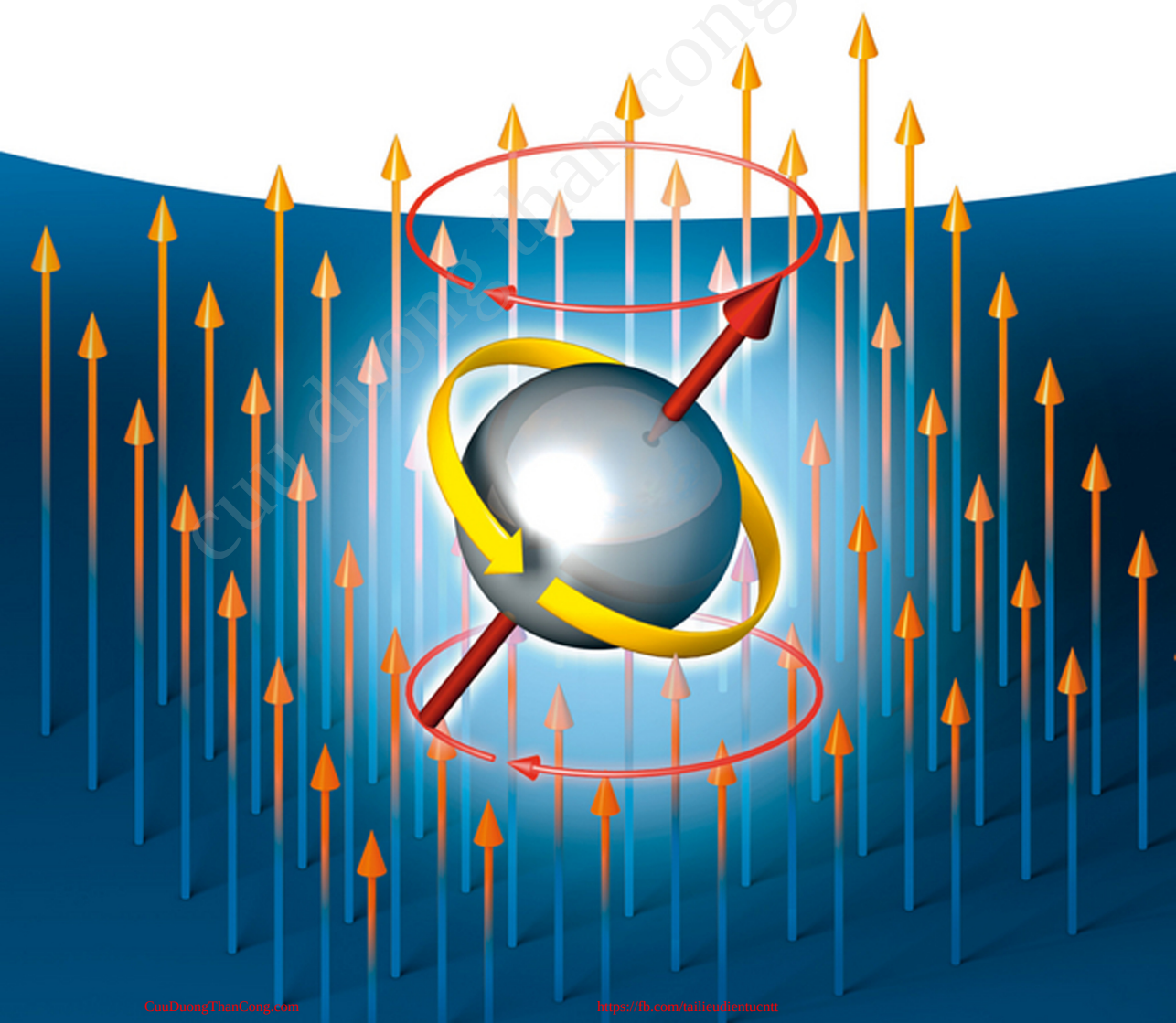


Harald Günther

NMR Spectroscopy

Basic Principles, Concepts
and Applications in Chemistry

Third Edition



cuu duong than cong . com

Harald Günther

NMR Spectroscopy

Related Titles

Zerbe, O., Jurt, S.

Applied NMR Spectroscopy for Chemists and Life Scientists

2013

ISBN: 978-3-527-32775-1 Hardcover

ISBN: 978-3-527-32774-4 Softcover

Friebolin, H.

Basic One- and Two-Dimensional NMR Spectroscopy

2011

ISBN: 978-3-527-32782-9

Pregosin, P. S.

NMR in Organometallic Chemistry

2012

ISBN: 978-3-527-33013-3

Keeler, J.

Understanding NMR Spectroscopy

2010

ISBN: 978-0-470-74609-7 Hardcover

ISBN: 978-0-470-74608-0 Softcover

Bertini, I., McGreevy, K. S., Parigi, G. (eds.)

NMR of Biomolecules Towards Mechanistic Systems Biology

2012

ISBN: 978-3-527-32850-5

Berger, S., Sicker, D.

Classics in Spectroscopy Isolation and Structure Elucidation of Natural Products

2009

ISBN: 978-3-527-32617-4 Hardcover

ISBN: 978-3-527-32516-0 Softcover

Harald Günther

NMR Spectroscopy

Basic Principles, Concepts, and Applications in Chemistry

Third, completely revised and updated edition

WILEY-VCH
Verlag GmbH & Co. KGaA

The Author

Prof. em. Dr. Harald Günther

Fakultät IV, OC II
Universität Siegen
D-57068 Siegen
Germany

■ All books published by **Wiley-VCH** are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <<http://dnb.d-nb.de>>.

© 2013 Wiley-VCH Verlag GmbH & Co.
KGaA, Boschstr. 12, 69469 Weinheim,
Germany

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

Hardcover ISBN: 978-3-527-33004-1

Softcover ISBN: 978-3-527-33000-3

Cover Design Formgeber, Eppelheim

Typesetting Laserwords Private Limited,
Chennai, India

Printing and Binding Markono Print
Media Pte Ltd, Singapore

Printed in Singapore

Printed on acid-free paper

Contents

Preface XV

1 Introduction 1

- 1.1 Literature 8
- 1.2 Units and Constants 9
- References 10

Part I Basic Principles and Applications 11

2 The Physical Basis of the Nuclear Magnetic Resonance Experiment.

Part I 13

- 2.1 The Quantum Mechanical Model for the Isolated Proton 13
- 2.2 Classical Description of the NMR Experiment 16
- 2.3 Experimental Verification of Quantized Angular Momentum and of the Resonance Equation 17
- 2.4 The NMR Experiment on Compact Matter and the Principle of the NMR Spectrometer 19
 - 2.4.1 How to Measure an NMR Spectrum 19
- 2.5 Magnetic Properties of Nuclei beyond the Proton 25
- References 27

3 The Proton Magnetic Resonance Spectra of Organic Molecules – Chemical Shift and Spin–Spin Coupling 29

- 3.1 The Chemical Shift 29
 - 3.1.1 Chemical Shift Measurements 32
 - 3.1.2 Integration of the Spectrum 35
 - 3.1.3 Structural Dependence of the Resonance Frequency – A General Survey 37
- 3.2 Spin–Spin Coupling 41
 - 3.2.1 Simple Rules for the Interpretation of Multiplet Structures 46
 - 3.2.2 Spin–Spin Coupling with Other Nuclei 49
 - 3.2.2.1 Nuclei of Spin $I = \frac{1}{2}$ 49

3.2.2.2	Nuclei of Spin $I > \frac{1}{2}$	51
3.2.3	Limits of the Simple Splitting Rules	52
3.2.3.1	The Notion of Magnetic Equivalence	52
3.2.3.2	Significance of the Ratio $J/\nu_0\delta$	56
3.2.4	Spin–Spin Decoupling	58
3.2.5	Two-Dimensional NMR – the COSY Experiment	60
3.2.6	Structural Dependence of Spin–Spin Coupling – A General Survey	62
	References	66
4	General Experimental Aspects of Nuclear Magnetic Resonance Spectroscopy	67
4.1	Sample Preparation and Sample Tubes	67
4.2	Internal and External Standards; Solvent Effects	70
4.3	Tuning the Spectrometer	74
4.4	Increasing the Sensitivity	78
4.5	Measurement of Spectra at Different Temperatures	81
	References	83
	Textbooks	83
	Review Articles	83
5	Proton Chemical Shifts and Spin–Spin Coupling Constants as Functions of Structure	85
5.1	Origin of Proton Chemical Shifts	86
5.1.1	Influence of the Electron Density at the Proton	87
5.1.2	Influence of the Electron Density at Neighboring Carbon Atoms	87
5.1.3	The Influence of Induced Magnetic Moments of Neighboring Atoms and Bonds	94
5.1.4	Ring Current Effect in Cyclic Conjugated π -Systems	101
5.1.5	Alternative Methods to Measure Diatropicity	110
5.1.6	Diamagnetic Anisotropy of the Cyclopropane Ring	113
5.1.7	Electric Field Effect of Polar Groups and the van-der Waals Effect	114
5.1.8	Chemical Shifts through Hydrogen Bonding	117
5.1.9	Chemical Shifts of Protons in Organometallic Compounds	119
5.1.10	Solvent Effects	120
5.1.11	Empirical Substituent Constants	121
5.1.11.1	Tables of Proton Resonances in Organic Molecules	122
5.2	Proton–Proton Spin–Spin Coupling and Chemical Structure	122
5.2.1	The Geminal Coupling Constant (^2J)	123
5.2.1.1	Dependence on the Hybridization of the Methylene Carbon	123
5.2.1.2	Effect of Substituents	124
5.2.1.3	A Molecular Orbital Model for the Interpretation of Substituent Effects on ^2J	126
5.2.2	The Vicinal Coupling Constant (^3J)	128
5.2.2.1	Dependence on the Dihedral Angle	129

5.2.2.2	Dependence upon the C–C Bond Length, $R_{\mu\nu}$	130
5.2.2.3	Dependence on HCC Valence Angles	132
5.2.2.4	Substituent Effects	133
5.2.3	Long-Range Coupling Constants (^4J , ^5J)	137
5.2.3.1	Saturated Systems	138
5.2.3.2	Unsaturated Systems	139
5.2.4	Through-Space and Dipolar Coupling	143
5.2.5	Tables of Spin–Spin Coupling Constants in Organic Molecules	144
	References	147
	Monograph	148
	Review Articles	148
6	The Analysis of High-Resolution Nuclear Magnetic Resonance Spectra	149
6.1	Notation for Spin Systems	150
6.2	Quantum Mechanical Formalism	151
6.2.1	The Schrödinger Equation	151
6.3	The Hamilton Operator for High-Resolution Nuclear Magnetic Resonance Spectroscopy	153
6.4	Calculation of Individual Spin Systems	155
6.4.1	Stationary States of a Single Nucleus A	156
6.4.2	Two Nuclei without Spin–Spin Interaction ($J_{ij} = 0$); Selection Rules	156
6.4.3	Two Nuclei with Spin–Spin Interaction ($J_{ij} \neq 0$)	158
6.4.3.1	The A_2 Case and the Variational Method	158
6.4.3.2	Calculation of the Relative Intensities	162
6.4.3.3	Symmetric and Antisymmetric Wave Functions	163
6.4.4	The AB System	164
6.4.5	The AX System and the First-Order Approximation	167
6.4.6	General Rules for the Treatment of More Complex Spin Systems	170
6.5	Calculation of the Parameters ν_i and J_{ij} from the Experimental Spectrum	174
6.5.1	Direct Analysis of the AB System	175
6.5.2	Spin Systems with Three Nuclei	177
6.5.2.1	The AB_2 (A_2B) System	177
6.5.2.2	The Particle Spin	181
6.5.2.3	The ABX System	182
6.5.3	Spin Systems with Four Nuclei – The $AA'XX'$ System	192
6.5.4	Computer Analysis	206
	References	209
	Textbooks	210
	Review Articles	210

7	The Influence of Molecular Symmetry and Chirality on Proton Magnetic Resonance Spectra	211
7.1	Spectral Types and Structural Isomerism	211
7.2	Influence of Chirality on the NMR Spectrum	216
7.3	Analysis of Degenerate Spin Systems by Means of ^{13}C Satellites and H/D Substitution	226
	References	229
	Review Articles	230

Part II Advanced Methods and Applications 231

8	The Physical Basis of the Nuclear Magnetic Resonance Experiment.	
	Part II: Pulse and Fourier-Transform NMR	233
8.1	The NMR Signal by Pulse Excitation	234
8.1.1	Resonance for the Isolated Nucleus	234
8.1.2	Pulse Excitation for a Macroscopic Sample	236
8.2	Relaxation Effects	239
8.2.1	Longitudinal or Spin–Lattice Relaxation	239
8.2.2	Transverse or Spin–Spin Relaxation	243
8.2.3	Experiments for Measuring Relaxation Times	247
8.2.3.1	T_1 Measurements – the Inversion Recovery Experiment	247
8.2.3.2	The Spin Echo Experiment	248
8.3	Pulse Fourier-Transform (FT) NMR Spectroscopy	249
8.3.1	Pulse Excitation of Entire NMR Spectra	250
8.3.2	The Receiver Signal and its Analysis	252
8.4	Experimental Aspects of Pulse Fourier-Transform Spectroscopy	254
8.4.1	The FT NMR Spectrometer – Basic Principles and Operation	254
8.4.1.1	The Computer and the Analog–Digital Converter (ADC)	254
8.4.1.2	RF Sources of an FT NMR Spectrometer	258
8.4.1.3	Transmitter and Signal Phase	259
8.4.1.4	Selective Excitation and Shaped Pulses in FT NMR Spectroscopy	260
8.4.1.5	Pulse Calibration	263
8.4.1.6	Composite Pulses	264
8.4.1.7	Single and Quadrature Detection	264
8.4.1.8	Phase Cycles	266
8.4.2	Complications in FT NMR Spectroscopy	267
8.4.3	Data Improvement	269
8.5	Double Resonance Experiments	272
8.5.1	Homonuclear Double Resonance – Spin Decoupling	272
8.5.2	Heteronuclear Double Resonance	273
8.5.3	Broadband Decoupling	275
8.5.3.1	Broadband Decoupling by CW Modulation	275
8.5.3.2	Broadband Decoupling by Pulse Methods	276
8.5.4	Off-Resonance Decoupling	277
	References	279

Textbooks 280
 Review articles 280

9	Two-Dimensional Nuclear Magnetic Resonance Spectroscopy	281
9.1	Principles of Two-Dimensional NMR Spectroscopy	281
9.1.1	Graphical Presentation of Two-Dimensional NMR Spectra	284
9.2	The Spin Echo Experiment in Modern NMR Spectroscopy	285
9.2.1	Time-Dependence of Transverse Magnetization	285
9.2.2	Chemical Shifts and Spin–Spin Coupling Constants and the Spin Echo Experiment	286
9.3	Homonuclear Two-Dimensional Spin Echo Spectroscopy: Separation of the Parameters J and δ for Proton NMR Spectra	289
9.3.1	Applications of Homonuclear ^1H J, δ -Spectroscopy	291
9.3.2	Practical Aspects of ^1H J, δ -Spectroscopy	294
9.4	The COSY Experiment – Two-Dimensional $^1\text{H}, ^1\text{H}$ Shift Correlations	296
9.4.1	Some Experimental Aspects of 2D-COSY Spectroscopy	300
9.4.2	Artifacts in COSY Spectra	302
9.4.3	Modifications of the Jeener Pulse Sequence	304
9.4.3.1	COSY-45	304
9.4.3.2	Long-Range COSY (COSY-LR)	305
9.4.3.3	COSY with Double Quantum Filter (COSY-DQF)	307
9.5	The Product Operator Formalism	309
9.5.1	Phenomenon of Coherence	309
9.5.2	Operator Basis for an AX System	311
9.5.3	Zero- and Multiple-Quantum Coherences	312
9.5.4	Evolution of Operators	313
9.5.5	The Observables	316
9.5.6	The COSY Experiment within the Product Operator Formalism	317
9.5.7	The COSY Experiment with Double-Quantum Filter (COSY-DQF)	320
9.6	Phase Cycles	322
9.6.1	COSY Experiment	324
9.7	Gradient Enhanced Spectroscopy	326
9.8	Universal Building Blocks for Pulse Sequences	329
9.8.1	Constant Time Experiments: ω_1 -Decoupled COSY	329
9.8.2	BIRD Pulses	329
9.8.3	Low-Pass Filter	330
9.8.4	z -Filter	331
9.9	Homonuclear Shift Correlation by Double Quantum Selection of AX Systems – the 2D-INADEQUATE Experiment	331
9.10	Single-Scan 2D NMR	336
	References	337
	Textbooks and Monographs	338
	Methods Oriented	338

Application Oriented	338
Review articles	338

10 More 1D and 2D NMR Experiments: the Nuclear Overhauser Effect – Polarization Transfer – Spin Lock Experiments – 3D NMR 341

10.1	The Overhauser Effect	341
10.1.1	Original Overhauser Effect	341
10.1.2	Nuclear Overhauser Effect (NOE)	343
10.1.3	One-Dimensional Homonuclear NOE Experiments	345
10.1.3.1	NOE Measurements of Relative Distances between Protons	345
10.1.3.2	NOE Difference Spectroscopy	346
10.1.4	Complications during NOE Measurements	348
10.1.5	Two-Dimensional Homonuclear Overhauser Spectroscopy (NOESY)	350
10.1.6	Two-Dimensional Heteronuclear Overhauser Spectroscopy (HOESY)	355
10.2	Polarization Transfer Experiments	357
10.2.1	SPI Experiment	357
10.2.2	INEPT Pulse Sequence	360
10.3	Rotating Frame Experiments	364
10.3.1	Spin Lock and Hartmann–Hahn Condition	364
10.3.2	Spin Lock Experiments in Solution	366
10.3.2.1	Homonuclear Hartmann–Hahn or TOCSY Experiments	366
10.3.2.2	One-Dimensional Selective TOCSY Spectroscopy	368
10.3.2.3	ROESY Experiment	369
10.4	Multidimensional NMR Experiments	371
	References	376
	Textbooks	376
	Review articles	376

11 Carbon-13 Nuclear Magnetic Resonance Spectroscopy 377

11.1	Historical Development and the Most Important Areas of Application	378
11.2	Experimental Aspects of Carbon-13 Nuclear Magnetic Resonance Spectroscopy	381
11.2.1	Gated Decoupling	382
11.2.2	Assignment Techniques	383
11.2.2.1	Multiplicity Selection with the Heteronuclear Spin Echo Experiment (SEFT, APT)	383
11.2.2.2	Polarization Transfer Experiments	387
11.2.2.3	Heteronuclear Two-Dimensional ^1H , ^{13}C Chemical Shift Correlation	389
11.2.2.4	The ^{13}C , ^{13}C INADEQUATE Experiment	398
11.2.2.5	Heteronuclear J , δ Spectroscopy	401
11.2.2.6	Assignment Techniques with Selective Excitation	403

11.2.2.7	Alternative Assignment Techniques	405
11.3	Carbon-13 Chemical Shifts	407
11.3.1	Theoretical Models	409
11.3.2	Empirical Correlations	418
11.4	Carbon-13 Spin–Spin Coupling Constants	420
11.4.1	Carbon-13 Coupling Constants and Chemical Structure	422
11.4.1.1	^{13}C , ^{13}C Coupling Constants	422
11.4.1.2	^{13}C , ^1H Coupling Constants	424
11.4.1.3	^{13}C , X Coupling Constants	427
11.5	Carbon-13 Spin–Lattice Relaxation Rates	428
	References	430
	Textbooks and Monographs	430
	Review articles	430
12	Selected Heteronuclei	431
12.1	Semimetals and Non-metals with the Exception of Hydrogen and Carbon	435
12.1.1	Boron-11	435
12.1.1.1	Referencing and Chemical Shifts	437
12.1.1.2	Polyhedral Boranes	438
12.1.2	Nitrogen-15	439
12.1.2.1	Referencing and Chemical Shifts	441
12.1.2.2	Spin-Spin Coupling	445
12.1.3	Oxygen-17	445
12.1.3.1	Referencing and Chemical Shifts	446
12.1.4	Fluorine-19	447
12.1.4.1	Referencing and Chemical Shifts	448
12.1.4.2	Spin-Spin Coupling	452
12.1.5	Silicon-29	454
12.1.5.1	Referencing and Chemical Shifts	454
12.1.5.2	Spin-Spin Coupling	457
12.1.6	Phosphorus-31	458
12.1.6.1	Referencing and Chemical Shifts	458
12.1.6.2	Spin-Spin Coupling	461
12.2	Main Group Metals	462
12.2.1	Lithium-6,7	462
12.2.1.1	Referencing and Chemical Shifts	463
12.2.1.2	Spin-Spin Coupling	463
12.2.2	Aluminum-27	468
12.2.2.1	Referencing and Chemical Shifts	469
12.2.3	Tin-119	471
12.2.3.1	Referencing and Chemical Shifts	472
12.2.3.2	Spin-Spin Coupling	473
12.3	Transition Metals	474
12.3.1	Vanadium-51	476

12.3.2	Platinum-195	480
12.3.2.1	Spin-Spin Coupling	482
12.3.3	Cobalt-59	482
12.3.4	Copper-63	484
12.3.5	Rhodium-103	485
12.3.6	Cadmium-113	488
12.3.7	Iron-57	489
12.3.8	Manganese-55	491
12.3.9	Molybdenum-95	492
12.3.10	Tungsten-183	492
12.3.11	Mercury-199	494
12.3.12	Osmium-187	496
	References	496
	Textbooks	498
	Monographs	498
	General Review Articles	498
	Selected Review Articles dealing with Individual Nuclei not cited Above	498

13 Influence of Dynamic Effects on Nuclear Magnetic Resonance Spectra 501

13.1	Exchange of Protons between Positions with Different Larmor Frequencies	501
13.1.1	Quantitative Description of Dynamic Nuclear Magnetic Resonance	504
13.1.2	Relationships to Reaction Kinetics	505
13.1.3	Approximate Solutions and Sources of Error	509
13.1.4	More Complex Exchange Phenomena	512
13.1.5	Application of Inversion-Recovery Experiments to the Determination of Rate Constants	513
13.1.6	Two-Dimensional Exchange Spectroscopy (EXSY)	514
13.1.7	Measurements of First-Order Rate Constants by Integration	516
13.2	Internal Dynamics of Organic Molecules	517
13.2.1	Hindrance to Internal Rotation	518
13.2.1.1	Bonds with Partial Double Bond Character	518
13.2.1.2	Substituted Ethanes	521
13.2.2	Inversion of Configuration	523
13.2.3	Ring Inversion	526
13.2.4	Valence Tautomerism and Bond Shifts	532
13.2.5	Dynamic Processes in Organometallic Compounds and Carbocations	542
13.3	Intermolecular Exchange Processes	549
13.4	Line Broadening by Fast Relaxing Neighboring Nuclei	554
	References	555

Textbooks 556
Review Articles 556

14	Nuclear Magnetic Resonance of Partially Oriented Molecules and Solid State NMR	557
14.1	Nuclear Magnetic Resonance of Partially Oriented Molecules	557
14.1.1	Nuclear Magnetic Resonance in Liquid Crystals	558
14.1.2	Other Alignment Methods – Residual Dipolar Couplings	565
14.2	High-Resolution Solid State Nuclear Magnetic Resonance Spectroscopy	568
14.2.1	Experimental Techniques of High-Resolution Solid State NMR Spectroscopy	570
14.2.1.1	Line Narrowing	570
14.2.1.2	Assignment Methods	576
14.2.1.3	Quadrupolar Nuclei	577
14.2.2	Applications of High-Resolution Solid State NMR Spectroscopy	580
14.2.2.1	Spin $\frac{1}{2}$ Nuclei	580
14.2.2.2	Quadrupolar Nuclei	584
14.2.2.3	Dynamic Processes	588
	References	589
	Textbooks	590
	Review Articles	590
15	Selected Topics of Nuclear Magnetic Resonance Spectroscopy	591
15.1	Isotope Effects in Nuclear Magnetic Resonance	591
15.1.1	Isotopic Perturbation of Equilibrium	595
15.2	Nuclear Magnetic Resonance Spectroscopy of Paramagnetic Materials	597
15.2.1	Contact Shifts	597
15.2.2	Pseudo-contact Shifts – Shift Reagents	599
15.3	Chemically Induced Dynamic Nuclear Polarization (CIDNP)	604
15.3.1	Energy Polarization (Net Effect)	605
15.3.2	Entropy Polarization (Multiplet Effect)	608
15.3.3	The Kaptein Rules	611
15.4	Diffusion-Controlled Nuclear Magnetic Resonance Spectroscopy – DOSY	612
15.4.1	Measurement of Diffusion Coefficients	612
15.4.2	Mixture Analysis by Diffusion-Ordered Spectroscopy (DOSY)	615
15.5	Unconventional Methods for Sensitivity Enhancement – Hyperpolarization	617
15.5.1	Hydrogenation Reactions and the Effect of <i>para</i> -Hydrogen	617
15.5.2	Optical Pumping – Xenon-129 NMR	621
15.5.3	Dynamic Nuclear Polarization	623
15.6	Nuclear Magnetic Resonance in Biochemistry and Medicine	625
15.6.1	Biomolecules	625

15.6.2	Peptides and Proteins	627
15.6.3	Nucleic Acids	634
15.6.4	Oligo- and Polysaccharides	636
15.6.5	Solvent Suppression	639
15.6.6	NMR of Body Fluids and <i>In-vivo</i> NMR Spectroscopy	640
15.6.7	NMR Imaging	642
	References	647
	Review Articles	648

Appendix 649

1	The “Ring Current Effect” of the Benzene Nucleus	649
2	Tables of Proton Resonance Frequencies and Substituent Effects $S(\delta)$	650
2.1	Substituent Effects $S(\delta)$ or SCS	652
3	Tables of ^1H , ^1H Coupling Constants	654
4	Chemical Shifts and Substituent Effects $S(\delta)$ of ^{13}C Resonances in Organic Compounds	659
5	The Hamiltonian Operator in Polar Coordinates	664
6	Intensity Distribution in A-multiplets Caused by n Neighbouring X-Nuclei with Spin $I = 1$ or $I = \frac{3}{2}$	664
7	Commutable Operators	665
8	The F_z Operator	665
9	Equations for the Direct Analysis of AA'BB' Spectra	666
10	Bloch Equations	667
11	Bloch Equations Modified for Chemical Exchange	668
12	Phase Behavior of Cross Peaks in 2D Nuclear Overhauser Spectroscopy (NOESY), Rotating-Frame Overhauser Spectroscopy (ROESY), and Total Correlation Spectroscopy (TOCSY) and Chemical Exchange (EXSY) Experiments	671
13	The International System (SI) of Units (MKSA System)	672
	References	673

Solutions for Exercises 675

Glossary 691

Index 695

Preface

When the first German edition of this textbook appeared in 1973, nuclear magnetic resonance was already a well established physical method in chemical research. In the years that followed, however, we witnessed unprecedented new developments of this technique with three outstanding advancements: the introduction of cryomagnets and the inventions of Fourier transform and multidimensional NMR. Further editions of this book covered these new aspects but the unbroken vitality of NMR required now a thorough revision of the last edition that was published in English in 1995.

The present text follows the original concept that tried to fill the reader with enthusiasm for applying NMR methods to solve chemical problems. Since this was not without success, the author kept this policy but has now considerably expanded the scope of this introduction. Furthermore, he took pains to eliminate errors contained in the last edition. After an Introduction, the first seven Chapters that concentrate on proton NMR are now united in Part I: *Basic Principles and Applications*. They are amended with new developments as, for example, the *nucleus independent chemical shifts* (NICS) and include the analysis of spin systems. They cover as before the basic theory of NMR and the material important for NMR beginners as well as for users primarily interested in the relations between NMR parameters and chemical structure. More emphasis was led on Fourier transform and high-field NMR and 2D experiments were introduced. Part II: *Advanced Methods and Applications* starts in Chapter 8 with a more detailed treatment of the physical background of NMR and of the pulse Fourier transform method. Chapters 9 and 10 are devoted to the introduction of advanced techniques like two-dimensional and nuclear Overhauser experiments. Chapter 11 deals with carbon-13 NMR and presents the heteronuclear 2D experiments. It also includes NMR results for *fullerenes*. A separate Chapter 13 then gives an overview of dynamic NMR.

The largest changes are the addition of the new Chapter 12 on NMR of selected *heteronuclei*, including *transition metals*. Chapter 14 on partially oriented molecules and solid state NMR has been complemented by a section on *residual dipolar couplings*, and Chapter 15 that contains—aside from the earlier accounts on NMR of *paramagnetic materials* and *chemically induced nuclear polarization* (CIDNP)—the description of special techniques like sensitivity enhancement by the use of *para-hydrogen* (PHIP), by *optical pumping* and by *dynamic nuclear polarization* (DNP).

Moreover, experiments based on diffusion processes as well as *diffusion-ordered spectroscopy* (DOSY) are described and a final section gives an introductory overview of NMR in *biochemistry* and *medicine*.

In treating the material presented care was taken to keep the inclusion of the physical and mathematical background at an acceptable limit, especially since excellent physics-oriented textbooks are available. The book has then certainly a “chemical touch”, as a reviewer of a former edition put it, but this is just what the author intended. In the same way the description of technical aspects of the NMR spectrometer and of its operation were confined to an introductory level, again, because monographs and textbooks that treat these topics in more detail are at hand.

A few changes compared to the earlier editions and points where the text differs from conventions used in other NMR books must be mentioned. The low-energy orientation of the nuclear magnetic moment was now changed to be that parallel to the positive z -axis of the Cartesian coordinate system and to the direction of the external field B_0 , that is with the α -state as the ground state. To avoid a negative Hamiltonian, the reverse order, which has no consequences on the appearance of the spectrum, was kept in Chapter 5 when treating the analysis of spin systems. Throughout the text the left-hand-rule is used to describe the action of magnetic fields B on nuclear spins and in the coherence level diagrams the receiver is set at $+1$.

During the preparation of the present edition, the author received numerous support and encouragement that is gratefully acknowledged. Prof. H. Ihmels provided continued access to computer equipment as did Dra P. Olivares Guerrero and Dr. T. Paululat critically reviewed Chapter 4. Special advice was given by Prof. B. Wrackmeyer and Drs. J. Keeler and J. Schraml and valuable help in acquiring literature came from Dr. N. Schlörer. Material for three figures was kindly contributed by Profs. R.K. Harris and H. Rüterjans and Dr. W. Baumann. As acknowledged in former editions, my coworkers supplied a great number of the figures and to those already mentioned there I have to thank Drs. R. Aydin, T. Fox, W. Frankmölle, S. Jost, S. Oepen, P. Schmitt, and J.R. Wesener for new material. I am also most grateful to Profs. R.R. Ernst and K. Wüthrich for supplying their photographs and to the Physics Departments of Harvard University and The University of Illinois at Urbana Champaign for the photographs of E.M. Purcell and P.C. Lauterbur. Additional photographic material was kindly provided by Bruker Biospin and Siemens AG. Thanks are also due to the people engaged in the production process of the book and to the publisher for their cooperation. Last but not least I wish to thank my wife for continuously assisting with patience and advice my efforts to finish this project.

Siegen, June 2013

H. Günther

1

Introduction

Of the important spectroscopic aids that are at the disposal of the chemist for use in structure elucidation, nuclear magnetic resonance (NMR) spectroscopy is one of the major tools. When, in December 1945 and in January 1946, two groups of physicists in the United States working independently – Edward M. Purcell, Howard C. Torrey, and Richard V. Pound at Harvard University on the US east coast and Felix Bloch, William W. Hansen, and Martin Packard at Stanford University in California – first succeeded in observing the phenomenon of NMR in solids and liquids they set the starting point for the unforeseen development of a new branch of science. The impact of their discovery was soon recognized and Bloch and Purcell received the Nobel Prize in Physics in 1952 (Figures 1.1 and 1.2).

At the beginning of the 1950s, the phenomenon was called upon for the first time in the solution of a chemical problem. Since then its importance has steadily increased – a situation highlighted by three additional Nobel Prizes: in 1991 to Richard R. Ernst from the Eidgenössische Technische Hochschule (ETH) Zürich, Switzerland, for his outstanding contributions to the development of experimental NMR techniques, in 2002 to Kurt Wüthrich from the same institution for his

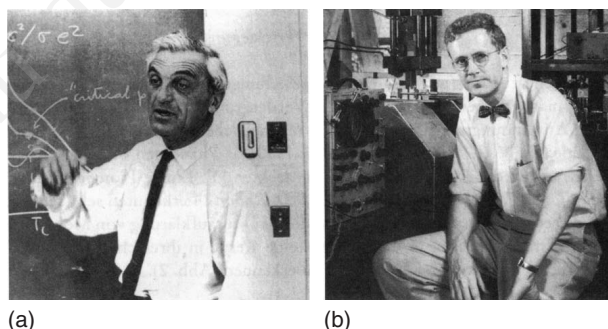


Figure 1.1 The founding fathers of nuclear magnetic resonance: Felix Bloch (1905–1983) (a) (Reprinted with permission from Reference [1]. Copyright 1985 International Society of Magnetic Resonance.) and Edward M. Purcell (1912–1997) (b). Courtesy of Physics Department, Harvard University.

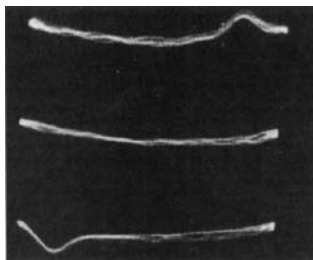


Figure 1.2 The first proton NMR signal from a water sample as seen on the screen of an oscilloscope by Bloch, Hansen, and Packard at Stanford University, California, USA, in January 1946 (Reprinted with permission from [2]. Copyright 1946 by the American Physical Society).

contributions to structural biology, and in 2003 to Paul C. Lauterbur from the University of Illinois at Urbana-Champaign, and Sir Peter Mansfield, University of Nottingham, UK, for the invention of NMR imaging, known today as magnetic resonance imaging (MRI).

The physical foundation of NMR spectroscopy lies in the magnetic properties of atomic nuclei. The interaction of the nuclear magnetic moment with an external magnetic field, B_0 , leads, according to the rules of quantum mechanics, to a nuclear energy level diagram, because the magnetic energy of the nucleus is restricted to certain discrete values E_i , the so-called *eigenvalues*. Associated with the eigenvalues are the *eigenstates*, which are the only states in which an elementary particle can exist. They are also called *stationary states*. Through a radiofrequency (RF) transmitter, transitions between these states can be stimulated. The absorption of energy is then detected in an RF receiver and recorded as a spectral line, the so-called *resonance signal* (Figure 1.3).

In this way a *spectrum* can be generated for a molecule containing atoms whose nuclei have non-zero magnetic moments. Among these nuclei are the proton, ^1H ,

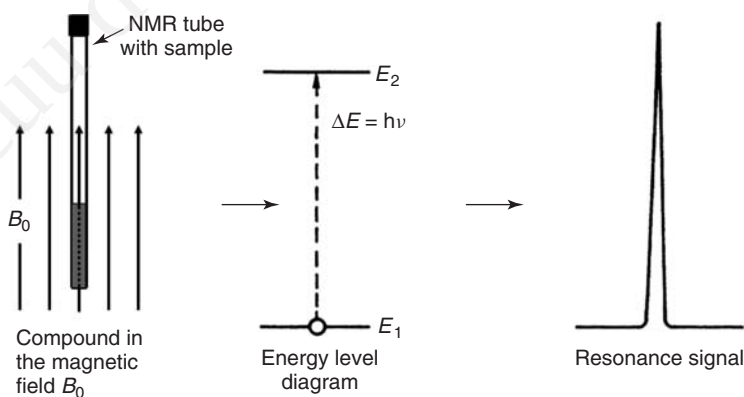


Figure 1.3 Formation of an NMR signal.

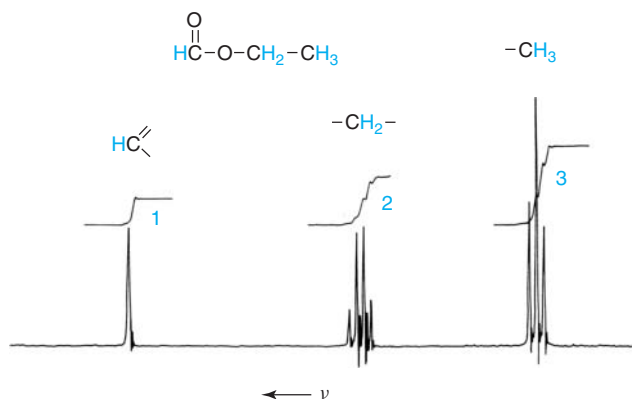


Figure 1.4 ^1H NMR spectrum of ethyl formate.

the fluorine nucleus, ^{19}F , the nitrogen isotopes, ^{14}N and ^{15}N , and many others of chemical interest. However, the carbon nucleus, ^{12}C , that is so important in organic chemistry has, like all other nuclei with even mass and even atomic number, no magnetic moment. Therefore, NMR studies with carbon are limited to the stable isotope ^{13}C , which has a natural abundance of only 1.1%.

To illustrate a NMR spectrum and its essential characteristics, the proton NMR spectrum of ethyl formate is reproduced in Figure 1.4. The spectrum was measured in a magnetic field of 1.4 T with a frequency ν of 60 MHz. In addition to the resonance signals observed at different frequencies, it shows a step curve produced by an electronic *integrator*. The heights of the steps are proportional to the areas under the corresponding spectral lines.

The following points should be noted:

- 1) Different resonance signals or groups of resonance signals are found for the protons. These arise because the protons reside in different chemical environments. The resonance signals are separated by a so-called *chemical shift*.
- 2) The area under a resonance signals is proportional to the number of protons that give rise to the signals. It can be measured by integration.
- 3) Not all proton resonances are simple (i.e., singlets). For some, characteristic splitting patterns are followed, forming triplets or quartets. This splitting is the result of *spin-spin coupling* – a magnetic interaction between different nuclei.

Empirically determined correlations between the spectral parameters, chemical shift and spin-spin coupling, on the one hand, and the structure of chemical compounds on the other hand form the basis for the application of proton and, in general, NMR to the *structure determinations* of unknown samples. In this respect the nuclear magnetic moment has proved itself to be a very sensitive probe with which one can gather extensive information. Thus, the chemical shift characterizes the chemical environment of the nucleus that is responsible for a signal. Integration of the spectrum allows one to draw conclusions concerning the relative numbers of nuclei present. Spin-spin coupling makes it possible

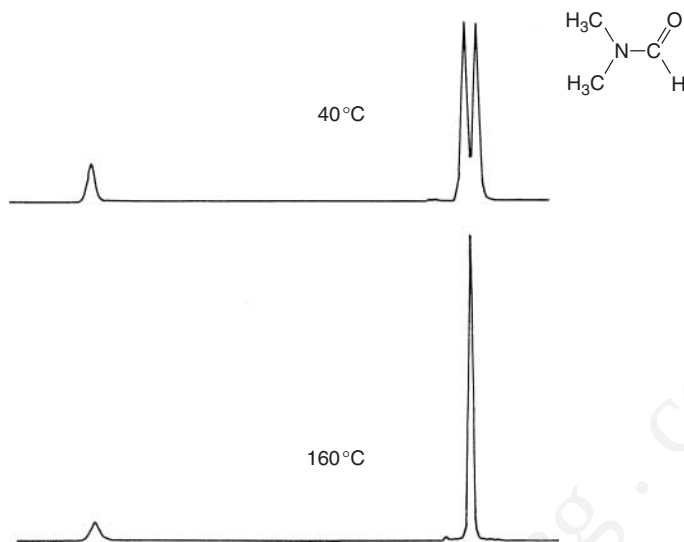
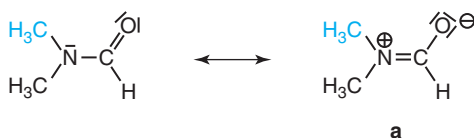


Figure 1.5 Temperature dependence of the ^1H NMR spectrum of *N,N*-dimethylformamide.

to define the positional relationship between the nuclei since the magnitude of this interaction – the coupling constant J – depends upon the number and type of bonds separating them. The multiplicity of the resonance signals and the intensity distribution within the multiplet are, moreover, in simple cases, as illustrated by the ethyl group of ethyl formate, clearly dependent upon the number of nuclei on the neighboring group.

Numerous additional applications of NMR have been developed. One of general importance is based on the observation that the NMR spectra of many compounds are temperature dependent and apparently sensitive to *dynamic processes*. Such a case is found with dimethylformamide, the spectrum of which shows a doublet for the resonance of the methyl protons at 40°C while at 160°C a singlet is observed (Figure 1.5).

The cause of this different behavior at the two temperatures is the high barrier to rotation about the carbonyl carbon–nitrogen bond (88 kJ mol^{-1}), which possesses partial double bond character as illustrated by the resonance form (a). The two methyl groups therefore have a relatively long life-time in different chemical environments, *cis* or *trans* to the carbonyl oxygen, and this leads to separate resonances. At higher temperatures the rate of internal rotation is increased and frequent interconversion of methyl groups between chemically different positions results, so that we are obviously no longer able to distinguish between them.



It follows that, for several molecules, the line shape of NMR signals is dependent upon dynamic processes and the *rates* of such processes can be studied with the aid of NMR spectroscopy. What is even more significant is that one can study fast reversible reactions that cannot be followed by means of classical kinetic methods. Thus, the progress achieved in the fields of fluxional molecules, like bullvalene, and in other areas, such as conformational analysis, would have been unimaginable without NMR spectroscopy.

NMR spectroscopy is also used successfully to study *reaction mechanisms* in all branches of chemistry. In these experiments, magnetic isotopes of hydrogen, carbon, or nitrogen (^2H , ^{13}C , ^{15}N) and many others can be used in labeling experiments that are devised to follow the fate of a particular atom during the reaction of interest. Labeling with radioactive carbon, ^{14}C , can be replaced today in many cases by labeling experiments with the stable but NMR active carbon isotope ^{13}C . Only where the highest sensitivity is indispensable does the use of the radiocarbon method still prevail.

The various aspects of the application of NMR to problems of inorganic, organic, and physical chemistry are supplemented by a remarkable variety of experimental techniques that lend a special position to NMR spectroscopy in comparison with other spectroscopic methods. In addition to the versatile physics of the NMR experiment, the large number of magnetic nuclei that are of significance to chemistry also contributes to this situation.

In the fields of organic chemistry and biochemistry, ^{13}C NMR plays a major role, but NMR investigations of ^{19}F , ^{15}N , and ^{31}P nuclei also yield valuable information. As is demonstrated in Figure 1.6 with the ^{13}C and ^{15}N NMR spectra of purine anion, the chemical shifts of these nuclei are sensitive to the chemical structure. With additional information from proton NMR, each position in the molecule is labeled with a reporter that provides data about bonding, structure, and reactivity.

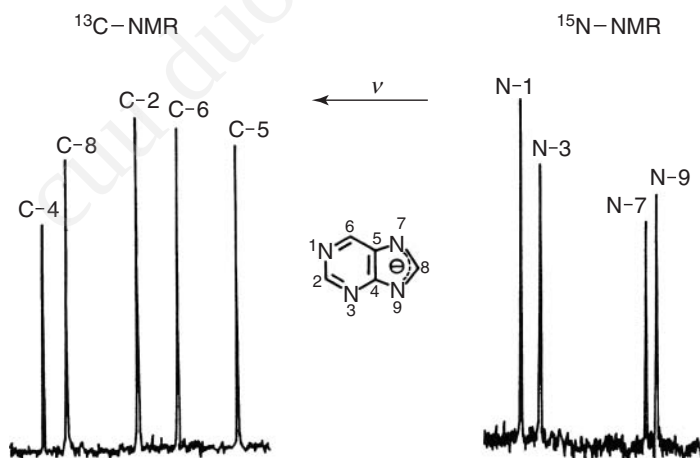


Figure 1.6 Carbon-13 (^{13}C) and nitrogen-15 (^{15}N) NMR spectra of the purine anion.

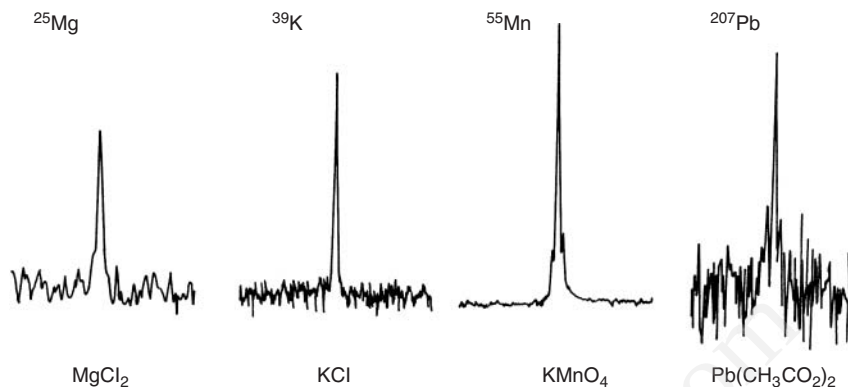


Figure 1.7 Nuclear magnetic resonance signals of metal nuclei.

For inorganic chemistry numerous metal nuclei are of interest and have become available for NMR experiments due to the rapid development of experimental techniques (Figure 1.7). Since nearly all elements of the Periodic Table contain a stable isotope with a magnetic moment, a large area is accessible for NMR investigations, even if the natural abundance of many of these isotopes is rather small.

Another innovation of general importance is *high-resolution NMR spectroscopy of solids*, which opened up new areas of structural research in inorganic and organic chemistry. Fast sample rotation and magnetization transfer from sensitive to insensitive nuclei – methods known as magic-angle spinning (MAS) and cross polarization (CP) – provide the basis for the measurement of chemical shifts and the study of dynamic processes even in solids.

All these topics have been accompanied by an improvement of existing, and the invention of completely new, measuring techniques. Three major events characterize this development:

- 1) Introduction of *cryomagnets* with high magnetic fields, B_0 , that are provided by a superconducting coil;
- 2) replacement of the continuous wave (CW) method by the pulse Fourier transform (PFT) method;
- 3) introduction of the concept of two-dimensional (2D) NMR.

These achievements have revolutionized practically all branches of NMR spectroscopy, for liquids as well as for solids:

- because the energy difference, ΔE , between the ground and excited state of NMR spectroscopy as well as the chemical shift are field dependent, the increase in B_0 has strongly improved *sensitivity* and *spectral dispersion*;
- while the older CW method used monochromatic signal excitation and the time needed to record a spectrum signal by signal was 250 or 500 s, the PFT method provides polychromatic signal excitation and the whole spectrum is measured in 1 s. The receiver signal is then analyzed mathematically by a Fourier transformation;

- two- and later *multidimensional NMR* became possible because special techniques of impulse spectroscopy allow the recording of NMR spectra with two or more independent frequency dimensions.

A 2D spectrum, for example, is characterized by two frequency axes, F_1 and F_2 , and the signals appear as frequency pairs (f_1, f_2) . In some experiments, the frequency axis F_2 only contains chemical shifts, while F_1 only contains spin–spin coupling constants. Both parameters are, therefore, separated by the 2D NMR experiment. For practical purposes spectra with chemical shift data on both frequency axes are the most important because they allow a so-called *shift correlation* between resonance frequencies of different nuclei and in this way a spectral assignment. One distinguishes homo- and heteronuclear shift correlations because F_1 and F_2 can contain frequencies of the same nuclides, for example, of protons, or of different nuclides, for example, of protons in F_1 and of carbon-13 in F_2 .

A homonuclear two-dimensional shift correlation, a so-called COSY spectrum (correlated spectroscopy), is shown in Figure 1.8 for the protons of ethyl formate. The new and important aspect is the observation of *cross peaks* that appear in addition to the normal spectrum recorded on the diagonal. Cross peaks have coordinates $F_1 \neq F_2$ and indicate spin–spin coupling between the respective nuclei, here those of the CH_2 and CH_3 group. Diagonal signals have the coordinates $F_1 = F_2$ and reproduce the 1D spectrum. The so-called *contour diagram* shown in Figure 1.8b gives a particularly clear demonstration of the characteristic cross peak positions.

COSY spectroscopy is important for the analysis of complex spectra with intensive signal overlap, where coupled nuclei can no longer be recognized on the basis of simple multiplet structures. Other 2D NMR spectra show cross peaks resulting from non-scalar interactions between nuclei that are close in space or that participate in a chemical exchange process. In this way information about atomic distances

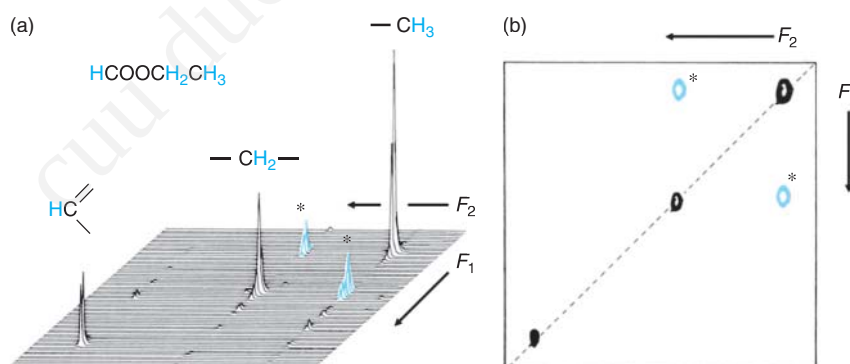


Figure 1.8 Two-dimensional $^1\text{H}, ^1\text{H}$ COSY spectrum of ethyl formate with the axes F_1 and F_2 with diagonal and cross peaks (the latter are marked with an asterisk, *); (a) stacked plot and (b) contour plot. The splitting due to spin–spin coupling is hidden in the line width.

or the mechanism of intramolecular dynamic processes becomes available. Two-dimensional NMR thus paved the way to successful investigation of the structures of complex molecules like natural products and biopolymers such as proteins or nucleic acids. In many cases even the complete three-dimensional structure could be derived solely on the basis of NMR data.

In summary, this short overview may convince the reader that NMR spectroscopy is an indispensable tool for all branches of chemistry. In addition, the method has its place in other sciences such as physics, biology, and even medicine, where in addition to the NMR imaging techniques the measurement of NMR spectra *in vivo* yields new information about body fluids or chemical processes in living tissue.

1.1

Literature

Numerous textbooks and monographs deal with NMR, ranging from physics to chemistry and biology to medicine. A complete bibliography is, therefore, beyond the limits of our introduction.

For the present textbook, we have adopted the following procedure: after each chapter we provide first a list with the original citations for material used in the text. Then, where required, selected textbooks or monographs are recommended for further reading, followed by a list of review articles on topics treated in the particular chapter. The following review series are frequently cited throughout the book:

- Webb, G.A. (ed) *Annual Reports on NMR Spectroscopy*, Elsevier, Amsterdam.
 Harris, R.K. and Grant, D.M. (eds) (1996) *Encyclopedia of Nuclear Magnetic Resonance*, John Wiley & Sons, Ltd, Chichester.
 Diehl, P., Fluck, E., Kosfeld, R., Günther, H., and Seelig, J. (eds) *NMR - Basic Principles and Progress*, Springer-Verlag, Berlin.
 Bodenhausen, G., Gadian, D.G., Meier, B.H., and Morris, G.A. (eds) *Progress in Nuclear Magnetic Resonance Spectroscopy*, Pergamon Press, Oxford.

To conclude this section, three classic books should also be listed:

- 1) Abragam, A. (1961) *The Principles of Nuclear Magnetism*, Clarendon Press, Oxford, 599 pp.
- 2) Ernst, R.R., Bodenhausen, G., and Wokaun, A. (1987) *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*, Clarendon Press, Oxford, 610 pp.
- 3) Pople, J.A., Schneider, W.G., and Bernstein, H.J. (1959) *High-Resolution Nuclear Magnetic Resonance*, McGraw-Hill Book Co., Inc., New York, 501 pp.

The first two books are physics-oriented and the last one was the first monograph with the emphasis on chemistry.

1.2

Units and Constants

The Système International (SI), based on the meter, kilogram, second, and ampere, is now accepted for all units of physicochemical quantities. Accordingly, SI units have generally been used in the present text. In chemistry, however, the old centimeter, gram, second (CGS) system is still in use and, of course, older textbooks and research papers employed this system. It seems, therefore, necessary to point out some of the main changes that occur when SI units are used:

- 1) For the magnetic field we use the symbol **B**, the magnetic induction field or magnetic flux density, a vector with magnitude *B*. The former use of **H** is incorrect, since this symbolizes the magnetic field intensity. The SI unit for the magnetic induction field is the tesla ($T = \text{kg s}^{-2} \text{A}^{-1}$), which is 10^4 times the electromagnetic unit, the gauss (G). Nevertheless, the simple expressions “magnetic field” or “field strength” are still in use when **B** is discussed.
- 2) The SI unit for energy is the joule ($J = \text{kg m}^2 \text{s}^{-2}$), and this replaces the calorie. Accordingly, activation energies are now given in kJ mol^{-1} , entropies in $\text{J K}^{-1} \text{mol}^{-1}$ (4.184 times the numerical values in kcal mol^{-1} or $\text{cal K}^{-1} \text{mol}^{-1}$, respectively).
- 3) The SI system uses rationalized equations. In these, the factors 2π or 4π appear where expected on geometrical grounds, that is, if the equation refers to situations where circular or spherical symmetry is involved.
- 4) The permeability of free space, μ_0 , often appears explicitly in SI equations.

Table 1.1 lists the constants that may be used for the physical relations given in the different chapters. In relevant situations we shall indicate which system is used.

Table 1.1 Constants for use in this book^{a,b}.

Symbol	Name	Magnitude	Unit
h	Planck's constant	6.625×10^{-34}	J s
e	Elementary charge	1.602×10^{-19}	C
m_e	Electron mass	0.9108×10^{-30}	kg
k or k_B	Boltzmann's constant	1.380×10^{-23}	J K ⁻¹
n_L	Loschmidt's number	6.0252×10^{23}	molecules mol ⁻¹
n_A	Avogadro's number	2.6870×10^{25}	gas molecules m ⁻³
μ_0	permeability of free space	$4\pi \times 10^{-7}$	kg m s ⁻² A ⁻²

^aMore information on units is given in Table A.7 (p. 672) in the Appendix.

^bTaken from reference [3]; please note that in the anglosaxon literature Loschmidt's number is called Avogadro's number.

References

1. Andrew, E.R. (1985) *Bull. Magn. Reson.*, 7, 81.
2. Bloch, F., Hansen, W.W., and Packard, M. (1946) *Phys. Rev.*, 70, 474.
3. Gerthsen, C., and Kneser, H.O. (1971) *Physik*, 11th ed., Springer, Berlin, p. 545.

Part I

Basic Principles and Applications

cuu duong than cong . com

2

The Physical Basis of the Nuclear Magnetic Resonance Experiment. Part I

Today's nuclear magnetic resonance (NMR) spectroscopy is characterized by Fourier transform (FT) spectroscopy and the use of superconducting magnets, so-called cryomagnets, with high magnetic fields. This chapter gives an elementary presentation of the method as applied to the proton, along with reference to the historical development of the technique. This presentation should suffice for the empirical and chemically routine application of the method, and as preparation for the material in Chapters 3–7. Chapter 8 gives a more detailed treatment of the physical principles.

2.1

The Quantum Mechanical Model for the Isolated Proton

The magnetic properties of atomic nuclei form the basis of NMR spectroscopy. We know from nuclear physics that several nuclei, among them the proton, possess *angular momentum*, $\mathbf{P}$, that in turn is responsible for the fact that these nuclei also exhibit a *magnetic moment*, $\boldsymbol{\mu}$. These two quantities are related through the expression:

$$\boldsymbol{\mu} = \gamma \mathbf{P} \quad (2.1)$$

where γ (in $\text{rad T}^{-1} \text{ s}^{-1}$), the *magnetogyric ratio*, is a constant characteristic of the particular nucleus. It can be positive or negative depending on the sense of nuclear rotation.

According to quantum theory, angular momentum and nuclear magnetic moment are *quantized*, a fact that cannot be explained by arguments based on classical physics. The allowed values or eigenvalues of the maximum component of the angular momentum in the z -direction of an arbitrarily chosen Cartesian coordinate system are measured in units of $\hbar$ ($h/2\pi$) and are defined by the relation:

$$P_z = \hbar m_l \quad (2.2)$$

with m_l as the *magnetic quantum number* that characterizes the corresponding

stationary or eigenstates of the nucleus. According to the *quantum condition*:

$$m_I = I, I - 1, I - 2, \dots, -I \quad (2.3)$$

the magnetic quantum numbers are related to the *spin quantum number*, I , of the respective nucleus; I can have half-integer or integer values up to $\frac{9}{2}$ (e.g., krypton-83, ^{83}Kr) or 3 (as for boron-10, ^{10}B), respectively. The total number of possible eigenstates or energy levels is equal to $2I + 1$.

The proton (^1H) has a spin quantum number $I = \frac{1}{2}$ and, consequently, can exist in only two eigenstates, also called *spin states* and characterized by the magnetic quantum numbers $m_I = +\frac{1}{2}$ and $m_I = -\frac{1}{2}$. With Eq. (2.1) we find for the z -component of its *magnetic moment*:

$$\mu_z = m_I \gamma \hbar \quad (2.4)$$

or:

$$\mu_z = \pm \frac{1}{2} \gamma \hbar = \pm \gamma \hbar I \quad (2.5)$$

The proton can therefore be pictured as a *magnetic dipole* – just called *spin* – that can exist in two different states.

In quantum mechanics, an atomic system is described by means of *wave functions* that are solutions of the well-known Schrödinger equation. For the purpose of the following discussion we introduce *eigenfunctions* α and β corresponding to the two eigenstates of the proton with $m_I = +\frac{1}{2}$ and $m_I = -\frac{1}{2}$, respectively. In Chapter 6 we shall describe in more detail the properties of these functions, since through them the energy of a spin system in a magnetic field can be determined. Here, they serve simply to label the two spin states.

The α and β states for the nuclei of spin quantum number $I = \frac{1}{2}$ have the same energy, that is, they are *degenerate*. Only in a static magnetic field B_0 is this degeneracy lifted as a result of the interaction of the nuclear magnetic moment μ with B_0 and both states have different energy (Figure 2.1). The potential energy of a magnetic dipole in the field B_0 directed along the positive z -axis of a Cartesian coordinate system is given by:

$$E = -\mu_z B_0 \quad (2.6)$$

and with Eq. (2.4) we have:

$$E = -m_I \gamma \hbar B_0 \quad (2.7)$$

The energy of the upper spin state, β ($m_I = -\frac{1}{2}$), that is, the excited state, is then $E_{-1/2} = +\frac{1}{2} \gamma \hbar B_0$ and that of the lower spin state, α ($m_I = +\frac{1}{2}$), that is, the ground

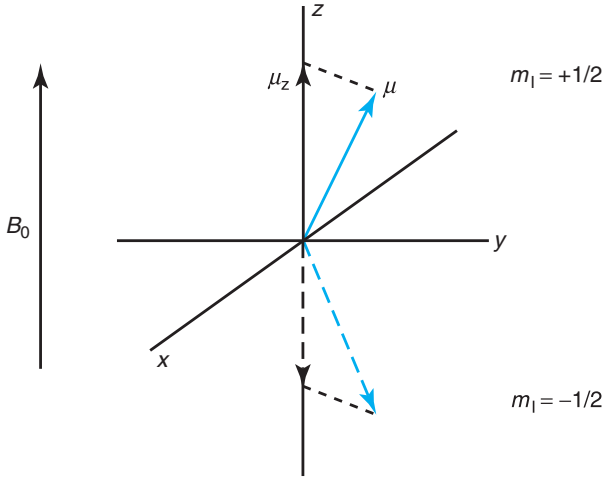


Figure 2.1 In the absence of a magnetic field the proton spin states have the same energy, that is, they are degenerate; in an external magnetic field B_0 the degeneracy is lifted and the parallel and antiparallel orientations relative to B_0 now have different energies. With the field B_0 in the positive z -direction, α with $m_l = +\frac{1}{2}$ is the low-energy or ground state while β with $m_l = -\frac{1}{2}$ is the high-energy or excited state.

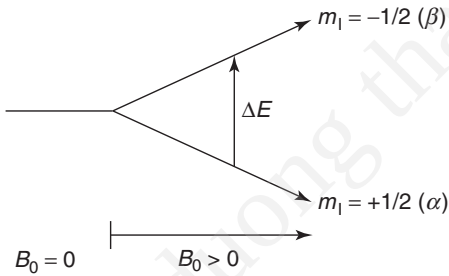


Figure 2.2 Energy separation between nuclear spin states without magnetic field and with increasing field strength B_0 (nuclear Zeeman splitting).

state, is $E_{+1/2} = -\frac{1}{2}\gamma\hbar B_0$. The energy difference (upper state minus lower state) is then given by:

$$\Delta E = \gamma\hbar B_0 \quad (2.8)$$

This energy separation between the states is proportional to the strength of the field B_0 (Figure 2.2) and is called *nuclear Zeeman splitting* in analogy to the splitting of electronic levels induced by a magnetic field, known as the *Zeeman effect*. It provides the necessary condition for the observation of a spectral line and, thus, forms the basis of the NMR experiment. According to the Bohr frequency condition,

$\Delta E = h\nu$, we need an energy quantum:

$$h\nu_0 = \gamma \hbar B_0 \quad (2.9)$$

or radiation of frequency:¹⁾

$$\nu_0 = \gamma B_0 \text{ or } \omega_0 = \gamma B_0 \quad (2.10)$$

to stimulate a transition to the state of higher energy. The energy is provided by the *transmitter coil* of the spectrometer and Eq. (2.10) describes the so-called *resonance condition*, where the radiation frequency exactly matches the energy gap. The NMR signal²⁾ observed with the *receiver coil* corresponds to the arrow in Figure 2.2 and ν_0 , the *Larmor frequency*, according to Eq. (2.10), varies with the strength of the B_0 field employed in the experiment. For protons with $\gamma_H = 2.675 \times 10^8 \text{ T}^{-1} \text{ s}^{-1}$ a field of 2.35 T yields $\nu_0 = 100 \text{ MHz}$ ($1 \text{ MHz} = 10^6 \text{ Hz}$), that corresponds to a wavelength, λ , of 3 m, which is typical for radio-waves at the ultrahigh frequency end of the radiofrequency (RF) region.

In a molecule the nucleus is surrounded by the electrons of the chemical bonds and the local magnetic field B_{local} is influenced by the chemical environment. As a consequence, its magnitude differs from that of B_0 . Thus, the resonance frequency also varies and this phenomenon is known as the *chemical shift*. It forms the basis for applications of NMR in chemistry and related fields. We shall discuss this aspect in detail in Chapters 3 and 5. For now we keep in mind that for a particular molecule we observe several NMR signals with different frequencies ν_i that constitute the NMR spectrum. This applies not only for the proton, but for other nuclei as well.

2.2

Classical Description of the NMR Experiment

Insight into the physics of NMR can also be gained if we consider the classical interaction of the particle spin with a magnetic field B_0 . This field attempts to align the magnetic moment μ with the field direction, but its angular momentum causes instead a precessional motion of μ around the field axis (Figure 2.3); μ thus behaves like a gyroscope under the force imposed by an angular momentum. For the angular velocity we have $\omega_0 = \gamma B_0$ and a magnetic field B_1 perpendicular to B_0 and rotating with the frequency $\omega_1 = \omega_0$ can effect the inversion of the magnetic moment; B_1 is provided by the electromagnetic radiation from the transmitter coil of the spectrometer. Again, we have the resonance condition for energy absorption with $\omega_0 = \gamma B_0$. More details about the physics of NMR will be presented in Chapter 8.

- 1) The frequency ν_0 is measured in hertz (Hz), while the angular frequency $\omega_0 (= 2\pi\nu_0)$ is measured in radians. We use in the following the angular frequency ω in equations related to the *physical background* of NMR and in sections with relevance to NMR *spectra* we use the frequency ν .
- 2) In molecular spectroscopy different terms are used to describe the spectra. One speaks of “bands” in ultraviolet and infrared spectroscopy but uses “signal” in nuclear magnetic resonance because the wavelengths are in the radiofrequency region (Figure 2.9). In addition, the term “line” is frequently used and, more recently, “peak” has become popular, in particular for 2D spectra.

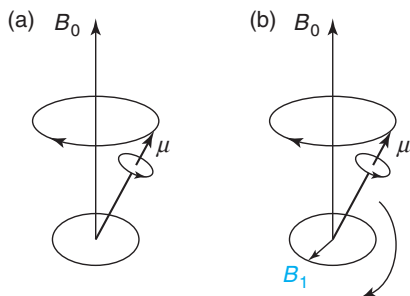


Figure 2.3 (a) Precessional motion of the nuclear magnetic moment μ around the external field B_0 and (b) a transverse field B_1 that causes inversion of μ (left-hand-rule: the thumb points along B_1 , the bend fingers show the sense of rotation of μ).

2.3

Experimental Verification of Quantized Angular Momentum and of the Resonance Equation

It seems appropriate to mention here two experiments of outstanding significance that verify the existence of nuclear magnetic moments and illustrate their behavior in a magnetic field as described above. They are the Stern–Gerlach experiment and the molecular beam experiment of Rabi, described in standard textbooks of physics.

Stern and Gerlach passed a stream of silver atoms, that in the ground state possess a total angular momentum of $\frac{1}{2}$, through a non-homogeneous magnetic field and found two discrete spots on the photographic plate used as a detector (Figure 2.4). The splitting of the beam of atoms is a direct consequence and a striking experimental documentation of the quantum nature of the magnetic energy of atoms. The magnetic moment of the individual silver atoms could be oriented either parallel or anti-parallel to the external magnetic field, that is, an atom

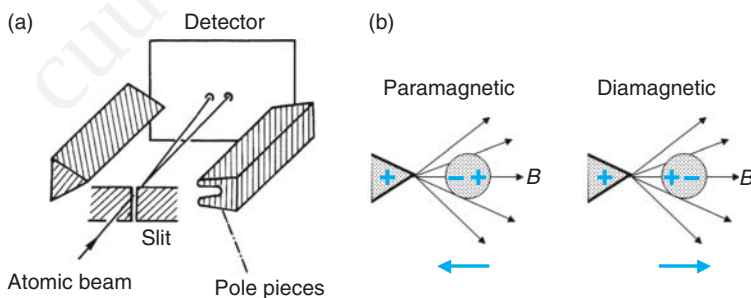


Figure 2.4 (a) Schematic representation of the Stern–Gerlach experiment; (b) behavior of paramagnetic and diamagnetic particles in an inhomogeneous magnetic field – the arrows indicate the direction of motion.

in the magnetic field would be either paramagnetic or diamagnetic. Paramagnetic and diamagnetic particles are, however, affected differently in an inhomogeneous magnetic field (Figure 2.4b). Because of the different field strengths at the dipole ends (illustrated by the density of the lines of force in the figure), one end of the dipole will be attracted or repelled more strongly than the other, resulting in a net accelerating force on the particle. If all orientations of the atomic moments relative to the magnetic field were allowed, as expected on the basis of classical theory, the experiment should yield a smear of silver atoms along a horizontal line. The observation of only two spots immediately tells us that only two distinct orientations, that is, two discrete values of magnetic energy, exist.

The quantization of magnetic energy demonstrated in this experiment is the result of the splitting of electronic states but it is also valid for nuclear spin states. This was demonstrated by the experiments of Rabi and his coworkers, who investigated the behavior of molecular beams (Figure 2.5). Only molecules for which the total electronic magnetic moment was zero were used in these experiments so that any observable magnetic effect had to be ascribed to the magnetic properties of the nuclei.

In the Rabi experiment a molecular beam enters the inhomogeneous magnetic field of magnet A, and, as described above for the Stern–Gerlach experiment, is split in two. Only the paramagnetic molecules following path *a* pass through the slit into the homogeneous field of magnet B and they are finally focused by the magnetic field of magnet C, the inhomogeneity of which is exactly opposite to that of A. The screen S serves as a detector that measures the intensity of the molecular beam focused at M. If one now irradiates the molecular beam in the region between the pole pieces of magnet B with RF radiation, there results at a particular frequency, depending upon the field strength of magnet B, a sharp decrease in the intensity of the molecular beam at M. At that frequency/field strength ratio the resonance condition 2.10 is met, the orientation of part of the nuclear magnetic moments changes through the absorption of energy, and these diamagnetic particles are diverted by the effect of the inhomogeneous field C along path *c* rather than proceeding along path *b* to the detector M.

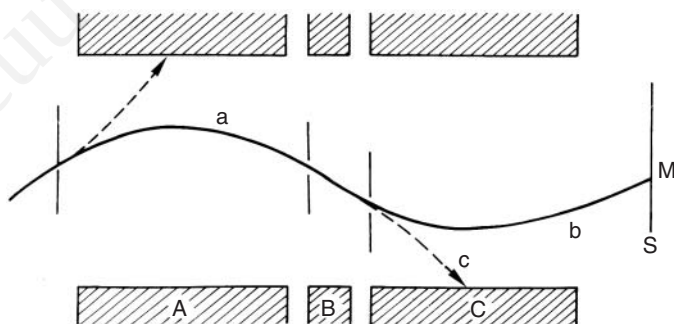


Figure 2.5 Principle of the experimental procedure used for detection of the resonance condition according to Rabi.

2.4

The NMR Experiment on Compact Matter and the Principle of the NMR Spectrometer

The significance of the experiments of the Bloch and Purcell groups mentioned in Chapter 1 is that they performed the NMR experiment for the first time on compact matter. With their discovery they laid the basis for observation of the chemical shift and its application in chemistry.

In a magnetic field B_0 the magnetic nuclei in both solids and liquids are distributed between their energy states. For a very large number of protons, such as, for example, exists in a macroscopic sample of hydrogen-containing material, the distribution of protons between ground and excited state is given by the Boltzmann relation:

$$\frac{N_\beta}{N_\alpha} = \exp\left(\frac{-\Delta E}{kT}\right) = \exp\left(\frac{-\gamma h B_0}{2\pi kT}\right) \approx 1 - \frac{\gamma h B_0}{2\pi kT} \quad (2.11)$$

where N_α and N_β are the numbers of nuclei in the ground and in the excited state, respectively, ΔE is the energy difference between these states, k is the Boltzmann constant, and T is the absolute temperature, in this context also called the *spin temperature* T_s . Since ΔE in the above case is very small, the number of nuclei in the lower state at equilibrium is only slightly larger than the number of nuclei in the higher state ($N_\alpha > N_\beta$). At a field strength of 2.35 T and room temperature, ΔE for protons is about 0.04 J mol^{-1} and the population excess in the lower state that determines the *probability* of a transition, and in this way the *sensitivity* of the experiment, amounts to only ca. 0.002 % or ~ 20 nuclei in 10^6 . Rather weak signals have thus to be detected in NMR spectroscopy. Equation (2.11) also tells us that the sensitivity of NMR experiments can be increased by raising the magnetic field strength and by lowering the temperature. The latter aspect is only of limited interest, but the use of stronger B_0 fields was a continuous challenge.

The most important parts of a NMR spectrometer are the magnet, the RF source, and the detector. The compound to be investigated is contained in a sample tube – a glass tube approximately 15 cm long and 5 or 10 mm in diameter – in the external magnetic field B_0 . A RF coil, the transmitter, yields the RF radiation and the stimulated signal is detected either through the same coil or through a separate coil, the receiver (single coil or cross coil type spectrometer). After amplification and transmission of the signal to an x,y plotter or a computer, the spectrum can be recorded and the resonance frequencies can be measured (Figure 2.6).

2.4.1

How to Measure an NMR Spectrum

In principle, two independent experimental techniques are available for the realization of an NMR experiment: CW (continuous wave) and FT NMR spectroscopy. Today the FT method is used exclusively – the reasons for this situation will become clear below – but for completeness we also describe briefly the older CW method. The basic procedures of both techniques will be discussed with the help of Figure 2.7.

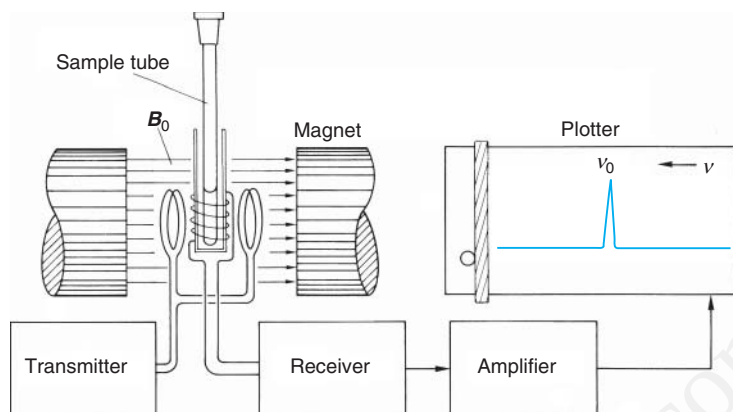


Figure 2.6 Schematic diagram of an NMR spectrometer with an electromagnet and separate transmitter and receiver coil (cross coil arrangement). An experimental arrangement of this type was used by Bloch, Hansen, and Packard for the first detection, in early January 1946, of proton NMR in liquids. Similar spectrometers, known as CW instruments and

equipped with iron magnets, served for several decades in NMR experiments, until they were replaced by Fourier-transform instruments with superconducting magnets. Please note that the direction of the magnetic field B_0 is perpendicular to the axis of the sample tube (see text below).

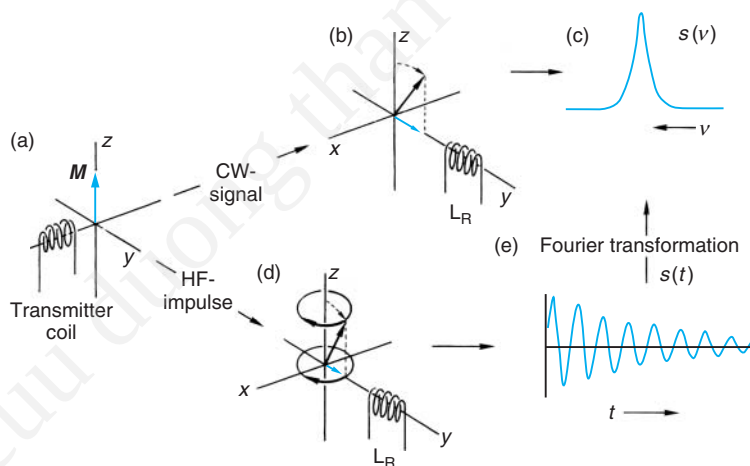


Figure 2.7 (a)–(e) NMR signal generation in CW and FT spectroscopy.

The notation CW means that during the recording of an NMR spectrum the frequency ν of a weak RF transmitter is varied continuously. The vector of the macroscopic magnetization of the sample, M (Figure 2.7a) that represents the excess of the individual nuclear magnetic moments μ in the ground state starts to deviate from its position on the z -axis through the action of the RF field B_1 produced along the x -axis by the transmitter coil (Figure 2.7b). This creates an x,y component, the so-called *transverse magnetization* that induces a signal in the

receiver coil L_R . The signal amplitude at maximum and at resonance ($\nu = \gamma B_0$) corresponds to the stationary state between nuclear *excitation* and *relaxation*, that is, the transfer of nuclei to the upper state and their return to the ground state. After resonance ($\nu > \gamma B_0$), the vector $\mathbf{M}$ again reaches its position on the z -axis after a precessional motion.

In the FT method, nuclear excitation is achieved through an RF pulse, a strong RF field (about 50 W) of short duration (typically 10–50 μs). The vector $\mathbf{M}$ will also be turned away from the z -axis in the direction of the y -axis. However, after the pulse, the RF radiation ends and only the magnetic field $\mathbf{B}_0$ acts upon $\mathbf{M}$, which starts a precession around the z -axis with the Larmor frequency characteristic of the particular nucleus (Figure 2.7d). The time signal induced in the receiver coil through this motion of the x, y component of $\mathbf{M}$, $S(t)$, the so-called *free induction decay (FID)*, fades away through relaxation (Figure 2.7e). Its Fourier transformation yields the frequency signal $S(\nu)$ that is identical with the CW signal. This procedure for the measurement of NMR spectra, used today exclusively, is also known as pulse Fourier transform (PFT) NMR spectroscopy.

Despite the fact that the FT method yields the spectrum only indirectly via the time signal $S(t)$, it has, compared to the CW method, a very important advantage. As we shall show in more detail in Chapter 8, the complete NMR spectrum can be excited with a single pulse and the corresponding time signal recorded within 1 s. In contrast, a CW spectrometer needs 250 s or more to record the spectrum since every signal has to be measured separately. This difference in measuring time was the main factor for the complete replacement of CW by FT NMR spectrometers after the invention of the FT method in 1966 by the Swiss physicist R.R. Ernst. Later it became clear that the possibilities of pulse FT NMR exceed by far that of the CW method because an enormous number of new experiments, never thought of before, could be developed.

From the simple form of Eq. (2.10) one sees immediately that resonance can in principle be realized in two ways: either by varying the frequency ν at constant field $\mathbf{B}_0$ or by varying the magnetic field strength B_0 while keeping the frequency ν_0 constant. The first procedure is called a *frequency sweep*, the second a *field sweep*. In the CW experiment both modes are possible but in the FT experiment there is no choice because pulse excitation always occurs at a constant field: the pulse provides RF over the total spectral width. This can be regarded as an instant frequency sweep.

Thus, the NMR spectrometer possesses all the elements that we also encounter in optical spectroscopy: radiation source, sample cell, and detector. Because the radiation we use comes from the RF region of the electromagnetic spectrum, the radiation source and detector are called the *transmitter* and *receiver*, respectively. However, a few more important differences have to be pointed out.

One difference is that the sample must be in a strong magnetic field before energy can be absorbed. Further, in the classic optical spectrometer the radiation is passed through a prism and thus is monochromatic. In the CW method the signal from the transmitter coil is also monochromatic, but in the FT experiment the radiation is polychromatic because a RF field $\mathbf{B}_1$ generated by an RF pulse has a broad frequency spectrum. Analysis of the receiver signal and its separation into

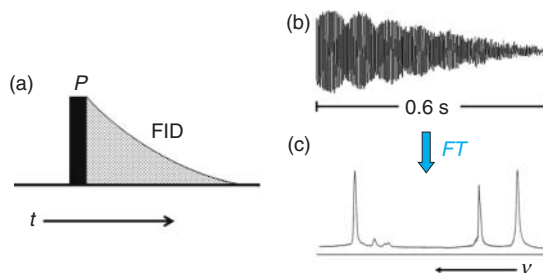


Figure 2.8 (a) Diagram of a FT NMR experiment; (b) FID for an NMR spectrum – its Fourier transformation yields the frequency spectrum (c) with the origin at the right-hand end.

individual resonance signals is then achieved via the mathematical procedure of Fourier transformation. A powerful computer is thus an important part of an FT NMR spectrometer.

We will see later that NMR experiments are described with simple diagrams that contain the necessary information to understand what is going on with the nuclear spins. The FT NMR experiment used today is represented as follows: a rectangular pulse P excites the spins and the receiver measures the FID, a frequency signal that decays through relaxation (Figure 2.8a). For a single line at the frequency ν_i the FID is a decaying oscillation as shown in Figure 2.7e, while for an NMR spectrum with n lines the FID results from the superposition of all line frequencies ν_1 to ν_n , including also the noise (Figure 2.8b). In practical spectroscopy the FID time signal is – except for spectrometer adjustments (Chapter 4) – not further evaluated and, after Fourier transformation, NMR spectra are exclusively presented as frequency spectra with individual resonance signals as in Figure 2.8c.

In Chapter 8 we will learn more about the details of the FT experiment that is the basis of modern NMR; here we only mention that on the t -axis different time scales are involved: the pulse has a length of the order of $10\ \mu\text{s}$ while the FID decay lasts about 1 s.

Furthermore, we note that in NMR spectroscopy there is a dramatic difference between the spectra of *solids* on the one hand and those of *liquids* or *solutions* on the other. In solids the rigid orientation of the nuclei with respect to the external magnetic field B_0 as well as to their neighboring nuclei leads to mechanisms that cause severe line broadening. For example, the variation, ΔB , in the local magnetic field at a nucleus caused by a nuclear magnetic moment μ in a distance r with an angle θ between the distance vector r and the direction of B_0 – called *dipolar coupling* – is given by:

$$\Delta B = \frac{\mu_0}{4\pi} (3 \cos^2 \theta - 1) \mu r^{-3} \quad (2.12)$$

where μ_0 is the permeability in free space. In a solid, the magnetic field therefore varies from place to place and the spectra of solids are characterized by lines that are several kilohertz wide and generally not easily analyzed.

In a liquid the factor $(3\cos^2\theta - 1)$ of Eq. (2.12) is reduced to zero because of the random thermal translational and rotational motions of the molecules, a fact that can be derived if the time average over $(3\cos^2\theta - 1)$ is replaced by the average obtained from $\Sigma_{x,y,z}(3\cos^2\theta_{x,y,z} - 1)/3$. The dipolar coupling between nuclei therefore cancels. Only in this situation do high-resolution NMR spectra with discrete resonance signals and with line widths smaller than 1 Hz result. One speaks, therefore, of *high-resolution* NMR spectroscopy.

Interestingly, however, according to Eq. (2.12) the dipolar coupling between nuclei also vanishes if $\theta = 54.7^\circ$ because $3\cos^2(54.7^\circ) - 1 = 0$. Thus, if one rapidly rotates the solid under examination, mostly a crystalline powder deposited in a so-called *rotor*, around an axis that forms the “magic” angle of 54.7° with the direction of the external field, one can eliminate the perturbing interaction since all distance vectors connecting magnetic moments would have the angle $\theta = 54.7^\circ$ as an *average* value. This technique – called magic-angle spinning (MAS) – forms the basis for a branch of NMR spectroscopy treated in more detail in Chapter 14: high-resolution NMR of solids.

Up to now we have concentrated our discussion of the NMR experiment on the process by which energy is absorbed. The equilibrium distribution of nuclei between spin states expressed in Eq. (2.11) presupposes, however, that excited nuclei can return to the lower spin state since, otherwise the population difference in the two states would tend to zero and the system would be *saturated*. As mentioned above, the process for the energy loss experienced by the nuclei in the excited state is called *relaxation*. In NMR it is caused by a loss of *x,y*-magnetization (*transverse relaxation*) as well as by a recovering of *z*-magnetization (*longitudinal relaxation*). Both mechanisms are responsible for the decay of the FID. The magnetic energy of relaxing nuclei is transferred to the environment as thermal energy and these nuclei return to the lower spin state. We shall consider this phenomenon in detail in Chapter 8. There we will learn that the dipole–dipole interaction introduced above provides in solution an efficient relaxation mechanism for many nuclei even if the effect of line splitting is eliminated. For the moment we will keep in mind that relaxation is as vital as absorption for the success of an NMR experiment.

As inferred above, the resonance frequency for protons and other nuclei lies in the region of radio-waves. In the electromagnetic spectrum, then, and in the series of well-known spectrometric methods, NMR spectroscopy takes its place at the long wavelength end (Figure 2.9).

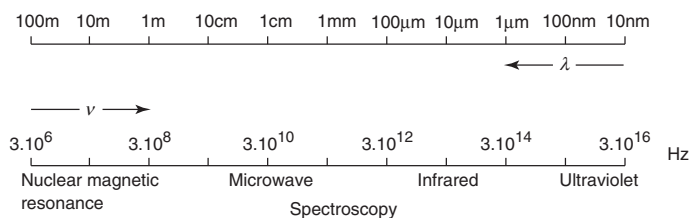


Figure 2.9 Electromagnetic spectrum.

While NMR spectroscopy was revolutionized by the introduction of the FT method, another modification was equally important, namely, replacement of the permanent and electromagnets by superconducting or cryomagnets. These are not magnets in the usual sense because the magnetic field is generated by a superconducting coil held at the temperature of liquid helium. This technique allows much higher magnetic fields, up to 17.5 T and more. For routine operations instruments with proton frequencies between 200 and 400 MHz, equivalent to a field strength of 4.70–9.35 T, respectively, are in use. Following Eq. (2.11), the sensitivity of the NMR experiment can thus be considerably improved because the lower spin state becomes more highly populated, that is, N_α increases. A further significant advantage of this development is the increase in spectral resolution because, as will become clearer in the next chapter, the chemical shift, which is the most important NMR parameter for chemical applications, is field-dependent and increases with increasing B_0 .

Figure 2.10 shows a schematic representation of a cryomagnet. An inner Dewar vessel contains the superconducting coil that is cooled by liquid helium to 2.3 K (-270°C). An outer Dewar vessel contains liquid nitrogen (77 K, -196°C). Both Dewars have to be refilled frequently, at an interval of about two weeks for nitrogen

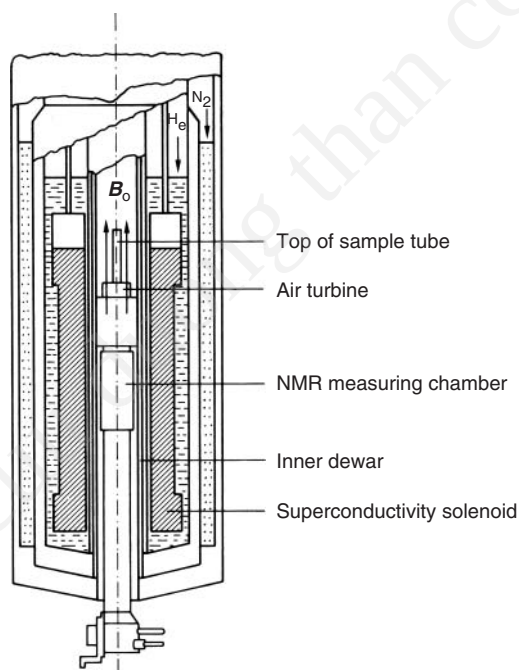


Figure 2.10 Schematic diagram of a superconducting or cryomagnet. The coil is located in a Dewar flask containing liquid helium; the Dewar flask, in turn, is cooled in liquid nitrogen. The sample tube is placed into the instrument

from above. In contrast to the older iron magnets, the lines of the external magnetic field B_0 are directed parallel to the long axis of the sample tube. (Courtesy Varian Associates, Palo Alto, CA, USA).

and up to several months for helium. The NMR tube is introduced into the magnet from above via a pneumatic system and the B_0 field direction coincides – as shown in Figure 2.1 – with the long axis of the sample cell, which is by 90° different from the arrangement with the electromagnet shown in Figure 2.6. The whole assembly with sample holder, air turbine, and transmitter and receiver coils in the NMR measuring chamber (Figure 2.10) is called the *probe* or the *probe-head*. Since measurements are made at room or even elevated temperature, insulation of the liquid helium chamber from the probe was an enormous engineering achievement. Instruments with various field strengths are in use and are classified by their proton NMR frequency (see Chapter 4).

2.5

Magnetic Properties of Nuclei beyond the Proton

Not all atomic nuclei possess magnetic moments and, furthermore, in the case of nuclei heavier than the proton, spin quantum numbers greater than $\frac{1}{2}$ are possible. The spin states of such nuclei are characterized, according to Eq. (2.2), by the magnetic quantum numbers $m_I = I, I - 1, I - 2, \dots -I$ and the energy level diagram for the deuteron ($I = 1$), for example, has the appearance illustrated in Figure 2.11.

Generally, for nuclei with even mass and even atomic number, the even–even nuclei, $I = 0$ and for all other nuclei $I \geq \frac{1}{2}$; I is an integral multiple of 1 for even–odd nuclei and for odd–odd and odd–even nuclei it is an integral multiple of $\frac{1}{2}$. Table 2.1 lists the nuclei that are most important for chemical applications, together with their relevant NMR properties. In particular, in addition to the NMR spectroscopy of the proton, the spectra of such nuclei as carbon-13 (^{13}C), nitrogen-15 (^{15}N), fluorine-19 (^{19}F), silicon-29 (^{29}Si), and phosphorus-31 (^{31}P) have been extensively investigated, and many metal nuclei are in reach today for NMR studies.

One can further see from Table 2.1 that all nuclei with $I > \frac{1}{2}$ possess a *nuclear quadrupole moment*, Q , as a result of non-spherical distribution of nuclear charge. These nuclei can, therefore, interact with electrical field gradients in the molecular environment – especially those due to the electron shell of the surrounding chemical bonds – and these interactions are of significance for relaxation phenomena. Further, in solids, because of the aforementioned interaction, even in the absence

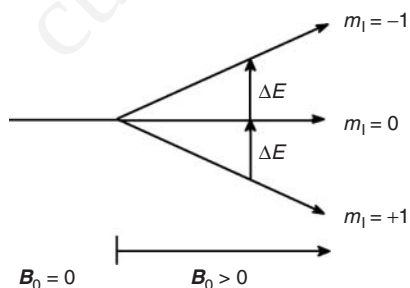


Figure 2.11 Energy levels for a nucleus of spin quantum number $I = 1$.

Table 2.1 Nuclear properties of nuclei important for chemical applications of NMR spectroscopy^a.

Nucleus	Spin quantum-number, I	Magnetogyric ratio, γ (10^7 rad $\text{T}^{-1} \text{s}^{-1}$)	Resonance frequency ν_0 (MHz at a field of 1 T)	Relative sensitivity at constant field	Natural abundance (%)	Quadrupole moment, Q (10^{-28} m^2)
^1H	$\frac{1}{2}$	26.7522	42.577	1.000	99.98	—
^2H	1	4.1066	6.536	0.009	0.0156	0.003
^{10}B	3	2.8747	4.574	0.020	19.9	0.085
^{11}B	$\frac{3}{2}$	8.5847	13.660	0.165	80.1	0.041
^{13}C	$\frac{1}{2}$	6.7283	10.705	0.016	1.108	—
^{14}N	1	1.9338	3.077	0.001	99.63	0.020
^{15}N	$\frac{1}{2}$	-2.7126	4.315	0.001	0.365	—
^{17}O	$\frac{5}{2}$	-3.6281	5.772	0.029	0.037	-0.004
^{19}F	$\frac{1}{2}$	25.1815	40.055	0.834	100.0	—
^{29}Si	$\frac{1}{2}$	-5.3190	8.460	0.008	4.70	—
^{31}P	$\frac{1}{2}$	10.8394	17.235	0.066	100.0	—

^aFor a complete list with the properties of the magnetic nuclei of the Periodic Table see Ref. [1].

of an externally applied magnetic field, such nuclei possess spin states of different energies, between which transitions can be stimulated. The stimulation and detection of these transitions is known as *nuclear quadrupole spectroscopy* or *resonance (NQR)*.

The *sensitivity* of a nucleus to investigation by an NMR experiment depends on the magnitude of its magnetic moment, μ , which determines the energy difference between the nuclear spin states and therefore, following Eq. (2.11), the population excess in the lower energy state. It can be shown that at constant field the signal strength should be proportional to:

$$I(I+1)\gamma^3 B_0^2 \quad (2.13)$$

an expression that also demonstrates the importance of strong static fields, B_0 . In practice the factor $B_0^{3/2}$ is found. In addition, the *natural abundance* is a critical factor. The NMR spectroscopy of ^{13}C and ^{15}N was thus severely hampered in the early years by the low concentration of these nuclei in molecules with natural isotopic distribution and it is only since the introduction of the FT technique that this problem has been overcome.

Today, the sensitivity of nuclei is characterized by their *receptivity* relative to the proton (R^{H}) or to carbon-13 (R^{C}). These parameters include the natural abundance N and are derived from Eqs. (2.13) and defined by Eq. (2.14):

$$R_X^Y = \left| \frac{\gamma_X^3}{\gamma_Y^3} \right| \frac{N_X I_X (I_X + 1)}{N_Y I_Y (I_Y + 1)} \quad (2.14)$$

where X stands for the nucleus of interest and Y for the proton or for carbon-13 [2]. In Chapter 11 and 12 we list *R*-values for nuclei discussed there.

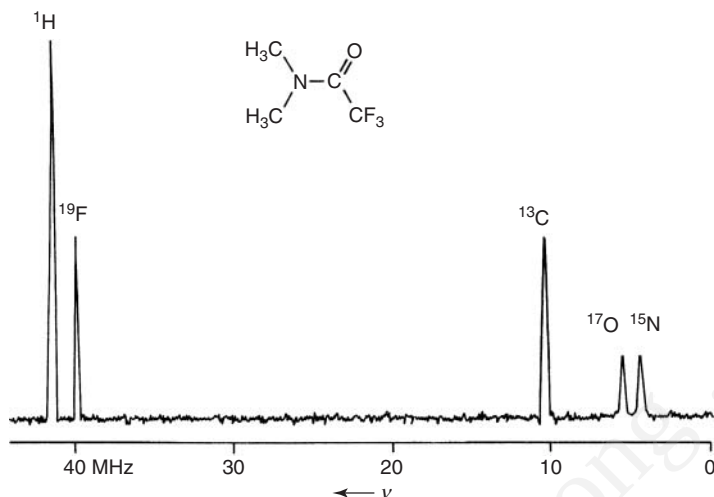


Figure 2.12 Hypothetical NMR spectrum of $[^{15}\text{N}]$ -*N,N*-dimethyltrifluoroacetamide with the magnetic nuclei ^{15}N , ^{17}O , ^{13}C , ^{19}F , and ^1H in a field of 1.0 T.

Aside from those nuclei listed in Table 2.1, numerous other nuclei have been detected by NMR. In practice, nearly all elements of the Periodic Table have an isotope that is NMR active and the resonance of which can be measured. Because of the sensitivity problem mentioned above – and also because of the sometimes large quadrupole moments for nuclei with $I > \frac{1}{2}$ that lead to fast relaxation and thus a shortening of the lifetime in the excited state – such measurements are by no means routine in all cases. These aspects and the NMR spectroscopy of other nuclei will be treated in more detail in Chapter 12.

We can summarize the above discussion of NMR spectroscopy as follows. The NMR experiment allows us to record the resonance signals of magnetic nuclei. Each type of nucleus is thereby characterized by its individual resonance frequency. In a “Gedanken experiment” for a hypothetical molecule such as $[^{15}\text{N}]$ -*N,N*-dimethyltrifluoroacetamide we might therefore expect the spectrum shown in Figure 2.12. To simplify the illustration, all nuclei were assumed to have the same sensitivity and the same natural abundance.

References

1. Harris, R.K. (1996) Nuclear spin properties and notation, in *Encyclopedia of Nuclear Magnetic Resonance*, (editors in chief D.M. Grant and R.K. Harris), Vol. 5, John Wiley & Sons, Ltd, Chichester, p. 3301.
2. Harris, R.K. and Mann, B.E. (1978) *NMR and the Periodic Table*, Academic Press, London, p. 4. The letter *D* is used there for the receptivity.

cuu duong than cong . com

3

The Proton Magnetic Resonance Spectra of Organic Molecules – Chemical Shift and Spin–Spin Coupling

So far we have been concerned with the magnetic resonance of a single nucleus and with explaining the physical basis of an NMR experiment. We will now turn our attention to the nuclear magnetic resonance spectra of organic molecules and in so doing will encounter two new phenomena: the *chemical shift of the resonance frequency* and the *spin–spin coupling*. These two phenomena form the foundation for the application of NMR spectroscopy in chemistry and related disciplines. They will be treated in the following sections.

3.1

The Chemical Shift

The hypothetical spectrum of [^{15}N]dimethyltrifluoroacetamide presented at the end of Chapter 2 may have suggested that NMR spectroscopy is employed for the detection of magnetically different nuclei in a compound. For at least two reasons this is not the case. First, experimental considerations make such an application difficult, if not impossible, since conditions and techniques must be modified to measure the resonance frequencies of different nuclei. Second, the elemental composition of organic compounds can be determined far more easily and accurately by other techniques such as elemental analysis or mass spectrometry.

The significance of NMR spectroscopy in chemistry is therefore not based on its ability to differentiate between elements, but on its ability to distinguish a particular nucleus with respect to its environment in the molecule. That is, one finds that the resonance frequency of an individual nucleus is influenced by the distribution of electrons in the chemical bonds. The value of the resonance frequency of a particular nucleus is therefore *dependent upon molecular structure*.

Using the proton to demonstrate this, a compound such as benzyl acetate, for example, will produce three different NMR signals, one each for the protons of the phenyl, methylene, and methyl groups (Figure 3.1). This effect, produced by the different chemical environments of the protons in the molecule, is known as the chemical shift of the resonance frequency or more simply as the *chemical shift*. Thus, with an applied magnetic field B_0 of 2.35 T, the proton resonances of a molecule do not occur at $\nu_0 = 100 \text{ MHz}$ but rather at $\nu_0 \pm \Delta\nu$, where $\Delta\nu$ for protons is

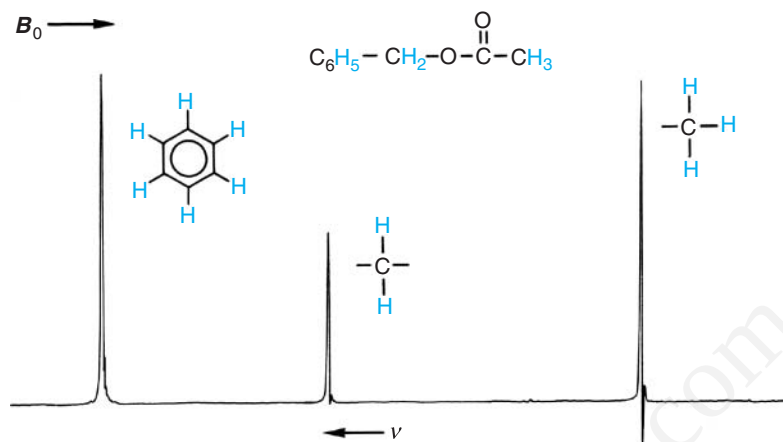


Figure 3.1 ^1H NMR spectrum of benzyl acetate; the chemical shift is measured in hertz and the frequency scale increases from right to left.

generally less than 1 kHz. Other magnetic nuclei are affected similarly, but with varying $\Delta\nu$, and this phenomenon forms the basis of applied NMR spectroscopy.¹⁾

In a first analysis, the chemical shift is caused by the electrons of the C–H bond in which the proton is involved. The external magnetic field, B_0 , induces circulations in the electron cloud surrounding the nucleus such that, following Lenz's law, a magnetic moment μ , opposed to B_0 , is produced (Figure 3.2). Thus, at the proton the applied field strength, B_0 , does not prevail or, in other words, the local field at the nucleus is smaller than the applied field. This effect corresponds to a magnetic shielding of the nucleus that reduces B_0 by an amount equal to σB_0 , where σ is known as the *shielding* or *screening constant* of the particular proton:

$$B_{\text{local}} = B_0(1 - \sigma) \quad (3.1)$$

The *shielding constant*, σ , is proportional to the electron density of the 1s orbital of the hydrogen atom and σB_0 is the magnitude of the secondary field induced at the proton. Because the local field at the nucleus is thus smaller than B_0 , the resonance condition is met at a lower frequency than might be expected. The screening of the nuclei that gives rise to the signals of the spectrum increases from left to right, which is opposite to the direction of the frequency scale. We also note that σ is anisotropic and for nuclei of molecules that have a fixed position in the magnetic field, and, like in solids, it has a directional dependence with respect to B_0 . In

1) In passing, the phenomenon of the chemical shift was discovered in 1950 by W.G. Proctor and F.C. Yu [1] as they tried to determine the magnetic moment of nitrogen-14 by using ammonium nitrate, NH_4NO_3 . They found two

resonance signals instead of *one* as they expected. For the physicists, this observation – a classical case of accidental discovery – was a nuisance, but its importance for chemistry was soon recognized.

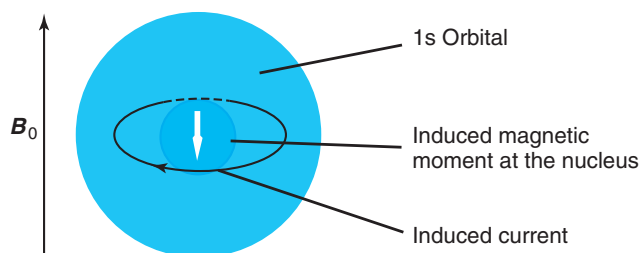


Figure 3.2 Shielding of a proton in a magnetic field B_0 .

mathematical terms, σ is a tensor that can be brought to diagonal form through a suitable transformation:

$$\sigma = \begin{vmatrix} \sigma_{11} & 0 & 0 \\ 0 & \sigma_{22} & 0 \\ 0 & 0 & \sigma_{33} \end{vmatrix} \quad (3.2)$$

In solids $\sigma_{11} \neq \sigma_{22} \neq \sigma_{33}$, but in liquids, because of the rotational motion, the chemical shift is measured as the trace of the symmetric matrix:

$$\text{tr} \sigma = \frac{1}{3}(\sigma_{11} + \sigma_{22} + \sigma_{33}) \quad (3.3)$$

Compared to NMR of solids, the situation is thus again much simpler for NMR in the liquid state.

In the case of an unperturbed spherical electron distribution – such as exists, for example, in a hydrogen atom – the induced circulation of charge leads to a pure diamagnetic effect. The value of σ can then be calculated by the Lamb formula [Eq. (3.4)] from the electron density $\rho(r)$ around the nucleus:

$$\sigma = \frac{\mu_0 e^2}{3m_e} \int_0^\infty r \rho(r) dr \quad (3.4)$$

where $\rho(r)$ itself is a function of the distance r from the nucleus and the other terms are well-known constants (see Table 1.1 on p. 9).

In molecules the situation is more complex, for here one must consider the electronic circulation within the entire molecule. In these cases it can be shown that the perturbation of the spherical symmetry of the electron distribution caused by the presence of other nuclei reduces the diamagnetic effect. This diminution can be treated as corresponding to a paramagnetic moment that strengthens the effect of the external field B_0 . The σ -value in molecules then corresponds to the sum of diamagnetic and paramagnetic components of the induced electronic motion:

$$\sigma = \sigma_{\text{dia}} + \sigma_{\text{para}} \quad (3.5)$$

Theoretical calculations of chemical shifts rely on advanced quantum chemical methods and are often restricted to small molecules. A practical approach for the treatment of the chemical shift in cases that are of immediate interest to the chemist is possible if the shielding is separated into local contributions and contributions

of neighboring atoms or groups that can be evaluated with the assistance of simple models or empirical correlations. These neighboring contributions may be represented by a third term, σ' , and from Eq. (3.5) it follows that:

$$\sigma = \sigma_{\text{dia}}^{\text{local}} + \sigma_{\text{para}}^{\text{local}} + \sigma' \quad (3.6)$$

where $\sigma_{\text{dia}}^{\text{local}}$ and $\sigma_{\text{para}}^{\text{local}}$ are now the local diamagnetic and local paramagnetic contributions to the shielding constant of the respective nucleus. A more detailed discussion of the term σ_{para} will be given when we treat NMR of heavier nuclei like ^{13}C , where the paramagnetic contribution to the shielding dominates (Chapters 11 and 12).

For protons, $\sigma_{\text{dia}}^{\text{local}}$ and σ' are of primary significance since theoretical calculations show that strong paramagnetic effects arise only for nuclei where energetically low-lying atomic orbitals are available and a mixing of ground state and excited state wave functions takes place through the external magnetic field. Thus, in the case of fluorine, for example, the dominant paramagnetic contribution to the chemical shift is essentially the result of the availability of low-lying p-orbitals.

This introduction to the relation between shielding constant and chemical structure will be expanded considerably in Chapter 5. Here we simply assert that in molecules σ for protons is always *positive* and for the magnitude of the local magnetic field at the nucleus the relation $B_{\text{local}} < B_0$ holds. For individual compounds, protons of certain groups are designated as *shielded* or *deshielded* relative to a reference line if their signals occur at lower or higher frequency, respectively. This can be seen in the spectrum of benzyl acetate (Figure 3.1), where relative to the methylene protons the methyl protons are shielded and the aromatic protons are deshielded. In cases such as this one often speaks of a *diamagnetic* or a *paramagnetic* shift, respectively, of the resonance signals.²⁾

3.1.1

Chemical Shift Measurements

Discussion of the differential shielding of individual protons assumes that a system of measurement for the chemical shift has been established. To specify the position of a resonance signal in an NMR spectrum it would, in principle, be possible to measure the strength of the external field, B_0 , or the absolute resonance frequency, ν , at which the resonance line of interest appears. These parameters are, however, unsuited for the characterization of the chemical shift because NMR spectrometers

2) Since the older CW spectra could be recorded by a field sweep experiment at constant frequency, the low-frequency region of the spectrum is associated with high magnetic field and signals found there are “upfield” from those at higher frequency because for a

shielded nucleus the B_0 field has to be high to meet the resonance condition that is based on the local field. On the other hand signals with high frequencies are “downfield” from those with low frequencies. These terms are still in use.

operate at different B_0 fields (e.g., with field strength B_0 of 2.3, 7.2, or even 13.8 T, to name only a few) and according to Eq. (2.10) the resonance frequency varies with B_0 . Furthermore, an absolute determination of the field strength or the resonance frequency is, while technically possible, not practical.

This problem is eliminated if one measures the position of the resonance signal *relative* to that of a reference compound or standard. In proton NMR the compound used under normal circumstances is *tetramethylsilane* (TMS), the 12 protons of which give a sharp signal that can be recorded simultaneously with the spectrum of the sample under investigation. Thus, a sample of benzyl acetate with a trace of TMS gives rise to the spectrum shown in Figure 3.3.

In a Fourier transform nuclear magnetic resonance (FT NMR) experiment the line frequencies relative to the reference signal, measured in hertz, are directly available after data processing because the NMR frequency of the standard TMS can be set as $\nu(^1\text{H}) = 0$. As frequencies of the order of hertz or kilohertz are easily measured with considerable precision, determination of the chemical shift is straightforward. Nevertheless, the frequency data have the disadvantage that their values, according to Eq. (2.10), are field dependent. For example, recording a spectrum at 2.35 T with a pulse frequency of 100 MHz would yield signals at 193, 500, and 722 Hz for the three groups of protons in benzyl acetate. In the fourfold stronger magnetic field of 9.40 T, we need a pulse frequency of 400 MHz to measure the proton resonances and observe the signals at 772, 2000, and 2888 Hz. Therefore, a dimensionless quantity, δ , has been introduced for the chemical shift that is defined as follows:

$$\delta = \frac{\nu_{\text{sample}} - \nu_{\text{standard}}}{\nu_0} \quad (3.7)$$

Here, ν_0 is the operating frequency of the spectrometer employed (e.g., 100 or 400 MHz) and since the difference $\nu_{\text{sample}} - \nu_{\text{standard}}$ amounts to hertz or kilohertz the

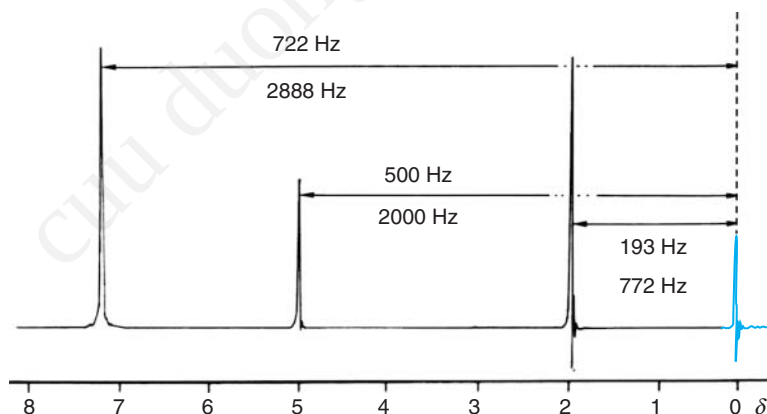
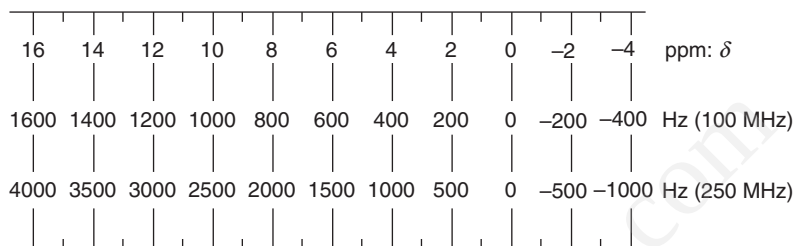


Figure 3.3 ^1H NMR spectrum of benzyl acetate in the presence of tetramethylsilane (red signal) as an internal standard. The frequencies of the signals (in hertz) relative to the standard signal at $\delta = 0$ ppm were measured with a 100 MHz spectrometer (upper numbers) and a 400 MHz spectrometer (lower numbers), respectively.

δ -values contain the factor 10^{-6} that is known as *parts per million (ppm)*. Thus, for the proton resonances of benzyl acetate, δ -values of 1.93, 5.00, and 7.22 ppm are found, regardless of whether the spectrum is measured at 2.35 T and 100 MHz or 9.40 T and 400 MHz. The relations between the frequency scale in hertz and the δ -scale in parts per million are again illustrated in the following diagram for two typical spectrometer frequencies of 100 and 250 MHz:



The absence of an absolute energy scale makes comparison of NMR spectra difficult if agreement cannot be reached upon a universal reference. The previously mentioned TMS fulfills the requirements that such a substance must meet. The TMS signal is an intense singlet, the chemical shift of which is different from most of the other proton resonances in organic molecules so that the superposition of a sample resonance signal with that of TMS is seldom observed. The substance is essentially chemically inert and it can easily be removed from the sample after recording the spectrum. The δ -scale of proton magnetic resonance is thus based on this reference compound. We must, however, emphasize that the δ -scale shown in Figure 3.3 does not imply that spectra end at 0.0 and 8.0 ppm. Larger δ -values as well as negative δ -values are quite common.

If, for technical reasons, ^1H δ -values refer to other reference compounds, such as cyclohexane, methylene chloride, or benzene, one usually labels the δ -value with an identifying subscript, for example, $\delta_{\text{C}_6\text{H}_6}$. The need to employ a different reference becomes obvious when the sample being investigated has a resonance signal that is superimposed on the TMS signal.

TMS is also used as standard in carbon-13 NMR spectroscopy, where it gives rise to a ^{13}C NMR signal at low frequency. However, for other nuclei it is often difficult to find a suitable standard and various compounds are used. To compare the results it is then necessary to convert data or to use a universal chemical shift scale, to be discussed in Chapter 12, that tries to solve this problem. Finally, in a general context δ -values should indicate the nucleus that they refer to by adding the respective nuclide in parenthesis, as, for example, $\delta(^1\text{H})$ or $\delta(^{19}\text{F})$. Furthermore, to record δ -values, the notation δ 6.5 (without “ppm”) or $\delta = 6.5$ ppm should be used.

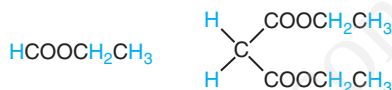
Individual contributions to the chemical shift of ^1H resonances caused by substituents will be symbolized in this text as $\Delta\sigma$ (ppm) as they represent changes in the shielding constant. A positive sign signifies an increase and a negative sign a decrease in shielding, which means a shift to low or high frequency, respectively, and small or large δ -values.

3.1.2

Integration of the Spectrum

With the establishment of the δ -scale, we are now able to assign a definite region in the spectrum to the protons in a particular structural element. Before proceeding, one more property of the NMR spectrum that may have already been noticed in reference to Figure 3.1 should be mentioned. The signals have different *intensities*. A more detailed examination shows that the area under the resonance signal is proportional to the number of protons that gives rise to that signal. An electronic *integrator* that is part of the spectrometer automatically produces a step curve such as that shown in Figure 3.4. The relative heights of the steps indicate a proton ratio in benzyl acetate of 5 : 2 : 3. This measurement yields valuable, and often crucial, additional information.

Notably, only the *relative number* of protons can be determined by integration. Thus, were it not for the chemical shift differences, ethyl formate and diethyl malonate, to choose only one example, would have identical spectra:



The integration of resonance signals finds important applications in analytical chemistry, where it allows us to determine the constitution of mixtures or the percentage of an impurity present. For example, the mass m_A of component A in a mixture can be determined if an amount m_B of a known substance B is added to a weighed sample of the mixture and signals assigned to A and B are integrated. In this case, the mass of A in the sample is given by:

$$m_A = m_B \times \frac{N_B}{N_A} \times \frac{A_A}{A_B} \times \frac{M_A}{M_B} \quad (3.8)$$

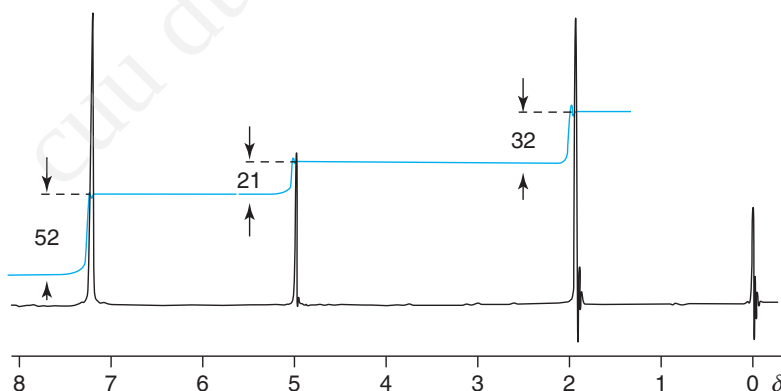


Figure 3.4 ^1H NMR spectrum of benzyl acetate with integration; step heights are given in millimeters.

where N is the number of protons responsible for the signals chosen, A is the area under the signals, and M_A and M_B are the molecular weights of A and B, respectively.

To illustrate the application of the integration of NMR signals, Figure 3.5 shows the partial spectrum of a mixture of methyl benzyl ether and toluene in a molar ratio of 1:1.491 (as determined by weighing). From the integration of the two methyl signals at δ 2.2 and 3.2, one obtains, as an average of five integrations, a molar ratio of $1:1.519 \pm 0.030$. The correct value lies within the error limit and the magnitude of the error (2%) is typical of the magnitude of errors in this type of determination (2–4%). Figure 3.5 also shows that, because of differences in line widths in the methyl resonances B and C, the *signal height* is not an accurate measure of the number of protons responsible for a signal.

Exercise 3.1

Determine the molar ratio of methyl benzyl ether to toluene by reference to the integration given in Figure 3.5 for the methylene protons of methyl benzyl ether and the methyl protons of toluene.

Exercise 3.2

The ^1H NMR spectrum of a mixture of chloroform, methylene chloride, and acetone is integrated and results in step heights of 10, 18, and 36 mm for the signals at δ 7.27, 5.30, and 2.17, respectively. In what molar ratio are the three substances present?

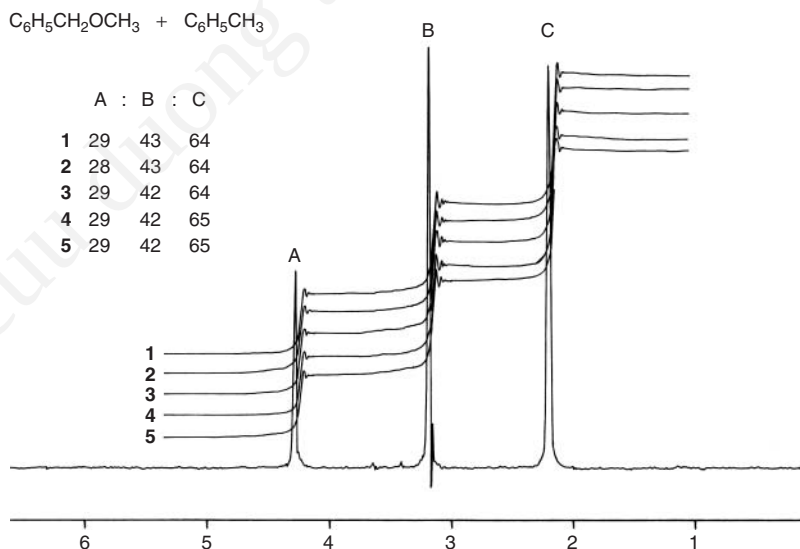


Figure 3.5 Partial ^1H NMR spectrum of a mixture of methyl benzyl ether and toluene in the region from δ 0 to 6 (A = CH_2 ; B = OCH_3 ; C = CH_3).

Table 3.1 Proton resonances (of protons in red) for selected organic compounds.

Compound	Formula	δ (ppm)
Cyclopropane	C_3H_6	0.22
Ethane	CH_3-CH_3	0.88
Ethylene	$CH_2=CH_2$	5.84
Acetylene	$HC\equiv CH$	2.88
Benzene	C_6H_6	7.27
Propene	$CH_2=CH-CH_3$	1.71
Propyne	$CH\equiv C-CH_3$	1.80
Acetone	$CH_3-CO-CH_3$	2.17
Cyclohexane	C_6H_{12}	1.44
Methyl chloride	CH_3Cl	3.10
Methylene chloride	CH_2Cl_2	5.30
Chloroform	$CHCl_3$	7.27
Ethanol	CH_3CH_2OH	1.22
	CH_3CH_2OH	3.70
	CH_3CH_2OH	2.58
Acetic acid	CH_3-COOH	2.10
	CH_3-COOH	8.63
Acetaldehyde	CH_3-CHO	2.20
	CH_3-CHO	9.80
Diethyl ether	$(CH_3CH_2)_2O$	1.16
	$(CH_3CH_2)_2O$	3.36
Ethyl acetate	$CH_3COOCH_2CH_3$	2.03
	$CH_3COOCH_2CH_3$	4.12
	$CH_3COOCH_2CH_3$	1.25
Trimethylamine	$N(CH_3)_3$	2.12
Triethylamine	$N(CH_2CH_3)_3$	2.42
Toluene	$C_6H_5-CH_3$	2.32
Benzaldehyde	C_6H_5-CHO	9.96

form hydrogen bonds. The presence of traces of acid or water promotes exchange processes that result in a shift of the proton resonance frequency. In addition, the shape of the resonance signal can also be changed by this chemical exchange and protons of $COOH$, NH_2 , and NH groups in particular very frequently show broad resonance signals that sometimes are hidden in the noise. Figure 3.7 shows as an example the spectrum of propionamide.

To complete this preliminary survey, Table 3.1 gives the δ -values of certain protons in a series of small organic molecules that are characteristic representatives of several classes of compounds.

Exercise 3.3

Figure 3.8 shows the integrated ^1H NMR spectrum of a mixture of toluene, methylene chloride, and benzene. Assign the resonances with the help of Table 3.1 and determine the molar ratio of the three compounds.

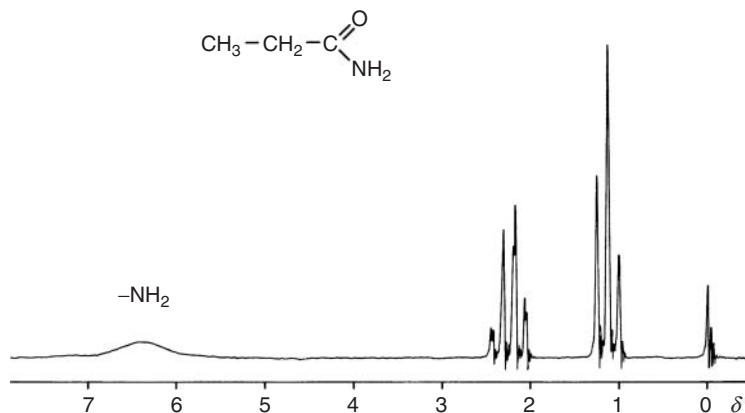


Figure 3.7 ^1H NMR spectrum of propionamide.

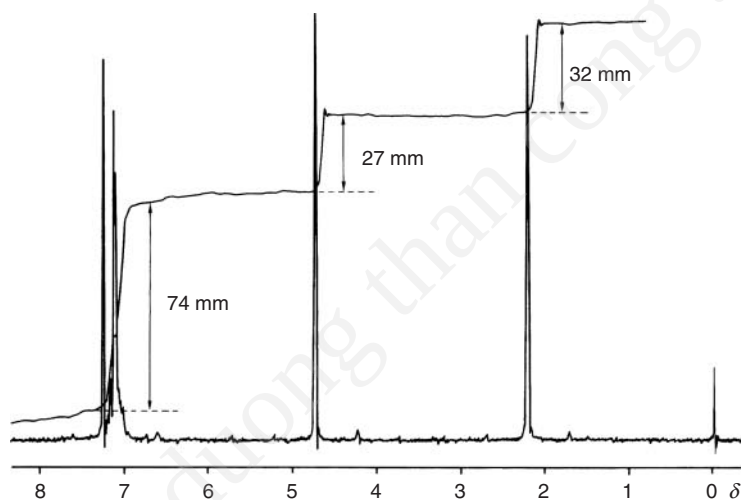


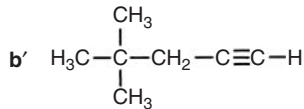
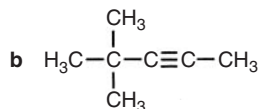
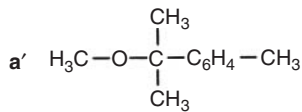
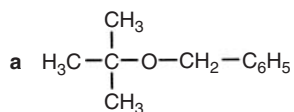
Figure 3.8 Integrated ^1H NMR spectrum of a mixture of toluene, methylene chloride, and benzene.

Exercise 3.4

For an unknown substance, signals are observed at δ 2.32 and 7.10 (area ratio 3 : 5) at a radiofrequency of 100 MHz. How large would the chemical shift difference (in hertz) be if the spectrum of the same substance were measured with a 270 MHz spectrometer? Which compound fits these data (molecular formula of C_7H_8)?

Exercise 3.5

What differences would be expected in the NMR spectra of the following pairs of isomers with respect to the position and areas under the resonance signals?



Exercise 3.6

Using the proton magnetic resonance spectra in Figure 3.9, determine the structure of compounds **a–j**. In addition to the molecular formula of each compound the

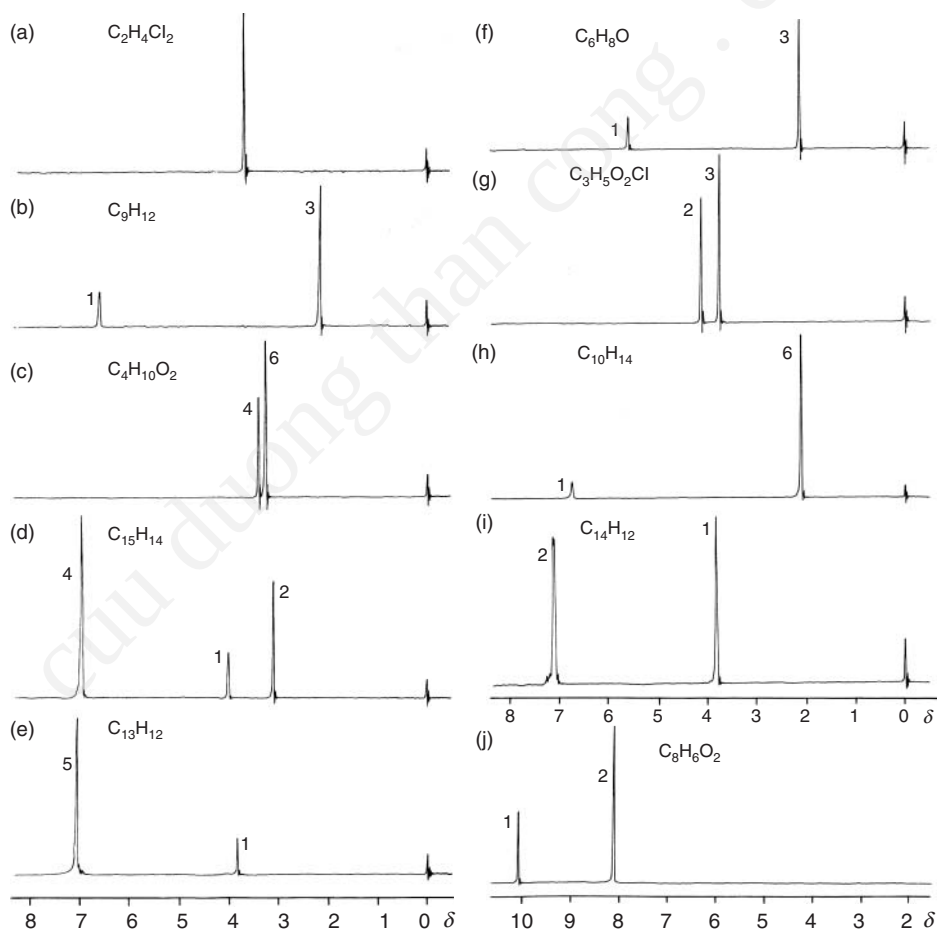


Figure 3.9 ^1H NMR spectra of various compounds.

relative areas of the signals are given. Note: the solution of the problems is facilitated if one first determines the double bond equivalents (DBEs) for each compound. For the compound $C_aH_b(O_c)$ the DBEs are given by:

$$DBE = \frac{(2a + 2) - b}{2}$$

3.2

Spin-Spin Coupling

In comparing the spectrum of benzyl acetate with that of ethyl formate (Figure 3.10), we notice not only a difference in the position of the resonance signals but also a difference in the *multiplicity* of the signals. In one case singlets are observed for both the methyl and methylene protons, and in the other the same type of protons give rise to a triplet and a quartet, respectively, each with a rather distinct intensity distribution. The cause of this fine structure is *spin-spin coupling*, a phenomenon discovered independently in several laboratories in 1950. It results from a magnetic interaction between individual protons that is not transmitted through space but

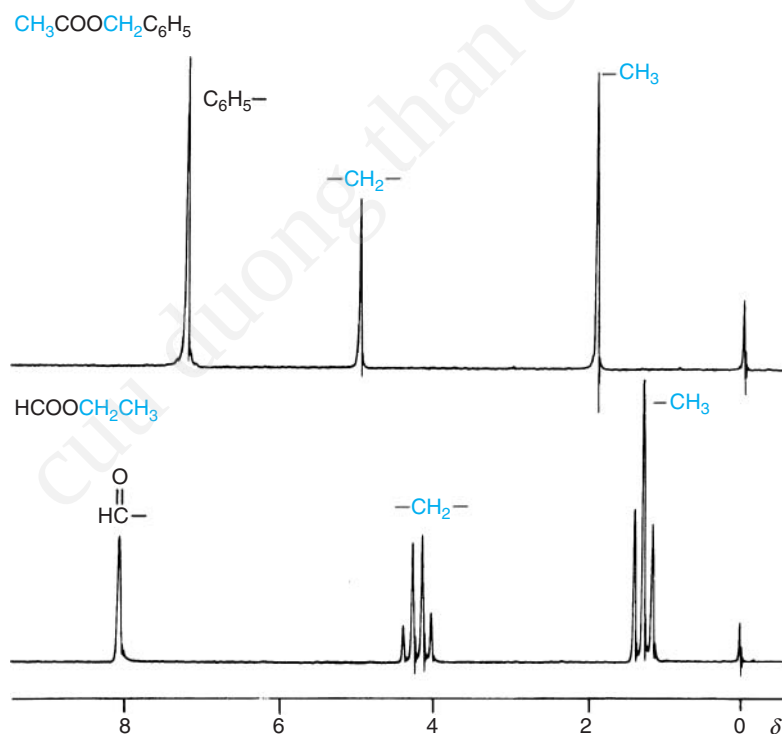


Figure 3.10 ^1H NMR spectra of benzyl acetate (top) and ethyl formate (bottom).

rather by the bonding electrons through which the protons are indirectly connected. Spin–spin coupling thus leads to *line splitting* of resonances.

Figure 3.11 shows schematically the coupling mechanism between a proton, ^1H (A), and a fluorine nucleus, ^{19}F (X), both spin- $\frac{1}{2}$ nuclei with a positive gyromagnetic ratio γ , in the hydrogen fluoride molecule. The magnetic moment of nucleus A causes a weak magnetic polarization of the bonding electrons that is transmitted by way of the overlapping orbitals and with observation of the Pauli-principle to nucleus X. As a consequence, depending on the spin state of A, the external field at X is either augmented or diminished; that is, the magnitude of the local magnetic field responsible for the resonance frequency of nucleus X varies and the NMR signal is split into a doublet. The same is true for nucleus A. Because the two spin states of A are almost equally probable, the lines of the doublet have the same intensity.

In the following, we will refer to nuclei between which a spin–spin interaction exists as a *spin system*. To characterize a spin system we use capital letters for different nuclei with subscripts, for example, AX_2 or A_3X_2 , that indicate their number. The relative chemical shift is shown by letters that are close neighbors in the alphabet or that are more separated, for example, ABC or AMX.

The energy, E , of the spin–spin interaction between two nuclei A and X is proportional to the scalar product of their nuclear magnetic moments μ_A and μ_X :

$$E \propto \mu_A \cdot \mu_X \quad (3.9a)$$

and with Eq. (2.5):

$$E = J_{AX} \hat{I}_A \cdot \hat{I}_X \quad (3.9b)$$

where $\hat{I}_A$ and $\hat{I}_X$ are the so-called nuclear spin vectors of both nuclei with components $\hat{I}_x$, $\hat{I}_y$, and $\hat{I}_z$ that we will meet again in Chapter 6. The proportionality

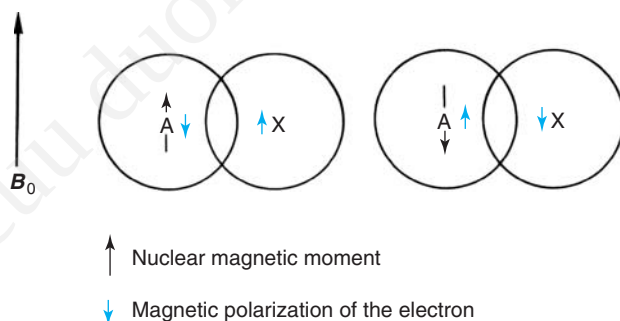


Figure 3.11 Schematic representation (Dirac vector model) of the nuclear spin–spin interaction through the bonding electrons in the HF molecule. The low-energy state, stabilized by the so-called Fermi-contact mechanism, corresponds to the antiparallel arrangement of nuclear and electron magnetic moments. The

Fermi-contact term depends on the electron density at the nucleus – hence the name “contact term” – and consequently only on the s-orbitals involved. (The arrows passing through the letter A represent the nuclear magnetic moment.)

constant, J_{AX} , is known as the *indirect or scalar coupling constant* between the nuclei A and X; J_{AX} is measured in hertz and is proportional to the product of the magnetogyric ratios of the nuclei. Because of $E = h\nu$, the right-hand side of Eq. (3.9b) is divided by h . Following Eq. (2.5), it can also be seen that J_{AX} contains the product of the magnetogyric ratios of the coupled nuclei and the factor $h/4\pi^2$. To eliminate this dependence a reduced coupling constant, K_{AX} , defined by:

$$K_{AX} = 4\pi^2 \frac{J_{AX}}{\gamma_A \gamma_X h} \quad (3.10)$$

is used sometimes if the magnitudes of coupling constants between different nuclei are compared or in order to compensate for the negative sign introduced by negative magnetogyric ratios. The units of K in the SI system are $\text{N A}^{-2} \text{m}^{-3}$.

An important consequence of Eq. (3.9) is that the energy of the coupling and consequently the coupling constant, unlike the chemical shift, is independent of the strength of the external magnetic field. These constants are therefore always expressed in frequency units (hertz). Because the coupling constant is independent of the spectrometer frequency, the separation between two lines in a spectrum can be identified as a coupling constant by measurements made at different B_0 fields. In the case of a spin–spin coupling the line splitting (in hertz) remains the same while in the case of chemical shifts it is changed. Indirect coupling constants can have either sign: they are positive if the antiparallel orientation of the two spins leads to the low-energy state and vice versa.

To reinforce our understanding of spin–spin coupling, the phenomenon of line splitting will be explained further by reference to the energy level diagram of a two-spin system with $\nu_A > \nu_X$ shown in Figure 3.12 (p. 44). First, we obtain four different *spin states* for two nuclei in an external field B_0 in the absence of spin–spin coupling ($J = 0$). That is, both nuclear spins can be oriented either parallel or antiparallel to B_0 and one can be parallel and the other antiparallel and vice versa (Figure 3.12a). Considering the transitions A_1 and A_2 where the A nucleus changes its spin orientation, we see from the length of the arrows that they have the same energy, that is, they are degenerate. Consequently, only one resonance line is observed. A similar result applies to the X nucleus (not shown in Figure 3.12).

In the presence of spin–spin coupling ($J > 0$) the energy of the states of the spin system, its eigenvalues, are, as a consequence of the coupling, either stabilized or destabilized according to the relative orientation of the nuclear magnetic moments. Following convention, the energy of the state with an antiparallel arrangement will be lowered by spin–spin coupling, while that of the state with parallel orientation will be raised if the coupling constant is positive. Thus the energy-level diagram in Figure 3.12b results. It can be seen that the transitions A_1 and A_2 are no longer degenerate and this has the effect of splitting the spectral line into a doublet with the frequency difference J_{AX} (Figure 13.2c). We note that for every transition only one spin flips. If we characterize the individual spin states by the spin functions α and β introduced in Chapter 2, we obtain the energy level diagram for an AX spin system shown in Figure 3.12d. An experimental AX system is shown below in Figure 3.25 (p. 61).

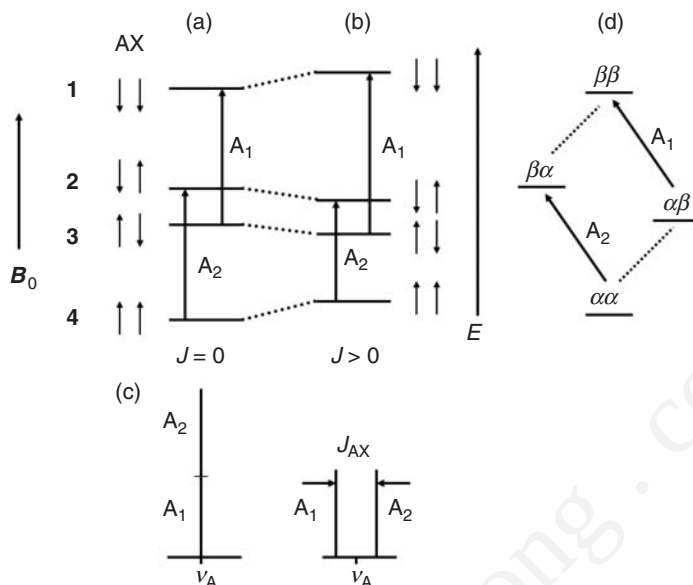


Figure 3.12 Nuclear magnetic energy level diagram for an AX two-spin system: (a) without spin–spin coupling; (b) with spin–spin coupling. Spin–spin coupling lowers the spin state energy in the case of antiparallel orientation of the spins for $J_{AX} > 0$, so that the eigenvalues

(2) and (3) are stabilized, while eigenvalues (1) and (4) with parallel spin orientation are destabilized. For clarity, only the lines of the nucleus A are shown; (c) NMR signals at ν_A ; (d) energy level diagram of an AX spin system with spin functions α and β .

Exercise 3.7

Copy Figure 3.12 and introduce the lines of the X nucleus in red. How large is the splitting between the lines X1 and X2?

A *quantitative* treatment of spin–spin coupling in the case of an AX system of two nuclei i and j and a coupling constant J_{ij} , is straightforward. As will be shown later, the eigenvalues of a spin system can be calculated using the simple equation:

$$E(\text{Hz}) = -\sum_{ij} v_i m_1(i) + \sum_{i < j} J_{ij} m_1(i) m_1(j) \quad (3.11)$$

With the resonance frequencies ν_A and ν_X , the coupling constant J_{AX} (all quantities in hertz), and the quantum numbers m_l we obtain for the states 1–4 of Figure 3.12:

$$(1) \downarrow\downarrow \equiv \beta\beta : E_1 = +\frac{1}{2}\nu_A + \frac{1}{2}\nu_X + \frac{1}{4}J_{AX}$$

$$(2) \downarrow\uparrow \equiv \beta\alpha : E_2 = +\frac{1}{2}\nu_A - \frac{1}{2}\nu_X - \frac{1}{4}J_{AX}$$

$$(3) \uparrow\downarrow \equiv \alpha\beta : E_3 = -\frac{1}{2}\nu_A + \frac{1}{2}\nu_X - \frac{1}{4}J_{AX}$$

$$(4) \uparrow\uparrow \equiv \alpha\alpha : E_4 = -\frac{1}{2}\nu_A - \frac{1}{2}\nu_X + \frac{1}{4}J_{AX}$$

The destabilization or stabilization of the eigenstates of the AX system as a result of spin-spin coupling thus amounts to $\pm\frac{1}{4}J_{AX}$, depending upon whether the orientations of the two nuclear moments are parallel or antiparallel. For the frequency of the spectral lines, by application of the selection rule $\Delta m_T = \pm 1$, where $m_T = \Sigma_i m_i$ is the *total spin* of the eigenstate under consideration, one obtains:

$$(3) \rightarrow (1) : E_1 - E_3 = \nu_A + \frac{1}{2}J_{AX} \quad \text{transition } A_1$$

$$(4) \rightarrow (2) : E_2 - E_4 = \nu_A - \frac{1}{2}J_{AX} \quad \text{transition } A_2$$

$$(2) \rightarrow (1) : E_1 - E_2 = \nu_X + \frac{1}{2}J_{AX} \quad \text{transition } X_1$$

$$(4) \rightarrow (3) : E_3 - E_4 = \nu_X - \frac{1}{2}J_{AX} \quad \text{transition } X_2$$

so that the line splitting at ν_A and ν_X equals exactly J_{AX} .

The rules for the treatment of spin-spin coupling based on Eq. (3.11) are called *first-order rules*. They are restricted to spin systems where the chemical shift between two nuclei or groups of nuclei, $\Delta\nu$ (hertz), is large compared to the coupling constant. This is true for the HF molecule where $\Delta\nu_{\text{HF}}$ amounts to several megahertz and J_{HF} to only 520 Hz. It still holds for the homonuclear A_2X_3 ^1H spin system in ethyl formate (Figure 3.10) where $\Delta\nu$ is about 180 Hz and $J = 7$ Hz. One speaks then of *weak* coupling. For other homonuclear spin systems $\Delta\nu$ is much smaller and often of the same order as the couplings constants (*strong* coupling). More complicated spectra then result that must be analyzed by more elaborate methods such as those discussed in Chapter 6. In these cases also the *sign* of the coupling constant, which can be positive or negative, is of importance. First-order spectra are unaffected by the sign of the coupling. As mentioned above, by definition the sign of the coupling constant is positive when the energy state with antiparallel arrangement of the two spins is lowered, as is shown in Figure 3.12.

For the chemical shift difference $\Delta\nu$ the notation $\nu_0\delta$ is also used; $\Delta\nu = \nu_0\delta$ follows from Eq. (3.7), where ν_0 is the resonance frequency of the particular nucleus and δ the shift difference between two signals of this nucleus in parts per million, that is in multiples of 10^{-6} . Thus, for a 100 MHz ^1H NMR spectrometer a shift difference of 2 ppm is equivalent to 200 Hz ($100 \times 10^6 \times 2 \times 10^{-6} = 200$).

The fact that spin-spin coupling is transmitted through chemical bonds makes the scalar coupling constant J a sensitive parameter for the types of bonds involved and for their spatial orientation in the molecule. Before we discuss the relationship of the magnitude of the $^1\text{H}, ^1\text{H}$ coupling constants and the structure of organic molecules in more detail, the simple rules that are used to interpret the splitting

patterns will be explained. These first-order rules are conceived as limiting cases of the quantum mechanical analysis of NMR spectra as we will treat them in Chapter 6. Their validity is therefore restricted and in connection with their introduction we should discuss a few points that will enable us to define the limits of their applicability.

3.2.1

Simple Rules for the Interpretation of Multiplet Structures

Let us consider once again the ethyl group in the spectrum of ethyl formate (Figure 3.10, p. 41). On the basis of the intensities of the signals the triplet and the quartet can be assigned to the methyl and the methylene groups, respectively. The number of lines in each group, that is, their multiplicity, is larger by just one than the number of protons in the neighboring group. This can be understood if we consider the possible combinations of the magnetic quantum numbers, $m_I(i)$, of the protons of each group. By employing the wave functions α and β to characterize the two possible spin states for individual protons the scheme given below results.

CH_2 group	m_T	CH_3 group	m_T
$\beta\beta$	-1	$\beta\beta\beta$	$-\frac{3}{2}$
$\beta\alpha$ $\alpha\beta$	0	$\beta\beta\alpha$ $\beta\alpha\beta$ $\alpha\beta\beta$	$-\frac{1}{2}$
$\alpha\alpha$	+1	$\beta\alpha\alpha$ $\alpha\beta\alpha$ $\alpha\alpha\beta$	$-\frac{1}{2}$
		$\alpha\alpha\alpha$	$-\frac{3}{2}$

The individual combinations are distinguished by means of their *total spin*, m_T , which characterizes the magnetic properties of the group of nuclei under consideration.

The fact that the three protons of the methyl group can exist in four different magnetic states leads, by analogy with the analysis made above for the two-spin system HF, to the observed quartet for the resonance of the methylene protons, where the 1 : 3 : 3 : 1 intensity distribution is a result of the relative probabilities of the different spin combinations with the same total spin.

Completely analogous considerations apply for the structure of the methyl proton resonance. Their generalization leads to the following rules that can easily be verified with the aid of Eq. (3.11):

- 1) For nuclei with spin quantum number $I = \frac{1}{2}$ the *multiplicity* of the line splitting equals $n + 1$, where n is the number of nuclei in the neighboring group. If another neighboring group is present with protons that have a chemical shift different from that of the protons in the first group, the effect of the second group must be considered separately. The sequence in which the effects of the protons in neighboring groups are considered is immaterial. Thus, if a nucleus

- 2) The *line separations* (in hertz) correspond to the coupling constants between the nuclei under consideration.
- 3) The *relative intensities* within a multiplet are given by the coefficients of the binomial expansion:

$$1 : \frac{n}{1} : \frac{n(n-1)}{2 \times 1} : \frac{n(n-1)(n-2)}{3 \times 2 \times 1} \dots$$

n = 0								1							
1							1	1							
2						1	2	1							
3					1	3	3	1							
4				1	4	6	4	1							
5			1	5	10	10	5	1							
6		1	6	15	20	15	6	1							

- 4) The *magnitude* of the spin–spin coupling between protons in general decreases as the number of bonds between the coupled nuclei increases. The coupling constant is finally reduced to the order of magnitude of the natural line width so that a splitting is no longer observed or *resolved*.
- 5) The *splitting patterns* are independent of the signs of the coupling constants. These must be determined by other means and we will come back to this aspect later.

The splitting patterns of a series of alkyl groups demonstrate the application of the above rules. The signal pattern of the ethyl group has already been discussed; to expand the series, Figure 3.13 (p. 48) shows the characteristic multiplets of a few other groups.

As is apparent from the foregoing discussion, the coupling constant, J , is determined in the spectrum by measuring the separation of adjacent lines in the multiplet under consideration. The observed splitting must then also be found in the multiplet of the neighboring group of protons. This is illustrated in Figure 3.14 (p. 49) for the three aromatic protons of 2,4-dinitrophenol. We use the rule of thumb that the magnitude of J decreases as the number of bonds between the coupled nuclei increases. This leads to the result that the assignments made should follow the order $J_{ac} < J_{ab} < J_{bc}$.

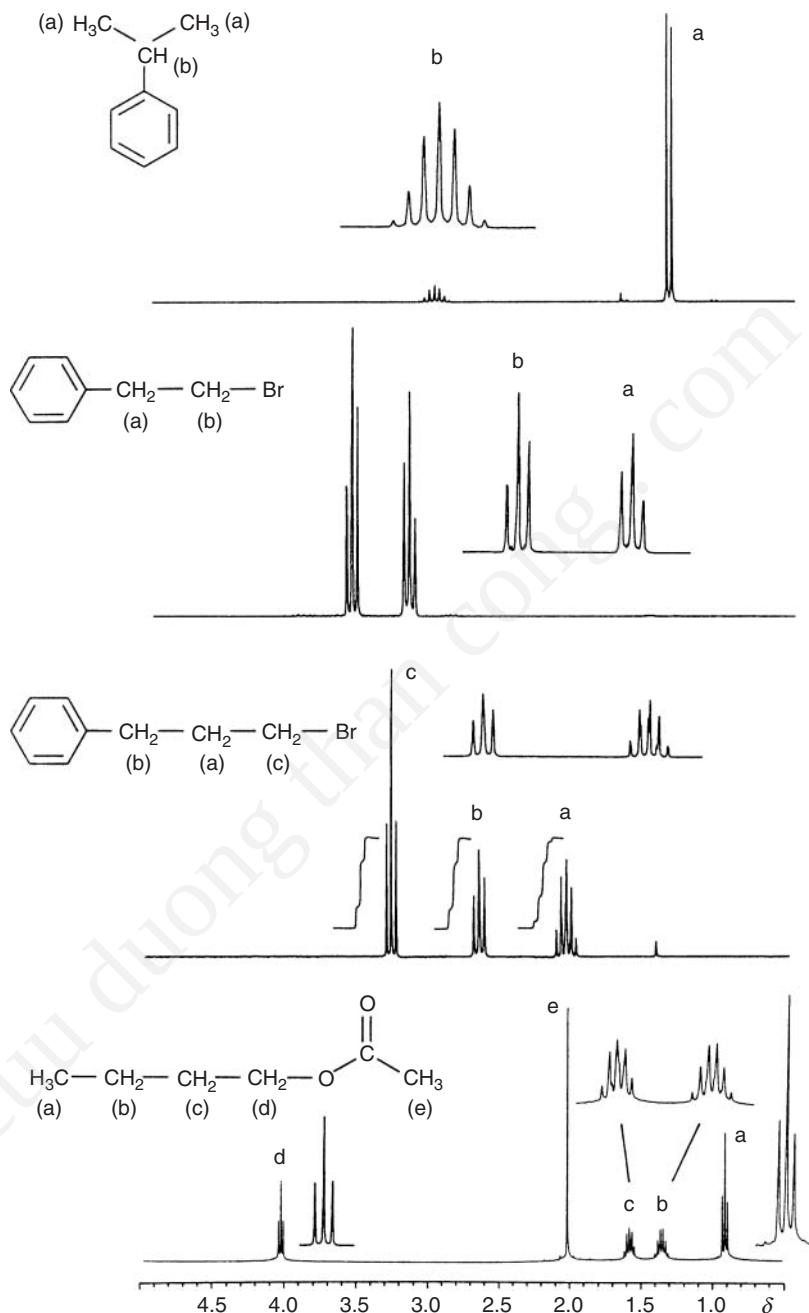


Figure 3.13 Characteristic splitting patterns in the ^1H NMR spectra of some alkyl groups at 200 MHz (upper three spectra) and 400 MHz (lowest spectrum).

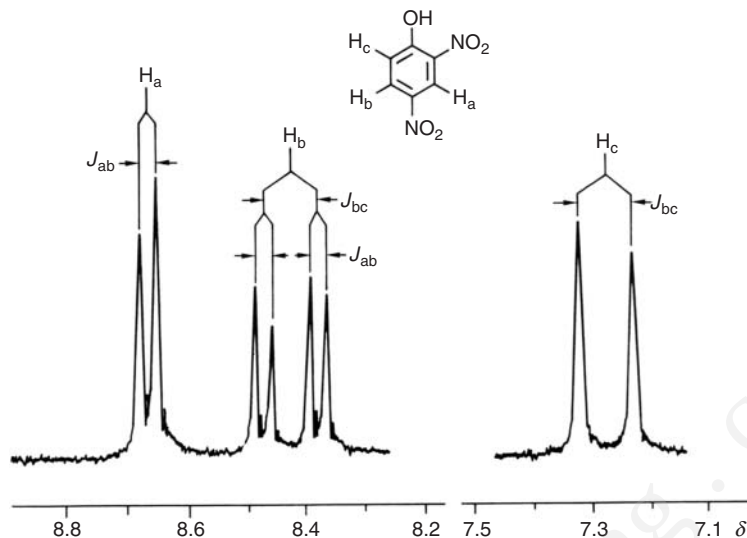


Figure 3.14 Signal splitting due to spin–spin coupling in the 100 MHz ^1H NMR spectrum of 2,4-dinitrophenol. One finds $J_{bc} = 9.1$ Hz and $J_{ab} = 2.8$ Hz; J_{ac} is not observed (rule 4).

3.2.2

Spin–Spin Coupling with Other Nuclei

3.2.2.1 Nuclei of Spin $I = \frac{1}{2}$

The aspects of spin–spin coupling discussed above are also valid for other nuclei with a spin quantum number $I = \frac{1}{2}$. For example, many first-order splittings are found in the ^{19}F NMR spectra of organofluorine compounds or in the ^{31}P NMR spectra of organophosphorus compounds. In addition, organofluorine and organophosphorus compounds possess mixed spin systems composed of protons and ^{19}F or ^{31}P nuclei, respectively. ^1H , ^{19}F , and ^1H , ^{31}P coupling constants then lead to line splittings in the ^1H , ^{19}F , and ^{31}P NMR spectra of these molecule (Figure 3.15 p. 50; see also Chapter 12).

In contrast to ^{19}F or ^{31}P nuclei, which both have a natural abundance of 100%, other nuclei with the spin quantum number $I = \frac{1}{2}$ are present in organic or organometallic molecules in small amounts. These nuclei are known as *rare nuclei*. Prominent examples of such nuclei are ^{13}C (1.1%) and ^{29}Si (4.7%), as well as several metal nuclei such as ^{199}Hg (16.9%), the cadmium isotopes ^{111}Cd and ^{113}Cd (12.9% and 12.3%, respectively), and also tin (^{117}Sn , 7.7%; ^{199}Sn , 8.8%) and platinum (^{195}Pt , 33.7%). Coupling of these nuclei to protons is observed only for those molecules that contain the NMR active isotope and the corresponding resonance signals are, therefore, of low intensity. They can be observed in the ^1H NMR spectrum of the particular compound as so-called *satellite lines*. Figure 3.16 (p. 50) shows as an example the proton resonance spectrum of bis(trimethylsilyl)mercury with satellites due to ^{13}C , ^{199}Hg , and ^{29}Si .

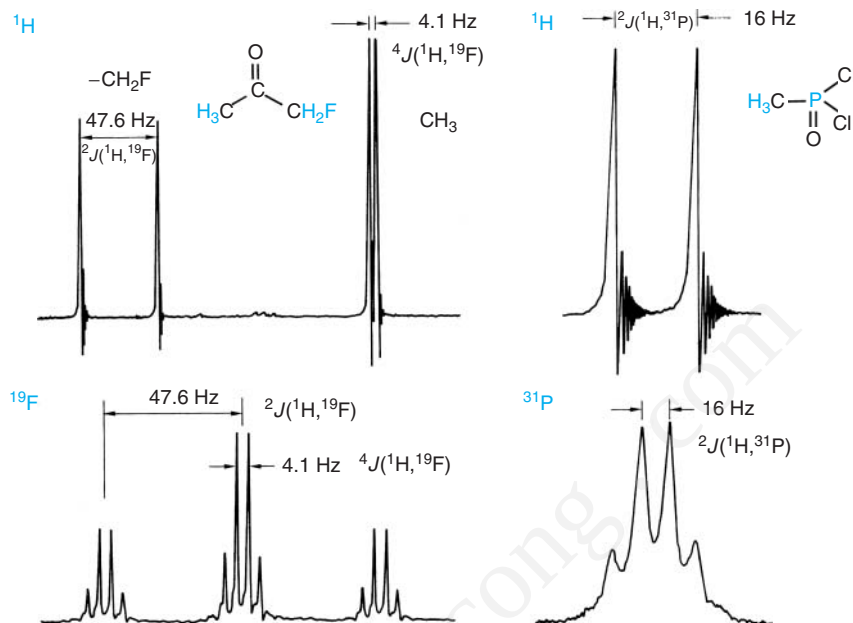


Figure 3.15 ^1H NMR and ^{19}F as well as ^{31}P NMR spectra of fluoroacetone and methylphosphorus dichloride, respectively [measuring frequencies 60 (^1H), 75.3 (^{19}F), and 32.3 (^{31}P) MHz].

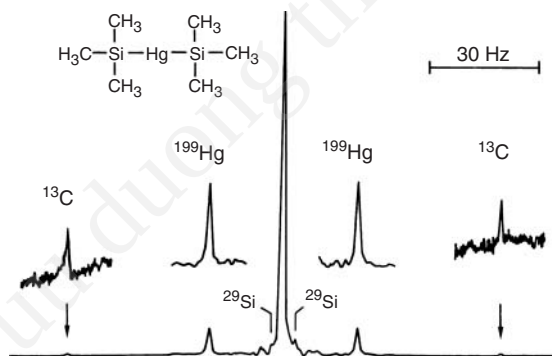


Figure 3.16 Satellite lines in the ^1H NMR spectrum of bis(trimethylsilyl)mercury: ^{13}C (1.1%), $^1J(^{13}\text{C}, ^1\text{H}) = 119.6$ Hz; ^{199}Hg (16.9%), $^3J(^{199}\text{Hg}, ^1\text{H}) = 40.7$ Hz; ^{29}Si (4.7%), $^2J(^{29}\text{Si}, ^1\text{H}) = 6.6$ Hz.

If the natural abundance of an NMR active nuclide falls below 1%, the observation of satellite spectra becomes difficult for sensitivity reasons. In these cases isotopic enrichment is necessary to observe the coupling constant of interest. The importance of ^{13}C satellites in ^1H NMR spectra for spectral analysis will be discussed in Chapter 7.

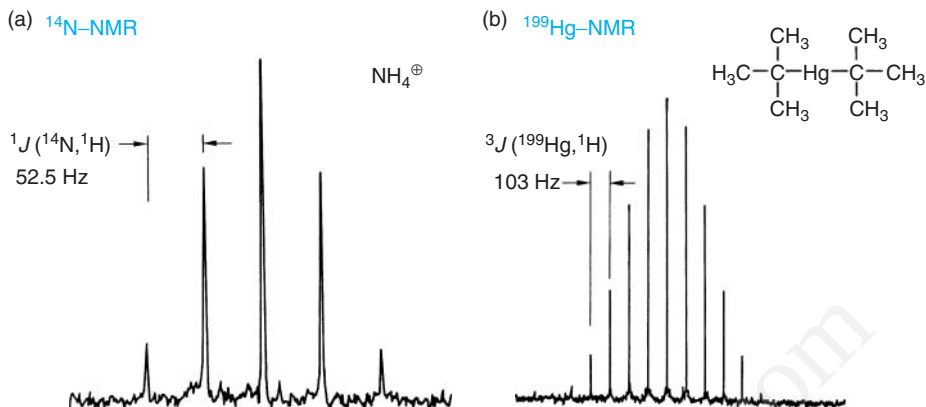


Figure 3.17 ^{14}N NMR spectrum of the ammonium ion (a) and ^{199}Hg NMR spectrum of di-*t*-butylmercury (b); measuring frequency 4.33 and 14.3 MHz, respectively. In (b) 8 of the 19 expected lines are not visible because of their low intensity.

In the spectra of rare isotopes, on the other hand, the line splitting that arises from coupling to the protons of the particular compound is always clearly visible. The splitting pattern corresponds in many cases to the first-order rules. As examples we show in Figure 3.17 the ^{14}N NMR signal of the ammonium ion and the ^{199}Hg resonance in di-*t*-butylmercury. The ^{13}C NMR spectrum of norbornane discussed later shows similar results (Figure 3.24, p. 60).

Exercise 3.8

Verify the intensity distribution found for the ^{14}N resonance of the ammonium ion in Figure 3.17 by writing a table with the possible spin functions for the four protons and inspection of Pascal's triangle.

3.2.2.2 Nuclei of Spin $I > \frac{1}{2}$

In cases in which spin-spin coupling involves a nucleus that has a spin quantum number I greater than $\frac{1}{2}$, the multiplicity and the intensity distribution of the splitting pattern deviates from the rules given above. For example, a neighboring deuteron or nitrogen-14 ($I = 1$) split a proton signal into a triplet, the lines of which have equal intensities. This follows from the fact that the possible orientations of the deuteron spin relative to an external field, namely, $m_I = +1, 0$, and -1 , are in practice equally probable. In general the multiplicity of an NMR signal caused by n neighboring nuclei is given by $2nI + 1$. Thus, a nucleus of spin $\frac{3}{2}$ with spin states of $m_I = -\frac{3}{2}, -\frac{1}{2}, +\frac{1}{2}$, and $+\frac{3}{2}$ splits the resonance line of a neighbor into four signals of equal intensity. Examples for this rule are found in Exercise 3.11 and the intensity distribution in spin multiplets caused by n neighboring nuclei with spin $I = 1$ or $I = \frac{3}{2}$ are shown in Section 6 (p. 664) in the Appendix.

Exercise 3.9

What multiplicity and intensity distribution should be expected according to the first-order rules for the nuclei designated a, b, c, and d in compounds 1–6? Consider coupling over only two or three bonds.

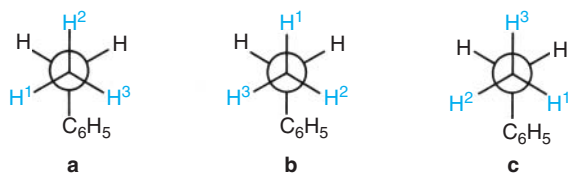
1 $\text{CH}_3\text{—OH}$ a b	4 $\text{CF}_3\text{—CHF—CH}_3$ a bc d
2 $(\text{CH}_3)_3\text{C—CH}_2\text{Br}$ a b	5 $(\text{CH}_3)_2\text{CH—O—CH}_2\text{—CH}_3$ a b c d
3 $\text{CH}_3\text{—CHCl—CH}_2\text{—O—CH}_3$ a b c d	6 CHDCl_2 ab

3.2.3

Limits of the Simple Splitting Rules**3.2.3.1 The Notion of Magnetic Equivalence**

As already mentioned, a few qualifying remarks are necessary concerning the validity of the first-order rules for analysis of the fine structure of nuclear magnetic resonance signals. The explanation often given leads one to the erroneous assumption that no spin–spin coupling occurs between protons within a group, for example, the three protons of a methyl group, because there is no indication of coupling between these protons in the spectrum. Therefore, we want to introduce a rule here that will be substantiated in detail later. It states: *The spin–spin coupling between magnetically equivalent nuclei does not appear in the spectrum.* By *magnetically equivalent* we mean that all of the nuclei under consideration possess the same resonance frequency and only *one* characteristic spin–spin interaction with the nuclei of a neighboring group. Nuclei with the same resonance frequency are called *isochronous*. They are usually also chemically equivalent, that is, they have identical chemical environments. Chemically equivalent nuclei are, however, not necessarily magnetically equivalent.

The protons of a methyl group are magnetically equivalent since, as a consequence of the rotation about the C–C bond, all three protons have the same time-averaged chemical environment and therefore the same resonance frequencies. The coupling constant to the protons of a neighboring CH_2 or CH group is likewise necessarily identical for each of the three protons, as the three conformations **a**, **b**, and **c** (shown below) are of equal energy and therefore equally populated. The geometric relation between the individual methyl protons and their neighbors that determines the magnitude of the coupling constant thus becomes identical for each of the three methyl protons.



The same arguments apply for the nine protons of a *t*-butyl group. With this group, however, it is possible in special cases to reduce the rate of rotation about the bond to the next carbon by cooling to low temperatures to such an extent that chemically different methyl groups can be distinguished in the NMR spectrum (Figure 13.11, p. 522).

Exercise 3.10

Figure 3.18 shows a series of splitting patterns for three different protons or proton groups that we shall identify as A, M, and X. Determine the coupling constants J_{AM} , J_{AX} , and J_{MX} and also the number of protons in each group by reference to the multiplicity and intensity distribution of the signals.

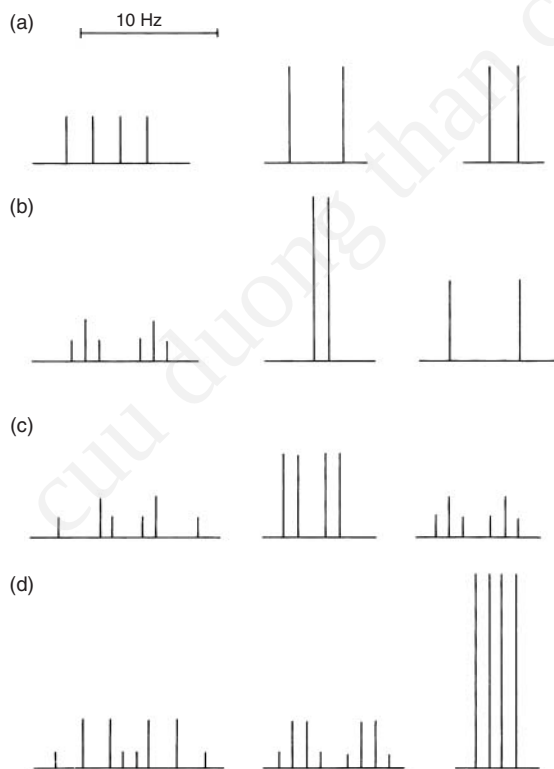


Figure 3.18 Series of splitting patterns for three different protons or proton groups.

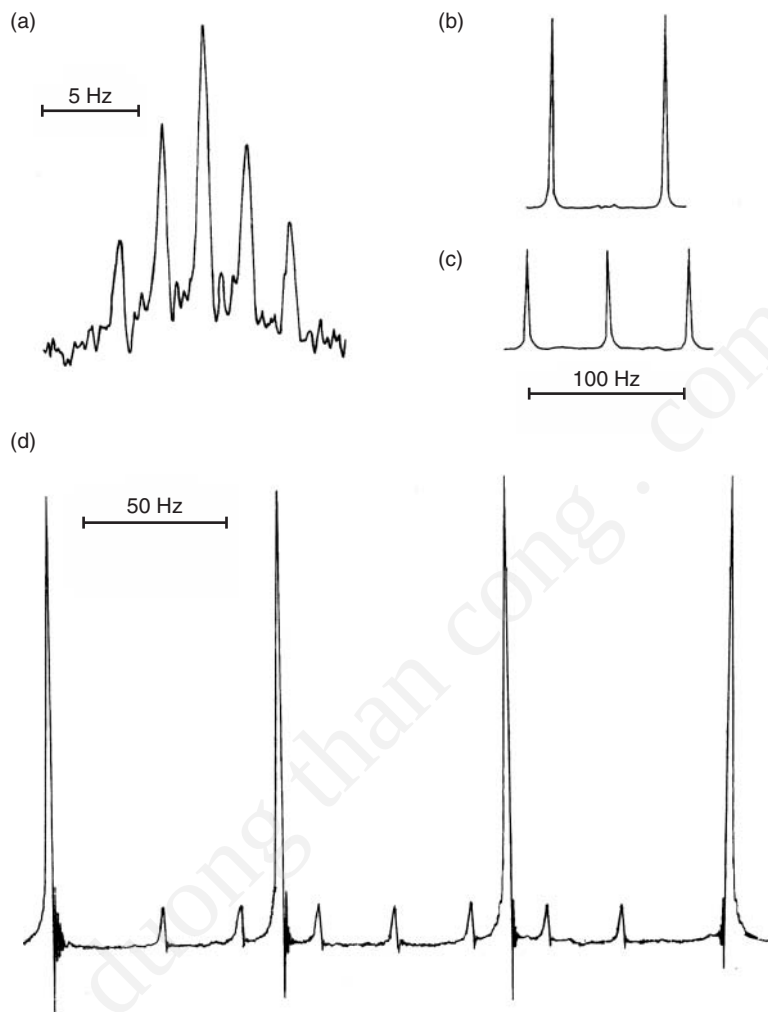


Figure 3.19 ^1H NMR of splitting patterns from different groups.

Exercise 3.11

Figure 3.19 above shows the ^1H NMR spectra of NaBH_4 , the CHD_2 group of $\text{C}_6\text{H}_5\text{CHD}_2$, and the ammonium ions $^{14}\text{NH}_4^+$ and $^{15}\text{NH}_4^+$. Assign the spectra, explain the multiplicity, and indicate the value of the coupling constants. Relevant nuclear properties may be found in Table 2.1, page 26.

In other compounds the magnetic non-equivalence of protons is often suggested by the structure. As Figure 3.20 shows, the protons in 1,1-difluoroethylene (1), as well as the two fluorine nuclei, are chemically equivalent but magnetically non-equivalent because two different coupling constants are observed. In such a case

$J_{13} \neq J_{14}$ or $J_{\text{cis}} \neq J_{\text{trans}}$. Similarly, there are two non-identical coupling constants, J_{13} and J_{14} , between the 1,2- and 3,4- protons in furan (2). The α and β protons are therefore magnetically non-equivalent. In difluoromethane (3), on the other hand, the protons as well as the fluorine nuclei are magnetically equivalent because of the tetrahedral geometry of this compound ($J_{13} = J_{14} = J_{23} = J_{24}$). In the customary notation for spin systems these different properties of nuclei are taken into account. As we shall explain later in detail in Chapter 6 (p. 194 and 204), the magnetic nuclei in 1,1-difluoroethylene (1) and in furan (2) represent AA'XX' systems while those in difluoromethane (3) are classified as an A_2X_2 system.

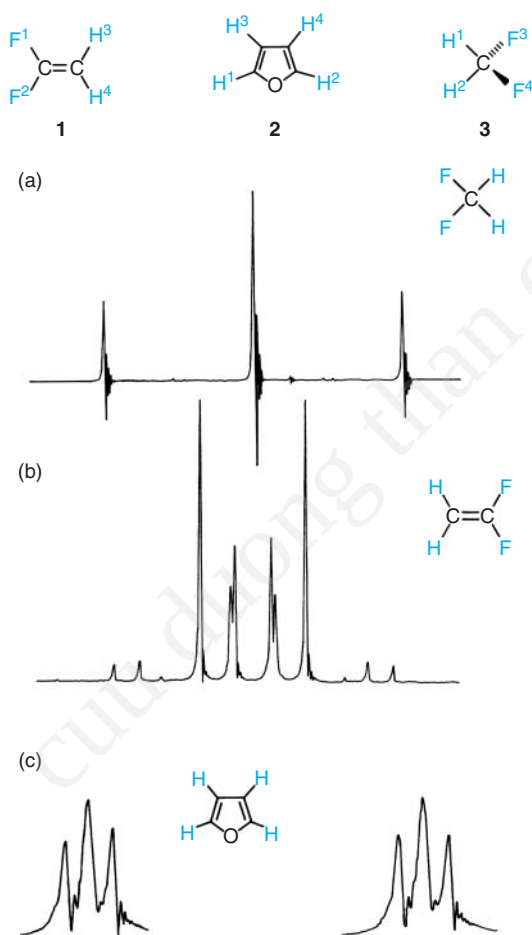


Figure 3.20 ^1H NMR spectrum of (a) difluoromethane (3), (b) 1,1-difluoroethylene (1) (after Reference [2]), and (c) furan (2).

In this context it is of significance that the first-order rules formulated above to explain the line splittings in NMR spectra apply only for groups of magnetically equivalent nuclei. If the nuclei in a group are not magnetically equivalent, individual coupling constants cannot be taken from the spectrum and the chemical shift can be determined from the center of the multiplet with sufficient accuracy without analysis only if the relation $J/\Delta\nu < 0.1$ holds (cf. Section 3.2.3.2, below). This is made readily apparent through comparison of the spectra of difluoromethane and 1,1-difluoroethylene. In the former (Figure 3.20a) we observe the expected triplet for the proton resonance while in the latter (Figure 3.20b) a complicated splitting pattern results. In this case the coupling constants can be determined only after a precise analytical procedure that will be considered in Chapter 6. In addition, we should emphasize that the presence of simple splitting patterns is not always a guarantee that the first-order rules can be applied. For example, in the NMR spectrum of furan one finds two triplets centered at δ 6.37 and 7.42 (Figure 3.20c) that, as we have already explained, may not be interpreted as indicating that the two α protons are equally coupled to the two β protons and that the coupling constant, J , corresponds to the 3.2 Hz that can be determined from the line separation. We shall return to the treatment of such *deceptively simple* cases in Chapter 6.

3.2.3.2 Significance of the Ratio $J/\nu_0\delta$

A further important restriction that must be applied to the first-order rules states that they can be employed with confidence only where the chemical shift difference, $\Delta\nu$ or $\nu_0\delta$ (Hz), of the individual groups of magnetically equivalent nuclei is large compared with the coupling constant connecting these groups. As mentioned above, we then speak of a *first-order* spectrum or of a case with *weak coupling*. If $\nu_0\delta$ is of the same order of magnitude as the coupling constant, more lines are observed in the spectrum than would be expected according to the first-order rules (Figure 3.21) and we have a case of *strong coupling*. Notably, the intensity distribution in the two groups of signals is also dramatically affected. The intensity of the lines nearest to the multiplet of the neighboring group is greatly enhanced while that of the other lines has decreased. This is called the *roof effect* and has considerable diagnostic value in the assignment of coupling constants as it indicates whether the resonance of neighboring protons coupled with a particular group lie at a higher or lower frequency than that of the group under consideration. An illustrative but less dramatic example is shown in Figure 3.14 (p. 49).

Increased multiplicity and altered intensity distribution are therefore indications of spectra of *higher order* that must be analyzed by more exact methods. In applying the first-order rules in the determination of chemical shifts and coupling constants one obtains only approximate values; the errors become larger as the ratio $J/\nu_0\delta$ increases.

It is, therefore, important that, because of the field dependence of $\nu_0\delta$, complicated spectra can be simplified by using high B_0 fields from superconducting magnets, and the introduction of spectrometers equipped with cryomagnets has greatly enlarged the number of first-order spectra from organic molecules. Figure 3.22 demonstrates the simplification that may be obtained at higher field

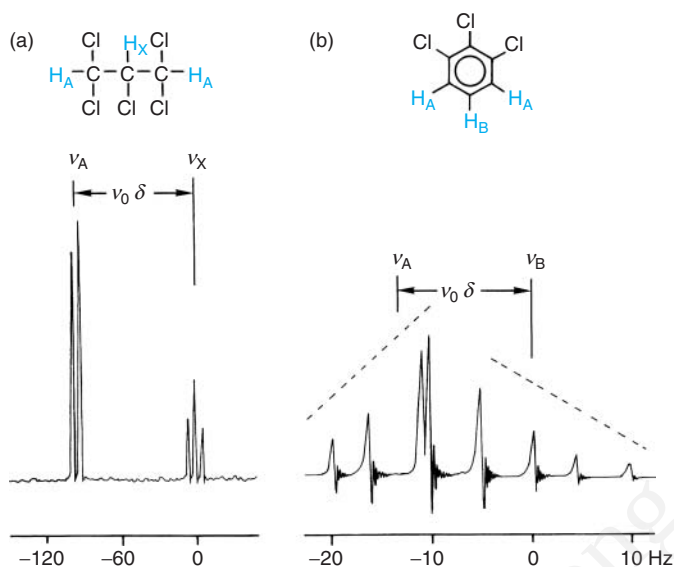


Figure 3.21 ^1H NMR spectrum of (a) 1,1,2,3,3-pentachloropropane and (b) 1,2,3-trichlorobenzene. The ratio $J/\nu_0\delta$ in the first case is 0.06 and first-order rules are applicable. In the second case $J/\nu_0\delta \approx 0.7$; first-order rules fail and the number of lines increases from five to eight.

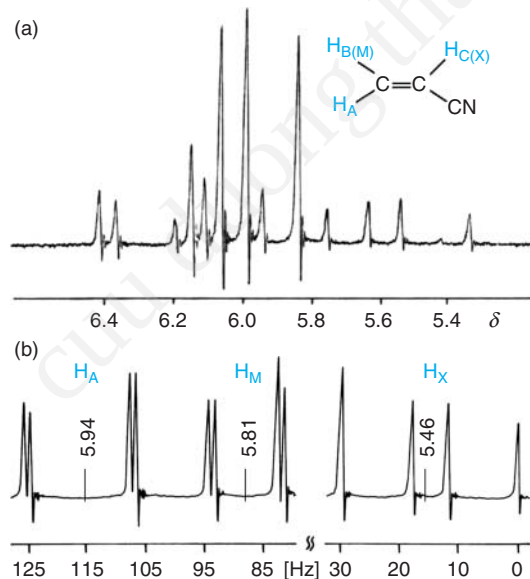


Figure 3.22 ^1H NMR spectra of acrylonitrile at 60 MHz (a) and 220 MHz (b); the δ -values below are given on a different scale.

strength with the spectra of acrylonitrile measured at 60 MHz (1.4 T) and at 220 MHz (5.1 T). At high field the complicated 60 MHz ABC spectrum has changed into a first order AMX spectrum.

Finally, it should be pointed out again that, unlike first-order spectra, all spectra of higher order depend upon the *relative* signs of the coupling constants, which can be obtained through a detailed spectral analysis. The signs of J couplings, the consideration of which is essential for a meaningful discussion of the experimental data, are included in our discussion in Chapter 5. They are based, in most cases, on the determination of the sign relative to that of the one-bond coupling between a ^{13}C nucleus and a proton that is positive.

3.2.4

Spin–Spin Decoupling

The interpretation of many NMR spectra from complex organic molecules, such as those from natural products, is often complicated through line splittings caused by scalar coupling and in cases of higher order spectra situations arise where by direct inspection even the chemical shifts can be determined only approximately. The possibility of simplifying complicated spectra by eliminating scalar spin–spin coupling experimentally is, therefore, of considerable practical importance. The techniques used for this purpose are known as *double resonance*.

Spin–spin decoupling rests on the application of a second radio frequency source B_2 in addition to the transmitter B_1 used for detection of the spectrum. Consider a spin system of two nuclei A and X with a scalar coupling $J(\text{A,X})$. If we observe the A nucleus with the transmitter B_1 while irradiating the X nucleus with the transmitter B_2 , the scalar coupling between A and X vanishes. The application of a strong B_2 source to the X resonance leads to a situation where the magnetization M_X of the X nucleus is driven to the y -axis of the coordinate system (cf. Figure 2.7). The vector μ_X is then quantized along the y -direction while the vector μ_A still points along the z -axis. The scalar product $\mu_A \cdot \mu_X$ and thus the energy of spin–spin coupling [Eq. (3.9)] will become zero. As a consequence, the line splitting for the A nucleus disappears.

Two examples may suffice to illustrate these facts. Figure 3.23 shows a spin–spin decoupling experiment with *trans*-ethyl crotonate. The resonances of the olefinic protons H_A and H_B are extensively split due to spin–spin coupling with the protons of the olefinic methyl group (Figure 3.23a). Upon irradiation of the resonance of the methyl group at the double bond with a second RF source, the spectrum simplifies to the expected AB system (Figure 3.23b). Since in this experiment the irradiated and the observed nucleus are from the same nuclide, the experiment is known as *homonuclear* decoupling experiment. Clearly, homonuclear decoupling experiments can be used as an assignment aid because upon irradiation of a certain multiplet A the line splittings for nuclei that are coupled to A are eliminated.

For spin decoupling a second independent RF source was used in the older CW mode to irradiate the resonance of the nucleus to be decoupled. FT spectrometers also have with a proton decoupler an independent RF source that is used for

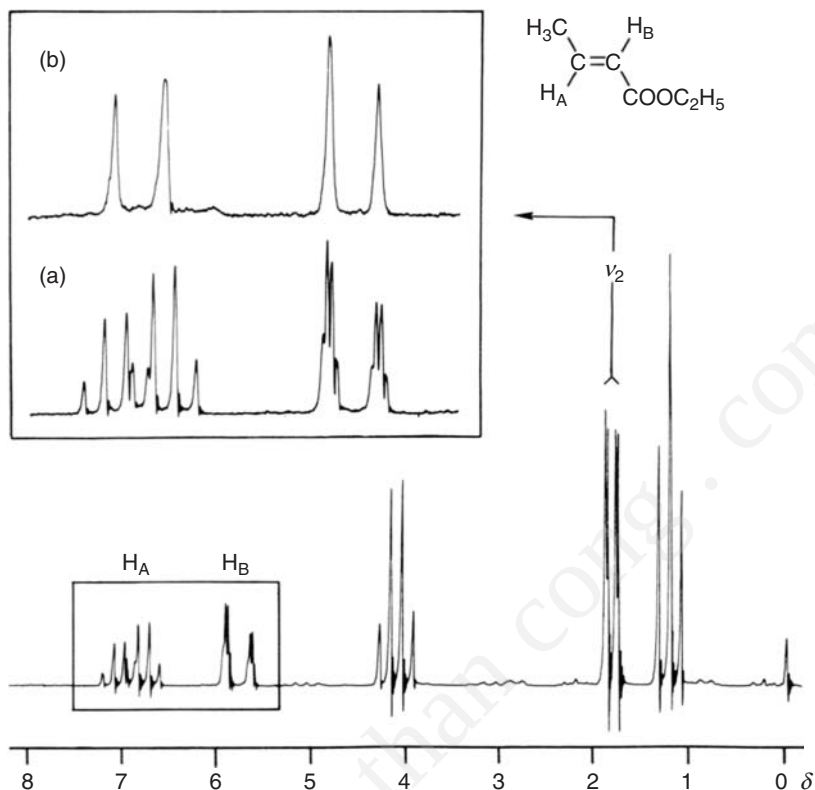


Figure 3.23 Spin-spin decoupling experiment with *trans*-ethyl crotonate: (a) single resonance spectrum of the olefinic protons and (b) double resonance spectrum with B_2 at the resonance of the olefinic methyl group ($\nu_2 = \nu_{CH_3}$).

homo- as well as heteronuclear decoupling experiments. In the pulse Fourier transform mode the proton decoupler, provided by a separate RF coil in the probe-head, yields a pulse modulated B_2 field in the proton regime that for homonuclear experiments is applied in a time-sharing procedure. This will be discussed in more detail in Chapter 8.

Figure 3.24 (p. 60) shows an example for a *heteronuclear* decoupling experiment with the ^{13}C NMR spectrum of norbornane, where the multiplets of the various ^{13}C resonances result from $^{13}C, ^1H$ coupling. However, if we record the ^{13}C NMR spectrum in the frequency range $\nu(^{13}C)$ (in this particular experiment 100 MHz) while irradiating at the same time the proton resonances in the frequency range $\nu(^1H)$ (here 400 MHz), all couplings disappear. The ^{13}C resonances are then recorded as singlets that can be assigned in this case immediately on the basis of their relative intensities. Because all proton resonances of norbornane have to be irradiated at once, the technique uses a strong B_2 field that covers the complete ^1H region and is called *broadband decoupling*. It has the additional advantage that the

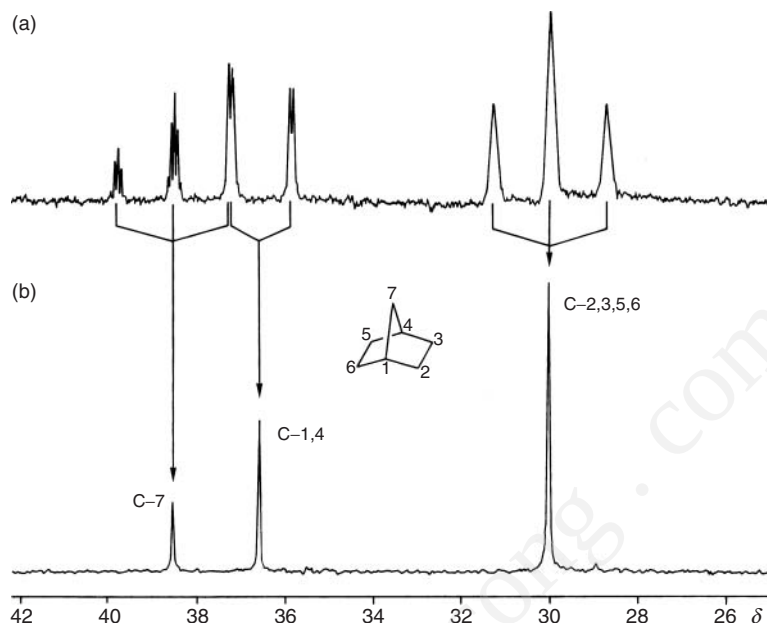


Figure 3.24 100 MHz ^{13}C NMR spectrum of norbornane without (a) and with (b) ^1H -decoupling; the δ -scale refers to the ^{13}C resonance of tetramethylsilane.

intensity of the ^{13}C signals increases because of the nuclear Overhauser effect, an important feature that we shall discuss in detail in Chapter 10.

3.2.5

Two-Dimensional NMR – the COSY Experiment

Having introduced the δ -scale of NMR spectra that runs in one dimension from low to high frequency, and the phenomenon of spin–spin coupling, it seems appropriate to introduce with the correlated spectroscopy (COSY) experiment the technique of two-dimensional (2D) NMR spectra.

A *two-dimensional* NMR spectrum is characterized by a square of *two* frequency scales that are labeled F_1 and F_2 . In the homonuclear COSY spectrum both scales are identical chemical shift scales of the same nuclide, for example, ^1H . Figure 3.25b shows a so-called contour plot for the 400 MHz ^1H COSY NMR spectrum of *trans*-chloroacrylic acid. The AX spectrum of the compound (Figure 3.25a) appears with the two doublets along the *diagonal peaks*. So far, no new information compared to that gained from the normal one-dimensional (1D) spectrum produced above is obtained. However, two *additional signals*, at coordinates $F_1 = \delta_A$; $F_2 = \delta_X$ as well as $F_1 = \delta_X$; $F_2 = \delta_A$ are observed. These are the so-called *cross peaks* that indicate coupling between the two resonances A and X – here already seen clearly in the 1D spectrum. The powerful feature of the COSY experiment is that *all* (or nearly all, see below) relationships between

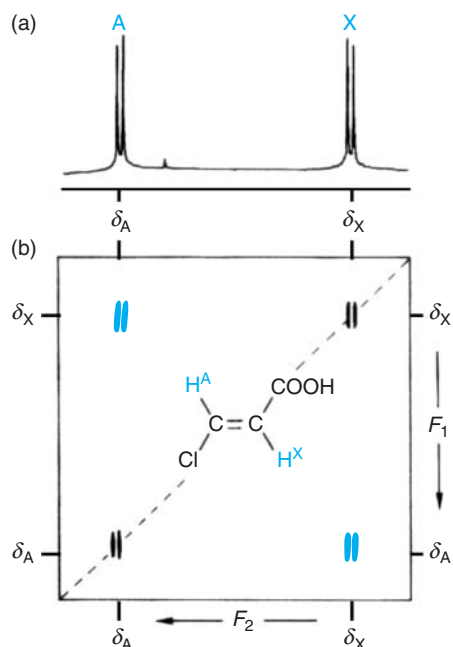


Figure 3.25 (a) 1D spectrum of an AX system; (b) COSY spectrum of the same system.

different nuclei of a certain molecule that are based on scalar spin–spin coupling are documented by cross peaks. Different frequency settings of a decoupler such as in the 1D spin-decoupling experiment described above are thus not necessary. The COSY experiment is therefore an important aid for spectral analysis and is superior to selective homonuclear decoupling, especially in cases of complicated spectra.

A COSY spectrum – as will be discussed in detail in Chapter 9 (Section 9.4, p. 296) – is measured by the FT method and consists of two pulses separated by the so-called *evolution time* t_1 , which is usually less than 1 s (Figure 3.26). This time interval is incremented (Δt of the order of ms) and the measurement repeated several times. Correctly speaking, the COSY spectrum is thus not the result of only *one* experiment but arises through a whole series of individual pulse experiments,

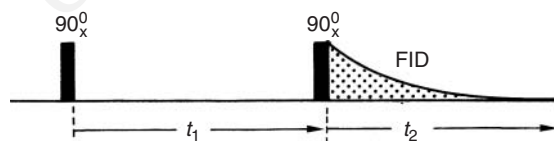


Figure 3.26 Pulse sequence of the homonuclear COSY experiment; the two 90° pulses are separated by the evolution time t_1 that is incremented in a series of successive experiments. The signals recorded in the detection time t_2

(free induction decay, FID) are stored after Fourier transformation. They show an amplitude modulation that contains the frequencies of the spectral parameters ν_i and J_{ij} that are obtained by a second Fourier transformation.

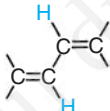
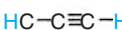
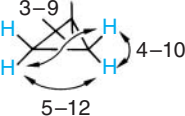
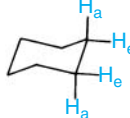
a property that is true for all 2D NMR techniques. The data are stored and subjected to two subsequent Fourier transformations. During the evolution time t_1 , magnetization is exchanged between coupled nuclei that results in an amplitude modulation of the different Fourier-transformed t_2 -signals. These data are Fourier-transformed again, which yields the diagonal and the cross peaks. The cross peaks of standard ^1H , ^1H COSY spectra are due to vicinal ^1H , ^1H coupling constants. A slight modification of the experiment allows optimization for long-range couplings that are in general smaller than 3 Hz (cf. p. 305 ff.).

3.2.6

Structural Dependence of Spin–Spin Coupling – A General Survey

Scalar spin–spin coupling constants are classified according to the number of bonds involved as *geminal* (two bonds, ^2J), *vicinal* (three bonds, ^3J), and *long-range* couplings (n bonds, $n > 3$, ^nJ) and we conclude this discussion with a general survey of the dependence of ^1H , ^1H coupling on molecular structure. For this purpose the most important types of coupling constants are summarized in Table 3.2. As these

Table 3.2 Typical values of ^1H , ^1H coupling constants in organic compounds.

			
12–20	0–3.5		
			
2–9	6–14	11–18	4–10
			
10–13	3–7	1–3	2–3
			
$J_o = 7\text{--}10$		$J_{aa} = 10\text{--}13$	
$J_m = 2\text{--}3$		$J_{ae} = 2\text{--}5$	
$J_p = 0.1\text{--}1$		$J_{ee} = 2\text{--}5$	

data show, coupling constants for protons cover a range of ca. 2 – 17 and are very sensitive to the geometry of the coupling path, that is, the stereochemistry of molecules.

The spin-spin interaction of olefinic protons offers a typical example. For a pair of isomers J_{trans} is always larger than J_{cis} . Similarly, we see that in cyclohexane $J_{\text{aa}} > J_{\text{ee}}$. In contrast, we observe $J_{\text{trans}} < J_{\text{cis}}$ in cyclopropane. In addition to coupling through a carbon skeleton, spin-spin interaction can be transmitted through heteroatoms in groups of the type H–C–O–H and H–C–N–H. *Long-range coupling* over more than three bonds is generally observed in unsaturated systems in which the π -electrons prove to be effective transmitters of magnetic information.

Finally, we note that the coupling constants of many molecules are influenced by conformational equilibria and other dynamic processes. The observed data are then average values that are formed on the basis of the mole fractions p , from the data of the individual conformers. In the simplest case of an equilibrium between two conformations A and B, the following equation holds:

$$J_{\text{exp}} = p_A J_A + p_B J_B \quad (3.12)$$

An analogous equation exists for chemical shifts. These relations are discussed in more detail in Chapter 13.

Exercise 3.12

Figure 3.27 presents a series of proton magnetic resonance spectra with significant signal splitting as the result of spin-spin coupling; frequency 60 MHz.

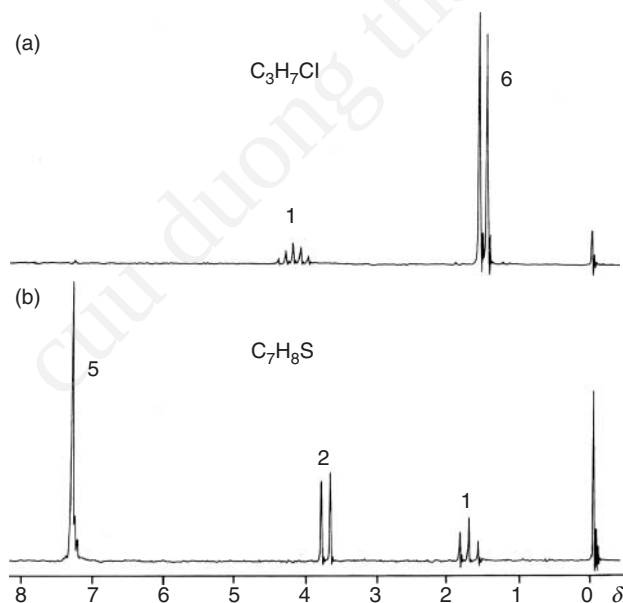


Figure 3.27 Proton magnetic resonance spectra with significant signal splitting as the result of spin-spin coupling.

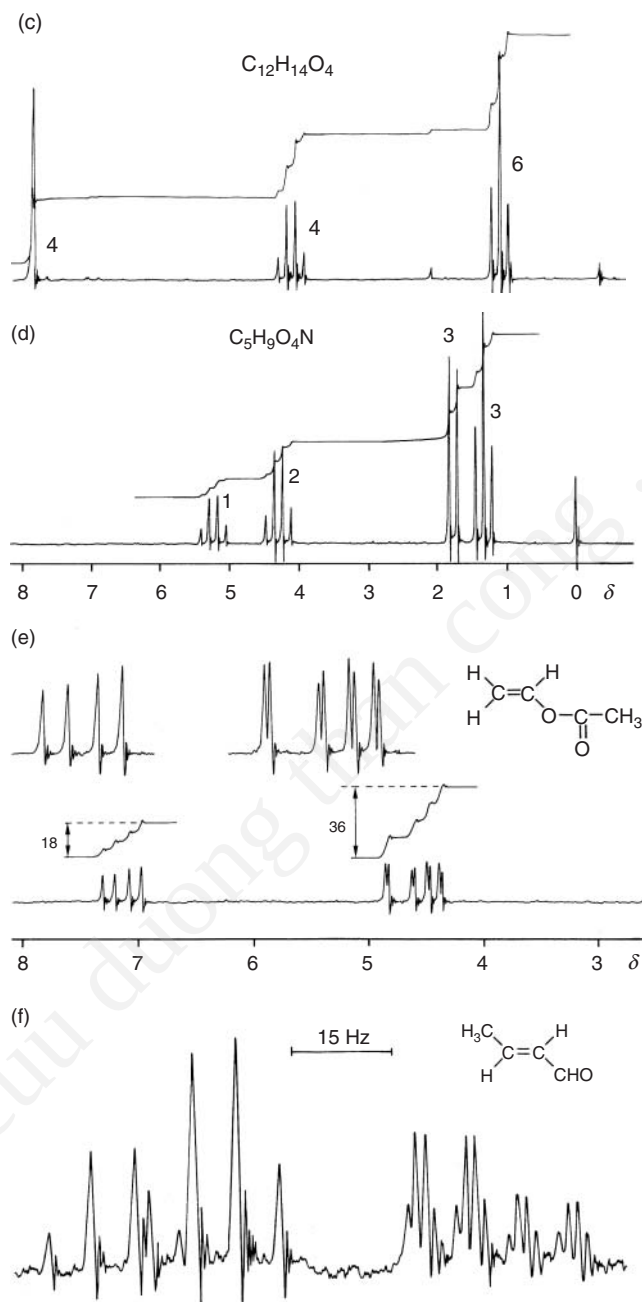


Figure 3.27 (continued)

- 1) Determine the structures of compounds (a)–(d).
- 2) Assign the signals in the 60 MHz spectrum of vinyl acetate (e) to the appropriate protons by means of determining the coupling constants.
- 3) Analyze the absorption of the olefinic protons in crotonaldehyde (f) and determine and assign the coupling constants. Which proton absorbs at higher frequency?

Exercise 3.13

Figure 3.28 (p. 65) shows the 90-MHz spectrum of the H^a and H^b protons of pyrimidine. Assign the resonances and determine the coupling constants.

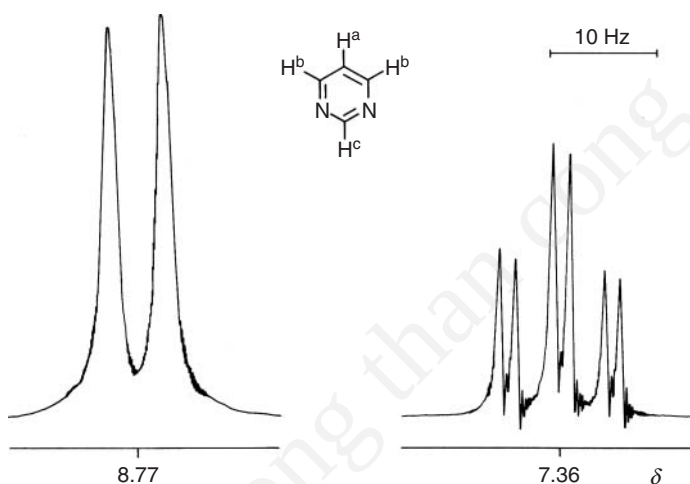


Figure 3.28 90-MHz ^1H NMR spectrum of the H^a and H^b protons of pyrimidine.

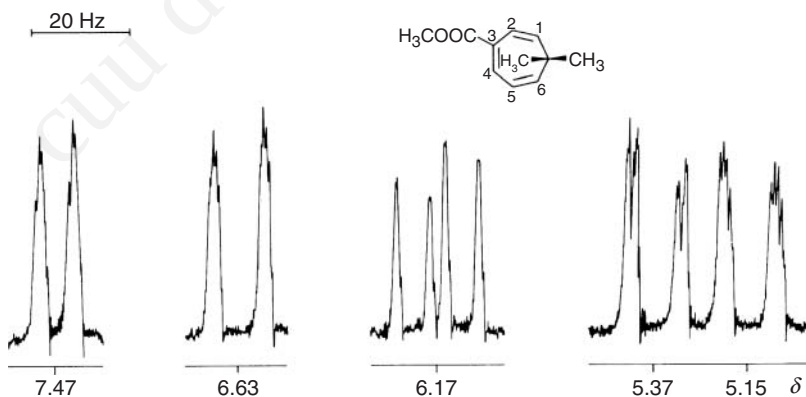


Figure 3.29 Olefinic resonances of thujic ester.

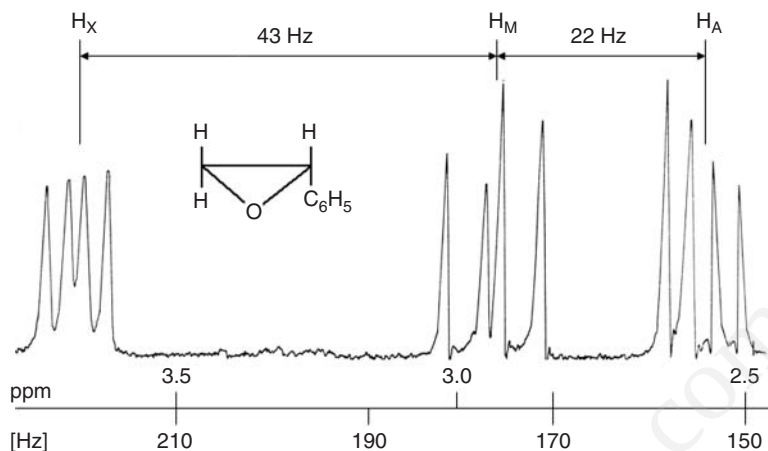


Figure 3.30 ^1H NMR spectrum of styrene oxide. Taken with permission from Reference [3]. Copyright 2013, Elsevier.

Exercise 3.14

Figure 3.29 (p. 65) shows the olefinic resonances of thujic ester. Assign the resonances to appropriate protons and estimate the vicinal coupling constants.

Exercise 3.15

Figure 3.30 shows the spectrum of styrene oxide with the chemical shift scale in hertz and parts per million. Assign the signals to the protons of the compound and estimate chemical shifts and coupling constants. At which frequency was the spectrum measured?

References

1. Proctor, W.G. and Yu, F.C. (1950) *Phys. Rev.*, **77**, 717.
2. Becker, E.D. (1980) *High-Resolution NMR*, 2nd edn, Academic Press, New York, p. 91.
3. Jackman, L.M. and Sternhell, S. (1969) *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd edn, Pergamon Press, Oxford, p. 126.

4

General Experimental Aspects of Nuclear Magnetic Resonance Spectroscopy

Having introduced the fundamental parameters of high-resolution nuclear magnetic resonance spectroscopy in the preceding chapter, we shall now examine more closely the experimental aspects of the technique.

4.1

Sample Preparation and Sample Tubes

Sample preparation in NMR spectroscopy is extremely simple. For ^1H NMR, obviously *solvents* that have no protons are preferred, but this limitation is not serious because of the ready availability of deuterated compounds. Furthermore, to stabilize the spectrometer the deuteron resonance is used in the so-called lock channel, described in more detail below. Therefore, deuterated solvents are used exclusively, and the most widely applied solvent for organic compounds is deuteriochloroform, CDCl_3 . For poorly soluble samples and for other applications an alternative series of deuterated solvents is available: $[\text{D}_6]$ dimethyl sulfoxide, $[\text{D}_6]$ acetone, $[\text{D}_3]$ acetonitrile, $[\text{D}_6]$ benzene, and D_2O . Table 4.1 summarizes the most frequently used solvents and their properties. A list with $\delta(^{13}\text{C})$ -values of solvents is given in the Appendix Table A.5, p. 659.

Another aspect of solvent selection arises in connection with the fact that in some cases the compound to be investigated is prepared in the NMR tube by the reaction of a starting material with the solvent or with a third component.

Protonated ketones are obtained in this way in trifluoroacetic acid, while simple carbenium ions were directly observed for the first time when aliphatic fluorides were reacted with antimony(v) fluoride in sulfur dioxide, resulting in the formation of the corresponding hexafluoroantimonate:



Similar results can be obtained with the so-called “magic acid,” a mixture of fluorosulfonic acid and antimony(v) fluoride. Obviously, in such cases the choice of solvent is considerably more than a routine decision and the NMR tube has served in these and other instances as a very useful “reaction flask” for organic chemistry.

Table 4.1 Properties of solvents used for NMR spectroscopy.^a

Solvent	Formula	Boiling point (°C)	Melting point (°C)	Magnetic volume susceptibility (χ_v) $\times 10^6$	$\delta(^1\text{H})$	$\delta(^{13}\text{C})$
[D]Chloroform	CDCl_3	60	−64.1	—	7.26 ^b	77.0
[D ₆]Dimethyl sulfoxide	CD_3SOCD_3	190	20.2	—	2.5 ^b	39.5
[D ₃]Acetonitrile	CD_3CN	79	−42	—	1.3	118.1
[D ₆]Acetone	CD_3COCD_3	55	−94.5	—	2.05	30.5
						205.1
[D ₂]Methylene chloride	CD_2Cl_2	39	−97	—	5.31 ^b	53.7
[D ₈]1,4-Dioxane	$\text{C}_4\text{D}_8\text{O}_2$	100	11	—	3.53 ^b	66.3
[D ₁₀]Diethyl ether	$\text{C}_4\text{D}_{10}\text{O}$	34.6	−116.3	—	1.07	14.5
					3.34	65.3
[D ₈]Tetrahydrofuran	$\text{C}_4\text{D}_8\text{O}$	64	−108.5	—	1.72 ^b	25.3
					3.57 ^b	67.2
[D ₁₂]Cyclohexane	C_6D_{12}	—	—	—	1.38	26.0
[D ₆]Benzene	C_6D_6	79	7.6	—	7.16 ^b	128.7
Heavy water	D_2O	101.4	3.8	−0.719	4.72 ^b	—
Sulfur dioxide ^c	SO_2	−10.0	−75.5	−0.812	—	—

^aAs a result of isotope effects, small differences between deuterated and non-deuterated compounds are observed for melting and boiling points as well as for $\delta(^{13}\text{C})$.

^bResidual ^1H NMR signal of partially deuterated material.

^cNot possible to lock.

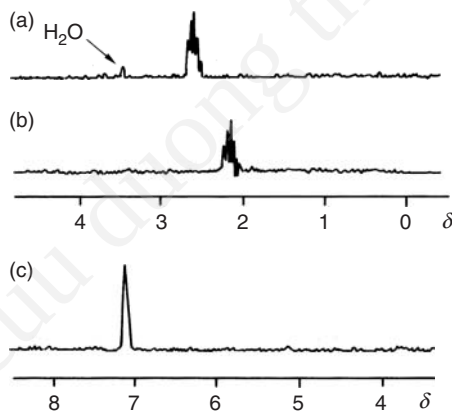


Figure 4.1 NMR absorptions of partially deuterated “impurities” in (a) [D₆]dimethyl sulfoxide, (b) [D₆]acetone, and (c) [D₆]benzene. Dimethyl sulfoxide is hygroscopic and therefore most samples are contaminated with a trace of water.

Notably, the small fractions (usually less than 0.5%) of only partially deuterated solvent molecules give rise to low-intensity signals in the spectrum. The signals produced by a few solvents are illustrated in Figure 4.1. The spin–spin splitting apparent in the cases of dimethyl sulfoxide and acetone arises through the

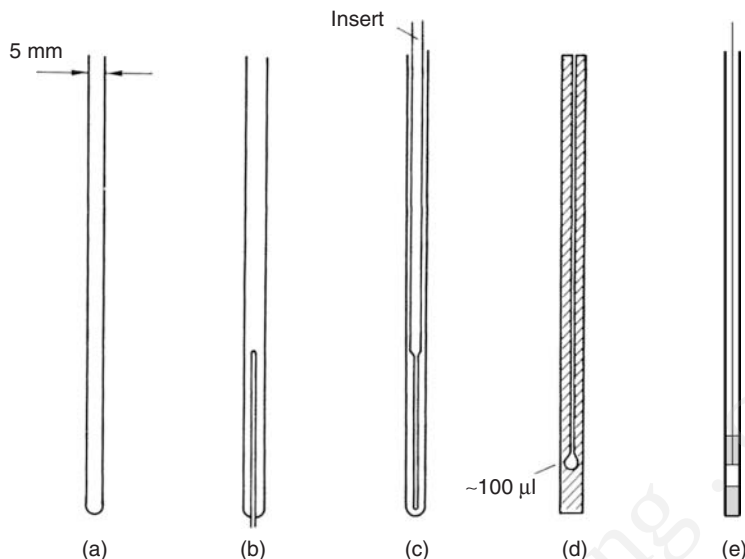


Figure 4.2 NMR sample tubes: (a) for measurement with an internal standard; (b) and (c) with capillaries for measurements with an external standard; (d) for microsamples; (e) Shigemi tube.

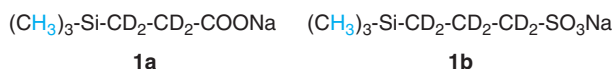
presence of the CHD_2 groups, that is, through the interaction of the proton with the two deuterons the total spin of which can take the m_T values of +2, +1, 0, -1, and -2 in the statistical ratio of 1 : 2 : 3 : 2 : 1. Except for a small high-field shift that originates from a deuterium induced isotope effect on the ^1H chemical shift, the proton resonance signals of partially deuterated solvents have the same δ values as those of the non-deuterated compounds.

To prepare a sample for measurement, about 5–10 mg or 10 μl of the substance are placed in the *sample cell* or *NMR tube*, a cylindrical glass tube about 17 cm long with a 5 mm outer diameter (Figure 4.2a), and dissolved by the addition of about 0.5 ml of solvent.

Finally, the *standard* or *reference compound*, usually tetramethylsilane (TMS), is added. Since this compound, because of its low boiling point (26°C) and its high vapor pressure, is difficult to handle in small amounts it is advantageous to have 5% (v/v) solutions of TMS in the most frequently used solvents on hand. Alternatively, the signal of the solvent can be used as reference and its frequency difference to TMS introduced into the software that controls the plotter. For insensitive nuclei like ^{15}N sample tubes with larger diameters are helpful if an appropriate probe-head is at hand. For measurements where only small amounts of the compound are available, special microcells like that shown in Figure 4.2d have been developed and tubes with diameters between 1 and 3 mm or so-called Shigemi tubes (Figure 4.2e) are used. In the normal sample cell (a) the solution should fill the tube to a height of 3–4 cm.

As with the choice of solvent, the choice of the standard depends upon the substance to be investigated. For example, with tetramethylsilane, for cyclopropane

derivatives and especially for silyl compounds a superposition of resonance and reference signals can result. In these cases cyclohexane, methylene chloride, or benzene can be used as a reference. In aqueous systems, 1,4-dioxane or *t*-butanol are applicable, but especially advantageous is the sodium salt of the partially deuterated $[D_4]3$ -(trimethylsilyl)propionic acid (**1a**), the ^1H NMR signal of which in aqueous and methanolic solutions is found at exactly $\delta = 0.00$, or the related $[D_4]2,2$ -dimethyl-2-silapentane-5-sulfonate (DSS, **1b**):



Generally, any substance for which the protons give rise to a signal of sufficient intensity is suitable as a reference. It is reasonable to wonder, though, to what extent measurements made with different reference compounds can be compared. Therefore, in the following section a few fundamental remarks are made concerning this subject.

4.2

Internal and External Standards; Solvent Effects

Following the classical electromagnetic equations the magnetic flux density B in a substance exposed to an external magnetic field consists of two terms:

$$B = \mu_0(H + M) \quad (4.1)$$

where H is the field strength of the applied field, M is the magnetization induced in the substance, and μ_0 is the permeability of free space, a constant equal to $4\pi \times 10^{-7} \text{ kg ms}^{-2} \text{ A}^{-2}$. The magnetization M is in turn dependent upon the external field strength according to:

$$M = \chi_v H \quad (4.2)$$

where χ_v is a dimensionless constant, the volume susceptibility, that is characteristic of the material. For diamagnetic substances χ_v is negative and in general is independent of the temperature. For NMR measurements the field strength that exists within the NMR tube is influenced by the magnetic susceptibility of the solvent. For this reason an *internal standard* is employed. That is, the reference substance and the sample are contained in the same solution so that both are exposed to the same magnetic environment and corrections of the experimental results are not necessary. On the other hand, with an *external standard*, when the reference substance is contained in a coaxial capillary separated from the volume that contains the sample (Figure 4.2b,c), the field strengths that exist in the capillary and the sample solution are different owing to the different volume susceptibilities. The chemical shifts recorded must then be corrected. For a cylindrical NMR tube the axis of which is parallel to the direction of the magnetic field, a situation met

for cryomagnets, the correction is given by:

$$\delta_{\text{cor.}} = \delta_{\text{exp.}} - \frac{4\pi}{3}(\chi_v^{\text{Standard}} - \chi_v^{\text{Sample}}) \times 10^6 \quad (4.3)$$

For iron magnets, where the sample cell is oriented perpendicular to the axis of the magnetic field, the factor $+2\pi/3$ instead of $-4\pi/3$ must be used. In the case of dilute samples, the volume susceptibility of the sample solution can be approximated as being equal to that of the solvent. Differences in δ values caused by the susceptibility effect can be as much as 1 ppm.

The observation of a frequency difference between measurements with internal and external standard suggests that the volume susceptibility of a solution can be determined by NMR. This is indeed the case. For this purpose a solution of a liquid L of unknown χ_v^L in a solvent S_0 of known χ_v^0 that has, preferably, only one NMR signal is placed in the inner capillary of an NMR tube of the type shown in Figure 4.2c. The outer compartment is then prepared with the same solvent S_0 and two signals of S_0 can be observed for the non-spinning tube. Their frequency difference $\Delta\nu$ (in Hz) is related to the difference in the volume susceptibilities by the equation:

$$\frac{\Delta\nu}{\nu_0} = -\frac{4\pi}{3}(\chi_v^i - \chi_v^0) \quad (4.4a)$$

and:

$$\chi_v^i = -\frac{3\Delta\nu}{4\pi\nu_0} + \chi_v^0 \quad (4.4b)$$

where χ_v^i is the volume susceptibility of the mixture in the inner capillary and ν_0 (in megahertz) is the spectrometer frequency. On the basis of Wiedemann's additivity law we find the unknown volume susceptibility χ_v^L with Eq. (4.5a), where ϕ^0 and ϕ^L are the volume fractions of the components in the mixture:

$$\chi_v^i = \phi^0\chi_v^0 + \phi^L\chi_v^L \quad (4.5a)$$

and

$$\chi_v^L = (\chi_v^i - \phi^0\chi_v^0)/\phi^L \quad (4.5b)$$

Alternatively, a sealed melting point capillary with the solution of L in S_0 can be placed in a normal NMR tube filled with S_0 and the spinning of the tube will now result in a coaxial arrangement. Before attempting any measurements, the tubes should carefully be calibrated. We will come back to this method when we discuss the diamagnetic anisotropies of aromatic compounds in Chapter 5.

It must be emphasized that while, with the aid of the internal standard, the susceptibility correction can be obviated, specific interactions between the solvent and the reference substance cannot be avoided. When, for example, chloroform is used as a reference substance in $[D_6]$ benzene as solvent, to consider an extreme case, the resonance signal of cyclohexane (concentration 20% v/v) is recorded at -4.96 ppm. With carbon tetrachloride as solvent and using the same reference the chemical shift is -5.80 ppm. The difference of 0.84 ppm between the two

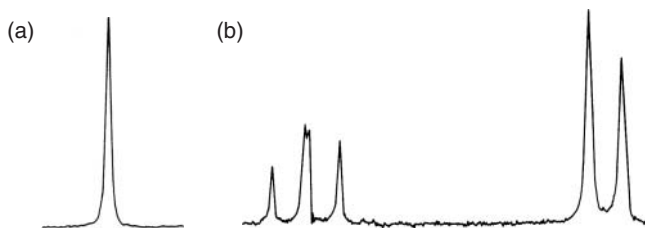


Figure 4.3 Concentration dependence of the CH_2OH group absorption of benzyl alcohol at 60 MHz in acetone as solvent: (a) acetone to benzyl alcohol ratio = 7:5 (v/v) and (b) pure benzyl alcohol.

measurements arises from the fact that chloroform associates with benzene in such a way that the chloroform proton is specifically shielded (cf. p. 118). If we now try to determine the “ δ -value” for cyclohexane on the basis of the above measurements by reference to the value for chloroform on the δ_{TMS} scale we obtain values of 2.31 (7.27–4.96) or 1.47 (7.27–5.80) ppm. Thus, only the measurement with carbon tetrachloride as solvent gives an acceptable result (cf. Table 3.1, p. 38). This example shows that measurements conducted in different solvents or with different reference compounds lead to equivalent results only when there are no *specific interactions* between the solvent and the reference substance or the sample. Solvent–standard combinations for which specific interactions of this kind are known or expected should therefore be avoided.

On the other hand, association effects can also be advantageous, since interactions of this type often lead to changes in the relative chemical shifts that influence the appearance of the spectrum. Furthermore, in addition to solvents, such changes can be caused by a simple concentration dependence of the resonance frequencies. For example, with a particular concentration of benzyl alcohol in acetone the resonance of the CH_2OH group appears as a singlet, while in pure benzyl alcohol the expected AB_2 system is observed (Figure 4.3). In the first case, determination of the coupling constant $J(\text{CH}_2\text{OH})$ is not possible. Thus, the concentration dependence of the chemical shift can be used to increase the information obtainable from the spectrum.

Especially in steroid chemistry, specific *solvent effects* have been systematically studied and used to advantage. Particularly valuable for this purpose is benzene because of its high diamagnetic anisotropy and its tendency to form specific complexes with the solute. If benzene is used instead of chloroform, the proton resonance signals of individual methyl groups in steroids can often be differentiated. Figure 4.4 provides an example with the spectra of 4,4-dimethyl-5 α -androstan-3-one. Acetone, because of its dipole moment, is also suitable for the production of specific solvent effects. Of course, if various NMR spectrometers with different field strengths are available in the laboratory, signal superposition may be removed by changing the spectrometer frequency.

The solvent dependence of spin–spin coupling is, in general, less marked than that of the resonance frequency, but in polar solvents variations of even this NMR parameter have been observed. Thus, in formaldoxime (2) and in

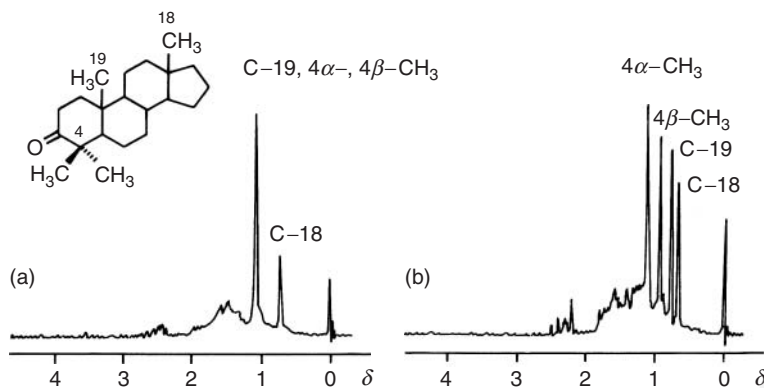
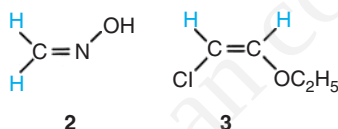


Figure 4.4 Aromatic solvent induced shifts (ASISs) in the ^1H NMR spectrum of 4,4-dimethyl-5 α -androstan-3-one: (a) deuteriochloroform and (b) benzene [1].

l-chloro-2-ethoxyethylene (3), to take two examples, changes in the geminal and vicinal coupling constants over two and three bonds, respectively, have been measured in the range of 7.6–9.9 and 4.2–6.3 Hz.



In addition, also notable is the property of dimethyl sulfoxide to slow down the exchange of protons of OH as well as NH and NH_2 groups. This solvent is therefore used to advantage when spin–spin interactions of the type $\text{H}-\text{C}-\text{O}-\text{H}$, $\text{H}-\text{C}-\text{C}-\text{O}-\text{H}$, or $\text{H}-\text{C}-\text{N}-\text{H}$ are to be investigated. These coupling constants, which depend on the stereochemistry of the bonds involved, cannot be determined in the presence of rapid proton exchange (cf. Chapter 13).

Finally, viscous solutions and paramagnetic impurities severely broaden and worsen the line width of NMR signals. In the first case molecular motion is slowed down and the averaging of magnetic field differences in the sample is less effective, leading to a faster decay of the transverse magnetization because, as we show later, the line width of the NMR signal is proportional to the factor $1/T_2^*$, where T_2^* is the transverse relaxation time due to field inhomogeneity. This effect is similar to the result for a non-rotating sample tube (see Figure 4.6 below).

In the presence of paramagnetic impurities, the lifetime of the excited spin states is shortened due to interactions with the fluctuating magnet fields that arise from unpaired electrons. This leads to an uncertainty in the measurement of the energy gap between ground and excited states and thus to line broadening. Because the magnetic moment of an unpaired electron is larger than the nuclear magnetic moment by a factor of about 10^3 , this mechanism is very effective and paramagnetic compounds can normally not be measured by NMR. Even the presence of trace amounts of oxygen, a paramagnetic molecule, shows the line broadening effect

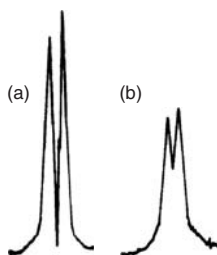


Figure 4.5 Influence of atmospheric oxygen on the shape of the resonance signal: shown is the second signal pair from the spectrum of 1,2-dichlorobenzene; (a) a degassed sample and (b) an air-containing sample. Both signals were recorded with the same spectrometer adjustments – only the field homogeneity was optimized.

(Figure 4.5) and for analyses of higher order spectra and the measurement of NMR parameters with a precision of better than 0.1 Hz the sample tubes have to be degassed on the vacuum line and sealed.

In conclusion, we mention that in some cases it is necessary to eliminate large solvent peaks from a spectrum that conceal the signals of interest and lead to baseline distortions. For example, in biological NMR or in NMR applications in medicine, quite often water cannot simply be replaced by deuterium oxide. *Solvent suppression* is thus an active field of NMR that we will treat in more detail in Chapter 15.

4.3

Tuning the Spectrometer

Modern nuclear magnetic resonance spectrometers are set up for pulse Fourier transform operation and are easy to handle for routine measurements, such that a spectrum can be obtained with a few adjustments. A number of excellent textbooks for detailed practical advice exist (see p. 83) and only a few general remarks about some basic requirements need be added here.

During many experiments fast rotation of the sample tube around its long axis is advisable. This is achieved by means of a small air turbine and has the effect of improving the field homogeneity because, as a result of the macroscopic movement of the sample, the individual nuclei are exposed to a time-averaged value of the external field B_0 , the magnitude of which varies within certain limits over the sample volume. As Figure 4.6 demonstrates for the resonance signal of TMS, this experimental trick is in many cases indispensable in obtaining sharp resonance signals with small line widths. As a result of spinning the sample tube *spinning side bands* appear on both sides of the principal signal and at equal distances from it. The difference in frequency between the central signal and the side bands is equal to the rotational frequency of the sample cell, so that at higher spinning frequencies the side bands move away from the central band and, in so doing, decrease in intensity. By correctly adjusting the spectrometer and with sufficient

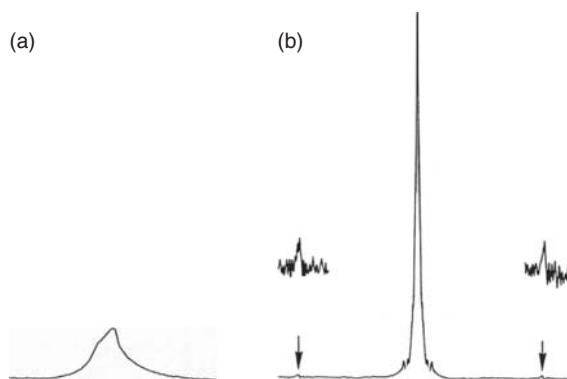


Figure 4.6 Effect of spinning the sample tube on the shape of the resonance signal: (a) without spinning and (b) with spinning (spinning side bands magnified).

rapid spinning of the sample the intensity of the side bands becomes so low that they do not affect the spectrum. In the extremely homogeneous magnetic fields of superconducting magnets spectra run with low-diameter sample cells can also be obtained in high quality without spinning.

Since the chemical shifts are field dependent, it is important that the field/frequency ratio of the particular spectrometer is constant during measurements. For this purpose a *lock channel* is installed. The continuous recording of a reference signal allows one to detect even very small changes in the magnetic field strength and corrections for a possible field drift can be applied. Modern spectrometers use a *heterolock* system with the deuterium (^2H) NMR signal of the deuterated solvents as *lock signal*.

An important condition for recording well-resolved NMR spectra is the homogeneity of the external magnetic field B_0 . Field homogeneity can be optimized using the ^2H lock signal that is recorded in the continuous wave (CW) mode and can be displayed on the spectrometer screen. Magnet homogeneity needs optimized field gradients in x , y , and z -directions. Currents in gradient coils, called *shim coils*, are used to correct these gradients, a procedure called *shimming*. With instruments that are regularly checked it is generally sufficient to optimize the z -gradient. Good field homogeneity is documented by the *wiggles* that follow the CW lock signal. The wiggles are a typical CW phenomenon that results from a precessional motion of the magnetization vector M after resonance (cf. Figure 2.7, p. 20). The RF field B_1 and M will rotate about the direction of B_0 at different rates. They will go alternately in and out of phase, thereby producing damped oscillations of the receiver signal. The longer the train of wiggles is the longer is the lifetime of the transverse magnetization, and the better the homogeneity of the field (Figure 4.7a). The signal shape should be symmetric if the sweep direction is changed (Figure 4.7b) and the signal phase should be pure absorption (Figure 4.7c).

Signal shape and phase can, of course, be monitored also with a FT signal received after Fourier transformation, but an alternative method for improving the resolution of the spectrometer is to optimize the signal intensity that is indicated

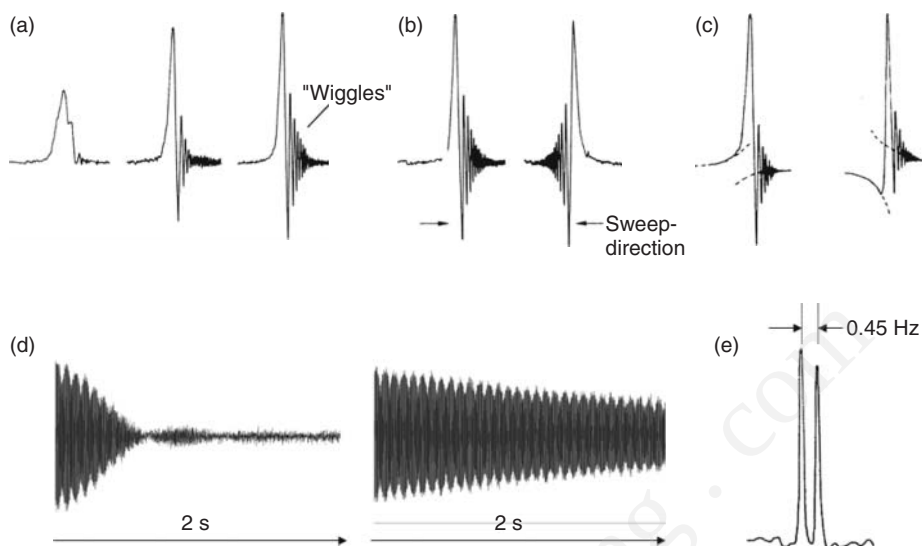


Figure 4.7 Influence of some instrument parameters on a CW signal, for example, the ^2H lock signal: (a) adjustment of the z-gradient; (b) symmetric signals for both sweep directions; (c) incorrect signal phase; (d) resolution enhancement by optimizing the free induction decay (FID); in the first trace the FID decayed within ~ 0.5 s because of poor field homogeneity; (e) resolution test with the second signal pair in the ^1H NMR spectrum of 1,2-dichlorobenzene measured in the FT mode; the resolution amounts to 0.45 Hz.

on the screen by the so-called *lock level* or the time of the free induction decay (FID) of the reference signal following pulse excitation (Figure 4.7d). This time signal is due to the transverse magnetization present after the pulse and its decay is strongly accelerated by field inhomogeneity (Chapter 8, p. 246).

In cases where great precision is required, the second pair of lines in the spectrum of 1,2-dichlorobenzene can be used to enhance further the performance of the spectrometer. For a well-adjusted instrument, the splitting here should approach the base line (Figure 4.7e). Thus, the better the *resolution* of a spectrometer the smaller the frequency difference between the two resonance signals that can still be separately recorded or *resolved*.

A perfect NMR line shape is necessary for good signal resolution and sensitivity and a widely used test for the NMR line shape provided by the spectrometer is the *hump test* that is performed with the ^1H NMR signal of chloroform (Figure 4.8). For this purpose the signal is measured with high sensitivity in order to detect the ^{13}C satellite lines that arise through $^{13}\text{C}, ^1\text{H}$ coupling in the $^{13}\text{CHCl}_3$ molecules that are present in natural abundance (1.1%); the coupling constant amounts to 215.2 Hz (see also p. 226 ff). The line width of the central signal is then measured at the height of the satellites (a) and at the basis (b); "a" should be less than 5 Hz and the ratio a : b about 0.4. The intensity of the rotational side bands should be smaller than that of the ^{13}C satellites.

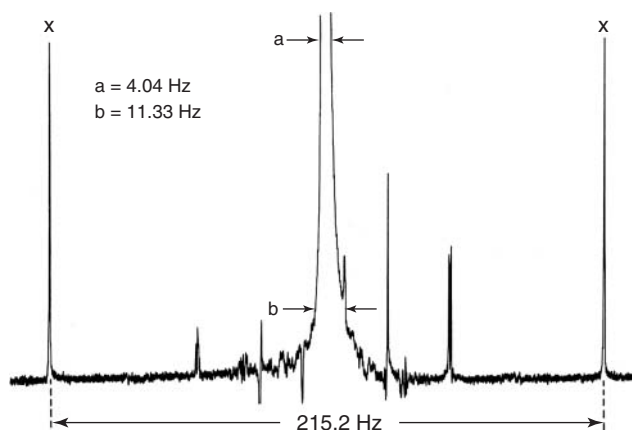


Figure 4.8 Hump test with the chloroform ^1H NMR signal on a 400 MHz FT NMR spectrometer. The ^{13}C satellites (x) belong to 1.1% $^{13}\text{CHCl}_3$. The splitting is caused by the $^{13}\text{C}, ^1\text{H}$ coupling constant over one bond. Typical signal widths that characterize the line shape are indicated (a and b).

The hump test is especially important as a test for perfect performance because measurements for other nuclei mean that the probe-head of the spectrometer (cf. Figure 2.10, p. 24), which contains the sample chamber and also, besides other electronic parts, the transmitter and receiver coils, as well as the tools of the lock channel, is often changed. Normally, the instrument is equipped with a probe-head for ^1H measurements or a so-called dual probe-head for measurements of two nuclei, mostly ^1H and ^{13}C , but other nuclei like ^{15}N , ^{19}F , ^{31}P , to name only a few, need different probe-heads. Aside from the “inner” coil tuned for the nucleus of interest and close to the sample tube for reasons of sensitivity, a second RF transmitter coil surrounding the inner coil is always included for proton decoupling. Over the years many probe-heads for special applications have been constructed (see below).

Before recording the FT spectrum, the pulse angle, receiver gain, and parameters that determine the spectral width and resolution are chosen by the operator. These aspects will be discussed in detail in Chapter 8 after a more complete description of the pulse Fourier-transform experiment.

After recording the spectrum it is *integrated*. For very exact integrations it is necessary to determine the average of several individual measurements (see Figure 3.5, p. 36). Further, the integration may be unreliable if the signals to be integrated vary considerably in their relative intensities. Thus, the number of methylene groups in an aldehyde of the general structure $\text{CH}_3-(\text{CH}_2)_n-\text{CHO}$ could not be determined with certainty if $n > 20$. Finally, for overlapping signals a separate integration is not possible with standard equipment. In these cases a curve analyzer may be used if the line shape of both signals is known.

Since frequency measurements are of central importance for NMR spectroscopy an independent check of the precision of the spectrometer is desirable. This is most

easily performed with the standard sample of chloroform and TMS in CDCl_3 . The difference between the resonance signals amounts to 7.27 ppm or the equivalent in hertz. The calibration of the spectra in Hz or ppm can be provided directly by the NMR software. As it is the most important experimental parameter, the measuring frequency that determines the relation Hz/ppm should always be checked and recorded on the spectrum. Finally, for routine measurements most spectrometers are equipped today with an automatic sample changer.

4.4

Increasing the Sensitivity

Compared to other spectroscopic methods, such as for instance ultraviolet (UV) or electron spin resonance (ESR) spectroscopy, NMR is relatively insensitive because of the small energy difference between ground and excited spin states (cf. p. 19). Therefore, an important goal of new experimental developments was always to minimize this disadvantage by improving the sensitivity. In particular, the NMR spectroscopy of rare nuclei like ^{13}C or ^{15}N could only be expected to become routine methods if progress in this direction was made.

If we look again at the Boltzmann distribution of the nuclear spins introduced on page 19 and the conclusions reached there, we see that raising the field strength of B_0 is the method of choice to increase the sensitivity. Accordingly, the signal-to-noise ratio, as defined for the quartet of the methylene protons in ethylbenzene in Figure 4.9, improves from about 50 : 1 to 800 : 1 if we use Eq. 2.13

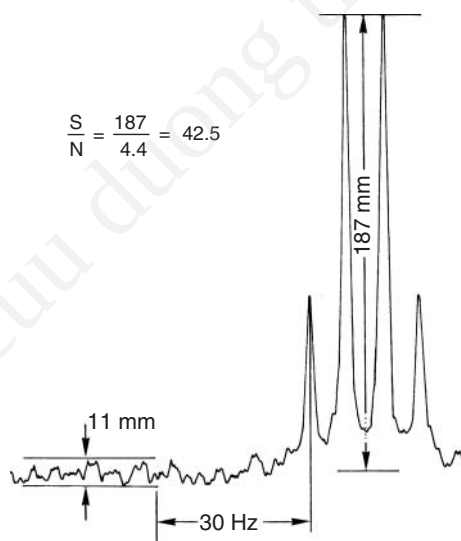


Figure 4.9 Sensitivity test on the methylene quartet of ethylbenzene (1% solution). The signal to noise ratio (S/N) is defined as the quotient of the average signal height, S , and the average noise level, N , which is determined by the relation $N = \text{noise height}/2.5$.

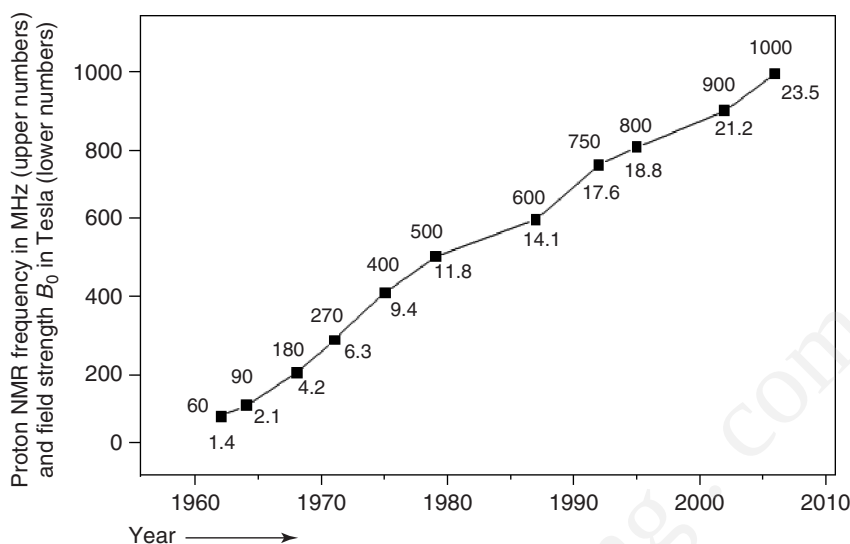


Figure 4.10 Increase of the ^1H NMR frequency and of the magnetic field strength through the development of superconducting magnets.

(p. 26) and compare a 100 MHz spectrometer with a 400 MHz spectrometer. This is equivalent to changing the field strength from 2.35 to 9.40 T.¹⁾

These relations were the driving force behind the development of superconducting magnets discussed in Chapter 2, which have now reached the considerable field strength of 23.5 T. This corresponds to a ^1H resonance frequency of 1000 MHz or 1 GHz (Figure 4.10; see also Figure 15.35, p. 639). Aside from increasing technological difficulties in the construction of such high-field magnets and the rising operational costs, this development is limited by the fact that even small molecules start to orient in high magnetic fields and the spectra will become much more complicated because of dipolar coupling (Chapter 14).

Early it was recognized that a further increase in sensitivity can be attained by spectral accumulation because, thereby, the electronic noise increases proportionally to $\sqrt{t}$ while the intensity of the signals increases proportionally to t , where t is the total observation time. By recording the spectrum several times and adding the results, the signal-to-noise ratio improves because signals originating from random noise vary in their intensity and, more importantly, their sign, whereas a true NMR absorption always gives a positive response of constant intensity. For spectral accumulation, the improvement is equal to $\sqrt{n}$, where n is the number of spectral traces that are added.

As briefly mentioned in Chapter 2, spectral accumulation was one of the major aspects that led to the complete displacement of the older CW method by FT NMR. The time taken to record an FT spectrum, that is, measuring the free induction

1) With $B_0^{3/2}$ instead of B_0^2 the enhancement is only half as large.

decay after pulse excitation, is of the order of 1 s, while a CW spectrum took at least 250 s to record. To accumulate several hundred FT spectra and, thereby, gain a 30-fold increase or more in signal-to-noise ratio takes a matter of minutes, even if a relaxation delay is included after each FID. The stability of modern spectrometers with respect to field strength and frequency allows spectral accumulation for hours and even days. This paved the way for the NMR spectroscopy of insensitive nuclei and of nuclei with low natural abundance, like ^{13}C or ^{15}N , as well as for time-consuming multidimensional experiments (2D, 3D). For sensitive nuclei, on the other hand, 1 mg of a compound or even less became sufficient for recording a ^1H NMR spectrum (Figure 4.11). Sample concentrations of 10^{-5} M, which were the domain of UV spectroscopy, are now also within the reach of NMR. Highly purified solvents have to be used for such measurements to avoid signals from impurities of low concentration or the residual protons of the deuterated solvent molecules.

For nuclei other than the proton, the so-called *heteronuclei*, a major step forward in sensitivity increase became possible through the *nuclear Overhauser effect*, which arises by NMR excitation (called in this case incorrectly decoupling) of neighboring, not necessarily chemically bound, protons. The basis of this effect is dipolar cross

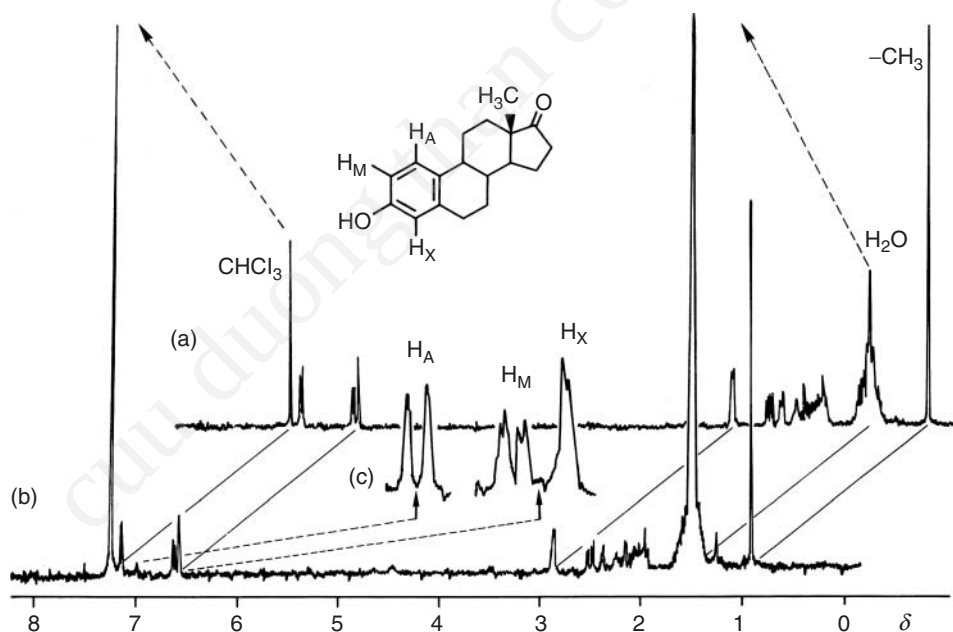


Figure 4.11 Fourier-transform ^1H NMR spectrum of estrone in CDCl_3 at 400 MHz: (a) concentration 3.7×10^{-3} M (weight 0.5 mg), measuring time 20 s; (b) concentration 3.7×10^{-4} M, measuring time 25 min; the signals of the residual CHCl_3 molecules in the solvent (0.04%) and the water traces disturb the spectrum; (c) enlarged signals of the aromatic protons from spectrum (b); one recognizes the *ortho*- and *meta*- $^1\text{H}, ^1\text{H}$ coupling that allows an assignment ($J_{\text{ortho}} > J_{\text{meta}}$, see Table 3.2, p. 62).

relaxation between nuclei that are close in space. For a heteronucleus X with positive magnetogyric ratio, γ_X , the intensity increase for excitation of nucleus A is given by $1 + \gamma_A/2\gamma_X$, which amounts for ^{13}C , for example, to 200% if we have A = ^1H ; $\gamma_A/2\gamma_X$ is known as the *Overhauser enhancement factor* η . Signals of X nuclei with negative γ factors, for example, ^{15}N or ^{29}Si , show negative enhanced signals if $|2\gamma_X| < \gamma_A$ holds. However, in unfortunate cases, competing relaxation mechanisms may lead to $\eta = -1$ and thus to signal loss. For the homonuclear case A = X = ^1H , the maximum enhancement is 50%. More details about this important subject will be presented in Chapters 10 and 11.

Finally, sensitivity gains were realized with the construction of special probe-heads. An early example is the inverse probe-head, where the receiver coil tuned for the insensitive nucleus of interest for example, ^{13}C , is the more sensitive inner coil close to the sample tube. More recently, NMR sensitivity has been improved significantly with the introduction of the *cryoprobe*, where the RF transmitter coil and the signal preamplifier, another electronic part of the probe-head, are cooled by a stream of helium gas to ~ 20 K. This technology takes advantage of the fact that the radio-frequency electronics will generate a more intense signal and less thermal noise at lower temperatures. The helium is used in a closed-loop cooling system, in which the gas is compressed in one chamber and allowed to expand in the second, thus making use of the Joule–Thomson effect. The NMR tube can be measured at room temperature only a few millimeters away from the cold RF coil assembly. Compared to the room temperature probe, the signal-to-noise ratio increases by a factor of about 4 and samples measured in the same amount of time need only 25% of the concentration. Further engineering led to a general-purpose cryoprobe prepared for the separate measurement of four different nuclei that cover the most abundant elements in organic, biological, and inorganic chemistry: fluorine, phosphorus, carbon, and hydrogen. Measurements for these nuclei can then be made without changing the probe-head. More sophisticated methods of sensitivity enhancement, like the use of *para*-hydrogen or the method of optical pumping, will be described in Chapter 15.

4.5

Measurement of Spectra at Different Temperatures

For several reasons it is desirable that NMR spectra can be recorded at different temperatures. The main application of variable-temperature NMR spectroscopy is in the area of temperature-dependent NMR line shapes, where information about rate processes, usually involving intramolecular dynamics, is obtained. This field – also called dynamic nuclear magnetic resonance (DNMR) – will be covered extensively in Chapter 13. In addition, it is possible to detect unstable intermediates at low temperatures, while on the other hand the solubility of a poorly soluble compound can be improved if elevated temperatures are used.

NMR spectrometers are routinely equipped with a *variable-temperature probe* permitting experiments between -150 and $+200^\circ\text{C}$. To accomplish this, a stream

of nitrogen gas is usually run through the probe after being brought to the desired temperature by an electric heater. For low-temperature measurements the gas is heated after it has passed through a Dewar vessel filled with liquid nitrogen ($T = -196^{\circ}\text{C}$). For high-temperature measurement the gas from a nitrogen tank is heated directly until the desired temperature for the experiment is reached. The temperature of the gas flow can be checked by using a thermocouple and regulated automatically. Other cooling systems for studies at very low temperature use the gas stream boiled off from a reservoir of liquid nitrogen to cool the sample chamber. The temperature is then controlled simply by varying the flow-rate.

Ideally, the *temperature measurement* should take place within the sample tube itself, but for technical reasons this is not always possible. In practice the temperature is determined by placing a thermocouple in the nitrogen stream directly below the NMR tube or by recording the spectra of standard samples of methanol or ethylene glycol both before and after the spectrum of the sample under investigation is measured. With these compounds – known as “NMR thermometers” – the chemical shift differences $\Delta\nu$ (in Hz), between the resonances of the CH_3 or the CH_2 protons, respectively, and the OH proton, are temperature dependent. Precise measurements have led to the following relationships, where ν_0 is the spectrometer frequency used in megahertz and the temperature is given in Kelvin:

Low temperature, methanol:

$$175\text{--}330\text{ K}; T = 403.0 - (29.46/\nu_0)|\Delta\nu| - (23.832/\nu_0^2)|\Delta\nu|^2 \quad (4.6)$$

High temperature, ethylene glycol:

$$310\text{--}410\text{ K}; T = 466.0 - (101.64/\nu_0)|\Delta\nu| \quad (4.7)$$

These equations result in errors of only about $\pm 0.5^{\circ}\text{C}$ for pure aerated samples of the two substances, in which the line splitting due to spin–spin coupling has been eliminated by the addition of a trace (0.03% v/v) of concentrated hydrochloric acid. Linear correlations are given in the original literature [2] for certain sections of the low temperature region. If deuterated methanol, CD_3OD (99.8%), is used the signals of the residual CD_2H and OH groups that belong to different molecules yield the following equation with an error of $\pm 0.7\text{ K}$ [3]:

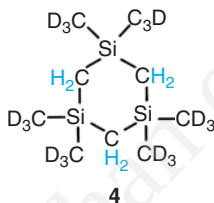
$$180\text{--}300\text{ K}; T = 398.7 - (26.94/\nu_0)|\Delta\nu| - (24.436/\nu_0^2)|\Delta\nu|^2 \quad (4.8)$$

The same sample was recommended for use in cryoprobes [4].

If the signals of methanol and ethylene glycol do not interfere with the spectrum of the sample under investigation, the most accurate temperature measurement in the region between -100 and $+140^{\circ}\text{C}$ is obtained by use of the NMR tube illustrated in Figure 4.2c, in which the capillary is filled with methanol or ethylene glycol. This has the advantage that temperature and spectrum are measured simultaneously. Generally, care must be taken during variable temperature studies using carbon-13 NMR because proton broadband decoupling may change the sample temperature.

An alternative method for temperature calibration of the probe head uses a set of liquid crystals with clearing points between 287 and 336 K. The FID of these samples sharply breaks down if the temperature drops below the clearing point where the compounds start to orient in the magnetic field [5] (cf. Chapter 14).

The *choice of solvent* presents special problems in variable-temperature measurements. At high temperatures dimethyl sulfoxide, hexachlorobutadiene, decalin, or nitrobenzene have been used successfully. Of course, the highly volatile TMS must be replaced in these experiments with a different reference substance. $[D_{18}]$ Cyclosilane (**4**) with a boiling point of 208°C and a singlet at δ 0.327 appears to be suitable. At low temperatures, $[D_6]$ acetone and carbon disulfide, perhaps mixed with chloroform, can be used down to about -100°C . Below -100°C , fluorinated hydrocarbons such as trifluorobromomethane and difluorodichloromethane are usually used. Dimethyl ether, preferentially fully deuterated, and carbon oxysulfide (*danger*: highly poisonous!) are also attractive because of their low freezing points (-138.5 and -138°C , respectively). Frequently only mixtures of several components lead to satisfactory results.



References

1. Bhacca, N.S. and Williams, D.H. (1965) *Application of NMR Spectroscopy in Organic Chemistry*, Holden Day, San Francisco, CA.
2. Van Geet, A.L. (1970) *Anal. Chem.*, **42**, 679; Van Geet, A.L. (1968) *Anal. Chem.*, **40**, 2227.
3. Hansen, E.W. (1985) *Anal. Chem.*, **57**, 2993.
4. Findeisen, M., Brand, T., and Berger, S. (2007) *Magn. Reson. Chem.*, **45**, 175.
5. Friebolin, H., Schilling, G., and Pohl, L. (1979) *Org. Magn. Reson.*, **12**, 569.
- Braun, S., Kalinowski, H.-O., and Berger, S. (2004) *200 and More Basic NMR Experiments*, Wiley-VCH, Weinheim.

Review Articles

- Laszlo, P. (1967) Solvent effects and nuclear magnetic resonance. *Prog. Nucl. Magn. Reson. Spectrosc.*, **3**, 231.
- Ronayne, J. and Williams, D.H. (1969) Solvent effects in proton magnetic resonance spectroscopy. *Annu. Rep. NMR Spectrosc.*, **2**, 83.
- Deutsch, J.L. and Poling, S.M. (1969) The determination of paramagnetic susceptibility by NMR. *J. Chem. Educ.*, **46**, 167.
- Webb, A.G. (2002) Temperature Measurements Using Nuclear Magnetic Resonance, *Annu. Rep. NMR Spectrosc.*, **45**, 1.

Textbooks

- Claridge, T.D.W. (1999) *High-Resolution NMR Techniques in Organic Chemistry*, Elsevier, Amsterdam.

cuu duong than cong . com

5

Proton Chemical Shifts and Spin–Spin Coupling Constants as Functions of Structure

In Chapter 3 it became clear that the dependence of proton resonance frequencies and spin–spin coupling constants on chemical structure leads to an abundance of important information that is of both theoretical and practical interest. The rapid development of NMR doubtlessly has been due in great part to the fact that it was recognized very early as a method of great utility in the solution of one of the central problems of chemical research – the determination of molecular structure. Each new measurement provided data that proved to be characteristic for a particular class of compounds or for a structural unit. Numerous empirical correlations between NMR parameters and molecular structure were discovered in this way. The wealth of experimental results also advanced our understanding of the theoretical basis of these correlations so that now most of these effects can be satisfactorily explained. Models based on laws of classical physics were developed to understand experimental trends long before quantum chemical calculations of chemical shifts and spin–spin coupling constants were practicable. Since then the development of these theoretical tools has made enormous progress. Different quantum chemistry programs – *semi*-empirical like CNDO (complete neglect of differential overlap) or INDO (intermediate neglect of differential overlap), but mostly *ab initio* methods like IGLO (individual gauge for localized orbitals) or the program packages GAUSSIAN or DeMon in combination with DFT (density functional theory) – allow the calculation of many NMR parameters with remarkable precision and yield deeper insight into their origin. Nevertheless, the models that we shall discuss in the following sections allow a quick rationalization of experimental findings in simple physical terms based on a huge amount of experimental observations. They are not, like many theoretical approaches, limited by the size of the molecule and are thus applicable even to complicated natural products. Furthermore, in practical work, the differences $\Delta\delta$ observed for chemical shifts can be readily explained in many cases by considering the factors discussed below. This is often more important than the calculation of absolute shift values.

5.1

Origin of Proton Chemical Shifts

Having provided a general summary of the characteristic absorption regions of the most important proton types in organic compounds in Figure 3.6 (p. 37), we shall now discuss, in terms of the approach introduced with Eq. (3.6) on p. 32, the individual contributions of different structural elements to proton chemical shifts. Since for protons, as previously mentioned, the local paramagnetic contribution to the screening constant, $\sigma_{\text{para}}^{\text{local}}$, is negligible because of the large energy gap between the 1s and the 2p orbitals, the ^1H chemical shift scale with only 10–15 ppm is rather small. In contrast, heavier nuclei often have δ -scales of several hundred parts per million (as will be discussed in Chapter 12).

In the past it was soon recognized that empirical concepts and models based on electrostatic or magnetostatic laws, like charge density, diamagnetic susceptibility, electric field effects, and steric – so-called van-der-Waals – effects allowed us to rationalize the large amount of ^1H data that became available. On the other hand, with the progress made in quantum chemistry and the calculation of chemical shifts it became clear that the mechanisms that determine the chemical shift are often more complicated than suggested by these classical models. Nevertheless, even in cases where the interpretation of the physical origin of the experimentally observed relationships needs revision, the predictions of the simple models have proved to be valid in most cases and helpful for the analysis of ^1H NMR spectra. We shall, therefore, discuss ^1H chemical shifts along these lines with comments on more recent results where necessary.

For protons we can confine ourselves at the outset, therefore, to the consideration of two effects:

- 1) The *local diamagnetic* contribution of the electron cloud around the proton under consideration ($\sigma_{\text{dia}}^{\text{local}}$);
- 2) the effect of *neighboring* atoms and groups in the molecule (σ').

Thus, within this approximation the influence of substituents and neighboring atoms is twofold: first, they will effect $\sigma_{\text{dia}}^{\text{local}}$ through changes of the electron density at the proton caused by inductive and mesomeric mechanisms and, second, electron circulations induced by the external field B_0 within these neighboring atoms and groups will give rise to magnetic moments, that is, secondary fields that change B_{local} at the proton. In addition, electric field and van-der-Waals effects may be considered, and also the influence of the surrounding medium. Consequently, any change in proton screening may be expressed as a sum of several terms:

$$\Delta\sigma = \Delta\sigma_{\text{dia}}^{\text{local}} + \Delta\sigma_{\text{magn}} + \Delta\sigma_{\text{el}} + \Delta\sigma_{\text{W}} + \Delta\sigma_{\text{med}} \quad (5.1)$$

where the last four contributions stand for the magnetic, electric field, van-der-Waals, and medium effects, respectively. For the following text, the reader should be aware of the relation $\Delta\sigma = -\Delta\delta$, that is, a higher shielding means smaller δ -values and vice versa.

5.1.1

Influence of the Electron Density at the Proton

As we have already mentioned, the diamagnetic contribution of the electron shell to the shielding of a nucleus may be calculated from the Lamb formula [Eq. (3.4), p. 31], which is strictly applicable, however, only in the case of spherical symmetry, that is, for the neutral hydrogen atom. Here a value of 17.8 ppm results for σ_{dia} . If inductive effects present in a molecule reduce the electron density in the hydrogen 1s orbital, deshielding is expected. Thus, the screening constants in the hydrogen halides, not unexpectedly, fall in the order $\sigma_{\text{HF}} < \sigma_{\text{HCl}} < \sigma_{\text{HBr}} < \sigma_{\text{HI}}$, with the proton in HI as the most shielded. In the gas phase one finds δ -values of +2.5, -0.45, -4.35, and -13.25 ppm, respectively, relative to the ^1H resonance of methane. This order is, however, also affected by the magnetic properties of the halide atoms.

5.1.2

Influence of the Electron Density at Neighboring Carbon Atoms

In organic compounds, protons are not usually bonded directly to electronegative elements. Nevertheless, their influence has far reaching effects through the carbon skeleton of a compound, and the charge density at the neighboring carbon atom becomes a determining factor for the resonance frequency of a proton. Results for the methyl halides illustrate the expected relationship between the proton chemical shift and the *electronegativity* of the substituents. As shown below, the δ -values found are consistent with the decreasing electronegativity of the halogens in the order $\text{F} > \text{Cl} > \text{Br} > \text{I}$.

	CH_3F	CH_3Cl	CH_3Br	CH_3I	CH_3H
$\delta(\text{CH}_3)$	4.13	2.84	2.45	1.98	0.13
E (Pauling)	4.0	3.0	2.8	2.5	2.1

Figure 5.1 gives a graphical representation of the electronegativity/chemical shift relation for alkyl halides. Linear relationships such as those shown suggest that NMR data can be used as a measure of electronegativities. Appropriate equations have indeed been proposed, but they must be used with caution because additional effects usually play an important role in determining proton resonance frequencies.

The significance of such other sources of proton shielding is demonstrated by observations made on the *ethyl* halides. In Figure 5.1 (line b) the expected change in the resonance frequency – high-frequency shift (less shielding) with increasing electronegativity – is noted for the methylene protons while the reverse trend is observed in line c for the methyl protons. In this case, owing to geometrical factors to be discussed later, the diamagnetic anisotropy of the C–H and C–X bonds is important and the magnetic contribution to the shielding constant, $\Delta\sigma_{\text{magn}}$, dominates.

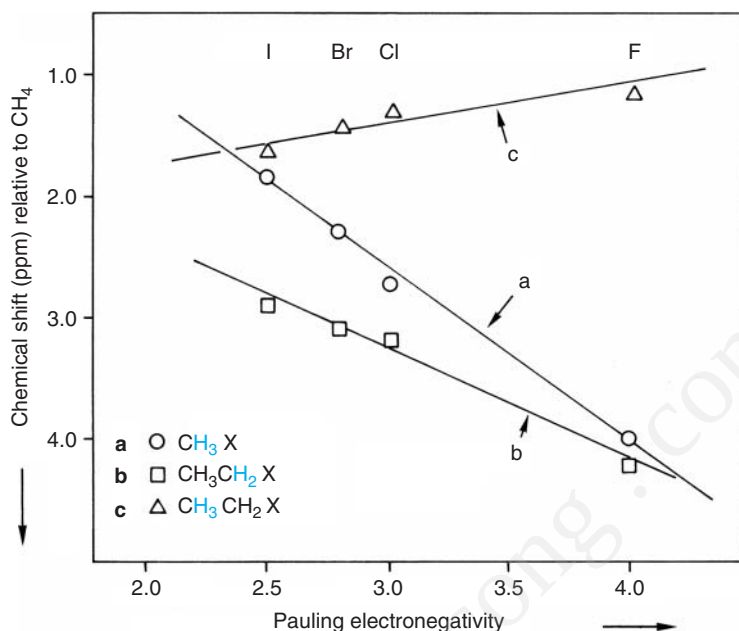


Figure 5.1 Correlation between the ^1H chemical shifts of alkyl halides and the electronegativity of the halogens.

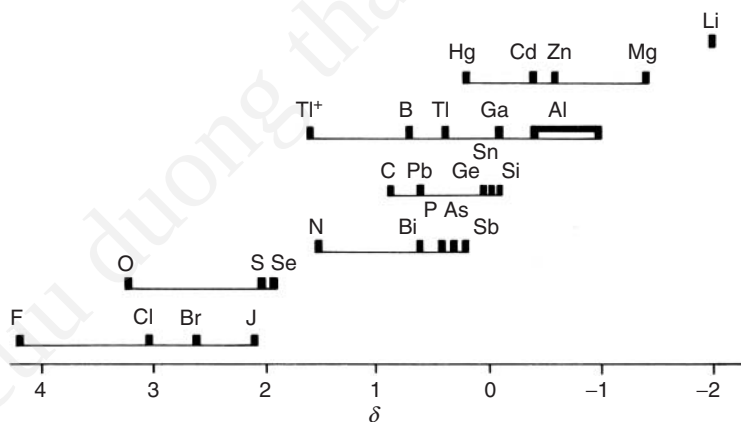


Figure 5.2 ^1H resonances of the methyl derivatives of the representative elements [1].

A similar correlation between the resonance frequency of the methyl protons and the polarity of the C–X bond exists for other methyl derivatives of the type CH_3X and Figure 5.2 provides a general summary of the phenomenon. Evidently, the increased shielding of the protons in the series $\text{X} = \text{Hg}, \text{Sn}, \text{Cd}, \text{Zn}, \text{Al}, \text{Mg}$, and Li parallels the growing ionic character of the corresponding metal–carbon bonds that, according to Pauling, amounts (in the above order) to 9, 12, 15, 18, 22, 35, and 43%.

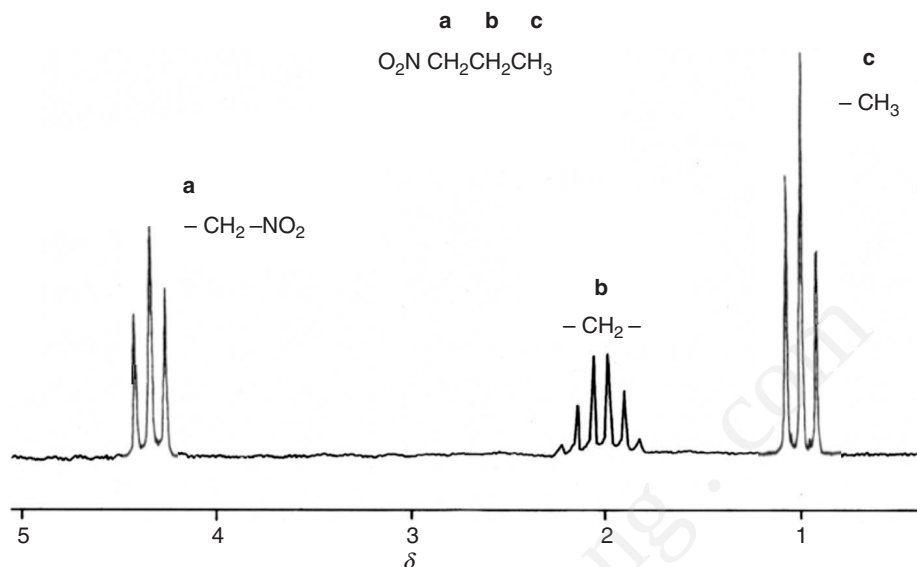
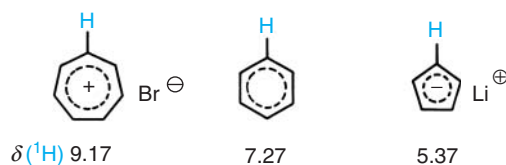


Figure 5.3 ^1H NMR spectrum of nitropropane.

Finally, the magnitude of the inductive effect and its propagation through the C–C bond framework is clearly illustrated with the spectrum of nitropropane (Figure 5.3). Here, $\Delta\delta$ values of 3.45, 0.72, and 0.12 ppm are found for the a-, b-, and c-protons, respectively, if the proton resonance frequencies of propane (δ_{CH_3} 0.91, δ_{CH_2} 1.33) are used as a reference.

In unsaturated compounds where the carbon of the C–H bond under consideration has a positive or a negative partial charge, shifts to higher and lower frequency, respectively, are observed. When the proton resonances of the tropylium cation and cyclopentadienyl anion are compared with that of benzene, $\Delta\delta$ values of +1.90 and -1.90 ppm result, the signs and magnitudes of which reflect the charge deficiency and the charge excess, respectively, of $\frac{1}{7}$ and $\frac{1}{5}$ of an electron per C atom.



This observation led to the discovery of a linear correlation between the π -electron density and the chemical shift of the protons in these compounds that also extends to other aromatic ions (Figure 5.4). From these data the following empirical relation was developed:

$$\Delta\sigma \cong 10.0 \Delta\rho \quad \text{or} \quad \Delta\delta \cong -10.0 \Delta\rho \quad (5.2)$$

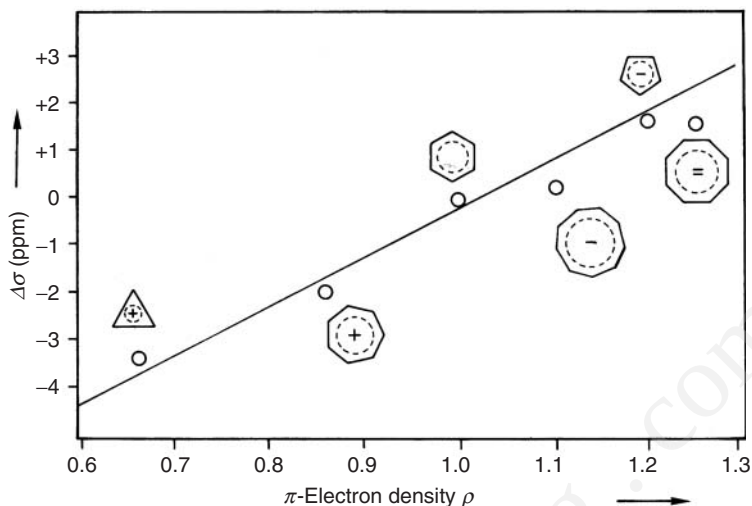


Figure 5.4 Relationship between proton resonance frequency and π -electron density at the carbon atoms in aromatic ions relative to benzene. Regression analysis of the data shown here yields $\Delta\sigma = 9.54\Delta\rho$ with a standard deviation of 0.65 ppm and a correlation coefficient of 0.993.

where $\Delta\sigma$ is the change in the shielding constant and $\Delta\rho$ is the change in the π -electron density relative to benzene ($\Delta\rho = \rho_{\text{sample}} - \rho_{\text{benzene}}$, where $\rho_{\text{benzene}} = 1.0$).

Physically, this effect can be interpreted as the influence of the electric field of the partial charge residing in the $2p_z$ orbital of the carbon atom on the electron cloud of the carbon-hydrogen bond. It results in a shift of the electrons either toward the carbon or toward the hydrogen and the proton is either deshielded or shielded, respectively.



The π -electron density is also significant for the resonance frequency of protons in *substituted* benzenes, notably for those in positions *ortho* and *para* to the substituents. Here too a linear correlation exists between the charge density changes $\Delta\rho$, obtained from Hückel molecular orbital (MO) calculations, and the changes in the proton shielding constant, $\Delta\sigma$ (Figure 5.5). In this case the proportionality constant is 12.7.

The simple Eq. (5.2) neglects the effect of charges from other atoms of the molecule – only the charge at the directly bonded carbon is considered. In addition, the ring current effect, discussed in Section 5.1.4, is assumed to be the same in all systems. We shall show in Section 5.1.7 that an approach based on the consideration of electric field effects allows a more complete analysis.

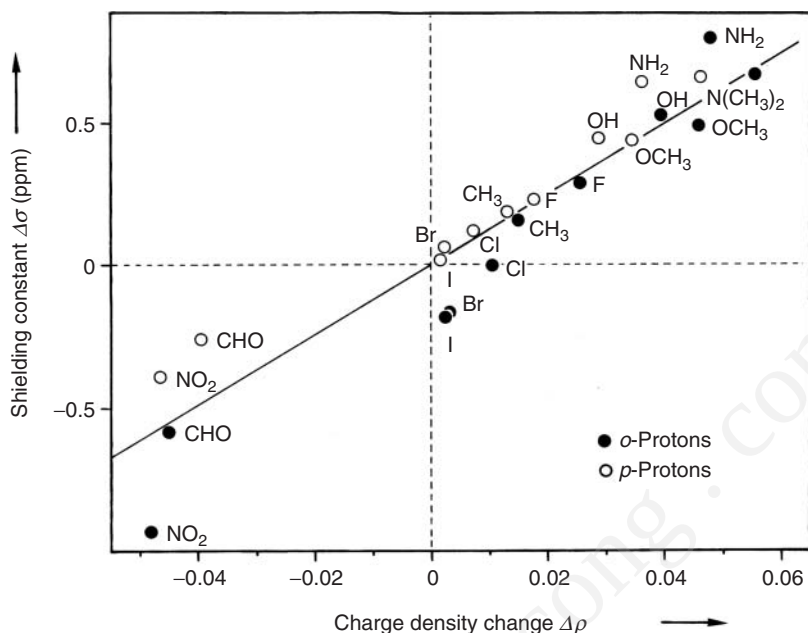
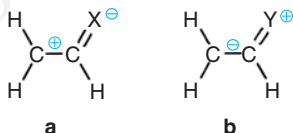
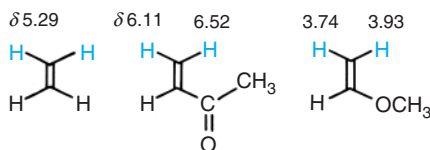


Figure 5.5 Correlation between the change in the shielding constants, $\Delta\sigma$, of *ortho*- and *para*-protons in monosubstituted benzenes and the corresponding electron density change $\Delta\rho = \rho(\text{C}_6\text{H}_5\text{X}) - 1.00$ [2].

Pronounced charge density effects for ^1H chemical shifts are observed in monosubstituted olefins, where strong substituents can lead to a considerable polarization of the π -bond. As shown by the mesomeric structures **a** and **b**, the $-M$ and the $+M$ -effect result in deshielding and shielding for the β -proton, respectively:



A comparison of the resonance frequencies in methyl vinyl ketone and methyl vinyl ether with the $\delta(^1\text{H})$ value of ethane documents this effect most clearly.



Unsurprisingly, therefore, olefinic protons in some cases are more strongly shielded than protons at saturated carbon atoms, as the spectrum of the bicyclic lactone shown in Figure 5.6 convincingly demonstrates.

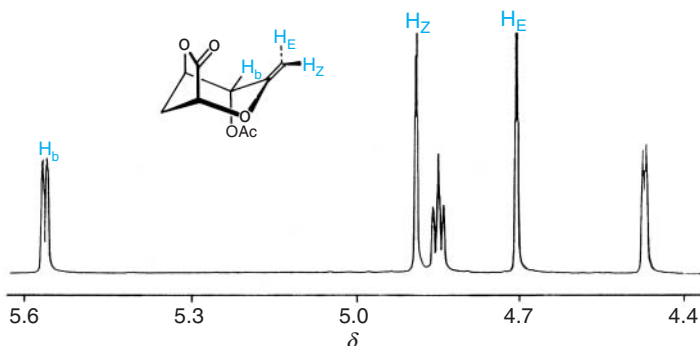


Figure 5.6 Partial 200 MHz ^1H NMR spectrum of a bicyclic lactone with strong shielding of the olefinic protons H_E and H_Z [3].

Table 5.1 Proton resonances in carbocations and carbanions.

$\text{H}_3\text{C}-\text{C}^+-\text{H}$ δ 5.06 13.50	$\text{H}_3\text{C}-\text{C}^--\text{CH}_3$ δ 4.35	$\text{C}_3\text{H}_7-\text{C}^+-\text{CH}_2-\text{CH}_2-\text{CH}_3$ δ 10.3 3.15 1.88 1.01
$[\text{CH}_2\equiv\text{CH}=\text{CH}_2]^+$ δ 8.97 9.64 8.97	$[\text{CH}_2\equiv\text{CH}=\text{CH}_2]^-$ δ 2.46 6.28 2.46	CH_3Li $\text{CH}_3-\text{CH}_2\text{Li}$ δ -1.3 1.33 -0.99 $(\text{CH}_3)_2\text{Mg}$ $(\text{CH}_3-\text{CH}_2)_2\text{Mg}$ δ -1.3 1.26 -0.64 $(\text{CH}_3-\text{CH}_2-\text{CH}_2)_2\text{Mg}$ δ 0.90 1.50 -0.57
$\text{C}_6\text{H}_5-\text{CH}_2\text{Li}$ δ_o 6.09 δ_m 6.30 δ_p 5.50	$\text{C}_6\text{H}_5-\text{C}^+(\text{CH}_3)_2$ δ 8.80 7.97 8.45	$\text{C}_6\text{H}_5-\text{N}^+(\text{CH}_3)_3$ δ 7.98 7.66 7.60

Analogous observations regarding charge density effects are made for saturated compounds; Table 5.1 summarizes some representative data for carbanions and carbocations. It can be seen that the protons in carbocations are strongly deshielded, but the influence of the positive charge in saturated systems decreases rapidly with the distance from the charged center. The data for the dimethyl carbocation and

the dipropyl-cyclopropenylum ion illustrate this effect. From the results for the allyl cation it can be concluded that, contrary to predictions of simple resonance theory or the Hückel MO model, the central carbon atom must bear considerable positive charge. In the allyl anion, to the extent that it exists in allylmagnesium bromide, it is seen that the negative charge is concentrated primarily at the terminal carbon atoms, doubtlessly as a consequence of electron repulsion. The saturated carbanions of organolithium and -magnesium compounds show strong shielding effects only for the α -protons with resonances at lower frequency than the tetramethylsilane (TMS) signal (negative δ -values). On the other hand, extensive delocalization of charge is again indicated by the δ -values of the aromatic protons in benzyllithium and phenyldimethyl carbenium ion, where the *ortho*- and *para*-protons are affected most. Noteworthy in this context is the comparison of the carbenium ion results with the δ -values of trimethylanilinium ion, where only a $+I$ effect is operative. While the resonance of the *meta*-protons is influenced least in the former, a substituent effect decreasing in the order *ortho* > *meta* > *para* is clearly recognized in the trimethylanilinium ion. In addition, the magnitude of the charge effect is much smaller.

To conclude our discussion, we mention that the chemical shifts in molecules like carboxylic or amino acids may show a strong dependence on pH that can be used for pK_a value determinations. For fast proton exchange an average spectrum is observed that results from the protonated and deprotonated species that are in equilibrium. Titration curves can then be obtained by NMR spectroscopy as shown in Figure 5.7 for alanine. Here, with increasing pH the doublet of the methyl

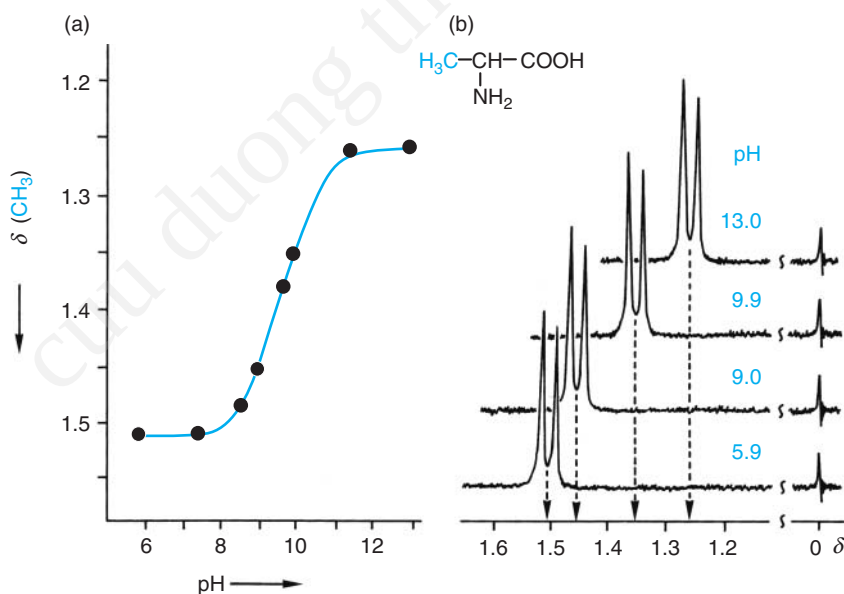


Figure 5.7 pH Dependence of the methyl ^1H resonance in alanine: (a) titration curve from a complete measurement series in H_2O ; (b) methyl ^1H signal at selected pH values.

proton resonance moves to lower frequency (Figure 5.7b). The inversion point of the titration curve (Figure 5.7a) yields a pK_a value of 9.6 because at a concentration ratio $[A^-]/[HA] = 1$ for anion and acid the pH is equal to the pK_a .

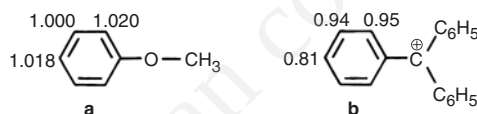
For more precise evaluations the use of the Henderson–Hasselbalch equation is to be preferred. The ratio $[A^-]/[HA]$ is then replaced by the quotient $(\delta_{\max} - \delta)/(\delta - \delta_{\min})$ [Eq. (5.3)]; $\delta_{\max}$ and $\delta_{\min}$ are the ^1H frequencies under acidic and basic conditions, respectively, which are independent of pH, and δ is the pH dependent shift:

$$pH = pK_a + \log \frac{\delta_{\max} - \delta}{\delta - \delta_{\min}} \quad (5.3)$$

If the logarithmic term of Eq. (5.3) is plotted against pH a straight line results and the pK_a value is obtained at the intersection with the abscissa.

Exercise 5.1

Calculate the δ -values of the protons in (a) anisole and (b) the triphenylmethyl cation on the basis of the given π -electron densities using Eq. (5.2) and $\delta(\text{benzene}) = 7.27$ as reference point. In addition, use 12.7 as the proportionality factor in (a) and compare the results with the experimental data in Table A.3 of the Appendix (p. 653).



5.1.3

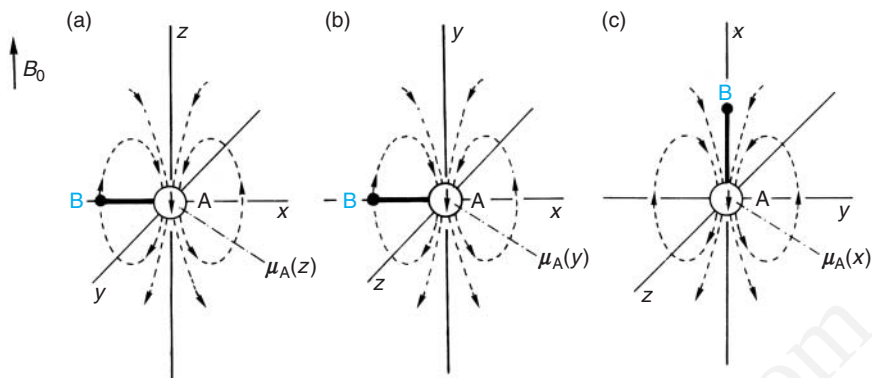
The Influence of Induced Magnetic Moments of Neighboring Atoms and Bonds

The diamagnetic shielding of a proton by its 1s electron density is relatively small compared with the shielding of nuclei of heavier atoms that have several filled inner electron shells. Therefore, additional effects that alter the local magnetic field responsible for the resonance frequency are much more significant in determining the chemical shift of the proton resonance than that of heavier nuclei. Among these effects magnetic dipoles induced by the external magnetic field B_0 at neighboring atoms or groups of atoms play an important role.

Let us first consider a *diatomic* molecule AB. Through the external field B_0 a magnetic moment μ_A , which we consider as a localized point dipole at the center of A, is induced. Its magnitude μ_A is proportional to the diamagnetic susceptibility, χ_A , of A and μ_A can be broken down in a Cartesian coordinate system into its components $\mu_A(x)$, $\mu_A(y)$, and $\mu_A(z)$. Its contribution to the shielding of the nucleus B is given by:

$$\Delta\sigma = \sum_{i=x,y,z} \chi_A^i (1 - 3\cos^2\theta_i) R^{-3} \quad (5.4)$$

where θ is the angle between the direction of $\mu_A(x,y,z)$ and the A–B bond axis and R is the distance between the center of A and the nucleus B (see diagram):



In the geometric arrangement (a) the secondary field at nucleus B is parallel to B_0 . The induced field thus augments the externally applied field and the resonance of B appears at higher frequency. The same situation develops when the direction of B_0 and the y-axis of the molecular coordinate system coincide (b). However, in arrangement (c) the induced field at B is opposed to B_0 and shielding results with a shift to lower frequency. In solution, the molecules of the sample undergo rapid rotation and averaging takes place. According to the factor $1 - 3\cos^2\theta$ in Eq. (5.4) the resulting net effect is zero¹⁾ as long as the components $\chi_A(x)$, $\chi_A(y)$, and $\chi_A(z)$ of the susceptibility χ_A have the same values, in which case the group A is said to be *magnetically isotropic*. When this is not the case, A possesses a *diamagnetic anisotropy* $\Delta\chi$ that, according to its orientation, can effect a paramagnetic or a diamagnetic shift of the resonance frequency of the nucleus B.

By means of the relation:

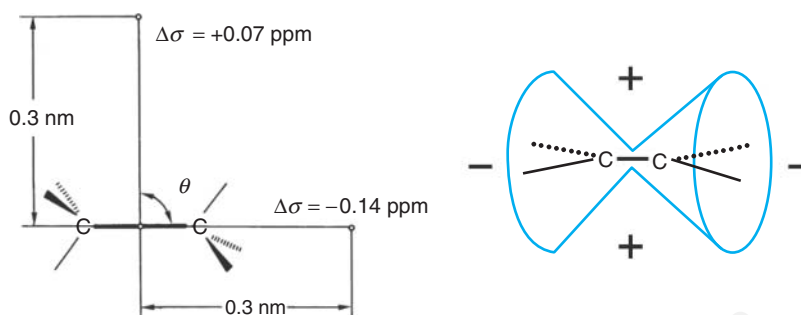
$$\Delta\chi = \chi_{\parallel} - \chi_{\perp} \quad (5.5)$$

the diamagnetic anisotropy of a group with an axial symmetry is defined as the difference between the susceptibilities parallel and perpendicular to the axis. The magnetic contribution to the chemical shift of individual protons can then be determined by the *McConnell equation*:

$$\Delta\sigma = \frac{1}{3}\Delta\chi(1 - 3\cos^2\theta)R^{-3} \quad (5.6)$$

if the magnitude and sign of the diamagnetic anisotropy $\Delta\chi$ of a group with axial symmetry is known. For example, for two points in the vicinity of a C–C single bond that are a distance $R = 0.3 \text{ nm}$ ($= 3 \times 10^{-10} \text{ m}$) from the center of the bond the results shown on the next page are obtained with a value of $\Delta\chi_{\text{C-C}} = 5.6 \times 10^{-36} \text{ m}^3 \text{ per molecule}^2)$ ($\theta = 0^\circ$ and 90° , respectively).

- 1) For $\theta = 90^\circ$ with A–B perpendicular to μ_i [situation (a) and (b)] we have $1 - 3\cos^2\theta = 1$; for $\theta = 0^\circ$ [situation (c)], $1 - 3\cos^2\theta = -2$.
- 2) Please note that our $\Delta\chi$ -values are given in e.m.u. per molecule while the literature data are often given per mole; they have then to be divided by 6.025×10^{23} (cf. Table 1.1 p. 9). In the SI system $\Delta\chi$ -values contain the factor 4π and the factor $1/4\pi$ appears then in Eqs. (5.4) and (5.6).

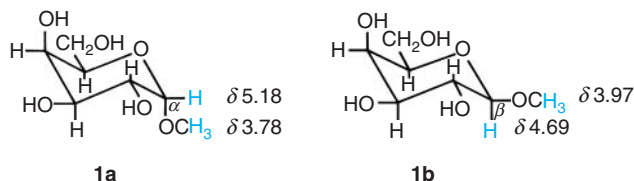


The results of Eq. (5.6) can be qualitatively represented by a shielding cone (see diagram) whose nodal plane ($\Delta\sigma = 0$) is fixed at the “magic angle” of 54.7° for that the factor $(1 - 3\cos^2\theta) = 0$. A positive sign indicates shielding and a negative sign deshielding.

Experimental verification of the proposed shielding behavior for the C–C single bond may be seen in the case of cyclohexane. Here, a difference of about 0.5 ppm exists between the resonance frequencies of the axial and equatorial protons that can be measured at low temperature where the rate of chair–chair interconversion (cf. p. 526) is slow on the NMR time scale. Obviously, H_a is more strongly shielded than H_e . One must emphasize, however, that such a simple picture neglects the effects of the other C–C bonds and those of the C–H bonds.



This differential influence on the ^1H resonance is an important aid in conformational analysis of six-membered rings. As the example of α - and β -D-methoxygalactose (**1a** and **1b**, respectively) shows, there is even a shielding effect for the protons of the axial methoxy group.



More recently, quantum chemical investigations have shown that the shielding properties of the C–C single bond are more complex than suggested by the simple shielding cone shown above. On this basis it was suggested that the different chemical shifts of the axial and equatorial proton in cyclohexane originate from

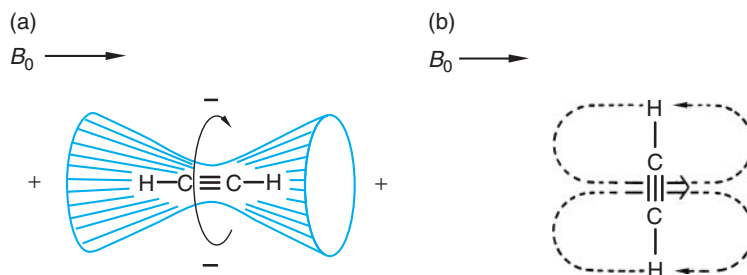


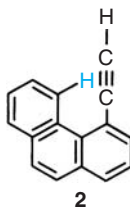
Figure 5.8 Schematic representation of the diamagnetic anisotropy effect of a triple bond.

hyperconjugative effects rather than from the diamagnetic anisotropy of the C2–C3 and C5–C6 single bond [4].

Significantly, almost all chemical bonds are magnetically anisotropic and models based on the McConnell equation were developed to predict their contributions to the proton shielding constants. Of the *multiple* bonds the C=C and the C=O double bonds and the C≡C and C≡N triple bonds possess particularly strong anisotropic effects on the chemical shifts of nearby protons. The special ^1H resonance position observed for acetylene at lower frequency than for the olefinic resonances, seen in the shift diagram Figure 3.6 (p. 37), can be understood within the McConnell approximation with a negative diamagnetic anisotropy. With a value of $\Delta\chi_{\text{C}\equiv\text{C}} = -27 \times 10^{-36} \text{ m}^3 \text{ molecule}^{-1}$ one calculates a shielding $\Delta\sigma$ of +3.66 ppm for a position on the bond axis ($\theta = 0^\circ$) 0.17 nm from the center of the bond. This is larger than the experimental difference between $\delta(^1\text{H})$ in ethene and acetylene (2.96 ppm, Table 3.1, p. 38) by 23% and underlines the approximate nature of the model calculation.

Another explanation of the experimentally observed low-frequency shift of acetylenic protons assumes an electron circulation or ring current around the bond induced by the external field (Figure 5.8). The result would be a magnetic dipole opposed to B_0 that leads to shielding. This idea corresponds to the ring current effect that we shall introduce below for the shielding properties of the benzene ring. If one considers the case in which the bond axis and the direction of B_0 are perpendicular (Figure 5.8b), the π -electron circulation is now hindered, a situation that leads to a paramagnetic moment in the center of the bond and, again, the protons are shielded. On the other hand, in the regions alongside the triple bond deshielding is expected.

Experimental evidence for this effect is found in 4-ethynylphenanthrene (2), where the chemical shift of H(5) is 1.71 ppm to higher frequency from the resonance of the same proton in phenanthrene itself. An alternative explanation, however, derived from theoretical calculations that support the general picture of the shielding cone shown in Figure 5.8 attributes this finding to a van-der-Waals effect – namely, compression of the electron clouds of the triple bond and the proton (see below). Similar considerations apply to the cyano group.



A drawback of the application of Eq. (5.6) is certainly the difficulty in obtaining bond-specific diamagnetic anisotropy data and the limitation of the model to axially symmetric groups. With $C=C$ and $C=O$ double bonds the situation is thus more complicated as a consequence of the fact that these groups have lost cylindrical symmetry. Experience has shown, however, that to a good approximation the shielding effects of both groups as well as those of the nitro group can be represented qualitatively by the diagrams given in Figure 5.9, and these are quite useful for the interpretation of ^1H NMR spectra. We note, however, that theoretical studies have shown that ^1H resonances from the region above the double bond may show high frequency shifts if the protons come close to the π -orbitals [5]. Orbital deformations lead then to deshielding, similar to the interaction discussed above for compound 2.

Thus, for compounds 3 and 4, with the protons of interest well above the double bond system, we find shielding and the resonance frequencies are shifted toward lower frequency. In cyclohepta-1,3,5-triene (5) the resonances of the methylene protons can be differentiated at low temperature (cf. p. 529). In this case the quasi-axial proton is more strongly shielded by the $C3=C4$ double bond. In the region of the nodal surface between shielding and deshielding reliable predictions concerning the influence of a double bond on the proton resonance frequency are difficult to make. This results on the one hand from the approximate nature of the shielding cones and, on the other hand, from the uncertainty with which the geometry of the molecule under investigation is usually known. For example, the resonance of the *syn* proton in norbornene (6) is found at higher frequency than that of the *anti* proton, while in substituted norbornenes this order is reversed, as the example of the isomeric pair 6a/6b shows.

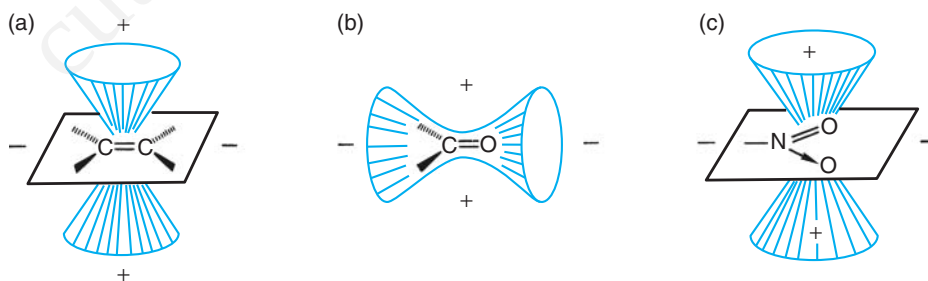
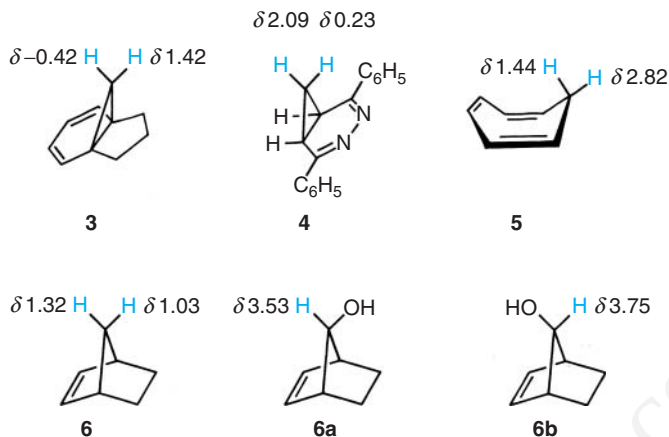
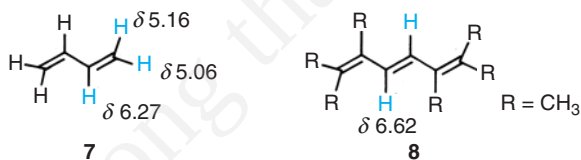


Figure 5.9 Schematic representation of the shielding effect of (a) a carbon–carbon double bond, (b) carbonyl group, and (c) nitro group.

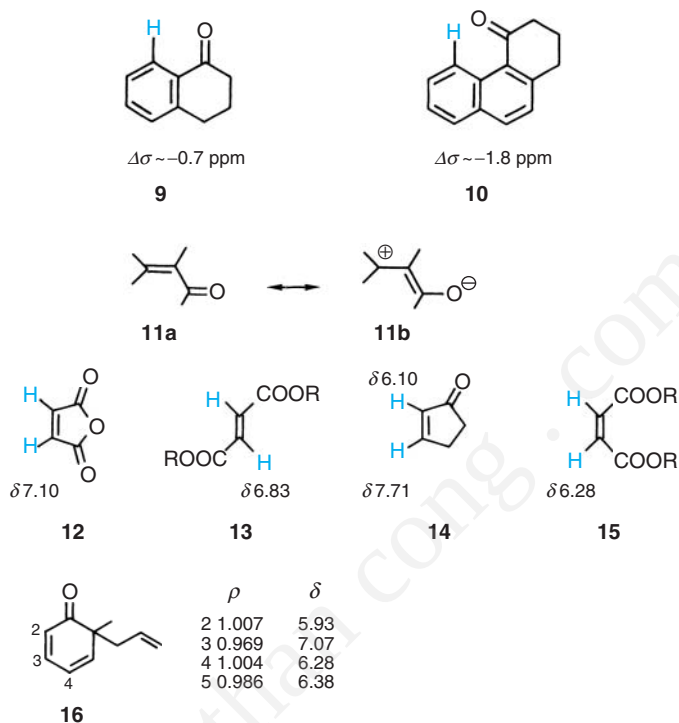


Olefinic protons are less shielded than protons in saturated hydrocarbons, an indication of the deshielding region in the plane of the C=C double bond, but the different carbon hybridization may also be important. The paramagnetic shift of the central protons in 1,3-butadiene (7) that exists almost completely in the planar *s-trans* conformation as well as the high δ -value of the vinyl proton resonance in 1,1,2,5,6,6-hexamethyl-1,3,5-hexatriene (8, R = Me) are, however, in good agreement with the predictions.



The particularly high frequency of the *aldehyde* proton resonance (ca. 10 ppm, cf. Table 3.1, p. 38) is the result of the combined electronic and magnetic effects. The dipole moment of this group possibly plays an additional role (cf. Section 5.1.6). In addition, compounds **9** and **10** distinctly show the deshielding effect of the C=O function on neighboring protons that lie in the nodal region of the π -bond.

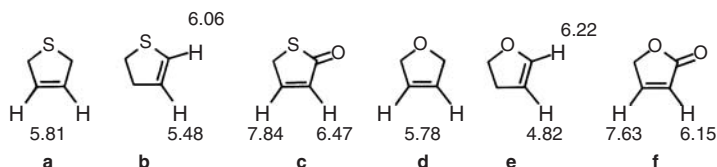
In α,β -unsaturated ketones and aldehydes the participation of resonance structures such as **11b** is of special significance. As a result, the chemical shift is dominated by electronic effects and the β -protons are strongly deshielded. In the case of malonic anhydride (**12**) mesomeric and anisotropic effects work in concert and the resonance frequency of the olefinic protons lies at very high frequency. In diethyl fumarate (**13**) and cyclopentenone (**14**), similar situations are found. In contrast, the olefinic protons of diethyl malonate (**15**, R = Et) are shielded because here the *cis*-position of the carbethoxy groups leads to steric hindrance and distorts the coplanar arrangement of the π -system, thereby reducing the charge transfer and the deshielding caused by the mesomeric effect.



Finally, electronic effects again dominate in the case of 2,4-cyclohexadiene-1-one **16**, where the proton resonance frequencies follow the calculated π -electron densities. Thus the proton H2 at the carbon atom with the largest charge density has the smallest δ value, while H3 bonded to the carbon with the lowest charge density is strongly deshielded. This brief analysis shows that, as a rule, only the consideration of all factors that are responsible for the variation of the shielding constants allows for a satisfactory interpretation of the experimental findings.

Exercise 5.2

Explain on the basis of the effects just discussed the chemical shifts of the olefinic protons in olefinic compounds a–f.



5.1.4

Ring Current Effect in Cyclic Conjugated π -Systems

A special case arises with the proton resonance of benzene. As will be shown in this section, the reduced shielding of aromatic protons as compared to olefinic protons can be explained by π -electron circulations that cover the entire molecule. In terms of this simple and very successful model, an aromatic molecule can be visualized as a current loop where the π -electrons are free to move on a circle formed by the σ framework. If these compounds are subjected to the external magnetic field B_0 , a diamagnetic ring current is induced. The secondary field resulting from this current can then be approximated by the field of a magnetic dipole opposed to B_0 and placed in the center of the ring (Figure 5.10). As a result, protons in the molecular plane and outside the ring are deshielded. Conversely, protons in the region above or below the plane of the ring are strongly shielded. If benzene is used as solvent, its diamagnetic ring current manifests itself even in a shielding of the ^1H resonances of the solutes.

The ring current concept, which neglects any chemical shift contributions from the σ -electrons of the C–C or C–H bonds, was introduced by L. Pauling to explain the strong increase in the diamagnetic susceptibility of aromatic compounds perpendicular to the ring plane. It was first formulated quantitatively for proton magnetic resonance by J. A. Pople. If the benzene ring is considered as a circular wire perpendicular to the direction of the field B_0 of magnitude B_0 , the π -electrons move around the framework of the σ -bonds with the Larmor frequency:

$$\omega = \frac{eB_0}{2m_e c} \quad (5.7)$$

where e (4.8×10^{-10} e.s.u.) and m_e (9.1×10^{-28} g) are the charge and the mass of the electron, respectively, and c is the velocity of light (3×10^{10} cm s $^{-1}$; we use here and below CGS units). The current intensity, i , for one electron is $i = e\omega/2\pi$ and

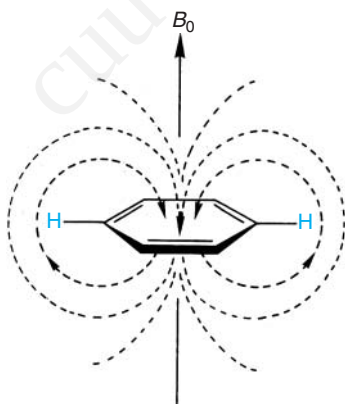


Figure 5.10 Secondary magnetic field of a benzene ring in the external magnetic field B_0 .

in a system with six electrons we have for the current intensity:

$$i = \frac{3e\omega}{\pi} = \frac{3e^2 B_0}{2\pi m_e c} \quad (5.8)$$

The magnetic properties of this ring current are now approximated as due to a magnetic dipole at the center of the ring, the magnitude of which is given by:

$$\mu = i\pi r^2 / c \quad (5.9)$$

or, in combination with Eq. (5.8), by:

$$\mu = \frac{3e^2 B_0 r^2}{2m_e c^2} \quad (5.10)$$

where r is the radius of the ring. The secondary magnetic field $B' = -B_0\sigma$ [see Eq. (3.1), p. 30] of this dipole at a proton located at a distance R from the center of the ring is μ/R^3 :

$$-B_0\sigma = \frac{3e^2 B_0 r^2}{2m_e c^2 R^3} \quad (5.11)$$

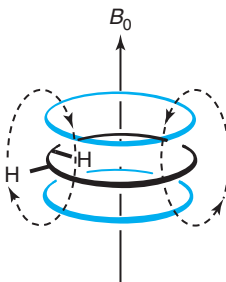
The contribution to the shielding constant is then given by:

$$\Delta\sigma = -\frac{e^2 r^2}{2m_e c^2 R^3} \quad (5.12)$$

where the statistical factor of 1/3 is introduced to account for the situation in which the plane of the ring is oriented parallel to B_0 and no ring current is induced.

With the known values for e , m_e , and c (see p. 9 and 101) as well as the data $r = 1.4 \text{ \AA}$ ($1 \text{ \AA} = 10^{-8} \text{ cm}$) and $R = 2.5 \text{ \AA}$, we have $\Delta\sigma = -1.76 \times 10^{-6}$ or $\Delta\delta = +1.76 \text{ ppm}$. This result compares well with the shift difference of 1.68 ppm between the resonance frequencies observed for the olefinic protons of cyclohexene ($\delta 5.59$) and the protons in benzene ($\delta 7.27$).

A more exact analysis avoids the point dipole approximation by considering that the density of the π -electrons is greatest where the carbon $2p_z$ orbitals overlap most strongly. This leads to two current loops, one above and one below the plane of the σ -bonds. For protons within the perimeter of the benzene ring an increased shielding results.



The magnitude of the induced field B' and the change in the shielding constant, $\Delta\sigma$, have been calculated and tabulated for the benzene nucleus. The Appendix

contains a graphical representation of these results that can be used to calculate the contribution of a phenyl group to the chemical shift of a proton in a compound of interest (p. 649). Moreover, by analogy with the simple ring current model, Eq. (5.6) can also be used for more distant protons with a value of $\Delta\chi = -50 \times 10^{-36} \text{ m}^3 \text{ molecule}^{-1}$ for the diamagnetic anisotropy of benzene, which is assumed to originate from the center of the ring.

Because of the inverse proportionality of $\Delta\sigma$ to R^3 , the ring current model allows a qualitative interpretation of the spectra of *polynuclear* aromatic compounds if the observed shift is considered to be the sum of the contributions of the individual rings. Thus, the α -protons in naphthalene resonate at higher frequency than the β -protons because the contributions of the two rings are more important at the α -position since the latter is closer to both rings. The order of the proton resonance frequencies in anthracene can be explained in the same fashion. Here one finds $\delta_\gamma > \delta_\alpha > \delta_\beta$ (Figure 5.11). The $\Delta\sigma$ values in these systems can be calculated with

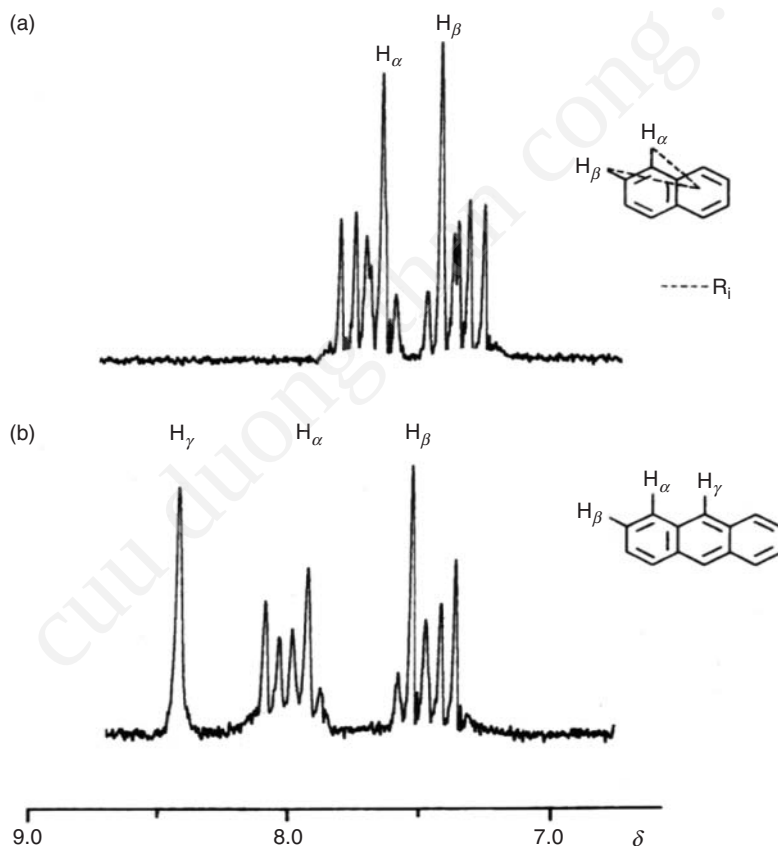


Figure 5.11 Correlation between the relative chemical shifts of the proton resonances in (a) naphthalene and (b) anthracene and the distance R_i of the proton from the center of a specific benzene ring.

the help of Eqs. (5.13a) and (5.13b):

$$\Delta\sigma = -\frac{e^2 r^2}{2m_e c^2} \sum_i R_i^{-3} \quad (5.13a)$$

or:

$$\Delta\sigma \text{ [ppm]} = -27.5 \sum_i R_i^{-3} \quad (5.13b)$$

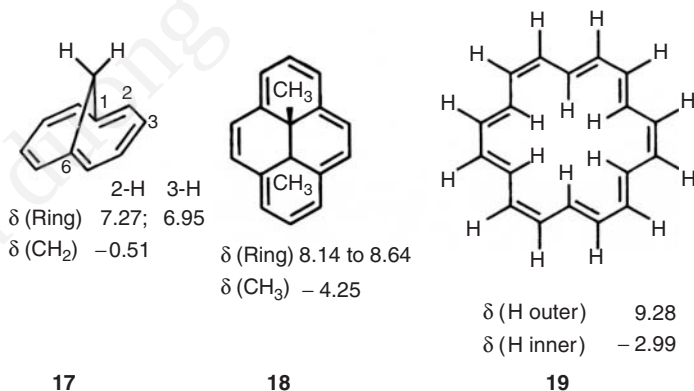
if R_i , the distance of the proton of interest from the center of the i -th ring, is given in Å. Thereby, the total effect is obtained as the sum of the contributions of individual benzene units.

Exercise 5.3

Calculate the ring current effect $\Delta\sigma$ (relative to benzene) for H4 and H9 in phenanthrene with the help of Eq. (5.13b).

In *non-alternating* hydrocarbons such as azulene the position of the individual proton resonances can be determined satisfactorily only if, in addition to the ring current effect, the different charge densities at the individual carbons are taken into consideration.

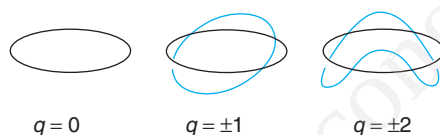
The results discussed above for benzene are fully supported by the proton resonance frequencies of the annulenes, a series of cyclic conjugated π -systems with more than six π -electrons. The three compounds 1,6-methano[10]annulene (**17**), *trans*-15,16-dimethyl-15,16-dihydropyrene (**18**), and [18]annulene (**19**) are presented here as examples.



Together with benzene, these molecules belong to the group of annulenes with $(4n + 2)$ π -electrons ($n = 0, 1, 2, \dots$) that, following the well known Hückel rule, possess aromatic character. The cyclic delocalization of the π -electrons in the ground state of these systems can therefore be demonstrated by means of NMR spectroscopy as a *ring current effect*. Since the secondary magnetic field of the ring current is diamagnetic, which is opposed to the direction of the external field B_0 , F. Sondheimer introduced the term *diatropic* for these systems.

How, on the other hand, do the annulenes with $4n$ π -electrons behave in a magnetic field? For these compounds quantum mechanical calculations predict a *paramagnetic ring current effect* with the opposite consequences for the proton resonance frequencies as in its diamagnetic counterpart discussed above. Protons within the perimeter or above are now deshielded, whereas those outside and in the plane of the ring are shielded.

This different behavior of $(4n + 2)$ and $4n$ π -electron systems can be rationalized with the help of a simple quantum mechanical model. Let us consider the movement of an electron along a circular path with a circumference L so that its wavelength λ can take only certain values. As a consequence of this, the electron can exist only in certain states, the so-called eigenstates. This phenomenon is similar to the situation postulated in Chapter 2 for the energy of a proton in an external magnetic field. For the electron to “fit” the circle, the condition $L = q\lambda$ with $q = 0, \pm 1, \pm 2$, etc. obviously must be met. This is the *quantum condition* for our problem and q is the quantum number that characterizes each eigenstate:



Following de Broglie, the momentum, p , of an electron is given by the relation $p = h/\lambda$, and the kinetic energy is then:

$$E = mv^2/2 = p^2/2m\lambda^2 = h^2q^2/2mL^2 \quad (5.14)$$

Accordingly, for each quantum number, q , there is a corresponding energy value, in units of $h^2/2mL^2$, the eigenvalue, and our model leads to the energy level diagram represented in Figure 5.12a.

If we choose the model of the “electron on a circle” to describe the π -electrons in cyclic conjugated systems, the energy level diagram must be filled with electrons according to the *Aufbau principle*, that is, with regard to the Pauli exclusion principle and Hund’s rule. Consequently, in a $(4n + 2)$ π -system a closed shell results (Figure 5.12a), and the occupied eigenstates or *orbitals* produce a diamagnetic contribution to the magnetic susceptibility. In contrast, in the $4n$ π systems the highest occupied orbitals contain only one electron each, the spins of which are unpaired (Figure 5.12b), and these compounds should be paramagnetic. Actually, neither cyclooctatetraene nor other $[4n]$ annulenes exhibit molecular paramagnetism. As a theorem formulated by H. A. Jahn and E. Teller states, the degeneracy of the highest occupied orbitals can be destroyed by a slight perturbation of the molecular symmetry, perhaps through alternating bond lengths, and this allows both electrons to occupy a single lower lying energy level. The resulting energy level diagram (Figure 5.12c) shows that now there is only a small energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) orbital. The respective energy difference is much smaller than the corresponding energy difference in the case of the $(4n + 2)$ π -systems. An interaction

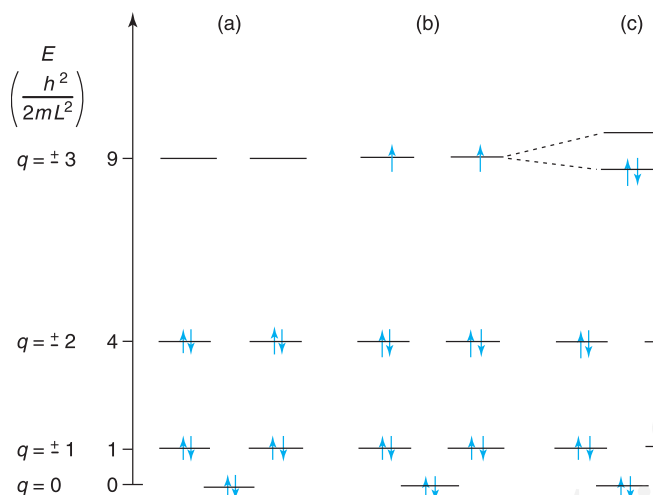


Figure 5.12 Energy level diagram for the model of an “electron on a circle.”

with the magnetic field B_0 will lead to a mixing of these electronic states and, as discussed later in Chapter 11, produce a strong paramagnetic contribution to the shielding constant σ since σ_{para} (cf. p. 31, 410) is proportional to $1/\Delta E$. This is larger in magnitude than the diamagnetic contribution of the lower orbitals so that the net result is a paramagnetic effect. Thus, in the case of $[4n]$ annulenes we speak – in analogy with the classical ring current model discussed at the outset – illustratively, but inaccurately, of a “paramagnetic ring current.” Clearly, this terminology does not imply that the electrons in $4n$ π -systems move in the other direction to those in $(4n + 2)$ π -systems, which would violate Lenz’ rule. Molecules that show a *paramagnetic* ring current effect are *anti-aromatic* and are called *paratropic*, whereas those with no ring current at all can be termed *atropic*.

A series of experimental observations confirm the theoretical prediction by the detection of paramagnetic ring current effects and we cite two particularly impressive examples. By reduction with metallic potassium, compound **18**, a $[14]$ annulene mentioned above, is converted into the doubly charged anion $\mathbf{18}^{2-}$ that has 16 π -electrons. In this compound the methyl protons resonate at δ 21.0 and the ring protons at δ -3.2 to -4.0 ppm. The dramatic difference between the spectra of the neutral $(4n + 2)$ π -system and its charged $4n$ π counterpart is illustrated in Figure 5.13. The different charge density affects to a first approximation only the ring protons, which due to this factor are subjected to an additional shielding of 1.4 ppm [Eq. (5.2)].

A similar observation was made for the dianion of 1,6-methano $[10]$ annulene ($\mathbf{17}^{2-}$), prepared by lithium reduction of the hydrocarbon, where – in contrast to the situation found for the diatropic hydrocarbon **17** – the ring protons are shielded (δ 1.59 and δ 3.07 in the α - and β -positions relative to the methano bridge), whereas the methylene protons at C11 suffer a high-frequency shift to δ 11.64 (Figure 5.14).

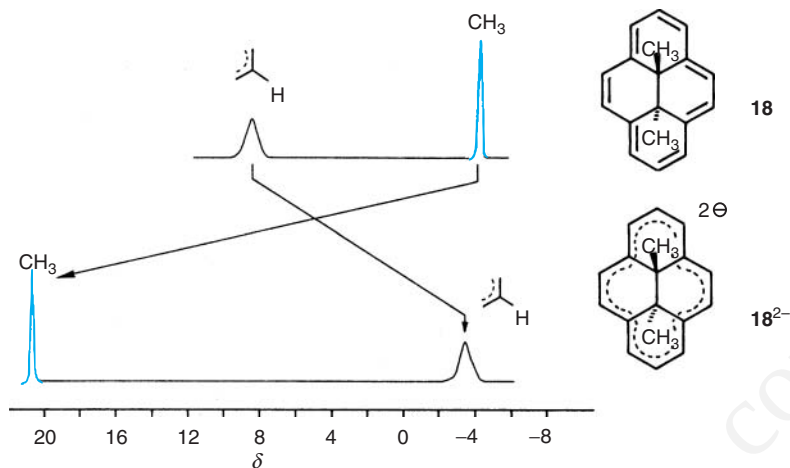


Figure 5.13 Schematic comparison of NMR spectra of annulenes **18** and **18²⁺**, which have 14 and 16 π -electrons, respectively.

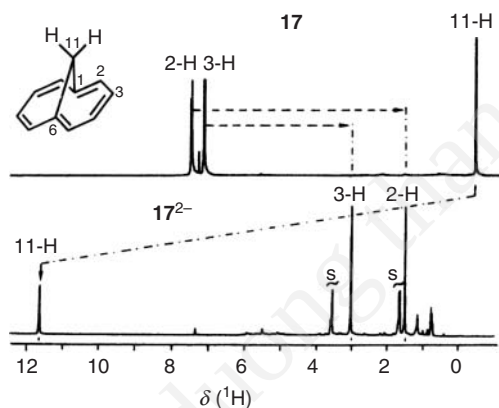


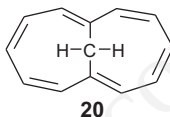
Figure 5.14 400 MHz ^1H NMR spectra of **17** and **17²⁺**; the δ -values observed for **17²⁺** are 1.59 and 3.07 ppm for 2,5,7,10-H and 3,4,8,9-H, respectively, and 11.64 ppm for the methylene protons [6].

Exercise 5.4

For the dilithium salt of naphthalene dianion that is formed by the reduction of the hydrocarbon with lithium metal in THF (tetrahydrofuran), ^1H resonance frequencies of δ 1.27 and 3.09 ppm are found. A Hückel MO calculation yields π -charge densities of 1.361 and 1.138 for the 1- and 2-position, respectively. Assign the ^1H NMR signals and calculate with the data of the hydrocarbon (Table A.1, p. 652) the experimental low-frequency shifts $\Delta\delta$ (1-H) and $\Delta\delta$ (2-H). Use Eq. (5.2) to estimate the contributions to these values of the negative charge density and the paramagnetic ring current effect in the 12π -system of the dianion.

Figure 5.15 illustrates the dependence of the ring current intensity, I , on the alternation of the bond lengths in cyclic π -systems as obtained by means of quantum mechanical calculations. As shown, with increasing bond alternation the paramagnetism decreases more rapidly than diamagnetism; conversely, however, the ring current intensity is substantially higher for delocalized paratropic $4n$ π -systems. Figure 5.13 obviously confirms these predictions since, if compared to chemical shifts in non-delocalized model compounds, for example, cyclohexene (5.59), the absolute chemical shifts in the dianion are considerably larger than in the hydrocarbon. For the 14π hydrocarbon **18** $\Delta\delta$ -values of 2–3 and –4 to –5 ppm result for the ring and methyl protons, respectively, while in the case of the 16π -system **18**²⁻ the shifts are –10 to –12 and 20 ppm, respectively, for these groups.

For neutral $[4n + 2]$ - and $[4n]$ annulenes, the two hydrocarbons 1,6-methano[10]annulene (**17**) and 1,7-methano[12]annulene (**20**) yield a striking example of the different shielding properties of diatropic and paratropic systems, especially for the region above the π -electron circle (Figure 5.16). The shift difference for the two CH_2 group amounts to nearly 7 ppm!



In addition, the two tricycloazines (**21**) and (**22**) represent a pair of compounds that clearly demonstrate the different behavior of diatropic and paratropic π -systems. The nitrogen atom here functions as a clamp that does not affect the resonance

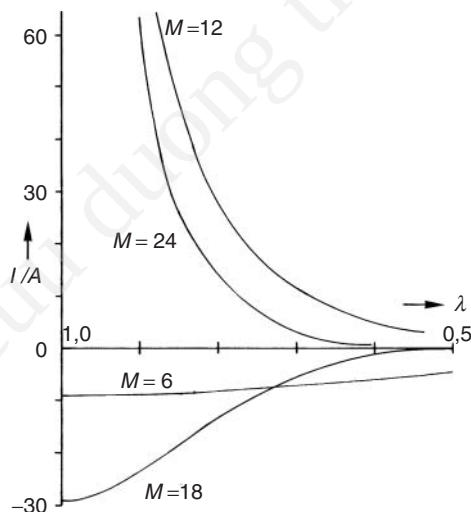


Figure 5.15 Ring current intensity, I , per unit area, A , in annulenes as a function of the alternation parameter, λ , which is a measure of the ratio of the resonance integrals, β , at adjacent carbon-carbon bonds. For completely equivalent bonds $\lambda = 1.0$. Negative signs signify diamagnetism; M indicates the number of π -electrons present [7].

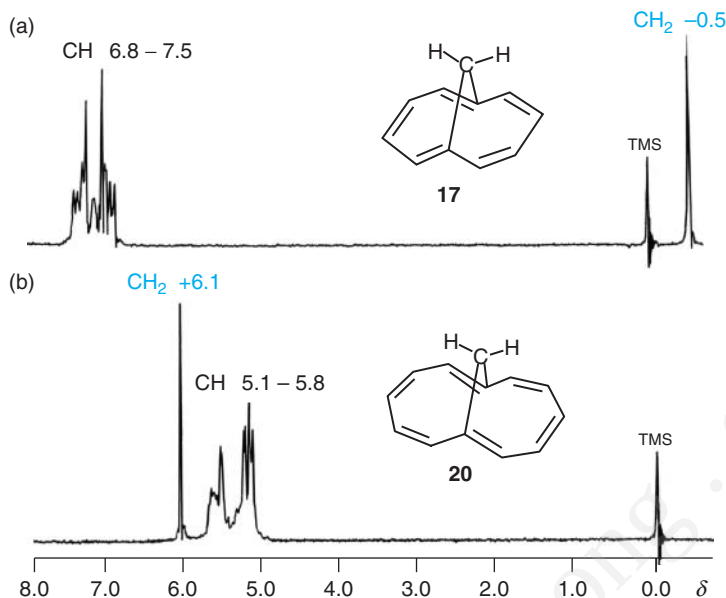
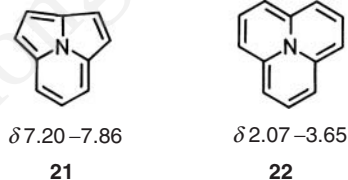


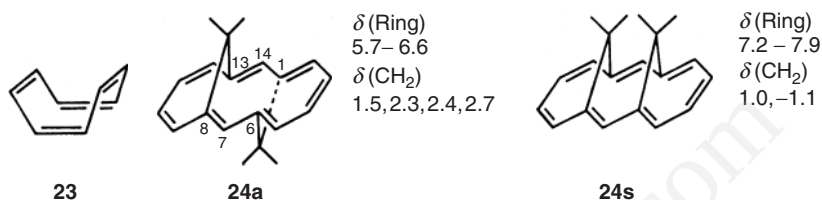
Figure 5.16 ^1H NMR spectra of (a) 1,6-methano[10]annulene (**17**) (b) and 1,7-methano[12]annulene (**20**) [8].

frequencies significantly. Relative to the $\delta(^1\text{H})$ of benzene (7.27 ppm) they are shifted to higher frequency in the case of the 10π -system **21** and to low frequency in the case of the 12π -system **22**, where, as expected (see Figure 5.15), the shift is again much larger. The same is true for the pair **17** and **17** $^{2-}$.



Nonplanar cyclic π -systems with pronounced bond alternation do not show a ring current effect since delocalization of the π -electrons is diminished or completely quenched. Thus, the protons of cyclooctatetraene that exists in the tub conformation **23**, have a resonance frequency of δ 5.80, which is practically identical to that of the protons of cyclohexa-1,3-diene (δ 5.85). In yet another example, comparison of the ^1H chemical shifts of 1,6;8,13-*syn*-bismethano[14]annulene (**24s**) with the data for the *anti*-compound **24a** leads to the conclusion that the ring current expected for the 14π -electron system **24a** on the basis of the number of its π -electrons does not exist. The resonance frequencies of the CH_2 groups of the *syn*-system **24s** exhibit the anticipated diamagnetic shift while the resonances of the methylene protons of **24a** are recorded as two AB systems in the region characteristic for allylic methylene groups such as that in cyclohepta-1,3,5-triene. Moreover, the deshielding of the

perimeter protons observed for **24s** is absent in **24a**. As examinations of models show, an extensive twisting of the carbon-carbon bonds between the centers 6, 7, 8 and 13, 14, 1 obviously hinders the effective overlap of the carbon $2p_z$ orbitals so that here, for the first time, a compound that has the correct number of π -electrons to satisfy the Hückel rule, and thus should be aromatic, exhibits olefinic characteristics [9]. We shall return to this interesting molecule in Chapter 13.



5.1.5

Alternative Methods to Measure Diatropicity

The general interest in aromatic compounds and the fascination that comes with the phenomenon of aromaticity since the days of Kekulé has stimulated much effort in finding aromaticity criteria. According to a proposal of J.A. Elvidge and L.M. Jackman, the presence of diatropic behavior should be taken as a qualitative NMR criterion for aromatic character. However, highly conjugated ring systems that lack cyclic delocalization of π -electrons or even olefins like **8** show resonances close to or even beyond the δ -value of benzene. A high-frequency shift may thus not be regarded as a conclusive indication of aromatic character. Furthermore, recent theoretical calculations have emphasized the importance of *localized* σ - and π -contributions to the chemical shifts in unsaturated systems. This is shown in Figure 5.17 where the positional dependence of individual contributions from CC- π -electrons, CC- σ -electrons, CH bonds, and core electrons to the magnetic shielding constant σ above the benzene ring is plotted. The results show that contributions from core electrons and CH bonds are of minor importance, whereas strong effects, of different sign however, come from the π - and σ -electrons.

Better suited to characterizing an unsaturated cyclic compound as diatropic seem data collected above or below the ring plane. To conclude this section we therefore describe two methods that use again magnetic properties to classify cyclic π -systems as aromatic or anti-aromatic in a more quantitative way.

The first is concerned with the exaltation of diamagnetic susceptibility, Λ , which can be measured with the NMR method and the coaxial sample tubes we introduced in Chapter 4 (p. 71). From the volume susceptibility of a compound, χ_v , one can calculate the molar susceptibility, χ_M , according to:

$$\chi_M = (\chi_v/\rho) \times M \quad (5.15)$$

where ρ is the density and M the molar mass. Comparing the experimental value with that derived from an increment system with individual contributions to χ_M by different types of chemical bonds and other structural features like lone

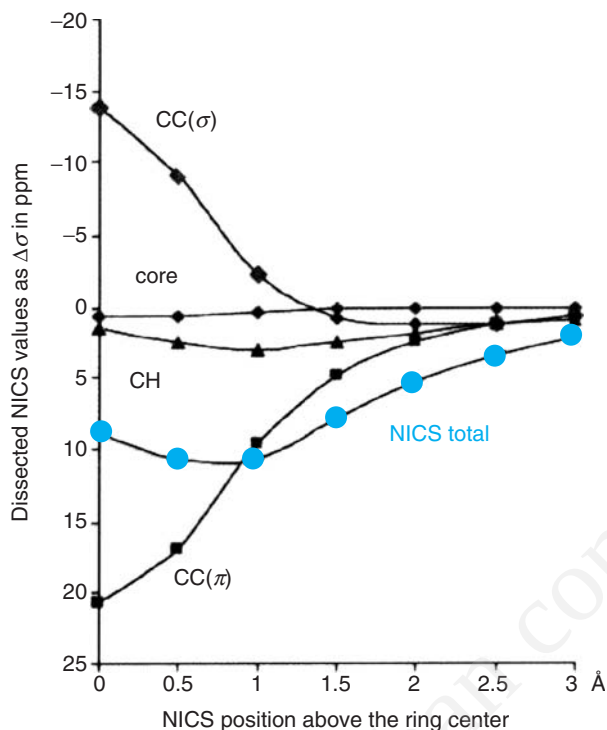
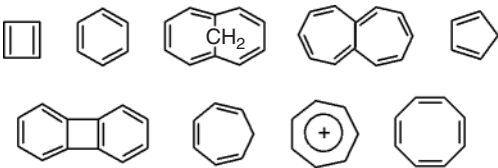


Figure 5.17 Calculated chemical shift contributions to the shielding constant σ at the ring center of benzene and up to 0.3 nm (3 Å) above; NICS-values as $\Delta\sigma$ in ppm [10]. These calculations do not imply the existence of a π -electron ring current (Adapted with permission from Reference [9a]. Copyright 2001 American Chemical Society).

pairs, one finds positive and negative deviations for Δ . The positive data come from an exaltation of the diamagnetic susceptibility and characterize the π -system as aromatic or diatropic, while negative values indicate reduced diamagnetism characteristic for anti-aromatic or paratropic systems. Table 5.2 shows the results for several typical cases with $|\Delta| > 5.0$ for diatropic compounds and $\Delta < 0.0$ for paratropic systems; values for $|\Delta|$ below 3.0 are not significant. The sign for Δ conforms to the sign convention for the NMR shielding constant σ with positive $\Delta\sigma$ -values for shielding (low-frequency shift) and negative $\Delta\sigma$ -values for deshielding (high-frequency shift).

The second approach is based on quantum chemical calculations of the properties of cyclic π -systems in a magnetic field. Using advanced methods for chemical shift calculations one can derive *nucleus-independent chemical shifts*, the so-called *NICS values* (Figure 5.17), at the center point and above for the ring system that is to be studied. Here, positive values signal aromaticity while negative values are found for anti-aromatic systems. The absolute magnitude of the calculated data varies somewhat if different quantum chemical programs are used and contains also contributions from the σ -bonds and from heteroatoms.

Table 5.2 Diamagnetic susceptibility exaltation, Λ , and NICS values of selected compounds; both data sets are from positions above or below the ring plane; NICS values are given as $\Delta\sigma$ values in ppm.

		
Compound	Diamagnetic susceptibility exaltation, Λ ($\times 10^6 \text{ cm}^3 \text{ mol}^{-1}$) ^a	NICS value ^b
Cyclobutadiene	−18	−27.6
Benzene	13.7	9.7
1,6-Methano[10]annulene	36.8	—
Heptalene	−6	−22.7 ^c
Cyclopenta-1,3-diene	6.5	3.2
Biphenylene	14	Six-membered ring: 5.1 Four-membered ring: −19
Cyclohepta-1,3,5-triene	8	—
Tropylium cation	17	7.6
Cyclooctatetraene	−0.9	−30.1 ^c

^aReference [11].

^bReference [12].

^cFor the hypothetical planar system.

Table 5.2 summarizes a few results of both methods described above. Please note that both models measure the diamagnetic effect either above or below the ring system or at its center and not at the position of the protons. For both situations the simple ring current model yields shielding and thus negative $\Delta\delta$ values for diatropic systems and deshielding and positive $\Delta\delta$ values for paratropic systems.

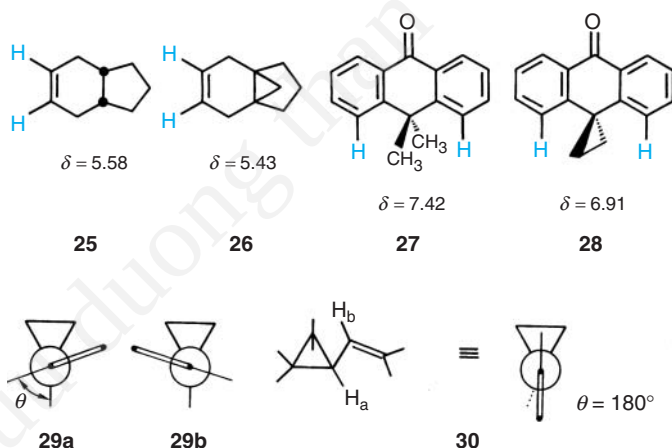
The data for cyclobutadiene clearly document its anti-aromaticity by large negative $\Delta\sigma$ values, while for benzene the expected positive values are observed. The 10π -system of 1,6-methano[10]annulene (17) shows an even stronger diatropicity. The $4n$ π -system of heptalene on the other hand, calculated with a planar structure, is again paratropic. The large difference between Λ and the NICS value supports the twisted nonplanar structure of this π -system. A similar difference is found between the Λ value for the tub conformation of cyclooctatetraene with virtually no cyclic delocalization of the π -electrons and the NICS value for the hypothetical planar system. Compared to the Λ method, the theoretical approach has the advantage that NICS values for partial structures can be derived. For biphenylene, for example, strong paramagnetism is thus found for the central four-membered ring, a fact not

apparent from the Δ value. Interestingly, cyclohepta-1,3,5-triene yields a relatively large positive Δ value that indicates neutral homoaromaticity. Indeed, the partial overlap of the lower halves of the carbon $2p_z$ orbitals at C1 and C6 of the tub conformation yields the diatropic character for this olefin (cf. p. 99). Finally, both methods demonstrate the diatropic nature of the tropylium ion.

5.1.6

Diamagnetic Anisotropy of the Cyclopropane Ring

In closing our discussion of ring currents in cyclic compounds, we consider the cyclopropane ring because it also possesses a diamagnetic anisotropy $\Delta\chi$ perpendicular to the plane of the ring. However, as a consequence of the different orientation of the C–H bonds, in comparison with those in benzene, a shielding of the ring protons of cyclopropane results, so that the resonance frequency of δ 0.22 is considerably lower than for other saturated cyclic hydrocarbons. The two pairs of compounds **25** and **26** and **27** and **28** illustrate this shielding effect of the three-membered ring, which can be explained with an electron circulation or ring current in the bent C–C σ -bonds. A value of $12 \times 10^{-36} \text{ m}^3$ per molecule has recently been derived for $\Delta\chi$ of the three-membered ring [13] and a classical ring current calculation exists [14].



Another example for the shielding behavior of cyclopropane is found in the temperature dependence of the resonance frequency of the proton H_b of vinyl cyclopropane (Figure 5.18). This compound exhibits a rapid and reversible equilibrium between two *gauche* and one *s-trans* conformer (**29a**, **29b** and **30**, respectively) in which the position of the vinyl group relative to the cyclopropane ring differs considerably. The strong diamagnetic shielding of H_b with decreasing temperature indicates that the conformation of lower energy, which is more highly populated, is the *s-trans* form in which the proton H_b is in the shielding region of the cyclopropane ring.

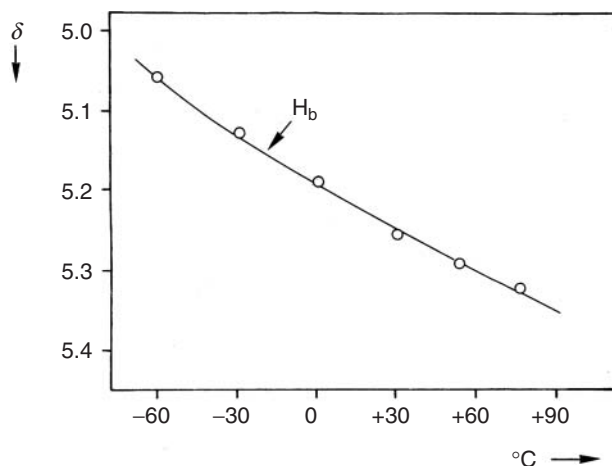


Figure 5.18 Temperature dependence of the resonance frequency of proton H_b in vinylcyclopropane [15].

5.1.7

Electric Field Effect of Polar Groups and the van-der-Waals Effect

Besides the previously discussed electronic and magnetic contributions to the chemical shift of proton resonances, two other effects that are in certain cases of substantial importance should be considered to complete our introduction to the origins of proton chemical shifts.

In molecules with highly polar groups it must be realized that the electric dipole moment may lead to a change of the charge density at particular protons because the charge cloud of the corresponding C–H bond can be distorted by electrostatic forces. Depending on the direction of the C–H bond relative to the electric field vector, the bonding electrons are shifted toward or away from the hydrogen atom with the result that the proton is either shielded or deshielded. This is similar to the effect of partial positive or negative charges at carbon atoms of C–H bonds discussed before (p. 90). As can be realized from Figure 5.19, the dipole moments in pyridine and nitrobenzene, for example, that have been localized at the nitrogen and at the center of the C–N bond of the nitro group, respectively, cause a deshielding of the protons because the electrons are shifted along the lines of force toward the positive end of the dipole.

According to the theory of Buckingham, this effect can be quantitatively described by the relation:

$$\Delta\sigma = -AE_z - BE^2 \quad (5.16)$$

where E_z is the component of the electric field in the direction of the C–H bond and E^2 is the square of the field strength at the proton. Both terms are calculated from the known relation for the field of an electric dipole μ and A and B are constants with values of $\sim 2.0 \times 10^{-12}$ and 10^{-18} (in e.s.u.), respectively, if μ is measured

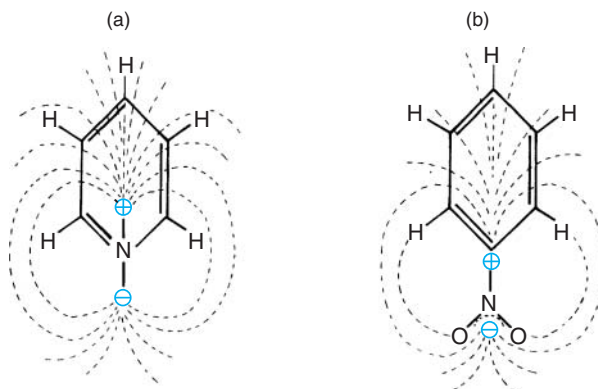
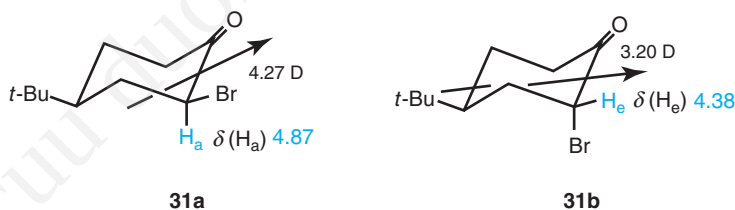


Figure 5.19 Electric field effect in (a) pyridine and (b) nitrobenzene.

in debye. The first term, the so-called linear electric field effect (LEFE), usually dominates; and the second term vanishes for larger distances (>0.2 nm). With Eq. (5.16), shielding contributions of -0.70 , -0.19 , and -0.14 ppm are calculated for the *ortho*-, *meta*-, and *para*-protons, respectively, in nitrobenzene, in qualitative agreement with the experimental results [-0.95 , -0.21 , and -0.33 , relative to $\delta(^1\text{H})$ in benzene]. An interesting manifestation of the importance of electric field effects for chemical shifts was found with the pair of 4-*t*-butyl-2-bromocyclohexanone (**31a**) and (**31b**), where the general rule that an axial proton in six-membered rings is more shielded than an equatorial proton is violated [16]. As seen in the formulae, the component of the electric field, E_z associated with the molecular dipole moment (arrows), increases the electron density in the cis-compound **31b** at H_e , but in the trans-compound **31a** the electrons of the C-H_a bond are shifted away from H_a leading to $\delta(\text{H}_a) > \delta(\text{H}_e)$.



With *ab initio* calculations, *A*-values for various molecules have been calculated and a refinement of the model considers the polarization of the medium by the polar solute, which leads to a so-called reaction field that also effects the shielding of the protons. However, we shall not consider this further here.

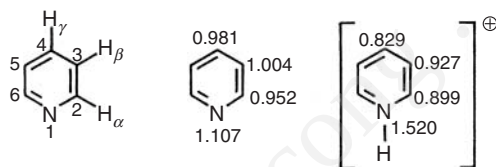
For practical applications with point charges in unsaturated and aromatic molecules, Eq. (5.17) has been derived from Eq. (5.16) [17]:

$$\Delta\sigma(\text{ppm}) = 0.125 \sum_i \frac{\Delta\rho_i}{R_i^2} \cos\theta_i - 0.170 \left(\sum_i \frac{\Delta\rho_i}{R_i^2} \right)^2 \quad (5.17)$$

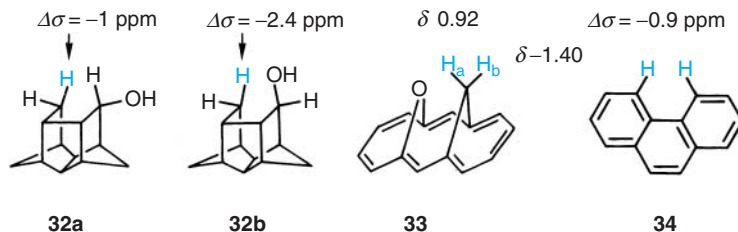
Here, $\Delta\rho_i$ is the excess elementary charge at atom i relative to $\rho = 1.0$, R_i (in nm) is the distance between atom i and the hydrogen atom, and θ is the angle between the C-H bond and the distance vector i, H . From the first term we can derive a verification of Eq. (5.2): for a C-H bond and a hypothetical charge excess of $\Delta\rho = 1.0$ at the carbon we find with $R = 0.11$ nm and $\theta = 0^\circ$ that $\Delta\sigma = 10.3$ ppm.

Exercise 5.5

Determine by means of Eq. (5.17) the expected change in the shielding of the γ -proton in the pyridinium ion on the basis of the indicated charge distribution. Consider the molecule to be a regular hexagon with bond lengths of 0.140 nm (C-C) and 0.110 nm (C-H).



The so-called *quadratic field effect* included in Eq. (5.16), BE^2 , is closely related to the van-der-Waals effect that arises when a steric interaction exists between a proton and a neighboring group (possibly another proton). In this case we predict that the electron cloud around the proton becomes deformed. The diminished spherical symmetry of the electron distribution causes a paramagnetic contribution to the shielding constant (cf. p. 31) that always results in a shift to higher frequency. First indications for this short-range effect, which follows a $1/R^6$ dependence, came from the observation of ^1H NMR gas-to-solution shifts $\Delta\delta$ of the order of 0.2–0.7 ppm for nonpolar molecules like cyclopentane in various solvents. Of other known examples the deshielding of the indicated protons in compounds **32–34** might be attributed substantially to the van-der-Waals effect. Heavy atoms with a large electron shell can show much larger van-der-Waals contributions to the chemical shift – for fluorine even up to 35 ppm.



5.1.8

Chemical Shifts through Hydrogen Bonding

As mentioned on page 37, no distinct region on the δ scale can be assigned to the resonances of exchangeable protons of OH or NH groups since the position of these resonance signals is strongly dependent upon medium and temperature. In general, the formation of hydrogen bonds leads to significant deshielding and thus shifts to high frequency, although formally the electron density and with it the shielding at the proton should be increased through the interaction with the free electron pair of the acceptor atom. The electrical dipole field of the hydrogen bond, which is formulated as a pure electrostatic attractive bond, however, appears to have the opposite effect. As is shown in Figure 5.20 for chloroform, there is a linear relationship between the deshielding of the chloroform proton and the dipole moment of the nonbonding orbitals of various acceptor atoms in different classes of compounds.

In the case of nitriles the chloroform proton resides within the shielding region of the triple bond (cf. p. 97) as shown in **35** (see next page). Accordingly, the data for nitriles in Figure 5.20 were corrected for the additional diamagnetic shift due to this arrangement. A similar effect exists in benzene, which acts as a π -electron donor. The chloroform proton in the benzene–chloroform complex (**36**) is therefore strongly shielded. Measurements in an inert solvent yield, at infinite dilution, for aromatics like benzene and 1,6-methano[10]annulene (**17**) shielding effects of 1.2 ppm for the chloroform proton. Even cyclohepta-1,3,5-triene shows $\Delta\sigma = +0.25$ ppm, whereas other olefins like cyclohexa-1,3-diene or cyclooctatetraene yield small

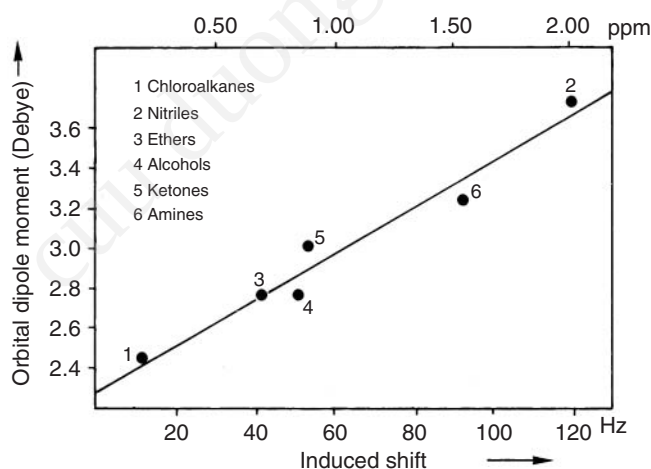


Figure 5.20 Correlation between the induced shift to higher frequency of the chloroform proton resonance frequency and the orbital dipole moment for different proton-acceptor atoms [18].

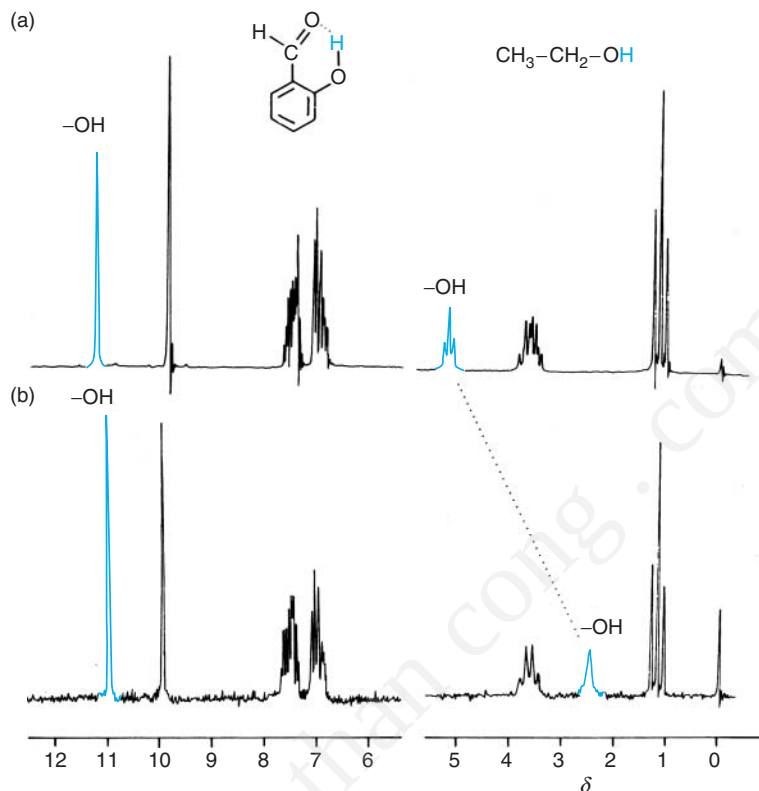
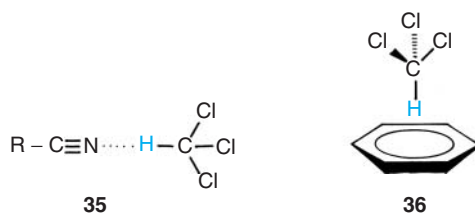


Figure 5.21 Concentration dependence of the proton resonance frequency of the hydroxyl protons of salicylaldehyde and ethanol: (a) neat and (b) 5% by volume in CCl₄.

negative $\Delta\sigma$ values of -0.2 and -0.15 ppm, respectively. This is, therefore, another simple test for the magnetic properties of cyclic π -systems.



Intra- and intermolecular hydrogen bonds can easily be distinguished by means of NMR spectroscopy as only in the latter case is the resonance frequency of the hydroxyl or amino proton strongly concentration dependent. As an illustration of this, the spectra of salicylaldehyde and ethanol at different concentrations are compared in Figure 5.21.

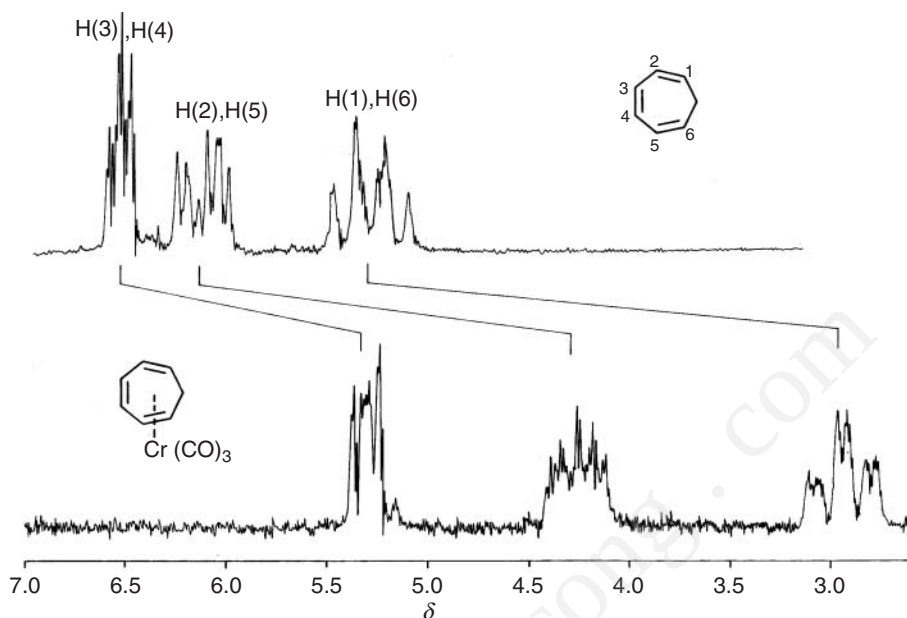


Figure 5.22 NMR spectra of the olefinic protons in cyclohepta-1,3,5-triene and in cyclohepta-1,3,5-triene chromium tricarbonyl.

5.1.9

Chemical Shifts of Protons in Organometallic Compounds

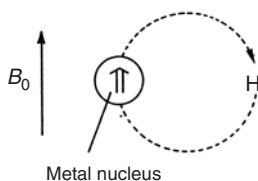
In Section 5.1.2 we discussed the shielding and deshielding of protons in charged species as a result of the electron density at the neighboring carbon atom. In this section the effect of metal carbonyl groups, as illustrated by the spectra of metal carbonyl π -complexes of olefins and aromatic compounds, will be described with reference to a few examples. As shown in Figure 5.22, complex formation leads to shielding of the protons at the coordinated carbon atoms of about 2–3 ppm. Different factors most probably cause this shielding. Certainly the presence of the metal plays a substantial role but the effect of the anisotropy of the metal carbonyl group and back-donation of electron density from the metal to the double bond may also be involved. Additional examples are compiled in Table 5.3 (p. 120). The corresponding proton resonances of the free ligands are collected in Table A.1 in the Appendix (p. 650 ff.).

Especially strong shieldings are observed for protons that are *directly* bonded to metals. Thus the resonance frequencies of the protons in transition metal hydride complexes are found in the region $\delta < 0$ ppm and in a few cases even at values up to -30 ppm. If in the complex the metal is positively charged the shielding is reduced, as expected. In protonated transition metal carbonyl complexes the formation of a metal–hydrogen bond, in contrast, again leads to an increased shielding of the proton. Table 5.3 also shows a few examples of these cases.

Table 5.3 Proton resonances in metal carbonyl π -complexes and in metal hydrides.

		δ 5.30 4.18 2.67	
	δ 4.89 δ 1.46 δ -0.03		δ 3.08 δ 4.94
δ 7.37 7.53 6.09 5.48		δ 7.07 7.30 7.49 5.68 4.92	
	δ -12.3		δ -6.3
	δ -2.1		δ -10.5
	δ -28.1		δ -18.6

To a large extent the asymmetrical charge distribution in the valence orbitals of the metals is responsible for the strong diamagnetic shift of the proton resonance in these compounds. The resulting paramagnetic moment deshields the metal nucleus but shields the proton as indicated below.



5.1.10

Solvent Effects

On page 86 the influence of the solvent as a factor contributing to the magnitude of the proton screening constant was mentioned, and here we want to include a brief

discussion of the significance of solvent effects that supplements the exposition made already in Section 2 of Chapter 4. In general, it can be assumed that all of the effects that we have discussed up to now on an *intramolecular* basis also play a role at the *intermolecular* level. It has been observed, for example, that the resonance signals of substances dissolved in aromatic solvents appear at higher field than when dissolved in aliphatic solvents. This effect has been ascribed to the diamagnetic ring current of benzene and its derivatives and stimulated the use of aromatic solvent induced shifts (ASISs) for spectral analysis. An example was shown on page 73. A similar influence of neighboring molecules, however, associated with both shielding and deshielding can be expected from the effect of the diamagnetic anisotropy of multiple bonds or the electrical field effect of molecules with large dipole moments. Solvent effects are particularly significant when intermolecular interactions in the solvent lead to the formation of weak complexes. On the basis of dipole–dipole or van-der-Waals interactions, certain steric orientations become favored with respect to others and, as a result, specific changes can be observed in the resonance frequencies of individual protons in the solute. This in turn can be used to obtain insight into the structure of such complexes, and NMR spectroscopy has proven to be an important method for the study of intermolecular interactions. The largest effects are found if data from the gas-phase are compared to data of the same compounds measured in solution.

For proton resonances the solvent effects are usually smaller than 1 ppm. We have already considered special applications and the consequences for the resonance frequency of the reference substance in Chapter 4. If one wishes to avoid complications caused by solvent effects, the use of “inert” solvents such as carbon tetrachloride and cyclohexane is recommended. On the other hand, concentration effects can be eliminated if several measurements at different sample concentrations are made and the data are extrapolated to infinite dilution. Only with the development of data accumulation by the Fourier-transform method have measurements become feasible for compounds with high vapor pressures in the gas phase, where intermolecular interactions are minimized.

5.1.11

Empirical Substituent Constants

The observation that the influence of substituents on the ^1H resonance frequency is to a first approximation *additive* was of great importance for the early interpretation of ^1H NMR spectra. On this basis it has been possible to derive empirical substituent constants $S(\delta)$ or *increments*, also known as substituent-induced chemical shifts (SCS), that in general allow satisfactory predictions of resonance frequencies. Of course, exceptions are to be expected when, because of strong electronic or steric interactions between the substituents, the condition for the additivity of $S(\delta)$ values, namely, their independence from the remainder of the molecule, is violated. Today the importance of such increment schemes has been diminished by the progress made in experimental assignment techniques, especially after the introduction of two-dimensional methods. It is thus more reliable to use these

experimental techniques to assign ^1H resonances. For completeness we mention in the Appendix (p. 652) the Shooley rule that was derived for aliphatic compounds, and shift increments for substituted benzenes.

5.1.11.1 Tables of Proton Resonances in Organic Molecules

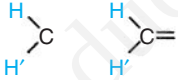
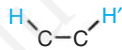
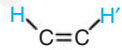
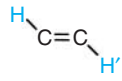
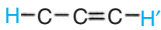
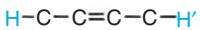
Proton resonance frequencies for different classes of organic compounds are tabulated in Table A.1 in the Appendix (pp. 650 ff.). This general survey can be used as a data source and as an aid in becoming familiar with the resonance frequencies to be expected in various situations.

5.2

Proton–Proton Spin–Spin Coupling and Chemical Structure

This section is devoted to discussion of correlations between scalar ^1H , ^1H coupling constants and chemical structure. A general survey of this subject has already been given in Table 3.2 (p. 62). For the following discussion, which deals in detail with the different types of spin–spin interactions, we shall use a classification indicating the number of bonds between the coupled nuclei (Table 5.4). Thus we differentiate between *geminal*, *vicinal*, and *long-range* coupling depending on whether the coupling occurs over *two*, *three*, or *more* bonds. The number of bonds, n , is used as a superscript in front of the symbol J . In unsaturated systems the position of the coupled nuclei relative to the double bond (*cis* or *trans*) can be indicated simultaneously by means of a subscript. In principle, there is no limit to the

Table 5.4 Classification of spin–spin coupling over n bonds.

Type of coupling	Classification	n	Symbol
	Geminal	2	^2J
	Vicinal	3	^3J
	Vicinal	3	$^3J_{cis}$
	Vicinal	3	$^3J_{trans}$
Long-range coupling:			
	Allylic	4	^4J
	Homoallylic	5	^5J

number of bonds over which coupling occurs, although it is seldom effective over more than five bonds and, in general, decreases in magnitude as n increases. Since in the following we deal exclusively with $^1\text{H}, ^1\text{H}$ coupling constants, the coupled nuclei, $^1\text{H}, ^1\text{H}$, are dropped for clarity and only the symbol ^nJ is used. Scalar coupling constants are independent of the magnetic field B_0 and are measured in hertz (Hz) (cf. p. 43). In addition, note that the signs of all ^3J and most ^5J values are positive while for ^2J and ^4J values they can be of either sign. For a systematic discussion of the dependence of the coupling constants on structure it is essential to consider their signs. How the sign of a coupling constant can be determined will be discussed in Chapter 6.

5.2.1

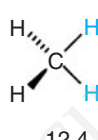
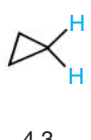
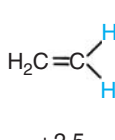
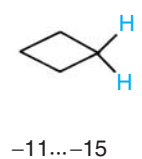
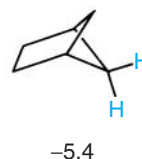
The Geminal Coupling Constant (^2J)

Following the spin–spin coupling over one bond in the hydrogen molecule, which amounts to 276 Hz and is of theoretical interest, the geminal coupling constants of CH_2 groups with values between -23 and $+42$ Hz form the class with the largest spin–spin interactions between protons. Many factors are responsible for the magnitude and the sign of ^2J .

5.2.1.1 Dependence on the Hybridization of the Methylene Carbon

In going from an sp^3 hybridized methylene group, as it exists in methane, to sp^2 hybridization in ethylene, the geminal coupling constant changes from -12.4 to $+2.5$ Hz. The coupling in the methylene group of cyclopropane, because of the special bonding situation in the three-membered ring,³⁾ has an intermediate value. Other strained ring systems exhibit ^2J values of up to -5.0 Hz while the geminal coupling in cyclobutane is not much different from that in methane (Table 5.5).

Table 5.5 Dependence of geminal $^1\text{H}, ^1\text{H}$ coupling (Hz) on carbon hybridization.

		
-12.4	-4.3	+2.5
		
-11...-15	-5.4	

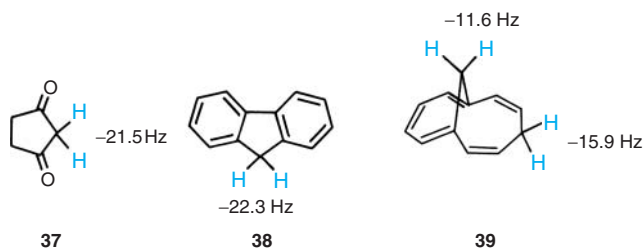
3) The Walsh model constructs cyclopropane with three CH_2 groups with sp^2 -hybridized carbon where the carbon $2p_z$ orbitals overlap to form a three-membered ring. We shall come back to this model again in Chapter 11.

5.2.1.2 Effect of Substituents

The ^2J values are subject to the influence of both α and β substituents. Table 5.6 presents characteristic data. It can be seen that an electronegative substituent at the methylene group in question leads to a positive change in the coupling constant. For sp^3 hybridized methylene groups the absolute value of the coupling constant therefore decreases. In polysubstituted methanes the effect of substituents, to a first approximation, is additive. The influence of oxygen in ethylene oxide results in a positive coupling constant for the methylene protons. The especially large positive value in formaldehyde is due to the additional influence of the non-bonded electron pairs on the oxygen atom. The steric orientation of *nonbonding electron pairs* relative to the orientation of the C–H bonds under consideration is also of significance in the case of sp^3 hybridized methylene groups. Comparison of the ^2J values in 1,3-dioxane with those in the conformationally more rigid formaldehyde dioxolane illustrates this effect. The lone pair effect is largest for an orientation parallel to the H,H distance vector.

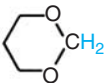
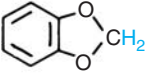
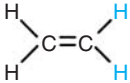
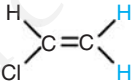
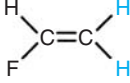
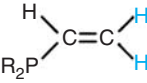
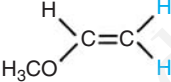
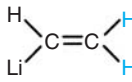
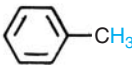
In contrast to the situation in the case of α -substituents, an electronegative β -substituent leads to a negative change in the coupling constant. The ^2J values in substituted ethylenes clearly indicate this. Conversely, an electropositive substituent such as lithium induces a positive change for the coupling constant that is found to be +7.1 in vinyl lithium. *Neighboring π -bonds* also have a considerable influence on the magnitude of geminal coupling constants. They cause a negative change, that is, the absolute value of the constants increases. Thus, the magnitude of the geminal coupling constant changes from 12.4 Hz in methane to 20.4 Hz in malononitrile. Notably, the effect of neighboring π -bonds on geminal coupling depends on the stereochemistry of the system under consideration, just as in the case of the effect of nonbonding electron pairs mentioned above. Theoretical studies and experimental data show that the effect of a neighboring π -bond on the geminal coupling constant is a function of the angle ϕ between the π -orbital and the C–H bond. This dependence is clearly illustrated in Figure 5.23 (p. 126). The largest effect is observed when the neighboring orbital and the distance vector between the two protons of the methylene group are parallel.

The ^2J values in cyclopentanedione (**37**) and fluorene (**38**) confirm this prediction, as does the relative magnitude of the two constants found for compound **39**.



The dependence of ^2J on the hybridization of the carbon atom mentioned earlier leads one to expect that a characteristic correlation also exists involving the H–C–H

Table 5.6 Influence of substituents on geminal $^1\text{H}, ^1\text{H}$ coupling constants (Hz).

1. α -Substitution		
CH_4	-12.4	 +5.5
CH_3Cl	-10.8	$\text{RN}=\text{CH}_2$ +16.5
CH_3Cl_2	-7.5	$\text{O}=\text{CH}_2$ +42.2
 +2.0		 -6
 ± 1.5		 0
2. β -Substitution		
 +2.5		 -1.4
 -3.2		 +2.0
 -2.0		 +7.1
3. Adjacent π bonds		
CH_3CN	-16.9	 -14.5
$\text{CN}-\text{CH}_2-\text{CN}$	-20.4	

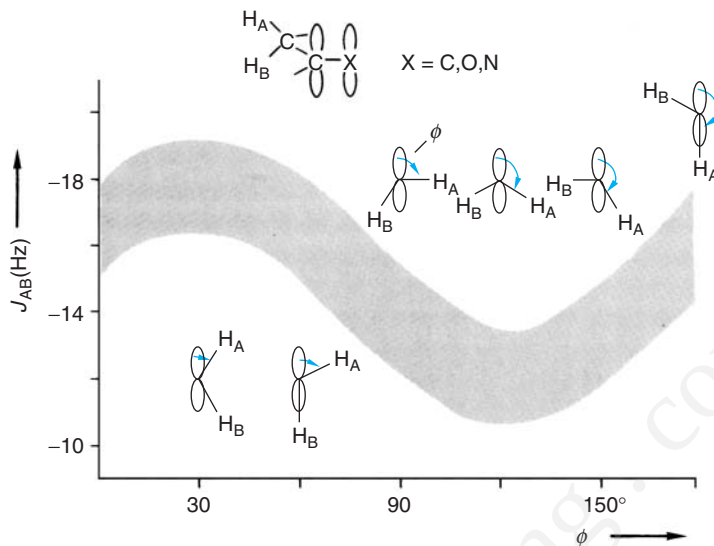


Figure 5.23 Perturbation of geminal $^1\text{H}, ^1\text{H}$ coupling by neighboring π -orbitals [19].

bond angle that might be used to obtain information on the corresponding C–C–C bond angle as well. However, as a result of the variety of substituent effects to which the geminal coupling constants are subject, such a relation cannot be formulated with the accuracy necessary for reliable predictions.

5.2.1.3 A Molecular Orbital Model for the Interpretation of Substituent Effects on ^2J

Let us now consider a MO model allowing the rationalization of substituent effects for geminal $^1\text{H}, ^1\text{H}$ coupling constants discussed above. It is based on the theoretical result that the coupling constant, $J(\text{H}, \text{H}')$, between two protons is proportional to the so-called mutual atom–atom polarizability, $\pi_{h,h'}$, of the two hydrogen 1s orbitals:

$$J(\text{H}, \text{H}') \propto \pi_{h,h'} \quad (5.18)$$

This polarizability is defined in MO theory through the relation:

$$\pi_{h,h'} = -4 \sum_i^{\text{occ.}} \sum_j^{\text{unocc.}} \frac{c_{ih} c_{ih'} c_{jh} c_{jh'}}{E_j - E_i} \quad (5.19)$$

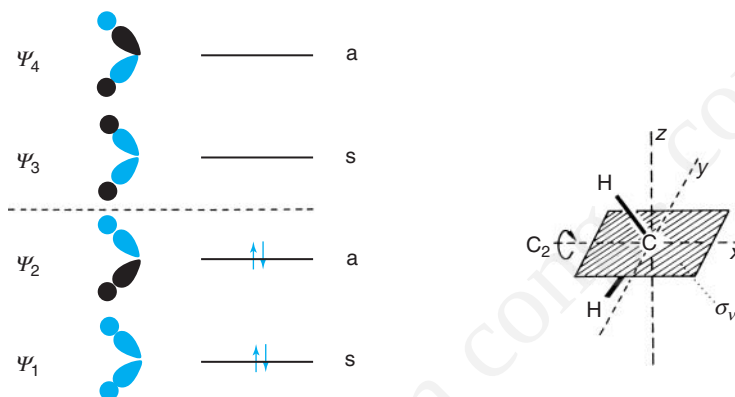
where c_{ih} , $c_{ih'}$, etc. are the coefficients of the 1s orbitals h and h' in the MOs ψ_i and ψ_j , which, as is well known, are formed by a linear combination of atomic orbitals:

$$\psi_i = c_{iA} \phi_A + c_{iB} \phi_B + \dots + c_{iN} \phi_N \quad (5.20)$$

E_j and E_i are the orbital energies and the summation includes all occupied and unoccupied MOs. Within the MO theory, atom–atom polarizabilities π_{ij} can be

used, for example, to determine the effect of a perturbation of the coulomb integral at the center i on the electron density at atom j .

For a CH_2 group we can construct MOs from four atomic orbitals if we use the two hydrogen 1s orbitals and two carbon hybrid orbitals, which can be either sp^2 or sp^3 . The following MO energy level diagram is obtained in which only the different signs of the coefficients c_{ih} , $c_{ih'}$, etc. symbolized by means of different color, are given:



The energy sequence of the MOs $\Psi_1 - \Psi_4$ follows from the number of bonding interactions between atomic orbital functions of the same sign. Relative to the symmetry plane σ_v of the CH_2 group the MOs can further be classified as either symmetric (s, reflection of Ψ_i yields Ψ_i) or antisymmetric (a, reflection of Ψ_i yields $-\Psi_i$).

The CH_2 moiety possesses four bonding electrons. In the ground state Ψ_1 and Ψ_2 are doubly occupied. Decisive in determining the magnitude of the coupling constants according to the proportionality [Eq. (5.18)] are the four possible electronic transitions A–D between the orbitals i and j . According to the signs of the coefficients c_{ih} , $c_{ih'}$, c_{jh} , and $c_{jh'}$, they lead with Eq. (5.19) to contributions $\pi_{h,h'}$ to the coupling with the following signs:

- A: transition from Ψ_1 to Ψ_3 : –
- B: transition from Ψ_1 to Ψ_4 : +
- C: transition from Ψ_2 to Ψ_3 : +
- D: transition from Ψ_2 to Ψ_4 : –.

In deriving the substituent effects on $^2J(\text{H}, \text{H}')$ it is only necessary to investigate how the coefficients c_{ih} and $c_{ih'}$ are influenced by substitution. In so doing it is important to note that the interaction between an orbital of the substituent and the MOs of the CH_2 group is governed by symmetry. Interaction is allowed only when both have the same symmetry relative to the symmetry plane σ_v shown above. Inductive effects through σ orbitals, oriented along the x -axis and therefore symmetric with respect to σ_v , will thus lead to changes in the coefficients

in the symmetrical orbitals Ψ_1 (and Ψ_3 , respectively) while a hyperconjugative interaction with a p_z orbital that is antisymmetric with respect to σ_v is restricted to the antisymmetric orbitals Ψ_2 (or Ψ_4 , respectively):



For substituents with a $-I$ effect we therefore expect a charge transfer out of Ψ_1 that will result in a decrease in c_{1h} and $c_{1h'}$. Since the sum of all the atomic orbitals employed in the formation of the MOs must remain constant, this means that at the same time the coefficients c_{3h} and $c_{3h'}$ in the symmetrical antibonding orbital Ψ_3 must become larger. According to Eqs (5.19) and (5.18) the contribution B to the geminal coupling decreases while that of C increases. A and D remain to a first approximation unchanged. Because of the smaller energy difference $E_3 - E_2$ the increase in C predominates and ^2J must become more positive. This is observed experimentally (Table 5.6). Obviously the opposite predictions apply for the $+I$ effect.

Following similar reasoning it can be predicted that in case of a *hyperconjugative* interaction *electron withdrawal* will decrease the contribution C and increase the contribution B while, to a first approximation, A and D are again unaffected. Because of the smaller energy difference for C the change in this contribution assumes greater importance, and the coupling becomes more negative. This prediction has also been confirmed experimentally (Table 5.6; Figure 5.23).

The striking increase in the magnitude of the geminal coupling in formaldehyde is an especially impressive example of the applicability of this simple MO model. Here the $-I$ effect of the oxygen atom and the hyperconjugative charge transfer from the nonbonding electron pairs on oxygen to the CH_2 group augment one another. Similarly, hyperconjugation in cyclic ethers leads to a positive change in ^2J . Finally, the conformational dependence of the effect of π -bonds and free electron pairs on ^2J described above can also be understood because of the fact that the electronic interaction of these groups with Ψ_2 obeys a $\cos \phi$ relation where ϕ is the angle between the z -axis and the axis of the substituent orbital.

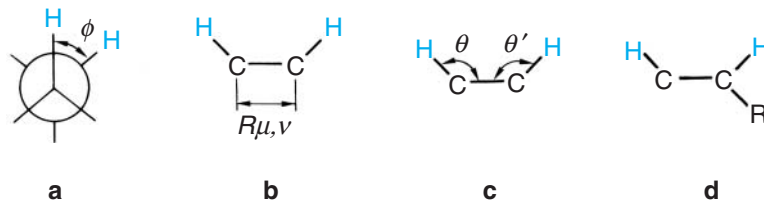
5.2.2

The Vicinal Coupling Constant (^3J)

There are extensive data on vicinal coupling constants and their relation to chemical structure. In agreement with the results of theoretical calculations it has been shown that the magnitude of ^3J , the sign of which was earlier found to be always positive, depends in essence upon four factors:

- 1) The dihedral angle, ϕ , between the C–H bonds under consideration (**a**);
- 2) C,C bond length, $R_{\mu\nu}$ (**b**);

- 3) H–C–C valence angles, θ and θ' (c);
- 4) electronegativity of the substituent R on the H–C–C–H moiety (d).



5.2.2.1 Dependence on the Dihedral Angle

The dependence of vicinal coupling constants on the dihedral angle, ϕ , first theoretically predicted independently by M. Karplus and H. Conroy, is represented in Figure 5.24. The curve shown – now known as a *Karplus curve* – is described by the relation:

$$^3J = A + B \cos \phi + C \cos 2\phi \quad (5.21)$$

where A , B , and C are constants with the values 4.22, -0.5 , and 4.5 , respectively. The experimental findings are in good qualitative agreement with calculations that were worked out for a H–C–C–H fragment and have since been confirmed by more elaborate theoretical methods. Experimental experience and more recent calculations have shown, however, that the ^3J values for $\phi = 0^\circ$ and 180° in general are about 2–4 Hz larger than predicted using the values given above for A , B , and C , and the new constants $A = 7$, $B = -1$, and $C = 5$, which improve the results, have been proposed. The original prediction that $^3J_{180} > ^3J_0$ is always

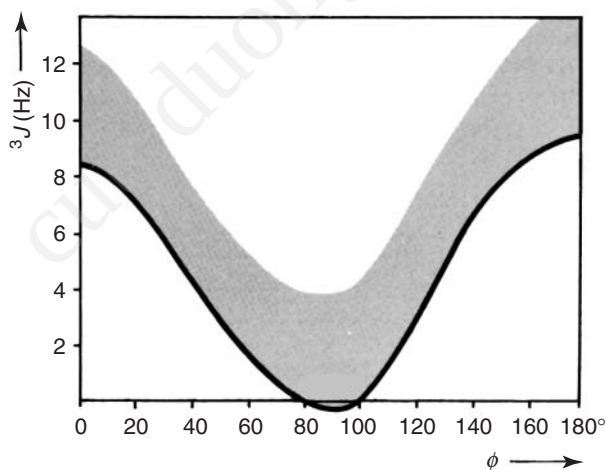


Figure 5.24 Karplus curve for the dependence of vicinal $^1\text{H}, ^1\text{H}$ coupling on the dihedral angle ϕ : black line, theoretical curve; shaded area, range of empirical results.

confirmed. Furthermore, specific Karplus equations have been derived that were experimentally calibrated for certain classes of compounds. It was also shown that Karplus-type equations not only hold for $^1\text{H}, ^1\text{H}$ coupling constants but are also valid for vicinal spin–spin interactions between other pairs of nuclei, such as, for example, $^{13}\text{C}, ^1\text{H}$, $^{19}\text{F}, ^{19}\text{F}$, or $^{31}\text{P}, ^1\text{H}$. Equation (5.21) thus describes a fundamental property of vicinal J coupling.

A series of important regularities is explained by the Karplus curve (Table 5.7). For example, in olefinic systems the coupling of protons in a trans situation is always greater than that between protons in a cis situation. A clear distinction between cis–trans isomers can therefore be made. In 1,2-disubstituted ethane the corresponding sequence $J_{\text{gauche}} < J_{\text{trans}}$ applies. Consequently, in the chair conformation of cyclohexane the coupling between two axial protons is larger than that between two equatorial protons or between an equatorial and an axial proton: $J_{\text{aa}} = 13.1$, $J_{\text{ae}} = 3.7$, and $J_{\text{ee}} = 3.0$ Hz (generally: $J_{\text{aa}} > J_{\text{ea}} \approx J_{\text{ee}}$) (see also Table A.4, p. 654 ff.). This is an important criterion in the conformational analysis of cyclohexane derivatives and carbohydrates. Thus, in the β -form of glucose the anomeric proton possesses, in addition to the higher shielding mentioned earlier (p. 96), a larger vicinal coupling constant than in the α -form, 7.4 versus 3.0 Hz (Table 5.7).

Special circumstances exist in the case of the three-membered ring. Here the dihedral angle for cis protons is 0° and that for trans protons is $\sim 130^\circ$. According to Figure 5.24 we would expect that $^3J_{\text{cis}} > ^3J_{\text{trans}}$, and this is always found experimentally for a pair of cis–trans isomers of a substituted cyclopropane. Analogous relations apply with oxirane and aziridine. For cyclobutane and cyclopentane derivatives, because of their greater flexibility, the dihedral angles are less well defined and an unequivocal assignment of the configuration on the basis of the ^3J values is, in general, not possible.

5.2.2.2 Dependence upon the C–C Bond Length, $R_{\mu\nu}$

In Figure 5.25 (p. 132) the vicinal coupling constants in unsaturated six-membered rings are plotted against the bond lengths, $R_{\mu\nu}$ (in nm) that were determined by X-ray structural analyses.

The dihedral angle in the compounds under consideration can be assumed to be 0° and, since for hydrocarbons no substituent effects are expected, the linear relation:

$$^3J = -351.0R_{\mu\nu} + 56.65 \quad (5.22)$$

can be understood as the result of changes in the C–C bond length. The ^3J values are therefore *very sensitive* to small differences in the C–C bond length and, if other factors are considered to be constant, can give information concerning the degree of bond alternation in cyclic π -systems. Since the π -bond order, $P_{\mu\nu}$, of HMO theory correlates linearly with the bond length $R_{\mu\nu}$, there also exists a linear relation between $P_{\mu\nu}$ and the ^3J values. For benzenoid aromatic compounds Eq. (5.23) holds:

$$^3J = 12.47P_{\mu\nu} - 0.71 \quad (5.23)$$

Table 5.7 Dependence of vicinal $^1\text{H}, ^1\text{H}$ coupling (Hz) on the dihedral angle, ϕ .

11.0	16.0	3.0	7.4	
15.8	12.3	3.9	9.0	9.3
	J_{12} (^2J) -12.0 J_{23} ($^3J_{gauche}$) 3.2 $J_{24} = J_{13}$ ($^3J_{gauche}$) 4.0 J_{14} ($^3J_{trans}$) 12.3			
<i>meta</i> -Cyclophan		J_{cis} 9.0	J_{cis} 9.4	
		J_{trans} 4.4	J_{trans} 4.2	
3.8	8.4	J_{cis} 11.2		
		J_{trans} 8.0		
$J_{12} = J_{34}$ ($^3J_{cis}$) 9.0	J_{12} ($^3J_{cis}$) 9.8			
J_{14} ($^3J_{trans}$) 10.0	J_{34} ($^3J_{cis}$) 8.6			
J_{23} ($^3J_{trans}$) 3.3	$J_{14} = J_{23}$ ($^3J_{trans}$) 6.7			

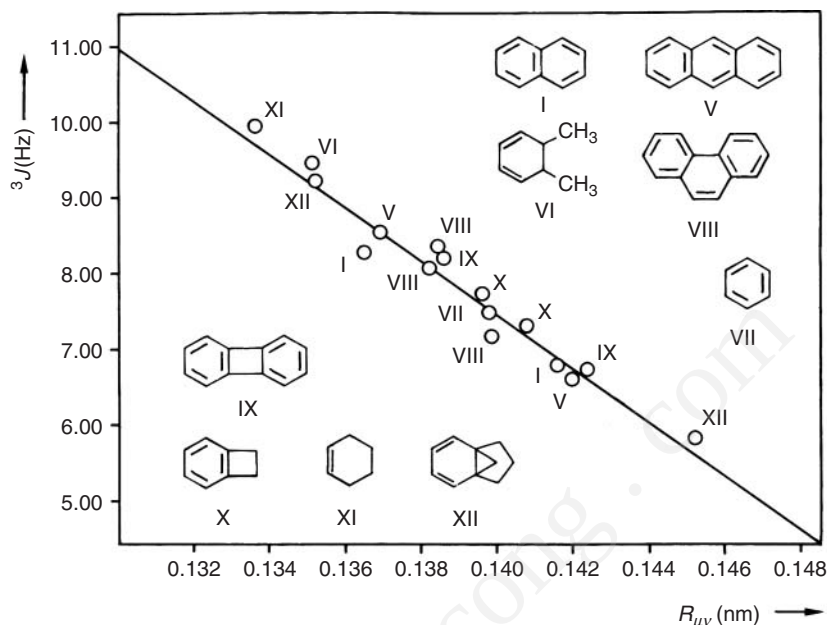


Figure 5.25 Relation between the vicinal $^1\text{H}, ^1\text{H}$ coupling and the C–C bond length, $R_{\mu\nu}$, in unsaturated six-membered rings [20]: I, naphthalene; V, anthracene; VI, *cis*-5,6-dimethylcyclohex-1,3-diene; VII, benzene; VIII, phenanthrene; IX, biphenylene; X, benzocyclobutene; XI, cyclohexene; and XII, tricyclo[4.3.1.0.^{1,6}]-2,4-decadiene.

Similar relations, but with different constants due to HCC valence angle changes (see below), have been derived from planar five- and seven-membered rings:

1) Five-membered rings:

$$^3J = -322.6R_{\mu\nu} + 48.45 \quad (5.24)$$

$$^3J = 7.12P_{\mu\nu} - 1.18 \quad (5.25)$$

2) seven-membered rings:

$$^3J = 367.4R_{\mu\nu} + 60.68 \quad (5.26)$$

$$^3J = 21.91P_{\mu\nu} - 3.85 \quad (5.27)$$

5.2.2.3 Dependence on HCC Valence Angles

The importance of the HCC valence angles for the magnitude of ^3J is best demonstrated with the vicinal *cis* coupling constants across the double bond in cyclic mono-olefins with different ring sizes. Here, a constant dihedral angle of 0° and the absence of substituent effects may be assumed. As is shown in Table 5.8 there is a steady increase in $^3J_{\text{cis}}$ on passing from cyclopropene to larger rings. Values as large as those found in acyclic olefins are observed in the eight-membered

Table 5.8 Dependence of vicinal $^1\text{H}, ^1\text{H}$ coupling (Hz) on the HCC angles θ and θ' .

	0.5 – 1.5		8.8 – 11.0		4.0
	2.5 – 3.7		9 – 12.6		7.5
	5.1 – 7.0		10 – 13		10.3

rings. We therefore conclude that a decrease in the HCC valence angles θ and θ' leads to an increase in ^3J . This observation is also supported by data from aromatic compounds.

5.2.2.4 Substituent Effects

In both saturated and unsaturated systems a decrease in the vicinal coupling is observed when an electronegative substituent is introduced at the H-C-C-H moiety. For substituted ethanes the relation between the change of electronegativity, $\Delta E = E(\text{X}) - E(\text{H})$, caused by the replacement of a hydrogen atom with a group X, and the coupling constant is given by:

$$^3J = 9.41 - 0.80\Delta E \quad (5.28)$$

For substituted ethylenes similar relations result:

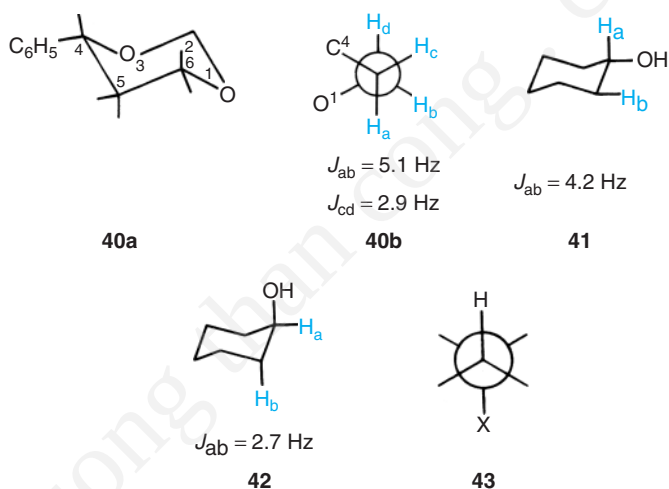
$$^3J_{\text{trans}} = 19.0 - 3.3\Delta E \quad (5.29)$$

$$^3J_{\text{cis}} = 11.7 - 4.7\Delta E \quad (5.30)$$

The data given below serve to illustrate these effects.

	^3J		$^3J_{\text{cis}}$	$^3J_{\text{trans}}$
$\text{H}_3\text{C}-\text{CH}_2-\text{Li}$	8.9		19.3	23.9
— SiR_3	8.0		14.6	20.4
—CN	7.2		10.0	16.9
—Cl	7.2		7.3	14.6
— OCH_2CH_3	7.0		7.0	14.1
— OR_2^+	4.7		4.7	12.8

As the different constants in Eqs (5.29) and (5.30) intimate, the steric orientation of the substituent X in the H–C–H moiety is also of significance. An example is found with 4-phenyl-1,3-dioxane (**40**). For this molecule conformation **40a** can be assumed because of the bulky phenyl substituent. The arrangement about the C5–C6 bond is represented by the Newman projection **40b**. Despite the possible flattening of the ring the dihedral angles ϕ_{cd} and ϕ_{ab} are equal. Nevertheless, J_{cd} is different from J_{ab} , as the experimental values given in formula **40b** show. Accordingly, the electronegativity effect of the oxygen seems to predominantly affect the H_d, H_c proton pair. Other findings, such as the coupling constants in the isomeric cyclohexanols (**41**) and (**42**), are consistent with the observation that the maximum effect of a substituent on the vicinal coupling constant results when the substituent is trans to one of the protons at the neighboring CH_2 group (**43**).



The torsional angle dependence of the substituent effect on vicinal coupling constants in substituted ethanes derived from these data is confirmed by MO calculations. The Karplus curves for ethane and fluoroethane shown in Figure 5.26 indicate that the introduction of an electronegative substituent shifts the curve so that an increase in the ^3J value results in some conformations (e.g., $\phi = 240^\circ$, $\theta = 120^\circ$). There are also experimental indications of this. It can be shown further that the substituent effect integrated over a complete rotation must lead to a diminution of the coupling constant that is obtained as the average of the couplings in all possible conformations. This conforms to the statement of the empirical relation [Eq. (5.28)].

Interestingly, theoretical investigations revealed a charge alternation for the continuation of the inductive effect along a carbon chain, contrary to the earlier belief, where an attenuation, but not a charge alternation, was implied. An alternation of the sign for ΔJ , the change of the coupling constant, can thus be expected.

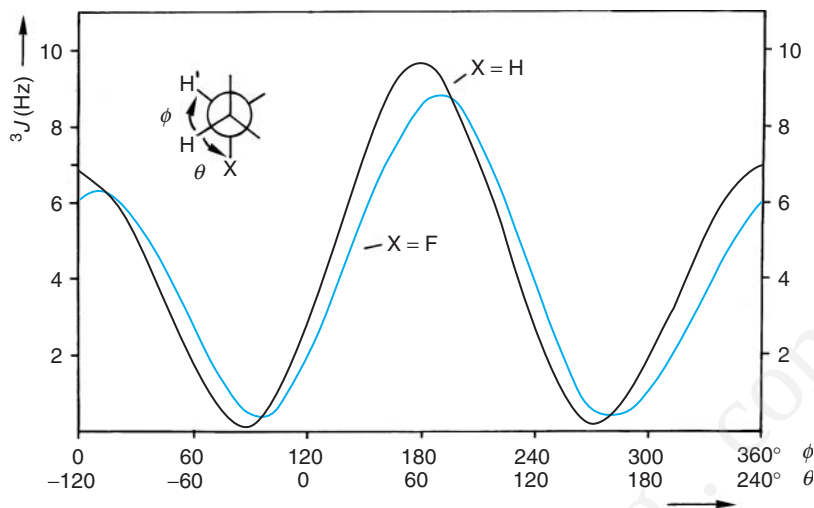
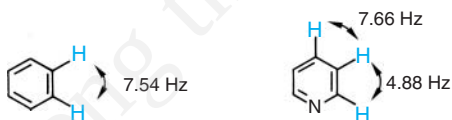


Figure 5.26 Effect of substituents on the vicinal $^1\text{H}, ^1\text{H}$ coupling in ethane as a function of torsional angle as derived from MO calculations [21].

These relations have been especially thoroughly investigated for monosubstituted benzenes. Figure 5.27 (p. 136) shows the increase found for the J_{23} coupling with the electronegativity of the substituent at C1. Similarly, a comparison of the ^3J values in benzene and pyridine is most illustrative.



While the influence of a substituent on the value of ^3J in a $\text{HC}-\text{CH}-\text{C}_\alpha\text{X}$ unit is clearly detectable, the effect of substituents three bonds away from the $\text{HC}-\text{CH}$ fragment, as in the unit $\text{HC}-\text{CH}-\text{C}_\alpha-\text{C}_\beta\text{X}$, can be demonstrated only through very precise measurements. Exact analysis of the spectra of monosubstituted benzenes leads to the relation:

$$^3J = 7.63 + 0.51\Delta E_\alpha - 0.10\Delta E_\beta \quad (5.31)$$

which confirms the alternating sign for ΔJ .

A special effect of substituents on vicinal coupling constants is observed in transition metal complexes of olefins and arenes. Here the $^3J_{\text{cis}}$ values at the complexed double bonds decrease upon complexation by about 2–3 Hz and the decrease in iron carbonyl complexes is larger than in complexes of either chromium or molybdenum. Table 5.9 (p. 136) presents data for a few of these compounds, and for the free ligands. In the iron carbonyl complexes of cyclobutadiene derivatives, the influence of the metal carbonyl groups means that the small vicinal coupling constant of the ring protons becomes zero in the complex.

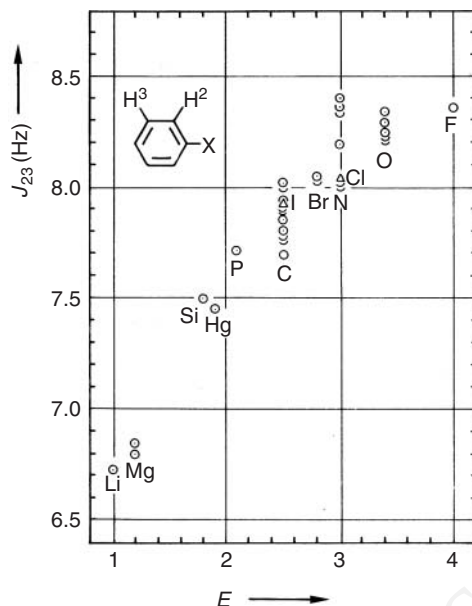


Figure 5.27 Dependence of the vicinal $^1\text{H}, ^1\text{H}$ coupling on the electronegativity of substituents in benzene derivatives [22].

Table 5.9 Vicinal $^1\text{H}, ^1\text{H}$ coupling constants (Hz) in transition metal complexes with organic ligands.

9.4	6.6	0	
J_{12} 8.9	8.4	8.2	7.8
J_{23} 5.5	6.8	7.0	5.0
J_{34} 11.2	8.4	8.5	7.8
J_{12} 8.3	6.7	6.9	7.2
J_{23} 6.9	6.1	8.3	8.1

5.2.3

Long-Range Coupling Constants (^4J , ^5J)

While the geminal and vicinal coupling constants usually have values of between 5 and 20 Hz and lead to easily recognizable line splitting in the spectra, most long-range couplings over four, five, and more bonds produce only small splittings of a few hertz or less. Therefore, these couplings were discovered only after the resolution of NMR spectrometers was greatly improved. Today, splittings of 0.2 Hz or even smaller are detectable without major difficulties and a wealth of structural and conformational information comes from long-range coupling constants. In general, this group of spin–spin interactions falls within the range 0.1–3.0 Hz, but larger values are not unusual.

For the interpretation of long-range coupling constants in unsaturated compounds a consideration of σ - and π -mechanisms has proved useful. The spin–spin interaction is then approximated as the sum of two quantities, $J(\sigma)$ and $J(\pi)$ that are transmitted via the σ and π -electrons, respectively.

The spin–spin interaction via σ -electrons – already shown schematically in Figure 3.11 – is again sketched in Figure 5.28a for a CH_2 group. The polarization of the electron spin at the nuclear spin of H_A is transmitted through the bonding system to the coupled nucleus H_X . For the spin orientations, the Pauli principle and Hund's rule apply. The two possible spin directions of H_A lead to two different polarizations at H_X and the H_X resonance is split in a doublet.

For the π -mechanism an analogous diagram can be prepared. Let us consider a CH group with an sp^2 hybridized carbon atom (Figure 5.28b). To a first

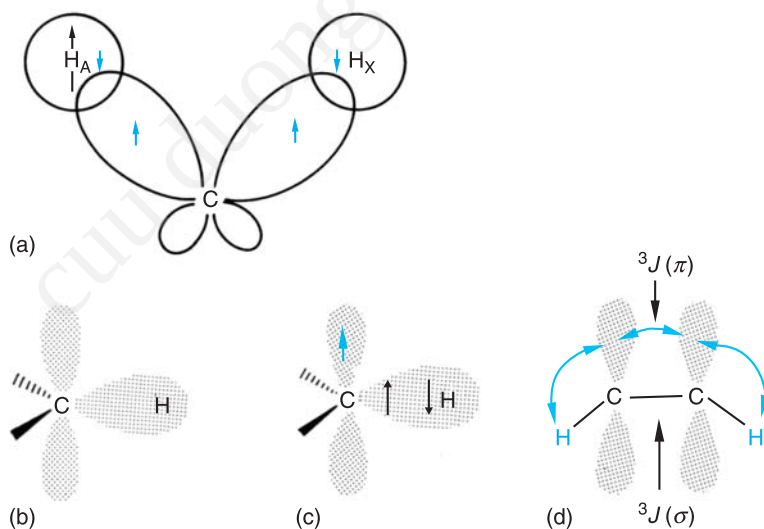


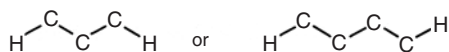
Figure 5.28 Schematic representation of the σ - and π -mechanism of spin–spin interaction between protons.

approximation, no interaction between the proton and π -electron in the carbon $2p_z$ orbital is possible since the proton lies exactly in the nodal plane of that orbital. From electron spin resonance (ESR) spectroscopy it is known, however, that this conclusion is not correct because the hyperfine splitting of ESR spectral lines in radical ions of π -systems comes about directly through a coupling of the unpaired electron residing in the carbon $2p_z$ orbital with the proton of the C–H bond. To explain this one assumes that the unpaired electron polarizes the two electrons in the CH σ -bond in such a way that the one with the parallel spin prefers to remain at the carbon atom (Figure 5.28c). Consequently, at the proton the opposite magnetic polarization, which can be oriented either parallel or antiparallel to the nuclear magnetic moment, predominates. The two possibilities are energetically different and as a result there is a splitting of the Zeeman levels of the electron and, consequently, a splitting of the ESR spectral lines.

We assume the same situation for the π -mechanism of spin–spin coupling in NMR spectroscopy with the difference that here the spin polarization originates at one proton. After transmission through the π -electrons it is detected at another proton. Even in the case of the simple double bond we can discuss a σ and a π -contribution to the vicinal coupling. This is represented schematically in Figure 5.28d. According to results of valence bond theory, the π -contribution to the vicinal coupling, $^3J(\pi)$, is proportional to the product of the ESR hyperfine coupling constants $a(\text{C–H})$, which are characteristic of the magnetic interaction between electron and nuclear spins in the $=\text{C–H}$ group. A detailed calculation shows that $J(\pi)$ in the case of vicinal coupling constitutes about 10% of the total effect. Since spin–spin interaction via the σ -electrons decreases rapidly with an increasing number of intervening bonds, the contribution of π -electrons to long-range coupling assumes a much greater importance. This is clearly shown by the results found in the case of unsaturated compounds. In the following section we first discuss the situation that exists in saturated compounds and then consider long-range coupling in unsaturated systems with special emphasis on the π -contribution to it.

5.2.3.1 Saturated Systems

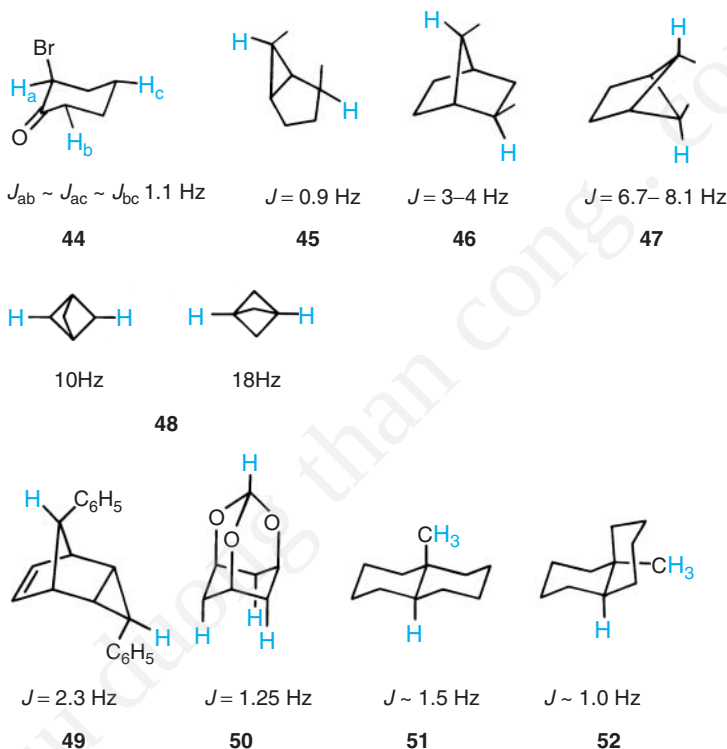
^4J and ^5J couplings are observed in saturated compounds, in particular when the C–H and C–C bonds exist in the zigzag arrangement of the form:



In the case of ^4J one speaks of the M- or a W-arrangement or -mechanism. For example, in α -bromocyclohexanone that exists in the chair conformation (**44**), spin–spin interactions of 1.1 Hz were found between the protons H_a , H_b , and H_c . In the bicyclic systems **45** and **46** the bonding arrangement of the coupled protons also meets the *M-criterion*. For the assignment of stereochemistry in isomeric *endo*- and *exo*-bicyclo-heptane derivatives the magnitude of ^4J is of importance since only the *endo* proton couples with the *anti* bridge proton. Especially large ^4J values are found in strained systems such as bicyclo[2.1.1]hexane (**47**) and

bicyclo[1.1.1]pentane (48). This is not surprising if one considers that in these compounds two or three routes are available for coupling between the protons compared with only one in the examples cited above.

^5J coupling is less frequently observed in saturated systems. As examples, compounds 49 and 50 are mentioned here. If the coplanar arrangement of the bonds is lost, the magnitude of ^4J and ^5J rapidly decreases. Nevertheless, in steroids the axial and equatorial orientation of angular methyl groups can still be distinguished on the basis of the different line width, despite methyl group rotation (51 and 52).



5.2.3.2 Unsaturated Systems

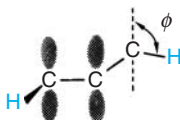
In compounds that contain π -bonds, both the σ - and π -contributions to the $^1\text{H}, ^1\text{H}$ coupling must be considered. For the latter, the valence bond calculations mentioned above lead to the following proportionalities between $J(\pi)$ and the ESR hyperfine coupling constants a that allow one to predict the sign of $J(\pi)$ and to estimate its magnitude:

$$\text{HC}=\text{CH}: {}^3J(\pi) \propto a(\dot{\text{C}}-\text{H}) \times a(\dot{\text{C}}-\text{H}) \quad (5.32)$$

$$\text{HC}=\text{C}-\text{CH}: {}^4J(\pi) \propto a(\dot{\text{C}}-\text{H}) \times a(\dot{\text{C}}-\text{C}-\text{H}) \quad (5.33)$$

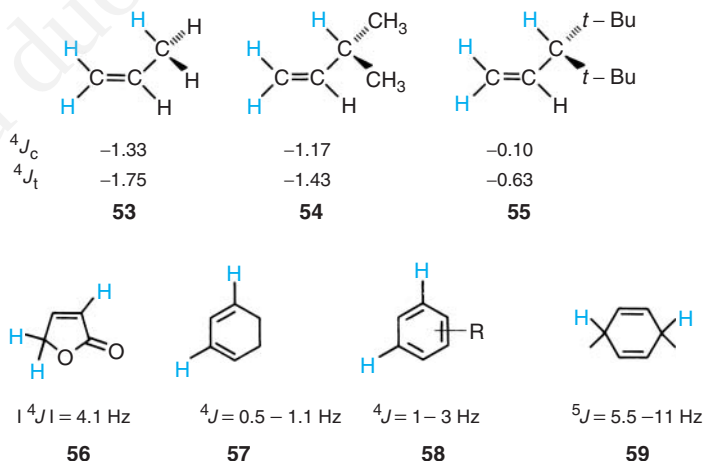
$$\text{HC}-\text{C}=\text{C}-\text{CH}: {}^5J(\pi) \propto a(\dot{\text{C}}-\text{C}-\text{H}) \times a(\dot{\text{C}}-\text{C}-\text{H}) \quad (5.34)$$

With $a(\dot{\text{C}}-\text{H}) = -65 \times 10^6$ Hz and $a(\dot{\text{C}}-\text{C}-\text{H}) = 150\cos^2\phi \times 10^6$ Hz, a *negative* sign results for ${}^4J(\pi)$ in an allyl group of the type $\text{HC}=\text{C}-\text{C}-\text{H}$ and, in addition, a dependence on the torsional angle, ϕ , is expected:



A large π -contribution to the coupling is consequently found in conformations with $\phi = 0^\circ$ and 180° while, because of the $\cos^2\phi$ term for the interaction between the CH bond and the $2p_z$ orbital. The π -contribution for $\phi = 90^\circ$ and 270° thus disappears.

In the propenes **53–55**, ${}^4J$ values have been observed that experimentally confirm the relations discussed above. Thus, the introduction of a large alkyl residue leads to a preference for the conformations shown where the angle ϕ is approximately 270° . Therefore, the π -contribution to the allylic coupling decreases in the series **53–55** and the magnitude of ${}^4J$ becomes smaller. These results also confirm that ${}^4J(\pi)$ has a negative sign. In *cyclic* systems such as the lactone **56**, very large ${}^4J$ values are often found since here the favored conformation is defined with $\phi \approx 0^\circ$ or 180° . On the other hand, for the arrangement with $\phi = 90^\circ$ we expect, according to these findings and the explanation given in Section 5.2.3.1, that ${}^4J(\sigma)$ should dominate and that the coupling constant should have a positive sign. Indeed, ${}^4J$ values of $+0.5$ to $+1.0$ Hz are found in cyclohexadienes (**57**). Of the same order and also with a positive sign is the coupling constant between *meta* protons in benzene derivatives (**58**).



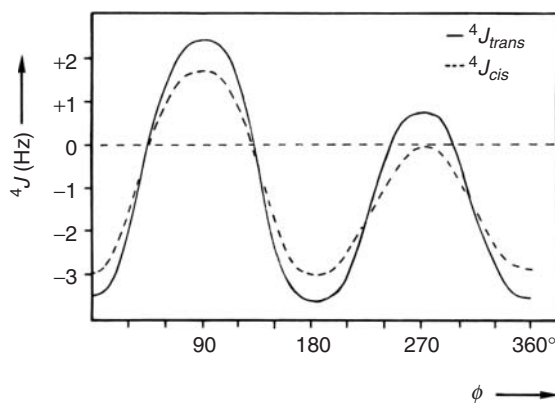


Figure 5.29 Conformational dependence of allylic $^1\text{H}, ^1\text{H}$ coupling [18].

Based on a series of experimental data, the dependence of $^4J_{\text{trans}}$ in a $\text{HC}=\text{C}-\text{C}-\text{H}$ fragment on the torsional angle, ϕ , can be represented as the sum of the positive $^4J(\sigma)$ and the negative $^4J(\pi)$ contribution (Figure 5.29). For $^4J_{\text{cis}}$ a similar result applies, but the large positive σ -contribution is absent for the conformation with $\phi = 90^\circ$.

For the *homoallylic* ^5J coupling observed in fragments of the type $\text{HC}-\text{C}=\text{C}-\text{CH}$ the conformational dependence is completely analogous to that discussed above for ^4J . Since, however, $^5J(\pi)$ has a positive sign [cf. Eq. (5.34)], σ - and π -contributions to ^5J augment one another. In favorable cases very large ^5J values can be observed, as in 1,4-dihydrobenzenes (**59**), where two routes are available for the transmission of spin information. In contrast, in benzene the *para* coupling is only 0.69 Hz.

In a series of unsaturated systems, couplings over five or more bonds are found that are probably transmitted largely over the σ -bonds that in these compounds assume the favorable zigzag arrangement mentioned in Section 5.2.3.1. These can include the couplings between H4 and H8 and H2 and H7, respectively, in naphthalene (**60**), and also similar interactions in heterocyclic systems such as **61**.

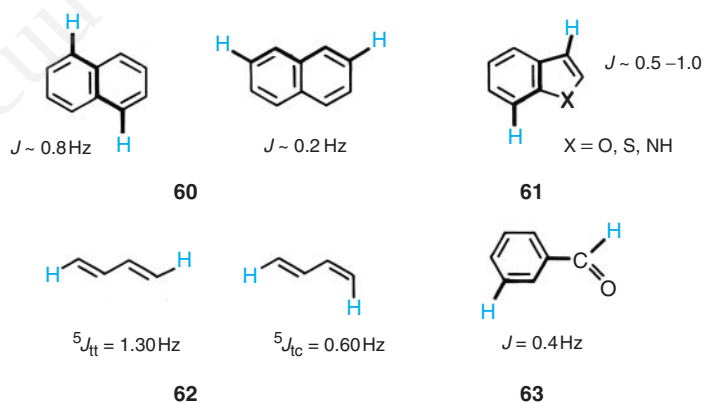
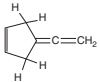
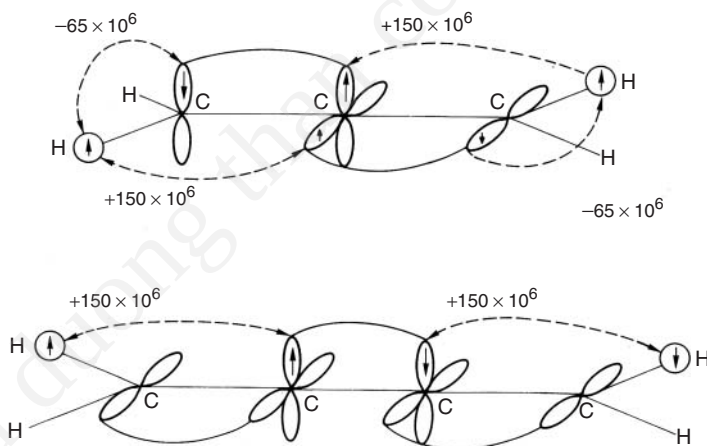


Table 5.10 Long-range $^1\text{H}, ^1\text{H}$ coupling (Hz) in selected polyacetylenes and allenes.

$\text{H}_3\text{C}-\text{C}\equiv\text{C}-\text{H}$	-2.93	$(\text{H}_3\text{C})_2\text{C}=\text{C}=\text{CH}_2$	3.0
$\text{H}_3\text{C}-\text{C}\equiv\text{C}-\text{CH}_3$	+2.7	$\text{H}_3\text{C}-\text{CH}=\text{C}=\text{CHCl}$	-5.8
$\text{H}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{H}$	+2.2	$\text{H}_3\text{C}-\text{CH}=\text{C}=\text{CHCl}$	+2.4
$\text{H}_3\text{C}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{H}$	-1.27		4.58
$\text{H}_3\text{C}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{CH}_3$	+1.3		
$\text{H}_3\text{C}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{CH}_2\text{OH}$	+0.4		

In addition, the larger value of $^5J_{\text{tt}}$ in 1,3-butadiene compared to the value of $^5J_{\text{tc}}$ can be attributed to the additional σ -contribution (62). Similarly, in the case of benzaldehyde it was shown that only the *meta* protons couple with the aldehyde proton (63), again an indication of the importance of $^5J(\sigma)$. In contrast, for polyacetylenes, allenes, and cumulenes long-range coupling arises almost exclusively through the π -mechanism. For allene and butatriene the interaction diagrams shown below can be formulated [23]:



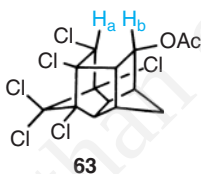
As the examples collected in Table 5.10 show, spin transmission through the π -system is very effective. With an increasing number of bonds only relatively small decreases of the coupling constants occur and even over nine bonds an interaction can be observed. Furthermore, the substitution of a terminal hydrogen in the $\text{CH}_3-(\text{C}\equiv\text{C})_x-\text{H}$ unit by a methyl group, formally a transformation of an allyl-type coupling into one of the homoallyl type, leads only to a sign change in the coupling constant while its magnitude remains unaffected. Actually, the sign changes for the examples given in Table 5.10 have not yet been verified experimentally, but they can be considered to be correct on the grounds of results obtained in other systems as well as on the basis of theoretical calculations.

5.2.4

Through-Space and Dipolar Coupling

Finally, we mention two mechanisms of spin–spin interaction that play only a limited or no role at all in the line splitting in high-resolution NMR spectroscopy.

The first mechanism is in principle only a variation of the spin–spin coupling transmitted by electrons treated in detail earlier. It has been detected in a few cases when, as the result of steric compression, an extensive nonbonding or van-der-Waals interaction of orbitals occurs. Transmission of magnetic information then results through a “short circuit” where no formal bonds are present. Thus, a coupling of 1.1 Hz is observed between the protons H_a and H_b in the case of compound **64**. Since the two nuclei are separated by six σ -bonds with an unfavorable geometry for conventional coupling, a direct spin–spin interaction between the two hydrogen 1s orbitals is very probable. This mechanism – known as *through-space coupling* – has greater significance for spin–spin coupling between a proton and a fluorine nucleus as well as between two fluorine nuclei and we come back to this feature in Chapter 12.



The second phenomenon – already briefly mentioned in Chapter 2 (p. 22) – involves the direct magnetic interaction of nuclear moments through space without the necessity of orbital contact. Its physical basis is thus completely different from that of the scalar spin–spin coupling discussed in this chapter. It leads to line broadening or splitting if the molecules assume a *fixed* or *partially fixed* orientation with respect to the direction of the external field B_0 . It is thus called *dipolar coupling*. As a consequence, the NMR spectra of *solids* have an entirely different appearance to those of liquids. As Eq. (2.12) suggests, distances between nuclei can then be determined from these spectra and the NMR of solids (also known as *wide-line NMR*) is an important experimental aid in structure determination. To simplify solid state spectra, dipolar coupling can be eliminated by magic-angle spinning (MAS, see Chapter 14). In liquids, the phenomenon of line splitting by dipolar coupling is only found if molecules are partially oriented, for example, in a liquid crystal medium. This will be elaborated further in Chapter 14. As already emphasized, in isotropic liquids *dipolar interactions* are still present. They constitute an important mechanism for nuclear relaxation by *cross relaxation* between different nuclei and form the basis of the nuclear Overhauser effect (NOE), as outlined later in Chapters 8 and 10. Only the *line splitting* is eliminated by the thermal motion of the molecules.

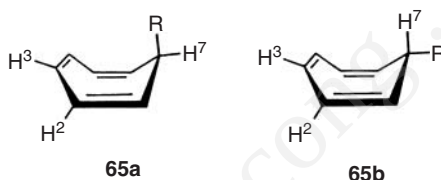
5.2.5

Tables of Spin–Spin Coupling Constants in Organic Molecules

As for the chemical shift, characteristic data for spin–spin coupling constants in different classes of organic compounds are collected in the Appendix (Table A.4, p. 654 ff.).

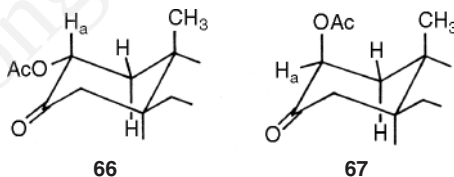
Exercise 5.6

Cycloheptatrienes that are monosubstituted in the 7-position can exist in either conformation **65a** or **65b**. Experimentally it was found that the allylic coupling constant J_{27} has a negative sign in 7-phenylcycloheptatriene. Which of the two conformations is consistent with this? In which conformation can a measurable homoallylic coupling J_{37} be expected?



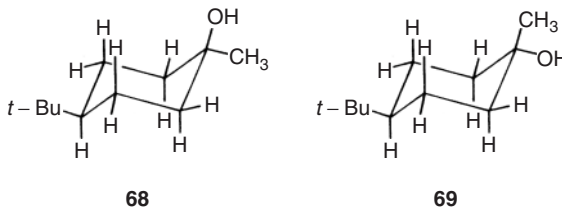
Exercise 5.7

Conformations **66** and **67** of the A ring of an acetylated steroid are to be differentiated. The signal for the proton H_a appears as a doublet of doublets with coupling constants of 13.1 and 6.6 Hz. Which conformation is consistent with this finding?



Exercise 5.8

The line widths of the methyl proton resonances in the isomeric 1-methyl-4-*t*-butylcyclohexanols (**68**) and (**69**) are 1.0–1.3 and 0.6–0.7 Hz, respectively. Explain this result and which assignment must be made?



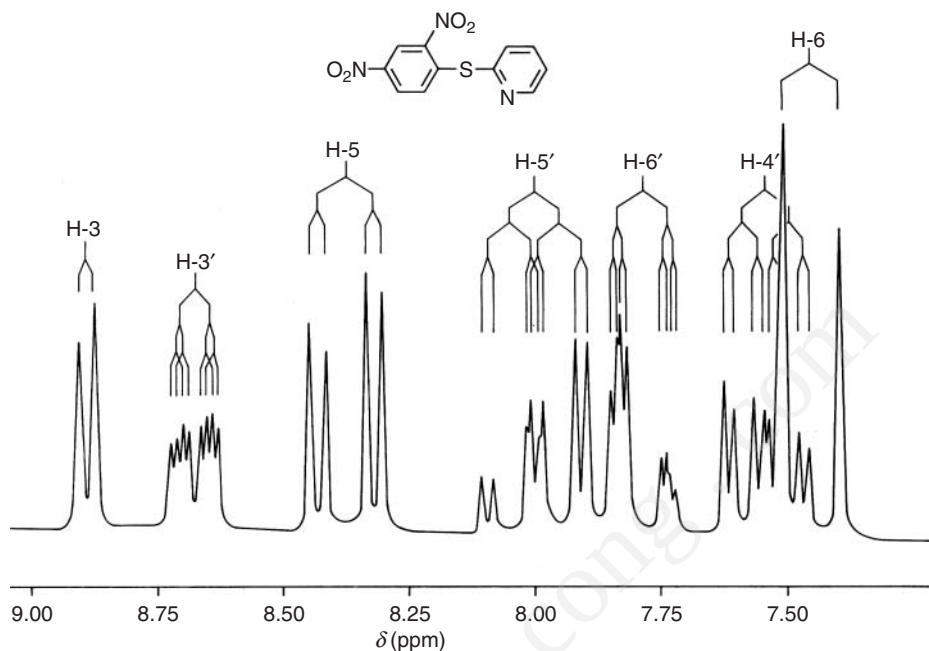
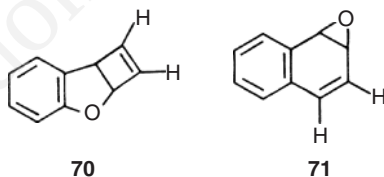


Figure 5.30 80 MHz ^1H NMR spectrum of 2,4-dinitrophenyl 2-pyridyl sulfide.

Exercise 5.9

The two structures **70** and **71** are proposed for an unknown compound. The vicinal coupling constant of the olefinic protons is 2.8 Hz. Which structure is correct?



Exercise 5.10

Figure 5.30 shows the 80 MHz ^1H NMR spectrum of 2,4-dinitrophenyl-2-pyridylsulfide. Assign the protons to the structural formula given and estimate the coupling constants.

Exercise 5.11

The ^1H NMR spectrum of 2,3-benzoxepine is given in Figure 5.31. Develop, on the basis of the integration and the splitting pattern, an assignment of the

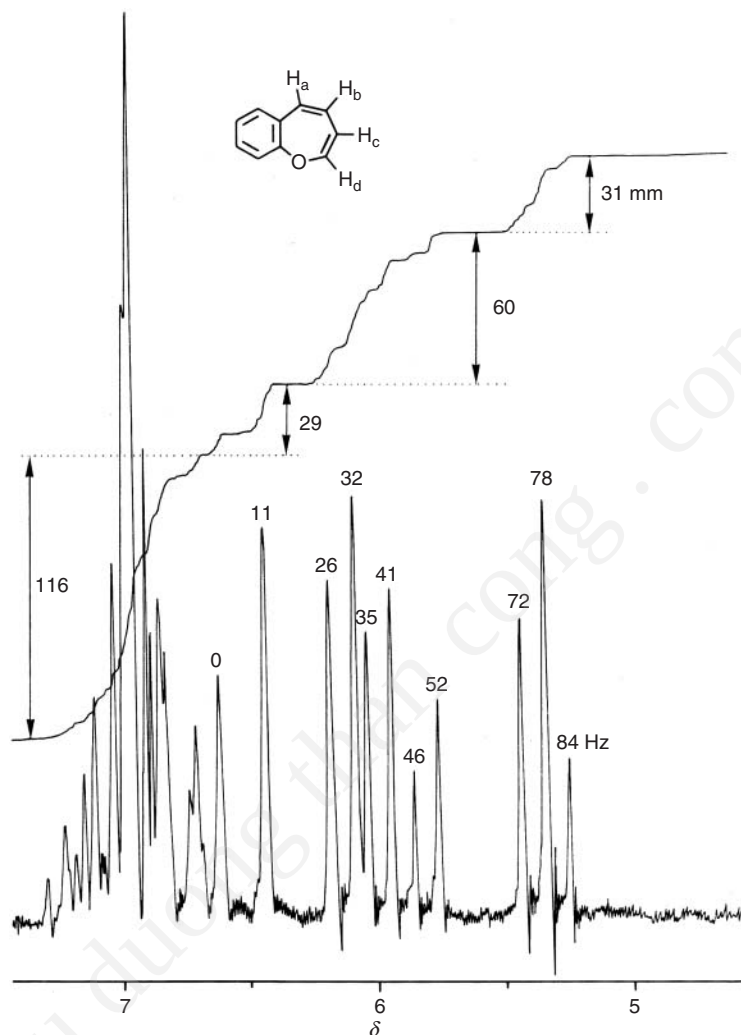


Figure 5.31 Proton magnetic resonance spectrum of 2,3-benzoxepine at 60 MHz.

resonance signals and determine the coupling constants in the olefinic portion of the molecule. Check if your assignment of the olefinic resonances is unequivocal. How could the correct solution be determined?

Exercise 5.12

Figure 5.32 shows the olefinic region of the proton NMR spectrum of a 6-chloro-1-trimethylsilylhexene. Determine the coupling constants and decide whether the spectrum is that of the *cis*-compound, the *trans*-compound, or a mixture of the two. In the latter case, estimate the *cis*/*trans* ratio.

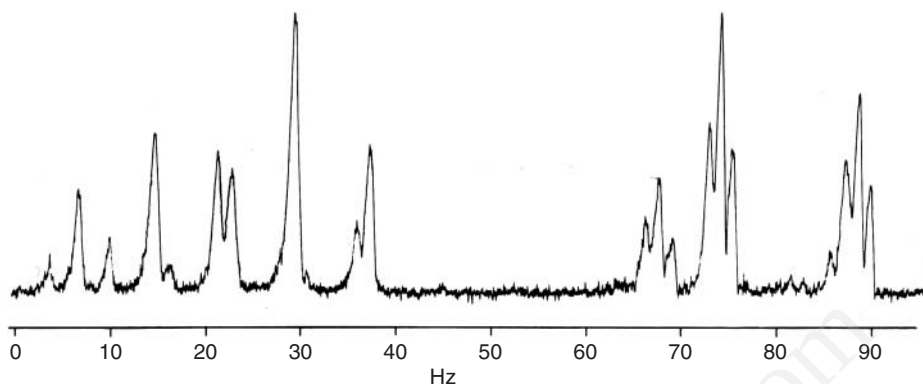


Figure 5.32 ^1H NMR spectrum of the olefinic protons of a 6-chloro-1-trimethylsilylhexene at 60 MHz.

References

1. Ham, N.S. and Mole, T. (1969) *Prog. Nucl. Magn. Reson. Spectrosc.*, **4**, 91.
2. Bremser, W. (1968) PhD thesis, University of Cologne.
3. Knowles, J.R. (1989) *Aldrichim. Acta*, **22**, 59.
4. Klod, S., Koch, A., and Kleinpeter, E. (2002) *J. Chem. Soc., Perkin Trans. 2*, 1506.
5. Martin, N.H., Allen, N.W. III, Ingrassia, S.T., Minga, E.K., and Brown, J.D. (1999) *Struct. Chem.*, **10**, 375.
6. Schmalz, D. and Günther, H. (1988) *Angew. Chem.*, **100**, 1754; *Angew. Chem., Int. Ed. Engl.*, **27**, 1692.
7. Pople, J.A. and Untch, K.G. (1966) *J. Am. Chem. Soc.*, **88**, 4811.
8. Christen, H.R., and Vögtle, F. (1988) *Organische Chemie*, 1st. ed., Vol. 1, O. Salle Verlag, Frankfurt, Verlag Sauerländer, Aarau, p. 152.
9. (a) Vogel, E. (1982) *Pure Appl. Chem.*, **54**, 1015. (b) Vogel, E., Haberland, U., and Günther, H. (1970) *Angew. Chem.*, **82**, 510; *Angew. Chem., Int. Ed. Engl.*, **9**, 513.
10. (a) Schleyer, P.v.R., Manoharam, M., Wang, Z.-X., Kiran, B., Jiao, H., Puchta, R., and Hommes, N.J.R.v.E. (2001) *Org. Lett.*, **3**, 2465. (b) Wannere, C.S. and Schleyer, P.v.R. (2003) *Org. Lett.*, **5**, 605.
11. Dauben, H.J. Jr., Wilson, J.D., and Laity, J.L. (1971) in *Non-Benzenoid Aromatics*, Vol. 2 (ed J. Synder), Academic Press, p. 167.
12. Schleyer, P.v.R., Maerker, C., Dransfeld, A., Jiao, H., and Hommes, N.J.R.v.E. (1996) *J. Am. Chem. Soc.*, **118**, 6317.
13. Abraham, R.J., Leonard, P., and Tormena, C.F. (2012) *Magn. Reson. Chem.*, **50**, 305.
14. Poulter, C.D., Boikess, R.S., Braumann, J.I., and Winstein, S. (1972) *J. Am. Chem. Soc.*, **94**, 2291.
15. DeMare, G.R. and Martin, J.S. (1966) *J. Am. Chem. Soc.*, **88**, 5033.
16. Wellman, M. and Bordwell, F.G. (1963) *Tetrahedron Letters*, 1703.
17. Schweizer, M.P., Chan, S.I., Helmkamp, G.K., and Ts'o, P.O. (1964) *J. Am. Chem. Soc.*, **86**, 696.
18. Friedrich, H.F. (1965) *Z. Naturforsch.*, **20b**, 1021.
19. Sternhell, S. (1969) *Quart. Rev.*, **23**, 236.
20. Pawliczek, J.B. and Günther, H. (1970) *Tetrahedron*, **26**, 1755.
21. Pachler, K.G.R. (1971) *Tetrahedron*, **27**, 187.

22. Castellano, S. and Sun, C. (1966) *J. Am. Chem. Soc.*, **88**, 4741.
 23. Karplus, M. (1960) *J. Chem. Phys.*, **33**, 1842.
- Monograph**
- Memory, J.D. and Wilson, N.K. (1982) *NMR of Aromatic Compounds*, John Wiley & Sons, New York, p. 252.
- Review Articles**
- Abraham, R.J. (1999) A model for the calculation of proton chemical shifts in non-conjugated organic compounds. *Prog. Nucl. Magn. Reson. Spectrosc.*, **35**, 85.
- Wolff, R. and Radeglia, R. (1996) Semiempirical chemical shift calculations, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 7 (editors in chief D.M. Grant and R.K. Harris), John Wiley & Sons, Ltd, Chichester, p. 4246.
- Gomes, J.A.N.F. and Mallion, R.B. (2001) Aromaticity and Ring Currents. *Chem. Rev.*, **101**, 1349.
- Lazzaretti, P. (2000) Ring Currents. *Prog. Nucl. Magn. Reson. Spectrosc.*, **36**, 1.
- Ronayne, J. and Williams, D.H. (1969) Solvent effects in proton magnetic resonance spectroscopy. *Annu. Rep. NMR Spectrosc.*, **2**, 83.
- Smith, S.L. (1972) Solvent Effects and NMR Coupling Constants. *Fortschr. Chem. Forsch.*, **27**, 117.
- Günther, H. and Jikeli, G. (1977) ^1H -NMR spectra of cyclic monoenes: hydrocarbons, ketones, heterocycles, and benzo derivatives. *Chem. Rev.*, **77**, 599.
- Thomas, W.A. (1997) Unravelling molecular structure and conformation - the modern role of coupling constants. *Prog. Nucl. Magn. Reson. Spectrosc.*, **30**, 183.
- Schaefer, T. (1996) Stereochemistry and long range coupling constants, in *Encyclopedia of Magnetic Resonance*, Vol. 7 (editors in chief D.M. Grant and R.K. Harris), p. 4571.
- Günther, H. (1996) Vicinal ^1H , ^1H coupling constants in cyclic π -systems, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 8 (editors in chief D.M. Grant and R.K. Harris), John Wiley & Sons, Ltd, Chichester, p. 4923.
- Sternhell, S. (1969) Correlation of interproton spin–spin coupling constants with structure. *Quart. Rev.*, **23**, 236.
- Barfield, M. and Chakrabarti, B. (1969) Long-range proton spin–spin coupling. *Chem. Rev.*, **69**, 757.
- Bothner-By, A.A. (1965) Geminal and vicinal proton–proton coupling constants in organic compounds, in *Advances in Magnetic Resonance*, Vol. 1 (ed J.S. Waugh), Academic Press, New York, p. 195.
- Hilton, J. and Sutcliffe, L.H. (1975) The through-space mechanism in spin–spin coupling. *Prog. Nucl. Magn. Reson. Spectrosc.*, **10**, 27.

6

The Analysis of High-Resolution Nuclear Magnetic Resonance Spectra

In Chapter 3 we introduced simple rules for the direct determination of chemical shifts and spin–spin coupling constants from proton NMR spectra. As already mentioned there, however, the application of these rules is limited to first-order spectra and the more complicated spin systems found in many cases can only be analyzed by quantum chemical methods. The increased use of high magnetic fields provided by superconducting magnets has improved the situation and first-order spectra that can be interpreted by inspection are met today quite frequently. On the other hand, spectra of higher order are now observed for structures that could not be analyzed by NMR before due to insufficient spectral resolution. In other words, many of the spin systems illustrated here with 60 or 100 MHz spectra are met today at 300 or 500 MHz measuring frequency for molecules like steroids, peptides, or carbohydrates. Furthermore, as a consequence of their particular spin Hamiltonian, quite a number of spin systems, such as, for example, the AA'XX' system, will never transform into a first-order spectrum even at the highest magnetic field available. The problem of accurate spin analysis is thus a permanent challenge for the NMR spectroscopist. The present chapter is, therefore, devoted to the quantum chemical basis of NMR spectral analysis. First we shall attempt to present the essential principles, treating later individual types of spectra, and finally several important generalizations. We will limit ourselves, however, to consideration of the more frequently encountered homonuclear spin systems of spin $I = \frac{1}{2}$ since a comprehensive treatment of the subject is beyond the scope of our introductory text.

The question that is of primary interest here can be formulated as follows: “How can the parameters – chemical shifts and coupling constants – of the spin system under consideration be derived from the spectrum?” To answer this question we must familiarize ourselves with the principles of the calculation of high-resolution NMR spectra. Therefore, the converse question: “How do the line frequencies and the line intensities in a spectrum follow from a known set of chemical shifts and coupling constants?” will be investigated first. That is, before we consider the *analysis* of a spectrum we want to understand its *synthesis*.

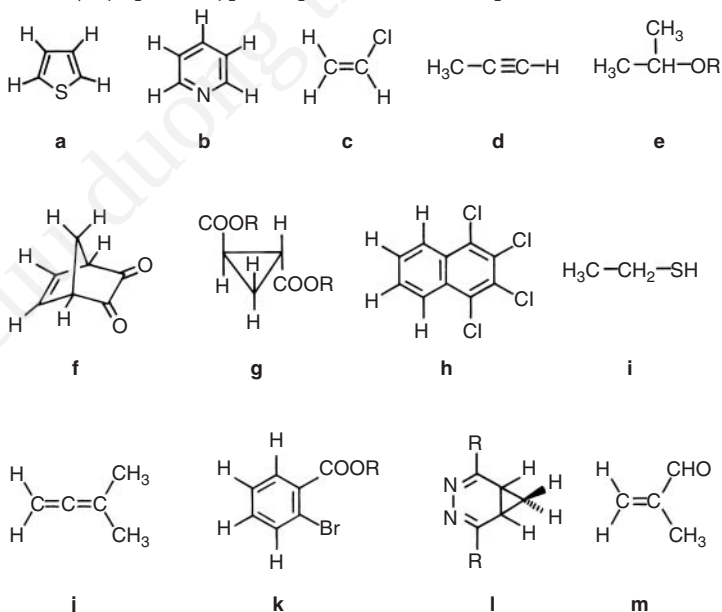
6.1

Notation for Spin Systems

The classification of different spin systems was briefly mentioned in Chapter 3; here we summarize the important points in more detail again. The notion *spin system* is used for a group of n nuclei that is characterized by no more than n resonance frequencies, ν_i , and $n(n-1)/2$ coupling constants, J_{ij} . This group does not interact magnetically with any other group of nuclei. Nuclei of equal chemical shift are labeled with the same capital letter and the number of such nuclei in the system is indicated by a subscript. Thus, the protons of an isolated methyl group form an A_3 system while those of an ethyl group constitute an A_3B_2 system. The relative chemical shifts of different nuclei in a spin system are indicated by the position in the alphabet of the labeling letter. For a CH_3CF_2 group the designation A_3X_2 is used to indicate the large difference between the chemical shifts of the protons and the fluorine nuclei. Magnetically non-equivalent nuclei such as the two protons and the two fluorine nuclei in 1,1-difluoroethene (cf. p. 55) and the two pairs of protons in 1,2-dichlorobenzene are distinguished by using primed letters. These two spin systems are an $AA'XX'$ system and an $AA'BB'$ system, respectively. Furthermore, whenever possible, the nuclei are labeled in such a fashion that the sequence of the letters in the alphabet matches the sequence of the resonance frequencies in order of decreasing frequency.

Exercise 6.1

Classify by spectral type the protons in the compounds **a–m**.



6.2

Quantum Mechanical Formalism

Since the nuclear spin is a non-classical property of atomic nuclei, we can solve the problem posed by the calculation of NMR spectra only with the aid of quantum mechanics and in the following sections we make a little excursion into quantum chemistry. Within the scope of this text we must introduce the necessary quantum mechanical principles and methods axiomatically since, on the one hand, we cannot presume a detailed knowledge of the theory by the reader and, on the other hand, we want to present as exact a derivation as possible. Our approach, however, has a certain rationale since quantum mechanics rests on postulates that can be neither proved nor rigorously derived mathematically. Instead they are based exclusively on experimental observations. Those readers who are familiar with the Hückel molecular orbital theory will soon discover that the formalism used there to calculate eigenvalues and wave functions of the electrons is the same that applies to the present problem. Several interesting parallels exist and a comparison of the two theories is very illuminating.

The fact that we can observe a nuclear magnetic resonance spectrum with distinct spectral lines demonstrates that the energy of a spin system in a magnetic field is *quantized*. Just like the individual nuclei, the spin system as a whole can exist only in certain states, the *stationary states* or *eigenstates*. The energies of these eigenstates, the *eigenvalues*, are determined by the interaction between the nuclei and the external magnetic field, B_0 , as well as by the spin–spin interaction of the nuclei with one another. Each eigenstate is characterized by a *wave function* or *eigenfunction*, Ψ .

The frequencies, f_{pq} , of the NMR signals correspond to the energy differences between the stationary states of the spin system. Their calculation therefore presupposes a knowledge of the eigenvalues E_p and E_q :

$$f_{pq} = \frac{1}{h}(E_q - E_p) \quad (6.1)$$

where h is Planck's constant. For the derivation of the relative intensities of the signals we must also know the eigenfunctions, Ψ , as will be shown later.

6.2.1

The Schrödinger Equation

We postulate that at the atomic level the relation between the energy, E , of a particle and its wave function, Ψ , can be described by the Schrödinger equation. In its simplest time-independent form, this equation can be written as a so-called eigenvalue equation:

$$\mathcal{H}\Psi = E\Psi \quad (6.2)$$

where $\mathcal{H}$ is the Hamilton operator or Hamiltonian. Its application on the eigenfunction, Ψ , yields the product of eigenvalue and eigenfunction. Equation (6.2) enables us to calculate the stationary energy states of one or more particles –

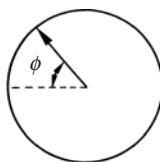
perhaps the electrons in a molecule or the magnetic nuclei of a spin system – as long as we know the Hamilton operator and the eigenfunctions. Since the energy of the system under consideration can be derived experimentally, E is called the *observable* appropriate to the particular Hamiltonian. The notion of the *operator* that we shall use in what follows requires a short explanation. Operators are, first of all, nothing more than instructions. The symbol $\mathcal{H}\Psi$ signifies only that an operation prescribed by the Hamilton operator (and not yet explained in detail) will be executed on the wave function, Ψ . In this sense the square root and the integral signs are also operators since they prescribe definite operations to be carried out on a certain function. Further, if a function is to be differentiated with respect to x the differential operator reads d/dx . From these examples, it is apparent that operators are always written at the left-hand side of the function to which they are to be applied. The exchange $\mathcal{H}\Psi \rightarrow \Psi\mathcal{H}$ therefore is not allowed.

The central problem of the theory of chemical bonding is the motion of the electrons in the potential field of the atomic nuclei and the other electrons in the molecule. In this case, the familiar Hamilton operator given in Eq. (6.3) is employed. Here the *Laplace operator* Δ stands for the kinetic and the operator $\hat{V}$ for the potential energy and m is the particle mass:

$$\mathcal{H} = \frac{-h^2}{8\pi^2 m} \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \right) + \hat{V} \quad (6.3)$$

The difficulties that prevent a simple treatment of the bonding problem according to Eq. (6.2) result principally from the complex form of the Hamilton operator, according to which the energy is a function of the coordinates of all of the electrons. For the model of an electron on a circle that we used in Chapter 5 (p. 105) these difficulties are drastically reduced. Therefore, it seems worthwhile demonstrating the application of Eq. (6.2) with this example.

Since the motion of the electron shall be confined to a circular path of radius r we can use exclusively the angle ϕ formed by the radius vector with an arbitrarily assumed starting point as the variable to characterize the position of the particle:



Further, the potential energy shall be zero so that the Hamilton operator, written in polar coordinates (see Appendix), assumes the following form:

$$\mathcal{H} = \frac{-h^2}{8\pi^2 m r^2} \times \frac{\partial^2}{\partial \phi^2} \quad (6.4)$$

The wave nature of the electron suggests that a sine or a cosine function should be used as the eigenfunction. Let us try $\Psi = N \sin q \phi$, so that Eq. (6.2) with the

substitution of Eq. (6.4) leads to:

$$\frac{-h^2}{8\pi^2mr^2} \times \frac{\partial^2}{\partial \phi^2} \times N \sin q\phi = E \times N \sin q\phi \quad (6.5)$$

which, on carrying out the operation, yields:

$$\frac{h^2}{8\pi^2mr^2} \times N \sin q\phi \times q^2 = E \times N \sin q\phi \quad (6.6)$$

From this it follows that:

$$E = \frac{h^2}{2mL^2} \times q^2 \quad (6.7)$$

if we substitute L for the circumference of the circle, $2\pi r$. The quantum condition $q = 0, \pm 1, \pm 2, \dots, \pm n$ results from the requirement that the eigenfunction for all values of ϕ must be unambiguous. Specifically, on the circle the condition $\Psi(\phi) = \Psi(2\pi + \phi)$ must hold. The eigenvalues E_0, E_1, E_2 , and so on accordingly correspond to the energies derived in Chapter 5. Let us consider further that the square of the eigenfunction Ψ_q is equal to the probability that the electron occupies a particular position on the circle so that:

$$\int_0^{2\pi} N^2 \sin^2 q\phi d\phi = \pi \quad (6.8)$$

For N , the so-called *normalization constant*, $1/\sqrt{\pi}$ is obtained since:

$$\int_0^{2\pi} \sin^2 q\phi d\phi = \pi \quad (6.9)$$

The eigenfunction is then:

$$\Psi_q = \sqrt{\frac{1}{\pi}} \sin q\phi \quad (6.10)$$

with $q = 0, \pm 1, \pm 2, \pm 3, \dots, \pm n$.

Exercise 6.2

Calculate with Eq. (6.2), the Hamilton operator derived from Eq. (6.3):

$$\mathcal{H} = \frac{-h^2}{8\pi^2m} \frac{\partial^2}{\partial x^2}$$

and the trial function $\Psi = N \sin ax$ the eigenvalues and the eigenfunctions of an electron that can move in a one-dimensional box of length L at the potential $V = 0$:

6.3

The Hamilton Operator for High-Resolution Nuclear Magnetic Resonance Spectroscopy

We now make use of the Schrödinger equation to solve the problem of interest to us – the determination of the energy levels of a spin system in a magnetic field.

The phenomenologically formulated Hamilton operator that applies here has the form:

$$\mathcal{H} = \mathcal{H}^{(0)} + \mathcal{H}^{(1)} = \sum_i v_i \hat{I}_z^{(i)} + \sum_{i < j} J_{ij} \hat{I}(i) \hat{I}(j) \quad (6.11)$$

in which the first term, $\mathcal{H}^{(0)}$, relates to the interaction of the nuclei with the external field, B_0 , and the second term in equation, $\mathcal{H}^{(1)}$, relates to the spin–spin coupling energy. For the formalism developed in this chapter it is more convenient to assume the direction of B_0 along the negative z-axis of the coordinate system. This results in a positive energy term $\mathcal{H}^{(0)}$ in the Hamilton operator. The wave functions α and β , on the other hand, represent then the upper and lower energy spin state, respectively, contrary to the formalism introduced in Chapter 5 and used in all other chapters except in the present. This change has no effect on the appearance of the spectra. The operator $\mathcal{H}^{(0)}$ contains the resonance frequencies v_i and $\mathcal{H}^{(1)}$ contains the coupling constants J_{ij} . $\mathcal{H}^{(1)}$ thus corresponds to Eq. (3.9b) introduced earlier for the energy of spin–spin interactions, while the form of $\mathcal{H}^{(0)}$ derives from the Eqs (2.6), (2.7), and (2.10) introduced in Chapter 2:

$$E = -\mu_z B_0 = -m_I \gamma h B_0 = -m_I h \gamma B_0 = -m_I h \nu_0$$

where m_I is now replaced by the operator $\hat{I}_z(i)$ and the sign is changed as described above. When divided by Planck's constant, h , the energy – as in the case of spin–spin interaction – is obtained in hertz, $E = v_i \hat{I}_z(i)$, and is measured as the coupling constants in hertz. Thus the factor $1/h$ in Eq. (6.1) disappears.

Turning now to the wave functions, we shall use here α and β for the two spin states with $m_I = +\frac{1}{2}$ and $m_I = -\frac{1}{2}$ for the antiparallel and parallel orientations of the nuclear magnetic moment with respect to the external magnetic field. Important properties of these functions will be introduced later.

The Hamilton operator [Eq. (6.11)] contains additional operators, namely, the nuclear spin operators $\hat{I}_z$ and $\hat{I}$. The vector $\hat{I}$ is defined by its components $\hat{I}_x$, $\hat{I}_y$, and $\hat{I}_z$. Their properties are introduced as postulates that tell us the results of their application on the wave functions α and β :

$$\hat{I}_x \alpha = \frac{1}{2} \beta \quad \hat{I}_y \alpha = i \frac{1}{2} \beta \quad \hat{I}_z \alpha = \frac{1}{2} \alpha \quad (6.12)$$

$$\hat{I}_x \beta = \frac{1}{2} \alpha \quad \hat{I}_y \beta = -i \frac{1}{2} \alpha \quad \hat{I}_z \beta = -\frac{1}{2} \beta$$

In addition, the complex combinations:

$$\hat{I}^+ = \hat{I}_x + i \hat{I}_y \quad (6.13)$$

and:

$$\hat{I}^- = \hat{I}_x - i \hat{I}_y \quad (6.14)$$

are introduced, known as *raising and lowering operator*, respectively. Their application to a wave function leads to the wave function of the eigenstate with the next higher or lower quantum number, respectively. The reader can verify this

statement by a straightforward application of $\hat{I}^+$ and $\hat{I}^-$ to the spin functions α and β . In Chapter 9 we will meet these operators again.

We note that the relations for the operator $\hat{I}_z$, can also be interpreted as eigenvalue equations: α and β are then eigenfunctions of $\hat{I}_z$ having eigenvalues $+\frac{1}{2}$ and $-\frac{1}{2}$, respectively; that is, the magnetic quantum numbers m_I introduced in Chapter 2 are the eigenvalues of the $\hat{I}_z$ operator.

Relative to the wave functions we want to stipulate further that they are *orthogonal* and *normalized*. Then:

$$\int \alpha \alpha \, dv = \int \beta \beta \, dv = 1 \quad (6.15)$$

and:

$$\int \alpha \beta \, dv = \int \beta \alpha \, dv = 0 \quad (6.16)$$

where the integral is over all space.

The obvious significance of these conditions is that an individual nucleus can exist in either the α or β state and that the probability of its existence in one of the two states, when integrated over all space, is exactly unity.

6.4

Calculation of Individual Spin Systems

In principle, we are now in the position to calculate the eigenvalues of any spin system by using Eq. (6.2) in conjunction with the rules formulated in Eq. (6.11) and the properties of the wave functions α and β defined by Eq. (6.12). It is important, however, to point out that only relative energies for the eigenstates of a spin system can be determined by means of the formalism we have developed. We have practically eliminated the question of the absolute energy values since we have introduced the resonance frequencies, ν_i , and the coupling constants, J_{ij} , as phenomenological parameters. This procedure obviated the much more complicated absolute determination of these quantities in which one encounters the same difficulties as in the exact treatment of chemical bonding since the Schrödinger equation must be solved for the unperturbed molecule before the shielding constants of the nuclei in the external magnetic field and the magnetic spin-spin interactions can be studied. However, knowledge of the relative energies of the eigenstates of a system is all that is necessary in spectroscopy since the spectral frequencies depend only on the energy difference of the eigenvalues.

Below we carry out the calculations for a few simple spin systems using the background developed in the preceding sections and, in doing so, we shall introduce additional important rules one by one.

6.4.1

Stationary States of a Single Nucleus A

This nearly trivial case will be considered at the outset for completeness. Here $\mathcal{H} = \mathcal{H}^{(0)}$ and it follows according to Eqs (6.2) and (6.12) that the energy of the stationary state of nucleus A, characterized by the wave function $\alpha(A)$, is given by:

$$\begin{aligned}\mathcal{H}^{(0)}\alpha(A) &= E_{+\frac{1}{2}}\alpha(A) \\ \nu_A \hat{I}_z(A)\alpha(A) &= E_{+\frac{1}{2}}\alpha(A) \\ \nu_A \frac{1}{2}\alpha(A) &= E_{+\frac{1}{2}}\alpha(A) \\ E_{+\frac{1}{2}} &= \frac{1}{2}\nu_A\end{aligned}$$

Analogously, for the β state of A we obtain $E_{-\frac{1}{2}} = -\frac{1}{2}\nu_A$ and the frequency for the transition of A from the β state to the α state is $E_{+\frac{1}{2}} - E_{-\frac{1}{2}} = \nu_A$ (upper state minus lower state).

6.4.2

Two Nuclei without Spin–Spin Interaction ($J_{ij} = 0$); Selection Rules

The system under consideration consists of two nuclei, A and B, that are individually characterized by the wave functions α and β . Four product functions identified by the sums, m_T , of the magnetic quantum numbers $m_I(A)$ and $m_I(B)$ – that is, the *total spin* introduced on p. 45 – serve to describe the stationary states:

$$\begin{aligned}(1) \quad \phi_1 &= \alpha(A)\alpha(B) \quad m_T = +1 \\ (2) \quad \phi_2 &= \alpha(A)\beta(B) \quad m_T = 0 \\ (3) \quad \phi_3 &= \beta(A)\alpha(B) \quad m_T = 0 \\ (4) \quad \phi_4 &= \beta(A)\beta(B) \quad m_T = -1\end{aligned}$$

The use of product functions should become clear by means of the following consideration. The Hamilton operators for the individual nuclei would be $\mathcal{H}_A$ and $\mathcal{H}_B$ respectively, so that for the system of two nuclei $\mathcal{H} = \mathcal{H}_A + \mathcal{H}_B$ and correspondingly the energy of the system would be $E = E_A + E_B$. Let us use the product function ϕ_1 so that the left-hand side of the Schrödinger equation would be $\mathcal{H}\alpha(A)\alpha(B) = \mathcal{H}_A\alpha(A)\alpha(B) + \mathcal{H}_B\alpha(A)\alpha(B)$. As long as no interaction exists between the nuclei we can consider the wave function $\alpha(B)$ as a constant with respect to the operation $\mathcal{H}_A\alpha(A)\alpha(B)$. Proceeding similarly with $\mathcal{H}_B\alpha(A)\alpha(B)$, we find that $\mathcal{H}_A\alpha(A) = E_A\alpha(A)$ and $\mathcal{H}_B\alpha(B) = E_B\alpha(B)$:

$$\begin{aligned}\mathcal{H}\alpha(A)\alpha(B) &= E_A\alpha(A)\alpha(B) + E_B\alpha(A)\alpha(B) \\ &= (E_A + E_B)\alpha(A)\alpha(B) \\ &= E\alpha(A)\alpha(B)\end{aligned}$$

that is, the product function ϕ_1 satisfies the Schrödinger equation $\mathcal{H}\phi_1 = E\phi_1$.

We can now calculate the energies of the four spin states of the two-spin system according to Eq. (6.2) using the product functions ϕ_1 , ϕ_2 , ϕ_3 , and ϕ_4 . Since there is

no coupling, $\mathcal{H} = \mathcal{H}^{(0)}$ and it follows that:

$$\begin{aligned} [v_A \hat{I}_z(A) + v_B \hat{I}_z(B)] \alpha(A) \alpha(B) &= E_1 \alpha(A) \alpha(B) \\ \left(\frac{1}{2} v_A + \frac{1}{2} v_B\right) \alpha(A) \alpha(B) &= E_1 \alpha(A) \alpha(B) \\ E_1 &= \frac{1}{2} (v_A + v_B) \end{aligned}$$

In the calculation it should be noticed that the operator $\hat{I}_z(A)$ is applied only to the wave function of nucleus A. Correspondingly, $\hat{I}_z(B)$ is effective only on $\alpha(B)$.

In analogous fashion we obtain:

$$\begin{aligned} E_2 &= \frac{1}{2} (v_A - v_B) \\ E_3 &= -\frac{1}{2} (v_A - v_B) \\ E_4 &= -\frac{1}{2} (v_A + v_B) \end{aligned}$$

Consequently, the energy level diagram for the two-spin system without spin–spin coupling has the structure shown in Figure 6.1. The frequencies of the lines correspond to the differences between the eigenvalues and the spectrum consists of two lines at v_A and v_B .

The transitions $(3) \rightarrow (2)$ or $(4) \rightarrow (1)$ are not considered because, according to the applicable *selection rules*, only those transitions that result in a unit change of the total spin of the wave function ($\Delta m_T = \pm 1$) are allowed. This corresponds to the plausible requirement that one quantum of energy can effect the reorientation of *only one* nucleus. Table 6.1a gives our results for the AB system without spin–spin coupling. We shall treat the derivation of the relative intensities of the individual transitions in Section 6.4.3.2.

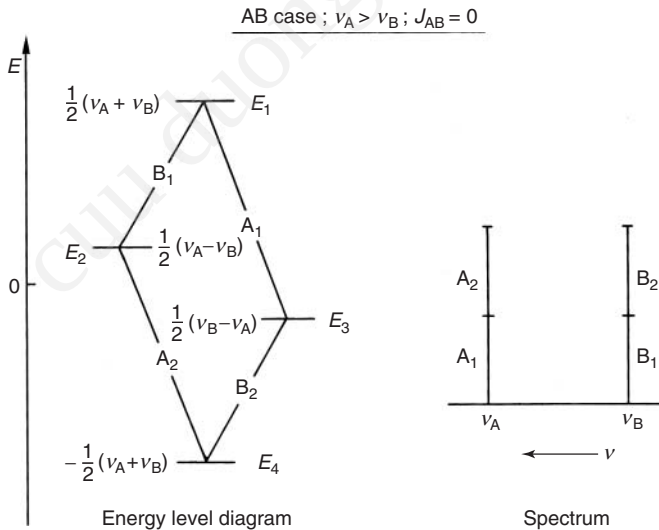


Figure 6.1 Energy level diagram and spectrum of the AB system with $J_{AB} = 0$.

Exercise 6.3

Form the product functions for a spin system of three nuclei and calculate the eigenvalues assuming that there is no spin–spin coupling.

For the calculation of the eigenvalues in the examples considered so far we were able to use the Schrödinger equation [Eq. (6.2)] directly. This was possible because the eigenfunctions of the corresponding systems were already available to us in the functions α and β or $\alpha\alpha$, $\alpha\beta$, $\beta\alpha$, and $\beta\beta$. This will not always be the case. On the contrary, in the future we shall usually face the problem of calculating the energy of a spin system by means of a trial function that is different from the true eigenfunction. It is here that a further postulate of quantum mechanics has its application. The energy of a spin system can be calculated using trial or approximate functions by means of the relation:

$$E = \frac{\int \Psi \mathcal{H} \Psi d\nu}{\int \Psi^2 d\nu} = \frac{\langle \Psi | \mathcal{H} | \Psi \rangle}{\langle \Psi | \Psi \rangle} \quad (6.17)$$

Equation (6.13) follows from Eq. (6.2) by multiplication by Ψ in the usual manner, followed by integration. The shorthand notation introduced here for the integral is due to Dirac.

6.4.3

Two Nuclei with Spin–Spin Interaction ($J_{ij} \neq 0$)

6.4.3.1 The A_2 Case and the Variational Method

We shall now introduce spin–spin coupling between the nuclei as an additional magnetic interaction so that the complete Hamilton operator [Eq. (6.10)] must be used for the calculation of the eigenvalues. From now on we must first determine whether the simple product functions ϕ_1 to ϕ_4 are suitable for the description of the stationary states, that is: Are they eigenfunctions?

Let us consider a two-spin system where the nuclei have the same resonance frequency ($\nu_A = \nu_B$) and that is therefore to be classified as an A_2 system. Here we obviously can no longer differentiate between the nuclei A(1) and A(2) and the product functions $\alpha(1)\beta(2)$ or $\beta(1)\alpha(2)$ can no longer be assigned unequivocally to the discrete states (2) and (3). In this context it is said that the states (2) and (3) mix with one another. It is therefore necessary to look for new wave functions for these states. On the other hand, however, the functions ϕ_1 and ϕ_4 are applicable for the states (1) and (4) since $\alpha(1)\alpha(2)$ and $\alpha(2)\alpha(1)$ as well as $\beta(1)\beta(2)$ and $\beta(2)\beta(1)$ obviously are identical.

What wave functions should now be chosen for the eigenstates (2) and (3)? The *variational method* of quantum mechanics is used in cases of this kind. The wave function for the corresponding eigenstate is first approximated by a *linear combination*. The states have certain characteristics of the product functions ϕ_2 and

ϕ_3 and thus can be described by the expression:¹⁾

$$\Psi_{2,3} = c_2(\alpha\beta) + c_3(\beta\alpha) \quad (6.18)$$

This trial function requires that we now calculate the energy according to Eq. (6.13) rather than according to Eq. (6.2) as was done earlier. The variational theorem states that the energy value, ε , so obtained can never be less than the actual value and will equal the actual value only when the trial function and the true wave function are identical. The best solution is thus obtained when the calculated energy of the system is minimized. Since we have not yet defined the coefficients c_2 and c_3 in our trial function we can conveniently establish as the condition for obtaining the best possible solution the requirement that:

$$\frac{\partial \varepsilon}{\partial c_2} = \frac{\partial \varepsilon}{\partial c_3} = 0 \quad (6.19)$$

In other words, the best solution is obtained when a variation of the coefficients no longer has the result of reducing the energy. Substituting Eq. (6.14) into Eq. (6.13) and performing the indicated operations leads to:

$$\varepsilon = \frac{\langle [c_2(\alpha\beta) + c_3(\beta\alpha)] | \mathcal{H} | [c_2(\alpha\beta) + c_3(\beta\alpha)] \rangle}{\langle [c_2(\alpha\beta) + c_3(\beta\alpha)] | [c_2(\alpha\beta) + c_3(\beta\alpha)] \rangle} \quad (6.20)$$

$$= \frac{c_2^2 \langle \alpha\beta | \mathcal{H} | \alpha\beta \rangle + c_2 c_3 \langle \alpha\beta | \mathcal{H} | \beta\alpha \rangle + c_3 c_2 \langle \beta\alpha | \mathcal{H} | \alpha\beta \rangle + c_3^2 \langle \beta\alpha | \mathcal{H} | \beta\alpha \rangle}{c_2^2 \langle \alpha\beta | \alpha\beta \rangle + c_2 c_3 \langle \alpha\beta | \beta\alpha \rangle + c_3 c_2 \langle \beta\alpha | \alpha\beta \rangle + c_3^2 \langle \beta\alpha | \beta\alpha \rangle} \quad (6.21)$$

To improve the clarity of the expression we use the following abbreviations:

$$\begin{aligned} H_{22} &= \alpha\beta | \mathcal{H} | \alpha\beta & H_{23} &= \alpha\beta | \mathcal{H} | \beta\alpha \\ H_{33} &= \beta\alpha | \mathcal{H} | \beta\alpha & H_{32} &= \beta\alpha | \mathcal{H} | \alpha\beta \end{aligned}$$

Imposing the implications of Eq. (6.12) and the identity $H_{32} = H_{23}$ we finally obtain:

$$\varepsilon = (c_2^2 H_{22} + 2c_2 c_3 H_{23} + c_3^2 H_{33}) / (c_2^2 + c_3^2) = u/v \quad (6.22)$$

In the sense of the above-defined criterion for the best solution, ε must be partially differentiated with respect to c_2 and c_3 . The rule for quotients leads to:

$$\frac{\partial \varepsilon}{\partial c_2} = \frac{1}{v} \left(\frac{\partial u}{\partial c_2} - \frac{u}{v} \times \frac{\partial v}{\partial c_2} \right) \quad (6.23)$$

Since the quotient u/v is equal to ε :

$$\frac{\partial \varepsilon}{\partial c_2} = \frac{1}{v} \left(\frac{\partial u}{\partial c_2} - \varepsilon \frac{\partial v}{\partial c_2} \right) = \frac{1}{c_2^2 + c_3^2} (2c_2 H_{22} + 2c_3 H_{23} - \varepsilon 2c_2) \quad (6.24)$$

To minimize ε with respect to c_2 , we equate $\partial \varepsilon / \partial c_2$ with zero. This can be satisfied only when the quantity in the parentheses is zero and we find that:

$$c_2(H_{22} - \varepsilon) + c_3 H_{23} = 0 \quad (6.25)$$

1) For clarity, here and in the future the indices of the wave functions α and β will be dispensed with. According to convention, the sequence of nuclei is always (1) (2) (3) ... (n).

Analogously, for $\partial\epsilon/\partial c_3 = 0$ (with $H_{23} = H_{32}$) we have:

$$c_2 H_{32} + c_3 (H_{33} - \epsilon) = 0 \quad (6.26)$$

Equations (6.25) and (6.26) obtained in this fashion are called *homogeneous linear equations* with the coefficients c_2 and c_3 as unknowns. They are also called *secular equations*. According to a theorem of algebra, a system of equations of this type possesses non-trivial, that is, non-zero, solutions for the coefficients only if the determinant of the system, known as *secular determinant*, is zero. In our case this requires that:

$$\begin{vmatrix} H_{22} - \epsilon & H_{23} \\ H_{32} & H_{33} - \epsilon \end{vmatrix} = 0 \quad (6.27)$$

Through the solution of this second-order determinant a quadratic equation is obtained from which the energy ϵ can be calculated.

To go through this calculation we must first introduce the elements H_{23} , H_{32} , H_{23} , and H_{33} explicitly in Eq. (6.27). With the aid of the Hamilton operator [Eq. (6.10)] we obtain:

$$H_{22} = \langle \alpha\beta | \mathcal{H} | \alpha\beta \rangle = \langle \alpha\beta | \mathcal{H}^{(0)} | \alpha\beta \rangle + \langle \alpha\beta | \mathcal{H}^{(1)} | \alpha\beta \rangle \quad (6.28)$$

We treat the individual terms separately and find that:

$$\begin{aligned} \langle \alpha\beta | \mathcal{H}^{(0)} | \alpha\beta \rangle &= \langle \alpha\beta | v_A \hat{I}_z(1) + v_A \hat{I}_z(2) | \alpha\beta \rangle \\ &= \langle \alpha\beta | (\tfrac{1}{2} v_A - \tfrac{1}{2} v_A) | \alpha\beta \rangle \\ &= 0 \\ \langle \alpha\beta | \mathcal{H}^{(1)} | \alpha\beta \rangle &= \langle \alpha\beta | J \hat{I}(1) \hat{I}(2) | \alpha\beta \rangle \\ &= J \langle \alpha\beta | \hat{I}_x \hat{I}_x + \hat{I}_y \hat{I}_y + \hat{I}_z \hat{I}_z | \alpha\beta \rangle \\ &= J (\langle \alpha\beta | \hat{I}_x \hat{I}_x | \alpha\beta \rangle + \langle \alpha\beta | \hat{I}_y \hat{I}_y | \alpha\beta \rangle + \langle \alpha\beta | \hat{I}_z \hat{I}_z | \alpha\beta \rangle)^2 \\ &= J (\tfrac{1}{4} \langle \alpha\beta | \beta\alpha \rangle + \tfrac{1}{4} \langle \alpha\beta | \beta\alpha \rangle - \tfrac{1}{4} \langle \alpha\beta | \alpha\beta \rangle) \\ &= -\tfrac{1}{4} J \end{aligned}$$

Thus $H_{22} = -\tfrac{1}{4}J$, and analogously we obtain $H_{33} = -\tfrac{1}{4}J$. Calculations for the off-diagonal elements proceed as follows:

$$\begin{aligned} H_{23} &= \langle \alpha\beta | \mathcal{H} | \alpha\beta \rangle = \langle \alpha\beta | \mathcal{H}^{(0)} | \alpha\beta \rangle + \langle \alpha\beta | \mathcal{H}^{(1)} | \alpha\beta \rangle \\ \langle \alpha\beta | \mathcal{H}^{(0)} | \alpha\beta \rangle &= \langle \alpha\beta | v_A \hat{I}_z(1) + v_A \hat{I}_z(2) | \beta\alpha \rangle \\ &= \langle \alpha\beta | (-\tfrac{1}{2} v_A + \tfrac{1}{2} v_A) | \beta\alpha \rangle \\ &= 0 \\ \langle \alpha\beta | \mathcal{H}^{(1)} | \alpha\beta \rangle &= \langle \alpha\beta | J \hat{I}(1) \hat{I}(2) | \beta\alpha \rangle \\ &= J (\langle \alpha\beta | \hat{I}_x \hat{I}_x | \beta\alpha \rangle + \langle \alpha\beta | \hat{I}_y \hat{I}_y | \beta\alpha \rangle + \langle \alpha\beta | \hat{I}_z \hat{I}_z | \beta\alpha \rangle) \\ &= J (\tfrac{1}{4} \langle \alpha\beta | \alpha\beta \rangle + \tfrac{1}{4} \langle \alpha\beta | \alpha\beta \rangle - \tfrac{1}{4} \langle \alpha\beta | \beta\alpha \rangle) \\ &= \tfrac{1}{2} J \end{aligned}$$

- 2) Here the scalar product $\hat{I} \hat{I}$ is resolved into $\hat{I}_x \hat{I}_x + \hat{I}_y \hat{I}_y + \hat{I}_z \hat{I}_z$ and the indices of the operators have been omitted for clarity.

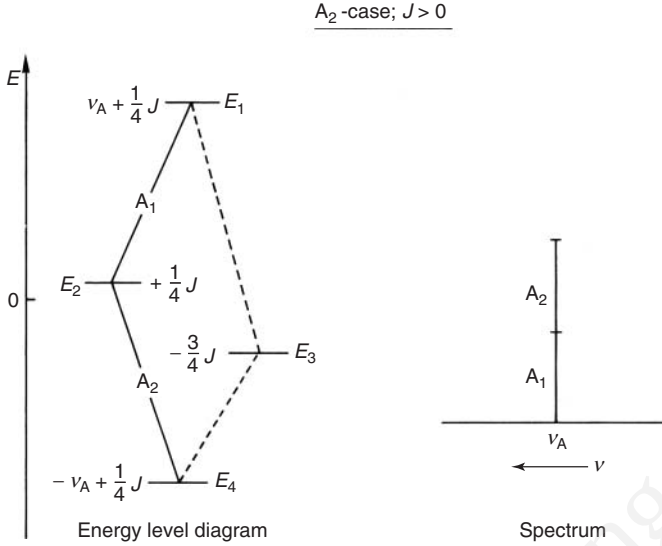


Figure 6.2 Energy level diagram and spectrum of the A_2 system.

H_{32} also equals $\frac{1}{2}J$ and the determinant reduces to:

$$\begin{vmatrix} -\frac{1}{4}J - \varepsilon & \frac{1}{2}J \\ \frac{1}{2}J & -\frac{1}{4}J - \varepsilon \end{vmatrix} = 0 \quad (6.29)$$

This leads to the quadratic equation $(-\frac{1}{4}J - \varepsilon)^2 - \frac{1}{4}J^2 = 0$ that has the solutions $\varepsilon_2 = +\frac{1}{4}J$ and $\varepsilon_3 = -\frac{3}{4}J$.

The variational method with the appropriate trial function $\Psi_{2,3}$ thus leads us to two energy values, one of which corresponds to a destabilization and the other to a stabilization of the system. The fact that two nuclei of equal resonance frequencies interact with one another through spin-spin coupling thus leads to a splitting of the energy values ε_2 and ε_3 that in the case $J = 0$ and $\nu_A = \nu_B$ were degenerate (cf. Section 6.4.2). We can state further without proof that the approximation of the variational method is sufficiently exact in the present case so that the energies ε_2 and ε_3 are the new eigenvalues E_2 and E_3 . Consequently, the energy level diagram for the A_2 case has the form shown in Figure 6.2. The eigenvalues E_1 and E_4 , $\nu_A + \frac{1}{4}J$ and $-\nu_A + \frac{1}{4}J$, respectively, result from substitution of the corresponding product functions $\alpha\alpha$ and $\beta\beta$ into Eq. (6.2) since the latter are always true eigenfunctions.

We now complete our consideration of the A_2 case with the calculation of the coefficients c_2 and c_3 in our linear combination Eq. (6.18). Substitution of the solution of E_2 in Eqs (6.15) and (6.16) results in:

$$\begin{aligned} c_2 \left(-\frac{1}{2}J\right) + c_3 \frac{1}{2}J &= 0 \\ c_2 \frac{1}{2}J + c_3 \left(-\frac{1}{2}J\right) &= 0 \end{aligned}$$

From this it follows that $c_2 = c_3$. As an additional equation for the unknown coefficient we employ the normalization condition Eq. (6.15) that also must hold for our linear combination. It requires that $\langle \Psi | \Psi \rangle = 1$ and this leads to the result that $c_2^2 + c_3^2 = 1$. Thus $c_2 = c_3 = 1/\sqrt{2}$ and the correct wave function has the form $\Psi_2 = (1/\sqrt{2})(\alpha\beta + \beta\alpha)$. Through substitution of E_3 we find that $c_2 = -c_3$ and in a manner analogous to that above it results that $\Psi_3 = (1/\sqrt{2})(\alpha\beta - \beta\alpha)$.

Thus, the two eigenstates with total spin $m_T = 0$ are characterized by different wave functions. In summary we can conclude that the variational principle leads us in our quest for the wave functions of the states (2) and (3) first to the energies of those states and from those energies to the coefficients c_2 and c_3 in the linear combination [Eq. (6.18)].

6.4.3.2 Calculation of the Relative Intensities

We have previously calculated transition energies by determining the differences in the eigenvalues of the corresponding spin system on the basis of the selection rule $\Delta m_T = \pm 1$. However, in so doing we did not concern ourselves with the relative intensities of the lines, that is, with the relative probabilities of the transitions. For the A_2 case we want to proceed differently and stipulate first that, in general, the relative intensity of a line is proportional to the square of the so-called *transition moment*, M , between the eigenstates under consideration. The transition moment between two stationary states Ψ_m and Ψ_n is defined by Eq. (6.30), in which the operator $\hat{I}_x$ is involved:

$$M = \langle \Psi_m | \sum_i \hat{I}_x(i) | \Psi_n \rangle \quad (6.30)$$

Applying Eq. (6.30) to the A_2 case we obtain the following relative intensities:

For the transition $\Psi_2 \rightarrow \Psi_1$:

$$\begin{aligned} M^2 &= \left\langle 1/\sqrt{2}(\alpha\beta + \beta\alpha) \middle| \hat{I}_x(1) + \hat{I}_x(2) \middle| \alpha\alpha \right\rangle^2 \\ &= \frac{1}{2} \left(\frac{1}{2} \langle \alpha\beta | \beta\alpha \rangle + \frac{1}{2} \langle \alpha\beta | \alpha\beta \rangle + \frac{1}{2} \langle \beta\alpha | \beta\alpha \rangle + \frac{1}{2} \langle \beta\alpha | \alpha\beta \rangle \right)^2 \\ &= \frac{1}{2} \end{aligned}$$

For the transition $\Psi_3 \rightarrow \Psi_1$:

$$\begin{aligned} M^2 &= \left\langle 1/\sqrt{2}(\alpha\beta - \beta\alpha) \middle| \hat{I}_x(1) + \hat{I}_x(2) \middle| \alpha\alpha \right\rangle^2 \\ &= \frac{1}{2} \left(\frac{1}{2} \langle \alpha\beta | \beta\alpha \rangle + \frac{1}{2} \langle \alpha\beta | \alpha\beta \rangle - \frac{1}{2} \langle \beta\alpha | \beta\alpha \rangle - \frac{1}{2} \langle \beta\alpha | \alpha\beta \rangle \right)^2 \\ &= 0 \end{aligned}$$

In the same fashion the calculations for the transitions $\Psi_4 \rightarrow \Psi_2$ and $\Psi_4 \rightarrow \Psi_3$ result in relative intensities of $1/2$ and 0, respectively. Transitions that involve the eigenvalue E_3 thus have an intensity of zero so that only two lines of the same frequency appear in the spectrum, that is, only a single line at ν_A is observed.

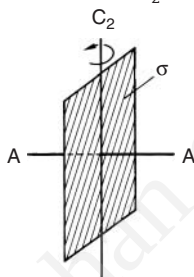
This is a confirmation of the earlier postulate that spin–spin coupling between magnetically equivalent nuclei does not affect the experimental spectrum.

Exercise 6.4

Calculate with wave functions of Table 6.1a and Eq. (6.30) the relative intensities of the transitions for the AB case assuming that there is no spin–spin interaction.

6.4.3.3 Symmetric and Antisymmetric Wave Functions

A consideration of the A_2 case proceeding on the basis of its symmetry leads to the same result and we will go through it because in so doing we will become acquainted with some important properties of operators. Neglecting the axis of rotation coincident with the internuclear axis, the A_2 group possesses a plane of reflection, σ , and a two-fold axis of rotation, C_2 , as symmetry elements:



Relative to these symmetry elements the eigenfunctions Ψ_2 and Ψ_3 are different. While Ψ_2 remains unchanged as a result of the symmetry operations, that is by an exchange of the two nuclei, Ψ_3 changes its sign. Thus, Ψ_2 and Ψ_3 are designated as symmetric and antisymmetric wave functions, respectively:

$$\begin{aligned} \frac{1}{\sqrt{2}}(\alpha\beta + \beta\alpha) &\xrightarrow{\sigma \text{ or } C_2} \frac{1}{\sqrt{2}}(\beta\alpha + \alpha\beta) \equiv \frac{1}{\sqrt{2}}(\alpha\beta + \beta\alpha) \\ \frac{1}{\sqrt{2}}(\alpha\beta - \beta\alpha) &\xrightarrow{\sigma \text{ or } C_2} \frac{1}{\sqrt{2}}(\beta\alpha - \alpha\beta) \equiv -\frac{1}{\sqrt{2}}(\alpha\beta - \beta\alpha) \end{aligned}$$

To the corresponding symmetry operations, reflection in σ or rotation around C_2 , an operator, $\hat{S}$, can be assigned that obviously must have the eigenvalues $s = +1$ and $s = -1$ since the eigenvalue equations $\hat{S}\Psi_2 = (+1)\Psi_2$ and $\hat{S}\Psi_3 = (-1)\Psi_3$ apply. Now, a theorem of quantum mechanics states that for two commuting operators $\hat{Q}$ and $\hat{R}$ (that is, $\hat{Q}\hat{R}\Psi = \hat{R}\hat{Q}\Psi$) expressions of the type $\langle \Psi_n | \hat{R} | \Psi_m \rangle$ vanish if Ψ_n and Ψ_m are eigenfunctions of the operator $\hat{Q}$ belonging to different eigenvalues q_n and q_m , that is, if the condition $q_n \neq q_m$ holds.

For the specific case of the transition probability in the A_2 system this statement means that the transitions $\Psi_3 \rightarrow \Psi_1$ and $\Psi_4 \rightarrow \Psi_3$ are “forbidden.” The proof hereof appears in the Appendix. Since the line intensity obviously must be independent of whether the symmetry operation is executed or not, the operators $\hat{S}$ and $\hat{I}_x$ must commute. Now, the wave functions Ψ_1 , Ψ_2 , and Ψ_4 are eigenfunctions of $\hat{S}$ for the eigenvalue $s = +1$ while Ψ_3 is an eigenfunction for the eigenvalue $s = -1$.

Thus the expressions $\langle \Psi_3 | \hat{I}_x | \Psi_1 \rangle$ and $\langle \Psi_4 | \hat{I}_x | \Psi_3 \rangle$ must vanish and [according to Eq. (6.18)] the intensity of the corresponding transitions must be zero.

The general conclusion to be drawn from this is that *transitions between wave functions of different symmetry are forbidden*. In this connection the eigenvalues of the operator $\hat{S}$ can also be considered as “good quantum numbers” that are not changed in the NMR experiment. As a further selection rule for allowed transitions, it follows that $\Delta s = 0$.

The results we have obtained for the A_2 system are tabulated in Table 6.1b,c (p. 168). The wave functions are labeled by their total spin, m_T , and their symmetry properties. As can be seen, the introduction of spin–spin coupling causes a destabilization of $\frac{1}{4}J$ for the symmetric states while in the antisymmetric state a stabilization of $\frac{3}{4}J$ results. This is in agreement with the tenets of valence theory concerning the coupling of electron spins in chemical bonds. The three symmetric spin functions describe the state of two particles that formally possess parallel spin orientations and consequently the spin quantum number of $I = 1$ with the magnetic quantum numbers $+1$, 0 , and -1 . These three functions represent a so-called *triplet state*.³⁾ The *singlet state* with $I = 0$, on the other hand, is characterized by the antisymmetric function a_0 , the stabilization of which justifies the well-known statement of the Pauli principle that the bonding state of two electrons is characterized by an antiparallel arrangement of their spins. The selection rules for the transitions in an A_2 system discussed above can also be expressed in this terminology. According to a general law of quantum mechanics, transitions between term systems of different multiplicity, that is, between singlet and triplet states in this context, are forbidden. On this basis *para*-hydrogen, for example, is metastable near 0 K for several months.

Identical conclusions to those derived for the A_2 system are also valid for other A_n systems of magnetically equivalent nuclei. The energy levels of the symmetric wave functions are equidistant and transitions including the antisymmetric states are forbidden. This explains the singlets observed for methylene chloride (A_2), methane (A_4), benzene (A_6), and for several other cases. We shall learn in Chapter 14, however, that partial orientation of these molecules in liquid crystals removes the degeneracy of the symmetric transitions and, aside from the dominant line splitting due to the dipolar coupling, the scalar coupling constants also become measurable.

6.4.4

The AB System

The variational principle and the relation Eq. (6.18) for determination of the transition moment also enable us to treat spin systems that are not simplified by restrictive conditions. Let us now turn to the AB system in which both parameters $\nu_0\delta$ and J are of comparable magnitude.

- 3) The multiplicity of a state (singlet, doublet, triplet, etc.) is determined by the spin quantum number, I , according to the formula $2I + 1$ (cf. the quantum condition Eq. (2.3), p. 14). It indicates the number of magnetic quantum numbers a state has and thus the number of possible orientations with respect to the direction of an external magnetic field.

We follow the treatment of the A_2 case completely up to the derivation of the determinant Eq. (6.29). Here the simplifying condition that $\nu_A = \nu_B$ does not hold and for the matrix elements H_{22} , H_{23} , and H_{33} the following expressions are obtained:

$$\begin{aligned} H_{22} &= \frac{1}{2}\nu_0\delta - \frac{1}{4}J \\ H_{23} &= H_{32} = \frac{1}{2}J \\ H_{33} &= -\frac{1}{2}\nu_0\delta - \frac{1}{4}J \end{aligned}$$

The determinant is then:

$$\begin{vmatrix} \left(\frac{1}{2}\nu_0\delta - \frac{1}{4}J\right) - E & \frac{1}{2}J \\ \frac{1}{2}J & \left(-\frac{1}{2}\nu_0\delta - \frac{1}{4}J\right) - E \end{vmatrix} = 0 \quad (6.31)$$

Expanding the determinant leads to the quadratic equation:

$$E^2 + \frac{1}{2}JE - \frac{1}{4}(\nu_0\delta)^2 - \frac{3}{16}J^2 = 0$$

that has solutions:

$$E_{2,3} = -\frac{1}{4}J \pm \frac{1}{2}\sqrt{J^2 + \nu_0\delta^2}$$

The eigenvalues E_1 and E_4 once more result from Eq. (6.2) and the product functions $\alpha\alpha$ and $\beta\beta$, respectively:

$$\begin{aligned} E_1 &= \frac{1}{2}(\nu_A + \nu_B) + \frac{1}{4}J \\ E_4 &= -\frac{1}{2}(\nu_A + \nu_B) + \frac{1}{4}J \end{aligned}$$

The next step is to calculate the coefficients in our trial function [Eq. (6.14)]. For this we first substitute the solution E_2 in Eq. (6.15). For brevity we let:

$$C = \frac{1}{2}\sqrt{J^2 + \nu_0\delta^2}$$

and obtain:

$$c_2\left(\frac{1}{2}\nu_0\delta - C\right) + c_3\frac{1}{2}J = 0$$

The calculations now necessary can be elegantly simplified if an angle 2θ defined by the following relations is introduced:

$$\nu_0\delta/2C = \cos 2\theta \quad \text{and} \quad J/2C = \sin 2\theta$$

It follows that:

$$c_2(1 - \cos 2\theta) - c_3 \sin 2\theta = 0$$

and:

$$c_2 = c_3 \sin 2\theta / (1 - \cos 2\theta)$$

Application of the identities $\sin(2\theta) = 2\cos(\theta)\sin(\theta)$ and $\cos(2\theta) = \cos^2\theta - \sin^2\theta$ leads to the result $c_2 = c_3 \cos(\theta)/\sin(\theta)$ and, with the aid of the normalization condition $c_2^2 + c_3^2 = 1$, the values $c_2 = \cos \theta$ and $c_3 = \sin \theta$ are obtained for the coefficients.

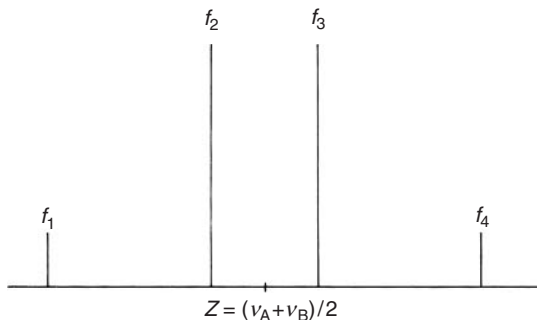


Figure 6.3 Spectrum of an AB system with $|J_{AB}| > 0$.

Substitution of E_3 in an analogous fashion results in the coefficients $c_2 = -\sin \theta$ and $c_3 = \cos \theta$. Thus, the correct wave functions for states (2) and (3) are:

$$\Psi_2 = \cos \theta(\alpha\beta) + \sin \theta(\beta\alpha)$$

$$\Psi_3 = -\sin \theta(\alpha\beta) + \cos \theta(\beta\alpha)$$

We now turn to the calculation of the relative intensities, where we again use relation Eq. (6.18). For the $\Psi_2 \rightarrow \Psi_1$ transition, for example, this yields:

$$\begin{aligned} M^2 &= \langle [\cos \theta(\alpha\beta) + \sin \theta(\beta\alpha)] | \hat{I}_x(A) + \hat{I}_x(B) | \alpha\alpha \rangle^2 \\ &= \frac{1}{4}(1 + \sin 2\theta) \end{aligned}$$

The relative intensities of the other transitions are obtained in analogous fashion.

The complete results of our consideration of the AB system are given in Table 6.1d. The spectrum consists of four lines that are arranged symmetrically about the center $(\nu_A + \nu_B)/2$. The outer lines of the AB quartet are of lower intensity than the central lines, a result we introduced empirically on p. 56 as the “roof effect.” The energy level diagram is different from that shown in Figure 6.1 only in that the eigenvalues are differently stabilized or destabilized and that the lines $A_1(f_1)$ and $A_2(f_2)$ and $B_1(f_3)$, and $B_2(f_4)$, respectively, are no longer degenerate.

To illustrate our conclusions derived for the AB system with a practical example, Figure 6.3 shows the spectrum calculated with the assumed parameters $\nu_0\delta = 15$ Hz and $J = 12$ Hz.

Exercise 6.5

In the preceding sections the expressions for the eigenvalues, wave functions, and transition probabilities were not explicitly derived in all cases. Confirm the results given by working through the necessary derivations.

Exercise 6.6

Calculate with the relations in Table 6.1d the line frequencies and intensities for an AB system with $\nu_0\delta = 20$ Hz and $J = 15$ Hz.

Exercise 6.7

Write the secular determinant according to the variational method for the linear combination $\Psi = c_2(\alpha\alpha\beta) + c_3(\alpha\beta\alpha) + c_4(\beta\alpha\alpha)$.

Exercise 6.8

For an AB system it is observed that $f_1 - f_2 = f_2 - f_3 = f_3 - f_4$.

- What is the ratio $\nu_0\delta/J$?
- Calculate the relative intensities of the lines.
- How can one determine that the signals do not comprise a first-order quartet?

6.4.5

The AX System and the First-Order Approximation

Having determined the eigenvalues and the eigenfunctions of the AB system, it would be of interest at this point to investigate the dependence of the line frequencies and intensities on the ratio of the parameters $\nu_0\delta$ and J .

Let us first discuss the case in which the *relative chemical shift* $\nu_0\delta$ is *very large compared with the coupling constant*. As a result of this the parameter C approaches $\frac{1}{2}\nu_0\delta$ and the expression $\sin 2\theta$ approaches zero. However, since $\sin(2\theta) = 2\sin(\theta)\cos(\theta)$, either $\sin\theta$ or $\cos\theta$ must be zero. Further, since $\sin^2\theta + \cos^2\theta = 1$, when $\sin\theta = 0$ it follows that $\cos\theta = 1$. The eigenfunctions and eigenvalues for this limiting case, classified as an AX case, are thus:

- (1) $\alpha\alpha \quad \frac{1}{2}(\nu_A + \nu_X) + \frac{1}{4}J$
- (2) $\alpha\beta \quad \frac{1}{2}(\nu_A - \nu_X) - \frac{1}{4}J$
- (3) $\beta\alpha \quad -\frac{1}{2}(\nu_A - \nu_X) - \frac{1}{4}J$
- (4) $\beta\beta \quad -\frac{1}{2}(\nu_A + \nu_X) + \frac{1}{4}J$

and the transition energies and the intensities for this system given in Table 6.1e are obtained in the usual manner.

We now go back a step further to the determinant Eq. (6.19) and see what the eigenvalues and the eigenfunctions of the states (2) and (3) would be if the off-diagonal elements H_{23} and H_{32} were neglected and set to zero:

$$\begin{vmatrix} H_{22} - E & 0 \\ 0 & H_{33} - E \end{vmatrix} = \begin{vmatrix} \left(\frac{1}{2}\nu_0\delta - \frac{1}{4}J\right) - E & 0 \\ 0 & \left(-\frac{1}{2}\nu_0\delta - \frac{1}{4}J\right) - E \end{vmatrix} = 0$$

Since a determinant becomes zero when the elements of one of its columns or rows are zero, we immediately obtain:

$$E_2 = H_{22} = \frac{1}{2}\nu_0\delta - \frac{1}{4}J$$

and:

$$E_3 = H_{33} = -\frac{1}{2}\nu_0\delta - \frac{1}{4}J$$

Table 6.1 Eigenfunctions, eigenvalues, transition energies, and transition probabilities for the two-spin systems of the A_2 , AB, and AX types.

Eigenfunctions	Eigenvalues	Transitions	Transition energy	Relative intensity
(a) AB case; $J_{AB} = 0$				
m_T				
(1) +1 $\alpha\alpha$	$\frac{1}{2}(\nu_A + \nu_B)$	(3) $\rightarrow$ (1) (A)	ν_A	1
(2) 0 $\alpha\beta$	$\frac{1}{2}(\nu_A - \nu_B)$	(4) $\rightarrow$ (2) (A)	ν_A	1
(3) 0 $\beta\alpha$	$-\frac{1}{2}(\nu_A - \nu_B)$	(2) $\rightarrow$ (1) (B)	ν_B	1
(4) -1 $\beta\beta$	$-\frac{1}{2}(\nu_A + \nu_B)$	(4) $\rightarrow$ (3) (B)	ν_B	1
(b) A_2 case; $J = 0$				
m_T				
(1) +1 $\alpha\alpha$	ν_A	(3) $\rightarrow$ (1) (A)	ν_A	1
(2) 0 $\alpha\beta$	0	(4) $\rightarrow$ (2) (A)	ν_A	1
(3) 0 $\beta\alpha$	0	(2) $\rightarrow$ (1) (A)	ν_A	1
(4) -1 $\beta\beta$	$-\nu_A$	(4) $\rightarrow$ (3) (A)	ν_A	1
(c) A_2 case; $J > 0$				
m_T				
(1) +1 $\alpha\alpha$	s_{+1}	$a_0 \rightarrow s_{+1}$ (A)	$\nu_A + J$	0
(2) 0 $(\alpha\beta + \beta\alpha)/\sqrt{2}$	s_0	$s_{-1} \rightarrow s_0$ (A)	ν_A	2
(3) 0 $(\alpha\beta - \beta\alpha)/\sqrt{2}$	a_0	$s_0 \rightarrow s_{+1}$ (A)	ν_A	2
(4) -1 $\beta\beta$	s_{-1}	$s_{-1} \rightarrow a_0$ (A)	$\nu_A - J$	0

(d) AB case: $J_{AB} > 0$					
m_T					
(1) +1	$\alpha\alpha$	$\frac{1}{2}(\nu_A + \nu_B) + \frac{1}{4}J_{AB}$	(3) $\rightarrow$ (1) (A) f_1	$\frac{1}{2}(\nu_A + \nu_B) + \frac{1}{2}J_{AB} + C^a$	$1 - \sin 2\theta$
(2) 0	$\cos \theta(\alpha\beta) + \sin \theta(\beta\alpha)$	$-\frac{1}{4}J_{AB} + C$	(4) $\rightarrow$ (2) (A) f_2	$\frac{1}{2}(\nu_A + \nu_B) - \frac{1}{2}J_{AB} + C$	$1 + \sin 2\theta$
(3) 0	$-\sin \theta(\alpha\beta) + \cos \theta(\beta\alpha)$	$-\frac{1}{4}J_{AB} - C$	(2) $\rightarrow$ (1) (B) f_3	$\frac{1}{2}(\nu_A + \nu_B) + \frac{1}{2}J_{AB} - C$	$1 + \sin 2\theta$
(4) -1	$\beta\beta$	$-\frac{1}{2}(\nu_A + \nu_B) + \frac{1}{4}J_{AB}$	(4) $\rightarrow$ (3) (B) f_4	$\frac{1}{2}(\nu_A + \nu_B) - \frac{1}{2}J_{AB} - C$	$1 - \sin 2\theta$
(e) AX case: $J_{AX} > 0$					
m_T					
(1) +1	$\alpha\alpha$	$\frac{1}{2}(\nu_A + \nu_X) + \frac{1}{4}J_{AX}$	(3) $\rightarrow$ (1) (A)	$\nu_A + \frac{1}{2}J_{AX}$	1
(2) 0	$\alpha\beta$	$\frac{1}{2}(\nu_A - \nu_X) - \frac{1}{4}J_{AX}$	(4) $\rightarrow$ (2) (A)	$\nu_A - \frac{1}{2}J_{AX}$	1
(3) 0	$\beta\alpha$	$-\frac{1}{2}(\nu_A - \nu_X) - \frac{1}{4}J_{AX}$	(2) $\rightarrow$ (1) (X)	$\nu_X + \frac{1}{2}J_{AX}$	1
(4) -1	$\beta\beta$	$-\frac{1}{2}(\nu_A + \nu_X) + \frac{1}{4}J_{AX}$	(4) $\rightarrow$ (3) (X)	$\nu_X - \frac{1}{2}J_{AX}$	1

$$^a C = \frac{1}{2} \sqrt{J^2 + \nu_0^2}.$$

Substitution of these solutions into the secular Eqs (6.15) and (6.16) leads – in conjunction with the normalization condition $c_2^2 + c_3^2 = 1$ – to values for the coefficients c_2 and c_3 of 1 and 0 for Ψ_2 and 0 and 1 for Ψ_3 , respectively. The wave functions are therefore $\Psi_2 = \alpha\beta$ and $\Psi_3 = \beta\alpha$.

Thus, neglect of the off-diagonal elements leads directly from the general AB case to the special AX case. Clearly, this simplification is justified only when these elements are substantially smaller than the diagonal elements. The appropriate situation is obtained when $\nu_0\delta \gg J$, a criterion we introduced on p. 45 for the application of the first-order rules. As can now be clearly understood, these rules are a special case resulting from the general derivation and strictly apply for very large chemical shifts only.

We encounter a second limiting case when the *relative chemical shift*, $\nu_0\delta$, becomes very small compared with the coupling constant, J . The parameter C then approaches J and $\sin 2\theta$ approaches 1. According to Table 6.1d the intensities of the lines f_1 and f_4 then decrease to the extent that the spectrum degenerates to that of an A_2 system, since in addition the transitions f_2 and f_3 coincide at $(\nu_A + \nu_B)/2$.

In practice, AB systems that closely approach the A_2 case are very often met. On the one hand, the center lines lie so close to one another that the spectral resolution is not sufficient to separate them. On the other hand, the intensity of the outer lines is so small that the sensitivity of the spectrometer does not allow their detection. Such spectra are termed “*deceptively simple*” spectra. The criteria for such spectra in the AB case are given by the relations:

$$\frac{(\nu_0\delta)^2}{2J} < \Delta \quad \text{and} \quad \frac{(\nu_0\delta)^2}{2J^2} < i$$

where Δ is the natural width of the spectral line and i is the lower limit of the detectable intensity. We shall encounter this phenomenon again in our discussion of other spin systems.

6.4.6

General Rules for the Treatment of More Complex Spin Systems

The preceding sections have shown how the eigenvalues and the eigenfunctions for stationary states with the same total spin can be obtained by means of the variational method. The same formalism can be used for more complex spin systems since the simple product functions of the type $\alpha\alpha \dots \beta$ always serve as the basis for the linear combinations. The method is thus very easily generalized.

First the Pascal triangle (p. 47) gives a systematic survey of the number of eigenstates and product functions, grouped according to their total spin, that are to be expected for a particular spin system with n nuclei of spin $I = \frac{1}{2}$. In general there are 2^n eigenstates for a system with n nuclei, so it is apparent that the number increases rapidly for more complex spin systems.

Thus, in the *three-spin* case the three basis functions $\alpha\alpha\beta$, $\alpha\beta\alpha$, and $\beta\alpha\alpha$ correspond to the m_T value $\frac{1}{2}$. Then the expression:

$$\Psi = c_2(\alpha\alpha\beta) + c_3(\alpha\beta\alpha) + c_4(\beta\alpha\alpha)$$

serves as our linear combination. More generally, in vector notation we have:

$$\Psi = \mathbf{c}_i \times \phi_i$$

where $\mathbf{c}_i$ is a row vector and ϕ_i is column vector:

$$\Psi = (c_1, c_2, \dots, c_n) \times \begin{pmatrix} \phi_1 \\ \phi_2 \\ \vdots \\ \phi_n \end{pmatrix}$$

Since the coefficients c_i convert the corresponding set of basis functions, ϕ_i , into eigenfunctions of the spin system they are termed *eigenvectors*. For the AB case there results for the states (2) and (3):

$$(\cos \theta, \sin \theta) \times \begin{pmatrix} \alpha\beta \\ \beta\alpha \end{pmatrix} \text{ and } (-\sin \theta, \cos \theta) \times \begin{pmatrix} \alpha\beta \\ \beta\alpha \end{pmatrix}.$$

Finally, from the Pascal triangle we also can obtain the theoretically possible number of lines for a spin system if the selection rule $\Delta m_T = \pm 1$ is observed. Of course, this number also includes the so-called *combination lines* for which the spin orientation of several nuclei is changed simultaneously and that are therefore forbidden (e.g., $\alpha\beta\beta \rightarrow \beta\alpha\alpha$). More correctly, the selection rule must be reformulated with respect to the magnetic quantum number, m_I , of the individual nuclei:

$$\sum_{i=1}^n \Delta m_I(i) = +1 \quad \text{with} \quad \Delta m_I(i) = 0, +1 \quad (6.32)$$

If we now apply the Hamilton operator Eq. (6.10) to the basis functions of a spin system of interest, we obtain the quantities $H_{11}, \dots, H_{kk}$ and $H_{12}, \dots, H_{kl}$ that most clearly can be arranged in the *Hamilton matrix*, $\hat{H}$. For a two-spin system this matrix has the form:

$$\hat{H} = \begin{vmatrix} H_{11} & 0 & 0 & 0 \\ 0 & H_{22} & H_{23} & 0 \\ 0 & H_{32} & H_{33} & 0 \\ 0 & 0 & 0 & H_{44} \end{vmatrix} \quad (6.33)$$

The following points deserve attention:

- 1) The *Hamilton matrix* is a square matrix and because of the identity $H_{23} = H_{32}$ (in general $H_{kl} = H_{lk}$) symmetric with respect to the principal diagonal.
- 2) The *off-diagonal matrix elements* between eigenstates with different total spins are zero. The matrix can therefore be factorized into submatrices:

$$\hat{H} = |H_{11}| \times \begin{vmatrix} H_{22} & H_{23} \\ H_{32} & H_{33} \end{vmatrix} \times |H_{44}|$$

This result is likewise a consequence of the theorem introduced earlier (p. 163) concerning commuting operators. Here the Hamilton operator and the operator $\hat{F}_z$ commute (cf. Appendix, p. 665) and the matrix elements $\langle \Psi_n | H | \Psi_m \rangle$ for eigenfunctions that belong to different eigenvalues n and m of F_z vanish.

- 3) If we subtract the energy E from the diagonal matrix elements H_{kk} and, after factorizing, set the individual factors equal to zero, secular determinants result of the general form:

$$|H_{kl} - \delta_{kl}E| = 0 \text{ with } \delta_{kl} = 1 \text{ for } k = l \\ \text{and } \delta_{kl} = 0 \text{ for } k \neq l$$

Because of point 2 above, their number is equal to the number of different m_T values of the corresponding spin system. Their dimensions follow clearly from the number of basis functions belonging to the respective total spin. They can also be determined directly by reference to the Pascal triangle. Solving the secular determinants yields the eigenvalues of the corresponding spin system and, via the secular equations, the eigenvectors as coefficients of the eigenfunctions.

- 4) Independent of the size of the spin system, the diagonal elements H_{11} and H_{kk} are always correct eigenvalues for the states with total spin $+n/2$ or $-n/2$ and the basis functions $\alpha\alpha \dots \alpha$ or $\beta\beta \dots \beta$ are correct eigenfunctions of these spin states.

The Hamilton matrix can be set up using the basis function ϕ_k for any spin system by the application of simple rules. For the diagonal elements:

$$\langle \phi_k | \mathcal{H} | \phi_k \rangle = H_{kk} = \sum_{i=1}^n v_i m_i(i) + \frac{1}{4} \sum_i \sum_{i < j} J_{ij} T_{ij}$$

with $T_{ij} = +1$ if the nuclei i and j have parallel spin in the corresponding basis function and $T_{ij} = -1$ if the nuclei i and j have antiparallel spin in the corresponding basis functions.

This formula corresponds to Eq. (3.11) (p. 44).

The off-diagonal elements between two basis functions ϕ_k and ϕ_l are given by:

$$\langle \phi_k | \mathcal{H} | \phi_l \rangle = H_{kl} = \frac{1}{2} J_{ij} U \text{ for } i \neq j$$

with $U = 1$ if ϕ_k and ϕ_l differ only by the exchange of the spin functions of the nuclei i and j (e.g., $\alpha\beta\alpha\beta$ and $\alpha\beta\beta\alpha$), and $U = 0$ in all other cases (e.g., $\alpha\beta\alpha\beta$ and $\beta\alpha\beta\alpha$).

Let us consider as an illustration of these rules the spin system of three nuclei A, B, and C. Here the complete set of the basis functions is:

$m_T = \frac{3}{2}$	$m_T = \frac{1}{2}$	$m_T = -\frac{1}{2}$	$m_T = -\frac{3}{2}$
(1) $\alpha\alpha\alpha$	(2) $\alpha\alpha\beta$	(5) $\alpha\beta\beta$	(8) $\beta\beta\beta$
	(3) $\alpha\beta\alpha$	(6) $\beta\alpha\beta$	
	(4) $\beta\alpha\alpha$	(7) $\beta\beta\alpha$	

Then, for the diagonal elements it follows:

$$H_{11} = \frac{1}{2}(\nu_A + \nu_B + \nu_C) + \frac{1}{4}(J_{AB} + J_{AC} + J_{BC})$$

$$H_{22} = \frac{1}{2}(\nu_A + \nu_B - \nu_C) + \frac{1}{4}(J_{AB} - J_{AC} - J_{BC})$$

$\vdots$

$$H_{88} = -\frac{1}{2}(\nu_A + \nu_B + \nu_C) + \frac{1}{4}(J_{AB} + J_{AC} + J_{BC})$$

and for the off-diagonal elements:

$$H_{12} = H_{13} = \dots H_{18} = 0$$

$$H_{23} = \frac{1}{2}J_{BC}$$

$$H_{24} = \frac{1}{2}J_{AC}$$

$$H_{34} = \frac{1}{2}J_{AB}$$

A simple example with the parameters:

$$\nu_A = -\nu,$$

$$\nu_B = 0,$$

$$\nu_C = \nu,$$

$$J_{AB} = J_{AC} = J_{BC} = J$$

then produces the Hamilton matrix:

$$\hat{H} = \begin{vmatrix} \frac{3}{4}J & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\nu - \frac{1}{4}J & \frac{1}{2}J & \frac{1}{2}J & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{2}J & -\frac{1}{4}J & \frac{1}{2}J & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{2}J & \frac{1}{2}J & \nu - \frac{1}{4}J & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\nu - \frac{1}{4}J & \frac{1}{2}J & \frac{1}{2}J & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{2}J & -\frac{1}{4}J & \frac{1}{2}J & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{2}J & \frac{1}{2}J & \nu - \frac{1}{4}J & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{3}{4}J \end{vmatrix}$$

Without going into the details of the mathematical treatment of such matrices here, we want to indicate a way that represents an alternative to the procedure of factoring the matrix into secular determinants as discussed above. It forms the basis for a series of computer programs for the treatment of quantum mechanical problems. The area of concern here is treated in mathematical textbooks under the rubric of the *eigenvalue problem*.

It can be shown that a quadratic matrix such as the Hamilton matrix $\hat{H}$ is linked through the matrix equation:

$$\hat{H}\hat{U} = \hat{U}\hat{D} \quad (6.34)$$

to the diagonal matrix $\hat{D}$ of the eigenvalues, that is, to a matrix with the elements $D_{kk} = E_k$ and $D_{kl} = D_{lk} = 0$.

The matrix $\hat{U}$ is a transformation matrix of a special kind that transforms, in the sense of Eq. (6.35), the matrix $\hat{H}$ into the diagonal form. Its special feature is that it is exactly the matrix of the eigenvectors so that it contains the coefficients $c_1, \dots, c_k$ of the linear combinations of the type shown in Eq. (6.18); $\hat{U}$ is called either *orthogonal* or *unitary* and Eq. (6.35) is a unitary transformation:

$$\hat{U}^{-1} \hat{H} \hat{U} = \hat{D} \quad (6.35)$$

For the eigenstates (2) and (3) of the A_2 system, for example, it follows according to Eq. (6.34) that:

$$\begin{bmatrix} -\frac{1}{4}J & \frac{1}{2}J \\ \frac{1}{2}J & -\frac{1}{4}J \end{bmatrix} \times \begin{bmatrix} \frac{1}{\sqrt{2}} & \frac{1}{\sqrt{2}} \\ \frac{1}{\sqrt{2}} & -\frac{1}{\sqrt{2}} \end{bmatrix} = \begin{bmatrix} \frac{1}{\sqrt{2}} & \frac{1}{\sqrt{2}} \\ \frac{1}{\sqrt{2}} & -\frac{1}{\sqrt{2}} \end{bmatrix} \times \begin{bmatrix} \frac{1}{4}J & 0 \\ 0 & -\frac{3}{4}J \end{bmatrix}$$

This can easily be verified by performing the indicated operations.

Standard mathematical procedures allowing us to diagonalize the Hamilton matrix $\hat{H}$ are available. Their application not only yields the diagonal matrix $\hat{D}$ of the eigenvalues, but also the matrix $\hat{U}$ of the coefficients. With that the eigenvalue problem is solved and the frequencies and intensities of the spectral lines can be calculated according to Eq. (6.1) or (6.18).

Since the mathematical formalism mentioned here can easily be programmed, spectra for various spin systems are most conveniently calculated using a digital computer. We shall return later to the programs that can be employed to calculate a theoretical spectrum from a set of resonance frequencies and coupling constants. Nevertheless, we shall already use the results of such calculations in the following sections to check the parameters we obtain in the analyses of spin systems.

6.5

Calculation of the Parameters ν_i and J_{ij} from the Experimental Spectrum

We now want to consider the question posed in the introduction of to this chapter: “How can the parameters of interest of the spin system under consideration, the chemical shifts and the coupling constants, be calculated from observed line frequencies and intensities?” That is, how is an experimental spectrum analyzed? Naively considered, this problem should be solved simply by a “reversal” of the mathematical derivations presented in the foregoing sections. This is possible in practice, however, only for a two-spin system, since only here we obtain second-order equations. In general all more complex spin systems yield equations of higher order that cannot be solved explicitly. A direct analysis in the sense indicated is thus impossible. There are, however, certain strategies that allow us to simplify the problem and second-order equations can be derived even for four-spin systems. How this can actually be done is illustrated in the following sections with several examples from the more common spin systems.

6.5.1

Direct Analysis of the AB System

Spectra of the AB type, an example of which is shown in Figure 6.4 for the aromatic protons in 1-amino-3,6-dimethyl-2-nitrobenzene, are encountered in a large number of organic compounds.

2-Bromo-5-chlorothiophene (1), 1-bromo-1-chloroethene (2), 2,5-dibromo-1,6-methano[10]annulene (3), and acetaldehyde dibenzyl acetal (4) represent additional examples. As Figure 6.5 illustrates, the appearance of the spectrum is determined by the ratio $J/\nu_0\delta$.

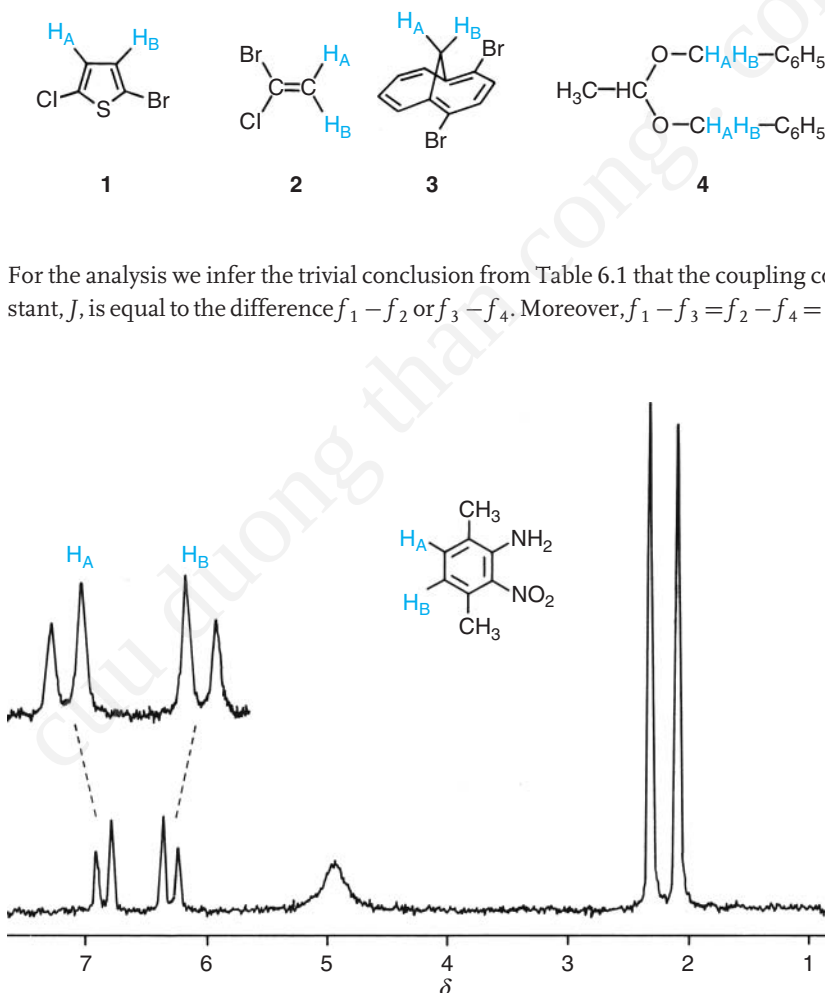


Figure 6.4 ^1H NMR spectrum of 1-amino-3,6-dimethyl-2-nitrobenzene at 60 MHz.

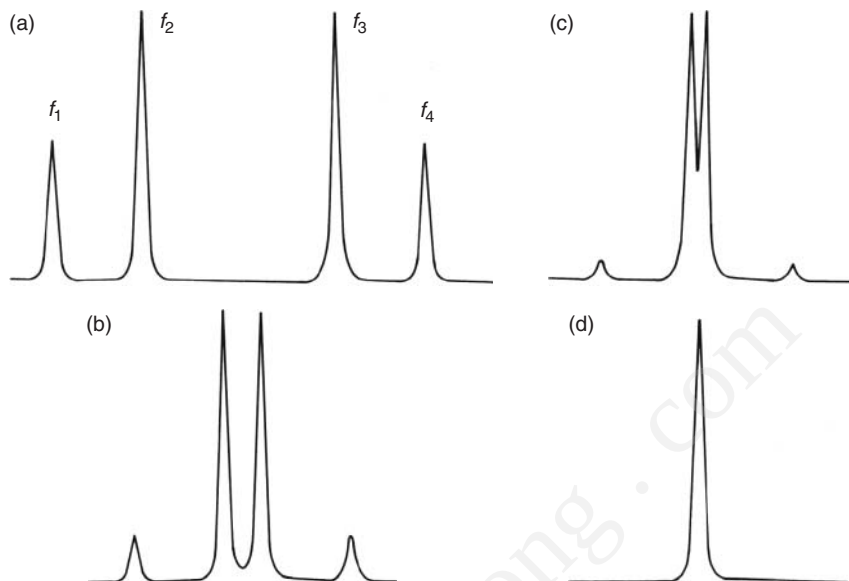


Figure 6.5 Dependence of the AB system on the ratio $J/\nu_0\delta$; spectra illustrated are for values of $J/\nu_0\delta$ of (a) 1:3, (b) 1:1, (c) 5:3, and (d) 5:1.

and, since $C = \sqrt{J^2 + \nu_0\delta^2}/2$, the relative chemical shift in an AB system is given by:

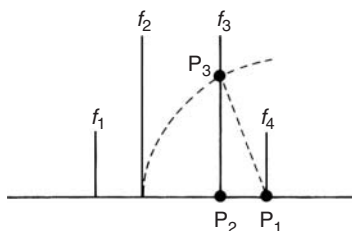
$$\begin{aligned}\nu_0\delta &= \sqrt{4C^2 - J^2} \\ &= \sqrt{(2C - J)(2C + J)} \\ &= \sqrt{(f_2 - f_3)(f_1 - f_4)}\end{aligned}$$

If Z is defined as the center of the multiplet, that is, the mid-point between f_1 and f_4 or f_2 and f_3 , then:

$$\nu_A = Z - \frac{1}{2}\nu_0\delta \quad \text{and} \quad \nu_B = Z + \frac{1}{2}\nu_0\delta$$

Further, as can be derived easily with reference to the expressions in Table 6.1 (pp. 168 and 169), for the ratio of the intensities we have $I_2/I_1 = I_3/I_4 = (f_1 - f_4)/(f_2 - f_3)$.

For the AB system there is also a geometric solution (Scheme 6.1). A circle with a radius $2C = f_2 - f_4 = \sqrt{J^2 + \nu_0\delta^2}$ is drawn about the point P_1 and there is thus obtained the rectangular triangle $P_1P_2P_3$. Since P_1P_2 is J , then – following Pythagoras – $P_2P_3 = \nu_0\delta$. The angle $\angle P_1P_3P_2$ is the angle 2θ introduced earlier (cf. p. 165).



Scheme 6.1

Exercise 6.9

Determine the resonance frequencies ν_A and ν_B for an AB system with the lines $f_1 = 38.5$, $f_2 = 28.0$, $f_3 = 20.5$, and $f_4 = 10.0$ Hz. In addition, calculate the relative intensities of the lines.

6.5.2

Spin Systems with Three Nuclei

The product functions tabulated on p. 172 according to their total spin serve as the basis for a general three-spin system. The variational method must be employed for the functions with total spin $m_T = +\frac{1}{2}$ and $m_T = -\frac{1}{2}$ in order to determine the correct eigenfunctions and eigenvalues. Only the basis functions $\alpha\alpha\alpha$ and $\beta\beta\beta$ are already eigenfunctions and the appropriate eigenvalues can be calculated by direct substitution in Eq. (6.2).

In the following we shall treat spin systems in which – because of special properties resulting from symmetry considerations or the existence of large relative chemical shifts between individual nuclei – we encounter simplifications that enable us to derive additional eigenfunctions directly from the basis functions without going through the complete variational calculation. The eigenvalues are then obtained by means of Eq. (6.2). In this manner the calculations for the three-spin system can be limited to quadratic equations so that explicit solutions for the spectral parameters can be obtained.

6.5.2.1 The AB_2 (A_2B) System

AB_2 spectra are observed for compounds that possess a two-fold axis of symmetry such as 2,6-dimethylpyridine (5) and 1,2,3-trichlorobenzene (6). Other examples are found in trisubstituted cyclopropanes with C_s symmetry (7, 8) and in benzylmalonic esters (9).

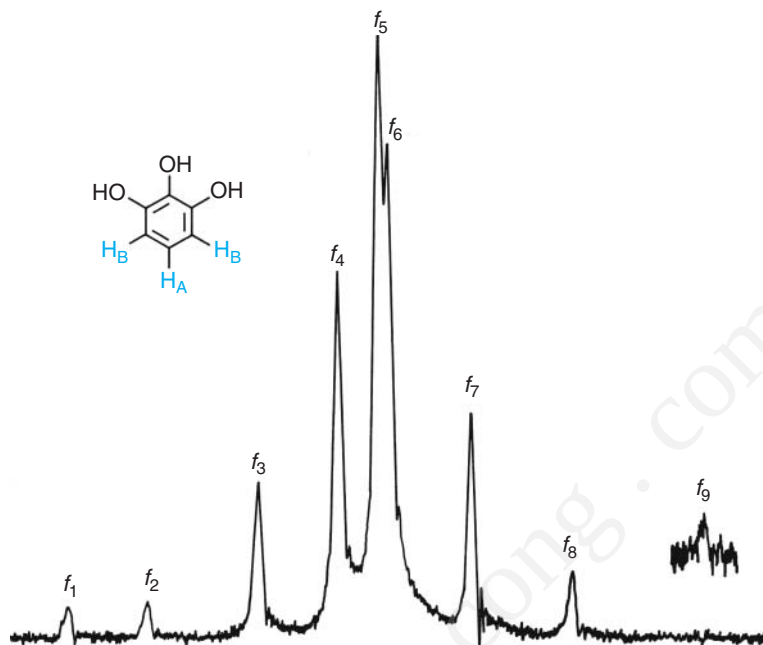


Figure 6.6 AB₂ system of the aromatic protons of pyrogallol (in chloroform) at 60 MHz.

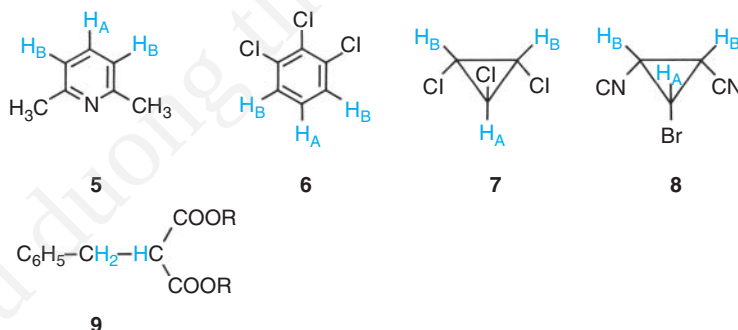


Figure 6.6 shows a typical AB₂ system. In general, seven or eight (at most, nine) transitions are observed, of which four ($f_1 - f_4$) are in the A portion. In the B₂ portion the lines f_7 and f_8 are well separated whereas f_5 and f_6 are often not resolved.

As we explained at the outset, the general case of a three-spin system is characterized by three resonance frequencies and three coupling constants.⁴⁾ In the process of the analysis of such a system two 3×3 secular determinants that arise through mixing of states with m_T values of $+\frac{1}{2}$ and $-\frac{1}{2}$ must be solved. This leads to third-order equations that cannot be explicitly solved for the parameters ν_i and J_{ij} .

4) Five parameters are sufficient since the appearance of the spectrum depends only on the relative chemical shifts.

Table 6.2 Basis functions of the AB_2 system according to symmetry.

Symmetric functions			
	A	B_2	m_T
(1) ϕ_1	α	$\alpha\alpha$	$+\frac{3}{2}$
(2) ϕ_2	α	$(\alpha\beta + \beta\alpha)/\sqrt{2}$	$+\frac{1}{2}$
(3) ϕ_3	β	$\alpha\alpha$	$+\frac{1}{2}$
(4) ϕ_4	α	$\beta\beta$	$-\frac{1}{2}$
(5) ϕ_5	β	$(\alpha\beta + \beta\alpha)/\sqrt{2}$	$-\frac{1}{2}$
(6) ϕ_6	β	$\beta\beta$	$-\frac{3}{2}$
Antisymmetric functions			
(7) ϕ_7	α	$(\alpha\beta - \beta\alpha)/\sqrt{2}$	$+\frac{1}{2}$
(8) ϕ_8	β	$(\alpha\beta - \beta\alpha)/\sqrt{2}$	$-\frac{1}{2}$

In the case of the AB_2 system this difficulty can be obviated if we make use of the results obtained for the A_2 case. The wave functions derived there can now be used for the magnetically equivalent nuclei of the B_2 group. Since α or β are the only possibilities for the wave function of the A nucleus, eight product functions are obtained as basis functions of the AB_2 system by simple multiplication. These are classified in Table 6.2 according to their symmetry and their total spin, m_T . If we recall that transitions between states of different symmetry are forbidden, it follows that a line in the A portion of the spectrum must correspond to the antisymmetric transition (8) $\rightarrow$ (7). Since the basis functions ϕ_7 and ϕ_8 are already eigenfunctions we obtain the eigenvalues E_7 and E_8 by direct substitution of ϕ_7 and ϕ_8 into Eq. (6.2). The result is $E_7 = \frac{1}{2}\nu_A - \frac{3}{4}J_{BB}$ and $E_8 = -\frac{1}{2}\nu_A - \frac{3}{4}J_{BB}$, so that the frequency of the transition is ν_A . Each AB_2 spectrum thus contains a line in the A part that is independent of the coupling constant J_{AB} and that directly yields the resonance frequency of the A nucleus. Further, the transitions in the following table are allowed ($\Delta m_T = 1$):

A lines ^a	B lines ^a	Combination line
(3) $\rightarrow$ (1)	(2) $\rightarrow$ (1)	(4) $\rightarrow$ (3)
(6) $\rightarrow$ (4)	(4) $\rightarrow$ (2)	
(5) $\rightarrow$ (2)	(6) $\rightarrow$ (5)	
	(5) $\rightarrow$ (3)	

^aThis classification holds rigorously only for the AX_2 limiting case.

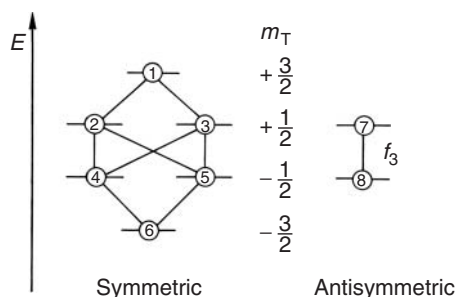


Figure 6.7 Energy level diagram of the AB_2 system.

The resulting energy level diagram is shown in Figure 6.7.

Of the symmetric basis functions, ϕ_1 and ϕ_6 are already eigenfunctions of the Hamilton operator and the corresponding eigenvalues can be calculated according to Eq. (6.2). The correct eigenfunctions Ψ_2 to Ψ_5 are determined by means of the variational method. Since only functions of the same total spin mix with one another, we obtain the following secular determinants:

$$\begin{vmatrix} H_{22} - E & H_{23} \\ H_{32} & H_{33} - E \end{vmatrix} \quad \text{and} \quad \begin{vmatrix} H_{44} - E & H_{45} \\ H_{54} & H_{55} - E \end{vmatrix}$$

The elements of these determinants ($H_{22} = \langle \phi_2 | \mathcal{H} | \phi_2 \rangle$, $H_{23} = \langle \phi_2 | \mathcal{H} | \phi_3 \rangle$, etc.) can be obtained explicitly so that the eigenvalues and the eigenvectors of the states (2) to (5) can be derived. We shall forego a complete treatment here that yields expressions for all of the frequencies and relative intensities of the AB_2 system.

From the results of such a direct analysis of the AB_2 system the following important rules are obtained:

$$\begin{aligned} \nu_A &= f_3 \\ \nu_B &= (f_5 + f_7)/2 \\ J_{AB} &= [(f_1 + f_4) + (f_6 - f_8)]/3 \end{aligned}$$

Since the coupling between the magnetically equivalent B nuclei does not influence the spectrum, the appearance of the AB_2 spectrum is dependent only on the ratio $J_{AB}/\nu_0\delta$ and thus the line frequencies and their intensities in such spectra can be tabulated on the basis of this ratio. In Figure 6.8 a few theoretical spectra are reproduced that illustrate the transition of an AB_2 spectrum, via the degenerate A_3 case, to an A_2B system. As earlier mentioned (p. 72), these spectral changes can be observed experimentally using benzyl alcohol.

The line f_9 deserves special attention. This is one of the combination lines mentioned previously that corresponds to the forbidden transition $\alpha\beta\beta \rightarrow \beta\alpha\alpha$. Its intensity is therefore generally very low (cf. Figure 6.6 and Exercise 6.10).⁵⁾

5) With the exception of transitions forbidden by symmetry, the selection rules, as well as other statements of quantum mechanics, possess only probability character.

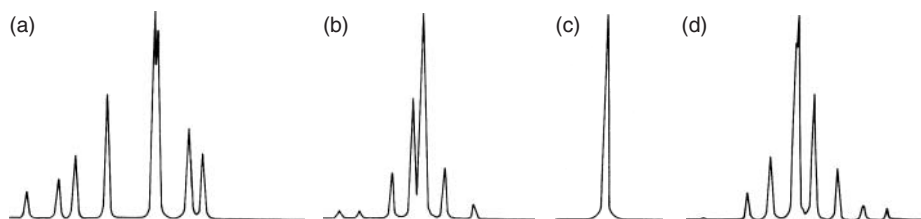
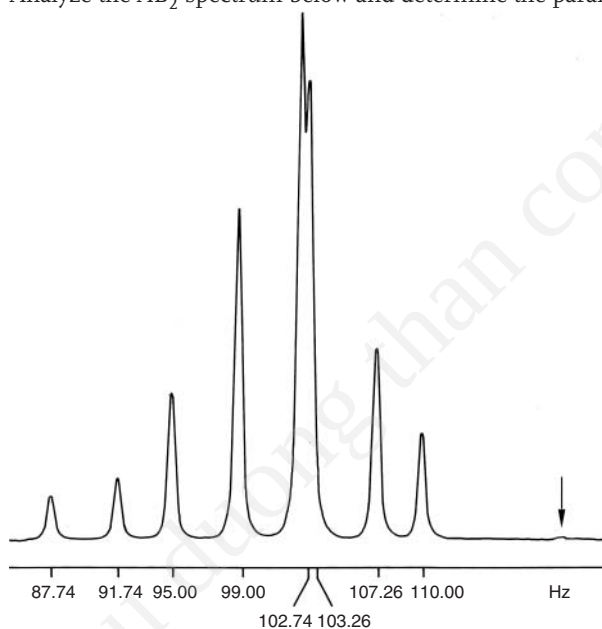


Figure 6.8 Transition from the AB_2 to the A_2B system: $\nu_0\delta =$ (a) 14.0, (b) 6.0, (c) 1.0, and (d) -8.0 Hz; $J = 6.0$ Hz in each instance.

Exercise 6.10

Analyze the AB_2 spectrum below and determine the parameters ν_A , ν_B , and J_{AB} .



6.5.2.2 The Particle Spin

We used the AB_2 system to illustrate the simplification that applies in the analysis when the symmetry present with magnetically equivalent groups is considered. A further important method for the treatment of equivalent nuclei that leads to the same result can also be illustrated using the AB_2 system. This involves the so-called *particle spin*.

If we consider the B_2 group as a simple particle its total spin I^* obviously must have the values 0 (for antiparallel spin orientations) or 1 (for parallel spin orientations); that is, the B_2 group exists either in a singlet (S) or a triplet (T) state. The A nucleus, because of its spin $\frac{1}{2}$, is in a doublet (D) state and accordingly is

Table 6.3 Basis functions of the AB₂ system.

m_T	Basis function	m_T	Basis function
	$A_{1/2}B_1$		$A_{1/2}B_0$
(1) $+\frac{3}{2}$	$D^{-3/2}T^{+1}$	(7) $+\frac{1}{2}$	$D^{+1/2}S^0$
(2) $+\frac{1}{2}$	$D^{+1/2}T^0$	(8) $-\frac{1}{2}$	$D^{-1/2}S^0$
(3) $+\frac{1}{2}$	$D^{-1/2}T^{+1}$		
(4) $-\frac{1}{2}$	$D^{+1/2}T^{-1}$		
(5) $-\frac{1}{2}$	$D^{-1/2}T^0$		
(6) $-\frac{3}{2}$	$D^{-3/2}T^{-1}$		

at one time bound to a hypothetical nucleus with spin quantum number 0 and at another time to one of spin quantum number 1. I^* is a good quantum number that is not changed by means of the NMR experiment. As a further selection rule for allowed transitions, it follows that $\Delta I^* = 0$. The spectrum can thus be considered to arise from two *subspectra* that are characterized by the notations $A_{1/2}B_0$ and $A_{1/2}B_1$ and that are completely independent of one another. The two subspectra are also known as the *irreducible representations* of the AB₂ system.

The eigenfunctions for the AB₂ system can now again be represented as product functions arranged according to total spin m_T (Table 6.3). In the $A_{1/2}B_0$ subsystem the B particle is not magnetic so that only one line, namely, the transition $A(\beta) \rightarrow A(\alpha)$ or $\Psi_8 \rightarrow \Psi_7$ can be observed. As can be seen immediately, the principle of particle spin leads to a considerable simplification in the treatment of spin systems with groups of n magnetically equivalent nuclei. If n is an even number there always exists a non-magnetic state for the group, while for uneven n the particle spin $I^* = \frac{1}{2}$ results. For AB_{*n*} systems a subspectrum of the A type is observed in the first case while in the second case an AB subspectrum results. The latter contains all the information characteristic of the spin system (ν_A , ν_B , and J_{AB}).

If we now turn to the Hamilton matrix for the general three-spin case, shown in Figure 6.9, the simplifications arising from the use of symmetry or the principle of the particle spin are evident. Notably, the indices of the matrix elements refer to the basis functions of p. 172 in the first case and to the functions in Tables 6.2 and 6.3 in the second case. Instead of two third-order submatrices, the Hamilton matrix now possesses only two second-order submatrices. We mention here that the particle spin approach belongs to the methods that are generally called “*subspectral analysis*.” In the following, subspectra will be characterized by small letters.

6.5.2.3 The ABX System

As another three-spin system we want to investigate the ABX system. As the notation indicates, this is a system in which two nuclei, A and B, having similar

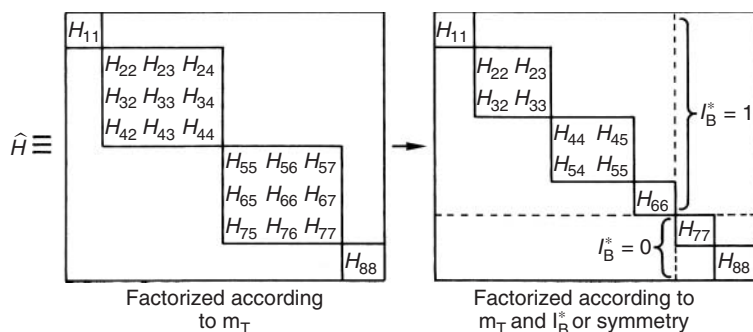
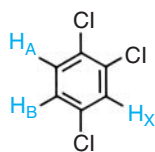
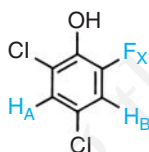


Figure 6.9 Hamilton matrix for the general three-spin-case factorized according to the total spin m_T and in addition according to the particle spin (cf. text).

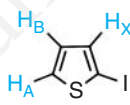
chemical shifts are coupled with a third nucleus, the resonance frequency of which is very different from ν_A and ν_B . The X nucleus in such systems is said to be weakly coupled and the A and B nuclei are said to be strongly coupled. The X nucleus is also called *passive spin*. Examples of such systems that are characterized by three resonance frequencies (ν_A , ν_B , and ν_X) and three coupling constants (J_{AB} , J_{AX} , and J_{BX}) are found in 1,2,4-trichlorobenzene (**10**), 2-fluoro-4,6-dichlorophenol (**11**), 2-iodothiophene (**12**), and styrene oxide (**13**).



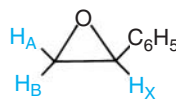
10



11



12



13

Another important principle is used in the analysis of these systems. It is known as the *X-approximation* and is based on the fact that those off-diagonal elements of the Hamilton matrix for the three-spin case that occur between states with different magnetic quantum numbers $m_I(X)$ of the X nucleus are negligibly small compared with the diagonal elements. Omitting these off-diagonal elements leads to a Hamilton matrix that is considerably simplified, as schematically illustrated below, where the indices of the elements refer to the basis functions in Table 6.4:

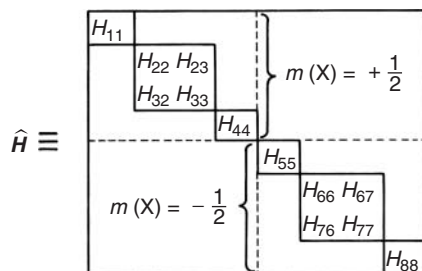
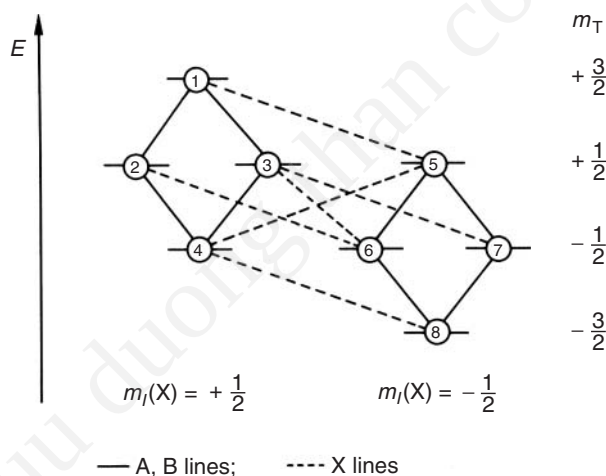


Table 6.4 Product functions of the ABX system.

$m_I(X) = +\frac{1}{2}$				$m_I(X) = -\frac{1}{2}$			
	A	B	X		A	B	X
m_T				m_T			
(1) $+\frac{3}{2}$	α	α	α	(5) $+\frac{1}{2}$	α	α	β
(2) $+\frac{1}{2}$	α	β	α	(6) $-\frac{1}{2}$	α	β	β
(3) $+\frac{1}{2}$	β	α	α	(7) $-\frac{1}{2}$	β	α	β
(4) $-\frac{1}{2}$	β	β	α	(8) $-\frac{3}{2}$	β	β	β
$\Downarrow$				$\Downarrow$			
(1) $\alpha\alpha$			α	(5) $\alpha\alpha$			β
(2) $\cos \theta (\alpha\beta) + \sin \theta (\beta\alpha)$			α	(6) $\cos \theta (\alpha\beta) + \sin \theta (\beta\alpha)$			β
(3) $-\sin \theta (\alpha\beta) + \cos \theta (\beta\alpha)$			α	(7) $-\sin \theta (\alpha\beta) + \cos \theta (\beta\alpha)$			β
(4) $\beta\beta$			α	(8) $\beta\beta$			β

**Figure 6.10** Energy level diagram of the ABX system.

In this table the basis functions are arranged separately according to the eigenvalues $m_I(X)$ of the operator $\hat{I}_z(X)$. As a result we get two sets of four functions each. These sets contain product functions for the AB part of the spin system that are identical with those already introduced as basis functions for the isolated AB system.

The AB portion of the ABX spectrum thus consists of two ab subspectra, one for each of the two $m_I(X)$ values of $+\frac{1}{2}$ and of $-\frac{1}{2}$. With respect to the transitions in each subspectrum, the X-nucleus is regarded as *passive spin*. The eigenvalues E_1 , E_4 , E_5 , and E_8 are immediately obtained through substitution of the corresponding

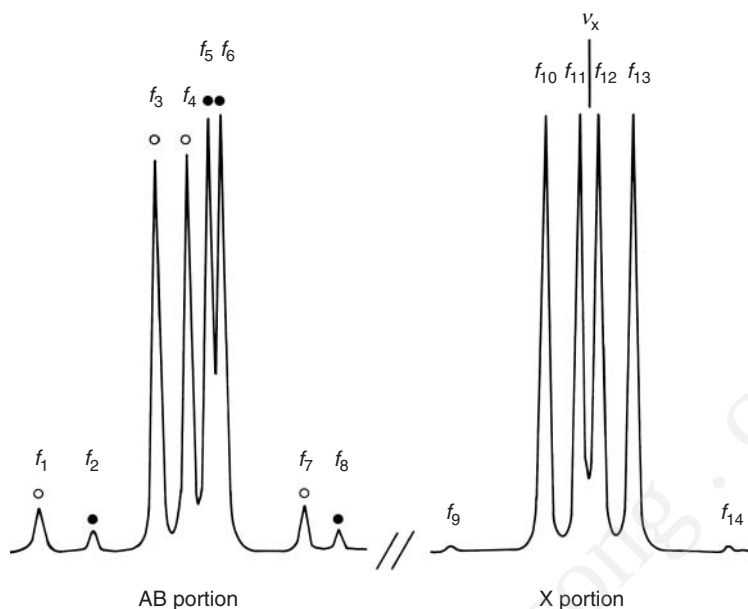


Figure 6.11 ABX system with the parameters $\nu_0\delta$ (AB) = 5.0 Hz, J_{AB} = 8 Hz, J_{AX} = 4.2 Hz, and J_{BX} = 1.8 Hz. The ab subspectra in the AB portion are identified by the open and closed circles. The parameters used are those of 2-chloro-3-aminopyridine. After Reference [1].

product functions $\alpha\alpha\alpha$, $\beta\beta\alpha$, $\alpha\alpha\beta$, and $\beta\beta\beta$ in Eq. (6.2), while it is only necessary to solve two second-order determinants for the determination of E_2 , E_3 , E_6 , and E_7 .

The advantage of the X approximation becomes most clear in the energy level diagram of the ABX system (Figure 6.10). For transitions within each subspectrum the spin orientation of the X nucleus is not changed.

The eigenvalues $m_I(X)$ of $\hat{I}_z(X)$ are to be considered good quantum numbers and as a special selection rule for allowed AB lines it follows that $\Delta m_I(X) = 0$. The spectrum is independent of the shift differences $\nu_A - \nu_X$ and $\nu_B - \nu_X$.

According to this analysis there are a total of eight AB and six X lines in the ABX system. Of these, the two arising from the transitions $\Psi_4 \rightarrow \Psi_5$ and $\Psi_6 \rightarrow \Psi_3$ are combination lines and in general are of low intensity. The X portion of the spectrum is symmetrical about ν_X (Figure 6.11).

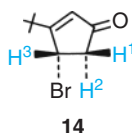
The principle of the approximation discussed here states in its generalized form that for a group X_n of n magnetically equivalent nuclei that are weakly coupled with nuclei of another group the eigenvalues $m_T(X)$ of the operator $\hat{F}_z(X) [= \sum_n \hat{I}_z(X)]$ are good quantum numbers. Therefore, for an ABX_2 system one would expect three ab subspectra and for an ABX_3 system one would expect four ab subspectra. The relative intensities of these subspectra can be obtained from the Pascal triangle (ABX, 1 : 1; ABX_2 , 1 : 2 : 1; ABX_3 1 : 3 : 3 : 1).

If the effect of the X nucleus is treated as a first-order perturbation, then the ab subspectra are characterized by the *effective Larmor frequencies*, ν^* . Specifically, in the ABX case we have:

$$\begin{aligned}\nu_a^* &= \nu_A + m_I(X)J_{AX} = \nu_A \pm \frac{1}{2}J_{AX} \\ \nu_b^* &= \nu_B + m_I(X)J_{BX} = \nu_B \pm \frac{1}{2}J_{BX}\end{aligned}\quad (6.36)$$

This approach is thus known as the *method of the effective Larmor frequencies*.

For analysis of the ABX system it is advantageous to proceed from the AB portion. There is the problem, though, of locating the two ab subspectra and analyzing them according to the rules of Section 6.5.1. To illustrate the procedure we present an example. Figure 6.12a shows the AB portion of the ABX system of protons H^1 , H^2 , and H^3 in 4-bromo-3-*t*-butylcyclopent-2-enone (**14**).



We observe that a line separation of 19.2 Hz occurs four times, that is, between the pairs f_1-f_3 , f_5-f_7 , f_2-f_4 , and f_6-f_8 . By consideration of the relative intensities it is possible to make the following assignments:

- ab subspectrum I: lines f_1, f_3, f_5 , and f_7 ;
- ab subspectrum II: lines f_2, f_4, f_6 , and f_8 .

Analysis of these subspectra according to the rules derived for AB spectra (Section 6.5.1) leads to the following results:

$\nu_a^* = 13.6 \text{ Hz}$	$\nu_a^{**} = 20.1 \text{ Hz}$
I. $\nu_b^* = 32.4 \text{ Hz}$	II. $\nu_b^{**} = 33.5 \text{ Hz}$
$J_{ab} = 19.2 \text{ Hz}$	$J_{ab} = 19.2 \text{ Hz}$

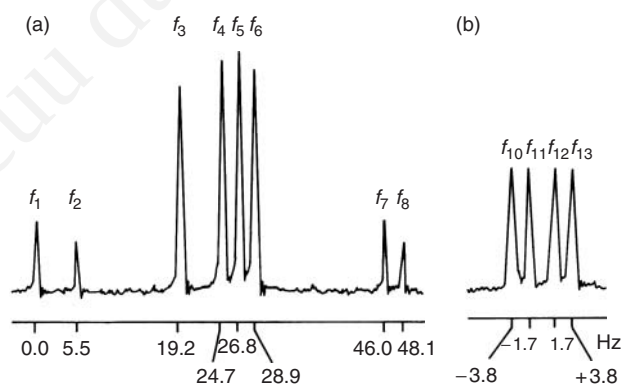


Figure 6.12 ABX spectrum of 4-bromo-3-*t*-butylcyclopent-2-enone (**14**): (a) AB portion, relative line frequencies in hertz; (b) X portion 60 MHz. After Reference [2].

If we now apply the relations [Eq. (6.36)] for the determination of ν_A , ν_B , J_{AX} , and J_{BX} , two solutions result since the relative assignment of the effective Larmor frequencies in the subspectra can be exchanged; that is one can combine $\nu_a^*(I)$ with $\nu_b^*(I)$ or $\nu_b^{**}(II)$:

Solution 1:

$$\begin{aligned}\nu_A &= 16.9 \text{ Hz} & J_{AX} &= 6.5 \text{ Hz} \\ \nu_B &= 33.0 \text{ Hz} & J_{BX} &= 1.1 \text{ Hz} \\ |J_{AB}| &= 19.2 \text{ Hz}\end{aligned}$$

Solution 2:

$$\begin{aligned}\nu_A &= 23.6 \text{ Hz} & J_{AX} &= 19.9 \text{ Hz} \\ \nu_B &= 26.3 \text{ Hz} & J_{BX} &= -12.3 \text{ Hz} \\ |J_{AB}| &= 19.2 \text{ Hz}\end{aligned}$$

This generally applies for each ABX system. We must therefore seek criteria by which the correct solution can be identified. The intensities of the lines in the X part of the spectrum enable us to do this. As we have already explained, the X portion of the spectrum consists of six lines symmetrically arranged about ν_X . Two of these lines have relative intensities of 1 and the frequencies $\nu_X \pm \frac{1}{2}(J_{AX} + J_{BX})$. Their separation thus directly yields the sum $J_{AX} + J_{BX}$. These lines are assigned to the transitions $\Psi_5 \rightarrow \Psi_1$ and $\Psi_8 \rightarrow \Psi_4$ and they constitute X subspectra with the effective Larmor frequencies:

$$\nu_X^* = \nu_X + \frac{1}{2}(J_{AX} + J_{BX}) \quad \text{and} \quad \nu_X^{**} = \nu_X - \frac{1}{2}(J_{AX} + J_{BX})$$

In the spectrum of compound **14** we observed only four lines of approximately equal intensity (Figure 6.12b). Of those, the lines f_{10} and f_{13} have the expected separation of 7.6 Hz. A decision about the correct solution can now be made by means of a computed spectrum (cf. Sections 6.4.6 and 6.5.4). Figure 6.13 (p. 188) shows the theoretical spectra obtained using the parameters of solutions 1 and 2. As can be seen, the *frequencies* of the lines are indeed virtually identical but the *intensities* indicate distinct differences. Accordingly, solution 2 can be discarded.

One can also forego a complete calculation of the spectrum and only compare the relative intensities of lines f_{10} and f_{11} of the X portion with one another. If we set the intensity of the line $f_{10} = 1$, then the intensity of the line f_{11} is given by Eq. (6.37), which we present here without proof. Since the line f_9 is not observed in our example, Eq. (6.37) of course cannot be applied:

$$I_{11} = [f_9^2 - 0.25(J_{AX} - J_{BX})^2] / (f_9^2 - f_{11}^2) \quad (6.37)$$

Exercise 6.11

A calculation made for the ABX system of compound **14** yields a value of 25.2 Hz as the frequency of line f_9 for both solutions. Calculate the intensity of the line f_{11} for both solutions using Eq. (6.37).

With solution 1 we now have the spectral parameters of the $H^1 - H^3$ protons. However, it is only with the aid of the empirical correlations discussed in Chapter 5

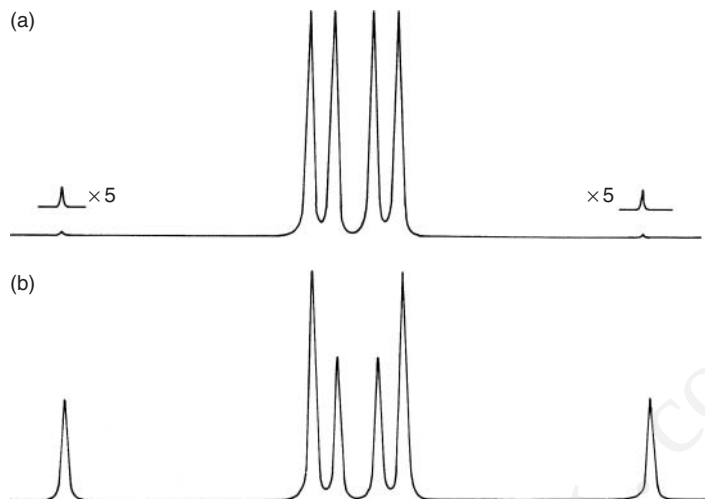


Figure 6.13 Theoretical X spectra of **14** for solutions 1 (a) and 2 (b).

that we are able to assign the spectrum since our analysis does not indicate which of the individual parameters ν_A , ν_B , etc. must be attributed to which proton. In addition, the relative sign of J_{AB} has not been determined by the analysis.

If we assume that the protons H^1 and H^2 should have similar resonance frequencies, H^3 is established as the X proton. Because $J_{AX} \gg J_{BX}$, it follows on the basis of the Karplus curve that $H^1 \equiv H_A$ and $H^2 \equiv H_B$ (p. 129). Furthermore, J_{AB} as a geminal coupling must be negative (p. 123 ff.).

With the ABX spectrum we encounter for the first time a spectral type in which, by means of Eq. (6.36), the *relative signs* of two coupling constants can be determined. In the AB case the spectrum is, as inspection of Table 6.1 shows, independent of the sign of the spin–spin coupling. Indeed, if the sign of J were reversed a different assignment of transitions would have to be made but the appearance of the spectrum would not change. This is also true for the AB_2 system.

Exercise 6.12

Calculate the two solutions for the ABX system of 2-fluoro-4, 6-dichlorophenol with reference to the AB portion shown in Figure 6.14.

How the relative signs of J_{AX} and J_{BX} can influence the appearance of an ABX spectrum can be seen from the two calculated spectra in Figure 6.15 (p. 190). The parameters used for the two systems are identical except for the relative signs of the coupling constants J_{AX} and J_{BX} . One further notes that the X portion of the spectrum is also sensitive to this difference. In contrast, the appearance of the spectrum is insensitive to the sign of J_{AB} .

The dependence of the ABX spectrum on the relative signs of the coupling parameters J_{AX} and J_{BX} leads to the expectation that, in general, there should

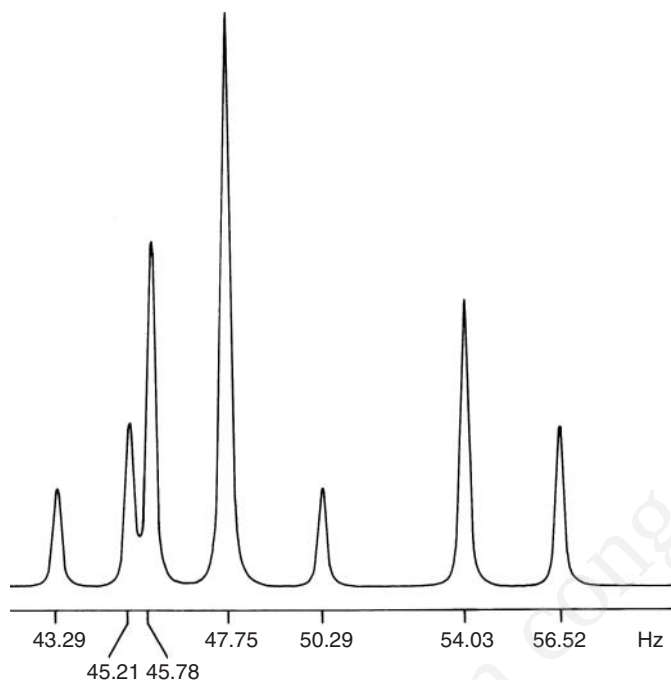


Figure 6.14 AB portion of the ABX spectrum of 2-fluoro-4,6-dichlorophenol.

be three different types of AB portions for ABX spectra. These are represented in Figure 6.16 (p. 190). In case (a), both ab subspectra are clearly separated. The relative signs of J_{AX} and J_{BX} must then be the same. In case (b), one ab subspectrum is framed by the other and consequently for both solutions the relative signs must be different. Finally, in case (c), the one most frequently observed, the two subspectra overlap and both the same and different signs are possible for the coupling constants J_{AX} and J_{BX} .

Not always are all 14 lines of the ABX spectrum observed. Sometimes one of the ab subspectra degenerates to a deceptively simple AB system, that is, to an A_2 system. An example of this is shown in Figure 6.17 (p. 191) for the 60-MHz spectrum of 1,2-dibromo-1-phenylethane. The AB portion exhibits only five lines. An approximate analysis of such a spectrum is possible since J_{AB} can be determined and this separation can be subtracted from the signal f_2 in order to define the outer lines of the second ab subspectrum.

With reference to a series of theoretical spectra, Figure 6.18 (p. 192) illustrates how the appearance of an ABX spectrum is influenced by the shift difference $\nu_A - \nu_B$ between the nuclei A and B. As expected, not only the AB portion but also the X portion of the spectrum is sensitive to this parameter. The fact that for all of these spectra $J_{AX} = 0$ deserves special attention. The multiplicity of the X portion in these examples is thus not the result of direct spin-spin interaction with the nucleus A and the nucleus B, as the incorrect application of the first-order rules

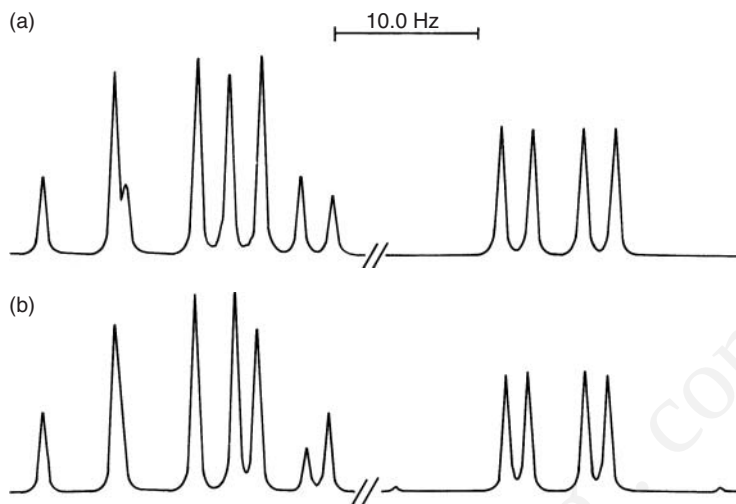


Figure 6.15 Theoretical ABX spectra with the following parameters:

(a) $\nu_0\delta(\text{AB}) = 10.0 \text{ Hz}$	(b) $\nu_0\delta(\text{AB}) = 10.0 \text{ Hz}$
$J_{\text{AB}} = 5.0 \text{ Hz}$	$J_{\text{AB}} = 5.0 \text{ Hz}$
$J_{\text{AX}} = 6.0 \text{ Hz}$	$J_{\text{AX}} = 6.0 \text{ Hz}$
$J_{\text{BX}} = 2.0 \text{ Hz}$	$J_{\text{BX}} = -2.0 \text{ Hz}$

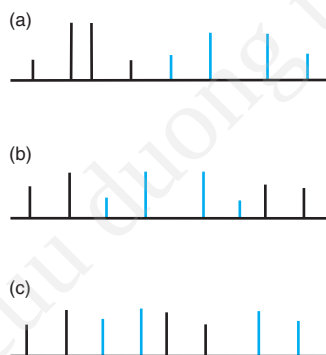


Figure 6.16 (a)–(c) AB parts of ABX spectra with different sign combinations for the passive couplings J_{AX} and J_{BX} .

would suggest. Therefore, the conclusion that $J_{\text{AX}} = J_{\text{BX}}$ cannot be drawn from the “triplet splitting” in case (d). In addition, the appearance of the A lines as doublets in case (b) is not caused by a finite coupling constant J_{AX} .

The phenomenon observed here has been called *virtual coupling* in order to indicate that the multiplicity of the X portion of an ABX system can be higher than a simple first-order approach suggests. This observation is not limited to

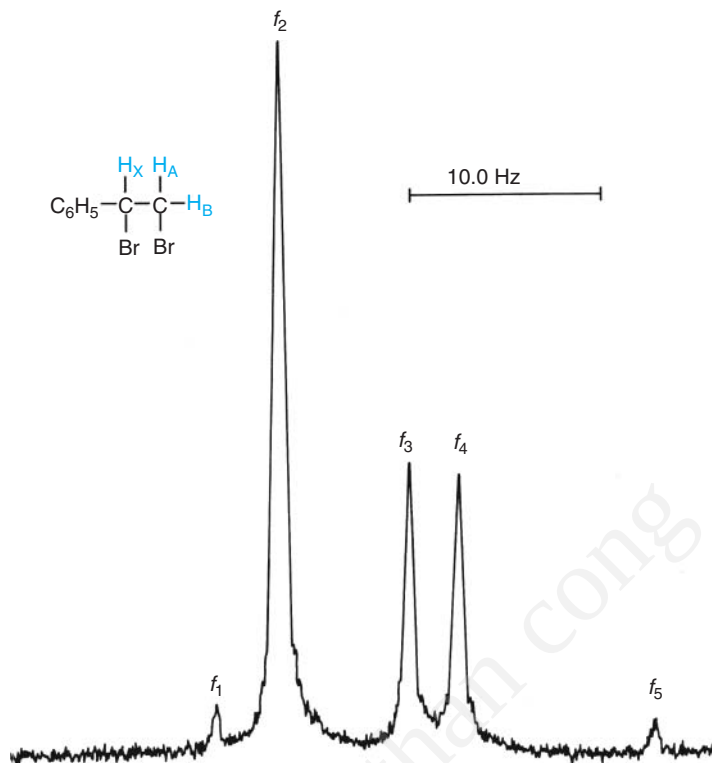


Figure 6.17 AB portion of the ABX spectrum of the aliphatic protons of 1,2-dibromo-1-phenylethane; 60 MHz.

ABX systems but is also encountered in other cases if one nucleus of a set of strongly coupled nuclei is additionally coupled to a third nucleus with a very different resonance frequency. The introduction of a special notation here seems superfluous, however, and in addition is misleading since the circumstances described merely demonstrate that the first-order rules may not be applied to the ABX system, a statement that follows immediately from the Hamilton matrix (p. 183). By no means is virtual coupling a special variety of spin–spin coupling or a property of the spin system that requires special treatment for analysis.

Exercise 6.13

Analyze the ABX spectrum of the aliphatic protons of L-asparagine shown in Figure 6.19.

The analyses of ABC systems often observed for vinyl groups turn out to be more difficult. Here no simplifying conditions apply and the maximum number of 15 theoretically possible transitions can be observed. Special procedures for direct analysis of these spectra are known but their treatment is beyond the scope of this book.

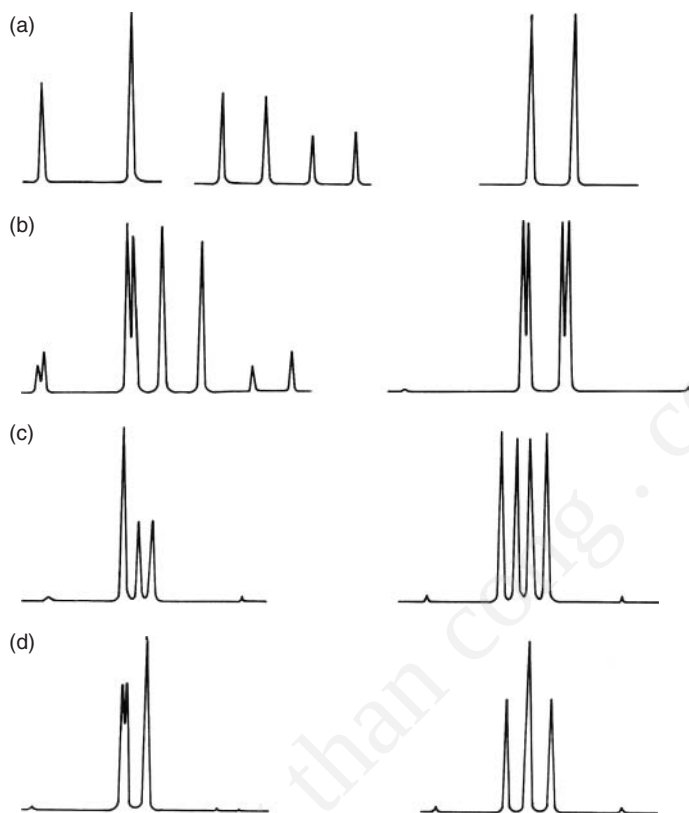


Figure 6.18 Dependence of the ABX system on the parameter $\nu_A - \nu_B$: left, the AB portion; right, the X portion. The following parameters apply in all examples: $J_{AB} = 15.7$ Hz, $J_{AX} = 0$ Hz, and $J_{BX} = 7.7$ Hz. The relative chemical shifts $\nu_0\delta$ (AB) amount to (a) 56.7, (b) 18.7, (c) 5.0, and (d) -0.6 Hz. Experimental data from 2-furfuryl-(2)-acrolein form the basis for the calculated spectra. After Reference [3].

6.5.3

Spin Systems with Four Nuclei – The AA'XX' System

For the general four-spin system we use 16 basis functions:

$m_T = +2$	$m_T = +1$	$m_T = 0$	$m_T = -1$	$m_T = -2$
(1) $\alpha\alpha\alpha\alpha$	(2) $\alpha\alpha\alpha\beta$	(6) $\alpha\alpha\beta\beta$	(12) $\alpha\beta\beta\beta$	(16) $\beta\beta\beta\beta$
	(3) $\alpha\alpha\beta\alpha$	(7) $\alpha\beta\alpha\beta$	(13) $\beta\alpha\beta\beta$	
	(4) $\alpha\beta\alpha\alpha$	(8) $\beta\alpha\alpha\beta$	(14) $\beta\beta\alpha\beta$	
	(5) $\beta\alpha\alpha\alpha$	(9) $\beta\alpha\beta\alpha$	(15) $\beta\beta\beta\alpha$	
		(10) $\beta\beta\alpha\alpha$		
		(11) $\alpha\beta\beta\alpha$		

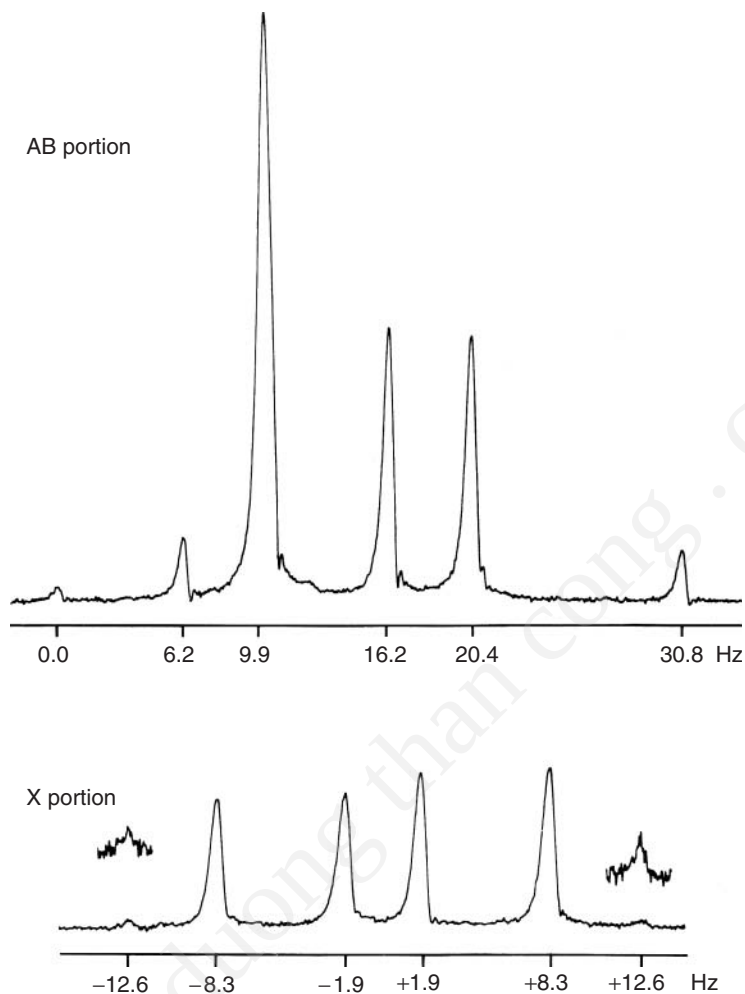
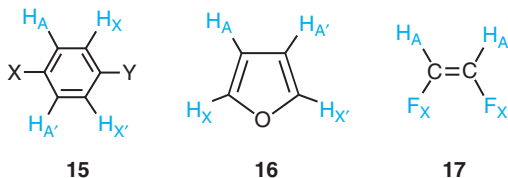


Figure 6.19 ABX spectrum of the aliphatic protons in L-asparagine; the X portion in this case lies at higher frequency; 100 MHz.

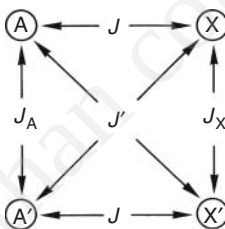
In this case the determination of the parameters of the system – four chemical shifts and six coupling constants – therefore requires the solving of one sixth-order and two fourth-order determinants. For the AA'XX' system that we want to treat here, however, the analysis can be simplified substantially by means of the principles discussed in the preceding sections.

We encounter AA'XX' systems in molecules such as *para*-disubstituted benzenes (15), furan (16), and 1,2-difluoroethene (17), to name only a few examples. Owing to the *chemical* equivalence of the two A and the two X nuclei, respectively, and also to

the molecular symmetry, they are characterized by only two resonance frequencies and four coupling constants, ν_A , ν_X , $J_{AA'}$ ($=J_A$), $J_{XX'}$ ($=J_X$), J_{AX} ($=J$), and $J_{AX'}$ ($=J'$):



The appearance of the spectrum is, by definition, independent of the difference $\nu_A - \nu_X$. Well-resolved spectra have 20 lines, 10 each for the AA' and the XX' parts. They are symmetric about the center and the AA' and the XX' portions are symmetric about ν_A and ν_X , respectively. Since $J \neq J'$, the nuclei of the A or the X groups are not *magnetically* equivalent. This means that despite the large relative chemical shift, $\nu_0\delta = \nu_A - \nu_X$, we cannot use first-order rules for analysis of the spectrum. The latter apply only for the special case when $J = J'$, classified as an A_2X_2 system. Here two triplets with intensity distributions of 1 : 2 : 1 are observed.



To construct the energy level diagram for the AA'XX' system we refer to the known functions of the A_2 case, s_{+1} , s_0 , s_{-1} , and a_0 (cf. Table 6.1), which, because of the symmetry in the AA'XX' system, can be used as basis functions for the AA' and the XX' groups. We then obtain suitable basis functions for the four-spin case by forming all possible products:

$$\phi_1 = s_{+1}(AA') \times s_{+1}(XX'); \quad \phi_2 = s_0(AA') \times s_{+1}(XX')$$

etc.

If we arrange these products according to their symmetry,⁶⁾ their total spin, and the magnetic quantum number, $m_T(XX')$, of the XX' group, we obtain Table 6.5 for the AA' portion. A completely analogous scheme is obtained for the XX' portion if the classification is made according to $m_T(AA')$.

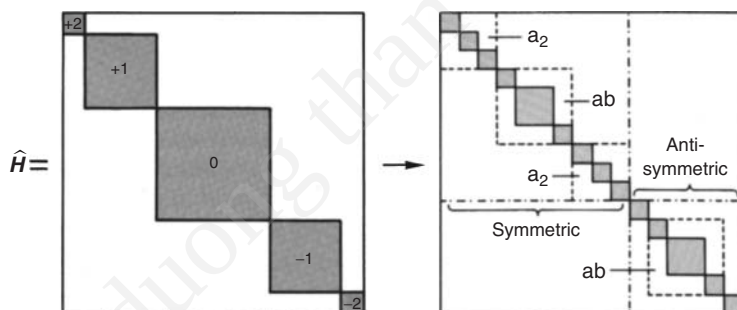
Consequently, the Hamilton matrix of the general four-spin case is drastically simplified. Instead of a 6×6 and two 4×4 submatrices, it now consists of only two

6) The general rule applies that the products of symmetric functions are symmetric, the products of antisymmetric functions are likewise symmetric, and the products of symmetric and antisymmetric functions are antisymmetric.

Table 6.5 Symmetry Functions of the AA' XX' System.

m_T Symmetric product functions			
+2	(1) $s_{+1}(AA')$ $s_{+1}(XX')$		
+1	(2) $s_0(AA')$ $s_{+1}(XX')$	(4) $s_{+1}(AA')$ $s_0(XX')$	
0	(3) $s_{-1}(AA')$ $s_{+1}(XX')$	(5) $s_0(AA')$ $s_0(XX')$	(6) $a_0(AA')$ $a_0(XX')$
-1		(7) $s_{-1}(AA')$ $s_0(XX')$	(8) $s_{+1}(AA')$ $s_{-1}(XX')$
-2			(9) $s_0(AA')$ $s_{-1}(XX')$
			(10) $s_{-1}(AA')$ $s_{-1}(XX')$
$m_T(XX')$	+1 a_2 subspectrum	0 ab subspectrum	-1 a_2 subspectrum
m_T Antisymmetric product functions			
+1	(11) $a_0(AA')$ $s_{+1}(XX')$	(12) $s_{+1}(AA')$ $a_0(XX')$	
0		(13) $a_0(AA')$ $s_0(XX')$	(14) $s_0(AA')$ $a_0(XX')$
-1		(15) $s_{-1}(AA')$ $a_0(XX')$	(16) $a_0(AA')$ $s_{-1}(XX')$
$m_T(XX')$	+1	0 ab subspectrum	-1

2×2 submatrices. The remaining elements are 1×1 matrices and already represent the correct eigenvalues:



Further inspection shows that the matrix contains only substructures that are known from the A_2 and AB cases and in the experimental spectrum for the AA' or the XX' portion we actually expect to find two subspectra of the a_2 type and two subspectra of the ab type. Thus, there results a total of 12 A and 12 X transitions eight of which (four pairs) are degenerate so that the number of experimental lines is reduced to a total of 20 (10 for each half spectrum). The energy level diagram for the AA'XX' system thus has the structure shown in Figure 6.20 (p. 196).

Since, as we have already noted, the spectrum is symmetric about the center $(\nu_A + \nu_X)/2$, we can limit our discussion to a consideration of one half spectrum. For this, Figure 6.21 (p. 197) shows the AA' portion of a theoretical spectrum that was calculated with the parameters $J_A = 9$ Hz, $J_X = 4$ Hz, $J = 8$ Hz, and $J' = 2$ Hz. The labeling of the lines follows from the nomenclature introduced by B. Dischler (see Appendix, p. 673, References [39] to [41]) and corresponds to that

in Figure 6.20. We may obviously assign the lines a , k and b , l to the a_2 -systems because of their high intensity. The two ab systems are represented by the lines c , d , e , and f and g , h , i , and j , respectively.

The relation between the spectral parameters of the subspectra (ν_a , ν_b , and J_{ab}) and those of the $AA'XX'$ system (J_A , J_X , J , and J') must now be established. For this it is necessary to calculate the eigenvalues to the functions introduced in Figure 6.20. Except for the four product functions ϕ_5 , ϕ_6 , ϕ_{13} , and ϕ_{14} , all of the other functions are already eigenfunctions and the Hamilton operator and the corresponding energies can be derived directly by the application of Eq. (6.2). It is to our advantage to make use of the following shorthand notation:

$$J_A + J_X = K$$

$$J_A - J_X = M$$

$$J + J' = N$$

$$J - J' = L$$

We then obtain the energies given in Table 6.6 (p. 198).

Exercise 6.14

Verify the results presented in Table 6.6 (p. 198).

The states (5) and (6) as well as (13) and (14) mix with one another. Their eigenvalues must therefore be determined according to the variational method. Besides the diagonal elements $H_{kk} = \langle \phi_5 | \mathcal{H} | \phi_5 \rangle$ and $\langle \phi_6 | \mathcal{H} | \phi_6 \rangle$ and $\langle \phi_{13} | \mathcal{H} | \phi_{13} \rangle$ and $\langle \phi_{14} | \mathcal{H} | \phi_{14} \rangle$ the off-diagonal elements $H_{kl} = \langle \phi_5 | \mathcal{H} | \phi_6 \rangle$ and $\langle \phi_{13} | \mathcal{H} | \phi_{14} \rangle$ must

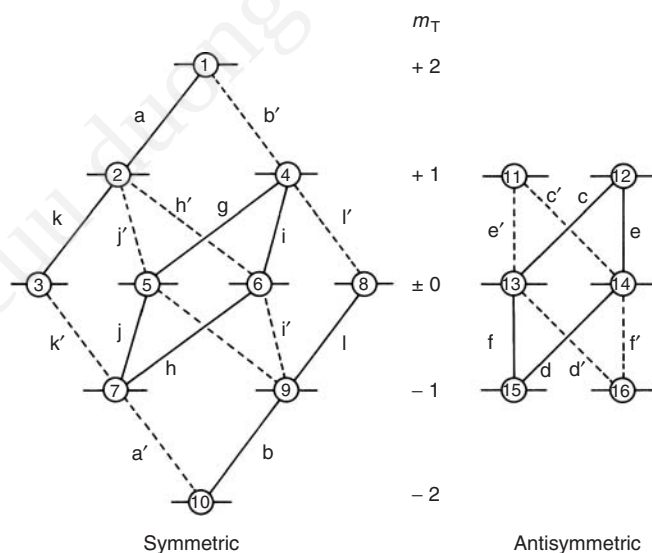


Figure 6.20 Energy level diagram of the $AA'XX'$ system.

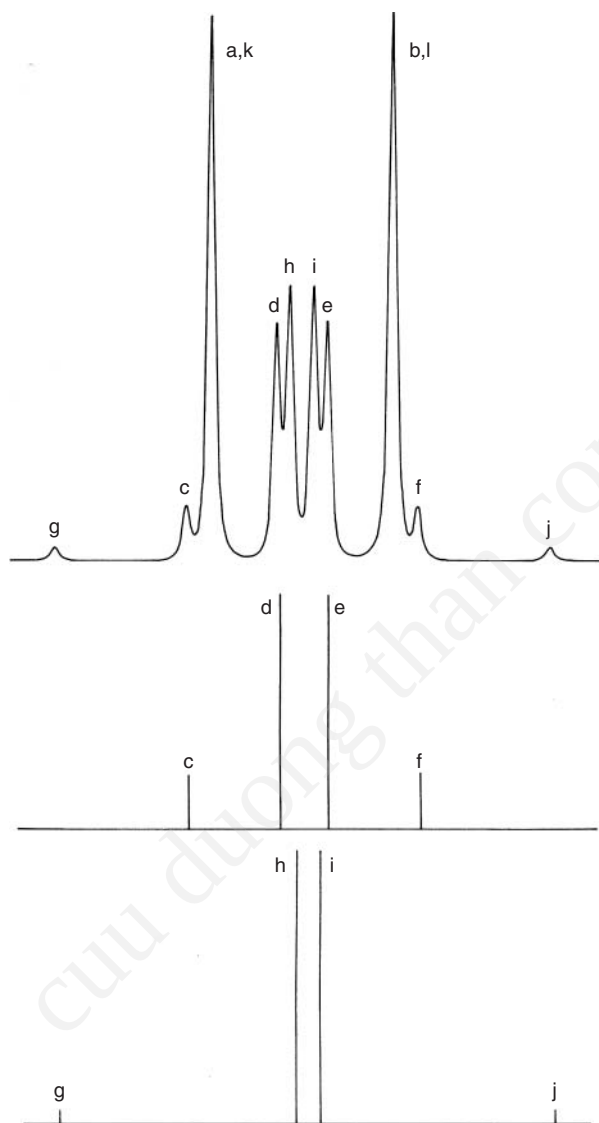


Figure 6.21 A half spectrum of an AA'XX' system; for clarity the ab subspectra (antisymmetric c, d, e, f; symmetric g, h, i, j) are shown separately.

also be calculated. Using the identity $H_{kl} = H_{lk}$ we obtain as determinants:

$$\begin{vmatrix} \frac{1}{4}K - E & -\frac{1}{2}L \\ -\frac{1}{2}L & -\frac{3}{4}K - E \end{vmatrix} = 0$$

for the symmetric ab subspectrum and, after addition of $\frac{1}{4}(K - M)$ to the diagonal elements:

$$\begin{vmatrix} -\frac{3}{4}M - E & -\frac{1}{2}L \\ -\frac{1}{2}L & -\frac{1}{4}M - E \end{vmatrix} = 0$$

for the antisymmetric case.

The energies of the states (5) and (6) or (13) and (14) are then:

$$E_{5,6} = -\frac{1}{4}K \pm \frac{1}{2}\sqrt{K^2 + L^2}$$

$$E_{13,14} = -\frac{1}{4}M \pm \frac{1}{2}\sqrt{M^2 + L^2}$$

If these expressions are compared with the solutions for the eigenvalues E_2 and E_3 of the AB system, it is quite obvious that the parameters K and M represent the effective coupling constants of the symmetric and antisymmetric ab subspectra, respectively, and that both ab subspectra are characterized by the effective chemical shift difference $\nu_0\delta = L$.

Together with the data in Table 6.5 and after subtraction of $\frac{1}{4}(K - M)$ from the eigenvalue $E_{13,14}$, the transition energies in Table 6.6 are obtained for the lines of the AA'XX' system. In the direct analysis of the AA'XX' system, on the other hand, identification of the subspectra is the central problem. If it is solved, the relations derived for the AB and the A_2 systems are applicable and the following equations hold:

$$N = a - b = k - l$$

$$M = c - d = e - f$$

$$K = g - h = i - j$$

$$L = \sqrt{(h - l)(g - j)} = \sqrt{(c - f)(d - e)}$$

Table 6.6 Eigenvalues of the AA'XX' system.

(1)	$\nu_A + \nu_X + \frac{1}{2}N + \frac{1}{4}K$	(9)	$-\nu_X + \frac{1}{4}K$
(2)	$\nu_X + \frac{1}{4}K$	(10)	$-\nu_A - \nu_X + \frac{1}{2}N - \frac{1}{4}K$
(3)	$-\nu_A + \nu_X - \frac{1}{2}N + \frac{1}{4}K$	(11)	$\nu_X - \frac{1}{4}K - \frac{1}{2}M$
(4)	$\nu_A + \frac{1}{4}K$	(12)	$\nu_A - \frac{1}{4}K + \frac{1}{2}M$
(7)	$\nu_X + \frac{1}{4}K$	(15)	$-\nu_A - \frac{1}{4}K + \frac{1}{2}M$
(8)	$\nu_A - \nu_X - \frac{1}{2}N + \frac{1}{4}K$	(16)	$-\nu_X - \frac{1}{4}K - \frac{1}{2}M$

Furthermore:

$$\begin{aligned}\nu_A \text{ or } \nu_X &= \frac{1}{2}(a + b) = \frac{1}{2}(k + l) \\ J_A &= \frac{1}{2}(K + M) \quad J = \frac{1}{2}(N + L) \\ J_X &= \frac{1}{2}(K - M) \quad J' = \frac{1}{2}(N - L)\end{aligned}$$

Exercise 6.15

Analyze the AA' portion of the AA'XX' system in Figure 6.22 (p. 200).

Exercise 6.16

Figure 6.23 (p. 200) shows the AA' portion of the AA'BB' system of the protons H¹–H⁴ in 2-methylbenzotriazole. Attempt an analysis of this system using the procedures we have derived for the AA'XX' system.

In connection with the treatment of the AA'XX' system developed so far a few important points should be emphasized. Through analysis of an AA'XX' system a differentiation between the parameters N and L , but not between K and M , can be made. This follows from the fact that we cannot define which ab subspectrum has to be assigned to the symmetric and which to the antisymmetric transitions. This can be achieved, however, as we will see later, if a double resonance technique is used. Thus, in general, only the relative signs of J and J' can be determined in an AA'XX' system. Further, the assignment of the parameters obtained by the analysis to the spin system under consideration deserves attention. Since the spectrum is

Table 6.7 Transition energies for the AA' nuclei of the AA'XX' system.

Transition	Eigenvalues involved	Frequency relative to ν_A
<i>a</i>	(2) → (1)	$\frac{1}{2}N$
<i>b</i>	(10) → (9)	$-\frac{1}{2}N$
<i>c</i>	(13) → (12)	$\frac{1}{2}M - \frac{1}{2}\sqrt{M^2 + L^2}$
<i>d</i>	(15) → (14)	$-\frac{1}{2}M - \frac{1}{2}\sqrt{M^2 + L^2}$
<i>e</i>	(14) → (12)	$\frac{1}{2}M + \frac{1}{2}\sqrt{M^2 + L^2}$
<i>f</i>	(15) → (13)	$-\frac{1}{2}M + \frac{1}{2}\sqrt{M^2 + L^2}$
<i>g</i>	(5) → (4)	$\frac{1}{2}K - \frac{1}{2}\sqrt{M^2 + L^2}$
<i>h</i>	(7) → (6)	$-\frac{1}{2}K - \frac{1}{2}\sqrt{M^2 + L^2}$
<i>i</i>	(6) → (4)	$\frac{1}{2}K + \frac{1}{2}\sqrt{M^2 + L^2}$
<i>j</i>	(7) → (5)	$-\frac{1}{2}K + \frac{1}{2}\sqrt{M^2 + L^2}$
<i>k</i>	(3) → (2)	$\frac{1}{2}N$
<i>l</i>	(9) → (8)	$-\frac{1}{2}N$

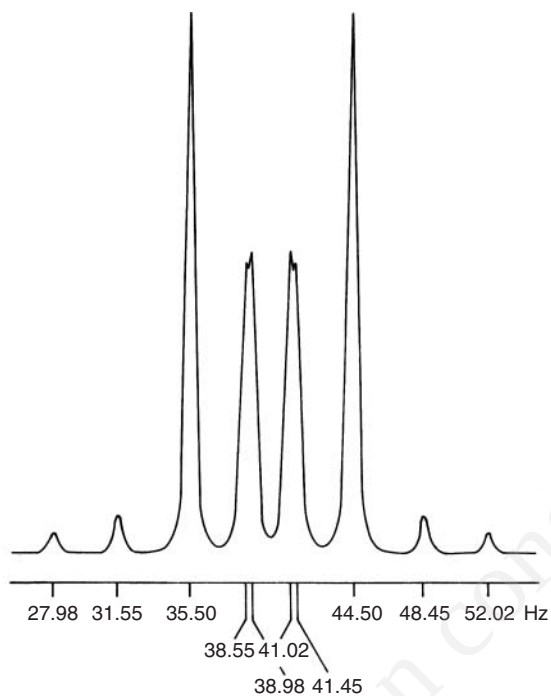


Figure 6.22 Spectrum of an AA'XX' system.

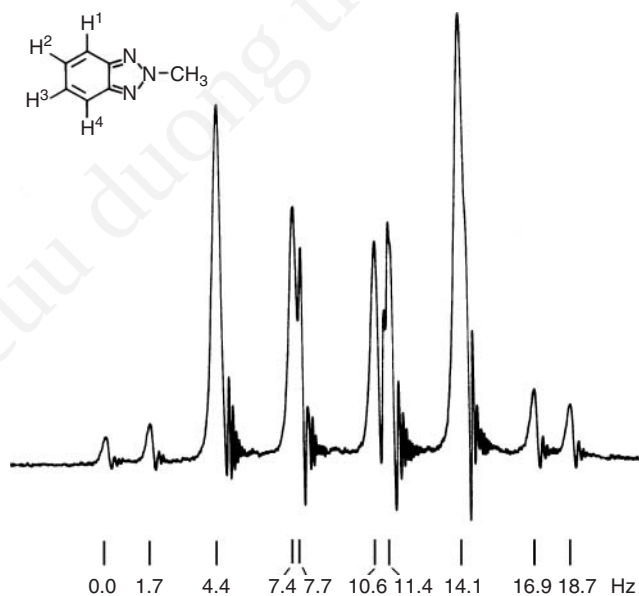


Figure 6.23 AA' portion of the AA'BB' system of protons H¹–H⁴ in 2-methylbenzotriazole.

not altered if we exchange ν_A and ν_X , neither the assignment of the resonance frequencies nor that of the coupling constants J_A and J_X and also J and J' is obvious. However, through comparison with known values obtained with similar compounds, this problem can be solved in most cases without difficulty.

With reference to the rules that we have established for AA'XX' systems the multiplicity and the intensity distributions in some typical spectra will now be discussed. Since we are concerned here with proton spectra it must be emphasized that, as in the case of 2-methylbenzotriazole, the criterion for the AA'XX' case – a very large chemical shift between the A and the X nuclei – is not always rigorously met. Correctly speaking, these systems should be classified as AA'BB' spectra, the characteristics of which we will consider briefly on page 200. For the examples treated here, however, the AA'XX' formalism is a very good approximation and since the essential features of the AA'XX' system reappear in the AA'BB' system the following discussion is justified.

As the first example let us consider the spectra of *para*-disubstituted benzenes. Representative of this class of compounds is the AA' portion of the four-spin system for the aromatic protons in 4-bromoanisole shown in Figure 6.24.

The spectrum can be interpreted easily if we consider the coupling constants expected for this molecule. The parameter N here consists of the relatively large *ortho* coupling (J) and the smaller *para* coupling (J'). The two a_2 subspectra are consequently separated by about 7–9 Hz (cf. Table 3.2, p. 62) and can immediately be assigned to the intense lines 1 and 2. It follows that the parameter L should be about 5–7 Hz since it represents the difference between the *ortho* and *para*

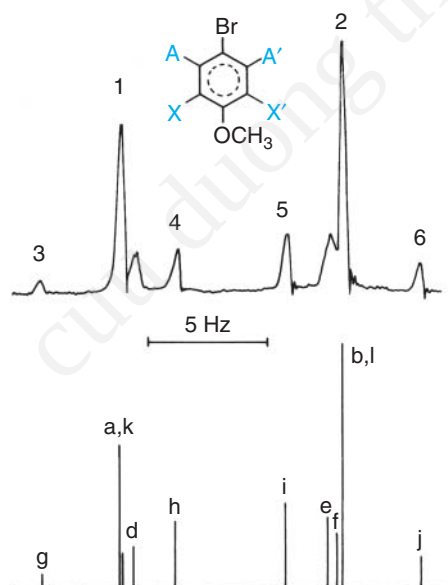
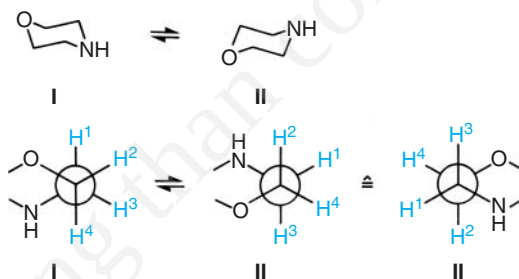


Figure 6.24 AA' portion of the AA'XX' system of the aromatic protons of 4-bromoanisole at 60 MHz; line c is nearly superimposed on a,k After Reference [4].

couplings. The effective coupling constants of the *ab* subspectra, the parameters K and M , differ considerably in the present case since the remaining two *meta* couplings (J_A and J_X) are similar in magnitude. Therefore, M is smaller than 1 Hz and a value of 4–6 Hz is expected for K . The symmetrical *ab* quartet (*g*, *h*, *i*, and *j*) can thus be assigned to the lines 3, 4, 5, and 6. In the antisymmetric *ab* subspectrum only the inner lines (*d* and *e*) are discernible. The outer lines (*c* and *f*) coincide with the a_2 subspectra and because of this the parameter M can be determined only approximately. Of importance for the characteristic appearance of the spectral type discussed here is the relatively large shift difference between the two proton pairs in the positions *ortho* to the bromine atom and the methoxy group. If the substituents *X* and *Y* become similar relative to their influence on the proton resonance, $\nu_0\delta$ decreases and consequently the *X* approximation is no longer applicable. The appearance of the spectrum becomes more complicated as it approaches the *AA'BB'* case.

For substituted ethanes of the type XCH_2CH_2Y , *AA'XX'* spectra are also observed. As an example, we consider morpholine. At room temperature rapid ring inversion occurs ($I \rightleftharpoons II$), effectively reducing the complicated four-spin system of the protons of the CH_2CH_2 groups to an *AA'XX'* system.



If we use Newman projections to represent these conformations we can show that:

- 1) The equilibrium $I \rightleftharpoons II$ has the effect of exchanging protons H^1 and H^2 for H^3 and H^4 , respectively, and consequently $\nu_1 = \nu_3 = \nu_A$ and $\nu_2 = \nu_4 = \nu_X$.
- 2) In addition to the two geminal coupling constants, $J_{13} = J_A$ and $J_{24} = J_X$, only two other time-averaged coupling constants are obtained, namely:

$$\begin{aligned}
 J &= \frac{1}{2}[J_{14}(I) + J_{14}(II)] = \frac{1}{2}(J_{trans} + J_{gauche}) \\
 &= \frac{1}{2}[J_{23}(I) + J_{23}(II)] = \frac{1}{2}(J_{gauche} + J_{trans}) \\
 J' &= \frac{1}{2}[J_{12}(I) + J_{12}(II)] = \frac{1}{2}(J'_{gauche} + J''_{gauche}) \\
 &= \frac{1}{2}[J_{34}(I) + J_{34}(II)] = \frac{1}{2}(J'_{gauche} + J''_{gauche})
 \end{aligned}$$

Thus the criteria for an *AA'XX'* system are met. The appearance of the spectrum here is determined by the large geminal coupling constants of about -10 Hz. Consequently, only K of the parameters K , L , M , and N becomes very large and M ,

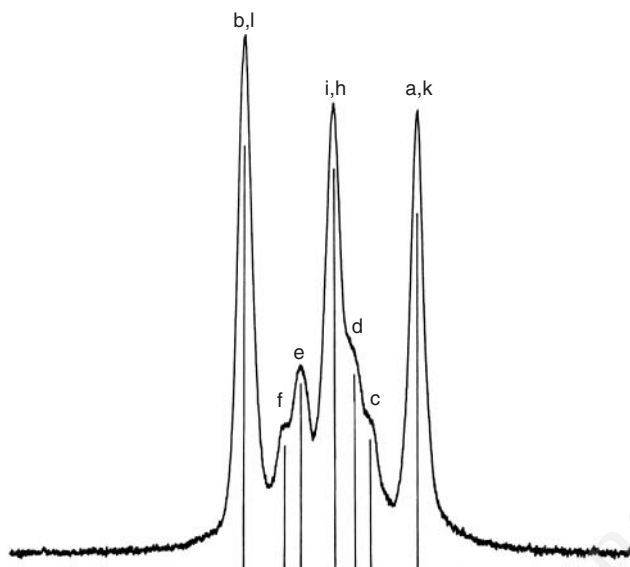


Figure 6.25 XX' portion of the $AA'XX'$ system of the methylene protons in morpholine at 100 MHz.

as the difference between two large values, becomes relatively small. Since $J > J'$ it follows that $N > L$. Therefore, in the symmetric quartet of the ab subspectra only the inner lines, h , and i , which sometimes degenerate to a singlet, are easily assignable, and the antisymmetric quartet should resemble an AX system (Figure 6.25). For $M \approx 0$ it degenerates to a doublet. The parameter K cannot be determined, so that from the coupling constants J_A and J_X only the difference (M) is accessible.

The special case of deceptively simple $AA'XX'$ system is found in furan (cf. Figure 3.20c and 6.26). The erroneous interpretation of this spectrum as an A_2X_2 system leads to the conclusion that $J = J'$, that is, that $L = 0$. This is the condition for the magnetic equivalence of the A and the X nuclei, respectively. In the case at hand this cannot be true since if it were the intensity ratio in both triplets would be 1 : 2 : 1. The simple appearance of the spectrum arises mainly from two sources. First, the inner lines of the ab subspectra (d , e , h , and i) are so close together that they cannot be resolved. Second, the intensities of the outer lines of the symmetric ab subspectrum lie below the limit of detection. In addition, the outer lines of the antisymmetric quartet are also of low intensity and very close to the intense lines a and k or b and l . Recording the spectrum with greater receiver gain makes these points clear (Figure 6.26, p. 204).

Another type of simplified $AA'XX'$ system is met if J_A or $J_X \approx 0$. In this case K becomes almost equal to M ($K \approx M$) and the ab subspectra degenerate to the extent that only six lines appear in the AA' and the XX' portion of the spectrum. The spectrum of the olefinic protons of the iron tricarbonyl complex of tricyclo[4.3.1.0^{1,6}]deca-2,4-diene provides an example of this (Figure 6.27, p. 204).

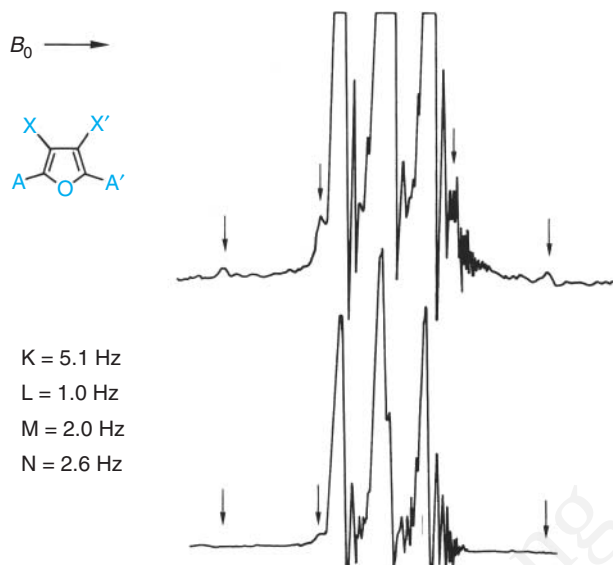


Figure 6.26 AA' part ^1H NMR spectrum of furan at 60 MHz. After Reference [4].

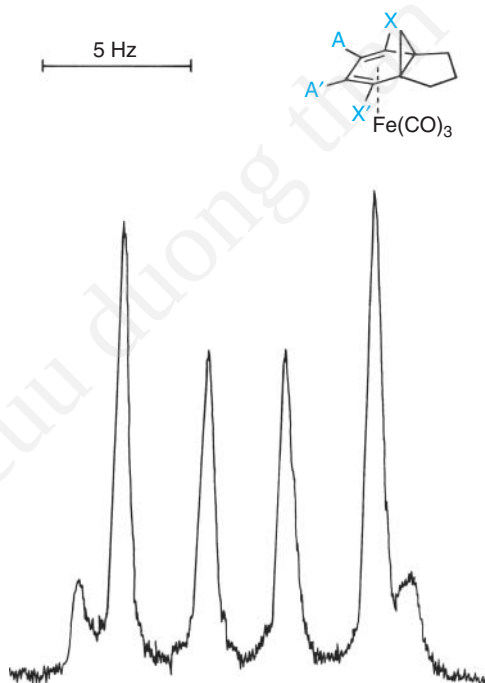


Figure 6.27 Half spectrum of the AA'XX' system of the olefinic protons of tricyclo[4.3.1.0^{1,6}]deca-2,4-dieneiron tricarbonyl. After Reference [5].

If the relative chemical shift between the A and X nuclei decreases, the spectrum changes gradually from the AA'XX' to the AA'BB' type. It is then sensitive to the chemical shift difference $\nu_0\delta$ (AB) and as a first indication of this new situation we note changes in the line intensities.

In the case of 4-bromoanisole (p. 201) these intensity changes are illustrated by the roof effect for the lines 1 and 2, which would not be expected for a true AA'XX' system as shown in Figure 6.21. The error that is made in this case by using the AA'XX' formalism is, however, rather small. By further diminishing the relative chemical shift, the error increases rapidly so that we finally must treat the spin system correctly as an AA'BB' system. The eigenvalues $m_T(BB')$ are then no longer good quantum numbers and a glance at Table 6.5 shows that a fourth-order determinant must be solved in the course of the analysis. Therefore, a straightforward *direct analysis* of the AA'BB' case is *not possible*. It can be shown, however, that the four unknown eigenvalues of the states (3), (5), (6), and (8) can be eliminated. Without going into the details of this procedure, we mention that this allows the derivation of equations that relate the measured line frequencies

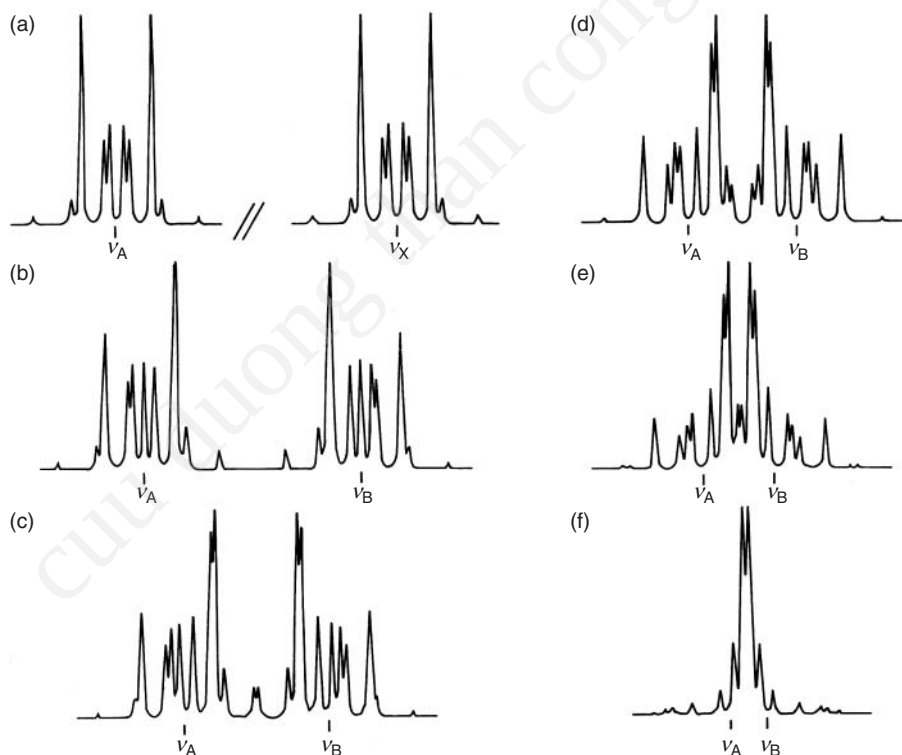


Figure 6.28 Dependence of the AA'BB' spectrum on the shift difference $\nu_0\delta$ (AB): (a) AA'XX' limiting case; $\nu_0\delta =$ (b) 30.0, (c) 20.0, (d) 15.0, (e) 10.0, and (f) 5 Hz. The following coupling parameters apply in all of the examples: $J = 8.2$ Hz, $J' = 1.5$ Hz, $J_A = 7.5$ Hz, and $J_B = 3.0$ Hz.

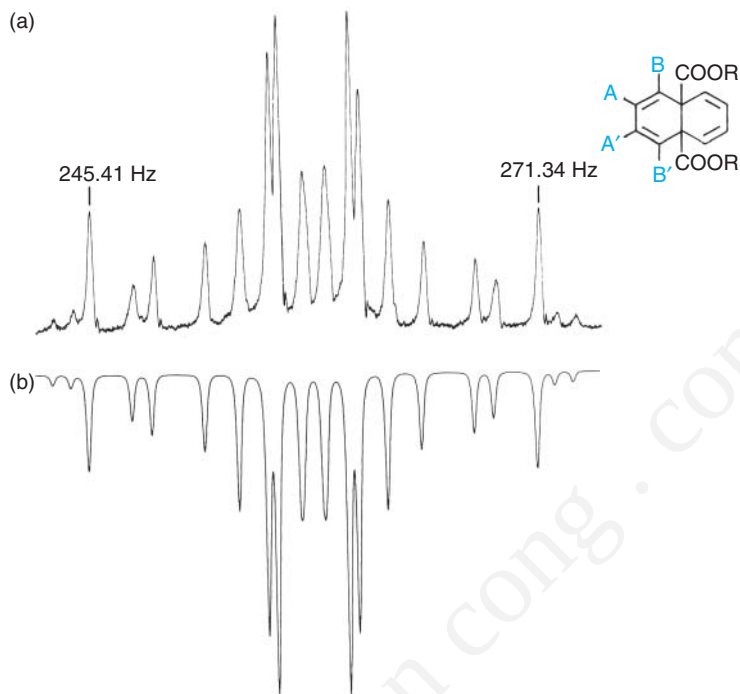


Figure 6.29 (a) Experimental and (b) calculated ^1H NMR spectrum of the olefinic protons of 9,10-dicarbethoxy-9,10-dihydronaphthalene (R = Et) at 60 MHz [6].

directly to the parameters of the spectrum (cf. Appendix, p. 666). Direct analysis is thus also possible for AA'BB' spectra.

Experimentally, the AA'BB' system can be recognized by the intensity distribution mentioned above, which results in progressively heightened intensities of the lines flanking the center ($(\nu_A + \nu_B)/2$) at the expense of the intensity of the outer lines. Consequently, AA'BB' systems show the roof effect but are symmetric about the center. Furthermore, the transitions *a* and *k* or *b* and *l* are no longer degenerate so that each half of the spectrum consists of 12 lines. Figure 6.28 (p. 205) shows the transition from the AA'XX' limiting case to the AA'BB' case with reference to a series of calculated spectra in which the relative chemical shift was decreased while the original values of the coupling constants were maintained.

6.5.4

Computer Analysis

As mentioned before, computers play an important role in the analysis of complicated spectra that arise from spin systems without symmetry or with a large number of nuclei. In these cases the simplifications discussed in the previous sections do not apply and computer programs are used to solve the eigenvalue problem. In addition, the results obtained by a direct analysis of a spin system

are always checked by comparing a calculated spectrum with the experimental spectrum. This comparison is a stringent test, especially since the line shape of the NMR signals can be simulated. Figure 6.29 produces such a comparison for the spectrum of the olefinic protons of 9,10-dicarboethoxy-9,10-dihydronaphthalene.

The solution of the eigenvalue problem formally presented in Section 6.4, that is, the calculation of transition frequencies and intensities on the basis of a given set of chemical shifts and coupling constants, can be easily programmed. Since for the more complicated spectra in general no explicit equations can be derived for the parameters, the “trial and error” procedure formed the basis of the earlier attempts of computer analysis. From the consideration of known data for similar compounds and possibly with the aid of recognizable or familiar features in the experimental spectrum – recurring line separations, for example – a set of trial parameters was estimated and in turn used to calculate a trial spectrum. Comparison of the calculated with the experimental spectrum suggested changes for chemical shifts and coupling constants in the initial set of parameters that were believed to improve the agreement between the calculated and the experimental spectrum. Depending upon the degree of complexity of the spectrum and the extent of the spectroscopist’s experience and sophistication, a set of parameters was finally reached that could be accepted as a solution of the problem since the spectrum calculated was consistent with the experimental one relative to the line positions as well as to the line intensities.

The disadvantages of this method are obvious. First, it is very tedious and time consuming in its application and, second, it lacks any indication that a further change of one or more parameters will not allow a still better fit between theory and experiment and thus a more exact analysis. Definite progress was therefore made when programs were developed that enabled the computer to perform the comparison between the calculated and the experimental spectra and criteria established that guarantee a convergence to the correct solution. From several approaches the one developed by S. Castellano and A.A. Bothner-By, known as LAOCOON⁷⁾ (least-squares adjustment of calculated on observed NMR transitions [7]), is generally used today and forms the basis of computer software that is commercially available for spectral analysis. Without going into the details of the mathematics of this program, we shall attempt to describe the essential principle.

The analysis starts with the calculation of a trial spectrum with a set of estimated starting parameters Δp_j . In the process of this calculation, that is, by the diagonalization of the Hamilton matrix set up according to the rules of Section 6.4.4, one obtains in addition to the eigenvalues the unitary matrix $\hat{U}$ of the eigenvectors. Next comes the very important step of assigning the lines of the experimental spectrum to the lines of the trial spectrum, that is, the investigator provides the computer with the information:

$$E_p - E_q = f_{pq} \quad (6.38)$$

7) This acronym signifies the effort necessary to unravel complicated NMR spectra.

where E_p and E_q are the calculated eigenvalues and f_{pq} is the experimentally measured energy difference. The basic idea is then that the best set of parameters is the one that leads to the smallest sum of the squares of the errors [Eq. (6.39)]:

$$\sum_{i=1}^k (f_{\text{exp.}} - f_{\text{calc.}})_i^2 \quad (6.39)$$

where k is the number of the measured lines and $f_{\text{exp.}} - f_{\text{calc.}}$ is the frequency difference between the observed and calculated transitions for the i -th line. For each of the parameters p_j then the following condition should hold:

$$\partial \sum_{i=1}^k (f_{\text{exp.}} - f_{\text{calc.}})_i^2 / \partial p_j = 0 \quad (6.40)$$

or:

$$-2 \sum_{i=1}^k (f_{\text{exp.}} - f_{\text{calc.}})_i \left(\frac{\partial f_{\text{calc.}}}{\partial p_j} \right)_i = 0 \quad (6.41)$$

If one assumes for small parameter changes a linear dependence of the frequencies one can write:

$$\Delta f_i = \left(\frac{\partial f_i}{\partial p_j} \right) \Delta p_j \quad (6.42)$$

and for the best solution:

$$\left(\frac{\partial f_i}{\partial p_j} \right) \Delta p_j = (f_{\text{exp.}} - f_{\text{calc.}})_i \quad (6.43)$$

That is, what we seek are those parameter changes: that make the experimental and the calculated frequencies equal.

Assignment of the experimental lines to the lines of the first calculated spectrum provides the computer with the information $f_{\text{exp.}} - f_{\text{calc.}}$. The partial derivatives are obtained from the eigenvalues of the trial spectrum in a manner we shall not discuss here. They are approximated just as the first parameter correction Δp_j . Various iteration cycles lead finally to convergence toward the correct solution (Figure 6.30). As one can easily see, the process of assignment is of crucial significance to the analysis since too many “incorrect” input data lead necessarily to erroneous results. In this connection it is interesting to ask whether the solution for a particular spin system is unique or whether perhaps several parameter sets exist that describe the experimental spectrum equally well within the limits of experimental error. Fortunately, only infrequently has the latter situation been found to be the case. The agreement between experiment and theory, not only with respect to frequencies but also with respect to intensities, therefore applies as the criterion for the correct solution. For the comparison it is thus advantageous to make use of the previously mentioned possibilities to simulate the natural line shapes of the NMR signals. Especially with strongly overlapping lines, an examination of the results of the spectral analysis is almost impossible without recourse to this aid.

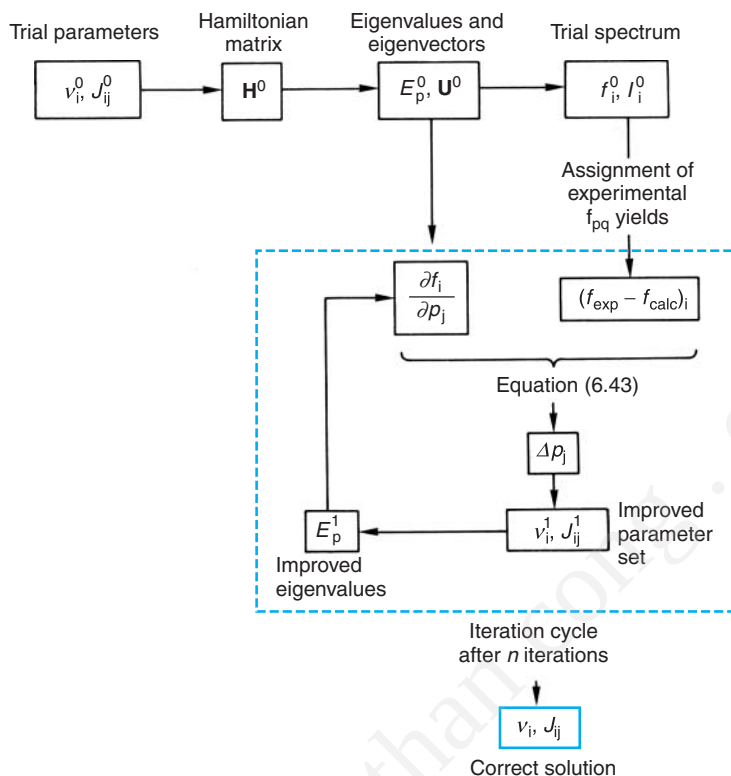


Figure 6.30 Dataflow in the LAOCOON program.

With the advent of more complicated spectra, in particular those of molecules partially oriented in liquid crystals that may consist of several hundred lines – a topic discussed in detail in Chapter 14 – the limits of traditional software for spectral analysis were soon recognized. Using more sophisticated mathematical methods several research groups succeeded later in the development of powerful programs, especially those that allow a completely automatic analysis of multiline spectra even without the use of intelligently guessed starting parameters. The interested reader may consult the first three review articles cited below for more information on this subject, which is beyond the limits of our introductory textbook.

References

1. Bovey, F.A. (1969) *Nuclear Magnetic Resonance Spectroscopy*, Academic Press, New York.
2. Garbisch, E.W. Jr., (1968) *J. Chem. Educ.*, **45**, 410.
3. Schaefer, T. (1962) *Can. J. Chem.*, **40**, 1678.
4. Grant, D.M., Hirst, R.C., and Gutowsky, H.S. (1963) *J. Chem. Phys.*, **38**, 470.
5. Bleck, W.E. (1969) PhD thesis, University of Cologne.
6. Günther, H. and Hinrichs, H.-H. (1967) *Justus Liebigs Ann. Chem.*, **706**, 1.

7. Castellano, S. and Bothner-By, A.A. (1964) *J. Chem. Phys.*, **41**, 3863.

Textbooks

- Abraham, R.J. (1971) *Analysis of High Resolution NMR Spectra*, Elsevier, Amsterdam, 324 pp.
Corio, P.L. (1966) *Structure of High-Resolution NMR Spectra*, Academic Press, New York, 548 pp.

Review Articles

- Corio, P.L. and Smith, S.L. (1996) *Analysis of High-Resolution Solution State Spectra*, in *Encyclopedia of Magnetic Resonance* (editors in chief R.K. Harris and D.M. Grant), vol. 2, John Wiley & Sons, Chichester, p. 797.
Stephenson, D.S. (1996) Analysis of spectra: automatic methods, in *Encyclopedia of Magnetic Resonance* (editors in chief R.K. Harris and D.M. Grant), vol. 2, John Wiley & Sons, Ltd, Chichester, p. 816.
Levy, G.C., Kerwood, D.J., and Ravikumar, M. (1996) Data processing, *Encyclopedia of Magnetic Resonance* (editors in chief R.K. Harris and D.M. Grant), vol. 3, John Wiley & Sons, Ltd, Chichester, p. 1548.
Hägele, G., Engelhardt, M., and Boenigk, W. (1987) *Simulation und automatisierte Analyse von Kernresonanzspektren*, VCH Publishers, Weinheim.
Diehl, P., Kellerhals, H., and Lustig, E. (1972) Computer assistance in the analysis of high resolution NMR spectra. *NMR Basic Princ. Prog.*, **6**, 1.
Günther, H. (1972) ^1H -NMR spectra of the AA'XX' and AA'BB' type—analysis and systematics *Angew. Chem., Int. Ed. Engl.*, **11**, 861.
Hofmann, R.A., Forsén, S., and Gestblom, B. (1971) Analysis of NMR spectra. *NMR Basic Princ. Prog.*, **5**, 1.
Garbisch Jr. E.W. (1968) Analysis of complex NMR spectra for the organic chemist. *J. Chem. Educ.*, **45**, 311, 402, and 480.
Diehl, P., Harris, R.K., and Jones, R.G. (1967) Sub-spectral analysis. *Prog. Nucl. Magn. Reson. Spectrosc.*, **3**, 1.

7

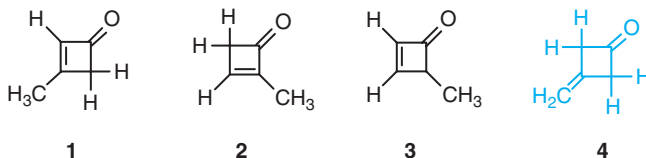
The Influence of Molecular Symmetry and Chirality on Proton Magnetic Resonance Spectra

The success of NMR spectroscopy in chemistry is due primarily to the fact that the information obtained from NMR spectra corresponds closely to the model-like thinking of chemists. The association of definite spectral regions with certain types of differently bonded protons such as “aromatic” and “olefinic,” and the multiplicity of the signals, provide information that can be transformed more easily into conceptions about structure and stereochemistry than can the absorption bands in infrared or ultraviolet spectra. Of special significance is the fact that the symmetry of a molecule, because of the sensitivity of NMR parameters to the molecular environment of the nuclei, is also reflected in the spectrum. As we explained in Chapter 3, it determines, for example, whether nuclei are magnetically equivalent. In particular the phenomenon of magnetic equivalence or non-equivalence (Chapter 3, p. 52) is closely related to molecular symmetry.

7.1

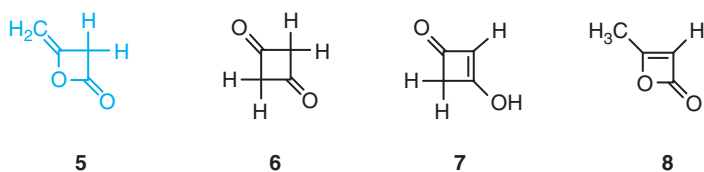
Spectral Types and Structural Isomerism

As in infrared spectroscopy, a *highly symmetric* compound can already be recognized from its NMR spectrum by the small number of signals it presents. Of the isomeric compounds 1–4 with the molecular formula C_5H_6O compound 4, which has two planes of symmetry and a twofold axis of rotation, produces only two signals with an intensity ratio of 2:1 and thereby can be differentiated from all of the other structures.

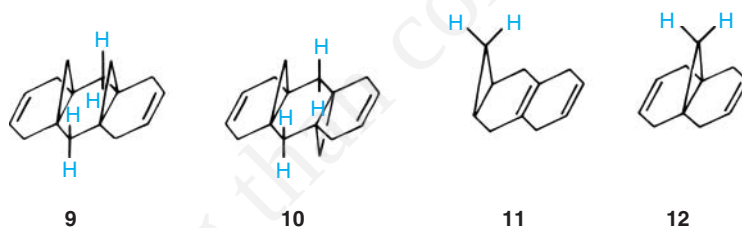


For the ketene dimer the proposed structures 6–8 can be immediately eliminated from consideration since only two groups of signals of equal intensity, due to

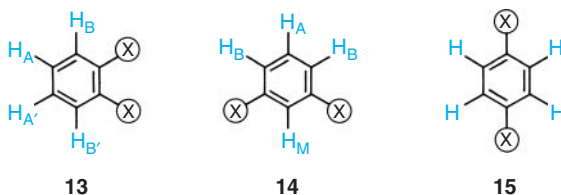
the olefinic and the aliphatic methylene protons, are observed in the spectrum of compound **5**. From the other structures one expects a singlet for **6**, three ^1H resonances for **7**, and two signals in the intensity ratio 1 : 3 for **8**.



In the case of bis-methylene adducts of the symmetrical hexahydroanthracene the possible *syn*- and *anti*-isomers (**9** and **10**, respectively) can be easily differentiated since on the one hand an AB system is expected for the central methylene groups while an A_2 system is expected on the other. In the same way the methylene adducts **11** and **12** can be differentiated, as an AB system for the cyclopropyl group of **11** and an A_2 system for the same group of **12** results. Moreover, the number of olefinic protons and the environment of the methylene groups in the six-membered ring are also different here.

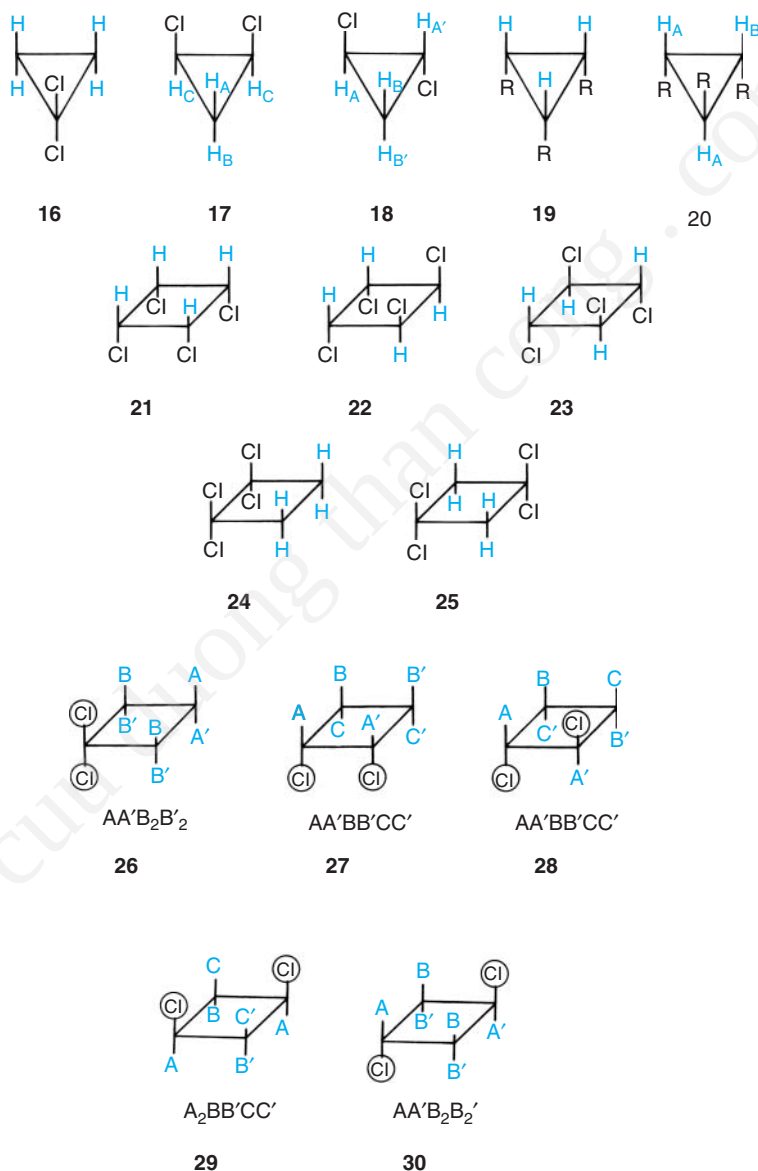


If, with respect to symmetry, we consider the spectra of disubstituted benzenes with two identical substituents, an unambiguous assignment of structure can be made without a detailed analysis through the mere classification of the spectra. Thus for the *ortho*-derivative (**13**) a spectrum of the $AA'BB'$ or $AA'XX'$ type is observed while for the *meta* and *para* derivatives (**14** and **15**) AB_2M and A_4 spectra, respectively, result.

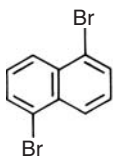
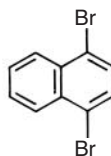


A similar situation is met in the case of disubstituted cyclopropanes with identical substituents, as shown, for example, with the three isomeric dichlorocyclopropanes (**16–18**) that have spectra of the A_4 , ABC_2 , and $AA'BB'$ type, respectively. For trisubstituted cyclopropanes with identical substituents the spectra are likewise clearly distinguished; for example, the two isomers **19** and **20** have A_3 - and

AB_2 -type spectra, respectively. Fewer favorable relationships exist in the case of cyclobutanes. The isomeric tetrachlorocyclobutanes **21–25** all have spectra of the A_4 type and individual structures cannot, a priori, be differentiated even though the resonance frequency of the protons in all five compounds is different. In the case of the isomeric dichlorocyclobutanes **26–30** the spectra are again of different symmetry, but they are so complicated that they cannot be interpreted without detailed analysis.



For dibromonaphthalenes **31** and **32** the assignment is again straightforward since for **31**, if one neglects $^1\text{H}, ^1\text{H}$ coupling over more than four bonds, depending on the spectrometer frequency used, an ABC or AMX system is expected, whereas the spectrum of **32** should exhibit an AA'BB' or AA'XX' and an A_2 system.

**31****32**

Exercise 7.1

Which spectral types do you expect for the protons in the following compounds?

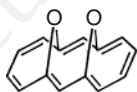
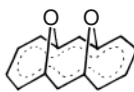
- cis*-cyclopropane-1,2-dicarboxylic acid
- trans*-cyclopropane-1,2-dicarboxylic acid
- 1,4-dichlorobenzene
- 2-chlorophenol
- 4-chlorophenol

Exercise 7.2

Sketch the ^1H NMR spectra of the three isomers of acetylpyridine.

Exercise 7.3

For 1,6;8,13-bis-oxido-[14]annulene only *one* AA'BB' system is observed for the perimeter protons. On the basis of this observation should the compound be assigned the structure (a) or (b)?

**a****b**

Exercise 7.4

1,4-Disila-octamethyl[6]radialene (**c**) can exist in the chair conformation (**d**) that has C_{2h} symmetry or in the twist conformation (**e**) with D_2 symmetry. Assign spectra 1 and 2 given in Figure 7.1 to **d** and **e**, respectively.

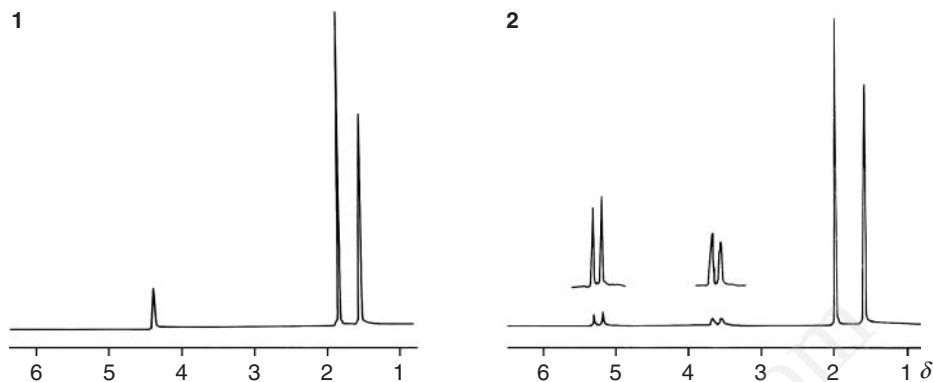
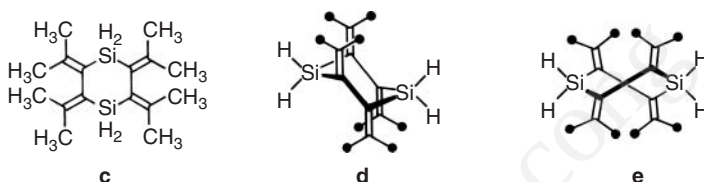


Figure 7.1 80 MHz ^1H NMR spectra of the two conformations of disila[6]radialene [1].



From the above considerations it can be concluded that compounds that have little or no symmetry will have more complex spectra than compounds that have a number of symmetry elements. Nevertheless, relatively simple spectra are often observed for high molecular weight natural products that are considered to be complicated in the chemical sense. In these cases groups of protons form isolated spin systems of A_2 , AB, AX, AB_2 , AX_2 , or ABX types that can be easily analyzed and assigned and only the symmetry of the group under consideration, and not the symmetry of the entire molecule, determines the spectral type. The prerequisite for the appearance of *subspectra* of this type is that the spin–spin interactions between the individual proton groups lie below the experimental limits of detection. The assignment of signals explained in the following example serves to illustrate this fact.

In the spectrum of flemingin B (Figure 7.2), an African drug, an AB_2 and two AB systems are recognized. The different coupling constants of 15.5 and 10.0 Hz allow an unambiguous assignment of the AB systems to the protons of the *trans* double bond and the C3=C4 double bond, respectively, while only one phenyl ring, namely (a), possesses the symmetry necessary for the AB_2 system. A singlet at δ 7.34 arises from the isolated proton at C7 while the broadened triplet at δ 5.12 comes from the olefinic proton of the side-chain, the resonance of which is split by the protons of the neighboring methylene group. The allylic spin–spin coupling with the methyl protons leads merely to a broadening of the signals. This is reflected in the methyl region for the signals at δ 1.63 and δ 1.57, which are assigned to the protons of the geminal methyl groups in the side-chain. The signals of the remaining methylene

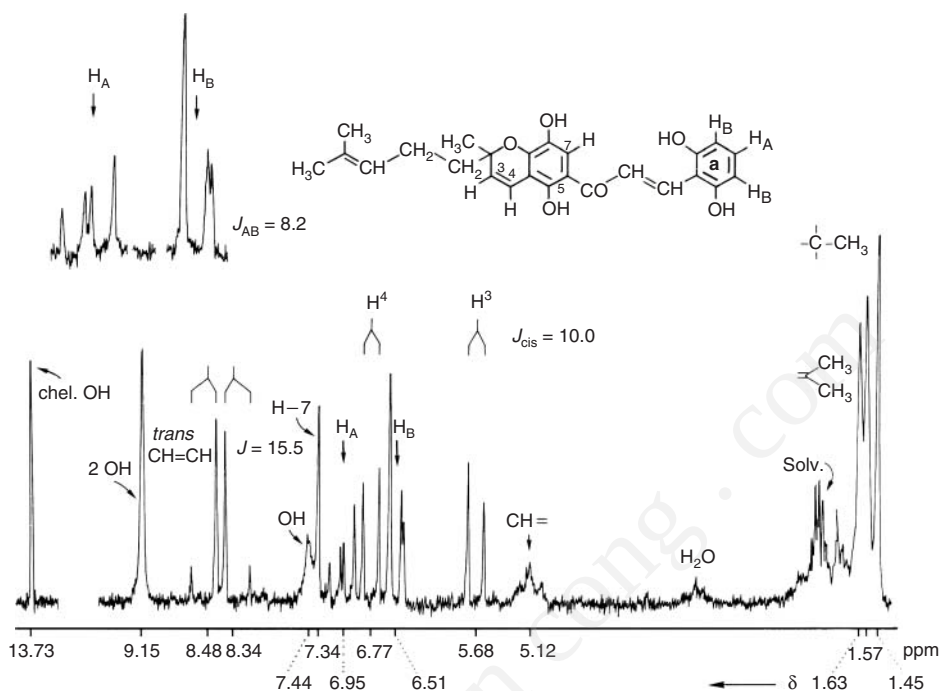


Figure 7.2 60 MHz proton resonance spectrum of a natural product (see text), in $[D_6]$ acetone [2].

protons at about δ 2.0 cannot be clearly distinguished since the protons of the incompletely deuterated solvent absorb here. Noteworthy is the low-field position of one of the OH resonances. This is the signal of the C5 hydroxyl group that can form a hydrogen-bond with the neighboring keto-function.

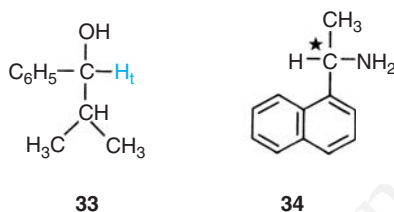
Clearly, the use a superconducting magnet with a much higher measuring frequency than 60 MHz would simplify the spectrum by removing signal overlap and the three subspectra would be transformed into AX and AX_2 spectra. Notwithstanding the high magnetic fields available today, however, higher than first-order spectra may be found for more complicated structures. First-order spectra are assigned with the help of 2D shift correlations, which were introduced briefly in Chapter 3 and will be discussed in detail later. Many coupling constants can then be identified and measured directly. The reader will find nice examples in Reference [3].

7.2

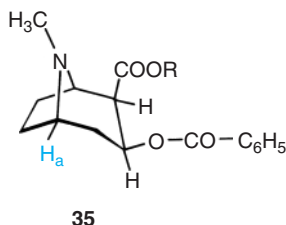
Influence of Chirality on the NMR Spectrum

Turning our attention to compounds with asymmetric centers we find that, just as with the other physical properties of optical antipodes – except for their

interaction with polarized light – the D- and the L-forms cannot be distinguished. Their NMR spectra are therefore superimposable and also correspond exactly to that of the racemate. However, it is possible through the use of *optically active solvents* to produce in a racemate a chemical shift between the signals of the two optical isomers. Thus, with a solution of phenylisopropylcarbinol (**33**) in D,L-naphthylethylamine (**34**) two equally intense doublets are observed for the resonance of the tertiary proton, H_t . Their separation amounts to 1.6 and 2.5 Hz at 60 and 100 MHz, respectively. Accordingly, the splitting must be the result of a difference in resonance frequencies since spin–spin coupling is independent of the field strength.



This finding does not contradict the introductory statement that enantiomers have identical NMR spectra since in optically active solvents, (+)SOL or (–)SOL, diastereomeric complexes D-X/(+)SOL and L-X/(+)SOL or D-X/(–)SOL and L-X/(–)SOL can form through intermolecular interaction between the solvent (SOL) and the dissolved substance, D,L-X, and lead to different spectra. The magnitude of the splitting depends upon the asymmetry or chirality of the solvent and also upon the degree of association between substrate and solvent and therefore upon the temperature. Thus, with 1-cocaine (**35**) the difference in the resonance frequencies for the proton, H_a , is 0.14 ppm when the spectra are measured at 20°C in 30% (v/v) solutions of (+)- and (–)-1-phenylethanol in carbon disulfide. At –40°C, on the other hand, a difference of 0.47 ppm is observed. This example also shows us that even when the optically active solvent is diluted with the optically inactive carbon disulfide the diastereomeric solvation effect is still observed.



As one can see immediately, integration of the NMR absorptions of the affected signals provides a means for determining the *optical purity* of incompletely resolved racemates. Another method consists of reacting the enantiomeric mixture

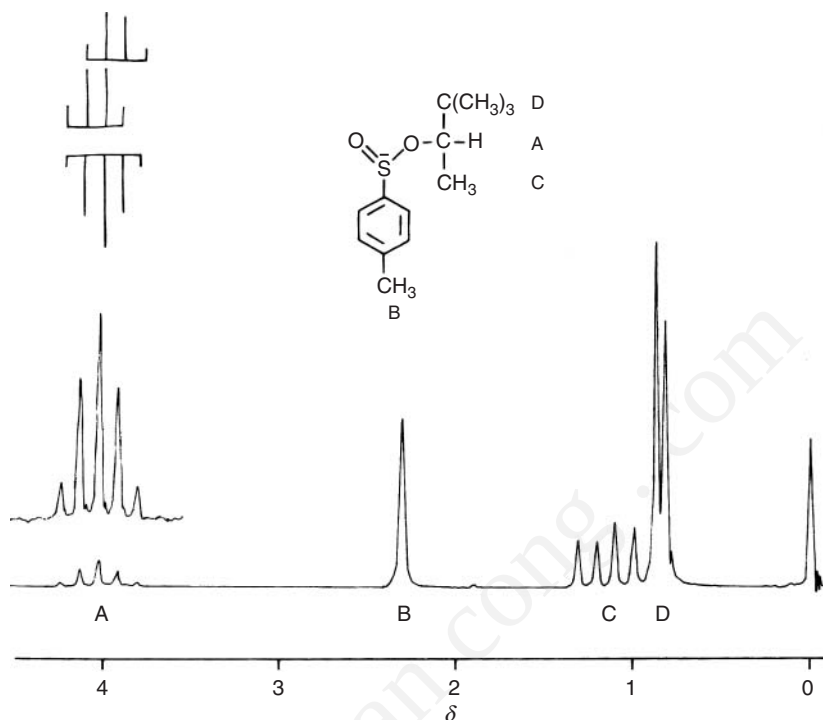


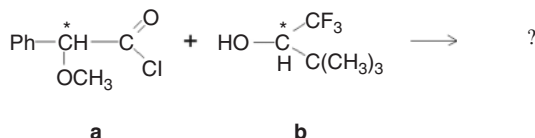
Figure 7.3 ^1H NMR spectrum of the product of the reaction of racemic *p*-toluenesulfinyl chloride with (*S*)-3,3-dimethyl-2-butanol [4].

under consideration with an optically active compound to form a mixture of diastereomeric products that can be investigated by integration of its NMR spectrum. Figure 7.3 shows the spectrum of the product (4-methylbenzenesulfinic acid 3,3-dimethylbutyl-2-ate) of such a reaction between racemic *p*-toluenesulfinyl chloride¹⁾ and pinacolone alcohol [(*S*)-3,3-dimethyl-2-butanol] that was nearly completely (97%) in the (*S*)-configuration. The product consisted of a mixture of two components, (+)A(+)B and (–)A(+)B, in which A and B represent the *p*-toluenesulfinyl and the pinacolone alcohol moieties, respectively. As the spectrum demonstrates, all of the resonances of the aliphatic protons, with the exception of that of the methyl group on the benzene ring, are duplicated. The two singlets of the *t*-butyl group and the doublets of the methyl group can be recognized especially clearly. The quartets of the tertiary proton overlap to form a quintet. Using this method it is even possible to determine the optical purity of compounds that owe their chirality merely to the substitution of a proton by a deuterium.

1) Note that the arylsulfinic acid chloride has a free electron pair at sulfur and therefore a quasi tetrahedral structure.

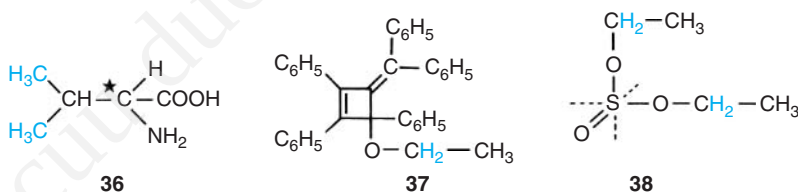
Exercise 7.5

Racemic acid chloride (**a**) is reacted with racemic carbinol (**b**). How many products do you expect? What is their stereochemistry and which ^1H NMR spectrum results?



Today, the use of chiral shift reagents – a topic discussed in more detail in Chapter 15 – is the method of choice to investigate racemic mixtures. The basic principle is the same as described above for the use of optically active solvents or the synthesis of diastereomers. However, their strong ability to form complexes in solution and the low concentration of the reagent usually needed to obtain the desired result make shift reagents much more attractive. In addition, a large variety of solvents can be used for the experiment.

Let us now investigate the intramolecular influence of optically active centers. If a molecule contains an *asymmetric* carbon atom the magnetic equivalence of neighboring protons or groups of protons can be destroyed. As a typical example, one finds two doublets at δ 0.90 and δ 0.83 for the CH_3 protons of the isopropyl group in L-valine (**36**). In another case, instead of the expected quartet, the CH_2 group of the ethoxy group in the methylene cyclobutene derivative **37** gives rise to a complex splitting pattern (Figure 7.4) resulting from an ABX_3 spectrum. Other chiral centers such as the sulfite group in diethyl sulfite (**38**) also have this effect. Its magnitude as well as the type of spectrum that is observed depends on the spectrometer field strength B_0 .



To explain these findings, we consider in Figure 7.5 a molecule of the general structure shown and its conformations **I–III**, which are represented as Newman projections.

As can be seen, H^1 and H^2 are always located in different chemical environments since even if fast methyl rotation prevails or if the populations of the three rotamers **I**, **II**, and **III** are equal (which is generally not the case), the non-equivalence between H^1 and H^2 remains because the position of the group R varies. In conformation **I** it resides between residues **a** and **c**, in conformation **II** between **a** and **b**, and in conformation **III** between **b** and **c**. For the proton resonance frequencies we then

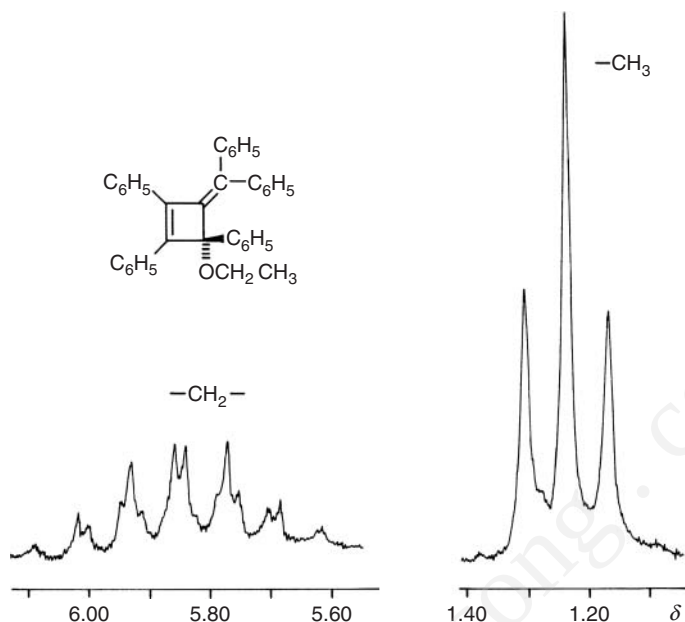


Figure 7.4 ^1H NMR spectrum of the ethoxy group in compound 37.

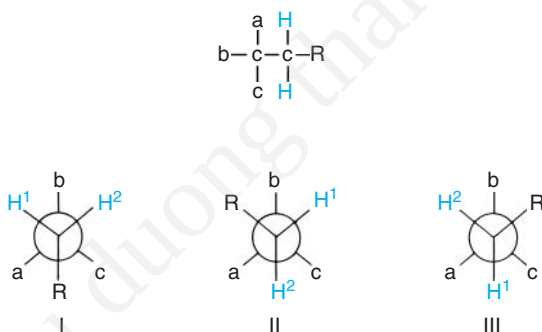
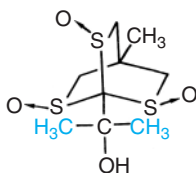


Figure 7.5 A general structure and its conformations I–III.

have $\nu_1(\text{I}) \neq \nu_2(\text{III})$, $\nu_2(\text{I}) \neq \nu_1(\text{II})$, and $\nu_2(\text{II}) \neq \nu_1(\text{III})$. If the substituent R is replaced by a hydrogen atom, this difference is eliminated and on the time average the protons of a rotating methyl group have the same resonance frequency, even if they are close to an asymmetric center (see also p. 53).

A compound for which the inherent asymmetric structural contribution to magnetic non-equivalence is independent of the populations of the individual conformations is the derivative of the “propeller” molecule 4-methyl-2,6,7-trithiabicyclo[2.2.2]octane-2,6,7-trioxide (**39**). The 2-hydroxyisopropyl group at the 1-position shows a shift difference of 0.04 ppm (in pyridine as solvent) for the

resonances of the methyl protons. The field dependence of the splitting (60 MHz, 2.3 Hz; 90 MHz, 3.6 Hz) proves that it is indeed a case of a difference in the resonance frequencies.



39

As the last example suggests, the phenomenon discussed here is not limited to molecules with optically active carbon atoms. Thus, in the general case shown in Figure 7.5 the residue (a) can be substituted by another CH_2R group, leading to a prochiral arrangement, as, for example, in acetaldehyde diethyl acetal, the spectrum of which is shown in Figure 7.6. In every case then, if a substituent of the general structure CX_2R is in the neighborhood of a prochiral $\text{CR}^1\text{R}^2\text{R}^3$ group or a chiral center the environments of the substituents X become non-equivalent, or *diastereotopic*. In contrast, groups whose environments are mirror images are designated as *enantiotopic*. The X–C–X angle between enantiotopic X groups is

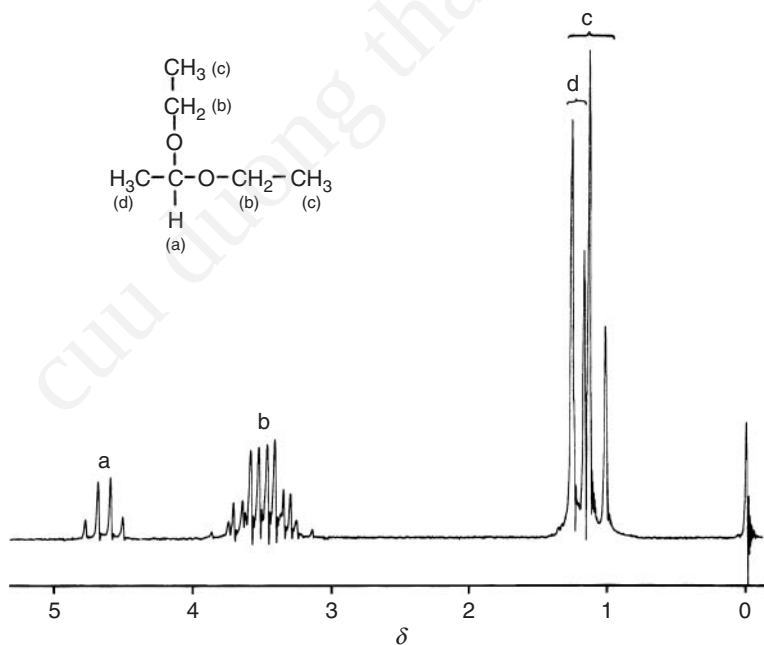
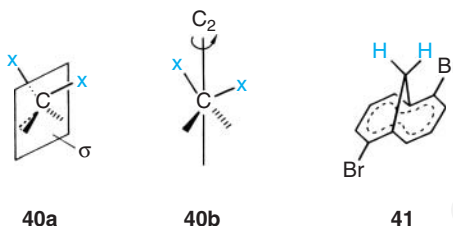
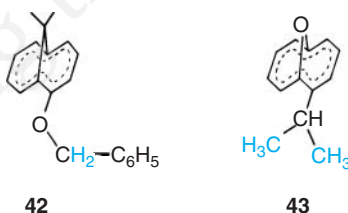


Figure 7.6 ^1H NMR spectrum of acetaldehyde diethyl acetal at 60 MHz.

therefore bisected by a mirror plane σ (**40a**). The X-groups are also equivalent if the particular molecule has C_2 symmetry and the C_2 axis passes through the carbon atom of the CX_2 moiety and is perpendicular to the line joining the X groups (**40b**). The A_2 system of the methylene protons in 2,7-dibromo-1,6-methano[10]annulene (**41**) provides an example.

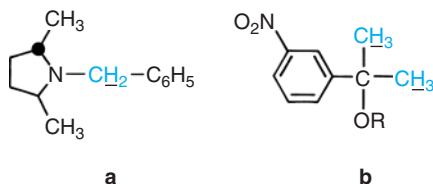


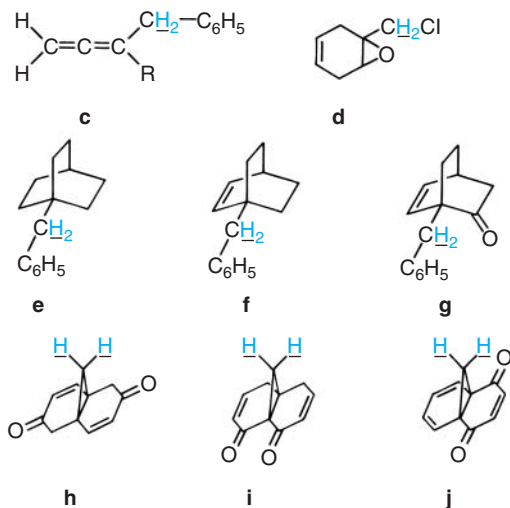
A CX_2R group can also serve as a probe to demonstrate the chirality of a larger ring system. Thus, one observes the expected AB system for the methylene protons of the benzyloxy group in 2-benzyloxy-1,6-methano[10]-annulene (**42**). Likewise, the non-equivalence of the methyl groups in 2-isopropyl-1,6-oxido[10]annulene (**43**) shows that this compound is not planar. Moreover, a rapid inversion of the oxygen bridge through the carbon perimeter can be excluded since this would result, on the time average, in an effective plane of symmetry and a consequent loss of chirality.



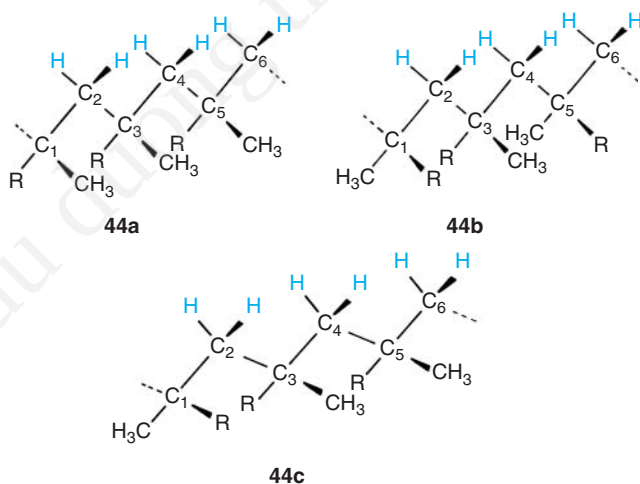
Exercise 7.6

Decide whether the indicated protons (underlined) in compounds **a–j** are enantiotopic or diastereotopic.





The sensitivity of the chemical shift to the symmetry of the molecular environment has also led to progress in polymer spectroscopy. This is revealed by observations made for poly(methyl methacrylate) polymer chains with different stereochemistry. Here we single out a sequence of six carbon atoms for which the conformations **44a–c** are conceivable.



These sequences are called “*triads*” since they are formed from three monomers and the linkage of the monomers is designated as isotactic (**44a**), syndiotactic (**44b**), and heterotactic (**44c**). If we limit ourselves to the first two systems it is easy to see that the methylene protons in **44a** should absorb as an AB system while in contrast

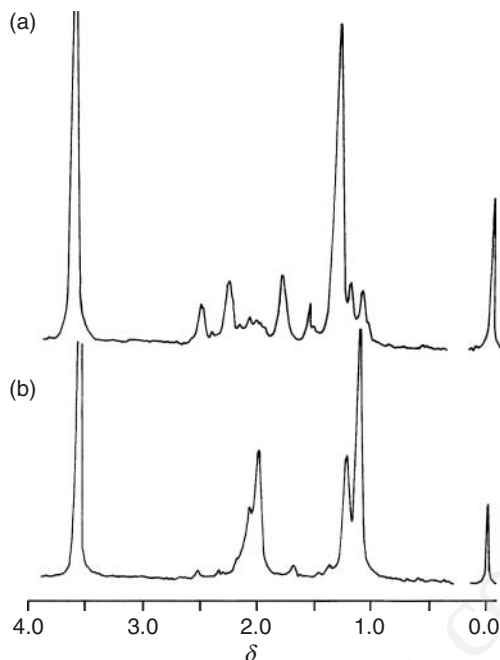
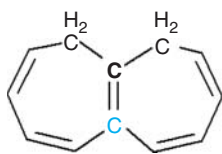


Figure 7.7 60-MHz ^1H NMR spectra of (a) isotactic and (b) syndiotactic poly(methyl methacrylate); the CH_2 resonance is centered at 2 ppm [5].

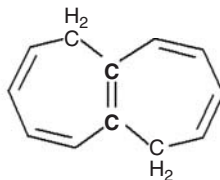
those in **44b** should absorb as an A_2 system, since in the latter case the $\text{C}_1-\text{C}_2-\text{C}_3$ segment possesses C_2 symmetry. As Figure 7.7 demonstrates, this prediction is confirmed by experiment.

Finally, to conclude the discussion of NMR spectra and molecular symmetry we emphasize that the observations described above are not confined to protons but are equally valid for other nuclei. For organic chemistry the carbon-13 nucleus is the most prominent representative of the so-called “heteronuclei” available for stereochemical investigations. The long measuring times necessary for ^{13}C NMR in the earlier days were certainly a drawback to using ^{13}C instead of ^1H NMR, but even today proton NMR is mostly preferred because of the high sensitivity of the proton chemical shift to neighboring group effects. Nevertheless, in anticipation of Chapter 11, where we deal at length with ^{13}C NMR, we mention that simple symmetry considerations such as those made at the beginning of this chapter for protons often show ^{13}C NMR to be superior to ^1H NMR. A few examples may be cited:

- The two isomers of dihydroheptalene, (**45a**) and (**45b**), both show four ^1H signals in the olefinic region and one methylene resonance. The chemical shifts are different but do not allow a differentiation. In contrast, a clear cut “*ab initio*” structure assignment is possible with ^{13}C NMR: **45a** shows *two* quaternary carbon signals, whereas **45b** only *one*.

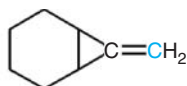


45a

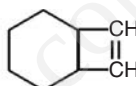


45b

- Compounds **46** and **47** can also be immediately distinguished by the number of olefinic ^{13}C resonances. Furthermore, for the dimer of cyclo-octatetraene (melting point 53°C) three structures (**48a–c**) were proposed. ^{13}C NMR gave rise to only four signals of equal intensity, which settled the problem in favor of structure **48c**.



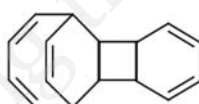
46



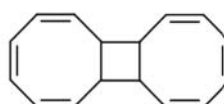
47



48a

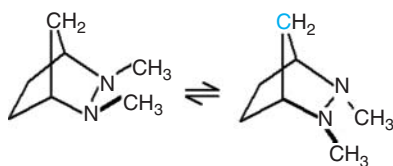


48b

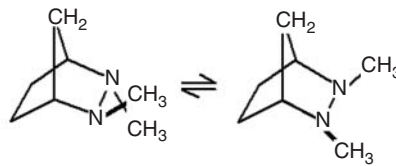


48c

- Finally, in the slow exchange limit the number of ^{13}C signals allows us to distinguish the two exchange systems **49** and **50**: *one* signal is observed for **50** and *two* for **49**.



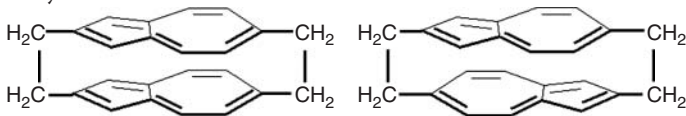
49



50

Exercise 7.7

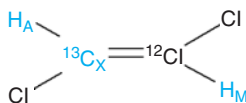
Can the two azulenophanes **a** (left) and **b** (right) be distinguished by ^1H , ^{13}C NMR, or by both?

**7.3****Analysis of Degenerate Spin Systems by Means of ^{13}C Satellites and H/D Substitution**

If the resonance signal of chloroform is recorded at high gain one observes a low-intensity singlet on both sides of the principal absorption separated by about 108 Hz from the main signal (see Chapter 4, Figure 4.8). The position of these weak signals is not dependent upon the spinning rate of the sample cell and therefore they are not spinning side bands. Instead, these signals are the so-called ^{13}C satellites of the chloroform signal.

Each organic compound contains 1.1% of the stable isotope ^{13}C in natural abundance. Thus, of 1000 chloroform molecules 989 are $^{12}\text{CHCl}_3$ and 11 are $^{13}\text{CHCl}_3$. Since ^{13}C has a nuclear spin of $I = \frac{1}{2}$ these molecules show a spin-spin interaction between ^{13}C and the proton that leads to the doublet splitting in the proton NMR spectrum. The same splitting is found in the ^{13}C NMR spectrum of $^{13}\text{CHCl}_3$.

The phenomenon of ^{13}C satellites can now be used to advantage to measure the coupling constants between magnetically equivalent protons of the A_n type that are not available from the spectra of ^{12}C molecules, as was shown before for the A_2 system (Chapter 6, p. 163 ff.). The condition is, however, that the protons are bound to different carbons. This will become clear with the example of *trans*-1,2-dichloroethene. As a consequence of molecular symmetry the protons in this compound form an A_2 system and the coupling constant $^3J_{\text{trans}}$ is not accessible.



However, if we consider molecules that have one ^{13}C nucleus, an AMX spin system with ^{13}C as the X-part is expected since $J(^{13}\text{C}-\text{H}_\text{A}) \gg J(^{13}\text{C}-\text{H}_\text{M})$. The effective Larmor frequencies of the protons are then:

$$\begin{aligned} \nu_\text{A}^* &= \nu_0 + \frac{1}{2}J(^{13}\text{C}\text{H}_\text{A}) \\ \nu_\text{M}^* &= \nu_0 + \frac{1}{2}J(^{13}\text{C}\text{H}_\text{M}) \end{aligned} \left\{ m_I(^{13}\text{C}) = +\frac{1}{2} \right.$$

$$\begin{aligned} \nu_\text{A}^{**} &= \nu_0 - \frac{1}{2}J(^{13}\text{C}\text{H}_\text{A}) \\ \nu_\text{M}^{**} &= \nu_0 - \frac{1}{2}J(^{13}\text{C}\text{H}_\text{M}) \end{aligned} \left\{ m_I(^{13}\text{C}) = -\frac{1}{2} \right.$$

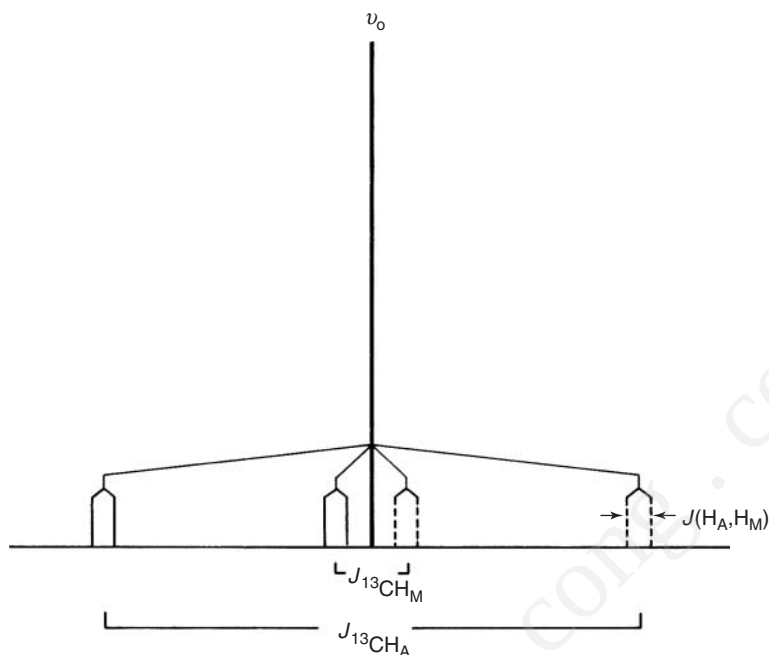


Figure 7.8 Schematic representation of the ^{13}C satellites in the ^1H NMR spectrum of *trans*-1,2-dichloroethene.

and in the proton spectrum we observe two AM subspectra for the ^{13}C satellites that are schematically represented in Figure 7.8 with the assumption that $J(^{13}\text{C}, \text{H}_\text{A})$ and $J(^{13}\text{C}, \text{H}_\text{M})$ have the same sign. These subspectra clearly contain the information J_AM that is the coupling of interest here. The signal of the ^{12}C molecules appears undisturbed at ν_0 .²⁾

The experimental spectrum of *trans*-1,2-dichloroethene (Figure 7.9) confirms the above analysis. Indeed, $J(^{13}\text{C}, \text{H}_\text{M})$ is approximately zero so that the two doublets in the neighborhood of the main signal are superimposed; $J(^{13}\text{C}, \text{H}_\text{A})$ and $J(^1\text{H}, ^1\text{H})$ are determined to be 199 and 12.5 Hz, respectively. For *cis*-1,2-dichloroethene one finds in an analogous experiment that $J(^1\text{H}, ^1\text{H}) = 5.3$ Hz. The differentiation between the two isomers on the basis of their vicinal coupling is therefore easily accomplished through observation of the ^{13}C satellites and the value of $J(^1\text{H}, ^1\text{H})$.

The analysis of ^{13}C satellite spectra also yields valuable information about spin–spin coupling in more complicated cases. For example, the ^1H NMR spectra of 1,4-dioxane and of benzene both yield a singlet. For the ^{13}C satellites, however, one observes an AA'XX' system and an ABB'CC'X system, respectively. This allows the determination of all $^1\text{H}, ^1\text{H}$ coupling constants through spectral analysis.

2) A possible isotope effect on the resonance frequency is neglected in this consideration.

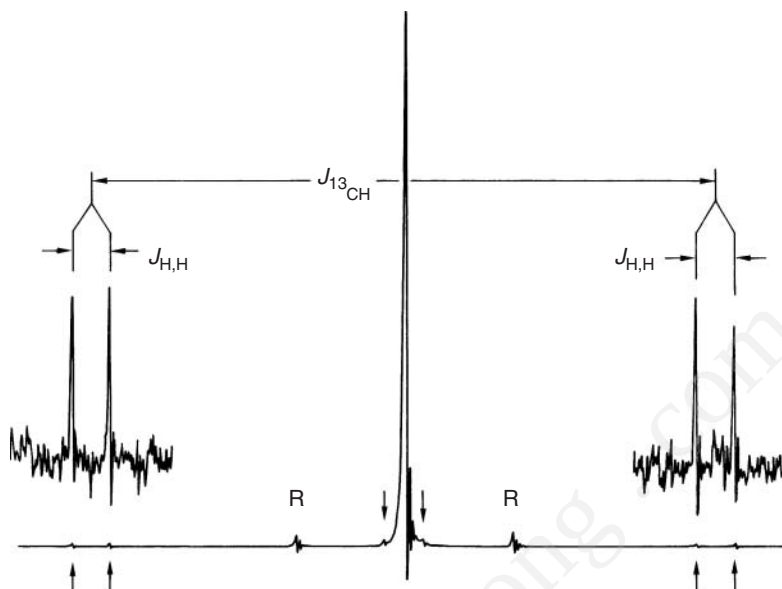
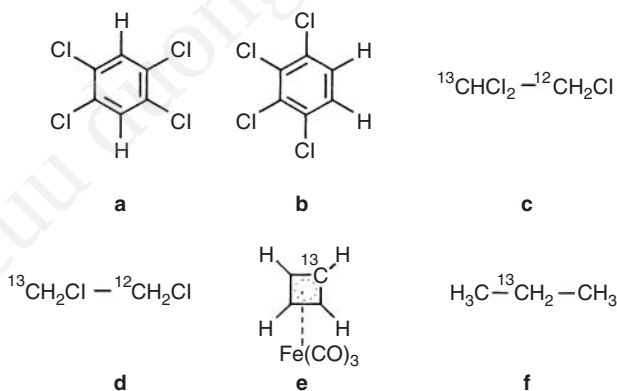


Figure 7.9 Experimental ^1H NMR spectrum of *trans*-1,2-dichloroethene with ^{13}C satellites; spinning side bands are labeled R; the *trans*- $^1\text{H}, ^1\text{H}$ coupling amounts to 12.5 Hz.

Exercise 7.8

Construct and classify the spectra of the ^{13}C satellites of the following molecules:



If the protons of interest are bound to the same carbon atom no information can be extracted from the ^{13}C satellites since both nuclei have the same $^{13}\text{C}, ^1\text{H}$ coupling constant and the ^{13}C satellite spectra are of the A_2X or A_3X type and independent of

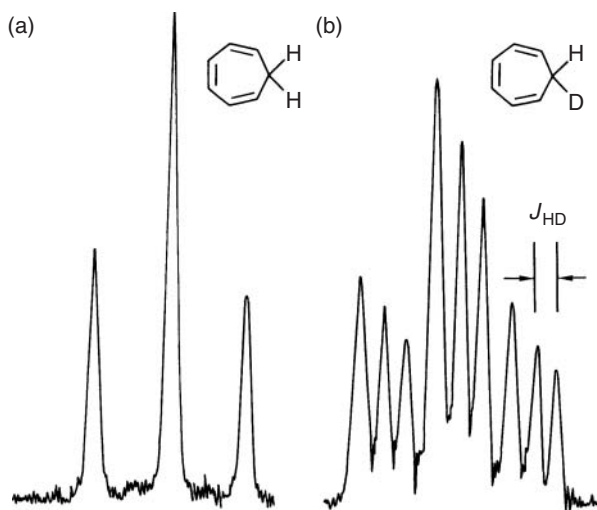


Figure 7.10 ^1H NMR absorption of the methylene protons in (a) cyclohepta-1,3,5-triene and (b) 7-deutero-cyclohepta-1,3,5-triene; $|^2J_{\text{H,D}}| = 2.0$ Hz and with Eq. (7.1) $|^2J_{\text{H,H}}| = 13.0$ Hz.

the spin–spin interaction within the A_2 or A_3 group. In the case of methylene and methyl groups this problem can be obviated by the substitution of a proton with a deuteron, ^2H . The $^1\text{H}, ^2\text{H}$ coupling constant can then be measured and converted into $J_{\text{H,H}}$ by Eq. (7.1):

$$J_{\text{H,H}} = (\gamma_{\text{H}}/\gamma_{\text{D}})J_{\text{H,D}} = 6.5144 J_{\text{H,D}} \quad (7.1)$$

Figure 7.10 illustrates the use of this strategy for the methylene protons of cyclohepta-1,3,5-triene, which are equivalent at room temperature as a consequence of fast ring inversion.

In conclusion, other magnetic nuclei also give rise to satellite spectra, as was shown in Figure 3.16 (p. 50). Thus, the ^1H resonance line of tetramethylsilane is always accompanied by the ^{29}Si satellites that arise through geminal $^1\text{H}, ^{29}\text{Si}$ coupling. The magnitude of the coupling constant here is 6.8 Hz. We shall consider other examples in Chapter 12.

References

1. (a) Maercker, A., Brauers, F., Brieden, W. and Engelen, B. (1989) *J. Organomet. Chem.*, **377**, C45–C51; (b) Brieden, W. (1990) PhD thesis, University of Siegen.
2. Cardillo, G., Merlinie, L., and Mondelli R. (1968) *Tetrahedron*, **24**, 497.
3. Berger, S. and Sicker, D. (2009) *Classics in Spectroscopy*, Wiley-VCH, Weinheim.
4. Raban, M. and Mislow, K. (1969) Modern methods of the determination of optical purity, in *Topics in Stereochemistry*, vol. 2 (eds N.L. Allinger and E.L. Eliel),

- Interscience Publishers, New York, pp. 199–230.
5. Bovey, F.A.(1969) *Nuclear Magnetic Resonance Spectroscopy*, Academic Press, New York, p. 170.
 - W. B. Jennings (1975) Chemical shift nonequivalence in prochiral groups. *Chem. Rev.*, **75**, 307.

Review Articles

- Parker, D. (1991) NMR determination of enantiomeric purity. *Chem. Rev.*, **91**, 1441.

Part II

Advanced Methods and Applications

cuu duong than cong . com

8

The Physical Basis of the Nuclear Magnetic Resonance Experiment. Part II: Pulse and Fourier-Transform NMR

After its discovery in 1945 nuclear magnetic resonance soon became one of the most powerful tools for structural research in chemistry. Nevertheless, before 1970 the number of nuclei that could be used for investigations was severely limited and structure determinations for larger molecules like complicated natural products or biological macromolecules were out of reach. New developments such as superconducting magnets that provided an increase in magnetic field strength and, in particular, the introduction of pulse Fourier-transform NMR paved the way for unprecedented progress and laid the basis for modern nuclear magnetic resonance.

Having treated in Part I the basic principles of the method and later the chemical applications of proton NMR, we now describe in Part II more advanced techniques that in large part are connected with the names of two scientists who have been awarded with the Nobel Prize for their outstanding contributions. We thus can introduce them as the pioneers of modern NMR.



Pioneers of modern nuclear magnetic resonance.

Richard R. Ernst (left, courtesy Prof. Ernst), born 1933 in Winterthur, Switzerland. Nobel Prize in Chemistry 1991 “for his contributions to the development of the methodology of high resolution nuclear magnetic resonance (NMR) spectroscopy.”

Kurt Wüthrich (right, courtesy Prof. Wüthrich), born 1938 in Aarberg, Switzerland. Nobel Prize in Chemistry 2002 (together with John B. Fenn and Koichi Tanaka) “for his development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution.”

NMR Spectroscopy: Basic Principles, Concepts, and Applications in Chemistry, Third Edition. Harald Günther. © 2013 Wiley-VCH Verlag GmbH & Co. KGaA. Published 2013 by Wiley-VCH Verlag GmbH & Co. KGaA.

In Chapter 2 the physical background of the nuclear magnetic resonance (NMR) experiment was described in terms of quantum theory and of classical physics. The classical description cannot explain the quantization of angular momentum, but the physical concepts behind the NMR experiment, the construction of the NMR spectrometer, and a large number of other aspects can be demonstrated most clearly by using the classical approach. In particular, the introduction of *pulse spectroscopy* in the area of high-resolution NMR, where it forms the basis of the Fourier transform (FT) technique, has emphasized the need to understand NMR experiments in terms of classical interactions between magnetic moments and magnetic fields. In fact, nuclear magnetism is not in the domain of either quantum mechanics or classical physics; rather, it forms an exercise for the combination of both concepts. In the following, we use the classical approach to describe the NMR experiment and, especially, the pulse experiment in more detail.

8.1

The NMR Signal by Pulse Excitation

8.1.1

Resonance for the Isolated Nucleus

Let us start again with the NMR experiment for the isolated nucleus that we described in Chapter 2 and that we now wish to inspect in more detail. The energy level diagram shown in Figure 1.3 (p. 2) for the two spin states of nuclei with spin $I = \frac{1}{2}$ has its classical equivalent in the parallel (ground state) and antiparallel (excited state) orientation of the z -component of the nuclear magnetic moment μ relative to the external magnetic field B_0 (Figure 2.1, p. 15). In this model absorption of energy via interaction between electromagnetic radiation and the nuclear moment leads to inversion of the magnetic vector μ (Figure 2.3, p. 17).

The magnetic dipole in a homogeneous magnetic field B_0 ¹⁾ experiences a torsional moment that attempts to align it with the direction of the field. The angular momentum of the nucleus, its *spin*, therefore causes a precessional motion of μ around the z -axis that can be easily understood according to the principles of gyration theory (Figure 8.1a). The angular velocity of this precessional motion, known as the *Larmor precession*, is given by $\omega_0 = -\gamma B_0$, since the vector ω_0 points into the negative z -direction. The Larmor frequency is thus $\omega_0 = -\gamma B_0$.

We know already that a RF field B_1 can affect the inversion of μ (Figure 8.1b). To achieve this, B_1 must be directed at right-angles to the x,y -component of μ and rotate in the x,y -plane with an angular velocity equal in sign and magnitude to the Larmor frequency. At this point it proves advantageous to introduce, in addition to the fixed coordinate system $C(x, y, z)$, known as the *laboratory frame*, a rotating

1) Here and in the following discussion B_0 will be again pointing in the positive z -direction of the Cartesian coordinate system. Please note further that we use the left-hand rule to describe the action of magnetic fields on magnetization vectors: the thumb points in the field direction, the bent fingers indicate the sense of rotation.

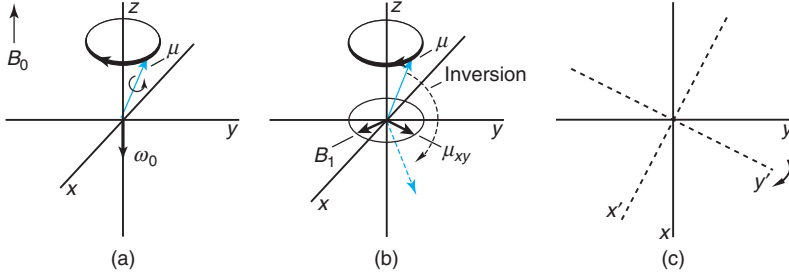


Figure 8.1 (a) Precession of the nuclear moment μ in the fixed laboratory system C; (b) effect of the rotating field vector B_1 on the nuclear moment μ ; (c) rotating and fixed coordinate systems C' and C.

coordinate system C' (x' , y' , z) (Figure 8.1c). In this *rotating frame*, as C' is called, the magnetic moment no longer feels the effect of the static magnetic field B_0 of magnitude B_0 but rather that of a magnetic field:

$$B' = B_0 + \frac{\omega}{\gamma} \quad (8.1)$$

where ω is the angular velocity of C' and ω/γ is a fictitious field B_f that exists only as a result of the relative motion of the coordinate systems C and C' . For $\omega=0$, B_f vanishes while for $\omega = -\gamma B_0$, B' becomes zero. This obviously corresponds to the statement that the vector assumes a fixed position in the rotating frame if ω is equal both in sign and magnitude to the Larmor frequency. The angular velocity and sign of rotation of C' then coincides with the precessional motion.

If we turn on the magnetic field B_1 , which is assumed stationary in the rotating frame and directed along the x' -axis perpendicular to B_0 (Figure 8.2a, p. 236), the effective field according to Eq. (8.1) is given by:

$$B_{\text{eff}} = B' + B_1 \quad (8.2a)$$

$$= B_0 + \frac{\omega}{\gamma} + B_1 \quad (8.2b)$$

$$= B_0 \left(1 - \frac{\omega}{\omega_0} \right) + B_1 \quad (8.2c)$$

The angle θ formed by B_{eff} with the z -axis is then defined by:

$$\tan \theta = \frac{B_1}{B_0 + \frac{\omega}{\gamma}} = \frac{B_1}{B_0 \left(1 - \frac{\omega}{\omega_0} \right)} \quad (8.3)$$

With the condition $B_0 \gg B_1$ for the magnitudes of the individual fields, variation of B_0 and thus the Larmor frequency ω_0 leads to the following situation:

- 1) If the magnitudes ω_0 and ω are very different, the effective field is aligned *parallel* to the z -axis because, according to Eq. (8.3), $\tan \theta$ becomes approximately equal to zero, that is, $\theta \approx 0^\circ$ or 180° for $\omega_0 \ll \omega$ or $\omega_0 \gg \omega$, respectively (note the condition $B_0 \gg B_1$ introduced above).

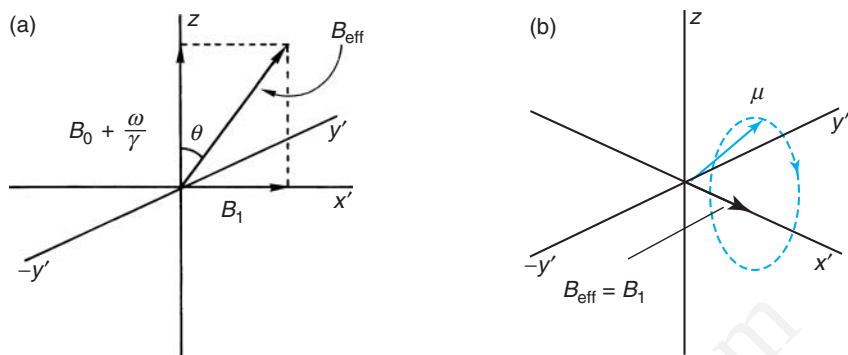


Figure 8.2 (a) Effective magnetic field, B_{eff} , in the rotating frame; (b) precession of the nuclear moment, μ , around B_1 .

- 2) On the other hand, if $\omega_0 \approx \omega$, $\tan \theta$ approaches infinity and $\theta = 90^\circ$; B_{eff} is then equal to B_1 and the vector μ precesses with frequency ω_1 around the direction of B_1 , that is, around the x' -axis (Figure 8.2b). Thus, μ passes from the ground to the excited state.

The situation described represents a typical resonance phenomenon, since a small perturbation of the system ($B_1 \ll B_0$) leads to a large variation. The system is affected by the perturbing field, however, only if the Larmor frequency and the frequency ω are identical.

Exercise 8.1

Derive the results obtained above on basis of Figure 8.2a by using the rule of Pythagoras.

In practice, the rotating field B_1 along the x' -axis of the rotating frame is generated by an oscillator – the transmitter coil of the spectrometer – on the x -axis of the fixed coordinate system C. A magnetic field B_x linearly polarized in the x -direction with frequency ω and amplitude $2B_1$ can be represented by two rotating components $B_1(r)$ and $B_1(l)$, one of which, $B_1(r)$, has the desired rotational sense and enforces the inversion of the vector μ . The other vector has practically no effect on the experiment (Figure 8.3).

8.1.2

Pulse Excitation for a Macroscopic Sample

The above model was based upon an isolated nucleus. We shall now attempt to extend our analysis to a macroscopic sample and thus to a large number of nuclei with a certain resonance frequency ω_0 .

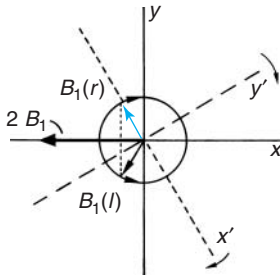


Figure 8.3 Resolution of a linearly polarized field with an amplitude of $2B_1$ into two rotating components $B_1(r)$ and $B_1(l)$.

After turning on the magnetic field B_0 , the spins are polarized into two populations and approach an equilibrium distribution between the two energy levels α and β with a small excess in the lower state (α). This process, which occurs within a certain time interval, T_1 , that we shall introduce below as the *longitudinal relaxation time*, yields, according to the Boltzmann distribution law, $N_\alpha > N_\beta$. The result of this process is the build-up of a macroscopic equilibrium magnetization $\mathbf{M}$ of magnitude M_0 , which is the resultant of individual magnetic moments of those nuclei that form the excess population of the ground state (Figure 8.4). Since the nuclear moments do not rotate in phase but are statistically distributed over a conical envelope, no component of the macroscopic magnetization in the x, y plane exists.

By means of a transmitter on the x -axis, a linearly polarized electromagnetic field B_1 of frequency ω and amplitude $2B_1$ stationary in the rotating frame is now generated as already described above. In a pulse experiment this is a B_1 field in the range of 0.01–0.4 T or about 10 kW. It is applied for only a short period, of the order of microseconds. Fields that fulfill these conditions are known as *radiofrequency impulses* or simply as *RF pulses*.

At resonance ($\omega = \omega_0$) an interaction between the individual nuclear moments and the field B_1 occurs that deflects $\mathbf{M}$ by an angle α from its equilibrium position along the z -axis. This in turn creates a finite transverse magnetization, M_y , in the y' -direction (Figure 8.5a, p. 238). In contrast to the case considered above for individual nuclear magnetic moments, here the vector $\mathbf{M}$ is not inverted because,

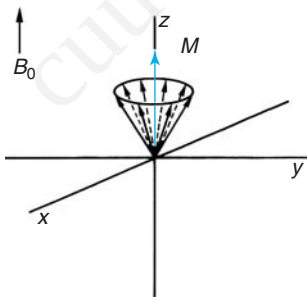


Figure 8.4 Longitudinal macroscopic magnetization $\mathbf{M}$ of magnitude M_0 as the resultant of the individual nuclear moments μ_i ; only the moments of the excess ground-state nuclei are shown.

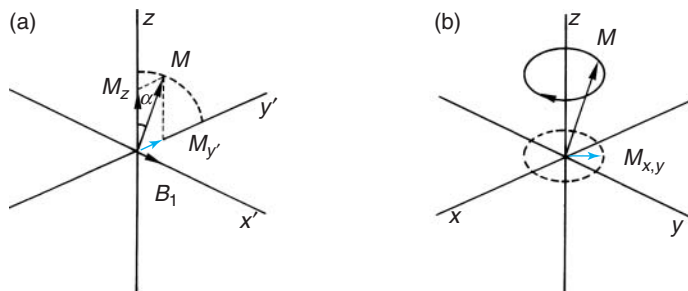


Figure 8.5 (a) Generation of the transverse magnetization, M_y by deflection of the vector M of magnitude M_0 ; (b) precession of the vector M in the fixed coordinate system, C.

depending on the pulse power or pulse duration, not all nuclear moments μ absorb energy. Consequently, in the fixed coordinate system, M executes a precessional motion around the z -axis (Figure 8.5b). The result is that the transverse magnetization, M_y , also rotates in the coordinate system C and is time-dependent on the y -axis of the laboratory frame. The precessional motion of the nuclei around the z -axis yields practically a linear polarized RF field in the y -direction. This is nothing other than an oscillator or transmitter with the Larmor frequency of the particular nuclei. Consequently, an alternating voltage can be detected in the receiver coil on the y -axis. This signal decays exponentially to zero with a time constant T_2^* . The receiver signal induced by the transverse magnetization is known as the free induction decay (FID) (Figure 8.6). The detected time signal is an emission signal, because the RF field B_1 is turned off before signal detection (therefore the adjective “free”).

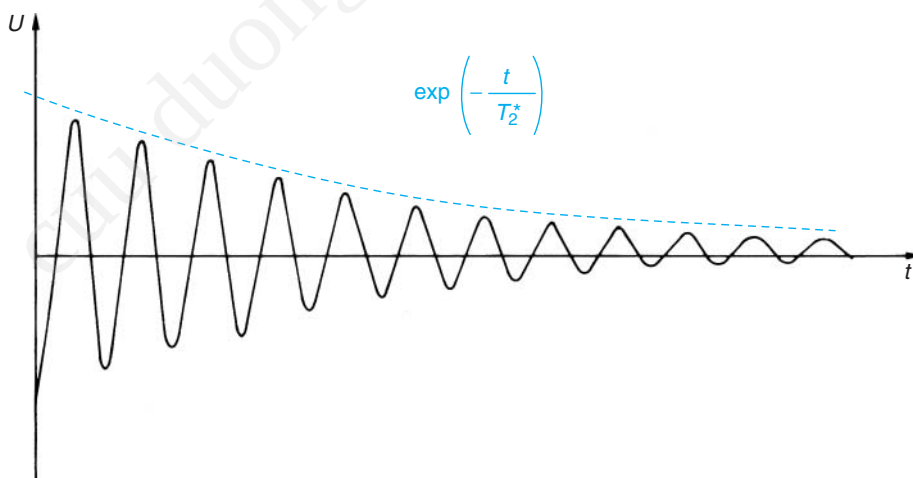


Figure 8.6 Time dependence of the voltage, U , induced in the receiver coil by the rotating component M_y (free induction decay).

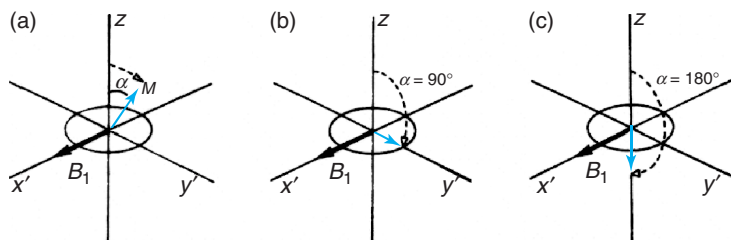


Figure 8.7 (a) Pulse angle α and position of the vector $\mathbf{M}$ in the rotating coordinate system after applying a $\mathbf{B}_1$ RF field in the x -direction; (b) 90°_x pulse; (c) 180°_x pulse; shown is the rotating frame and the rotating field vector $\mathbf{B}_1(r)$ of Figure 8.3.

The *pulse* or *flip* angle α (in radians) for $\mathbf{M}$ (Figure 8.5a) is given by the relation:

$$\alpha = \gamma B_1 t_p \quad (8.4)$$

where γB_1 is the *amplitude* or *power* of the pulse and t_p its *length* or *width*. Both can be varied to obtain certain flip angles of interest (Figure 8.7). One of these is $\alpha = \pi/2$ or 90° , where the total magnetization is in the x,y -plane along the y' -axis of the rotating frame and the signal has its maximum intensity. Another is $\alpha = \pi$ or 180° , where $\mathbf{M}$ is inverted and points into the negative z -direction. This corresponds to an inverse polarization of the spin system and formally to a negative spin temperature if we remember the Boltzmann distribution law (p. 19). RF fields that yield these angles are called $\pi/2$ - or 90° and π - or 180° pulses. A subscript is used to indicate the direction of the $\mathbf{B}_1$ field, for example, 90°_x or 180°_x for $\mathbf{B}_1(x)$.

8.2

Relaxation Effects

After perturbation through an external force, a physical system tries to return to its equilibrium state that it occupied before. This process is called *relaxation*. It is not an instantaneous event, but takes a finite time and occurs exponentially.

For the NMR experiment we have shown above that two macroscopic magnetizations can be distinguished: the longitudinal magnetization along the z -axis and the transverse magnetization in the x,y plane. Both are subject to relaxation phenomena, that is, their magnitudes are time-dependent. This aspect is discussed in the following sections.

8.2.1

Longitudinal or Spin–Lattice Relaxation

Before exposing the spins of a sample to the external magnetic field $\mathbf{B}_0$ they are in a non-equilibrium state because both spin states are equally populated and $M_0 = 0$. The build-up of the equilibrium magnetization, M_0 , controlled by the Boltzmann distribution law [Eq. (2.11), p. 19], starts after the sample is placed in the field $\mathbf{B}_0$

and requires a certain time T_1 . The variation of the z component of the macroscopic magnetization obeys a first-order differential equation:

$$dM_z/dt = (M_0 - M_z)/T_1 \quad (8.5)$$

where $1/T_1$ is the rate constant for the transition of the perturbed system to the equilibrium state. During the time T_1 , energy is transferred from the spins that start to occupy the ground state to the environment, the so-called *lattice*. This process, characterized by Eq. (8.5), is called *longitudinal or spin-lattice relaxation*. Accordingly, T_1 is known as the *longitudinal or spin-lattice relaxation time*. At the end of this period, M_0 is established and the system is prepared for the NMR experiment.

Applying now an RF pulse the action of the RF field B_1 reduces or completely eliminates the z -magnetization by deflecting the vector $\mathbf{M}$ from the z -axis. In terms of quantum chemistry, nuclei are excited to the higher energy state. The system then tries to restore the normal Boltzmann distribution and $\mathbf{M}$ finally returns to the z -axis to reach again its equilibrium value M_0 . During this process, also characterized by T_1 , nuclei are transferred from the excited state to the ground state and energy is again transmitted to the surrounding medium, the lattice. The system is then ready for a second RF pulse. Longitudinal relaxation thus plays an important role in the observation of the NMR phenomenon, especially if spectral accumulation, a standard technique in FT NMR, is used.

By which mechanism is energy exchanged between the lattice and the nuclear spin system? Rotational and translational motions of a molecule in a liquid occasion a fluctuating, that is, time-dependent magnetic field that can be described simply as magnetic noise. This fluctuating field possesses components Bt_x and Bt_y with frequency ω_0 that satisfy the resonance condition and can stimulate transitions between the stationary states of the nuclear spin system; in other words, they act as built-in RF transmitters. The magnetic energy received by the lattice is then transformed into thermal energy. In general terms, the effect on the relaxation rate constant can be expressed by Eq. (8.6):

$$R_1 = \frac{1}{T_1} = \left(\frac{\mu_0}{4\pi} \right) \frac{2 \gamma^2 \langle Bt \rangle^2 \tau_c}{(1 + \omega_0^2 \tau_c^2)} \quad (8.6)$$

where μ_0 is the permeability of free space, $\langle Bt \rangle^2$ is the mean-square average of the fluctuation of the local magnetic field that is produced by the molecular motions, and τ_c is the *correlation time* characterizing these motions, with large values for slow motions and vice versa; τ_c corresponds roughly to the average time a molecule needs to progress through one radian. The quotient:

$$J(\omega) = \frac{\tau_c}{1 + \omega_0^2 \tau_c^2} \quad (8.7)$$

is called the *spectral density function* and can be associated with the frequency distribution of the molecular motions. Because of their τ_c dependence, spin-lattice relaxation data can give valuable information about molecular dynamics.

The magnitude of T_1 has important consequences for the width of the NMR signal. Short relaxation times broaden the resonance signals, because the lifetime

of nuclei in the excited state is decreased. This causes an uncertainty in the determination of the energy difference and is a manifestation of the Heisenberg uncertainty principle:

$$\Delta E \Delta t \approx \hbar \quad (8.8)$$

which states that for the measurement of an energy difference, ΔE , a minimum lifetime Δt of the system is necessary. Since $\Delta E = h\Delta\nu$, we have $\Delta\nu\Delta t \approx 1/2\pi$ and Eq. (8.8) implies an uncertainty in the frequency measurement of $1/2\pi\Delta t$. The NMR line width will thus be of the order of $1/\Delta t$ or $1/T_1$.

According to Eq. (8.6), for very rapid motions, $\omega_0^2\tau_c^2 \ll 1$ and R_1 becomes frequency-independent and is directly proportional to τ_c :

$$R_1 = \frac{1}{T_1} = \frac{\mu_0}{4\pi} 2\gamma^2 \langle Bt \rangle^2 \tau_c \quad (8.9)$$

This situation is known as the *extreme narrowing limit*. With increasing τ_c , the relaxation rate constant R_1 increases while T_1 decreases. As the correlation time approaches ω_0^{-1} (remember that τ_c has the time unit s, while the frequency unit is radians $^{-1}$ or s $^{-1}$), T_1 goes through a minimum at $\tau_c = \omega_0^{-1}$ and we have:

$$R_1^{\min} = \frac{1}{T_1^{\min}} = \frac{\mu_0}{4\pi} \frac{\gamma^2}{\omega_0} \langle Bt \rangle^2 \quad (8.10)$$

Beyond this critical value a further increase of τ_c leads to fluctuations slower than the Larmor frequency and relaxation becomes less effective with the consequence that T_1 increases again (Figure 8.8). The T_1 minimum depends on the field strength of B_0 and shifts to smaller values of τ_c and larger values of T_1 with stronger magnetic fields.

Different physical phenomena exist that are responsible for the presence of the fluctuating magnetic fields mentioned above. For spin $\frac{1}{2}$ nuclei, the dominant origin is dipolar coupling, even if, as mentioned on p. 22, this does not lead to a

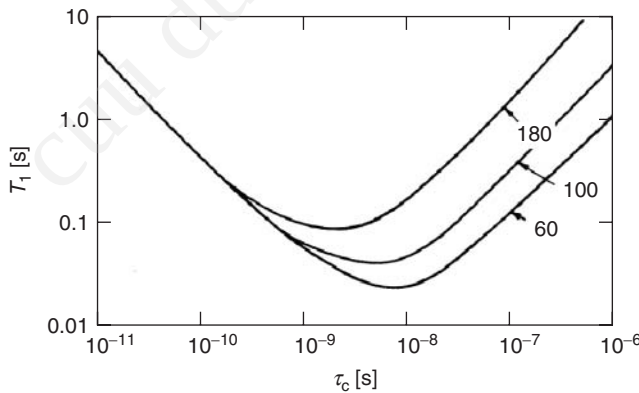


Figure 8.8 Dependence of the relaxation time T_1 on the correlation time τ_c for molecular motion and the field strength B_0 in megahertz [1].

line splitting; T_1 is, therefore, also called *dipolar* or *dipole–dipole relaxation time*. The characteristic correlation times for this interaction are that of rotational and translational motion. If the spins belong to the same molecule, only rotational motion, characterized by τ_c , is important. For small molecules τ_c is typically of the order of 10^{-11} s. This situation is met with nuclei shielded against their environment, as for instance ^{13}C nuclei, where relaxation processes based on *intramolecular* interactions dominate. For this situation, theory yields, in the extreme narrowing situation ($\omega_0^2 \tau_c^2 \ll 1$), for the dipolar relaxation of a $^{13}\text{C}, ^1\text{H}$ AX spin system the relation:

$$R_1^{\text{DD}} \propto \gamma_{\text{C}}^2 \gamma_{\text{H}}^2 r_{\text{CH}}^{-6} \tau_c \quad (8.11)$$

which includes the $^{13}\text{C}, ^1\text{H}$ distance, r_{CH} . For a C–H fragment, with a bond length of 0.15 nm (1.5 Å), in an organic molecule, we find relaxation rate constants of ca $10\text{--}10^3 \text{ ms}^{-1}$ which corresponds to dipole-dipole relaxation times, T_1^{DD} , of ca. 1–100 s. We come back to this topic in Chapter 11. The relaxation time T_1^{DD} (*intra*) is inversely controlled by the correlation time for rotational motion, τ_c , and *increases* at higher temperatures when τ_c *decreases* and *decreases* upon intermolecular association and high viscosity when τ_c *increases*; R_1^{DD} shows the opposite trends.

Because protons normally occupy positions at the molecular surface, their relaxation is strongly determined by *intermolecular* interactions and is thus diffusion-controlled. T_1 values are normally around 10 s and a line width contribution of 0.1 Hz or less results. However, in the presence of paramagnetic substances the relaxation times are much shorter. This is because T_1 theoretically is inversely proportional to the square of the effective mean square magnetic moment μ_{eff} that gives rise to the above-mentioned fluctuating fields:

$$\frac{1}{T_1} \propto \mu_{\text{eff}}^2 \quad (8.12)$$

and the magnetic moment of an unpaired electron is larger than the nuclear magnetic moment by a factor of about 10^3 . T_1 may thus be smaller than 10^{-1} s and the resonance lines become very much broadened. Even the presence of trace amounts of oxygen (O_2), a paramagnetic molecule, causes the line broadening effect, as shown in Figure 4.5 (p. 74).

This variation of T_1 is also illustrated by the longitudinal relaxation times measured for the protons of benzene under different experimental conditions (Table 8.1). An especially long relaxation time T_1 is observed in carbon disulfide, a

Table 8.1 Longitudinal proton relaxation times T_1 for benzene (s).

State of benzene	T_1
Degassed (20°C)	19.9
In CS_2 (11 vol.%, degassed)	60.0
In CS_2 in the presence of air	2.7

molecule with only a few magnetic nuclei (1.1% ^{13}C , 0.76% ^{33}S), but the presence of atmospheric oxygen considerably accelerates the spin–lattice relaxation process. The corresponding relaxation rate constants R_1 are 0.05, 0.017, and 0.37 s^{-1} .

On the other hand, short relaxation times are in some cases desirable, as we will show later. They can raise the efficiency of FT NMR experiments where spectral accumulation is generally used and a relaxation delay serves for the recovery of the original magnetization. This can be achieved by adding a so-called *relaxation reagent* to the sample, a trace of a paramagnetic compound like $\text{Cr}(\text{acac})_3$ (chromium acetylacetonate). However, the additive must not lead to chemical shift changes (see also Chapter 15).

Another relaxation mechanism of general importance is *quadrupolar relaxation*. As already mentioned on p. 25, nuclei with spin quantum numbers $I > \frac{1}{2}$, possess a charge distribution that is not spherically symmetric. These nuclei therefore have an electric quadrupole moment, Q , that interacts with the electric field gradient at the nucleus and in this way contributes to the relaxation. This interaction is electrical rather than magnetic. For the halogen nuclei chlorine, bromine, and iodine, for example, this mechanism is so effective that these nuclei, although they have large magnetic moments, are practically non-magnetic for the purpose of high-resolution NMR. For deuterium (^2H) and nitrogen-14 (^{14}N) quadrupolar relaxation is less important and resonance lines of these nuclei can be observed more easily. Those of ^{14}N ($Q = 2 \times 10^{-29}\text{ m}^2$) are, however, mostly broadened (half-width up to several hundred hertz), whereas those for ^2H are broadened less because of the smaller quadrupolar moment ($Q = 2.77 \times 10^{-30}\text{ m}^2$). We will find out more about this relaxation mechanism in Chapter 12.

We mention briefly without going into detail that, in addition to dipolar and quadrupolar relaxation, three other spin–lattice relaxation mechanisms can be found in special situations. One is *spin rotation relaxation*, which is observed for small fast rotating spherical molecules like SF_6 or PCl_3 where a local magnetic field originates from the bonding electrons. Fluctuations result from molecular collisions. In other cases, a large anisotropy of the chemical shift, $\Delta\sigma$, can give rise to fluctuating fields caused by molecular rotation (*relaxation by chemical shift anisotropy*). In this case T_1 is proportional to the square of the magnetic field B_0 . Finally, there exists *relaxation by scalar coupling* for IS spin systems if S has a relaxation rate that is fast compared to $2\pi J(I, S)$.

8.2.2

Transverse or Spin–Spin Relaxation

In the description of the NMR experiment we have learned that, in addition to the z -magnetization, there exists a second magnetization in the x, y plane, termed *transverse* or *x, y -magnetization* ($M_{x,y}$). It seems reasonable therefore to introduce a second relaxation time, T_2 , the so-called *transverse relaxation time*, especially since it turns out that the time dependence of $M_{x,y}$ usually differs from that observed

2) In units of $e \times 10^{-28}\text{ m}^2$, where e is the charge of the proton.

for M_z ; T_2 is also known as the *spin–spin relaxation time* after the mechanism responsible for transverse relaxation (energy transfer between individual spins), which will be discussed below.

Another justification for the introduction of T_2 comes from considerations of the line width of the NMR transitions. As mentioned above, longitudinal relaxation usually contributes less than 0.1 Hz. Nevertheless, observed line widths are larger and may amount to several kilohertz in the case of solids. It is therefore convenient to define another characteristic time T_2 , shorter than T_1 , to deal with this situation.

In the simplest case, for liquids $T_2 = T_1$ if, after resonance, the x,y -component of the magnetization vanishes at the same rate as the longitudinal magnetization attains its previous value M_0 along the z -axis, in other words, T_2 can never be longer than T_1 . On the other hand, the transverse magnetization can be reduced without the simultaneous increase of the z -magnetization ($T_2 < T_1$). As in the case of spin–lattice relaxation, fluctuating fields can interact with the transverse component $M_{x,y}$, thereby reducing its magnitude. Whereas time dependent fields B_{t_x} and B_{t_y} , stationary in the rotating frame, interact with M_z , $M_{x,y}$ can interact not only with B_{t_x} and B_{t_y} but also with B_z . The component B_z , however, is static in the laboratory frame; thus, transverse relaxation can also originate from the presence of static dipolar fields.

An important mechanism for transverse relaxation is based on an energy transfer within the spin system. Any transition of a nucleus between its spin states changes the local field at nearby nuclei at the correct frequency to stimulate a transition in the opposite direction (*flip-flop* mechanism). The lifetime of the spin states will be shortened by this process and this contributes to the NMR line width in a manner similar to the spin–lattice relaxation process. The total energy of the spin system does not change, however, and transverse relaxation of this kind can be regarded as an entropy process. Spin–lattice relaxation, on the other hand, is classified as an enthalpy process.

In solids transverse relaxation is strongly affected by the static dipolar fields present. In the absence of motion, each spin experiences a slightly different local field as a result of dipolar interactions with its neighbors. If we remember that the transverse magnetization $M_{x,y}$ is a macroscopic quantity that can arise only if the individual magnetic moments in the sample have the same Larmor frequency, it is clear that the spread in Larmor frequencies resulting from the different local fields will destroy $M_{x,y}$. Graphically this process can be described as a fanning out of the vector $M_{x,y}$ (Figure 8.9). As a consequence of this different mechanism, T_2 does not increase with increasing τ_c as shown in Figure 8.10 for T_1 . Instead, it approaches a limiting value typical for a solid.

In non-viscous liquids and for small and medium-sized molecules, the inhomogeneity, ΔB_0 , of the magnetic field B_0 is by far the most important factor for the time dependence of $M_{x,y}$. Exposure of the individual nuclear spins to different external field strengths $B_0 \pm \Delta B_0$ will result in a spread of their Larmor frequencies and in a fanning out process for $M_{x,y}$ that is completely analogous to the one shown in Figure 8.9. To avoid the resulting line broadening, each determination of an

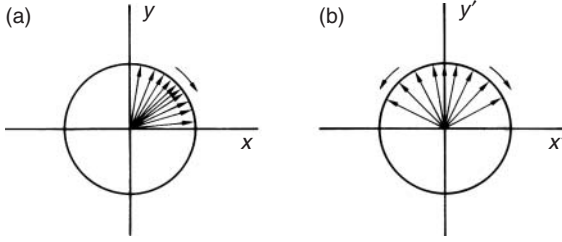


Figure 8.9 Transverse relaxation: (a) in the laboratory; (b) in the rotating frame.

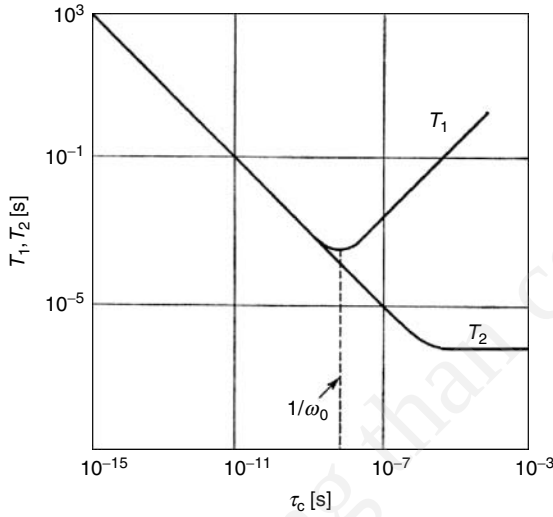


Figure 8.10 Comparison of the T_1 and T_2 dependence on the correlation time τ_c . (Taken with permission from Ref. [2]. Copyright 1959, McGraw-Hill Book Company.)

NMR spectrum should be preceded by optimizing the field homogeneity through an adjustment of the field gradients (cf. Chapter 4).

According to the quantitative classical treatment of the resonance process [cf. Appendix, p. 668, Eq. (A15b)], for small amplitudes of the B_1 field, that is, for $\gamma^2 B_1^2 T_1 T_2 \ll 1$, the resonance signal is described by:

$$I(\omega) = \frac{\text{constant} \times B_1 T_2}{1 + (\omega_0 - \omega)^2 T_2^2} \quad (8.13)$$

The signal intensity at resonance ($\omega = \omega_0$) is then directly proportional to the transverse relaxation time:

$$I(\omega_0) = \text{constant} \times B_1 T_2 \quad (8.14)$$

Including B_1 in the constant, it follows for the intensity at half the signal height that:

$$I_{1/2} = \text{constant} \times \frac{1}{2} T_2 \quad (8.15)$$

As this value for $I_{1/2}$ must also satisfy Eq. (8.13), it follows that:

$$\frac{T_2}{2} = \frac{T_2}{1 + (\omega_0 - \omega_{1/2})^2 T_2^2} \quad (8.16)$$

and one obtains:

$$\omega_0 - \omega_{1/2} = \frac{1}{T_2} \quad \text{or} \quad \Delta_{1/2} = \frac{2}{T_2} \quad (8.17)$$

where $\Delta_{1/2}$ is the line width of the resonance signal at half-height (Figure 8.11). Since the decay of $M_{x,y}$ is caused by field inhomogeneity and natural spin-spin relaxation as well, one usually writes:

$$\Delta_{1/2} = \frac{2}{T_2^*} \quad \text{with} \quad \frac{1}{T_2^*} = \frac{\gamma \Delta B_0}{2} + \frac{1}{T_2} \quad (8.18)$$

where the first term stands for the inhomogeneity contribution to the line width and the second term for the true transverse relaxation. In hertz one has $\Delta_{1/2} = 1/\pi T_2^*$ if T_2^* is measured in seconds. Equation (8.13) describes a *Lorentz curve* and the signal is said to have a *Lorentzian line shape*.

Finally, slow motion will shorten T_2 , while T_1 shows the opposite effect (Figure 8.10). As with the large line widths found for solids, the broad lines observed in viscous media and for large, slowly tumbling molecules like polymers or biological macromolecules are a result of short T_2 values [see Eq. (8.18)].

A very effective reduction of the transverse relaxation time occurs when the nuclei under consideration periodically change their Larmor frequency. This is of great importance for chemistry since in the case of intra- and intermolecular dynamic processes, such as proton transfers, conformational equilibria, or valence tautomerism, rapid and reversible variations of the resonance frequencies, called *chemical exchange*, can occur for particular protons and other nuclei, as we shall see in Chapter 13. In cases where this is the dominant mechanism for transverse relaxation, reaction rates can be derived from the temperature-dependent T_2 values that are related to the line widths. To eliminate other line width contributions not caused by chemical exchange, the natural line width of a reference signal that is not involved in the exchange process is subtracted from the measured line width.

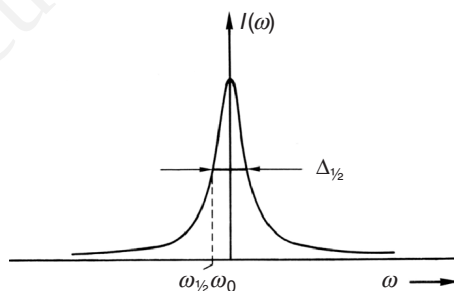


Figure 8.11 Lorentzian line shape of the NMR signal with line width at half-height, $\Delta_{1/2}$.

Chemical kinetics can thus be studied with the help of NMR spectroscopy and the method plays an important part in research on rapid reversible reactions.

Finally, we mention that an additional relaxation time, $T_{1\rho}$, will be discussed in Chapters 10 and 14. It describes *relaxation in the rotating frame* and is connected to so-called spin-lock experiments that form the basis of important methods in NMR of liquids and of solids.

8.2.3

Experiments for Measuring Relaxation Times

We return to the aspect of pulse excitation with the discussion of two experiments that illustrate the application of RF pulses and their practical use.

8.2.3.1 T_1 Measurements – the Inversion Recovery Experiment

As briefly mentioned above, T_1 values for individual nuclei have been recognized as significant parameters related to the dynamic properties of molecules and longitudinal relaxation times T_1 for carbon-13 and other nuclei are measured frequently. From the various methods available for T_1 determinations we shall describe only the most often used inversion recovery experiment.

Let us first consider the macroscopic magnetization $\mathbf{M}$ in the rotating coordinate system (Figure 8.12a).³⁾ A 180°_x pulse at the beginning of the experiment brings the vector $\mathbf{M}$ into the negative z -direction (Figure 8.12b). As a result of spin-lattice relaxation the value of $\mathbf{M}$ decreases (Figure 8.12c), passes through zero (Figure 8.12d), begins to increase in the positive z -direction (Figure 8.12e), and finally reaches its initial value. If we characterize the situations (Figure 8.12c–e) by the times τ_1 , τ_0 , and τ_2 after the 180°_x pulse, the magnetization can be detected by 90°_x pulses at τ_1 and τ_2 that align $\mathbf{M}$ along the negative or positive y -direction, respectively. The two signals differ in phase by 180° and thus lead to an emission and absorption line, respectively. At time τ_0 no signal can be observed since here the sample is not magnetized. For this situation the following relation holds:

$$\tau_0 = T_1 \ln 2 = 0.693 T_1 \quad (8.19)$$

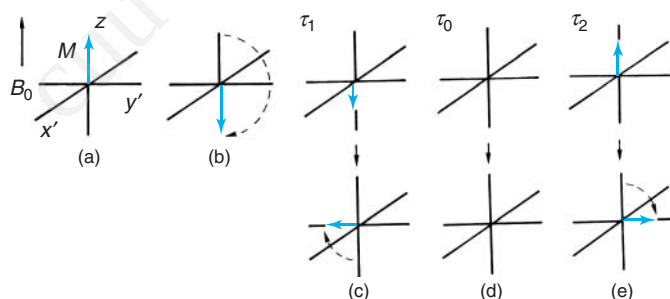


Figure 8.12 Inversion-recovery experiment for T_1 measurements.

3) From now on x and y refer to the rotating frame of reference if not stated otherwise.

and from it the relaxation time T_1 can be determined. Alternatively, T_1 can be obtained more accurately from a semilogarithmic plot of the intensity changes $M_0 - M_z$ against τ , since from Eq. (8.5) one derives by integration:

$$\ln(M_0 - M_z) = \ln 2 M_0 - \tau/T_1 \quad (8.20)$$

An application of such an experiment is shown in Figure 8.13 for the ^1H NMR signal of benzene. Each spectral trace is the result of the pulse sequence $180_x^\circ - \tau - 90_x^\circ$ applied to the sample, and the delay time τ was varied from 0.1 to 50 s. From the plot shown a τ_0 of 2.25 s can be estimated that leads, according to Eq. (8.13), to a value for T_1 of about 3 s.

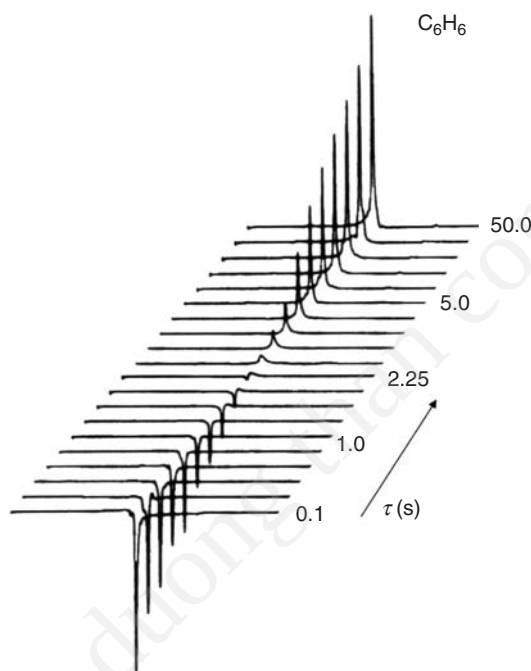


Figure 8.13 Inversion-recovery experiment for the ^1H NMR signal of benzene.

8.2.3.2 The Spin Echo Experiment

The physics of this experiment can best be understood by reference to the diagrams shown in Figure 8.14. Figure 8.14a shows the macroscopic magnetization vector $\mathbf{M}$ along the z -axis of the laboratory system. A pulse in the x -direction of the rotating frame leads to a deflection of the vector as discussed above. If one chooses a 90_x° pulse, $\mathbf{M}$ ends up along the y -axis (Figure 8.14b). As a result of the inhomogeneity of the $\mathbf{B}_0$ field the individual nuclear spins begin to fan out and the magnitude of the transverse magnetization decreases (Figure 8.14c). After a certain time τ , a 180_x° pulse is applied so that all vectors are turned around into the negative y -direction (Figure 8.14d). Now, however, their relative motion follows a course

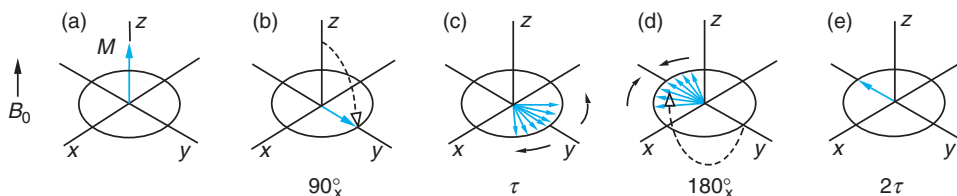


Figure 8.14 Spin echo experiment

such that after a time 2τ they are focused along the $-y$ -axis (Figure 8.14e). The resultant transverse magnetization can then be detected in the receiver coil as a signal, the so-called *spin echo*. The experiment is conveniently formulated as a *pulse sequence*:

$$90_x^\circ \text{-----} \tau \text{-----} 180_x^\circ \text{-----} \tau \text{-----} \text{FID} \quad (8.21)$$

From the above analysis it becomes clear that the intensity of the spin echo should depend only on the true transverse relaxation rate, that is, the irreversible loss of transverse magnetization during the period 2τ , since contributions of the field inhomogeneity to the fanning out process for the elementary spins have been eliminated by the refocusing process. If this were true, the echo amplitude should be proportional to $\exp(-2\tau/T_2)$. In practice, diffusion processes complicate the situation by changing the positions of the spins in the magnetic field, thereby increasing the spread of the Larmor frequencies. However, this complicating factor can be eliminated in an elegant manner if, instead of using a single 180_x° pulse at time τ , one uses a whole sequence of such pulses at $\tau, 3\tau, 5\tau$, etc. (Carr–Purcell pulse train). It was possible to show that the decrease in the amplitude of the spin echo, which in turn is recorded again at $2\tau, 4\tau, 6\tau$, etc. is now proportional to $\exp(-t/T_2)$ and the effect of diffusion becomes negligible if the interval τ between the pulses is small. Inaccuracies due to imperfections of the 180_x° pulse ($180^\circ \pm \varphi$) can be avoided by using 180_y° pulses where these deviation cancel CPMG (Carr–Purcell–Meiboom–Gill) experiment.

8.3

Pulse Fourier-Transform (FT) NMR Spectroscopy

The foregoing description of two pulse experiments was introduced to show how strong RF fields can be used to move the magnetization vector $\mathbf{M}$ in certain directions of the coordinate system and to follow its relaxation behavior. Many other experiments of this type exist, especially ones using certain pulse sequences on both liquid and solid samples. These form the basis of the branch of NMR spectroscopy known as *pulse spectroscopy*. The most important application of pulse spectroscopy developed after 1966, when it was recognized by R.R. Ernst and W.A. Anderson that RF pulses can also be used to excite the different signals of

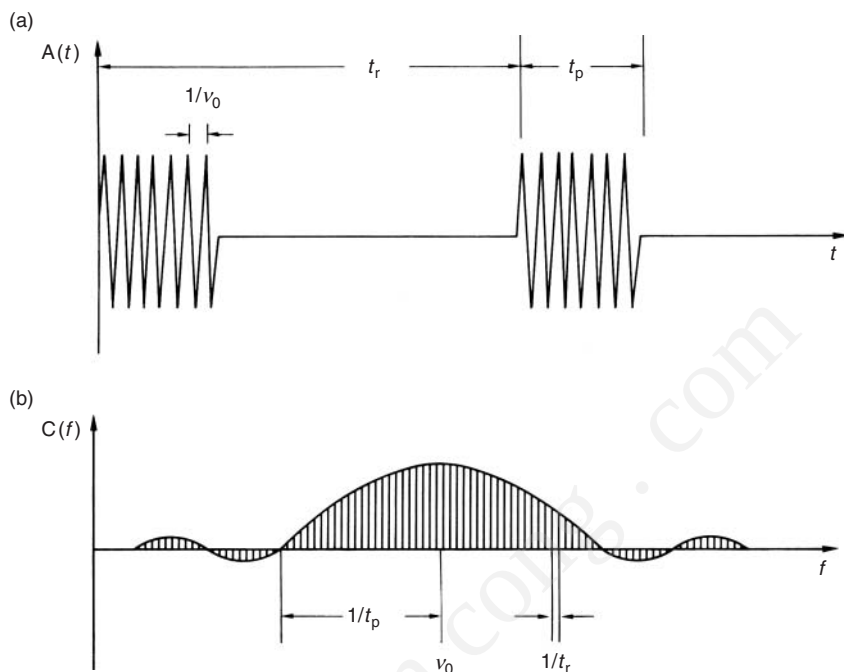


Figure 8.15 (a) Sequence of RF pulses of frequency ν_0 with width t_p and repetition time t_r ; (b) the corresponding frequency components.

normal high-resolution NMR spectra simultaneously and after means were found to analyze the signals detected after such an excitation.

8.3.1

Pulse Excitation of Entire NMR Spectra

If a strong RF field is applied to the spin system repeatedly for short periods, a situation results where nuclei with Larmor frequencies ν_i within a certain range $\Delta\nu$ can be excited simultaneously. The reason for this is that a pulse or a pulse-modulated RF field with a carrier frequency ν_0 , that is, a train of pulses with frequency ν_0 and small width t_p , produces side bands within a range $\pm 1/t_p$ and separated by a frequency difference $1/t_r$, where t_r is the repetition time for the individual pulses. This is illustrated most clearly in Figure 8.15 where the pulse train shown on a time scale in Figure 8.15a has the frequency spectrum shown in Figure 8.15b.

Two points require special attention. On the one hand, the time function of Figure 8.15a, that is, the pulse train with the repetition time t_r and the pulse width t_p , has an equivalent frequency function that is shown in Figure 8.15b on the frequency scale. On the other hand, such an experiment obviously can be seen as an application of a large number of B_1 fields of different frequency ν_i . Thus, the

experiment corresponds in principle to having a multichannel spectrometer with numerous transmitters distributed equally over the spectral range of interest and available for simultaneous excitation of all resonance lines. That strong RF fields can indeed be used for this purpose follows from Figure 8.2a, which yields:

$$B_{\text{eff}}^2 = \left(B_0 + \frac{\omega}{\gamma} \right)^2 + B_1^2 \quad (8.22)$$

and gives the magnitude of the effective field B_{eff} as:

$$B_{\text{eff}} = \frac{1}{\gamma} \sqrt{4\pi^2(\nu_i - \nu_0)^2 + (\gamma B_1)^2} \quad (8.23)$$

(note that $\omega = 2\pi\nu$ and $B_0 = -\omega_0/\gamma$). For large B_1 fields satisfying the condition $\gamma B_1 \gg 2\pi\Delta\nu$, the term $(\nu_i - \nu_0)$ can be neglected and the following approximate relationship results:

$$B_{\text{eff}} \approx B_1 \quad (8.24)$$

For nuclei having resonance frequencies within the range $\Delta\nu$ the magnetization thus precesses about B_1 . For a 90° pulse ($\gamma B_1 t_p = \pi/2$), the above condition for γB_1 is met if:

$$t_p \ll 1/4\Delta\nu \quad (8.25)$$

Accordingly, small pulse widths, typically a few microseconds, are necessary. For $\Delta\nu = 10$ kHz, for example, we have $t_p = 25 \mu\text{s}$ and a standard pulse length of $10 \mu\text{s}$ yields a sweep width $\Delta\nu$ of 25 kHz.

The same conclusions can be drawn from another inspection of Figure 8.15b, where the relationship between the frequency range and the number of the side bands, on the one hand, and the parameters t_p and t_r , on the other, is illustrated. Pulse excitation in high-resolution NMR thus requires small t_p values (for a large frequency range) and large t_r values (for a high density of side bands). In the limit, if t_p increases $\Delta\nu$ will be reduced to zero and the side bands disappear. We then have a situation similar to that in the traditional continuous wave (CW) experiment with continuously applied B_1 field (cf. p. 20). On the other hand, if t_r decreases, the frequency difference between the individual side bands will increase until finally again we have CW conditions with excitation at a single frequency.

We now ask, what is the advantage of this excitation technique compared to the older CW spectroscopy? This is explained by a simple consideration. Suppose an NMR spectrum of width 500 Hz shows ten lines of 0.5 Hz half-width. To record this spectrum in the CW mode, we typically choose a sweep time of 250 or 500 s. Only 2% of this sweep time, however, is used to record the information of interest, since this is the time we need to measure the resonance signals. The remaining time is actually wasted recording the noise. With the single transmitter of the traditional CW spectrometer, however, there was no alternative means of recording an unknown spectrum other than by sweeping slowly through the spectral range, checking point by point if absorption occurs or not. Only the pulse technique gives us a method that allows us to reduce enormously the time necessary for this part

of the experiment by exciting all resonances at once. In practice, our RF field has become polychromatic.

8.3.2

The Receiver Signal and its Analysis

Next, we must consider what signal we detect after such an excitation and how we can analyze it. If we remember the comparison made in Chapter 2 between NMR and optical spectroscopy, we conclude that, if polychromatic excitation is used, we obviously need a device equivalent to the prism in optical spectroscopy.

To understand this part of the experiment as well, let us first discuss the receiver signal more closely. For a single line we record the FID shown in Figure 8.16. We know already that the envelope of this curve is determined by T_2^* but the time interval between the maxima of this decaying sine function also has a definite meaning: it corresponds to the reciprocal of the frequency difference $\Delta\nu_i$ between the pulse frequency ν_0 and the Larmor frequency ν_i of the resonance line that is excited. Hence, this curve, recorded on a time scale, contains all the information needed to characterize the NMR signal also on the frequency scale, because $\Delta\nu_i$ gives us the position of the line (with respect to ν_0) and T_2^* determines the line shape. In Figure 8.16 it is shown that recording the time dependence of the decaying x,y -magnetization is thus fully equivalent to recording the spectrum in the traditional way on the frequency scale, but requires less than 1 s.

It is important to realize that the two forms of the NMR signal shown in Figure 8.16 are two representations of the same data set. One representation is on a time scale or in the *time domain* and the spectral trace is a function of time, $f(t)$. The other representation is on a frequency scale or in the *frequency domain* and the spectral trace is a function of frequency, $F(\nu)$. A transformation from one domain into the other is possible through a well-known mathematical operation: the Fourier transformation. In this sense, the FID and the frequency spectrum form a Fourier transform pair.

In mathematical terms, the two representations of the receiver signal are given by the expressions:

$$f(t) = \int_{-\infty}^{+\infty} F(\nu) \exp(-i2\pi\nu t) d\nu \quad (8.26)$$

for the time domain function $f(t)$ and:

$$F(\nu) = \int_{-\infty}^{+\infty} f(t) \exp(+i2\pi\nu t) dt \quad (8.27)$$

for the frequency domain function $F(\nu)$, where $i = \sqrt{-1}$. The transformation of $f(t) \rightarrow F(\nu)$ is achieved point by point following the relation:

$$F_j = \frac{1}{N} \sum_{k=0}^{N-1} T_k \exp\left(\frac{-2\pi i j k}{N}\right) \quad (8.28)$$

where F_j is the j -th point in the frequency domain, T_k is the k -th point in the time domain, and N is the total number of points. Equation (8.28) can be executed by a

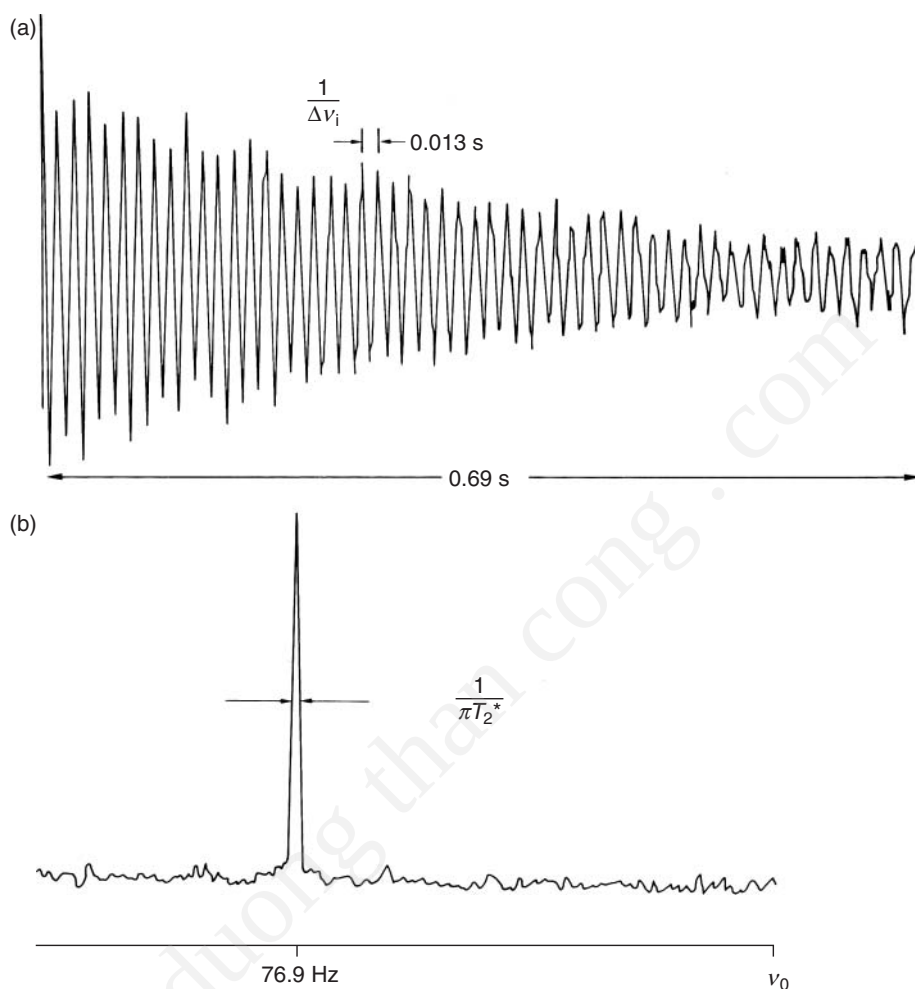


Figure 8.16 Receiver signal of a single NMR line: (a) in the time domain as free induction decay (FID) and (b) in the frequency domain as Lorentz curve. Compared to the voltage recorded in Figure 8.6, the signals are now also modulated by noise.

small computer using a standard algorithm derived by Cooley and Tukey (details of which are beyond the scope of this discussion). For the following considerations it is adequate to know that the mathematical operation indicated, and viewed much as a “black box,” fulfills the requirements of the prism and allows us to analyze the receiver signal and pick out the frequencies responsible for the FID.

In practice, the FID of an NMR spectrum is much more complicated than the function shown in Figure 8.16a since it results from a superposition of the FIDs of *all* individual resonance lines, including the noise. An example of such an *interferogram* is given in Figure 8.17a (p. 255). Nevertheless, it may be stored in

digital form in the memory of the computer of the FT spectrometer and later transformed into the frequency domain spectrum.

Since data collection is now so fast, requiring about 1 s or less, it is of course advantageous to accumulate data before carrying out the Fourier transformation. Recording several hundred transients takes only a matter of minutes and hence the signal-to-noise ratio can be increased considerably (Figure 8.17). This made FT NMR the standard experimental technique for NMR spectroscopy. In particular, the NMR of less sensitive nuclei such as carbon-13 or nitrogen-15 profited enormously from the new technique and this field has since made substantial progress. What, at an early stage, may have seemed to be a special experimental aid for selected applications soon developed into the most powerful tool of present-day NMR spectroscopy and has opened up new areas of application. Pulse spectroscopy also forms the basis for two-dimensional (2D) NMR spectroscopy, which will be treated in Chapter 9. In the remaining sections of the present chapter, the most important experimental aspects and requirements of pulse FT NMR experiments are discussed in more detail.

8.4

Experimental Aspects of Pulse Fourier-Transform Spectroscopy

8.4.1

The FT NMR Spectrometer – Basic Principles and Operation

The basic principles of an FT NMR spectrometer are best explained with the aid of a simplified block diagram such as that given in Figure 8.18 (p. 256). Its different parts will be discussed in the following sections.

8.4.1.1 The Computer and the Analog–Digital Converter (ADC)

The most prominent feature of the FT NMR spectrometer is the *digital computer* that plays a central role in the experimental set-up. It controls both the transmitter and the receiver, stores, and processes the incoming data and transfers the results to display units such as the oscilloscope or the recorder. The software provides the necessary basis for the commands given to the computer by the operator through an input device, a keyboard, a mouse, or a light pen. Practically all functions of the spectrometer – from the transmitter to the printer – are included in this program and are thus under computer control.

The computer itself is characterized by two important parameters that define its storage capacity: *the number of memory locations* (*x*-axis) and the *word length* (*y*-axis). Memory locations are counted in multiples of K, which stands for $2^{10} = 1024$. Computers with a memory of 12K can be regarded as the absolute minimum requirement for an FT spectrometer; 4K is reserved for the software, including the FT routine, and 8K is available for the actual data. Since the Fourier transformation yields the real and imaginary part of the frequency domain function, the two have to be separated and for the final spectrum, which corresponds to the real part, 4K

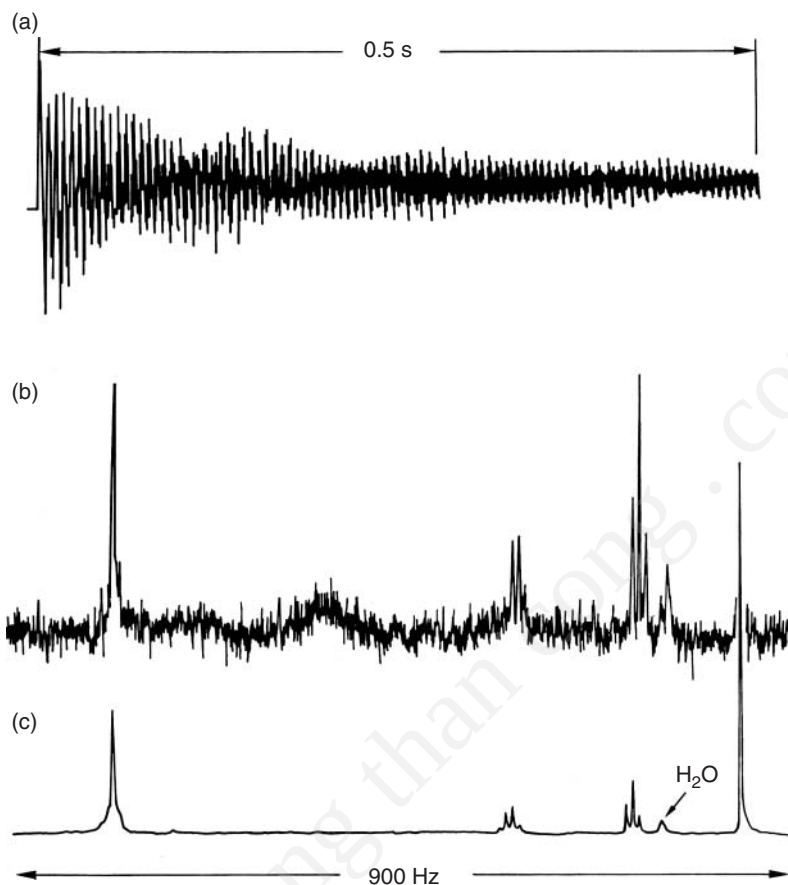


Figure 8.17 ^1H Fourier transform (FT) NMR spectrum of a 0.1% solution of ethylbenzene: (a) free induction decay; (b) conventional CW spectrum, sweep time 1000 s; (c) FT spectrum of 1000 transients of 1 s each.

data points can be used. Modern NMR instruments are equipped with computers of a memory capacity of at least 64 or 128K, mostly considerably more. Hard disks or tape units lead to external storage capacities in the megabyte range.

The word length determines the amount of data or its magnitude that can be stored in each memory location. Its unit is the bit (*binary digit*), and the number of bits defines the word length. The information, usually a number as a result of a measurement, is stored in binary form, where each decimal number is expressed as the sum of powers of two; for example, $7 = 2^0 + 2^1 + 2^2$. Each bit is a dual unit that can take the value 1 or 0, indicating whether the particular power of two is necessary to represent the decimal number in question or not. With a word length of 4 bits, for example, the largest decimal number that can be stored is 15, which in binary representation takes the form 1111 ($2^0 + 2^1 + 2^2 + 2^3$). In general, for n

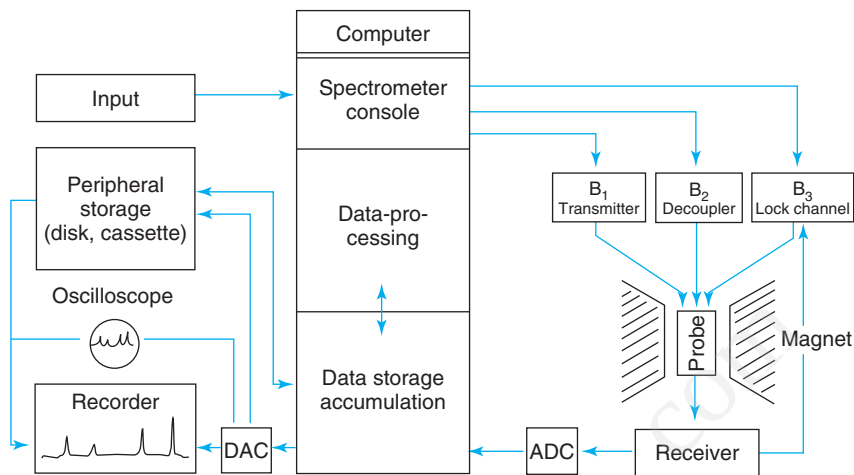


Figure 8.18 Block diagram of an FT NMR spectrometer.

bits the largest possible decimal number that can be represented is $2^n - 1$ since one bit must be provided for sign information.

From the foregoing it is clear that the raw data somehow must be converted from analog into digital form before they are acceptable to the computer. This is accomplished by means of an analog-to-digital converter (ADC), also known as a *digitizer*. This device samples the FID at regular time intervals and converts each voltage measured into a binary number that can be stored in the corresponding memory location of the computer. Two important aspects have to be considered: one is the *resolution* of the ADC, measured in bits, the other is the *sampling rate*.

With a voltage range normally covering ± 10 V, a 12-bit resolution for the ADC means that the voltage is measured in steps of $10\,000/(2^{12} - 1) = 2.44$ mV. The integers thus produced are then converted into binary numbers. Data points below one step, in our case 2.44 mV, are not detected. The word length of the ADC, in addition to that of the computer, is therefore important for the *dynamic range* available, that is, the capacity to detect weak signals in the presence of strong signals. For the present example of a 12-bit ADC, the limit is given by the intensity ratio $2^{12} : 1 = 4096 : 1$; for an ADC with a 4-bit resolution this ratio is only $16 : 1$. Full use of the dynamic range of the ADC is therefore advisable in order to characterize the FID correctly. On the other hand, it also follows that for data accumulation the word length of the computer must exceed the resolution of the ADC, otherwise memory overflow will result with a consequent loss of information. This is a particular property of the FT experiment that follows from the fact that the frequency domain spectrum is the result of the transformation of the entire free-induction decay. “Chopping off” part of the FID falsifies the time domain function and may destroy the frequency domain spectrum completely.

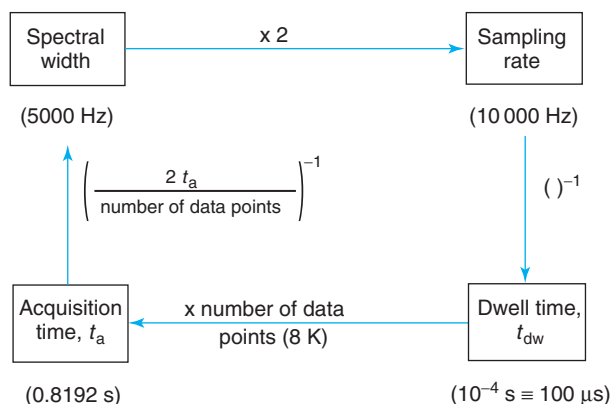


Figure 8.19 Interrelation of experimental parameters in FT NMR.

A further point of interest is the rate of data collection in the time domain. Here we remember that the free-induction decay contains frequency components $\Delta\nu_i$ given by the difference between the pulse frequency ν_0 and the frequency of the NMR signal of interest, ν_i . According to the *Nyquist theorem* of information theory, to characterize properly each $\Delta\nu_i$ at least two data points per cycle must be measured. Therefore, the sampling rate is determined by the spectral width we choose to investigate. If a range of 5 kHz is of interest, data must be collected at a rate of 10 000 points s^{-1} or 10 kHz. If, to use another example, the sampling rate is only 5 kHz, the highest frequency that can be recorded is 2500 Hz.

In addition to sampling rate and dynamic range there are several other, not necessarily independent, parameters connected with certain aspects of data collection in FT NMR. One of these is the *dwell time*, t_{dw} , that is, the time used to produce a particular data point. It is given by the reciprocal of the sampling rate. Thus, for a spectral width of 5 kHz, $t_{\text{dw}} = 10^{-4}$ s or 100 μs . Given a computer storage of 8K, the total time during which a FID can be measured in this particular example is then 0.82 s. This time interval is known as the *acquisition time*. It is important to realize that spectral width, sampling rate, dwell time, and acquisition time are all interrelated and, for a given experimental set-up, it is not possible to change one of these parameters without affecting the others. Sampling more slowly, for example, decreases the spectral width and an increase in acquisition time at a given computer storage is possible only if the dwell time is reduced through an increase in the sampling rate. The sometimes confusing interrelations of these parameters just discussed are illustrated graphically with a numerical example in Figure 8.19.

After FT we again store the results in the computer, and the available number of memory locations now becomes critical for the resolution of the frequency domain spectrum. Before this curve can be recorded, a digital-to-analog converter (DAC) must be applied. In the example chosen above, the 4K data points available for the spectral range of 5 kHz yield a digital resolution of 1.22 Hz for the frequency spectrum, no matter how good the actual resolution due to magnet homogeneity

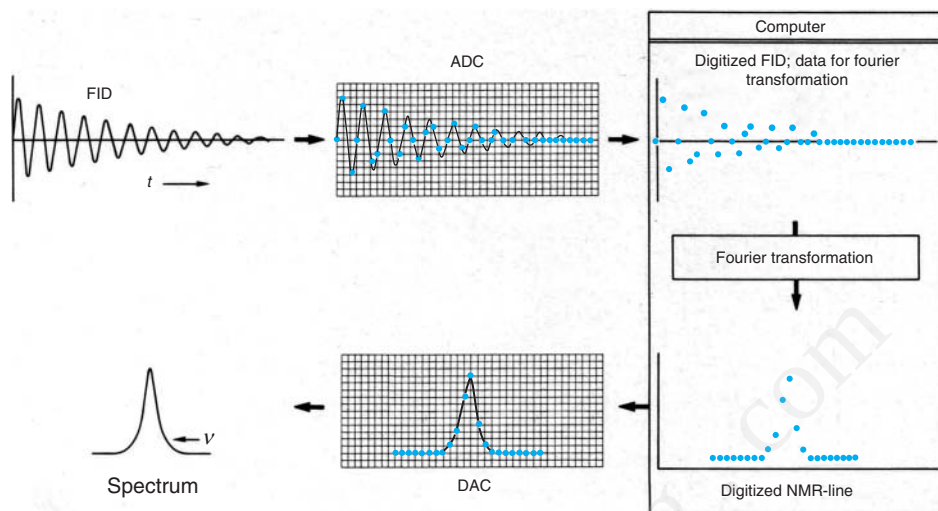


Figure 8.20 Data flow chart for an FT NMR experiment.

was. Limited computer space, therefore, may severely affect the quality of the spectrum, especially as far as small line splittings are concerned.

In summary, the data flow and transformation, beginning with the FID, through the ADC, the computer, the DAC, and finally to the recorder, where the conventional NMR signal is displayed, is represented in graphical form in Figure 8.20.

8.4.1.2 RF Sources of an FT NMR Spectrometer

Several aspects concerned with the RF sources of the FT NMR spectrometer require special attention. Data accumulation over large time intervals requires high field/frequency stability and an internal heterolock system that usually employs the ^2H resonance of a deuterated solvent (CDCl_3 , C_6D_6 , etc.) is therefore essential. The lock channel operates in the CW mode. Furthermore, to allow double resonance experiments of various types, a second RF source of variable frequency should be available. Finally, the pulse transmitter provides the RF power for the nucleus of interest. It usually has a fixed value for γB_1 and is characterized by the width t_p (in microseconds) necessary for a 90° pulse of a standard sample. Typical values for $t_p(90^\circ)$ range from a few microseconds for protons to up to $100\ \mu\text{s}$ for the less sensitive nuclei with small magnetogyric ratios. Whereas the maximum signal results from a 90° pulse, small flip angles are advisable for data accumulation in order to reduce the recovery time for the z -magnetization, which is governed by spin-lattice relaxation. As can be seen from Figure 8.5a (p. 238) the induced transverse magnetization along the y -axis, M_y , present after deflection of vector $\mathbf{M}$ of magnitude M_0 , is equal to $M_0 \sin \alpha$. At the same time the z -magnetization is reduced to a value of $M_0 - M_0 \cos \alpha$. For small flip angles ($\alpha < 30^\circ - 50^\circ$), we have $\sin \alpha > (1 - \cos \alpha)$ and the detected signal is much larger than the loss of longitudinal magnetization. For the optimal pulse angle, known as the *Ernst angle*,

the following equation holds:

$$\cos \alpha = \exp \left(-\frac{t_r}{T_1} \right) \quad (8.29)$$

The *delay time* between individual pulses – for a sequence of 90° pulses of the order of five times T_1 – and consequently the *repetition time* for the experimental sequence can thus be shortened considerably.

A further, though much shorter, delay time (of the order of one or two times t_{dw}) is necessary to allow for the recovery of the receiver after application of the strong RF pulse, because a strict orthogonal arrangement of transmitter and receiver coil is in practice not achieved. Part of the RF power will also reach the receiver, even if time sharing is used, a technique where transmitter and receiver are turned on and off alternately. Finally, as will be discussed below, the correct setting of the pulse frequency with respect to the spectral range is of crucial importance for the results. Figure 8.21 summarizes the sequence of an FT experiment in graphical form.

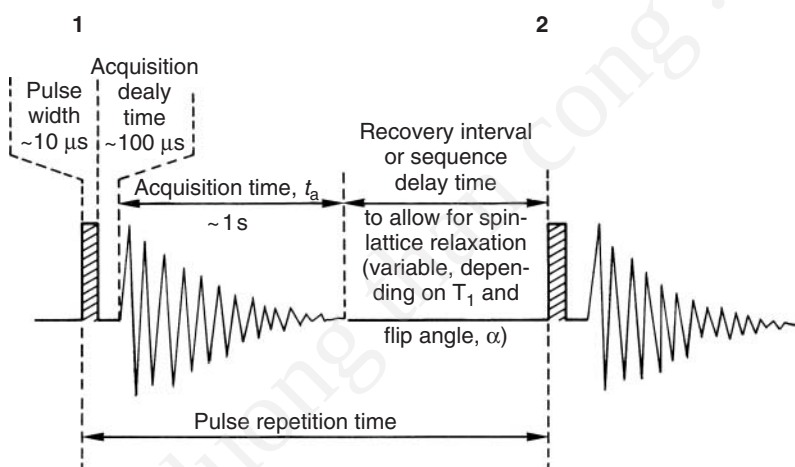


Figure 8.21 Time sequence in FT NMR with data accumulation.

8.4.1.3 Transmitter and Signal Phase

Modern FT NMR spectrometers are equipped with pulse transmitters that can generate transverse magnetization in each direction of the x,y -plane of the laboratory frame. The orientation of the respective vector, $M_{x,y}$, is known as its *phase*, which is measured relative to the y -axis of the rotating frame. The vector orientation at the time when data accumulation starts determines the phase of the time signal as well as that of the frequency signal after Fourier transformation. These relations are illustrated in Figure 8.22 (p. 260). Because NMR spectrometers are equipped with phase-sensitive detectors the dispersion signals with phase errors of 90° or 270° can be suppressed.

A special feature of the FT NMR experiment is the *frequency dependent phase error* that results after Fourier transformation of the time domain data. It originates

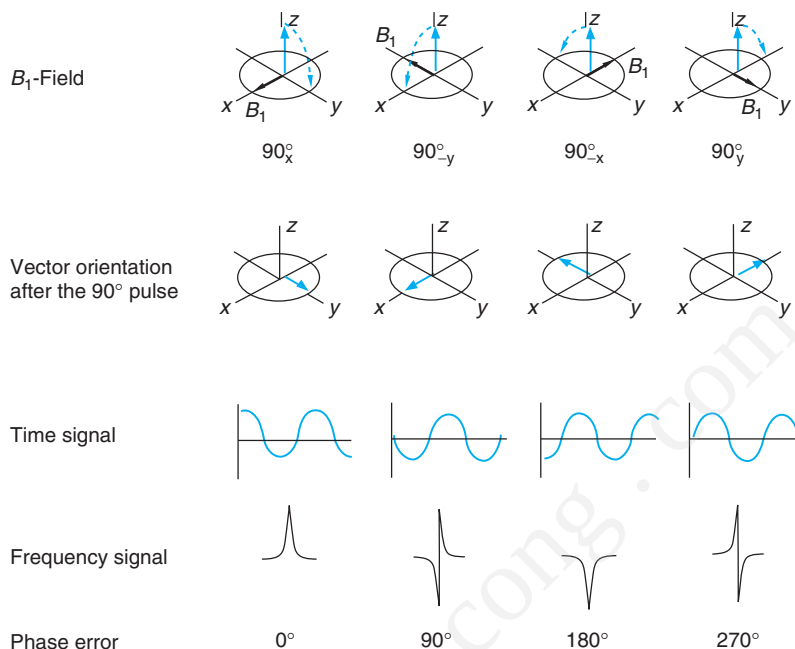


Figure 8.22 Relationship between the phase of the B_1 field, the orientations of the transverse magnetization vector after a 90° pulse, and the phases of the respective time and frequency signals in a FT NMR experiment. Please note that Larmor precession moves the vector $M_{x,y}$ clockwise; through the 90° pulse the vector I_z is transformed into I_y , I_x , I_{-y} , and I_{-x} .

from the delay time necessary for receiver recovery. During this time the individual cosine components of the free-induction decay progress by different phase angles, thus giving rise to phase shifts in the transformed signals. A straightforward correction of this effect can be made by multiplying the NMR line shape by a frequency-dependent phase factor, which is a standard routine in the FT program. Figure 8.23 illustrates this aspect.

Phase errors can also be caused by insufficient power of the pulse transmitter. As shown in Figure 8.15, the intensity of the Fourier components decreases with their distance from the carrier frequency. For large spectral widths the condition $B_{\text{eff}} \approx B_1$ is then not valid for all frequencies. Accordingly, for some frequencies B_{eff} makes an angle θ with the z -axis that is smaller than 90° . Since the vector I_z rotates around B_{eff} , a phase error arises that is dependent on the frequency offset (Figure 8.24).

8.4.1.4 Selective Excitation and Shaped Pulses in FT NMR Spectroscopy

As discussed on p. 21, the basis of FT NMR spectroscopy is polychromatic signal excitation. This means that the RF field always extends over the whole frequency range. These particular pulses are called *hard pulses* and their t_p is in

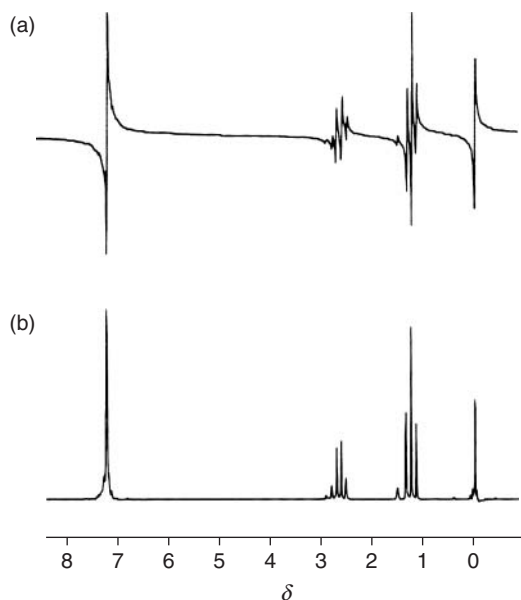


Figure 8.23 Phase correction for a FT NMR spectrum: (a) ^1H NMR spectrum of ethylbenzene after Fourier transformation with frequency dependent phase errors; (b) the same spectrum after phase correction.

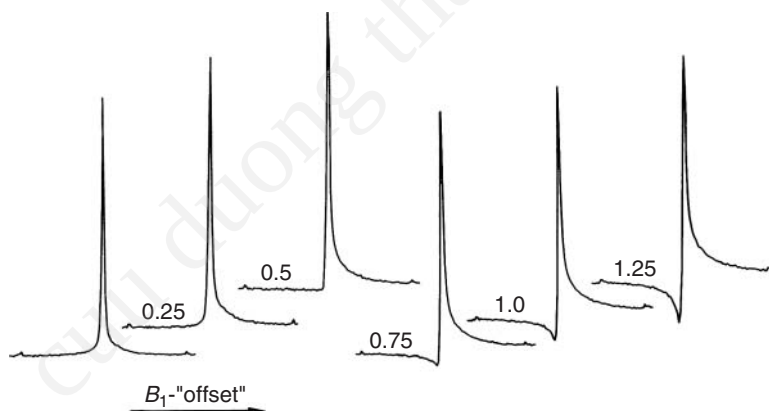


Figure 8.24 Phase error resulting from frequency offset in units of B_1 .

the microsecond range. In several cases, however, it is desirable to use selective or *soft pulses* with a small frequency range, for instance if solvent signals are to be saturated or if certain resonances are to be excited selectively. Soft pulses have t_p values in the millisecond range and several approaches have been developed to overcome the difficulties associated with the limited band width, for example, uniform pulse power over the excitation range to avoid phase errors.

In the case of heteronuclear experiments the decoupler channel provides the simplest means for the generation of selective 180° ^1H -pulses. For example, ^{13}C resonances can be observed while at the same time the proton magnetization of one particular ^{13}C -satellite in the ^1H spectrum is inverted by a short application of the ^1H transmitter [selective population inversion (SPI), cf. p. 357 ff.]. This experiment is used for ^{13}C NMR assignments and will be discussed in more detail in Chapter 10 (p. 357). For homonuclear cases, on the other hand, selectivity can be achieved, for example, by the application of GAUSS pulses or by the *delays alternating with nutation for tailored excitation* (DANTE) pulse sequence.

GAUSS pulses have, as their name implies, instead of the common rectangular envelope the shape of a Gauss curve and relatively long pulse times (60–100 ms). To achieve the Gauss envelope, the pulse amplitude must be controlled during the pulse time. A narrow excitation range results and the pulse power readily falls off with the frequency offset (Figure 8.25). Special pulse transmitters have been developed for this purpose and the spectrometer must be equipped with a waveform generator. The simple GAUSS pulse has a number of imperfections and sometimes phase errors may arise, but several alternatives with improved performance are available, but we will not discuss this more technical aspect in detail.

The DANTE sequence, used earlier, does not need special equipment. Selective excitation is achieved here through a train of n rectangular pulses with small repetition times, t_r , and small pulse angles α . Such pulse modulation of the carrier frequency corresponds to frequency spectrum with side bands separated by $1/t_p$ that can be regarded as selective pulse transmitters (Figure 8.26). The carrier frequency of the pulse transmitter has to be arranged in such a way that signals, which are not to be excited, fall into the gaps between the side bands. For a selective 90° pulse one chooses $\alpha = 90/n$. Typical values are $t_r = 2$ ms, $n = 200$, and $\alpha = 0.45^\circ$.

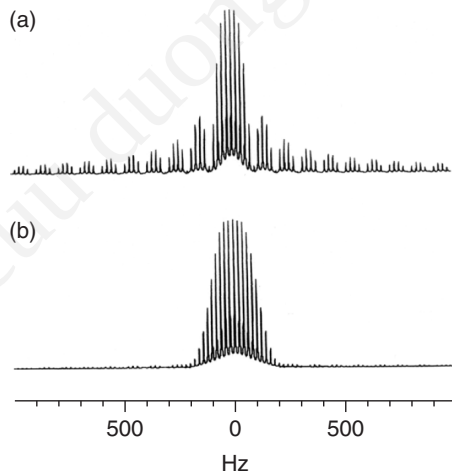


Figure 8.25 Absolute value frequency domain excitation profiles for (a) a rectangular pulse and (b) a Gaussian shaped pulse. (Reproduced by permission from Reference [3]. Copyright Elsevier 1999).

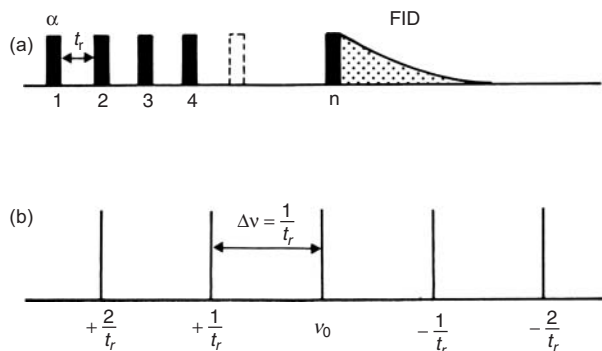


Figure 8.26 DANTE pulse sequence for selective excitation (a) and corresponding frequency spectrum (b).

This technique finds applications, for example, in the excitation of individual spin multiplets or in several one-dimensional measuring techniques that are based on selective pulses (cf. Chapter 11).

8.4.1.5 Pulse Calibration

The success of modern NMR experiments depends to a great extent on the precision with which certain pulse angles can be experimentally verified. Pulse angle calibration, that is, calibration of the pulse length used by the particular transmitter to produce a desired pulse angle α , is of great practical importance. This relation should be checked quite often, in 2D NMR before each experiment. In principle, several methods are available for this purpose, but we will mention only the most widely used, namely, determination of the pulse time for the 360° pulse.

In a series of measurements, where the conditions for sensitivity enhancement and phase correction are kept constant, the singlet of a standard sample, for example, benzene, is measured. Starting with small pulse angles α , which means short pulse lengths t_p , the signal amplitude increases and becomes negative after going through zero at t_p for $\alpha = 180^\circ$ (Figure 8.27). A second zero transition is then found at t_p for $\alpha = 360^\circ$.

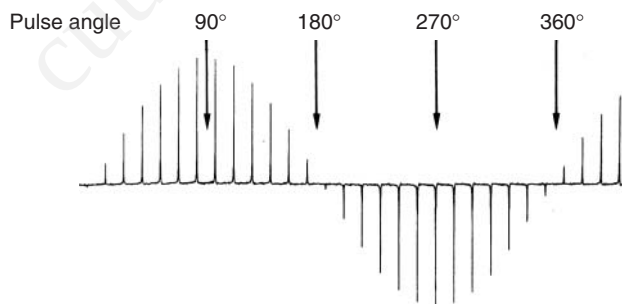


Figure 8.27 Dependence of signal amplitude of transverse magnetization on the pulse angle α .

To avoid offset effects, the carrier frequency is positioned directly at or close to the frequency of the signal used for calibration. Since approximate data for the pulse lengths in the frequency range of interest are normally available, results are obtained most quickly with the $t_p(360^\circ)$ search because it requires the shortest relaxation delays.

8.4.1.6 Composite Pulses

Even with modern instruments and notwithstanding careful pulse calibration, small pulse errors are unavoidable. These errors result from the offset effects as well as from field inhomogeneity and limited RF power. Additional means to correct for these imperfections are, therefore, of general importance. The most effective is the method of composite pulses, where the desired pulse angle results after the application of several individual pulses. For example, a 180° pulse that inverts longitudinal magnetization can be replaced by the sequence $90_x^\circ - 180_y^\circ - 90_x^\circ$. This *pulse sandwich* reduces the error in the pulse time from up to 20% to 1% during an inversion-recovery experiment (Figure 8.28). To eliminate, at the same time, offset effects more extensive *pulse clusters* have been developed.

8.4.1.7 Single and Quadrature Detection

As described on page 250, the Fourier components that arise during pulse excitation extend to frequency ranges above and below the carrier frequency.

Because positive and negative frequency differences cannot be distinguished after Fourier transformation of the data, it is necessary to position the pulse transmitter at the upper or lower limit of the sweep range of interest if only one detector is used. This experimental set-up is called *single detection*. It has the disadvantage that half of the transmitter power is lost and the sweep range that can be excited with uniform pulse power is limited. The addition of noise by frequency folding – to be discussed in Section 8.4.2 – from the unused region of the pulse spectrum must be prevented by the application of frequency filters.

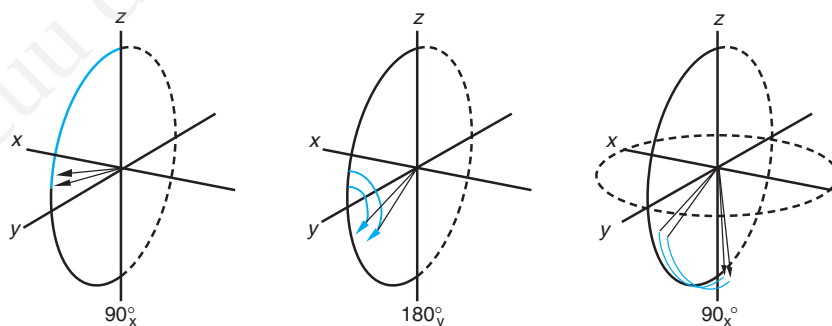


Figure 8.28 Illustration of the principle of *composite pulses* with the example of a $90_x^\circ - 180_y^\circ - 90_x^\circ$ sandwich for the inversion of longitudinal magnetization M_z ; errors in the pulse length are largely removed.

The alternative method of *quadrature detection* that is employed in all modern spectrometers avoids these disadvantages. The carrier frequency is now positioned in the center of the spectral window. Two phase-sensitive detectors with a phase difference of 90° are employed and this arrangement allows one to determine the sign of the measured frequency relative to the frequency of the carrier. To understand the principle of this technique, imagine the projections of the rotating transverse magnetization on one or two axes of the rotating coordinate system, respectively. With single detection on one axis we observe only one-dimensional oscillations. With double detection on two axes in quadrature, the sense of rotation and, therefore, the relative sign of the frequency can be determined. Frequencies of different sign behave like sine or cosine functions (Figure 8.29). Their individual Fourier transformation yields frequency pairs, which, if added, eliminate one frequency. Consequently, in comparison to single detection the Nyquist frequency during quadrature detection is given by half of the sweep width (SW) and the dwell time is thus $1/\text{SW}$ instead of $1/2 \text{ SW}$ as for single detection (Figure 8.19).

Instrumental imperfections can lead to a situation where signal selection by quadrature detection is not completely successful. So-called quad-images are then observed at $+\nu$ or $-\nu$. They can, however, be recognized by their different phase properties. Their intensity seldom exceeds 1% of the true lines. Therefore, this

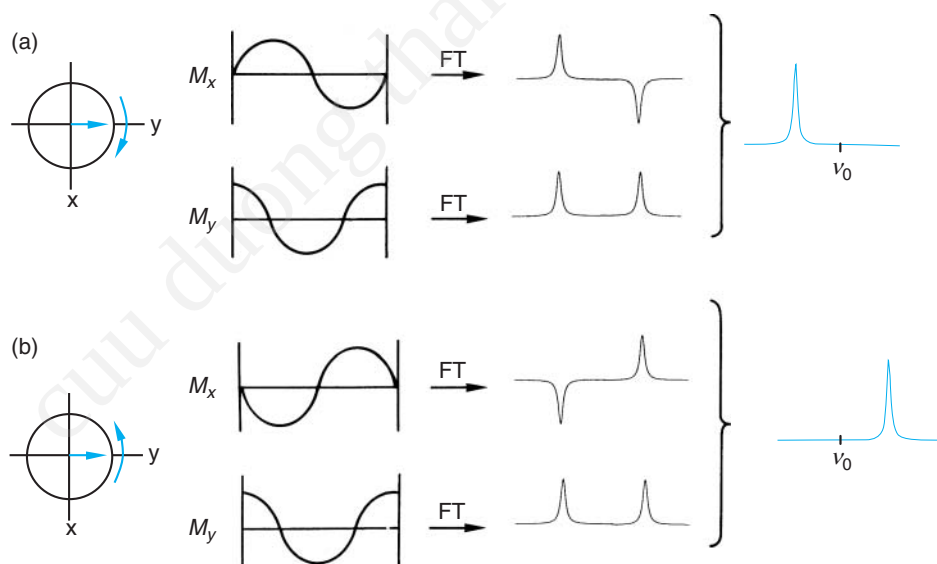


Figure 8.29 Principle of quadrature detection; (a) for a vector $\mathbf{M}$ that rotates clockwise, we detect on the x-axis a positive sine and on the y-axis the positive cosine; (b) if $\mathbf{M}$ rotates anti-clockwise, we detect on the

x-axis a negative sine and on the y-axis again a positive cosine; the result of the Fourier transformation of the signals and addition of the frequency spectra are also shown [4].

problem is only important with intensive signals, for example, those of solvents. In addition, hardware errors that lead to quad-images and several other artifacts can be removed or greatly attenuated by the method of phase cycles.

8.4.1.8 Phase Cycles

As mentioned above, with modern NMR spectrometers transmitter and detector phases can be varied and adjusted to the needs of the individual experiments. It is therefore possible, in particular by a certain choice for the receiver phase, to select signals of interest and suppress unwanted signals or artifacts. This is achieved by the use of *phase cycles*, the principle of which will be illustrated with two examples.

Many artifacts that result from inaccuracies of the experimental parameters can be eliminated by a simple 180° transmitter *phase shift*. Such a variation allows us, for instance, to eliminate error signals that arise from an inaccurate pulse length. In an inversion recovery experiment, for example, an imperfect 180°_x pulse produces transverse magnetization along the $+y$ -axis that affects the result of T_1 measurement. If, however, in every second experiment a 180°_{-x} pulse is used, in other words the transmitter phase is shifted by 180° , $-y$ -magnetization results and the disturbing transverse magnetization is eliminated by adding the individual experiments.

The artifact of quad-images mentioned above can be eliminated if the signals of the two receiver channels are interchanged in order to improve the balance. This is achieved by a 90° phase shift of the transmitter that leads to a situation where in the second experiment a negative cosine signal enters channel 1 and a positive sine signal enters channel 2 (Figure 8.30). The cosine signal is then multiplied by (-1) and stored in memory block B, while the sine signal from channel 2 is stored in memory block A. After adding the results of experiment 1 and 2 both signals in A and B contain components that passed from both transmitter channels. An additional 180° phase shift leads to further improvements.

The complete phase cycle, known as CYCLOPS (*cyclically ordered phase cycle*), is composed of *four* individual experiments that are collected in the table below.

	transmitter phase	Code	Receiver signal		Memory location	
			Channel 1	Channel 2	A	B
			M_x	M_y		
(1)	x	0	$\sin \omega t$	$\cos \omega t$	M_x	M_y
(2)	y	1	$-\cos \omega t$	$\sin \omega t$	M_y	$-M_x$
(3)	$-x$	2	$-\sin \omega t$	$-\cos \omega t$	$-M_x$	$-M_y$
(4)	$-y$	3	$\cos \omega t$	$-\sin \omega t$	$-M_y$	M_x
					$4\sin \omega t$	$4\cos \omega t$

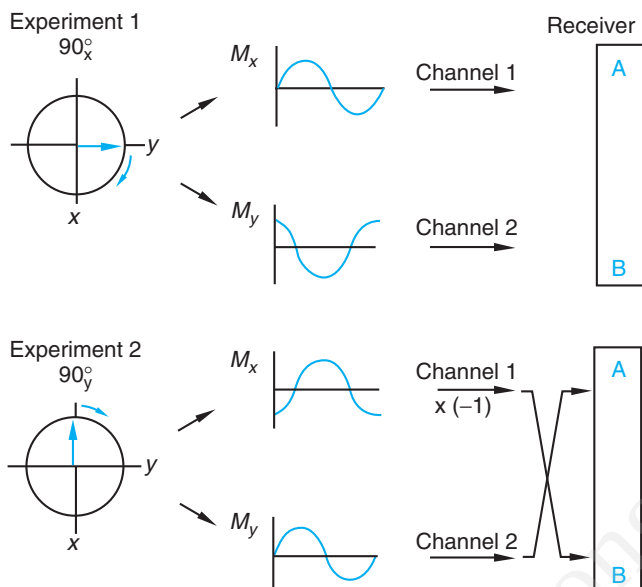


Figure 8.30 Transmitter and receiver phase during the CYCLOPS phase cycle for experiments (1) and (2) of the table on p. 266 [4].

The phases of the receiver channels are fixed on the $+x$ - and $+y$ -axis, respectively. Because of the phase shift for the transmitter, the signals have to be stored in such a way that signal addition results. This necessitates, as described above, multiplication by (-1) in four cases. As one sees, the resulting signal always contains two components that have passed through channel 1 and two that have passed through channel 2. Any existing imbalance of the two channels is thereby reduced.

8.4.2

Complications in FT NMR Spectroscopy

From the foregoing discussion it appears that a number of complications and perhaps disadvantages are typical of the FT method. One of the most common is known as *frequency folding*, which results from an improper choice of the spectral width with regard to the actual spectrum to be investigated. If there is a signal outside this range at a higher frequency $\Delta\nu + \delta\nu$, following the Nyquist theorem, it cannot be recognized. It can be shown, however, that the data points resulting from this frequency are treated by the computer as if they belonged to a frequency $\Delta\nu - \delta\nu$. Hence the term “*folding*” is used, since transformation faithfully produces a signal at $\Delta\nu - \delta\nu$ in the frequency domain. This is illustrated in Figure 8.31 (p. 268).

With normal FT NMR it is therefore in general difficult, if not impossible, to investigate smaller spectral regions separately. In such cases the possibility of frequency folding has to be considered. In addition, the elimination of strong

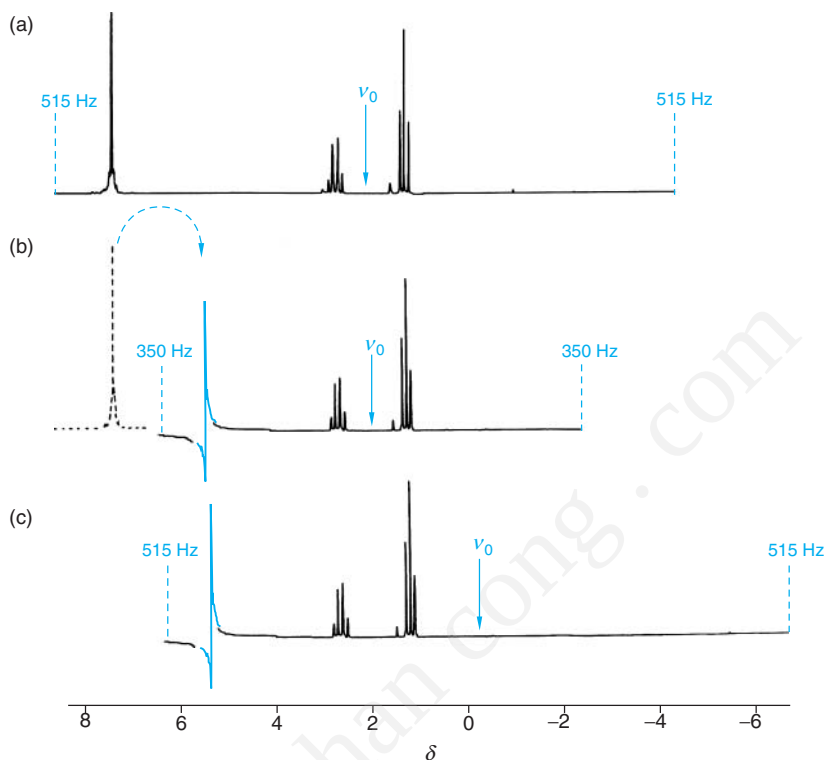


Figure 8.31 Frequency folding in FT NMR spectroscopy as demonstrated with the 80 MHz ^1H NMR spectrum of ethylbenzene observed with quadrature detection: (a) Nyquist frequency +515 Hz; (b) Nyquist frequency +350 Hz, spectral window too small; (c) Nyquist frequency +515 Hz as for (a) with, however, the wrong choice of the transmitter position. As in the cases shown, the folded signals can be recognized mostly by the phase error that remains after phase correction. This criterion is, however, not always valid, especially in ^{13}C NMR spectroscopy.

solvent lines presents a problem. In particular, strong signals may cause a storage overflow during data accumulation. Special techniques are therefore necessary to deal with these shortcomings.

The phenomenon of frequency folding is also important with respect to the noise present at higher frequencies outside the spectral range. To prevent a fold-back of these data that would add to the noise in the spectral range, *filtering* devices that attenuate these signals are employed.

Another aspect related to the spectral width and the computer capacity arises with the FT NMR of nuclei covering a large chemical shift range (^{19}F , ^{31}P). In addition to the pulse power, the sampling rate must be high in these cases and the acquisition time may be severely limited by the available computer space. Distorted signals may then result from truncated free-induction decay (Figure 8.32, p. 271). Furthermore, the digital resolution in the frequency domain decreases.

For a small $\Delta\nu$, on the other hand, provided that there is no frequency folding, the digital resolution improves. However, the acquisition time increases and the conditions for data accumulation become less favorable. Thus in FT NMR high sensitivity can be achieved only at the expense of resolution and vice versa.

A point of special interest that should be included here concerns *intensity measurements* in FT spectra. Errors can arise from various sources, such as low pulse power or a pulse sequence with insufficient delay times. In the first case, the power distribution of the B_1 field over the spectral range varies and different pulse angles for the individual resonance signals result. Since the magnitude of the induced transverse magnetization is a function of the pulse angle, the intensities become distorted. If, on the other hand, the pulse repetition for data accumulation is too fast, nuclei with high T_1 values that need a longer relaxation delay suffer from incomplete recovery of their z-magnetization and their intensities are systematically recorded too low. To avoid such shortcomings, the experimental settings must be carefully checked. In general, then, determination of the correct integrals requires great care in FT NMR.

Problems with intensive solvent signals with respect to the dynamic range (see p. 256) are met today in ^1H FT NMR spectroscopy only if non-deuterated solvents have to be used. This is the case, for example, during measurements on biochemically or biologically interesting samples that have often to be performed in H_2O instead of D_2O . Of the various techniques available to suppress the water signal, among them a number of pulse sequences, two relatively simple methods have been found useful in practice: *presaturation* and the *selective inversion recovery* experiment (p. 247). In the first case the H_2O resonance is saturated just before the measurement of the spectrum of interest with a strong B_1 field, and in the second case the remaining spectrum is excited when the inverted H_2O signal just passes through zero intensity. We come back to this topic in Chapter 15.

8.4.3

Data Improvement

FT NMR spectroscopy provides several techniques that can be used to improve the experimental results in order to achieve better resolution or a more favorable signal-to-noise ratio. For this purpose several mathematical operations can be applied to the time domain data before Fourier transformation.

It turns out, for example, that after half of the acquisition time, which is usually of the order of 1 s, most of the signals have decayed to zero owing to transverse relaxation. The free-induction decay then primarily contains noise. This can be drastically reduced if each data point of the FID is multiplied by an exponential function $\exp(-j\text{TC}/N)$ where TC is an empirical time constant, j the number of the particular data point, and N the total number of data points. This corresponds to a multiplication of the time signal with the function:

$$F_E = \exp(-t/a) \quad (8.30)$$

As the exponent indicates, the higher data points are more strongly affected, thus reducing the noise. The effective transverse relaxation rate, $1/T_2^*$, which determines the time dependence of the FID signal and the half width of the NMR signal in the frequency domain [see Figure 8.11 and Eq. (8.18)], is then governed by the following relation:

$$(1/T_2^*)' = 1/T_2^* + 1/a \quad (8.31)$$

Of course, the apparently shorter T_2 leads to an artificial line broadening, but this can usually be accepted for the benefit of a better signal-to-noise ratio. The result obtained with this procedure is illustrated below in Figure 8.34. The best compromise between the reduction of the signal-to-noise ratio and line broadening is generally obtained if we choose $a = T_2^*$. In this case the time constant in Eq. (8.30) is equal to the decay time of the FID.

In ^1H NMR spectroscopy the procedure described is less important due to the high sensitivity available, especially since information about small spin–spin couplings may be lost through line broadening effects. In the field of NMR spectroscopy of insensitive and rare nuclei, such as, for example, ^{13}C , the method is, however, of great importance in order to detect signals of low intensity (Figure 8.32d).

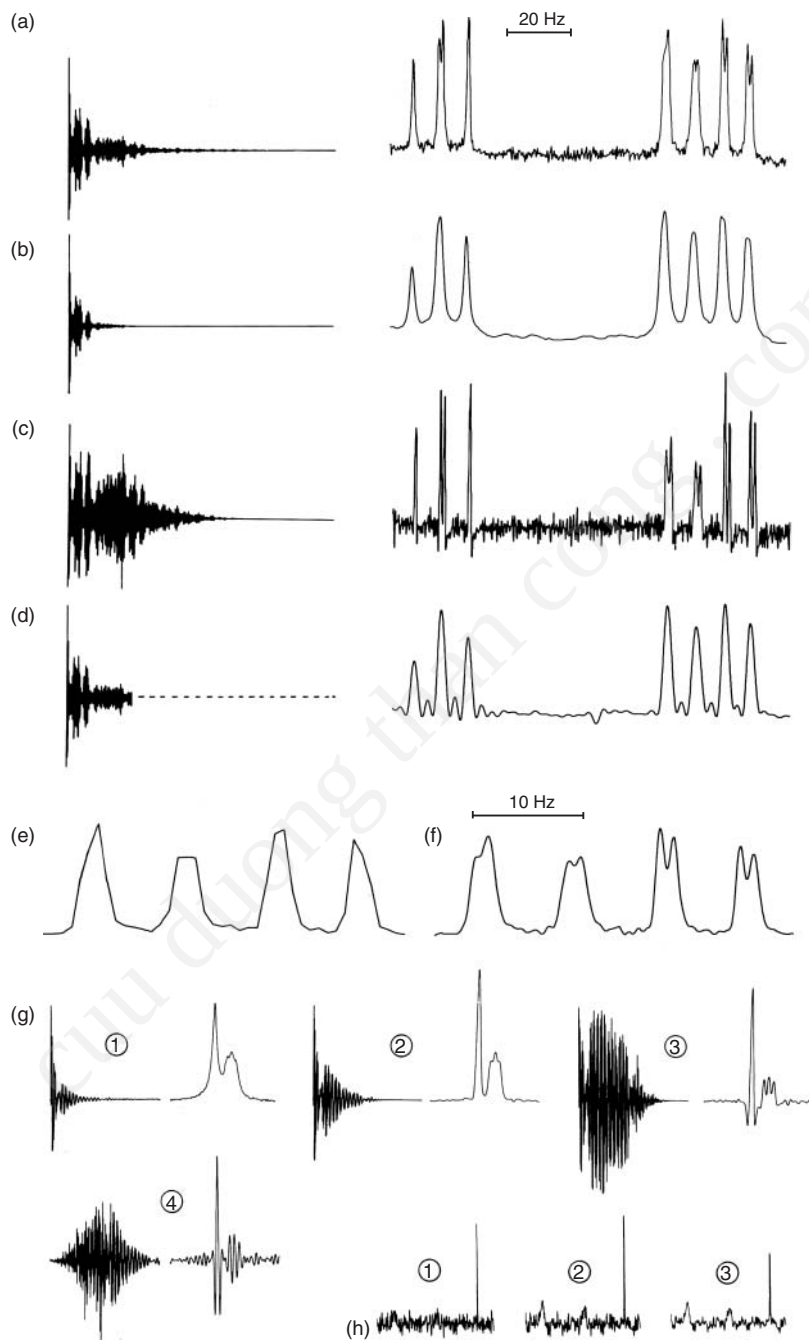
In some cases, multiplication of the FID by an exponential function with a positive exponent, $\exp(t/a)$, may be desirable to improve the resolution at the expense of the signal-to-noise ratio. The most effective function for resolution enhancement is the product function:

$$F_G = \exp\left(\frac{t}{a}\right) \exp\left(-\frac{t^2}{b}\right) \quad (8.32)$$

for which the parameters a and b are determined empirically. The first term corresponds to resolution enhancement by exponential multiplication, as discussed above, while the second term corresponds to a Lorentz–Gauss transformation of the signal. This leads to narrow lines that can show artifacts, however, at the basis.

Figure 8.32 Aspects of data treatment in FT NMR spectroscopy; the time and frequency domain signals of the ^1H AMX spin system of perylene dianion are used for demonstration in the examples (a)–(f); (a) time and frequency domain signal with 8K data points; (b) influence of exponential multiplication; line broadening 1 Hz – the time domain signal is artificially damped, the signal-to-noise ratio is improved, small signal splittings are lost; (c) Lorentz–Gauss transformation for resolution enhancement; (d) truncated time domain signal; the base line shows oscillations; (e) signal distortions in the frequency domain as a consequence of an insufficient number of data points (2K data points, digital resolution 0.78 Hz/point); (f) improvement of spectrum

(e) by zero filling to 16K data points (digital resolution 0.09 Hz per point); the density of data points can be observed at the monitor and the possibility of improving the digital resolution by zero filling may thus be checked; (g) line shape changes after extreme Lorentz–Gauss transformations using Eq. (8.32) with the example of a singlet and a triplet: (1) without data treatment; (2) $a = 0.318$, $b = 0.309$; (3) $a = 0.159$, $b = 1.41$; and (4) $a = 0.106$, $b = 0.252$; the a -values correspond to a decrease in line width of -1.0 , -2.0 , and -3.0 Hz [cf. Eq. (8.32)]; (h) detection of two broadened ^{13}C singlets of low intensity by exponential multiplication using Eq. (8.30): (1) without data treatment; (2) $a = 0.0637$; and (3) $a = 0.0318$; the a -values correspond to line broadening effects of 5 and 10 Hz, respectively.



A disadvantage is that small signals may be lost in the noise and the peculiar signal shape prevents correct integration of the spectrum (Figure 8.32c, g).

As a result of data treatment by application of Eq. (8.32), certain regions of the time domain signals are enhanced or attenuated (Figure 8.32). The functions used for this purpose are, therefore, also called *window functions* or *weighting functions*. They also play an important role in two-dimensional NMR spectroscopy (Chapter 9).

Resolution enhancement may also be effected in the frequency domain if enough computer space is available to add several memory blocks of zeros to the FID (*zero-filling*). This provides a larger number of data points in the frequency domain and allows for a better reproduction of the signals without affecting the acquisition time. This is especially important for accurate intensity measurements as well as for resolution enhancement with the Lorentz–Gauss transformation.

8.5

Double Resonance Experiments

We conclude this chapter by describing an important group of experiments that are known as *double resonance experiments*. Such experiments may differ with respect to their specific application; however, a general and typical feature of all double resonance experiments is that besides the transmitter B_1 a second RF field B_2 is applied to the spin system. The field B_2 has then to be included into the Hamilton operator:

$$\mathcal{H} = \sum_i (\nu_i - \nu_2) \hat{I}_z(i) + \sum_{i < j} J_{ij} \hat{I}(i) \hat{I}(j) - \sum_i \gamma_i B_2 \hat{I}_x(i) \quad (8.33)$$

The results of such experiments can vary widely, depending upon the frequency and amplitude of B_2 .

8.5.1

Homonuclear Double Resonance – Spin Decoupling

The classical double resonance experiments for *spin decoupling* in ^1H NMR spectra, where a transmitter B_2 of frequency ν_2 is positioned with sufficient power at the resonance of a certain nucleus X while the spectrum is observed with the transmitter B_1 , has already been introduced in Chapter 3 (p. 58 ff.). It leads to a simplification of NMR spectra by removing the multiplet structure of individual resonances that is due to scalar spin–spin interactions with X. This facilitates spectral interpretations and yields at the same time, on the basis of the relations between the magnitude of homonuclear ^1H , ^1H spin–spin coupling constants and chemical structure, an assignment for individual resonances. In these experiments a small displacement of the A resonance, called the *Bloch–Siegert shift*, may occur if the decoupler field B_2 at ν_X is strong and the chemical shift difference $\nu_A - \nu_X$ is small. Today, homonuclear ^1H , ^1H decoupling as an assignment aid is

practically completely replaced by the two-dimensional COSY experiment, which will be discussed in detail in the following chapter.

Here we only mention that spin decoupling can also be performed in an FT experiment by using a time-sharing procedure. One takes advantage of the fact that to record a data point of the FID only a fraction of the dwell time is needed. The receiver and the decoupler channel can thus be synchronized in such a way that decoupling is applied between data collection. Because of the short dwell time interval, which is in the microsecond region, the B_2 field is practically pulse modulated. A center band at ν_2 and side bands in a distance $1/t_{\text{dw}}$ result because the relation $t_r = t_{\text{dw}}$ holds. For $t_{\text{dw}} \rightarrow 0$ the experiment is identical to CW decoupling. In both cases the result is the same: all line splittings that are due to couplings with the irradiated nucleus are removed.

Without going into the details of a rigorous treatment, the results of a spin-decoupling experiment can be rationalized on the basis of the classical model for the NMR experiment. This implies that the frequency ν_2 of the second RF field coincides with the Larmor frequency of the X nucleus and we have $B_{\text{eff}} = B_2$, that is, the vector μ_X precesses around B_2 and thus around the x' -axis of the rotating frame. Consequently, μ_A is directed practically perpendicular to the vector μ_X . The nuclear spin vectors $\hat{I}(A)$ and $\hat{I}(X)$ are then quantized along the z - and the x' -axis, respectively. They are thus orthogonal and their scalar product, that is, the scalar spin-spin coupling according to Eq. (3.9a), vanishes.

8.5.2

Heteronuclear Double Resonance

The previously described variety of double resonance techniques is carried out on nuclei of a single type and therefore the term *homonuclear* double resonance is applied. The extension to different nuclei leads to *heteronuclear* double resonance, which differs from the homonuclear technique only in that the frequency difference $\nu_2 - \nu_1$ lies in the megahertz range. The second field B_2 is most advantageously produced by a separate transmitter such as a quartz-controlled frequency synthesizer. Such experiments are useful for the simplification of spectra that are complicated by heteronuclear spin-spin coupling such as $J(^1\text{H}, ^{19}\text{F})$ or $J(^1\text{H}, ^{31}\text{P})$. The line broadening caused by ^{14}N that is due to unresolved coupling to this quadrupolar nucleus can also be eliminated (Figure 8.33, p. 274) so that the spectra can be analyzed more easily. In the consideration of a specific pair of nuclei, for example, ^1H and ^{19}F , a notation has been developed to indicate which nucleus is observed and which is decoupled. The case in which fluorine is irradiated and the proton resonance is observed would be represented as $^1\text{H}\{^{19}\text{F}\}$.

Double resonance experiments of the type $^1\text{H}\{^2\text{H}\}$ (or $^1\text{H}\{\text{D}\}$) in connection with the synthesis of partially deuterated compounds are an important aid in the simplification of proton resonance spectra. For example, the eight-proton spin system of naphthalene can be transformed into an $AA'BB'$ system if one synthesizes 1,2,3,4-tetradeuteronaphthalene and performs a $^1\text{H}\{\text{D}\}$ double resonance experiment (Figure 8.34, p. 274).

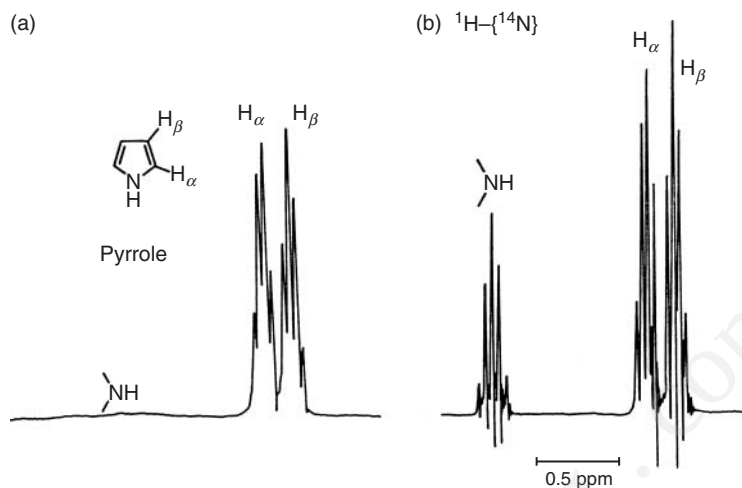


Figure 8.33 ^1H NMR spectrum of pyrrole: (a) without and (b) with simultaneous irradiation of the ^{14}N nucleus; note the dramatic difference for the NH resonance. Reproduced from Joel-Kontron, *Technical Bulletin*.

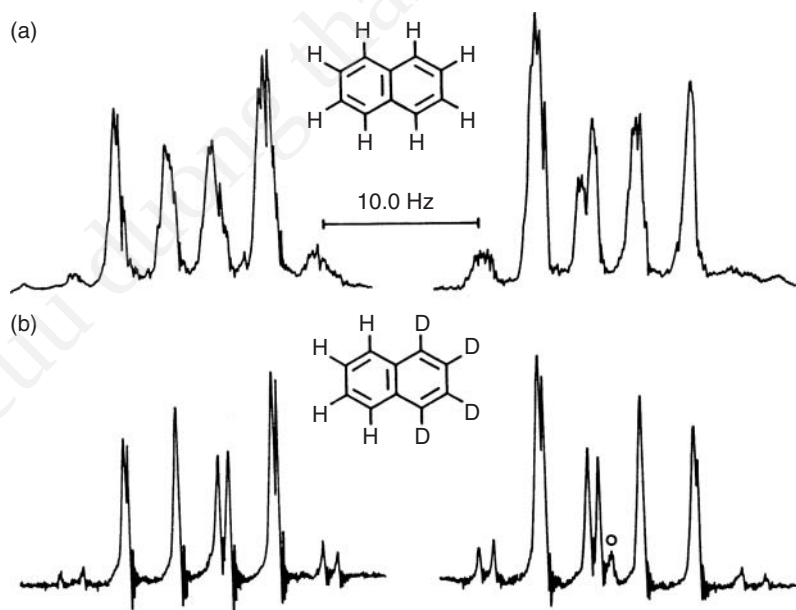


Figure 8.34 ^1H NMR spectra of (a) naphthalene and (b) 1,2,3,4-tetradeuterionaphthalene with deuterium decoupling; 100 MHz; at o signal of unknown impurity [5].

8.5.3

Broadband Decoupling

8.5.3.1 Broadband Decoupling by CW Modulation

The technique of broadband decoupling represents an important development in the field of heteronuclear double resonance. The limits of the conventional heteronuclear decoupling technique are met very soon if it proves necessary to irradiate a larger spectral region. Since the amplitude of the B_2 field cannot be increased indefinitely, its application is confined to relatively small parts of the spectrum. In the case where the resonances of the heteronucleus extend over a range of many parts per million, as, for example, in the case of ^{19}F , complete decoupling would be impossible. The method of choice then becomes broadband decoupling. Here modulation techniques of various kinds are used to effectively produce a frequency band that extends over several kilohertz and covers the whole spectral area of the nucleus that is to be decoupled. The most widely known technique was *noise decoupling*, where a noise generator is employed to produce the desired effect. Phase modulation techniques can be used just as effectively. The power of the method is demonstrated in Figure 8.35 for an $^{19}\text{F}\{^1\text{H}\}$ experiment. In comparison with the standard procedure, because of the width of the frequency band, this experiment is far less sensitive to the correct choice of ν_2 . To achieve complete spin decoupling, however, it is important that the amplitude of the B_2

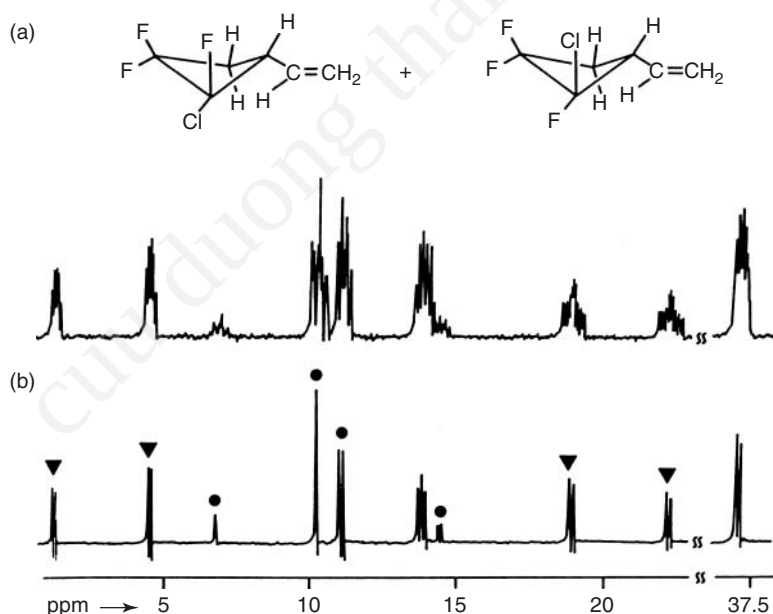


Figure 8.35 ^{19}F resonance spectra of a mixture of two isomeric cyclobutane derivatives: (a) normal spectrum; (b) with proton-noise decoupling. The “AB systems” of the CF_2 groups in the two isomers are denoted with different symbols [6].

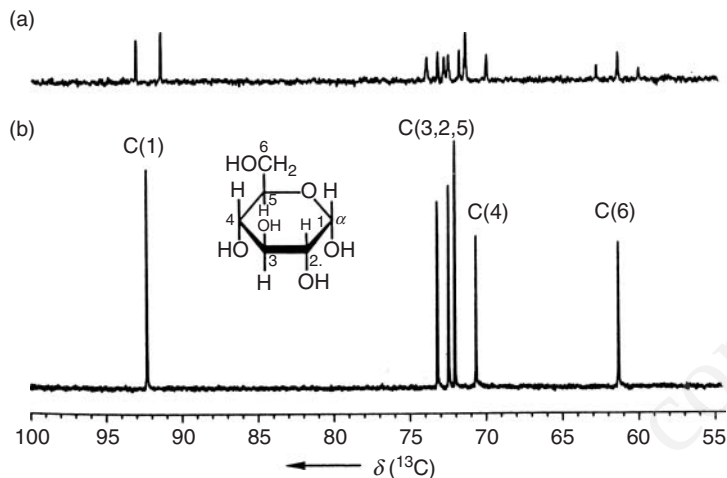


Figure 8.36 100 MHz ^{13}C NMR spectrum of α -D-glucose in DMSO-d_6 without (a) and with (b) ^1H broadband decoupling.

field is large enough to encompass the complete spectral region of the particular nucleus.

Broadband decoupling found its application routinely in ^{13}C NMR spectroscopy (cf. Chapter 11), where ^{13}C NMR spectra are measured with broadband ^1H decoupling. An additional bonus of this experiment is an intensity enhancement for the ^{13}C resonances that has two sources. Firstly, the collapse of multiplet structures into singlets improves the signal-to-noise ratio in a straightforward manner. Secondly, the ^1H decoupling is accompanied by an intensity increase for the ^{13}C resonance that amounts to 200%. The reason for this is the so-called nuclear Overhauser effect (NOE), which we discuss in detail in Chapter 10. The effect of ^1H -broadband decoupling is demonstrated in Figure 8.36 with the example of the ^{13}C NMR spectrum of α -D-glucose.

8.5.3.2 Broadband Decoupling by Pulse Methods

As an unwanted side effect, the application of strong RF fields for spin decoupling can lead to a considerable temperature rise in the sample, especially if high power is necessary to decouple a large frequency range. Sample cooling is a straightforward measure to prevent uncontrolled temperature changes, but alternative decoupler methods are available that are less critical in this respect. A breakthrough was possible by introducing spin decoupling techniques that are based on the spin echo experiment. As shown in Figure 8.37 (p. 277), the evolution of transverse X magnetization observed in the case of a heteronuclear scalar coupled AX spin system, for example, ^1H , ^{13}C , can be reversed by a $180^\circ(\text{A})$ pulse at time τ . Digital detection of the A-magnetization at times 2τ , 4τ , 6τ , etc. yields data for a decoupled X-resonance. While the two doublet components still possess different

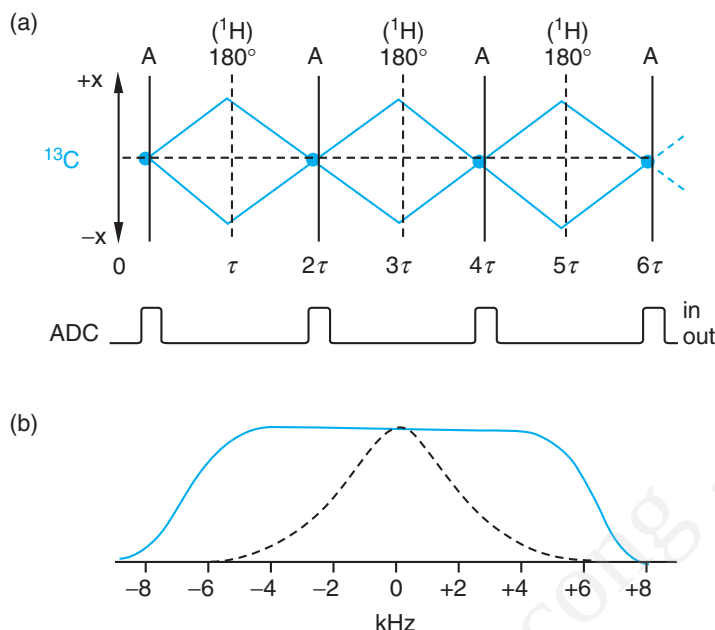


Figure 8.37 (a) Time dependence of transverse X-magnetization of an AX system with application of a train of 180° (A) pulses. The gating of the analog to digital converter (ADC) shows the data acquisition. (b) Comparison of the band width of the decoupler field during conventional modulation technique (---) and pulse decoupling (—).

Larmor frequencies $\pm J/2$, the transmitter does not recognize this difference since the magnetization is only measured when both vectors are superimposed.

The important practical aspect of this spin flip method, called *MLEV* after its inventor M. Levitt, is the fact that the frequency range for the decoupled spin is three times as large as in experiments with conventional modulation techniques (e.g., noise modulation) (Figure 8.37b). Broadband decoupling of nuclei with large chemical shift ranges, such as ^{19}F or ^{31}P , can thus be more easily performed. Further developments of this technique on the basis of composite pulses that greatly eliminate pulse errors have considerably improved the results. The methods used today are known under the acronyms WALTZ-16 and GARP and *heteronuclear composite pulse decoupling* is a standard sequence segment in multidimensional NMR experiments. Furthermore, these techniques also produce the NOE enhancement mentioned above (see Table 8.2 (p. 278) for other methods).

8.5.4

Off-Resonance Decoupling

In addition to the gain in sensitivity discussed above, several techniques of heteronuclear spin-spin decoupling provide important experimental possibilities

Table 8.2 Selective composite-pulse sequences for broadband decoupling [3].

Sequence	Bandwidth (γB_2)	Application
Continues wave	<0.1	Selective decoupling only
MLEV16	1.5	^1H decoupling
WALTZ-16	2.0	High-resolution ^1H decoupling
DIPSI-2	1.2	Very high-resolution ^1H decoupling
GARP	4.8	X nucleus decoupling
SUSAN	6.2	X nucleus decoupling

for the assignment of NMR signals of various heteronuclei. One of these methods, known as *off-resonance decoupling*, was used extensively in the early days of ^{13}C NMR. Today, polarization transfer methods of pulse NMR have replaced these experiments, but we describe them briefly here for completeness.

As the name indicates, off-resonance decoupling is really a partial decoupling technique that uses a strong RF field in the ^1H NMR region with a frequency ν_2 just “off” the resonance signals to be irradiated. The important aspect of this experiment becomes clear immediately if we realize that in such a partial decoupling experiment the line splittings are still visible. Of course, these splittings are smaller than the coupling constants, but the typical multiplet structure of certain resonances is retained. In the case of ^{13}C , it turns out that all of the smaller ^{13}C , ^1H coupling constants (geminal, vicinal, long range) are eliminated, whereas the line splittings caused by the larger one-bond coupling constants are retained. As a consequence, ^{13}C resonances in an off-resonance ^1H -decoupling experiment show first-order multiplicity and can thus be distinguished. Quartets, triplets, doublets, and singlets are observed for primary (CH_3), secondary (CH_2), tertiary (CH), and quaternary carbon atoms, respectively. Figure 8.38 shows an example.

From the theory of off-resonance decoupling an approximate equation that relates the residual splitting J_R to the frequency offset $\Delta\nu$ and the unperturbed coupling constant J_0 can be derived:

$$\Delta\nu = \gamma B_2 J_R (J_0^2 - J_R^2)^{-\frac{1}{2}} \quad (8.34)$$

This equation was used earlier to interrelate ^1H and ^{13}C spectra of a certain compound. For this purpose, the ^1H decoupler is swept through the proton spectrum and the J_R values measured for individual ^{13}C resonances are plotted against the decoupler position. Extrapolation to $J_R = 0$, that is, complete decoupling, yields the resonance frequencies of the ^{13}C attached protons. Today, two-dimensional ^1H , ^{13}C shift correlations are used for this purpose.

An additional decoupling technique, known as a *gated decoupling* and most frequently applied also in ^{13}C NMR, will be treated in Chapter 11.

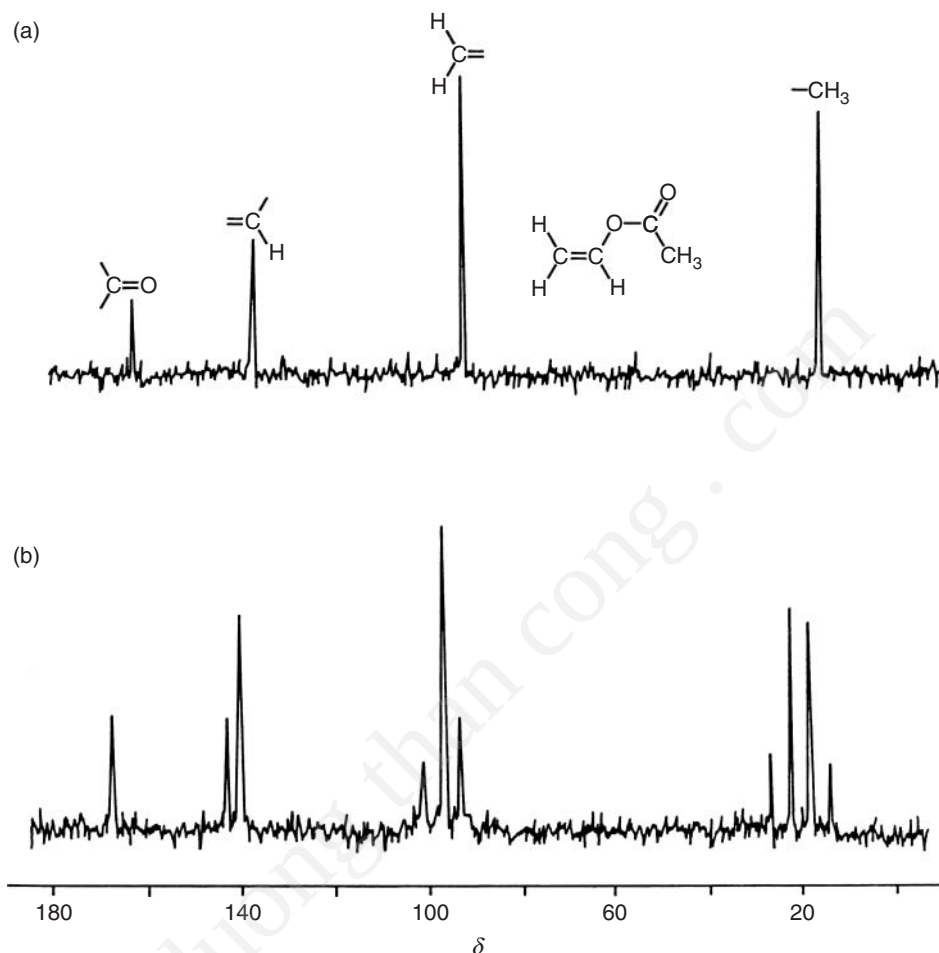


Figure 8.38 Off-resonance ^1H -decoupled ^{13}C -NMR spectrum of vinyl acetate with resonances for the carbonyl-, methine-, methylene-, and methyl carbon at 167.2, 141.8, 96.8, and 20.2 ppm, respectively, relative to the ^{13}C resonance of TMS (not shown): (a) ^1H -decoupled and (b) off-resonance ^1H -decoupled; frequency offset 3 kHz.

References

1. Wehrli, F.W. and Wirthlin, T. (1976) *Interpretation of Carbon-13 NMR Spectra*, Heyden, London, p. 134.
2. Pople, J.A., Schneider, W.G., and Bernstein, H.J. (1959) *High-resolution Nuclear Magnetic Resonance*, McGraw-Hill, New York, p. 205.
3. Claridge, T.D.W. (1999) *High-Resolution NMR Techniques in Organic Chemistry*, Elsevier, Amsterdam, p. 351, 347.
4. Derome, A.E. (1987) *Modern NMR Techniques for Chemistry Research*, Pergamon Press, Oxford, p. 77 ff.

5. Pawliczek, J.B. and Günther, H. (1970) *Tetrahedron*, **26**, 1755.
6. Ernst, R.R. (1966) *J. Chem. Phys.*, **45**, 3845.

Textbooks

- Claridge, T.D.W. (1999) *High-Resolution NMR Techniques in Organic Chemistry*, Elsevier, Amsterdam, 382 pp.
- Harris, R.K. (1986) *Nuclear Magnetic Resonance Spectroscopy*, Longman, Harlow, 250 pp.
- Shaw, D. (1984) *Fourier Transform NMR Spectroscopy*, 2nd Ed., Elsevier, Amsterdam, 304 pp.
- Müllen, K. and Pregosin, P.S. (1976) *Fourier Transform NMR Techniques: A Practical Approach*, Academic Press, London, 149 pp.

Freeman, R. (1987) *A Handbook of Nuclear Magnetic Resonance*, Longman, Harlow, 312 pp.

Slichter, C.P. (1990) *Principles of Magnetic Resonance*, 3rd Ed., Springer-Verlag, Berlin, 397 pp.

Farrar, T.C. and Becker, E.D. (1971) *Pulse and Fourier Transform NMR*, Academic Press, New York, 115 pp.

Review articles

- Traficante, D.D. (1996) Relaxation: An Introduction, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 6, (eds in chief D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester, UK, p. 3988.
- Shaka, A.J. and Keeler, J. (1987) Broadband spin decoupling in isotropic liquids, *Progr. NMR Spectrosc.*, **19**, 47.

9

Two-Dimensional Nuclear Magnetic Resonance Spectroscopy

As already mentioned in the Chapter 1, no other development has influenced magnetic resonance spectroscopy in the last 30 years so profoundly as the concept of two-dimensional (2D) NMR spectroscopy. This technique, which emerged from an idea of the Belgian physicist J. Jeener, has been developed for applications primarily in the laboratories of R.R. Ernst and R. Freeman. Today it forms the basis for a large number of experiments in all branches of nuclear magnetic resonance. It induced not only major improvements for the determination of the important spectral parameters chemical shift and spin–spin coupling but also paved the way for the discovery of completely new facets in the properties of spin systems.

The present chapter describes the idea of 2D NMR and two basic homonuclear 2D experiments: J -resolved or J, δ -spectroscopy and the correlation spectroscopy (COSY) experiment. In Section 9.5, the simplest formalism for the theoretical interpretation of 2D spectroscopy is introduced. Further 2D methods, like nuclear Overhauser spectroscopy (NOESY) or exchange spectroscopy (EXSY) as well as heteronuclear shift correlations, will be treated in Chapters 10 and 11.

9.1

Principles of Two-Dimensional NMR Spectroscopy

The 2D NMR experiment belongs to the area of Fourier transform and pulse spectroscopy. It is basically characterized by three time intervals: preparation, evolution, and detection (Figure 9.1a). In a number of 2D experiments a further interval is added before detection, the so-called mixing time (Figure 9.1b).

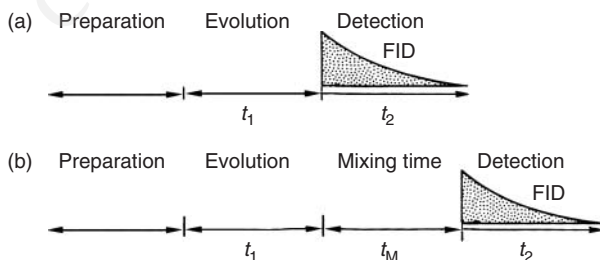


Figure 9.1 (a), (b) Time scales of 2D NMR experiments.

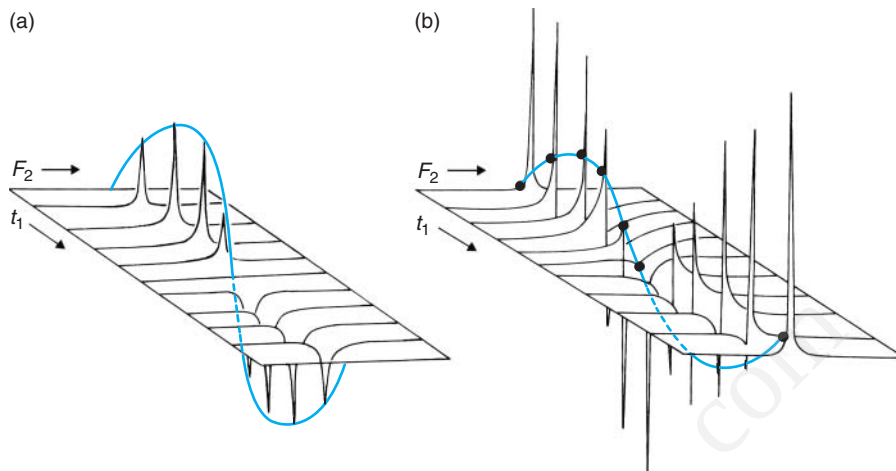


Figure 9.2 Amplitude and phase modulation [(a) and (b), respectively] in 1D spectra after a systematic increase of the evolution time t_1 .

During the preparation time the spin system of interest is prepared for the experiment, for example, by application of decoupler experiments or simply by the generation of transverse magnetization through a 90° pulse. In the evolution time t_1 it then develops under the influence of different factors, such as, for example, Larmor precession or scalar spin–spin coupling, before a signal is detected during the detection time t_2 .

The sequence described in Figure 9.1a does not yet constitute a 2D NMR experiment. Only if in a series of experiments the sequence is repeated with a systematic variation of the evolution time t_1 by adding time increments Δt_1 , and if after the first Fourier transformation of the resulting t_2 signals a number of one-dimensional spectra are obtained in the frequency domain F_2 that show a modulation in amplitude or phase, can a second Fourier transformation be applied. The data of these spectra are then transformed with respect to the time axis t_1 . A frequency axis F_1 results that now contains the frequencies of those mechanisms that have been effective during the evolution time t_1 and that caused the observed modulation of signal amplitude or signal phase (Figure 9.2). If for instance spin–spin coupling was effective during t_1 and Larmor precession during t_2 , F_1 contains coupling constants while the chemical shifts appear on the frequency axis F_2 . Resonance frequencies and spin–spin coupling constants that are a priori indistinguishable in a conventional 1D NMR spectrum can thus be separated and presented on two distinct frequency axes.

Even if the idea of two-dimensional NMR spectroscopy is basically simple, experience tells us that the principles are quite new and, initially, difficult to understand. Therefore, the concise description given above will be supplemented by additional explanations.

Let us state again that a 2D NMR experiment is possible only after a series of n one-dimensional spectra has been measured. Thereby the evolution time

is systematically increased by adding time increments Δt_1 : normally, 32 1D experiments are used as a minimum, but 128, 512 or more single 1D experiments are not uncommon. We shall see later what effect the number of t_1 increments has on the final spectrum.

The experimental data of such a series of 1D experiments are not individually Fourier transformed but rather stored in the computer memory. They yield a data matrix that is characterized by two time axes, t_1 and t_2 . The 2D spectrum is thus a function of two variables, $S(t_1, t_2)$. A first Fourier transformation with respect to t_2 yields $S(t_1, F_2)$. This function must be seen as a series of 1D spectra, the signals of which are modulated with respect to their amplitude or phase (Figure 9.2). There exists a periodical behavior along t_1 characterized by a frequency that can be obtained through a second Fourier transformation with respect to the time axis t_1 . The final 2D spectrum is thus a function of two frequencies variables: $S(F_1, F_2)$. These relations are illustrated in Figure 9.3.

Only the detection time is a real time axis in a 2D experiment, which means that real free induction decay (FID) signals are only detected in t_2 . In contrast, the FID for the Fourier transformation along t_1 is constructed point by point. Therefore, the t_1 increments Δt_1 determine the Nyquist frequency in the F_1 domain. Thus a value of 1 ms for Δt_1 means, for example, that along t_1 frequencies of 1 kHz can be recognized if quadrature detection is used in t_1 . The t_1 increment Δt_1 thus corresponds to the dwell time of the t_1 dimension. Quadrature detection in t_1 can be achieved through certain phase cycles that yield a phase shift of 90° for the receiver signal (see p. 325). Two experiments must then be performed for each t_1 increment.

From our description of two-dimensional NMR spectroscopy one can easily conclude that, normally, long measuring times are required for 2D NMR spectra. This is also because, nearly always, 90° excitation pulses are used. Therefore, after each individual t_1 experiment a relaxation delay is necessary to provide uniform starting conditions. Furthermore, data accumulation has to be used also in 2D NMR experiments to achieve sufficient sensitivity. Finally, the mass of data that has to be mathematically processed is much larger than in the one-dimensional

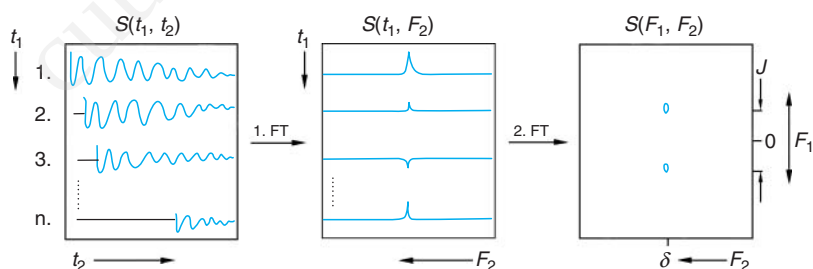


Figure 9.3 Data flow in a 2D NMR experiment: after the first Fourier transformation along t_2 amplitude-modulated signals with a frequency F_2 result; the second Fourier transformation yields the modulation frequency F_1 , the scalar coupling J , and a signal at f_1, f_2 .

experiment. Without modern computers, especially efficient data storage capacities, two-dimensional NMR spectroscopy would not be practicable.

9.1.1

Graphical Presentation of Two-Dimensional NMR Spectra

For the presentation of the results of a two-dimensional NMR experiment several choices are available. The total spectrum can be reproduced either in a sort of perspective diagram (3D or stacked plot) as shown in Figure 9.4a and already known from T_1 experiments (Figure 8.13, p. 248) or as contour diagram as shown in Figure 9.4b. The latter is better suited for data analysis.

Besides the two representations mentioned one can plot the rows or columns of the two-dimensional data matrix $S(F_1, F_2)$ as pseudo-1D spectra. This is especially advisable if signals of small intensity are to be detected that often disappear in the noise of the contour diagram. In addition, projections of the 2D spectrum on the frequency axes F_1 or F_2 are possible. We shall come back to these aspects during discussion of the individual experimental methods. We should mention here, however, that the separation of the real and imaginary part of the spectrum after Fourier transformation that is necessary to derive phase sensitive spectra is

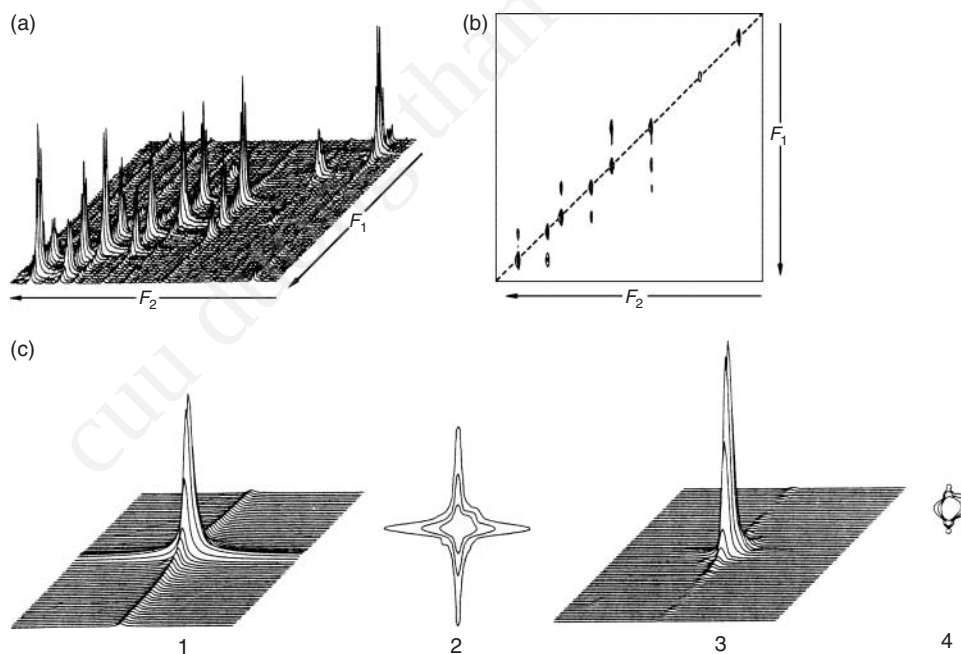


Figure 9.4 (a) 2D NMR spectrum as stacked plot; (b) the same spectrum as a contour plot; (c) stacked plot and contour diagram of the line shape of a 2D NMR singlet in magnitude calculation (1, 2) and after data treatment with a sine function (3, 4).

by no means trivial in 2D NMR spectroscopy. Quite often, therefore, 2D signals are displayed in the so-called *magnitude* or *absolute value* representation that uses the square root of the sum of the squares of real (Re) and imaginary (Im) parts:

$$M = \sqrt{\text{Re}^2 + \text{Im}^2} \quad (9.1)$$

This representation has, however, the disadvantage that the NMR signals are strongly broadened near the baseline in comparison to the Lorentzian signals that result from the real part of the Fourier-transform data. Signals of low intensity that are close to intensive signals are thus often lost. It is therefore important that techniques that allow us to record *phase sensitive* 2D spectra have been introduced and phase sensitive representations of 2D NMR spectra are today generally preferred.

A major practical aspect of 2D NMR spectroscopy is data processing by the application of filter functions or weighting functions that improve the NMR line shape (see also p. 269). Most widely used are sine functions of the form $\sin(\pi t_2/t_{\max})$ or $\sin^2(\pi t_2/t_{\max})$ (sine-bell, sine-bell squared) that have their maximum at $t_2 = t_{\max}/2$. In this way the dispersive parts of the 2D signals are suppressed (Figure 9.4c). A wrong selection of the maxima of such functions can, however, lead to the situation that broad signals are eliminated. This problem can be overcome if functions that have their maximum shifted to smaller values of t_2 (shifted sine bell, shifted sine bell squared) are used. Filter functions are indispensable if magnitude spectra are processed.

9.2

The Spin Echo Experiment in Modern NMR Spectroscopy

Before discussing different techniques of 2D NMR spectroscopy in detail, some aspects of the spin echo experiment, $90_x^\circ \cdots \tau \cdots 180_x^\circ \cdots \tau \cdots \text{FID}$, introduced in Chapter 8, will be discussed. This experiment has emerged as one of the important building blocks of 2D pulse sequences. In connection with our explanations we shall also treat several relations that are of general importance in understanding multiple pulse experiments.

9.2.1

Time-Dependence of Transverse Magnetization

As outlined in Chapter 8, the transverse magnetization $M_{x,y}$ generated in an FT NMR experiment is subject to changes caused by different mechanisms. Because all modern one- and two-dimensional NMR experiments incorporate an evolution time and thus require delayed data detection (Figure 9.1), it is illustrative to study the time-dependence of $M_{x,y}$ in more detail. During the evolution time the magnitude and direction of $M_{x,y}$ are subject to the influence of four different factors:

- 1) transverse relaxation,
- 2) inhomogeneity of the magnetic field B_0 ,
- 3) Larmor precession,
- 4) scalar spin–spin coupling.

Mechanisms (1) and (2) determine the line widths of the NMR signals through the effective transverse relaxation time T_2^* . In this respect, true transverse relaxation leads to an unavoidable signal loss. In practice, however, the inhomogeneity contribution to the effective transverse relaxation rate is by far the most important factor. This effect can largely be eliminated through the spin echo experiment, as discussed on p. 249. Spin echo spectra are therefore distinguished by narrow lines, since the influence of field inhomogeneity has been eliminated.

9.2.2

Chemical Shifts and Spin–Spin Coupling Constants and the Spin Echo Experiment

Transverse relaxation and field inhomogeneity, factors (1) and (2) of our list above, can now be excluded from the following discussions of individual pulse sequences because they are not related to the spin physics that govern these experiments. Larmor precession and scalar spin–spin coupling of the nuclei involved are the parameters of interest.

After excitation of the spins, the transverse magnetization components that correspond to the individual signals of different Larmor frequency in the NMR spectrum of interest are separated by Larmor precession (factor 3). Delayed data detection then causes the phase error already discussed (p. 268). If time intervals of the order of milliseconds are involved, as in many 2D experiments, the spin echo experiment is used for phase correction. Generally, with this technique all effects that arise from different Larmor frequencies can be refocused. Figure 9.5 illustrates this application of the spin echo experiment with a simple example.

On the other hand, transverse magnetization is in many cases affected by scalar spin–spin coupling with neighboring nuclei of the same or of a different nuclide (homo- or heteronuclear spin–spin coupling). After excitation a separation of transverse magnetization into magnetization vectors sets in that corresponds to the individual components of spin multiplets (doublets, triplets, etc.). In a coordinate system that rotates with the Larmor frequency of the nucleus in question the situation for a doublet or triplet is illustrated in Figure 9.6a,b, respectively. Within the X approximation, in the case of the doublet the rotation of the vector $A1$ is induced by the X-nucleus with α -spin, and that of vector $A2$ by the X-nucleus with β -spin.

If we turn our attention to the spin echo experiment for scalar-coupled spin systems, in the simplest case of an AX system different situations can be envisaged (Figure 9.7, p. 288). For a *homonuclear* AX spin system the 180° pulse after the interval τ is not selective – it affects the A- as well as the X-nucleus. The A-vectors are rotated around the x -axis and at the same time their sense of rotation with respect to the z -axis is inverted, because the 180° pulse interchanges the spin states of the X-nucleus. Therefore, after the time 2τ refocusing is not observed

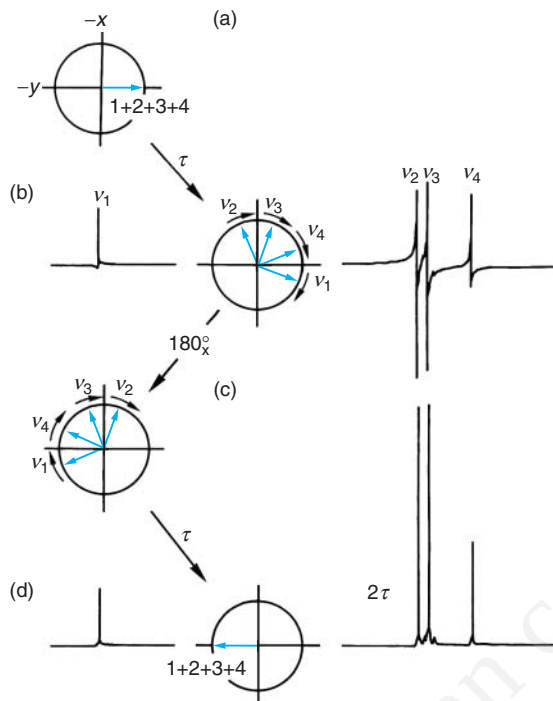


Figure 9.5 Phase correction by a spin echo experiment ($90^\circ_x \cdots \tau \cdots 180^\circ_x \cdots \tau$ —FID) of four resonance lines of different Larmor frequencies: (a) situation after the excitation pulse along $+x$; (b) after a time τ , the individual components of the macroscopic magnetization have progressed differently in their precession around the field axis because of their different Larmor

frequencies; data detection yields a spectrum with frequency-dependent phase errors; (c) a 180°_x pulse at τ inverts the vectors and leads to a new superposition after the time 2τ , the *spin echo*. The phase errors in the recorded spectrum disappear (d) (to observe an absorption spectrum at $+y$, an additional phase correction of 180° was applied).

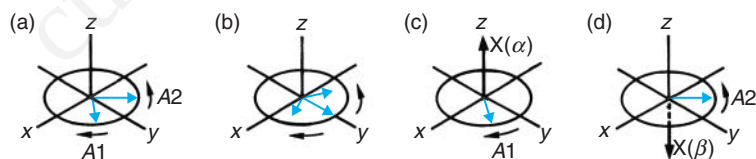


Figure 9.6 Effect of scalar spin–spin coupling J_{AX} on the transverse magnetization of the A-nucleus in the rotating coordinate system with $\omega_1 = \omega_A$, that is, under “on-resonance” conditions for the A-nucleus: (a) AX system; the effective Larmor frequencies of the vectors A_1

and A_2 amount to $+J_{AX}/2$ and $-J_{AX}/2$, respectively; (b) AX_2 system; the relative frequencies of the vectors are $+J_{AX}$ and $-J_{AX}$ for the outer lines of the A-triplet, the center line stays on the y -axis; (c) rotation of A_1 around the $X(\alpha)$ -spin; (d) rotation of A_2 around the $X(\beta)$ -spin.

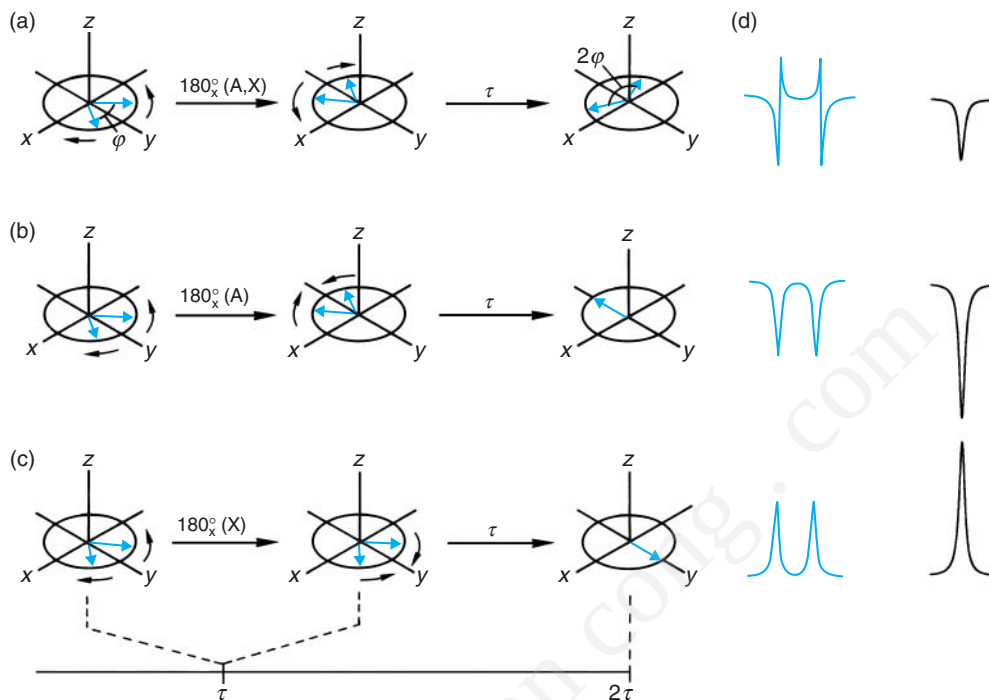


Figure 9.7 Spin echo experiments with an AX system; the vector diagram is shown for the A-nucleus after the first τ delay; each experiment starts with a 90° pulse at $\tau = 0$ (not shown in the diagram); (a) homonuclear case; (b)

heteronuclear case with a 180°(A) pulse; (c) heteronuclear case with a 180°(X) pulse; (d) spin echo signals without (left-hand side) and with (right-hand side) X-decoupling.

(Figure 9.7a). Instead, both doublet components have a phase difference that depends on the angle φ and, therefore, on the time τ .

In the *heteronuclear* case two variants are possible. If the A-nucleus is observed and the 180° pulse is applied in the A-region, refocusing of the A-vectors occurs on the $-\gamma$ -axis after a time 2τ (Figure 9.7b). For a 180° pulse in the X-region, however, Figure 9.7c is valid: the spin inversion for the X-nucleus interchanges the sense of rotation for the components of the A-doublet and refocusing after time 2τ is observed on the $+\gamma$ -axis. Finally, as a third alternative – not shown in the figure – an experiment can be performed in the heteronuclear case where an A- and an X-pulse are applied simultaneously. The situation is then completely similar to the homonuclear case, as shown in Figure 9.7a.

If a detector on the $+\gamma$ -axis is switched on at time 2τ , the spin echo signal of the A-nucleus is a doublet with anti-phase dispersion character in case (a). For case (b) we obtain an in-phase doublet with emission, and in case (c) we have an in-phase doublet with absorption character. If X-decoupling is applied during A-detection, (a) yields a signal with an amplitude that depends on the angle φ that is reached on the

time τ ; (b) and (c) yield singlets in emission or absorption, respectively (Figure 9.7d).

Exercise 9.1

Draw the detected signal for the homonuclear spin echo experiment without and with X-decoupling, as shown in Figure 9.7a, for angles $\varphi = 90^\circ$, 180° , and 270° .

Exercise 9.2

Derive in analogy to Figure 9.7 diagrams for spin echo experiments that use a 180_y° pulse.

Exercise 9.3

Redraw the diagrams shown in Figure 9.7 for the “off-resonance” situation with $\nu(A1) > \nu(A2) > \nu_0$.

9.3

Homonuclear Two-Dimensional Spin Echo Spectroscopy: Separation of the Parameters J and δ for Proton NMR Spectra

The first two-dimensional experiment that will be discussed in more detail is a *homonuclear* experiment that provides us with the possibility to observe two of the most important parameters of NMR spectra, namely, resonance frequencies δ and scalar coupling constants J , separately on two distinct frequency axes. In the resulting 2D NMR spectrum the coupling appears only in the F_1 domain, while the chemical shift is confined to the F_2 domain. This result is achieved with the ^1H pulse sequence [Eq. (9.2)]:

$$90_x^\circ \text{-----} \frac{t_1}{2} \text{-----} 180_x^\circ \text{-----} \frac{t_1}{2} \text{-----} \text{FID } (t_2) \quad (9.2)$$

which is illustrated in graphical form in Figure 9.8a (p. 290). It starts with signal excitation by a 90_x° pulse, followed by the evolution time t_1 that is divided by a 180_x° pulse. Finally, the signal is detected in t_2 .

For a simple ^1H , ^1H two-spin system of the AX-type with resonance frequencies ν_A and ν_X and the scalar coupling J_{AX} it is possible to describe this experiment within the framework of the classical Bloch vector picture already used in Chapter 8 to illustrate the effect of RF pulses on the macroscopic magnetization $\mathbf{M}$ (Figure 9.8b). However, if compared to the simple FT NMR experiment the important new aspect is the evolution time t_1 . During this time interval, transverse magnetization is affected by the mechanisms discussed in Section 9.2.2.

The pulse sequence described by Eq. (9.2) is nothing else than a spin echo experiment as shown in Figure 9.7a, and the rules developed above apply: defocusing of the transverse magnetization by field inhomogeneity and the effects of chemical

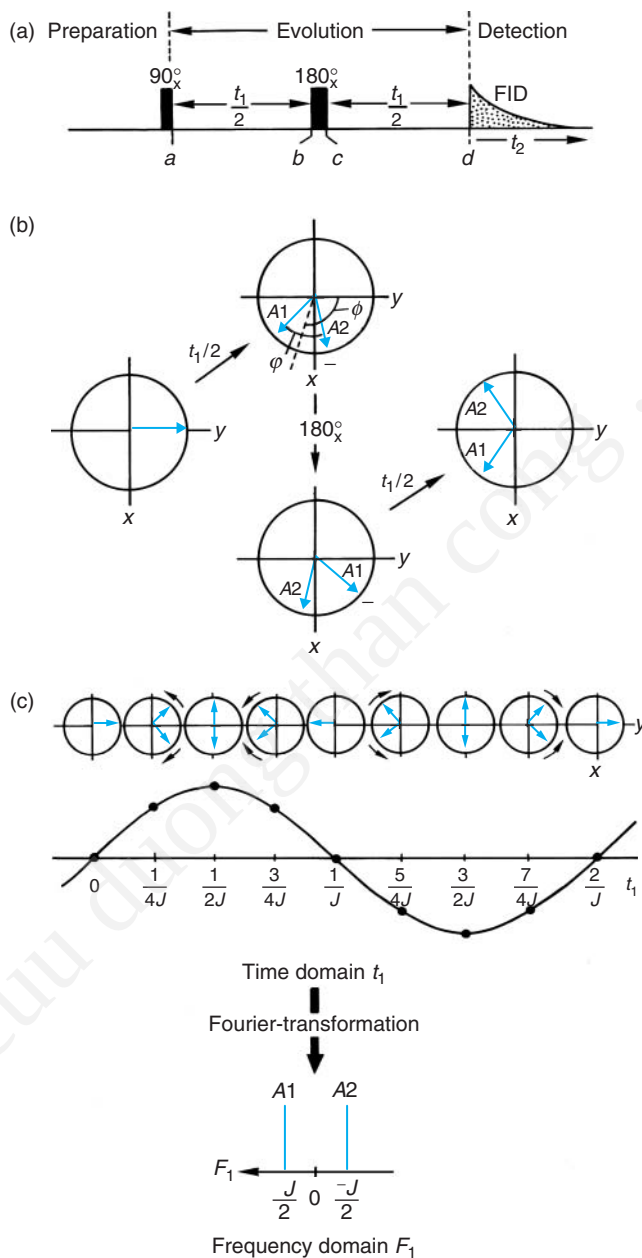


Figure 9.8 (a) Pulse sequence for homonuclear two-dimensional spin echo spectroscopy (J, δ or J -resolved spectroscopy). (b) Vector diagram for the A nucleus of an AX system: after excitation transverse magnetization develops under the influence of Larmor frequencies and spin–spin coupling. The vectors **A1** and **A2** of the A-doublet move clockwise around the z-axis (Larmor precession, angle ϕ) and fan out (spin–spin coupling, effective Larmor frequencies $\nu(\mathbf{A1}) > \nu(\mathbf{A2})$, symbolized by + and –, angle φ). The non-selective 180°_x pulse rotates the vectors around the x-axis and interchanges the spin states of the X-nucleus and as a consequence the effective Larmor frequencies for **A1** and **A2**. In the second half of the evolution time the effects of Larmor precession and of field inhomogeneity (not shown here) are eliminated and **A1** and **A2** are symmetrically oriented with respect to the y-axis. They show a phase error of $\pm\Delta\varphi$, the magnitude of which is t_1 -dependent. (c) Phase error $\Delta\varphi$ of one component of the A-doublet relative to the y-axis during the evolution time t_1 ; please note that the angular frequency of each vector is $J/2$; $2/J$ is the time a vector needs to return again on the +y-axis. The second Fourier transformation yields the frequencies $\pm J/2$.

shifts are eliminated; the effect of spin–spin coupling, however, remains. Thus, during the time interval t_1 – if we neglect true transverse relaxation – the spin system is subject only to the influence of scalar spin–spin coupling. For the vectors **A1** and **A2** of the A-doublet a phase error results at the end of the evolution time that is dependent on t_1 . The signals are then measured in a series of experiments with different t_1 values. They are thus phase modulated. The modulation frequency for each of the two vectors is just half the frequency of the spin–spin coupling, $J_{AX}/2$, and can be determined by a second Fourier transformation of the data in the frequency domain F_1 (Figure 9.8c).

We now turn to the detection time t_2 and the frequency domain F_2 of the 2D spectrum. The receiver signal decays as usual with a time constant T_2^* . It contains, however, the resonance frequencies *and* the frequencies of the spin–spin couplings, because during t_2 both are effective. Therefore, our experiment so far did not eliminate the frequencies of the scalar coupling constants from the F_2 domain. After the second Fourier transformation the two-dimensional data matrix thus looks like the contour diagram shown in Figure 9.9a (p. 292): the spin multiplets are aligned along diagonals that are inclined with respect to F_2 by 45° . The coupling information from F_2 is, however, eliminated in a very simple manner. We just tilt the data matrix along the F_2 axis (Figure 9.9b). Projection of the 2D signals on the frequency axes F_1 and F_2 now yields spectra that contain only coupling or chemical shift information, respectively, and the separation of the two parameters J and δ is complete (Figure 9.9c,d).

9.3.1

Applications of Homonuclear $^1\text{H}, J, \delta$ -Spectroscopy

The NMR experiment described above is known as *J-resolved* or *J, δ -spectroscopy*. Its main field of application is in the analysis of crowded spectra, where spin multiplets of different protons strongly overlap. An example is given in Figure 9.10 (p. 293) with a spectrum of a mixture of *n*-butyl bromide and *n*-butyl iodide. In the 1D spectrum of the mixture only the triplets of the CH_2 groups adjacent to the

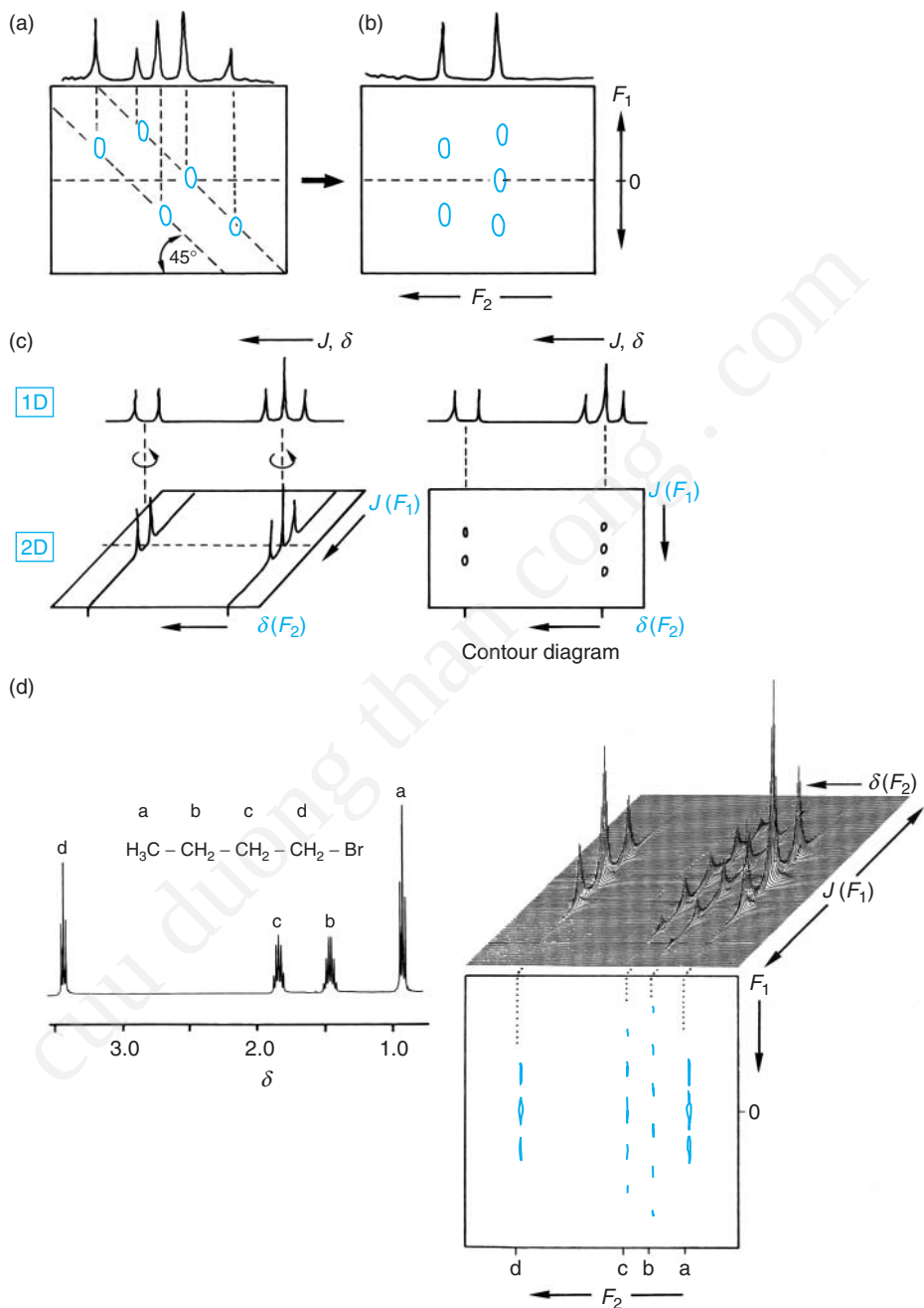


Figure 9.9 Data treatment during homonuclear J, δ spectroscopy; (a) data matrix after twofold Fourier transformation; (b) data matrix after tilting along F_2 ; (c) comparison of a conventional 1D NMR spectrum and a 2D J, δ -spectrum with separate frequency axes for chemical shifts and spin–spin coupling constants; (d) 400 MHz ^1H -NMR spectra of *n*-butyl bromide: 1D spectrum and 2D J, δ -spectrum as stacked and as contour plot; recording parameters: F_2/t_2 : sweep width 1602.5 Hz, 4K data points, 32 scans, relaxation delay 11 s; F_1/t_1 : $\Delta t_1/2 = 10 \text{ ms} \hat{=} 25 \text{ Hz}$ sweep width, 64 experiments $\hat{=} 64$ data points, zero-filling to 256 data points yielded a digital resolution of 0.2 Hz per Pt; total measuring time 8 h.

halogen atoms are resolved at 400 MHz. In contrast, the contour diagram of the 2D spectrum shows all multiplets separated, even the triplets of the CH_3 groups, and the F_1 traces of the 2D data matrix yield well-resolved line patterns ready for analysis. An interesting aspect of 2D J, δ -spectra is the possibility of producing “ ^1H -decoupled” ^1H NMR spectra by F_2 axes projections of the data (Figure 9.10b). This allows us to determine the chemical shifts of all ^1H resonances directly without multiplet analysis.

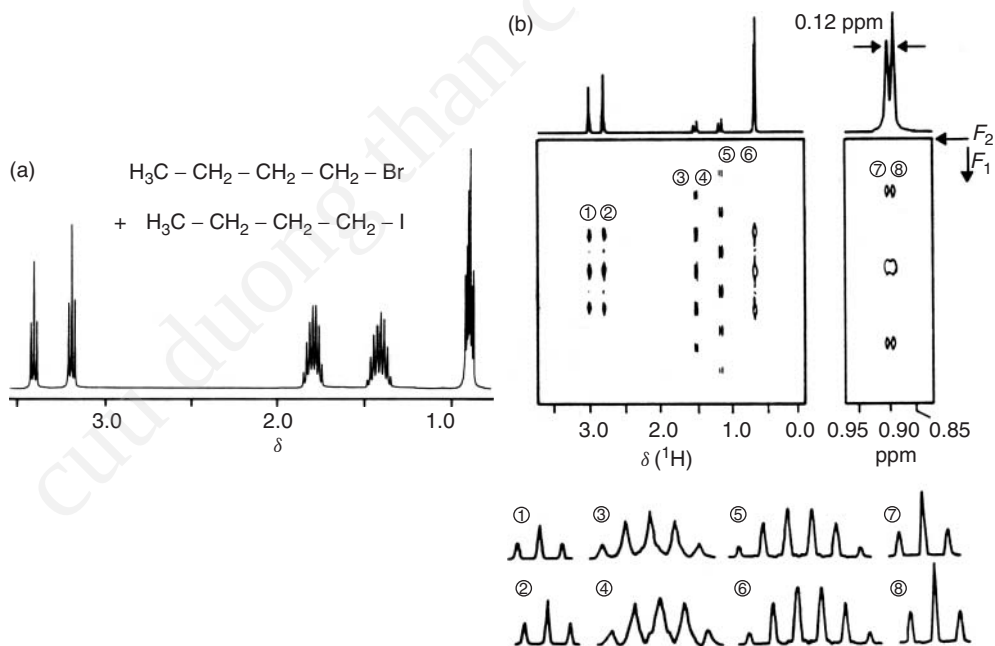


Figure 9.10 (a) 400 MHz 1D ^1H NMR spectrum of a mixture of *n*-butyl bromide and *n*-butyl iodide; (b) above, contour diagram of the 2D- J, δ -spectrum with F_2 projection as “ ^1H -decoupled” ^1H spectrum that shows only

singlets at the chemical shift values; below, F_1 cross-sections of the individual multiplets (methyl signals are shown also on an expanded scale [1]).

The most important applications of homonuclear J, δ -spectroscopy can be expected where strong multiplet overlap is observed for weakly coupled spin systems. This situation is met quite frequently with natural products or biomolecules that contain alicyclic partial structures with a large number of methylene groups. Sometimes severe spectral overlap is also met for stereoisomers, where the chemical shifts may differ only slightly. Besides (*E,Z*)-isomers, mixtures of diastereomers, as well as racemic or partially resolved optically active samples in chiral solvents (formation of diastereomeric solvation complexes), belong to this group. ^1H J, δ -spectroscopy can thus be a valuable analytical tool in the field of stereoselective synthesis.

Coupling constants to heteronuclei like ^{19}F or ^{31}P are treated in 2D ^1H J, δ -spectra like resonance frequencies, because the 180° ^1H pulse does not affect the spin states of these nuclei. The effect of such couplings on transverse proton magnetization is, therefore, eliminated at the end of the t_1 interval (see Figure 9.7b). The line splitting due to $^1\text{H}, \text{X}$ couplings then appears on the F_2 axis, as shown in the spectrum of Figure 9.11c. This example also demonstrates the advantage of spin echo spectroscopy: small line widths through elimination of field inhomogeneity. Singlet signals of solvents are not modulated by coupling and in the 2D J, δ -experiment they appear on the shift axis with the coordinates $F_1 = 0, F_2$. Using special techniques, like signal saturation in the preparation time, they can be eliminated.

9.3.2

Practical Aspects of ^1H J, δ -Spectroscopy

Because $^1\text{H}, ^1\text{H}$ spin–spin coupling constants are generally smaller than 15 Hz, the width of spin multiplets seldom exceeds 30 Hz. A spectral window of 50 ± 25 Hz is, therefore, in most cases sufficient for the F_1 domain in J, δ -spectroscopy. If quadrature detection is used, the Nyquist frequency in F_1 then amounts to 25 Hz and the dwell time, that is the t_1 increment, is 20 ms. With 64 t_1 experiments a $t_1(\text{max})$ value of 1.28 s results, and the digital resolution in F_1 is 0.78 Hz pt. It can be improved by zero-filling before Fourier transformation. An improvement through a larger number of t_1 increments is not practicable, because the resulting increase in evolution time would strongly diminish the signal intensity in t_2 due to transverse relaxation effects. As the data in Figures 9.9 and 9.11 demonstrate, the long relaxation delay contributes strongly to the overall experimental time of J, δ -spectroscopy.

Similarly, if high resolution in F_1 is needed to resolve small couplings, the increased number of t_1 increments leads to long measuring times.

The signals originally detected in homonuclear J, δ -spectroscopy with the coordinates $F_2 \pm J/2$ and $F_1 \pm J/2$ are transformed by the data treatment discussed above into signals at $F_2, F_1 \pm J/2$, and the $F_1 = 0$ axis divides the spectrum. Zero-filling (see above) and the use of filter functions lead to improved line shapes. Several artifacts in 2D J, δ -spectra that are a consequence of imperfect pulse lengths

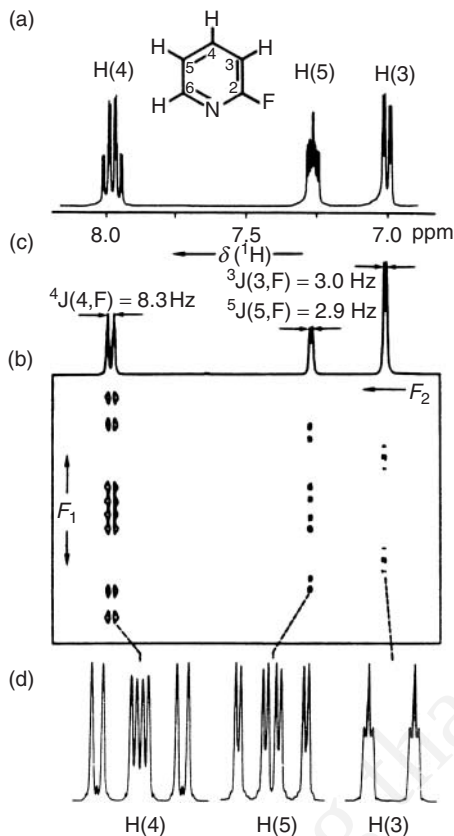


Figure 9.11 Homonuclear J -resolved 2D ^1H NMR experiment for H(3), H(4), and H(5) in 2-fluoropyridine (1.4 M in acetone- d_6): (a) 1D ^1H NMR spectrum; (b) 2D contour plot; (c) F_2 projection; (d) traces parallel to F_1 . The F_2 frequency axis contains the ^1H , ^{19}F -coupling constants, while the F_1 -axis shows only the ^1H , ^1H couplings. The traces along F_1 show ^{19}F -decoupled ^1H multiplets, while the F_2 projection shows the “ ^1H -decoupled” ^1H

spectrum that now displays the ^1H , ^{19}F couplings. The following experimental data were used: $\Delta t_1 = 26.4$ ms (this corresponds to $\text{SW}_1 = 37.9$ Hz); $\text{SW}_2 = 606$ Hz; data matrix $F_1 \times F_2 = 128 \times 1\text{K}$; sine filter functions in F_1 and F_2 ; 16 scans for each t_1 experiment; 10 s relaxation delay; total measuring time 7.2 h. The ^1H , ^1H coupling constants are $J(3,4) = 8.26$, $J(3,5) = 0.76$, $J(3,6) = 0.76$, $J(4,5) = 7.23$, $J(4,6) = 2.02$, and $J(4,6) = 4.92$ Hz [1].

(phantom or ghost signals) can be eliminated by the phase cycle EXORCYCLE that we will not, however, discuss here.

The greatest disadvantage of J , δ -spectroscopy must be seen in the relatively long measuring times, which are usually larger than those of other 2D NMR methods. Furthermore, strongly coupled spin systems show several artifacts that prevent a simple analysis of the spin multiplets. Today, 2D J , δ -spectroscopy is thus used less frequently.

Aside from the *homonuclear* J -resolved spectroscopy we also have *heteronuclear* J -resolved spectroscopy. This technique is useful for the measurements of, for example, ^{13}C , ^1H coupling constants and will be discussed briefly in Section 10.4 of Chapter 10 and later again in Chapter 11 (p. 401).

9.4

The COSY Experiment – Two-Dimensional ^1H , ^1H Shift Correlations

We now return to the COSY experiment, which was briefly introduced in Chapter 3 (p. 60 and Figure 3.25, p. 61). It is also known as the *Jeener experiment* after its inventor, the Belgian physicist J. Jeener, and is certainly one of the most important measuring techniques of two-dimensional ^1H NMR spectroscopy, but is also of vital interest for the NMR of other abundant nuclei like boron-11, fluorine-19, or phosphorus-31.

We recall that the COSY pulse sequence contains only two 90°_x pulses ($P1$ and $P2$), separated by the evolution time t_1 ; after the second 90°_x pulse, signal detection occurs by the receiver (R) in the time interval t_2 (Figure 9.12).

Here, both frequency axes contain chemical shifts and so-called *cross peaks* indicate which nuclei are spin–spin coupled. The experiment is based on scalar spin–spin coupling, as is J, δ -spectroscopy discussed in the preceding section. The determination of spin–spin coupling constants, however, is usually not the major object of COSY spectroscopy – it is primarily used to obtain structural information via the spin connectivities revealed by the cross peaks. In this sense, the COSY experiment is the two-dimensional equivalent of the one-dimensional selective spin–spin decoupling experiment. The exact measurement of coupling constants via COSY spectra is not trivial (see below) and more advanced versions of the basic experiment are necessary for this purpose. We come back to this point in due course.

As was shown in Figure 3.25 (p. 61), the 2D spectrum for an AX-system shows *diagonal signals*, centered at coordinates $F_1 = F_2 = \nu_A$ and $F_1 = F_2 = \nu_X$, as well as off-diagonal signals, the so-called *cross peaks*, centered at $F_1 = \nu_A$, $F_2 = \nu_X$ and $F_1 = \nu_X$, $F_2 = \nu_A$. The cross peaks correlate the chemical shifts ν_A and ν_X and indicate scalar coupling between the A and the X nucleus. This leads in more complicated cases to a direct assignment of adjacent protons and yields important information about molecular structure, as shown in Figure 9.13 for *o*-nitroaniline. Since in a COSY spectrum chemical shifts are measured in F_1 and F_2 , these spectra can be called δ, δ -spectra, in analogy to the classification of J -resolved spectra as J, δ -spectra.

Besides the Larmor frequencies the frequency axes F_1 and F_2 of a COSY spectrum also contain the frequencies of the homonuclear scalar spin–spin interactions

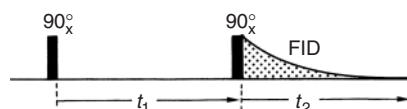


Figure 9.12 Pulse sequence of the COSY experiment: $P1$, t_1 , $P2$, t_2 (FID).

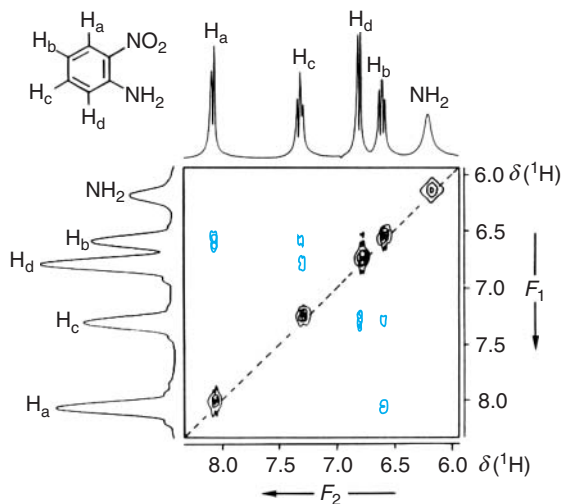


Figure 9.13 COSY spectrum of *o*-nitroaniline measured with the pulse sequence $[90^\circ_x \cdots t_1 \cdots 90^\circ_x, t_2 \text{ (FID)}]$ with cross peaks for vicinal neighbors and projections on both frequency axes; δ values in parts per million. The NH_2 resonance shows no cross peaks. As mentioned below, the spectral resolution in F_1 and F_2 differs; measurement time 2 h [2].

because during the evolution time as well as the detection time both parameters, the chemical shifts and scalar couplings, operate. The spectral resolution in both frequency domains, however, is not necessarily the same, because in F_1 it depends on the number of t_1 increments used, and is therefore limited (cf. p. 283). Under conditions of high resolution a fine structure is observed for the diagonal as well as for the cross peaks of a COSY spectrum from which scalar spin–spin coupling constants can be extracted (Section 9.4.1). The intensity distribution within the cross peaks, however, follows rules that differ from those that govern the intensities of the multiplets in 1D spectra. Furthermore, in the case of crowded spectra, signal overlap can lead to the elimination of cross peak components. The assignment of line splittings to certain spin–spin coupling constants in more complex 2D spectra, therefore, is by no means trivial and it is not surprising that for most practical applications the structural information that comes from the correlation of chemical shifts is by far the most important aspect. This is convincingly shown in Figure 9.14 (p. 298) with the assignment of the protons of an [18]annulene.

A correct interpretation of the COSY pulse sequence on the basis of the Bloch vector model is not feasible and the systematic development of the spin physics behind this experiment must be postponed until discussion of the basic theory in Section 9.5. However, with a simple, qualitative picture the origin of the diagonal and the cross peaks in a 2D COSY spectrum can be rationalized. For this purpose let us first look at the singlet signal of a nucleus A that is not spin–spin coupled. The first 90° pulse of the COSY sequence produces transverse A magnetization $\mathbf{M}(A)$ that rotates around the z -axis. The second 90° pulse moves the y -part of $\mathbf{M}(A)$ into the negative

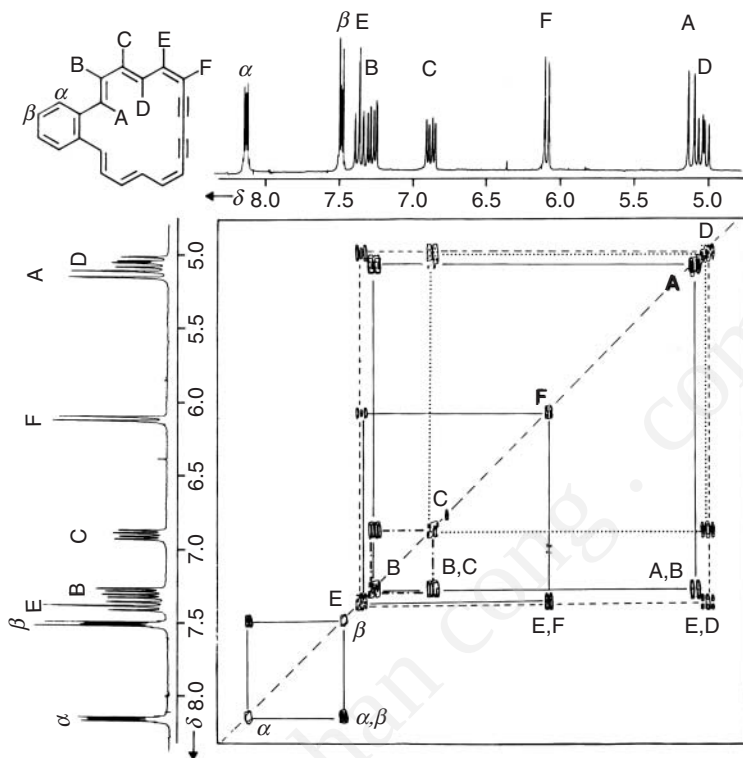


Figure 9.14 $^1\text{H}, ^1\text{H}$ COSY spectrum of 9,11-bisdehydrobenzo[18]annulene; measuring time 4 h; only cross peaks based on vicinal $^1\text{H}, ^1\text{H}$ -coupling constants were detected [3].

z direction, while the x -part remains in the x,y plane for detection. The intensity of the detected signal depends on the orientation of the vector $\mathbf{M}(A)$ at the end of the evolution time, which is determined by the Larmor frequency ν_A . The signal amplitude is thus modulated with this frequency during t_1 and double Fourier transformation yields in both dimensions the frequency ν_A , which is a diagonal signal.

Exercise 9.4

Illustrate the situation discussed above in graphical form (because scalar coupling is absent, Bloch vector pictures can be used).

In the presence of spin–spin coupling the second 90° pulse not only affects transverse magnetization but also leads to population changes for the various transitions in the spin system. In this way magnetization is exchanged between all nuclei that are mutually coupled and their signals are amplitude-modulated in a series of t_1 experiments by the frequencies of the neighboring nuclei. This mechanism, which cannot be represented by classical vector diagrams, leads to the cross peaks of the 2D spectrum at ν_i, ν_j and ν_j, ν_i .

In comparing the COSY experiment with the one-dimensional decoupling experiments discussed in Chapter 3, we note that 2D spectroscopy yields the complete information about coupled nuclei in the spectrum of interest and the spectroscopist does not need to decide which resonance should be irradiated by the B_2 field of the decoupler. The two-dimensional method is thus superior to the 1D technique and is indispensable, not only for complicated spectra but also for routine applications. We must point out, however, that with the standard COSY experiment generally only cross peaks that arise from coupling constants that are larger than about 3 Hz are observed. To detect cross peaks that are due to long-range couplings, the COSY sequence has to be modified as described in Section 9.4.3. Routine ^1H , ^1H COSY spectra are thus dominated by geminal and vicinal coupling constants. Furthermore, with regard to the time of the experiment, a 1D decoupling experiment might be preferable if only one or two connectivities have to be checked.

Practical applications of COSY experiments are further illustrated in Figure 9.15. It shows the multiplets in the spectrum of a mixture of *n*-butyl bromide and *n*-butyl iodide, already discussed in Section 9.3.1, and their assignment by COSY

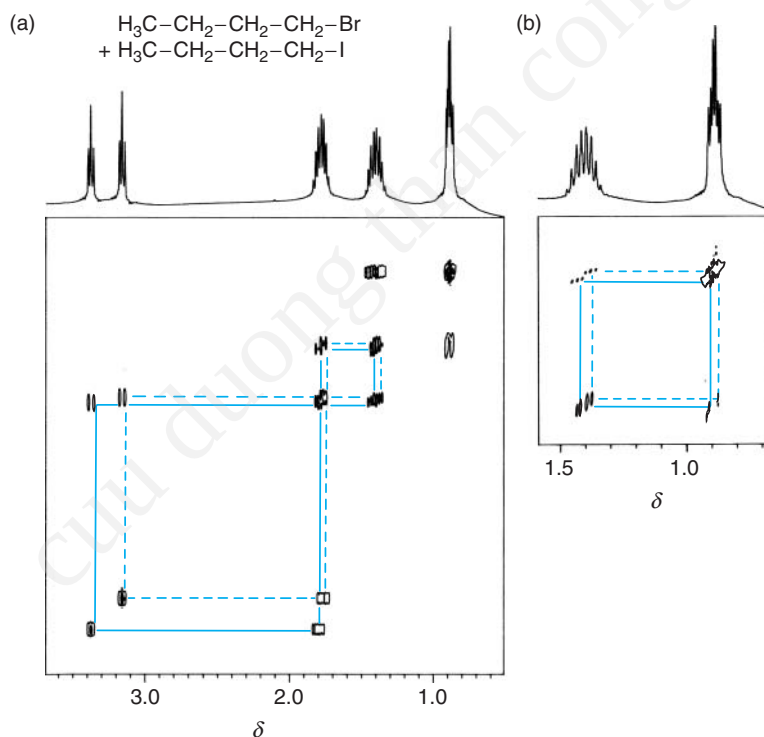


Figure 9.15 (a) 400 MHz ^1H , ^1H COSY spectrum of a mixture of *n*-butyl bromide and *n*-butyl iodide (about 1 : 1, see Figure 9.10); the sweep width was 3.18 ppm; 1K data points in F_2 ; 128 t_1 -experiments, measuring time 2.5 h; data treatment with sine functions in both dimensions; (b) enlarged low-frequency section without data treatment.

spectroscopy. This information is not available from the J, δ -spectrum in Figure 9.10. It is found that the low-frequency as well as the high-frequency components of the overlapping multiplets are correlated by cross peaks. Owing to low digital resolution a decision in the case of the methyl group signals, where the chemical shift difference amounts to only 0.12 ppm or 48 Hz, requires an enlarged spectrum (Figure 9.15b). Since the COSY experiment only yields relative assignments, the absolute assignment must be based on the known shift data for alkyl halides. According to this information the low-frequency signals belong to *n*-butyl iodide. Again, only cross peaks based on vicinal $^1\text{H}, ^1\text{H}$ -coupling constants were detected.

9.4.1

Some Experimental Aspects of 2D-COSY Spectroscopy

In contrast to J, δ -spectroscopy, a considerably larger spectral window in the F_1 -dimension must be chosen in δ, δ -spectroscopy, because the sweep width in F_1 is now determined by the chemical shift scale of a nucleus and not by the width of a spin multiplet. Since for a correlation experiment lower resolution can be tolerated and the spectra are often processed in the absolute value mode, 128 or 256 t_1 increments suffice in most cases for the detection of cross peaks. As a consequence, the digital resolution in a COSY spectrum is normally lower in F_1 than in F_2 (cf. Figure 9.13).

The aspect of digital resolution is more critical if scalar coupling constants are to be determined from the fine structure of the cross peaks. It is then necessary to use *phase-sensitive* detection. For a simple AX-system, Figure 9.16 shows the result of a COSY experiment that was processed in the phase-sensitive mode. All signals appear on both frequency axes. The cross peaks show four lines arranged in a quartet and separated by $J(A, X)$. In the case of an additional nucleus as in an AMX system, each line would again split into four peaks by the additional couplings $J(A, X)$ and $J(M, X)$ with the result of 16 lines. One can easily imagine that cross peaks in situations where a manifold of couplings is active are difficult, if not impossible, to interpret. In addition, different phase behavior for cross peaks and diagonal peaks is found: cross peaks are detected partly in absorption and partly in emission while diagonal peaks are detected in dispersion. In the case of low digital resolution, cross peaks can thus be partly or completely eliminated.

As already mentioned, problems related to the signal phase present difficulties in 2D NMR spectroscopy, because double Fourier transformation in principle produces four components for the frequency function $S(F_1, F_2)$: $S(\text{real}, \text{real})$, $S(\text{imaginary}, \text{imaginary})$, $S(\text{real}, \text{imaginary})$, and $S(\text{imaginary}, \text{real})$. Their separation is obviously more complicated than the separation of real and imaginary part in 1D NMR. The same is true for quadrature detection, which presents no problem for the time domain t_2 but is principally more difficult in the t_1 domain, where it is impossible to measure simultaneously two signals. Here, several tricks must be used that will be looked at again in Section 9.6.1 after we have introduced further details of the COSY experiment. For now we just note that two procedures – developed independently by D. J. States, R. A. Haberkorn, and

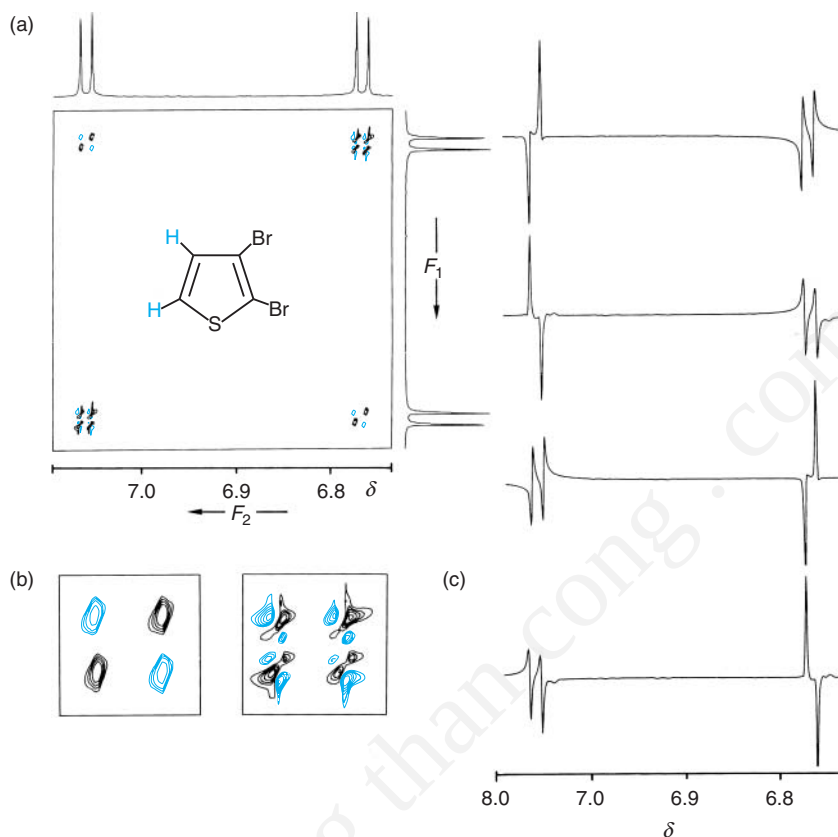


Figure 9.16 Phase-sensitive COSY spectrum of the AX-system of 2,3-dibromothiophene ($J = 5.8$ Hz) with complete resolution of all signals: (a) total spectrum; (b) enlargement of cross and diagonal peaks; (c) traces through the two-dimensional data matrix parallel to F_2 .

D. J. Ruben (we use the acronym SHR) and by D. Marion and K. Wüthrich (known by the acronym TPPI, *time proportional phase increment*) – yield pure signal phases. They should be used if an analysis of the cross peak fine structure is desirable. More recent developments, however, based on field gradients (cf. Section 9.7) are even more attractive, because they achieve quadrature detection within less experimental time.

A simple relation between cross peak intensity and the magnitude of the scalar spin–spin coupling involved does not exist. As can be shown theoretically (see p. 319), cross peaks develop according to:

$$S(\nu_A, \nu_X) \propto \sin(\pi J t_1) \sin(\pi J t_2) \quad (9.3)$$

They can be enhanced by filter functions that have a maximum after the interval $1/2J$. This procedure not only yields an intensity increase, as compared to the intensity of the diagonal peaks, but also allows, within certain limits, a selection

with respect to the magnitude of J . Sometimes, cross peaks can be identified only after careful examination of the 2D spectrum with contour diagrams at various intensity levels. For a detailed analysis of COSY spectra cross sections through the 2D data matrix parallel to both frequency axes are very useful. They often yield more reliable information than the contour plots, because in the resulting pseudo-1D spectra cross peaks can be distinguished more easily from the noise. The following factors can be responsible for failures to detect cross peaks and should be kept in mind: small coupling constants, cross peak elimination because of low digital resolution, and inadequate filter functions or acquisition times that are too short with respect to the time development of cross peak magnetization.

9.4.2

Artifacts in COSY Spectra

Artifacts in 2D COSY spectra are the so-called *axial peaks* that appear parallel to the F_2 dimension at $F_1 = 0$ (Figure 9.17a). They result from longitudinal relaxation during the evolution time. The z -magnetization that is generated in this way is transformed into transverse magnetization by the second 90° pulse of the COSY sequence. This magnetization is not amplitude modulated and after Fourier transformation appears at $F_1 = 0$. Using a simple phase cycle by alternating the phase of the second 90° pulse (P_2), they can be eliminated. Together with the CYCLOPS cycle for quadrature detection in t_2 (see p. 266), the simplest phase cycle for the COSY experiment (P_1 , P_2 , R) thus amounts to: (000) (020) (111) (131) (222) (202) (333) (313).¹⁾

Exercise 9.5

Draw vector pictures to explain the origin of axial peaks.

2D COSY spectra very often suffer from the phenomenon of t_1 noise. Various instrumental instabilities during the measurement (e.g., unstable pulse power or field/frequency lock) cause during a series of t_1 -experiments a statistical, noise-like modulation of the 2D signals. This leads to noise that extends parallel to F_1 at the frequency of the F_2 signals (Figure 9.17a). The intensity of t_1 -noise is proportional to the intensity of the respective 1D signal and, therefore, is particularly large in the case of solvent peaks. By careful adjustment of all instrumental parameters these artifacts can be minimized. Elimination is possible by *symmetrization*, a software operation with the 2D data matrix that takes advantage of the symmetry of the COSY spectrum (Figure 9.17b). Data points that do not appear in symmetrical pairs with respect to the diagonal are thereby eliminated. In many cases, however, false cross peaks are produced by this technique. For instance, if two t_1 noise signals have just the coordinates i, j and j, i they will give rise to an artificial cross peak. This technique must thus be executed with great care.

1) For the explanation of this code see the table on p. 266; the choice of the receiver phase will become clear in Section 9.6.1.

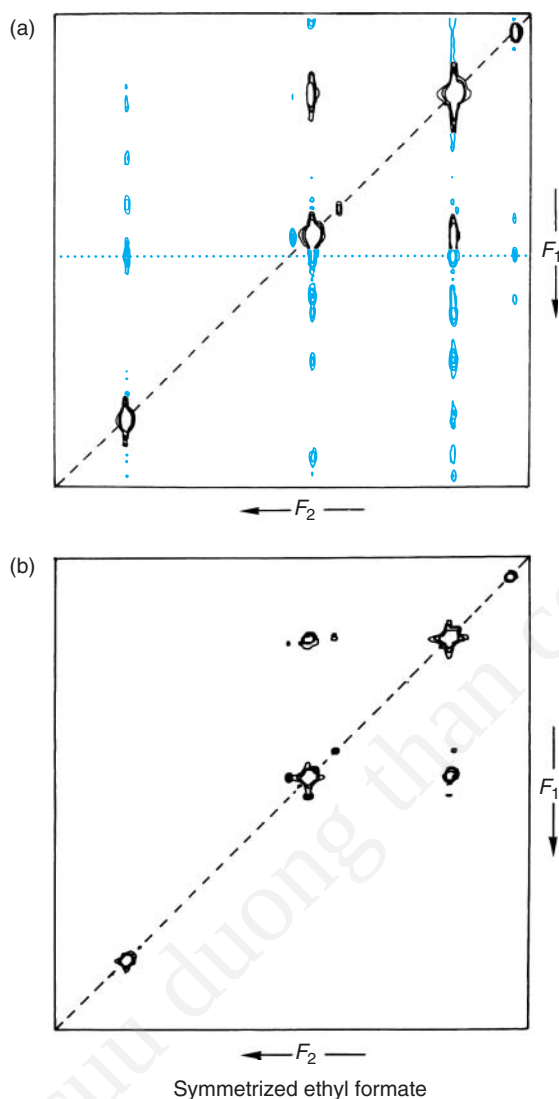


Figure 9.17 (a) Artifacts in a ^1H , ^1H COSY spectrum of ethyl formate, $\text{HCOOCH}_2\text{CH}_3$, (red signals): axial peaks parallel to the F_2 axis at $F_1 = 0$ (· · ·) and t_1 noise parallel to the F_1 axis; (b) the same spectrum after symmetrization of the data matrix.

The time necessary for a routine COSY spectrum is in the case of modern high field instruments relatively short and amounts to usually less than 1 h with standard samples. Even shorter measuring times have become possible by the application of gradient enhanced COSY spectroscopy, a technique that will be described in Section 9.7. In any case, of course, if high digital resolution in F_1 is desirable, a lengthening of the experiment is unavoidable.

9.4.3

Modifications of the Jeener Pulse Sequence

The COSY pulse sequence has been modified with different intentions. Three important variants – COSY-45, COSY-LR (*COSY longrange*), and COSY-DQF (COSY double quantum filter), shown as diagrams in Figure 9.18 – will be discussed in the following section; a fourth one, ECOSY, which has important applications in the field of biopolymers, is introduced in Chapter 15.

9.4.3.1 COSY-45

If the frequency difference between coupled nuclei in the 1D spectrum is small, the COSY cross peaks appear close to the diagonal and overlap with diagonal peaks occurs. In such cases the pulse sequence COSY-45 is useful, where the second 90_x° pulse is replaced by a 45_x° pulse (Figure 9.18a):

$$90_x^\circ \text{-----} t_1 \text{-----} 45_x^\circ, \text{FID} (t_2) \quad (9.4)$$

One can show theoretically (see Exercise 9.10, p. 321) that this reduces the intensity of the diagonal signals with respect to the intensity of the cross peaks. Possible overlaps can thus be diminished or even avoided. Furthermore, the smaller pulse angle introduces non-symmetric cross peaks. Normally, these are arranged in a square-like fashion. Smaller pulse angles lead to a rhombic distortion, where the orientation of the large diagonal depends on the relative sign of the coupling constants. Thus, COSY-45 spectroscopy allows determination of the relative signs of scalar spin–spin interactions and, for example, the discrimination between vicinal and geminal ^1H , ^1H coupling constants (cf. Chapter 5). An example is

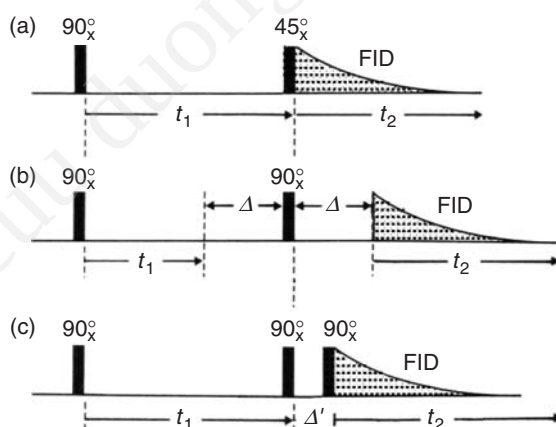


Figure 9.18 Modifications of the COSY experiment: (a) COSY-45 for the reduction of diagonal signals; (b) long-range COSY (COSY-LR) to emphasize small couplings; the delay Δ is in the ms-region; (c) COSY with double quantum filter (COSY-DQF) to eliminate singlet signals; the delay Δ' is an interval in the μs region.

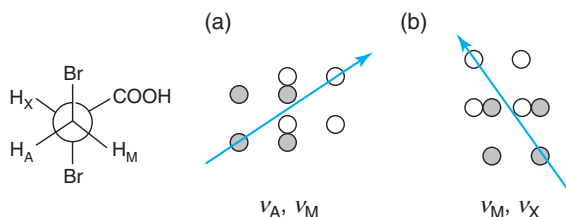


Figure 9.19 Selected cross peaks from the COSY-45 spectrum of 2,3-dibromopropionic acid (schematic); due to the X-approximation ($\nu_\text{o}\delta \gg J$) the cross peak structure is simplified and only two subspectra with four signals each are observed. From the three spins A, M, and X one is always a passive spin (cf. p. 183). For cross peak (a) between A and M the spin X is the passive one and two passive couplings exist: $J(\text{A},\text{X})$ and $J(\text{M},\text{X})$; the cross peak

diagonal points to the right-hand corner. For cross peak (b) between M and X the A spin is the passive one and the two passive couplings are $J(\text{A},\text{M})$ and $J(\text{A},\text{X})$; the cross peak diagonal points to the left upper corner. The relative sign between the passive couplings in the two pairs is thus different. Since $J(\text{A},\text{X})$ and $J(\text{M},\text{X})$ as vicinal couplings have a positive sign, the geminal coupling constant $J(\text{A},\text{M})$ has a negative sign (cf. p. 123 ff.) [4].

shown in Figure 9.19 with selected COSY-45 cross peaks from the spectrum of 2,3-dibromopropionic acid.

9.4.3.2 Long-Range COSY (COSY-LR)

With organic compounds proton spectra are normally dominated by geminal and vicinal coupling constants. These interactions with magnitudes between 5 and 15 Hz also determine the COSY spectra. If *correlations via long-range couplings* are of interest, special provisions have to be made. For small couplings of less than 5 Hz, due to the relatively slow development of cross peak magnetization, the following relation should be satisfied:

$$t_1(\text{max}) = t_2 = T_2 \quad (9.5)$$

This can be achieved by the introduction of a fixed delay Δ in the evolution and detection time that is before and after the second pulse of the COSY sequence (Figure 9.18b):

$$90^\circ_x \text{-----} t_1 \text{-----}, \Delta, 90^\circ_x, \Delta, \text{FID } (t_2) \quad (9.6)$$

With T_2 values of 0.2–0.6 s for protons the value for Δ amounts to 50–500 ms. To illustrate this experiment, Figure 9.20 (p. 306) shows again a COSY spectrum for *o*-nitroaniline, this time measured with the pulse sequence shown in Eq. (9.6). Contrary to the COSY-90 experiment, where the cross peaks arise from vicinal couplings (Figure 9.13, p. 297), cross peaks for ^4J coupling constants between meta-protons are now observed; 125 ms was chosen for the Δ delay. As one sees, a number, but not all of the vicinal correlations are also detected. With unknown compounds it is, therefore, advisable to measure first a COSY-90 or COSY-45 spectrum to identify the vicinal and geminal correlations, before the sequence in

Eq. (9.6) can be used to verify long-range correlations by careful comparison of these spectra.

Exercise 9.6

Consider why Eq. (9.6) cannot be satisfied by an increase of the t_1 increment.

Interestingly, in this context, cross peaks can be detected even if the 1D spectrum does not show any line splittings, that is, when the coupling is of the order of the half width of the 1D signal. This aspect is of practical importance in several cases. Examples are spectra of organic ligands of paramagnetic complexes where even the vicinal interactions in the 1D spectrum are not resolved due to severe paramagnetic line broadening. Figure 9.20b shows another application of the pulse sequence in Eq. (9.6), where the extremely small couplings between deuterons that are not resolved in the 1D ^2H spectrum are detected via the cross peaks in the $^2\text{H}, ^2\text{H}$ COSY experiment. From the pyridine ^1H data (Table A.4, p. 658) one calculates vicinal interactions of the order of ~ 1 Hz by the equation $J(^2\text{H}, ^2\text{H}) = [\gamma(^2\text{H})/\gamma(^1\text{H})]J(^1\text{H}, ^1\text{H}) = 0.154J(^1\text{H}, ^1\text{H})$ [cf. Eq. (7.1), p. 229].

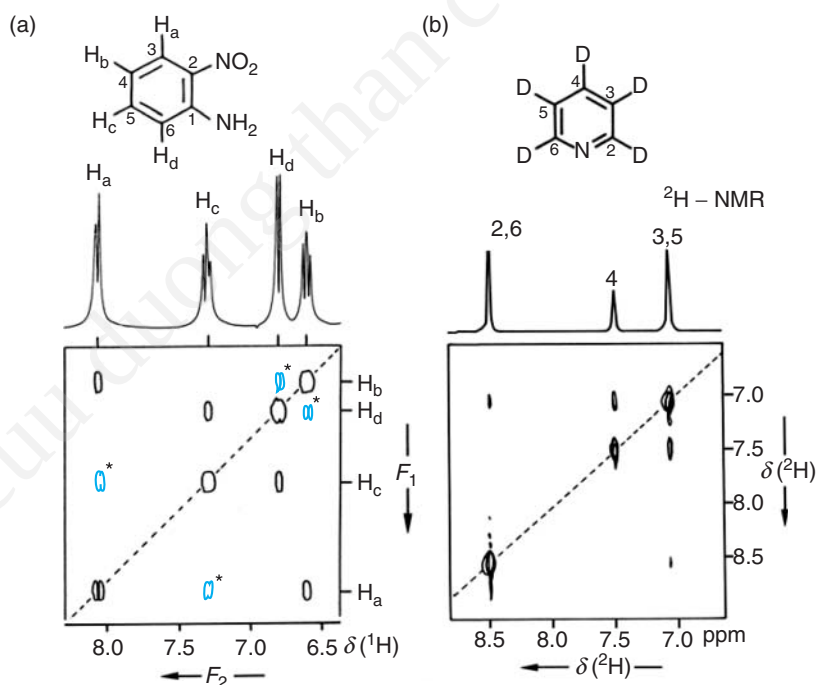


Figure 9.20 (a) 400 MHz $^1\text{H}, ^1\text{H}$ COSY-LR spectrum for *o*-nitroaniline measured with the pulse sequence given in Eq. (9.6) and $\Delta = 125$ ms; cross peaks for ^4J -correlations (indicated with an asterisk) [2] and (b) 61.42 MHz $^2\text{H}, ^2\text{H}$ COSY-LR spectrum for $[\text{D}_5]\text{pyridine}$ [5].

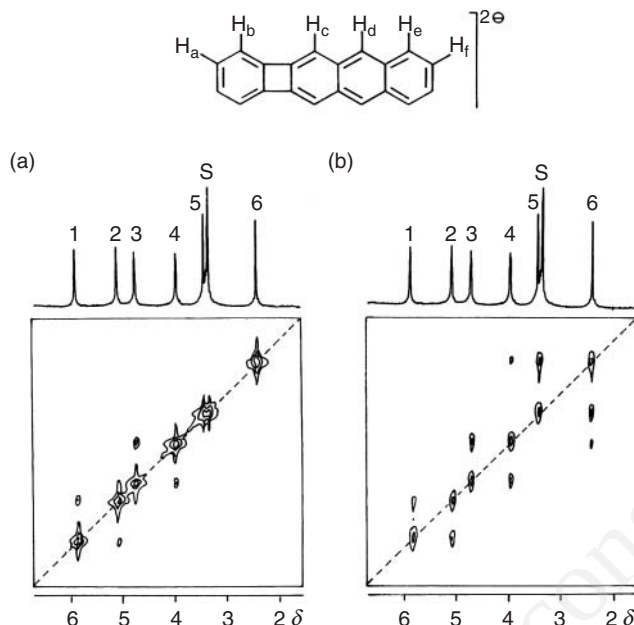


Figure 9.21 400 MHz ^1H , ^1H COSY spectra of naphthobiphenylene dianion; S = solvent signal [6].

Exercise 9.7

Figure 9.21 shows the COSY-90 and the COSY-LR ^1H NMR spectrum of naphthobiphenylene-dianion [(a) and (b), respectively]. Assign the signals 1–6 to the protons $\text{H}_a - \text{H}_f$ (S = solvens tetrahydrofuran).

9.4.3.3 COSY with Double Quantum Filter (COSY-DQF)

To eliminate perturbing singlet signals from solvent molecules, COSY-DQF (Figure 9.18c) is particularly suitable:

$$90_x^\circ \text{-----} t_1 \text{-----}, 90_x^\circ, 90_x^\circ, \text{FID} (t_2) \quad (9.7)$$

As we shall derive later, the introduction of a third 90° pulse allows us to detect coupled spin systems, while the singlet signals are suppressed. These experiments are based on the fact that only in a spin system that consists of two or more scalar coupled nuclei with different chemical shifts can detectable *double quantum phenomena*, so-called *double-quantum coherences*, arise. In this case two nuclei change their spin states at the same time. The double-quantum coherence associated with two coupled nuclei A and X is selected via the phase cycle or by the use of field gradients and detected after transformation into single quantum coherence (SQ). Besides the elimination of singlet signals, this experiment also reduces the diagonal signals that are partly eliminated because of their anti-phase

character. In total, the COSY-DQF experiment has only half the sensitivity of the standard COSY-90 experiment, but this disadvantage is outweighed by the spectral simplifications obtained.

An application of the COSY-DQF experiment is shown in Figure 9.22 with the spectra of a sample of (*Z*)- and (*E*)-2-chloroacrylic acid that contains CHCl_3 . The diagonal signal of the solvent is eliminated in the COSY-DQF experiment, as documented by the appropriate F_1 trace of the data matrix (Figure 9.21d). The experiment has importance also in measurements of aqueous solutions of peptides

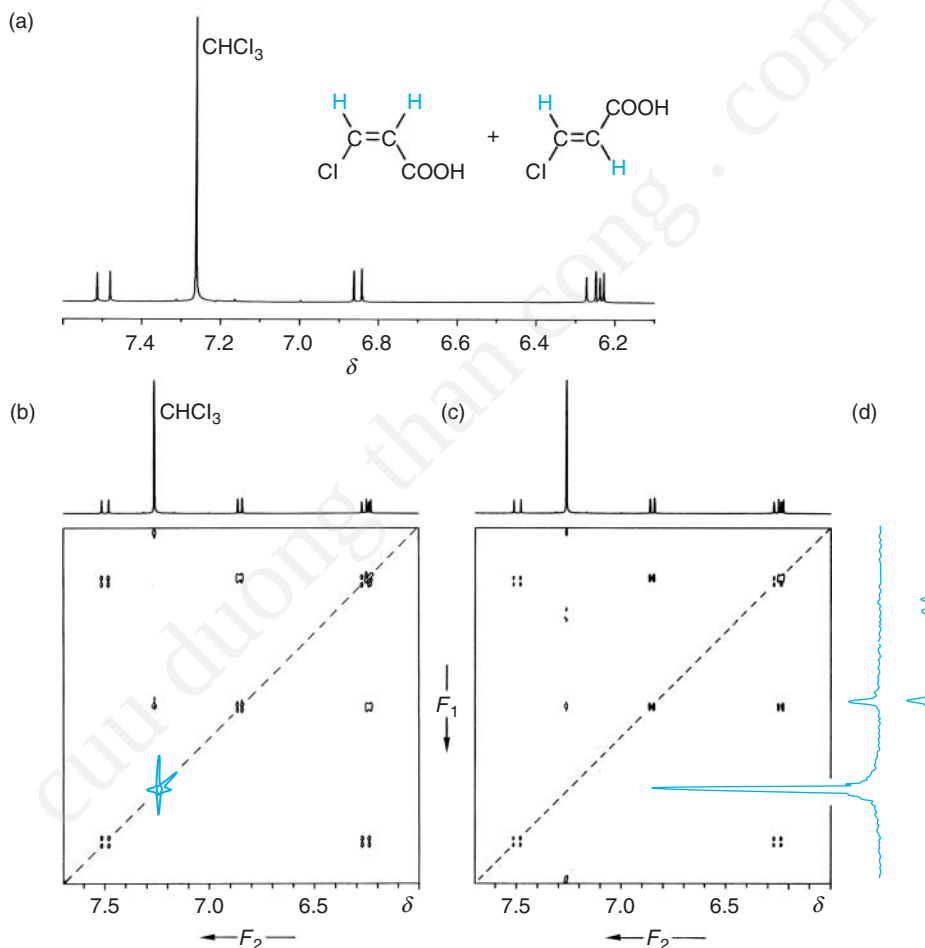


Figure 9.22 400 MHz ^1H NMR spectra of a mixture of (*Z*)- and (*E*)-2-chloroacrylic acid in $\text{CDCl}_3/\text{CHCl}_3$: (a) 1D spectrum; (b) COSY-90 spectrum with 128 t_1 -experiments of 32 accumulations each, measuring time 3 h; (c) COSY-DQF spectrum with 128 t_1 -experiments of 64 accumulations each, measuring time 6 h; (d) F_1 -traces of spectra (b) (left) and (c) (right) at the ^1H frequency of CHCl_3 .

and proteins, where the large water signal has to be eliminated. Its theoretical background will be discussed further in the next section.

9.5

The Product Operator Formalism

The Bloch vector model describes the action of the external magnetic field B_0 and the radiofrequency field B_1 on the nuclear magnetization vector within the framework of classical physics and is only valid for isolated nuclei without spin–spin interactions. For an adequate description of pulse sequences, where scalar spin–spin coupling is important, quantum mechanical methods have to be used instead. Calculation of the effect of pulse sequences on spin systems of the AX type or those of higher order is thereby based on the time-dependent Schrödinger equation. Contrary to the analysis of spin systems treated in Chapter 6 on the basis of the Schrödinger equation for stationary states, the time dependence of the spin system under the effect of the appropriate Hamilton operator must now be taken into account. Before, only energy differences and transmission probabilities between the stationary states of the spin system were important. Even the effect of the RF field B_1 could be neglected. The Schrödinger equation for the double resonance experiment (p. 272) was already supplemented by this term. In the case of pulse sequences, during the evolution time the effects of RF pulses, chemical shifts, and spin–spin coupling constants have to be included as well as relaxation processes during the complete pulse sequence. The quantum theoretical tool available to deal with this situation is *density matrix theory*. This is a mathematical technique used in theoretical chemistry and we assume that most of our readers will not be familiar with this formalism. In addition, the application of density matrix calculations for the cases of interest in the present context is lengthy and not practical for larger spin systems. Therefore, we take advantage of a simplified procedure, introduced by R.R. Ernst and others and known as *product operator formalism*. It serves to calculate observable magnetizations and to explain the spin physics of pulse sequences. It is based on Cartesian nuclear spin operators $\hat{I}_{xyz}$, already known from Chapter 6, as well as on products of these quantities. The procedure is limited in its applications to weakly coupled spin systems, which means first-order spectra, and neglects all relaxation effects. In the following section we shall develop its basic principles and later on apply the method to the COSY sequence and several of its modifications as well as to a number of other pulse sequences. All our discussions are related to the rotating frame of reference.

9.5.1

Phenomenon of Coherence

Before we discuss the basic principles of the product operator formalism, let us first introduce the important phenomenon of *coherence* that plays a central role in pulse NMR. In principle, a coherence between two spin states corresponds

to the transition in the NMR energy level diagram, discussed in Chapter 6, and thus to transverse magnetization. However, the term is more general, because it describes all possible mechanisms for the exchange of spin population between different states, in particular transitions that cannot be observed directly in the experimental spectrum. For example, relaxation transitions with $\Delta m_T = \pm 2$, as well as the double and zero-quantum or combination lines, belong to this group. Through such pathways spin population can be exchanged, as we shall discuss in Chapter 10 in connection with the nuclear Overhauser effect, but observable NMR signals do not necessarily result in a direct way. During certain pulse sequences “invisible” coherences of this type play an important role, but only coherences that obey the quantum chemical selection rules can be detected directly.

Coherences can arise between all eigenstates that belong to the same irreducible representation of the symmetry group of the nuclear spin system. Coherences between eigenstates of different symmetry are forbidden. Within the framework of density matrix theory, coherences correspond to the non-diagonal elements σ_{kl} between the eigenstates $|k\rangle$ and $|l\rangle$. This means that the state function $\varphi(t)$ of the system is a coherent superposition of these and other eigenstates and, therefore, not an eigenfunction of the time-dependent Hamilton operator. In the field of nuclear magnetic resonance, coherences between more than two states, however, are not important. The order of a coherence, p_{kl} , corresponds to the difference Δm of the magnetic quantum numbers of the eigenstates connected by the particular coherence: $p = 0$ for zero-quantum coherences and longitudinal z -magnetization, $p = 1$ for single quantum coherences, $p = 2$ for double-quantum coherences. During a pulse sequence all coherences can be excited, but only coherences of the order $p = 1$ are detectable.

An important aspect of modern pulse NMR is the transformation of coherences during a pulse sequence and a change of their order. The notion of coherence order is then replaced by the term *coherence level* that also has a sign. The sign results from the raising and lowering operators $\hat{I}^+$ and $\hat{I}^-$, respectively, that we introduced already in Chapter 6 (p. 154, see also Section 9.5.3). For example, transverse x -magnetization of the coherence order $p = 1$, represented by the nuclear spin operator $\hat{I}_x$ as described below, can be expressed, following Eq. (9.11a), by $\hat{I}^+$ and $\hat{I}^-$. A 90° pulse that produces transverse x -magnetization thus leads to coherences of the level $+1$ (for $\hat{I}^+$) and -1 (for $\hat{I}^-$). Double quantum coherences are characterized by the products $\hat{I}^+ \hat{I}^+$ and $\hat{I}^- \hat{I}^-$ and, therefore, the coherence levels $+2$ and -2 exist. A different sign of the coherence level indicates a difference in the sense of evolution for the respective operator that is a different rotational sense in the coordinate system.

The fate of coherences during a pulse sequence is best illustrated by a coherence level diagram (Figure 9.23). It documents the *coherence transfer pathway* during the pulse sequence that starts always at the zero level corresponding to longitudinal z -magnetization. The first pulse of a sequence produces coherences of the order $p = \pm 1$. If a certain coherence is to be detected finally as a signal, the coherence transfer pathway must end at the level $+1$, which in our convention is the coherence level of the receiver (see legend below to Figure 9.24).

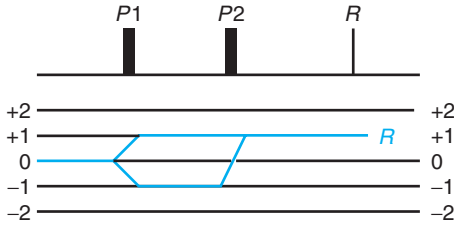


Figure 9.23 Coherence level diagram of a pulse sequence with two pulses P1 and P2 and the receiver R at the level +1; the first pulse produces coherences at levels +1 and -1, the second pulse, for example, changes one coherence level from -1 to +1 and leaves the other untouched; how these changes can be achieved will be discussed below.

9.5.2

Operator Basis for an AX System

The complete set of operators that can be derived for a spin system of N spin $\frac{1}{2}$ nuclei on the basis of the density matrix theory contains 4^N components. For a two-spin system of AX type, to which we will limit ourselves here, the following operators, which operate only on a particular spin A or X, result:

$$\hat{I}_x(A) \quad \hat{I}_y(A) \quad \hat{I}_z(A) \quad (9.8a)$$

$$\hat{I}_x(X) \quad \hat{I}_y(X) \quad \hat{I}_z(X) \quad (9.8b)$$

$$2\hat{I}_x(A)\hat{I}_x(X) \quad 2\hat{I}_x(A)\hat{I}_y(X) \quad 2\hat{I}_x(A)\hat{I}_z(X) \quad (9.8c)$$

$$2\hat{I}_y(A)\hat{I}_x(X) \quad 2\hat{I}_y(A)\hat{I}_y(X) \quad 2\hat{I}_y(A)\hat{I}_z(X) \quad (9.8d)$$

$$2\hat{I}_z(A)\hat{I}_x(X) \quad 2\hat{I}_z(A)\hat{I}_y(X) \quad 2\hat{I}_z(A)\hat{I}_z(X) \quad (9.8e)$$

As one sees, nuclear spin operators for the individual nuclei appear as single operators and as products²⁾. The 16th operator, not shown above, is the unity operator.

The importance of the one-spin operators has already been demonstrated in Chapter 6: $\hat{I}_z(A)$ and $\hat{I}_z(X)$ represent longitudinal, $\hat{I}_x(A)$, $\hat{I}_x(X)$ and $\hat{I}_y(A)$, $\hat{I}_y(X)$ transverse A- and X-magnetization, respectively. Within the framework of the product operator formalism these operators have two functions. On the one hand they correspond to the coherences of the spin system and on the other hand they behave as operators in the true sense and transform these coherences. This is known as *coherence transfer*. For the transfer pathways, coherence selection rules exist, for example:

- 1) Coherence transfer can only occur between states of the same symmetry.
- 2) In a weakly coupled spin system coherence can be exchanged between different spins only in the presence of scalar coupling.

2) The factor 2 allows for normalization

9.5.3

Zero- and Multiple-Quantum Coherences

The more general term *coherence* provides the basis for a discussion of magnetization components that cannot directly be observed. To characterize these contributions, we use the raising and lowering operator, $\hat{I}^+$ and $\hat{I}^-$, respectively, where $i = \sqrt{-1}$:

$$\hat{I}^+ = \hat{I}_x + i\hat{I}_y \quad (9.9a)$$

$$\hat{I}^- = \hat{I}_x - i\hat{I}_y \quad (9.9b)$$

Application of these operators to spin functions and observing the rules given on p. 154, Chapter 6 yields the spin functions of the next higher or next lower magnetic quantum number n , for example:

$$\hat{I}^+\alpha = [\hat{I}_x + i\hat{I}_y]\alpha = \frac{1}{2}\beta - i^2\frac{1}{2}\beta = \beta \quad (9.10)$$

hence, the terms *raising operator* and *lowering operator*. A double-quantum coherence, where two nuclei change their spin orientation at the same time is then characterized by the products $\hat{I}^+\hat{I}^+$ or $\hat{I}^-\hat{I}^-$ ($\Delta m_T = \pm 2$), while products of the form $\hat{I}^+\hat{I}^-$ or $\hat{I}^-\hat{I}^+$ describe zero-quantum coherences ($\Delta m_T = 0$). In the energy level diagram of an AX system these coherences arise between the states $\alpha\alpha$ and $\beta\beta$ and $\alpha\beta$ and $\beta\alpha$, respectively (see p. 44).

From Eqs (9.9a) and (9.9b) one obtains on the other hand:

$$\hat{I}_x = \frac{1}{2}(\hat{I}^+ + \hat{I}^-) \quad (9.11a)$$

$$\hat{I}_y = \frac{1}{2i}(\hat{I}^+ - \hat{I}^-) \quad (9.11b)$$

For the operator products with two transverse components the following equations result:

$$2\hat{I}_x(A)\hat{I}_x(X) = \frac{1}{2} \left[\hat{I}^+(A)\hat{I}^+(X) + \hat{I}^+(A)\hat{I}^-(X) + \hat{I}^-(A)\hat{I}^+(X) + \hat{I}^-(A)\hat{I}^-(X) \right] \quad (9.12a)$$

$$2\hat{I}_y(A)\hat{I}_y(X) = -\frac{1}{2} \left[\hat{I}^+(A)\hat{I}^+(X) - \hat{I}^+(A)\hat{I}^-(X) - \hat{I}^-(A)\hat{I}^+(X) + \hat{I}^-(A)\hat{I}^-(X) \right] \quad (9.12b)$$

$$2\hat{I}_x(A)\hat{I}_y(X) = \frac{1}{2i} \left[\hat{I}^+(A)\hat{I}^+(X) - \hat{I}^+(A)\hat{I}^-(X) + \hat{I}^-(A)\hat{I}^+(X) - \hat{I}^-(A)\hat{I}^-(X) \right] \quad (9.12c)$$

$$2\hat{I}_y(A)\hat{I}_x(X) = \frac{1}{2i} \left[\hat{I}^+(A)\hat{I}^+(X) + \hat{I}^+(A)\hat{I}^-(X) - \hat{I}^-(A)\hat{I}^+(X) - \hat{I}^-(A)\hat{I}^-(X) \right] \quad (9.12d)$$

All these terms contain double- and zero-quantum contributions, namely, the products $\hat{I}^+(A)\hat{I}^+(X)$ or $\hat{I}^-(A)\hat{I}^-(X)$ for $\Delta m_T = \pm 2$ (spin change in the same sense) and $\hat{I}^+(A)\hat{I}^-(X)$ and $\hat{I}^-(A)\hat{I}^+(X)$ for $\Delta m_T = 0$ (spin change in the opposite sense). Through a linear combination of these terms pure double or zero-quantum coherences result:

Double quantum coherence:

$$\frac{1}{2} \left[2\hat{I}_x(A) \hat{I}_x(X) - 2\hat{I}_y(A) \hat{I}_y(X) \right] = \frac{1}{2} \left[\hat{I}^+(A) \hat{I}^+(X) + \hat{I}^-(A) \hat{I}^-(X) \right] = \text{DQ}_x \quad (9.13a)$$

$$\frac{1}{2} \left[2\hat{I}_x(A) \hat{I}_y(X) + 2\hat{I}_y(A) \hat{I}_x(X) \right] = \frac{1}{2i} \left[\hat{I}^+(A) \hat{I}^+(X) - \hat{I}^-(A) \hat{I}^-(X) \right] = \text{DQ}_y \quad (9.13b)$$

Zero-quantum coherence:

$$\frac{1}{2} \left[2\hat{I}_x(A) \hat{I}_x(X) + 2\hat{I}_y(A) \hat{I}_y(X) \right] = \frac{1}{2} \left[\hat{I}^+(A) \hat{I}^-(X) + \hat{I}^-(A) \hat{I}^+(X) \right] = \text{ZQ}_x \quad (9.13c)$$

$$\frac{1}{2} \left[2\hat{I}_y(A) \hat{I}_x(X) - 2\hat{I}_x(A) \hat{I}_y(X) \right] = \frac{1}{2i} \left[\hat{I}^+(A) \hat{I}^-(X) - \hat{I}^-(A) \hat{I}^+(X) \right] = \text{ZQ}_y \quad (9.13d)$$

9.5.4

Evolution of Operators

During a pulse sequence operators are transformed, which means they are time dependent due to the action of several factors. Within the framework of our model, three factors have an important effect:

- 1) RF pulses,
- 2) Larmor precession, that is, chemical shifts,
- 3) scalar spin-spin coupling.

How these different factors act on various magnetization components will be derived with the simple example of the Cartesian operators $\hat{I}_x$, $\hat{I}_y$, $\hat{I}_z$ (Figure 9.24).

Let us start for this purpose with the z-operator $\hat{I}_z$. This operator can be treated as classical magnetization. Unsurprisingly, therefore, $\hat{I}_z$ is transformed through a 90°_x pulse into $\hat{I}_y$ (Figure 9.24).³⁾ This transformation can be written as follows:

$$\hat{I}_z \xrightarrow{90^\circ_x} \hat{I}_y \quad (9.14)$$

- 3) For the convention chosen here see the legend to Figure 9.24.

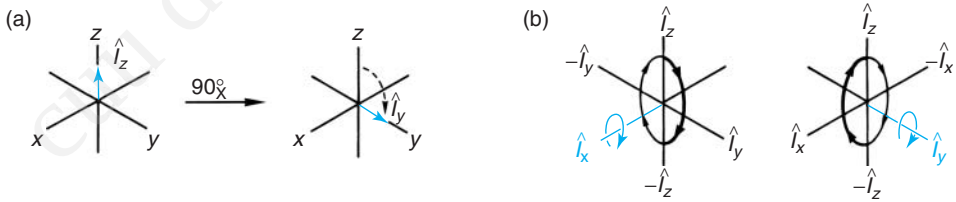


Figure 9.24 Effect of RF pulses on the operators $\hat{I}_z$, $\hat{I}_x$, and $\hat{I}_y$. We choose here the coordinate system in agreement with Chapter 8 and the effect of the B_1 -field for nuclei with a positive γ -factor is predicted by the left-hand rule (see p. 17). Transverse magnetization then rotates clockwise: $+M_y \rightarrow +M_x \rightarrow -M_y \rightarrow -M_x$. In the literature and the original publication by

Sørensen, Eich, Levitt, Bodenhausen, and Ernst (see Review Articles) the right-hand rule and anticlockwise rotation of transverse magnetization is used. The reader must be aware of differences in signs, therefore, if he or she compares results. The same applies to the choice of the receiver level, where we use +1 while others use -1.

The term of the respective *Hamilton operator* that is responsible for the transformation described is written above the arrow and is called the *propagator*. Note that the propagator also contains an operator. The operators thus appear, as already mentioned, in active as well as in passive form.

Similar effects arise with 90° pulses in other directions of the coordinate system:

$$\hat{I}_z \xrightarrow{90^\circ \hat{I}_y} -\hat{I}_x \quad (9.15)$$

$$\hat{I}_z \xrightarrow{90^\circ (-\hat{I}_x)} -\hat{I}_y \quad (9.16)$$

$$\hat{I}_z \xrightarrow{90^\circ (-\hat{I}_y)} \hat{I}_x \quad (9.17)$$

On the other hand, a 90°_x pulse on the operator $\hat{I}_x$ and $\hat{I}_y$ yields:

$$\hat{I}_x \xrightarrow{90^\circ \hat{I}_x} \hat{I}_x \quad (9.18)$$

$$\hat{I}_y \xrightarrow{90^\circ \hat{I}_x} -\hat{I}_z \quad (9.19)$$

If we choose a different pulse angle $\alpha < 90^\circ$ it follows:

$$\hat{I}_z \xrightarrow{\alpha \hat{I}_x} \hat{I}_z \cos \alpha + \hat{I}_y \sin \alpha \quad (9.20)$$

These equations hold for A as well as X magnetization. For clarity, we have dropped the index here. Figure 9.24 (p. 313) shows the relations discussed in graphical form.

Exercise 9.8

Formulate the effect of 90° pulses in the $+\gamma$ - and $-\gamma$ -direction on $\hat{I}_x$ and $\hat{I}_y$.

Since the effect of RF pulses is instantaneous (pulse duration is neglected), the propagators used so far do not contain the evolution time t_1 . This changes if we turn our attention to the effect of Larmor precession. The propagator for this case is simple. It must contain the Larmor frequency of the respective nucleus, the evolution time t_1 , and the operator $\hat{I}_z$, since transverse magnetization rotates around the z-axis. Indeed, we can derive the propagator for the Larmor precession as well as the propagator for scalar spin-spin coupling from the Hamilton operator, Eq. (6.10), introduced in Chapter 6. For weakly coupled spin systems of first order and with the relation $\omega = 2\pi\nu$, a simple rearrangement of terms transforms Eq. (6.10) into Eq. (9.21) [remember that for an AX system only the z-operator is responsible for scalar spin-spin interaction; compare Eq. (3.11), p. 44]:

$$\mathcal{H} = \sum_i \omega_i \hat{I}_z(i) + \sum_{i < j} \sum \pi J_{ij} 2\hat{I}_z(i)\hat{I}_z(j) \quad (9.21)$$

If the evolution time t_1 is now added to the various terms, the propagators for Larmor precession become $\omega_A t_1 \hat{I}_z(A)$ and $\omega_X t_1 \hat{I}_z(X)$, respectively, and for the spin-spin coupling $\pi J_{AX} t_1 2\hat{I}_z(A)\hat{I}_z(X)$; $\omega_A t_1$, $\omega_X t_1$, and $2\pi J_{AX} t_1$ are angles in radians.

The operators are then transformed under the action of the propagators for Larmor precession, remembering Eq. (9.20), according to:

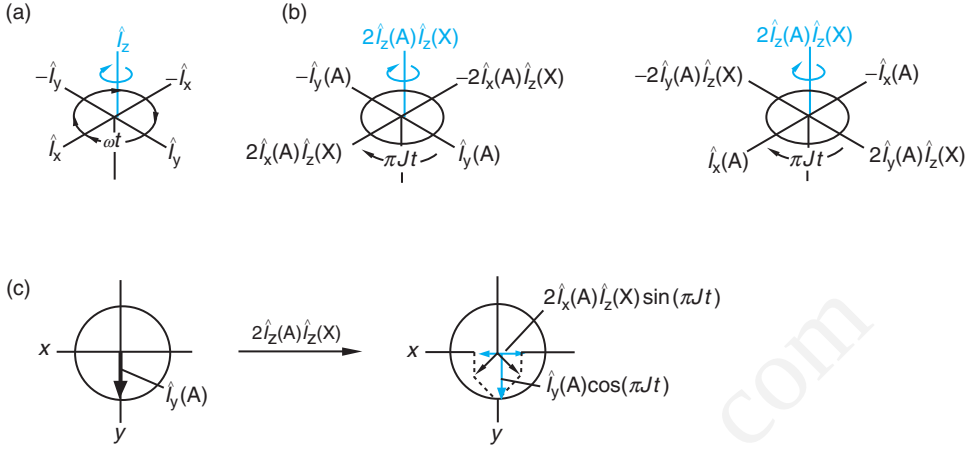


Figure 9.25 (a) Evolution under the influence of Larmor precession; (b) evolution under the influence of scalar spin–spin coupling; (c) in-phase and anti-phase magnetization.

$$\hat{I}_x(A) \xrightarrow{\omega_A t_1 \hat{I}_z(A)} \hat{I}_x(A) \cos \omega_A t_1 - \hat{I}_y(A) \sin \omega_A t_1 \quad (9.22a)$$

$$\hat{I}_y(A) \xrightarrow{\omega_A t_1 \hat{I}_z(A)} \hat{I}_y(A) \cos \omega_A t_1 + \hat{I}_x(A) \sin \omega_A t_1 \quad (9.22b)$$

These transformations, illustrated in graphical form in Figure 9.25a, can also be regarded as z-pulses. It is immediately clear that the $\hat{I}_z$ operator is invariant with respect to the Larmor propagator.

Finally, we study the effect of scalar spin-spin coupling. Again, the effect is restricted to the $\hat{x}$ - and $\hat{y}$ -operators, and with the propagator derived above the following transformations, illustrated in Figure 9.25b, result⁴⁾:

$$\hat{I}_x(A) \xrightarrow{\pi J_{AX} t_1 2\hat{I}_z(A)\hat{I}_z(X)} \hat{I}_x(A) \cos(\pi J_{AX} t_1) - 2\hat{I}_y(A)\hat{I}_z(X) \sin(\pi J_{AX} t_1) \quad (9.23a)$$

$$\hat{I}_y(A) \xrightarrow{\pi J_{AX} t_1 2\hat{I}_z(A)\hat{I}_z(X)} \hat{I}_y(A) \cos(\pi J_{AX} t_1) + 2\hat{I}_x(A)\hat{I}_z(X) \sin(\pi J_{AX} t_1) \quad (9.23b)$$

$$2\hat{I}_x(A)\hat{I}_z(X) \xrightarrow{\pi J_{AX} t_1 2\hat{I}_z(A)\hat{I}_z(X)} 2\hat{I}_x(A)\hat{I}_z(X) \cos(\pi J_{AX} t_1) - \hat{I}_y(A) \sin(\pi J_{AX} t_1) \quad (9.23c)$$

$$2\hat{I}_y(A)\hat{I}_z(X) \xrightarrow{\pi J_{AX} t_1 2\hat{I}_z(A)\hat{I}_z(X)} 2\hat{I}_y(A)\hat{I}_z(X) \cos(\pi J_{AX} t_1) + \hat{I}_x(A) \sin(\pi J_{AX} t_1) \quad (9.23d)$$

Accordingly, the product operators appear in the propagator only after scalar spin–spin coupling is introduced. A further interesting and important aspect must be emphasized: the fanning out of the two transverse magnetization vectors of a doublet caused by the coupling produces – as a resultant of the counter rotating doublet components – two types of : (i) magnetization of the same phase on the starting axis [first term in Eqs (9.23a) and (9.23b)] and (ii) magnetization of opposite phase on the orthogonal axis [second term in Eqs (9.23a) and (9.23b)]. These

4) Note that for the calculation of the second term in Eqs (9.23c) and (9.23d) the relation $\hat{I}_z \hat{I}_z = \frac{1}{4}$ was used.

magnetization components are called *in-phase magnetization* and *anti-phase magnetization*. Both are continuously interconverted during evolution (Figure 9.25c). Only in-phase magnetization, however, contributes to macroscopic magnetization, since anti-phase magnetization cancels.

For evolution of the double- and zero-quantum coherences introduced above [Eqs (9.13a–9.13d)], the following rules hold. Pure double-quantum coherence develops with the sum of the Larmor frequencies. This yields:

$$DQ_x \xrightarrow{[\omega_A \hat{I}_z(A) + \omega_X \hat{I}_z(X)] t_1} DQ_x \cos(\omega_A + \omega_X)t_1 + DQ_y \sin(\omega_A + \omega_X)t_1 \quad (9.24)$$

Pure zero-quantum coherence, on the other hand, develops with the difference of the Larmor frequencies:

$$ZQ_x \xrightarrow{[\omega_A \hat{I}_z(A) - \omega_X \hat{I}_z(X)] t_1} ZQ_x \cos(\omega_A - \omega_X)t_1 + ZQ_y \sin(\omega_A - \omega_X)t_1 \quad (9.25)$$

With respect to scalar spin-spin coupling between nuclei that contribute to the particular coherence, multiple-quantum product operators are invariant.

9.5.5

The Observables

The magnetization detected in t_2 is, finally, the important aspect if the product operator formalism is used to describe certain pulse sequences. Consequently, we are interested to learn more about the meaning of the various operator products that we obtain as a result of the calculations. In this respect the following rules are important:

- 1) Only products that contain a single transverse component $\hat{I}_x$ or $\hat{I}_y$ yield observable signals. Examples are the one-spin operators $\hat{I}_x(A)$ or $\hat{I}_y(A)$.
- 2) Products with more than one transverse component correspond to zero- or multiple-quantum coherences and cannot be detected. Examples are $2\hat{I}_y(A)\hat{I}_x(X)$ or $2\hat{I}_x(A)\hat{I}_y(X)$.
- 3) Products that contain one transverse component and one or several z-terms correspond to signals in anti-phase. For example, the operator product $2\hat{I}_x(A)\hat{I}_z(X)$ represents an A doublet with one absorption and one emission line, that is, a phase difference of 180° between the two doublet components. The integrated intensity of such a doublet is zero.

During the various pulse experiments the operators develop under the influence of different propagators. While Larmor frequencies and scalar spin-spin couplings are important in all cases where an evolution time or fixed time delays are involved, the transformations caused by the application of RF pulses lead to immediate coherence transfers. A number of examples may illustrate this point:

- 1) Transformation of anti-phase A-magnetization into anti-phase X-magnetization:

$$2\hat{I}_x(A)\hat{I}_z(X) \xrightarrow{90^\circ[\hat{I}_y(A)+\hat{I}_y(X)]} -2\hat{I}_z(A)\hat{I}_x(X) \quad (9.26)$$

$$2\hat{I}_y(A)\hat{I}_z(X) \xrightarrow{90^\circ[\hat{I}_x(A)+\hat{I}_x(X)]} -2\hat{I}_z(A)\hat{I}_y(X) \quad (9.27)$$

- 2) Transformation of anti-phase A magnetization into zero- and multiple- quantum coherences:

$$2\hat{I}_x(A)\hat{I}_z(X) \xrightarrow{90^\circ[\hat{I}_x(A)+\hat{I}_x(X)]} 2\hat{I}_x(A)\hat{I}_y(X) \quad (9.28)$$

These transfers play an important role during the Jeener experiment that we shall discuss in the following section. With the analysis of this pulse sequence we apply the relations developed so far to a specific example to illustrate the practical application of the product operator formalism.

9.5.6

The COSY Experiment within the Product Operator Formalism

For the Jeener pulse sequence of the COSY experiment as applied to a homonuclear AX system:

$$90^\circ_x \text{-----} t_1 \text{-----} 90^\circ_x, \text{FID} (t_2) \quad (9.29)$$

a product operator calculation will now be carried out. During the different steps, outlined below, the actual state of the spin system is characterized by the so-called *density operator* σ_i ($i = 0, 1, 2$, etc.):

- 1) In the preparation period pulse excitation transforms z-magnetization (σ_0) into transverse magnetization (σ_1):

$$\begin{aligned} \sigma_0 &= \hat{I}_z(A) + \hat{I}_z(X) \\ &\downarrow 90^\circ[\hat{I}_x(A) + \hat{I}_x(X)] \\ \sigma_1 &= \hat{I}_y(A) + \hat{I}_y(X) \end{aligned}$$

- 2) Transverse magnetization develops during the evolution time under the influence of Larmor precession and spin-spin coupling into the state σ_2 . We shall analyze these steps separately and combine in-phase and anti-phase magnetizations:

$$\begin{aligned}
& \sigma_1 \\
& \downarrow \omega_A t_1 \hat{I}_z(A) + \omega_X t_1 \hat{I}_z(X) \text{ (Larmor precession)} \\
\sigma_2 &= \hat{I}_y(A) \cos \omega_A t_1 + \hat{I}_x(A) \sin \omega_A t_1 + \hat{I}_y(X) \cos \omega_X t_1 + \hat{I}_x(X) \sin \omega_X t_1 \\
& \downarrow \pi J_{AX} t_1 2 \hat{I}_z(A) \hat{I}_z(X) \text{ (spin-spin coupling)} \\
\sigma_2 &= \text{in-phase magnetization :} \\
& [\hat{I}_y(A) \cos \omega_A t_1 + \hat{I}_x(A) \sin \omega_A t_1 + \hat{I}_y(X) \cos \omega_X t_1 \\
& + \hat{I}_x(X) \sin \omega_X t_1] \cos(\pi J_{AX} t_1) \\
& \text{anti-phase magnetization :} \\
& [2 \hat{I}_x(A) \hat{I}_z(X) \cos \omega_A t_1 - 2 \hat{I}_y(A) \hat{I}_z(X) \sin \omega_A t_1 + 2 \hat{I}_z(A) \hat{I}_x(X) \cos \omega_X t_1 \\
& - 2 \hat{I}_z(A) \hat{I}_y(X) \sin \omega_X t_1] \sin(\pi J_{AX} t_1)
\end{aligned}$$

3) The second 90°_x pulse that is known as the *mixing pulse*, produces the state σ_3 :

$$\begin{aligned}
& \sigma_2 \\
& \downarrow 90^\circ [\hat{I}_x(A) + \hat{I}_x(X)] \\
\sigma_3 &= \left. \begin{aligned} & -\hat{I}_z(A) \cos \omega_A t_1 \\ & + \hat{I}_x(A) \sin \omega_A t_1 \\ & -\hat{I}_z(X) \cos \omega_X t_1 \\ & + \hat{I}_x(X) \sin \omega_X t_1 \end{aligned} \right\} \times \cos(\pi J_{AX} t_1) \\
& \left. \begin{aligned} & + 2 \hat{I}_x(A) \hat{I}_y(X) \cos \omega_A t_1 \\ & + 2 \hat{I}_z(A) \hat{I}_y(X) \sin \omega_A t_1 \\ & + 2 \hat{I}_y(A) \hat{I}_x(X) \cos \omega_X t_1 \\ & + 2 \hat{I}_y(A) \hat{I}_z(X) \sin \omega_X t_1 \end{aligned} \right\} \times \sin(\pi J_{AX} t_1)
\end{aligned} \tag{9.30}$$

As one can see, anti-phase A magnetization has been transformed into anti-phase X magnetization and vice versa. This explains the expression “mixing pulse.”

From the terms in Eq. (9.30) observable transverse magnetization, σ_3^{obs} , can now be derived if we drop, on the basis of rules 1–3 discussed in Section 9.5.5, the expressions that contain only the $\hat{I}_z$ operator and operator products with two transverse components, thereby selecting only terms with *one* transverse component:

$$\begin{aligned}
\sigma_3^{\text{obs}} &= [\hat{I}_x(A) \overset{\textcircled{1}}{\sin \omega_A t_1} + \hat{I}_x(X) \overset{\textcircled{2}}{\sin \omega_X t_1}] \cos(\pi J_{AX} t_1) \\
& + 2 \hat{I}_z(A) \overset{\textcircled{3}}{\hat{I}_y(X) \sin \omega_A t_1} + 2 \hat{I}_z(X) \overset{\textcircled{4}}{\hat{I}_y(A) \sin \omega_X t_1} \sin(\pi J_{AX} t_1)
\end{aligned} \tag{9.31}$$

This magnetization then evolves during the detection time t_2 , again under the influence of Larmor precession and spin–spin coupling. Remembering that only in-phase components contribute to the macroscopic magnetization, we can analyze the situation during t_2 by a straightforward application of Eqs (9.22) and (9.23) to the individual terms of Eq. (9.31). To facilitate this analysis we introduce the following shorthand notations: $\sin \omega_A t_1 = \sin A1$; $\sin \omega_X t_2 = \sin A2$;

$\sin(\pi J_{AX}t_1) = \sin J1$; $\sin(\pi J_{AX}t_2) = \sin J2$; and similar expression for the cosine terms and ω_X , respectively.

Starting with term ① that represents transverse A-magnetization, we have:

- 1) Larmor precession:

$$\hat{I}_x(A) \sin A1 \cos J1 \xrightarrow{\omega_A t_2 \hat{I}_z(A)} \hat{I}_x(A) \sin A1 \cos J1 \cos A2 - \hat{I}_y(A) \sin A1 \cos J1 \sin A2$$

- 2) spin-spin coupling:

$$\xrightarrow{\pi J_{AX} t_2 \hat{I}_z(A) \hat{I}_z(X)} \hat{I}_x(A) \sin A1 \cos J1 \cos A2 \cos J2 - \hat{I}_y(A) \sin A1 \cos J1 \sin A2 \cos J2 \quad (9.32)$$

An analogous result is obtained for the X-magnetization, the second term in Eq. (9.31). This leads to the following predictions for the expected 2D spectrum: the first two terms in Eq. (9.31) represent A- and X-magnetization that is modulated during both the evolution time t_1 and the detection time t_2 with $\omega_A + \pi J_{AX}$ and $\omega_X + \pi J_{AX}$, respectively. After Fourier transformation this yields multiplets at $F_1 = F_2 = \omega_A$ and ω_X , respectively, that lie on the diagonal and, due to their cosine dependence on J_{AX} during t_1 and t_2 , possess in-phase structure.

We now turn to terms ③ and ④ in Eq. (9.31). Term ③ represents anti-phase X-magnetization that develops during t_2 as follows⁵⁾:

- 1) Larmor precession:

$$2\hat{I}_z(A)\hat{I}_y(X) \sin A1 \sin J1 \xrightarrow{\omega_A t_2 \hat{I}_z(X)} 2\hat{I}_z(A)\hat{I}_y(X) \sin A1 \sin J1 \cos X2 + 2\hat{I}_z(A)\hat{I}_x(X) \sin A1 \sin J1 \sin X2$$

- 2) spin-spin coupling:

$$\begin{aligned} &\xrightarrow{\pi J_{AX} t_2 2\hat{I}_z(A)\hat{I}_z(X)} \\ &2\hat{I}_z(A) \hat{I}_y(X) \sin A1 \overset{\textcircled{5}}{\sin J1 \cos X2 \cos J2} + \hat{I}_x(X) \sin A1 \sin J1 \overset{\textcircled{6}}{\cos X2 \sin J2} \\ &+ 2\hat{I}_z(A) \hat{I}_x(X) \sin A1 \overset{\textcircled{7}}{\sin J1 \sin X2 \cos J2} - \hat{I}_y(X) \sin A1 \sin J1 \overset{\textcircled{8}}{\sin X2 \sin J2} \end{aligned} \quad (9.33)$$

Terms ⑥ and ⑧ of Eq. (9.33) are the observable in-phase magnetization components that arise from the third term in Eq. (9.31). They have a different chemical shift in t_1 and t_2 (modulation by $\sin \omega_A$ and $\cos \omega_X$ and $\sin \omega_A$ and $\sin \omega_X$, respectively). This yields after Fourier transformation a cross peak multiplet at $F_1 = \omega_A$ and $F_2 = \omega_X$ with anti-phase structure in both time dimensions (sine dependence on J_{AX}). A similar analysis for the fourth term that represents anti-phase A-magnetization shows that it yields the symmetrical cross peak at $F_1 = \omega_X$ and $F_2 = \omega_A$.

5) Note that for the calculation of terms ⑥ and ⑧ in Eq. (9.33) the relationship $\hat{I}_z(A)\hat{I}_z(A) = \frac{1}{4}$ was used.

Exercise 9.9

Develop an equation similar to Eq. (9.33) for the t_2 evolution of antiphase A-magnetization [term ③ in Eq. (9.31)].

Because of the different modulation by πJ_{AX} (cosine and sine, respectively) there is in total a 90° phase difference between the diagonal and the cross peaks. Thus, the diagonal peaks are dispersive, while the cross peaks are detected in absorption (or emission). The experimental spectrum shown in Figure 9.16 (p. 301) confirms these relationships. If the magnitude representation of the signals is used (cf. p. 285) the phase information is completely lost. The danger of a partial cancelling of the cross peaks in the case of small couplings, however, remains.

9.5.7

The COSY Experiment with Double-Quantum Filter (COSY-DQF)

This experiment uses the following pulse sequence (cf. Figure 9.18, p. 304):

$$90_x^\circ \text{-----} t_1 \text{-----} 90_x^\circ, 90_x^\circ, t_2 \quad (9.34)$$

Its analysis can therefore start with the density operator σ_3 of the COSY experiment [Eq. (9.30)]. A further simplification results from the fact that the complete single-quantum, zero-quantum, and single-quantum anti-phase coherences can be eliminated by an appropriate phase cycle or by the use of field gradients Section 9.7. Consequently, only double-quantum coherences remain after the second 90° pulse. To select these coherences, let us first rearrange Eq. (9.30), where the magnetization is expressed as a linear combination of pure double and zero-quantum coherence, with the help of Eqs (9.13a–9.13d). This yields:

$$2\hat{I}_x(A)\hat{I}_y(X) \cos \omega_A t_1 = \frac{1}{2} \{ [2\hat{I}_x(A)\hat{I}_y(X) + 2\hat{I}_y(A)\hat{I}_x(X)] - [2\hat{I}_y(A)\hat{I}_x(X) - 2\hat{I}_x(A)\hat{I}_y(X)] \} \cos \omega_A t_1 \quad (9.35a)$$

$$2\hat{I}_y(A)\hat{I}_x(X) \cos \omega_X t_1 = \frac{1}{2} \{ [(2\hat{I}_x(A)\hat{I}_y(X) + 2\hat{I}_y(A)\hat{I}_x(X)) + [2\hat{I}_y(A)\hat{I}_x(X) - 2\hat{I}_x(A)\hat{I}_y(X)] \} \cos \omega_X t_1 \quad (9.35b)$$

and we then obtain the modified density operator:

$$\begin{aligned} \sigma_3 = & [-\hat{I}_z(A) \cos \omega_A t_1 + \hat{I}_x(A) \sin \omega_A t_1 - \hat{I}_z(X) \cos \omega_X t_1 + \hat{I}_x(X) \sin \omega_X t_1] \cos(\pi J_{AX} t_1) \\ & + \left(\frac{1}{2} \{ [2\hat{I}_x(A)\hat{I}_y(X) + 2\hat{I}_y(A)\hat{I}_x(X)] - [2\hat{I}_y(A)\hat{I}_x(X) - 2\hat{I}_x(A)\hat{I}_y(X)] \} \cos \omega_A t_1 \right. \\ & + \left. \frac{1}{2} \{ [2\hat{I}_x(A)\hat{I}_y(X) + 2\hat{I}_y(A)\hat{I}_x(X)] + [2\hat{I}_y(A)\hat{I}_x(X) - 2\hat{I}_x(A)\hat{I}_y(X)] \} \cos \omega_X t_1 \right. \\ & \left. + 2\hat{I}_z(A)\hat{I}_y(X) \sin \omega_A t_1 + 2\hat{I}_y(A)\hat{I}_z(X) \sin \omega_X t_1 \right) \sin(\pi J_{AX} t_1) \end{aligned} \quad (9.36a)$$

and with Eqs (9.13a–d):

$$\begin{aligned}\sigma_3 = & [-\hat{I}_z(A) \cos \omega_A t_1 + \hat{I}_x(A) \sin \omega_A t_1 - \hat{I}_z(X) \cos \omega_X t_1 + \hat{I}_x(X) \sin \omega_X t_1] \cos(\pi J_{AX} t_1) \\ & + [\frac{1}{2}(DQ_y - ZQ_y) \cos \omega_A t_1 + \frac{1}{2}(DQ_y - ZQ_y) \cos \omega_X t_1 \\ & + 2\hat{I}_z(A)\hat{I}_y(X) \sin \omega_A t_1 + 2\hat{I}_y(A)\hat{I}_z(X) \sin \omega_X t_1] \sin(\pi J_{AX} t_1)\end{aligned}\quad (9.36b)$$

For the double-quantum coherence that has passed the phase cycle unhindered and that finally remains while all longitudinal, zero-quantum, and anti-phase SQ terms are cancelled, we find:

$$\begin{aligned}\sigma_3^{DQ} = & \{\frac{1}{2}[2\hat{I}_x(A)\hat{I}_y(X) + 2\hat{I}_y(A)\hat{I}_x(X)] \cos \omega_A t_1 \\ & + \frac{1}{2}[2\hat{I}_x(A)\hat{I}_y(X) + 2\hat{I}_y(A)\hat{I}_x(X)] \cos \omega_X t_1\} \sin(\pi J_{AX} t_1)\end{aligned}\quad (9.37)$$

or:

$$\sigma_3^{DQ} = (\frac{1}{2}DQ_y \cos \omega_A t_1 + \frac{1}{2}DQ_y \cos \omega_X t_1) \sin(\pi J_{AX} t_1) \quad (9.38a)$$

The third 90° pulse with constant $-x$ -phase then produces single-quantum magnetization:

$$\begin{aligned}\sigma_4^{SQ} = & \{\frac{1}{2}[2\hat{I}_x(\overset{\textcircled{1}}{A})\hat{I}_z(X) + 2\hat{I}_z(\overset{\textcircled{2}}{A})\hat{I}_x(X)] \cos \omega_A t_1 \\ & + \frac{1}{2}[2\hat{I}_x(\overset{\textcircled{3}}{A})\hat{I}_z(X) + 2\hat{I}_z(\overset{\textcircled{4}}{A})\hat{I}_x(X)] \cos \omega_X t_1\} \sin(\pi J_{AX} t_1)\end{aligned}\quad (9.38b)$$

that evolves during t_2 under the action of chemical shifts and spin–spin coupling. We shall forego here a detailed treatment like the one performed above for the COSY experiment, since already by inspection of Eq. (9.38b) we can derive the following result: the diagonal peaks (terms $\textcircled{1}$ and $\textcircled{4}$, modulated by ω_A and ω_X in t_1 and t_2 , respectively, are detected in both dimensions as anti-phase doublets, since the corresponding magnetization is modulated with $\sin(\pi J_{AX})$ during t_1 as well as t_2 [note the different origin of the diagonal peaks in the COSY- and the COSY-DQF experiment, cf. Eqs (9.30) and (9.36)]. This leads, as for the cross peaks, to partial signal cancellation in the case of signal overlap if the line width is of the order of the coupling. Because the single-quantum magnetization (singlet signals) is already eliminated by the phase cycle, in total a reduction of the diagonal peaks results.

The terms $\textcircled{2}$ and $\textcircled{3}$ on the other hand represent anti-phase X- and A-magnetization that is modulated during t_1 with ω_A and ω_X and during t_2 with ω_X and ω_A , respectively, yield cross peaks with, however, only half the intensity of the standard COSY experiment [cf. Eq. (9.31)]. The reduction of the diagonal peaks is, therefore, achieved only at the expense of sensitivity.

Exercise 9.10

Analyze the results of COSY experiments with variable pulse angles $\beta = 0^\circ$, 90° , and 180° for the mixing pulse with the help of the general results given in

Eq. (8.2.3) on p. 407 of the monograph by Ernst, Bodenhausen, and Wokaun (first ed., see the Literature at the end of this chapter, p. 338).

9.6

Phase Cycles

The usefulness of phase cycles for the elimination of artifacts in 1D and 2D NMR spectra has already been mentioned. For multiple pulse experiments phase cycles play a far more fundamental part, because signal selection that is essential for the success of most 2D experiments can be achieved with the help of phase cycles. This aspect is only inadequately or not at all expressed in the general diagrams that are drawn for pulse sequences. Consequently, phase cycles are often regarded as a technical detail of minor importance. In connection with the product operator formalism we shall, therefore, underline the vital role phase cycles can play in 2D NMR and demonstrate with a number of simple examples how phase cycles for multiple pulse experiments can be constructed. An alternative technique for signal selection that has several advantages if compared to phase cycling is the use of gradient pulses to be discussed in the next section.

For the discussion of the phase cycling technique, the coherence level diagram introduced in Figure 9.23 is helpful. It shows the coherence transfer pathway and allows us to determine the phases of the participating coherences for every step in a pulse sequence. The important aspect is that the various pulses not only change the coherence level but also the phase of the coherence. In this respect the following rule is important:

If the pulse phase is changed by $\Delta\theta$, those coherences, for which the pulse induces a coherence level shift $\Delta p = p_2 - p_1$, change their phase ϕ by $\Delta p \times \Delta\theta$:

$$\Delta\phi = \Delta p \times \Delta\theta \quad (9.39)$$

This relation is illustrated with several examples in Figure 9.26a.

The principle of signal selection by phase cycles is most clearly illuminated with the simple case shown in Figure 9.26. Assume that from two coherences A and B shown in Figure 9.26b, which arrive at the coherence level +1 on different pathways, only one shall be detected as signal. In the case of A, double-quantum magnetization is involved (level +2); in the case of B, the pulse transforms zero-quantum magnetization into single-quantum magnetization. Consequently, the coherence level shifts are $\Delta p(A) = -1$ and $\Delta p(B) = +1$. Now, in a series of four experiments, the results of which are finally added, the phase of the pulse P_1 be shifted by 90° . The coherence phases $\phi(A)$ and $\phi(B)$, on the basis of the rule given above [Eq. (9.39)], then shift as shown in Figure 9.26c. If we are interested in the A signals, the receiver phase $\theta(R)$ must follow the phase of coherence A, $\phi(A)$. The B signals are then cancelled. With constant receiver phase, complete signal cancellation for A and B results.

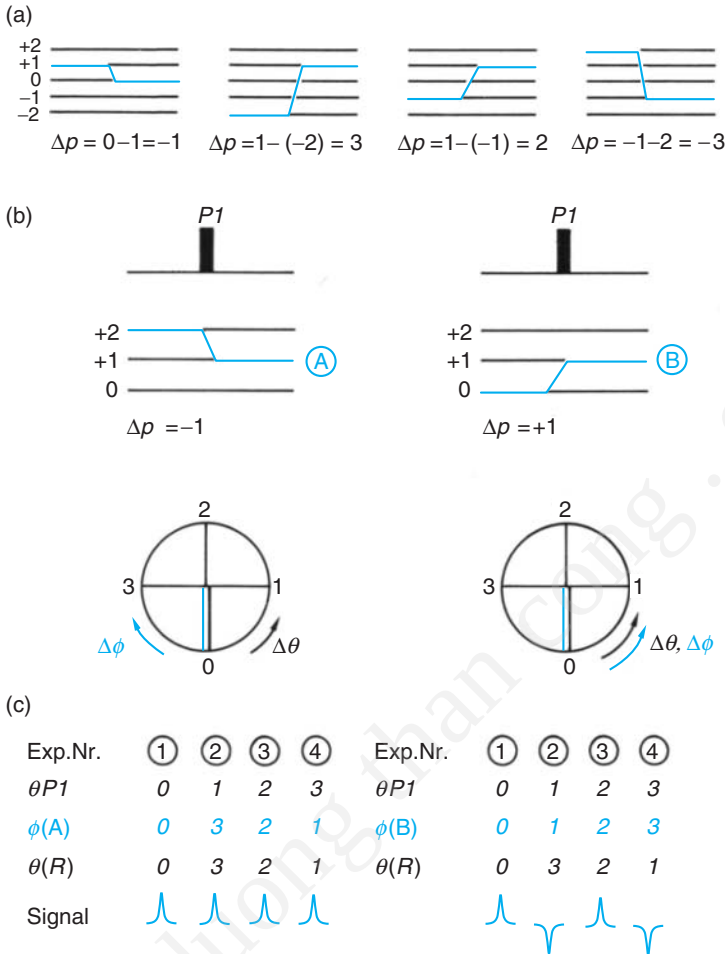


Figure 9.26 (a) Coherence level shifts $\Delta p = p_2 - p_1$; (b) coherence level diagram for two coherences that reach the receiver level +1 on different pathways; (c) analysis of the coherence and receiver phase for a phase cycle of four different experiments 1–4 for coherence A with $\Delta p = -1$ and coherence B with $\Delta p = +1$; the phase code used was introduced in Chapter 8 (p. 266).

To derive phase cycles for certain pulse sequences, the coherence pathways in the coherence level diagram must be inspected. Let us remember first that we start always at level 0 and that the first pulse $P1$ produces coherences with levels +1 and -1. The next pulse $P2$ then already excites all possible coherences for the spin system under consideration (Figure 9.27a). Phase cycling, however, puts us into the position to decide which of these coherences later reach the receiver level +1. The phase cycle thus has the function of a filter that can be passed only by the desired coherences.

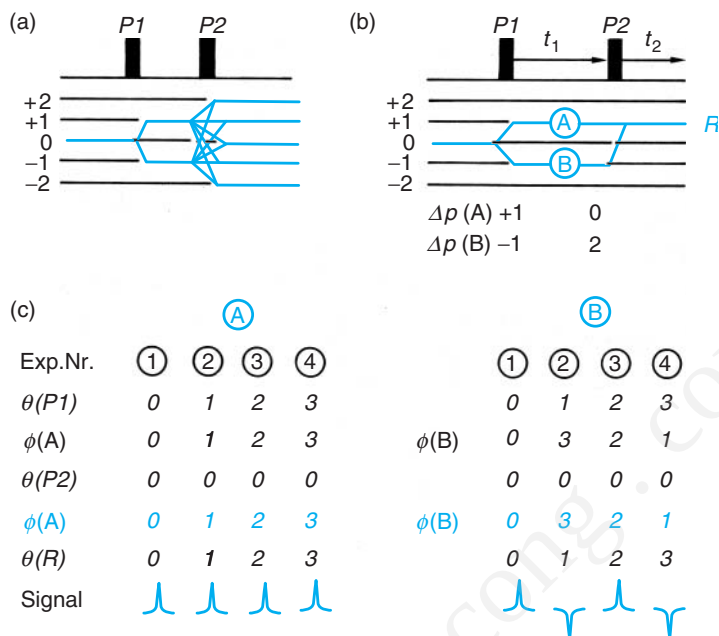


Figure 9.27 (a) Time-development of coherences in a pulse sequence; (b) coherence pathways for the COSY-90 experiment; and (c) analysis of a phase cycle for the detection of coherence A in the COSY-90 experiment.

9.6.1

COSY Experiment

As an exercise for the application of the relations discussed so far, let us analyze the COSY experiment, Eq. (9.29) (p. 317). The appropriate coherence level diagram is shown in Figure 9.27b. After the second 90° pulse we select those coherences that end at the receiver level +1. Other coherences are not shown because they do not yield detectable magnetization.

Because of their different history, the coherences at the receiver level +1 have different phases. For coherence A, the coherence level shifts are +1 and 0, whereas coherence B has experienced shifts of -1 and +2. According to the rule formulated above, phase shifts for the pulses P1 and P2 will thus influence the coherence phases differently. As above, pulse phase shifts of 90° are used with a code of 0, 1, 2, and 3 for relative phase differences of 0° , 90° , 180° , and 270° , respectively (Chapter 8).

The effect of the pulse phase shifts on the coherence of interest can be most easily read off from a graphical diagram of the type shown in Figure 9.27c for the coherences that arise in the COSY experiment. In the particular phase cycle shown only the phase of the first 90° pulse P1 is changed. During four single experiments, all run with the same t_1 -value, the phase of P1 then takes the values 0, 1, 2, and 3.

For the coherence A with $\Delta p = +1$, according to Figure 9.26c, the values 0, 1, 2, and 3 result ($\Delta\phi = \Delta p \times \Delta\theta!$). Since the phase of the second 90° pulse remains constant and we have no coherence level shift, $\Delta\phi = 0$ results. The receiver phase $\theta(R)$ is adjusted to detect an absorption signal with the cycle (0123). For coherence B, however, $\Delta p = -1$ for the first pulse and the coherence phase now follows the cycle (0321). The second pulse $P2$ with constant phase again has no further effect ($\Delta p = +2$, but $\Delta\theta = 0$). With the given receiver phases 0123 this leads to a cancellation of the corresponding signal. On the other hand, a receiver phase cycle (0321) would allow us to detect coherence B and to eliminate coherence A.

Exercise 9.11

Draw the receiver signals for both coherences A and B if the alternative receiver phase cycle (0321) for the first pulse $P1$ is used and analyze the result for a situation where only the phase of $P2$ is changed.

The two signals that arise in the COSY experiment are known as an *anti-echo signal* or *P-type signal* (coherence A in Figure 9.27b,c) or as an echo signal (also called *coherence transfer echo*) or *N-type signal* (coherence B in Figure 9.27b,c). The abbreviations *P* and *N* result from the sense of rotation of the coherences during the evolution time that is positive ($p = +1$) or negative ($p = -1$), while the term “echo” derives from the coherence order change from -1 to $+1$ for B; no change is involved for A. For the representation of COSY spectra one uses echo selection (coherence B) and the diagonal runs from the left-hand lower corner to the right-hand upper corner. Quadrature detection in F_1 requires two signals with a phase difference of 90° for each t_1 value. In the older procedure, these two signals are combined into one FID that converts the amplitude modulation into a phase modulation. This is achieved with the phase cycle for *P*- or *N*-type selection discussed above. For *N*-type selection, according to Figure 9.27, the required receiver phases are (0321). The pairs of scans 1, 2 and 3, 4 introduce the necessary phase shift, while the pairs 1, 3 and 2, 4 cancel axial peaks. However, this method does not lead to pure signal phases in both dimensions and the spectra have to be processed in the magnitude mode (cf. p. 285).

For true phase sensitive COSY experiments the SHR or TPPI method (p. 301) have to be used. In the former, the number of t_1 experiments is doubled and a 90° phase shift for one pulse of the COSY sequence is introduced between both data sets that are then stored as the real and imaginary part, respectively, of the t_1 -FID. In the alternative approach that is based on the Redfield quadrature detection method, which we did not discuss here, the phase of one pulse is incremented in 90° steps together with t_1 , hence the name *time proportional phase increment*. A version that uses field gradients is mentioned in Section 9.7.

9.7

Gradient Enhanced Spectroscopy

Apart from the construction of more sophisticated pulse sequences for the detection of spin correlations and magnetization transfer processes, the progress made in developing new experimental methods has also shown that the traditional phase cycling techniques discussed in the preceding section can be replaced in many of the important 2D experiments by the use of linear B_0 field gradients, a basic element of the NMR imaging method (cf. Chapter 15).

If, after a 90°_x excitation pulse, a linear B_0 field gradient ΔG_z is applied for a time t_G along the z -axis to the ensemble of spins present in the NMR sample tube, the Larmor frequencies of nuclei in different volume elements v_i vary by $\omega + \Delta\omega_i$ because the amplitude of the effective field varies by $B_0 + \Delta B_i$. Consequently, macroscopic transverse magnetization is defocused and the NMR signal destroyed (Figure 9.28b). This is not surprising as we have emphasized earlier (Chapter 4) that field homogeneity is a prerequisite for the detection of NMR signals.

In the case of a *short* gradient pulse, however, where t_G is in the order of a few milliseconds, the signal can be recovered and a so-called gradient echo (Figure 9.26d) is detected. For this purpose, within a time where diffusion is negligible, the spin system is subjected to a second field gradient with the same amplitude but of opposite polarity, $-\Delta G_z$ (Figure 9.26c). This is true if we deal exclusively with single-quantum coherences (SQ).

Imagine now a situation where, in addition to SQ coherence, double-quantum coherence (DQ) is generated, such as, for example, by application of two successive 90°_x pulses as in the case of a COSY experiment. A first gradient pulse ΔG_z after the 90°_x excitation pulse and just before the mixing pulse then changes the Larmor frequencies to $\omega + \Delta\omega$, while a second gradient pulse ΔG_z after the mixing pulse yields $\omega_{SQ} = \omega + 2\Delta\omega$ for the SQ coherence but $\omega_{DQ} = \omega + 3\Delta\omega$ for the double-quantum coherence (remember that DQ created by the mixing pulse rotates with

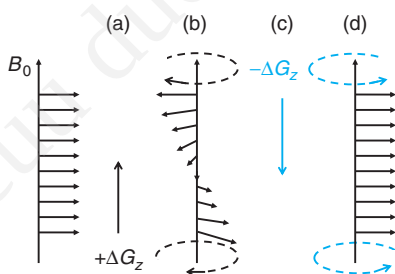


Figure 9.28 A magnetic field gradient, $+\Delta G_z$, applied along the z -axis of the external field B_0 destroys the transverse magnetization $M_{x,y}$ because the Larmor frequency varies along the z -direction (a), (b). The dephasing of the individual spins can be eliminated and the original $M_{x,y}$ signal recovered if a second field

gradient with a polarity opposite to that of the first, $-\Delta G_z$, is applied before diffusion sets in, (c) and (d). In the case of diffusion the $M_{x,y}$ signal will be diminished or completely destroyed because the spins have changed their position on the B_0 field axis.

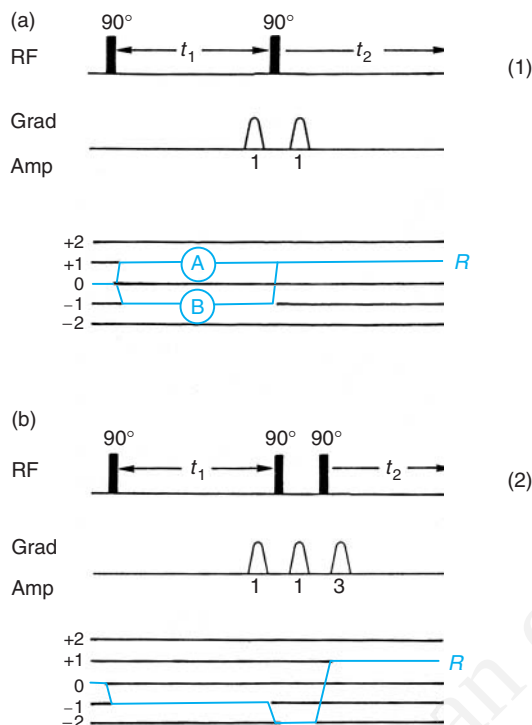


Figure 9.29 Pulse sequences for gradient enhanced COSY (a) and COSY-DQF (b) spectroscopy.

twice the Larmor frequency). Selective rephasing of SQ or DQ can then be achieved by applying a reverse gradient pulse with amplitude $2\Delta G_z$ or $3\Delta G_z$, respectively.

With gradient pulses matched to the requirements of the particular pulse sequence and the type of magnetization, signal selection is possible by initiating defocusing and refocusing processes. Pulsed field gradients can also be used to eliminate, or *purge* completely, unwanted magnetization, for example, transverse magnetization that arises from an incomplete 180° pulse of z -magnetization.

Let us now discuss with the example of the COSY experiment how field gradients can be used for the selection of coherence pathways. The rotational sense of the dephasing caused by the gradient pulse, + or -, is thereby determined by the sign of the coherence order p . On page 325 we have shown how echo selection (coherence B) is achieved with a simple phase cycle that requires, however, four individual experiments for one t_1 increment. Using field gradients, the same result is obtained already with *only one* experiment by applying pulse sequence (1) shown in Figure 9.29a. Thereby, the effect of the gradient is governed by the product of coherence order and gradient strength, $p \times \Delta G_z$.

The first gradient pulse causes dephasing of coherence B (coherence order $p = -1$) by $-\Delta G_z$ and of coherence A ($p = +1$) by $+\Delta G_z$. After the mixing pulse, coherence B is transferred to coherence level +1 and the second gradient pulse

of the same amplitude applied just before signal detection leads to a dephasing effect of $+\Delta G_z$ that exactly cancels the effect of the first gradient pulse. Thus, coherence B can be detected. On the other hand, for coherence A we have $p = +1$ during t_1 and after the mixing pulse again $p = +1$ and the dephasing amounts to $+2\Delta G_z$. The result is an elimination of coherence A and the technique allows quadrature detection in F_1 . Using alternatively $+$ and $-$ for the second gradient pulse ΔG_z , coherences A and B that have an opposite sense of rotation, can be stored separately and this allows quadrature detection in F_1 . In addition, other unwanted parts of the magnetization (t_1 -noise, axial peaks) are also dephased, thereby improving the quality of the spectrum. We note further that coherence selection by the field gradient technique occurs for each FID and does not rely on the addition or subtraction of signals as required by the conventional phase cycling technique. The method is thus time-saving and furthermore less sensitive to hardware instabilities because dephasing of unwanted signals occurs even if the gradients are not perfectly adjusted.

In quantitative terms, for the effect Φ of a linear B_0 field gradient pulse on a particular coherence we have:

$$\Phi = z p \gamma \Delta G_z t_G \quad (9.40)$$

where z is the distance (in cm) of an individual spin from the gradient origin, p is the coherence order, γ the gyromagnetic ratio ($\text{rad T}^{-1} \text{s}^{-1}$), ΔG_z the gradient strength (T cm^{-1}), and t_G (in s) the gradient pulse time. The requirement for detection of the desired magnetization in pulse sequences with several applied field gradients obviously is $\sum \Phi = 0$. Since, if the effect of gradients in a certain pulse sequence are considered, z , γ , and t_G are constant, Eq. (9.40) simplifies to $\Phi = p \times \Delta G_z$ as already stated above. Please note that now the *coherence order* p is important, while in Eq. (9.39) of the phase cycling procedure the *coherence level shift* Δp was decisive.

Coherence selection is also important for the COSY-DQF experiment and can be achieved with the gradient technique by the pulse sequence of Figure 9.29b. To see how this sequence works we follow the coherence pathway $0 \rightarrow (-1) \rightarrow (-2) \rightarrow (+1)$ for the *N*-type signal. Application of the first gradient pulse leads to a dephasing proportional to $(-1) \times \Delta G_z$ that increases after the second gradient pulse of the same amplitude to $(-3) \times \Delta G_z$. The desired echo is finally generated by a refocusing gradient $(+3) \times \Delta G_z$ that is applied after SQ magnetization has been re-established by the third 90_x° pulse. The *P*-type signal that follows the coherence pathway $0 \rightarrow (+1) \rightarrow (+2) \rightarrow (+1)$, on the other hand, dephases with $(+6) \times \Delta G_z$.

Exercise 9.12

Discuss the consequences of pulse sequence (2) in Figure 9.29 for the remaining double-quantum coherences as well as for the zero- and single-quantum coherences of the COSY-DQF experiment shown in the Figure given in the Solution to Problems.

Today, the gradient technique has been installed in most pulse sequences for homo- and heteronuclear shift correlations and, as compared to the phase cycling technique, improves these experiments with respect to the suppression of artifacts as well as to the measuring time necessary and thus leads to a better signal-to-noise ratio. To avoid chemical shift evolution during t_G due to the action of B_0 the gradient can be applied in combination with a spin echo experiment that refocuses this effect and phase errors can be avoided. A drawback may arise for measurements of small molecules in solvents of low viscosity where diffusion losses of the signal can occur that lead to incomplete refocusing. We shall learn later that this actually forms the basis for the measurement of diffusion coefficients by NMR.

9.8

Universal Building Blocks for Pulse Sequences

As we discuss more advanced pulse sequences in the following chapters, we shall see that the spin echo experiment (p. 248) is repeatedly used as an important building block that refocuses inhomogeneity and chemical shift effects. Similarly, in a heteronuclear sequence a simple $180^\circ(X)$ - or $180^\circ(A)$ -pulse can be introduced at the center of a time interval to decouple the X from the A nuclei and vice versa. In the following, we discuss briefly four other important building blocks frequently used in modern pulse NMR spectroscopy. Figure 9.30 (p. 330) gives a graphical representation of these experiments.

9.8.1

Constant Time Experiments: ω_1 -Decoupled COSY

In the COSY-90 sequence (Figure 9.12, p. 296), homonuclear coupling operates during t_1 and t_2 . Accordingly, splittings due to spin–spin coupling appear in both frequency dimensions, F_1 and F_2 . Homonuclear decoupling in F_1 requires that J -modulation of transverse magnetization during t_1 is eliminated. This is achieved by introducing a non-stationary 180°_x pulse in a constant time interval, Δ , between the two 90°_x pulses (Figure 9.30a). Because the 180°_x pulse affects both the A and the X nucleus, the evolution of coupling within the constant time interval Δ is unaffected and identical for every t_1 experiment. Hence, there is no signal modulation by J -coupling. On the other hand, chemical shift effects are refocused during t_1 , but evolve during the remaining interval $\Delta - t_1$ that is the true evolution time. Clearly, by shifting the 180°_x pulse, $\Delta - t_1$ is incremented. The result is a ω_1 -decoupled COSY spectrum that yields in F_1 a “ ^1H -decoupled ^1H spectrum” that is a singlet for every proton resonance. Resolution in F_1 is thus greatly improved and the ^1H chemical shifts are immediately available.

9.8.2

BIRD Pulses

For a heteronuclear AX system it is often important to separate transverse magnetization due to coupled spins from magnetization of uncoupled or weakly coupled

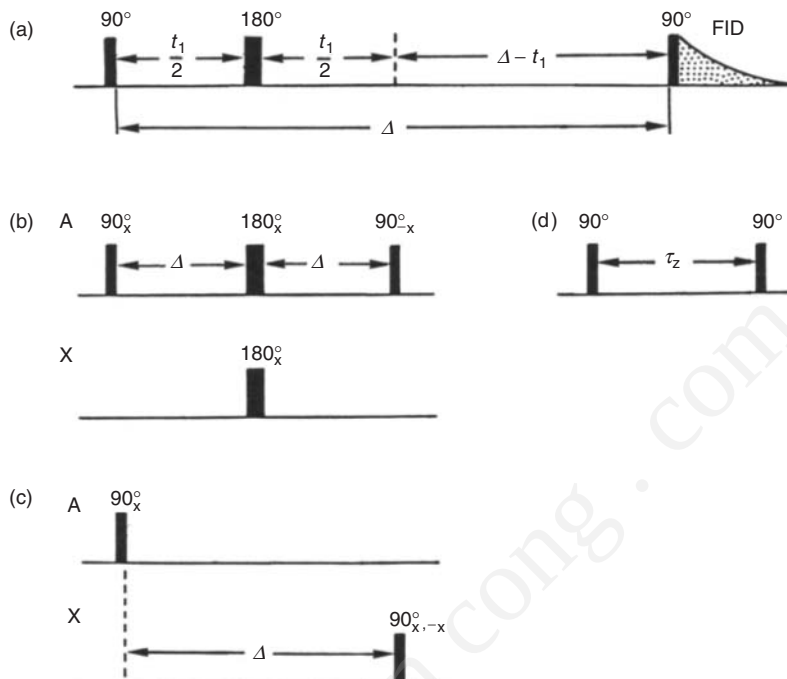


Figure 9.30 Building blocks for modern pulse sequences: (a) the “constant time” experiment for ω_1 -decoupled COSY spectroscopy; (b) the BIRD pulse; (c) low-pass filter; (d) z-filter.

spins. For this purpose the *pulse sandwich* shown in Figure 9.30b can be used. If the delay Δ is set equal to $1/2J(\text{AX})$, coupled A-magnetization $\hat{I}_y(\text{A})$ evolves to form anti-phase A-magnetization $2\hat{I}_z(\text{X})\hat{I}_x(\text{A})$. The 180°_x pulses change the sense of rotation and after the second Δ delay this magnetization is refocused along the $+\gamma$ -axis and transferred into $+z$ -magnetization by the 90°_{-x} pulse. Uncoupled or only weakly coupled A-magnetization, on the other hand, evolves according to the following scheme:

$$\hat{I}_z \xrightarrow{90^\circ_x} \hat{I}_y \xrightarrow{\Delta} \hat{I}_y \xrightarrow{180^\circ_x} -\hat{I}_y \xrightarrow{\Delta} -\hat{I}_y \xrightarrow{90^\circ_{-x}} -\hat{I}_z \quad (9.41)$$

and is thus selectively inverted. This sequence is known as a “*bilinear rotation operator*” or *BIRD pulse*.

9.8.3

Low-Pass Filter

Another building block for heteronuclear AX situations that separates magnetization of coupled spins from those of non-coupled or weakly coupled spins employs two 90° pulses separated by a delay Δ (Figure 9.30c). For $\Delta = 1/2J(\text{A,X})$, anti-phase

magnetization that evolved after the first 90° pulse is transformed into double-quantum magnetization that changes sign with the phase change for the second $90^\circ(X)$ pulse. Addition of two experiments destroys this magnetization, while that of uncoupled A spins is essentially unchanged and that of weakly coupled spins is only slightly reduced because evolution to anti-phase magnetization is here much slower.

9.8.4

z-Filter

An efficient way to select a desired magnetization component and purge a pulse sequence from undesired coherences is the so-called z-filter. It consists of a 90°_x pulse pair separated by a delay τ_z (Figure 9.30d). The first pulse is used to transform a desired transverse magnetization into z-magnetization. During the following delay τ_z all remaining transverse components oscillate and are effectively eliminated if experiments performed with different τ_z values are co-added. The desired magnetization that was stored on the z-axis during τ_z is transformed into transverse magnetization suitable for detection by the second 90°_x pulse.

9.9

Homonuclear Shift Correlation by Double Quantum Selection of AX Systems – the 2D-INADEQUATE Experiment

After becoming familiar with the phenomenon of double-quantum coherence, another correlation experiment based on double-quantum magnetization will now be discussed. It was originally developed for ^{13}C NMR spectroscopy to facilitate the recognition of neighboring ^{13}C pairs in natural abundance, an ambitious project indeed considering that these pairs occur in only 1 molecule out of a total number of 10 000! The experiment, originally performed in the 1D version, is known as INADEQUATE (*incredible natural abundance double quantum transfer experiment*) and we consider this further in Chapter 11. In the following we describe the 2D version with applications to pairs of abundant spins like coupled protons, where it does not suffer from low sensitivity.

The basic idea of the INADEQUATE pulse sequence is to use a two-dimensional experiment to separate overlapping, weakly coupled two-spin systems of the AX type. The separation then yields a unique assignment. Since in a chain of NMR active nuclei each spin, with the exception of those at the chain ends, has two neighbors and, therefore, participates in two different AX spin systems, the identification of the AX systems reveals the spin connectivities in a particular molecular structure.

Each AX system is characterized by its Larmor frequencies ν_A and ν_X as well as by the double quantum frequency $\nu_{\text{DQ}} = \nu_A + \nu_X - 2\nu_0$ (ν_0 = transmitter frequency). On a frequency axis $F_1 = \nu_{\text{DQ}}$ it can thus be distinguished from all other systems with different ν_{DQ} -values, if in a two-dimensional spectrum the F_2 -axis contains

the Larmor frequencies ν_A and ν_X , and the F_1 frequency axis the double quantum frequency ν_{DQ} .

In principle, the experiment can be performed with the following pulse sequence:

$$90^\circ_x \text{---} 1/4J_{AX} \text{---} 180^\circ_x \text{---} 1/4J_{AX} \text{---} 90^\circ_x \text{---} t_1 \text{---}, \text{FID } (t_2) \quad (9.42)$$

We shall use this sequence to illustrate the spin physics behind the experiment more closely. For practical applications several modifications are necessary that will be discussed later.

An analogy between the INADEQUATE and the COSY-DQF experiment may be seen if the pulse sandwich of the preparation period, $90^\circ_x \text{---} 1/4J \text{---} 180^\circ_x \text{---} 1/4J \text{---} 180^\circ_x$ that is in essence a spin echo sequence followed by a 90°_x pulse, is regarded as equivalent to the first two 90° pulses of the COSY-DQF sequence. During the evolution time t_1 that follows, double-quantum magnetization evolves that is converted into observable SQ magnetization by a 90° pulse as read pulse. A more detailed analysis is possible within the framework of the product operator formalism.

Let us start with longitudinal A and X magnetization and the 90°_x excitation pulse:

$$\begin{aligned} \sigma_0 &= \hat{I}_z(A) + \hat{I}_z(X) \\ \downarrow 90^\circ_x [\hat{I}_x(A) + \hat{I}_x(X)] \\ \sigma_1 &= \hat{I}_y(A) + \hat{I}_y(X) \end{aligned}$$

The effect of the delay $1/4J_{AX}$, 180°_x , $1/4J_{AX}$ can easily be visualized with the help of the classical Bloch vector picture: the components of the A and the X doublet fan out and will be turned around the x -axis by the 180°_x pulse. Because this pulse is non-selective, it exchanges the spin states of the A as well as the X nucleus. Consequently, the doublet components continue to fan out until they are in anti-phase on the x -axis after the second $1/4J_{AX}$ interval. In this way pure anti-phase A and X magnetization is produced and phase differences that result from differences in the Larmor frequencies are eliminated by the 180°_x pulse. Accordingly, the density operator σ_2 results:

$$\sigma_2 = 2\hat{I}_x(A)\hat{I}_z(X) + 2\hat{I}_z(A)\hat{I}_x(X)$$

Exercise 9.13

Derive σ_2 with the help of Eq. (9.23b) (p. 315).

The next 90°_x pulse yields:

$$\begin{aligned} \sigma_3 &= 2\hat{I}_x(A)\hat{I}_y(X) + 2\hat{I}_y(A)\hat{I}_x(X) \\ &= (1/i)[\hat{I}^+(A)\hat{I}^+(X) - \hat{I}^-(A)\hat{I}^-(X)] \end{aligned}$$

that is pure double-quantum coherence of the order $p = 2$ and -2 that develops during the evolution time t_1 according to Eq. (9.24) with the sum of the Larmor frequencies $\omega_A + \omega_X$. The frequency axis F_1 thus contains the double quantum

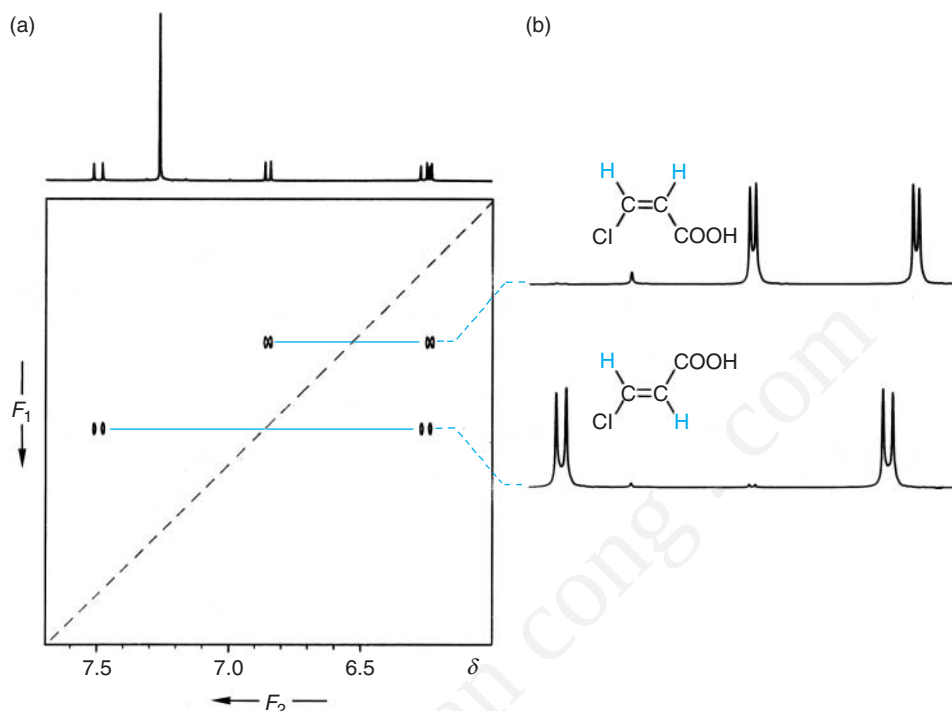


Figure 9.31 2D INADEQUATE $^1\text{H}, ^1\text{H}$ NMR spectrum of a mixture of (Z)- and (E)-2-chloroacrylic acid at 400 MHz (olefinic region): (a) contour diagram and (b) F_2 -traces of the two AX-systems. For the $1/4J$ delay (23 ms) the average of the two vicinal $^1\text{H}, ^1\text{H}$ -coupling constants ($J_{\text{cis}} = 8.4$, $J_{\text{trans}} = 13.4$ Hz) was used.

frequencies of the AX systems. Transformation of the double-quantum coherence into detectable transverse magnetization is achieved by the last pulse:

$$\begin{aligned} \sigma_3 & \\ \downarrow 90^\circ [\hat{I}_x(A) + \hat{I}_x(X)] & \\ \sigma_4 = -2\hat{I}_x(A)\hat{I}_z(X) - 2\hat{I}_z(A)\hat{I}_x(X) & \end{aligned}$$

that generates anti-phase A and X magnetization, which are detectable as an anti-phase doublet at ν_A and ν_X , respectively. Using magnitude representation, positive signals are obtained.

Figure 9.31 shows the result of a 2D-INADEQUATE experiment for the mixture of (E)- and (Z)-2-chloroacrylic acid in $\text{CDCl}_3/\text{CHCl}_3$ discussed already with its COSY-DQF spectrum on p. 308. Both AX systems are clearly separated and the centers of both spectra fall on a line with the inclination 2; since their F_2 frequency is $(\nu_A + \nu_X)/2$, their F_1 frequency, however, is $\nu_A + \nu_X$. As in the COSY-DQF experiment the solvent signal (one-quantum magnetization) is eliminated.

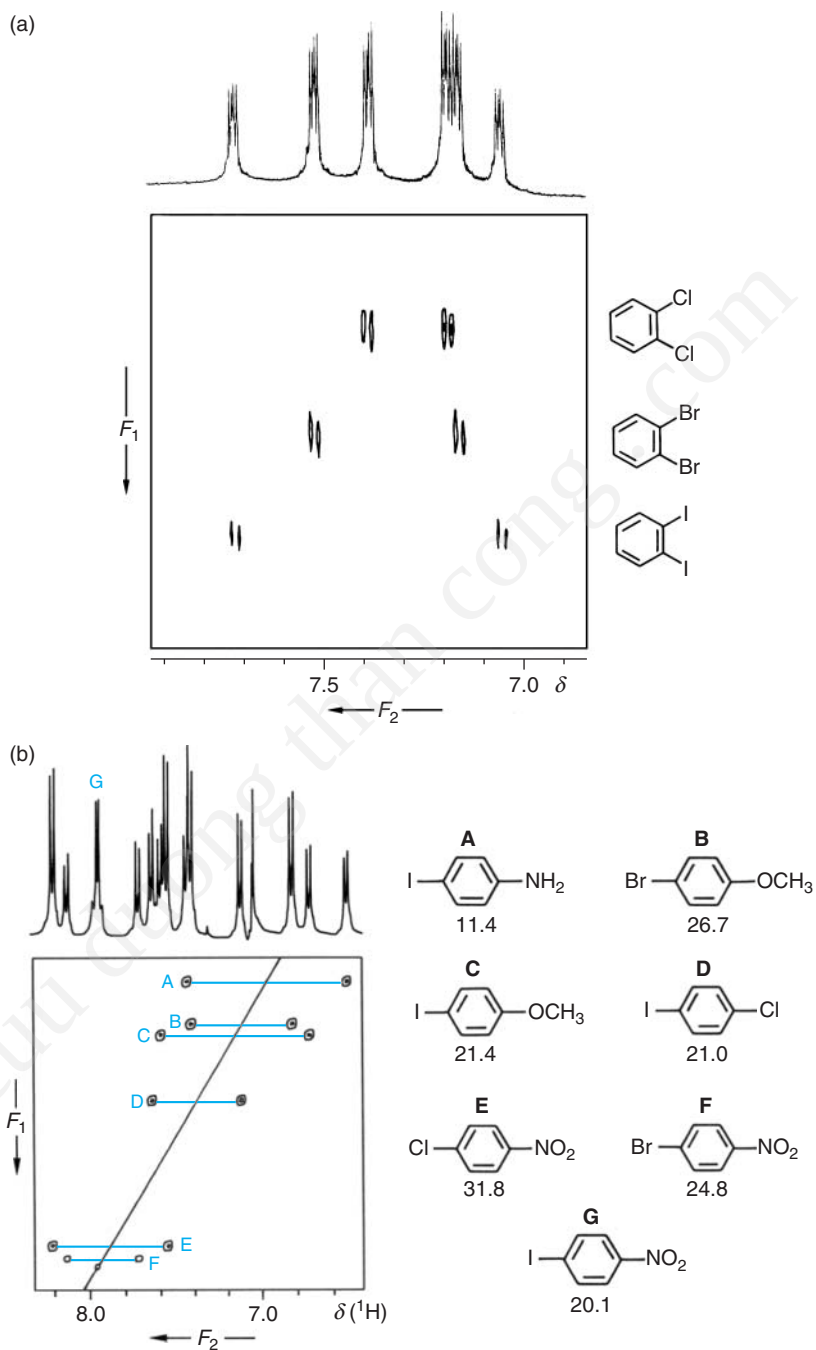


Figure 9.32 (a) Contour diagram of the 400 MHz 2D-INADEQUATE ^1H NMR spectrum of a mixture of *o*-dichloro-, *o*-dibromo-, and *o*-diiodobenzene with 1D spectrum. For the 2D experiment the following parameters were used: 64 t_1 increments, 32 scans each; sweep width in F_1 500 Hz, in F_2 1 kHz, $1/4J$ -delay 40 ms (optimized for the N -parameter of about 6 Hz); 2 s relaxation delay, digital resolution in F_1 1.95 Hz per pt, in F_2 7.8 Hz per pt; measuring time 2.7 h. (b) 400 MHz 2D INADEQUATE ^1H spectrum of seven *p*-disubstituted benzenes **1–7** (weight in millimoles below formulae); the strongly coupling spin system **7** leads only to a diagonal peak [7].

As compared to Eq. (9.42), the pulse sequence of the 2D-INADEQUATE experiment is somewhat modified for practical applications. A 135° read pulse eliminates unwanted signals that arise in cases where the A and/or the X nucleus are further coupled to a third nucleus. In addition, for any t_1 value a second sequence is applied, where a phase shift of 90° for the detected signal results. In this way quadrature detection in F_1 is achieved. The phase cycle of the INADEQUATE experiment is relatively complicated, since it combines the selection of double-quantum magnetization with the CYCLOPS cycle for quadrature detection and the suppression of axial signals. As in other cases, signal selection is simplified by the use of gradient pulses.

In comparison to the standard COSY experiment that yields practically the same correlation information, the 2D-INADEQUATE experiment has the advantage that diagonal signals are absent. Its dependence on the $1/4J_{AX}$ delays may be seen as a disadvantage. In addition, small coupling constants will lead to long measuring times. However, the experiment is not very sensitive to the correct choice of J_{AX} , and AX systems with similar couplings can be detected simultaneously without difficulties. For larger spin systems, where more than two protons are involved (e.g., AMX-systems), magnetization transfer to so-called passive spins, only weakly coupled to the A or X nucleus, yields additional signals. As mentioned above, a variation of the read pulse angle eliminates these peaks. In general, satisfactory results for ^1H , ^1H INADEQUATE spectra can always be expected if the structure of interest is dominated by vicinal coupling constants.

The usefulness of the 2D-INADEQUATE experiment for the analysis of mixtures will be demonstrated with two examples where strong signal overlap prevents the assignment and identification of individual spectra. In Figure 9.32a,b spectra of the AA'XX'-type, as are found in *ortho*- or *para*-disubstituted benzenes, have been separated by a 2D-INADEQUATE experiment in the form of a "spin chromatography." An N -parameter (cf. p. 196) of 6 Hz was chosen to adjust the $1/4J_{AX}$ delay. Even the spectra of seven components could be separated in not more than 30 min (Figure 9.32b).

The possibility of evaluating vicinal proton connectivities for spectral assignments is finally demonstrated in Figure 9.33 (p. 336) with the results of a 2D-INADEQUATE experiment for the ^1H NMR spectrum of adenosine (Figure 9.33a), where the assignment of the ribose protons is achieved, which have vicinal coupling constants of the order of 3.0–9.7 Hz. With an $1/4J$ -delay of 83 ms, which corresponds to a coupling of 3 Hz, all neighboring protons can be recognized

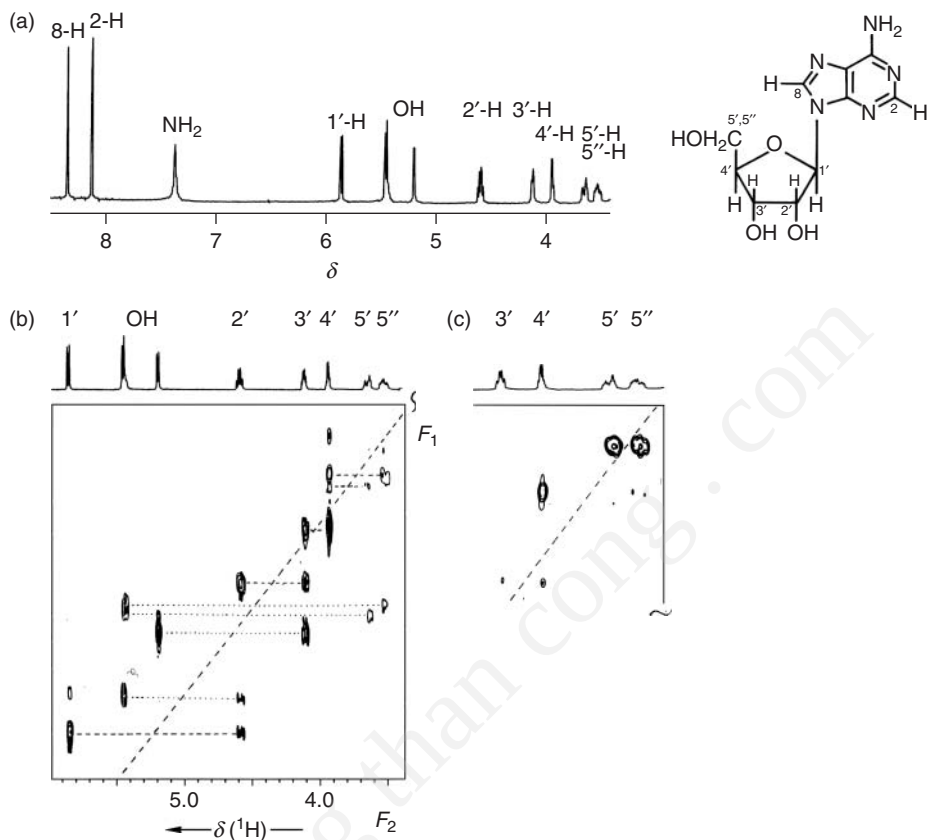


Figure 9.33 2D-INADEQUATE ^1H NMR spectrum of adenosine at 400 MHz; solvent DMSO- d_6 : (a) 1D spectrum; (b) 2D-INADEQUATE spectrum in the ribose region with $1/4J = 83$ ms ($\cong 3$ Hz coupling); (c) part of the 2D-INADEQUATE spectrum with $1/4J = 50$ ms ($J = 5$ Hz).

(Figure 9.33b). Only the signals due to the geminal protons 5'-H and 5''-H are not detected. The coupling amounts here to 12.7 Hz and a second experiment with $1/4J = 50$ ms had to be performed (Figure 9.33c). Interestingly, assignment of the OH signals is also feasible, because in the solvent dimethyl sulfoxide the hydroxyl protons exchange slowly and couple with the protons at the ribose ring.

9.10

Single-Scan 2D NMR

The introduction of 2D and multidimensional homo- and heteronuclear NMR spectroscopy has enlarged enormously the area of NMR applications and opened

the way for completely new experimental techniques. One must admit, however, that it has also increased the measuring times. The development of methods that reduce the time necessary for such experiments is therefore of vital interest to NMR spectroscopists. The goals of this activity can be twofold: (i) reduction of the number of spectral accumulations necessary for enhancement of weak signals, which is achieved, for example, by various NOE or INEPT experiments, and (ii) reduction of the time taken to measure the series of t_1 experiments required by a 2D NMR spectrum. To conclude this chapter we thus want to mention briefly an approach that addresses the second aspect and can help to solve these time problems, namely, *single-scan* 2D NMR

The idea behind this approach - which might surprise the reader who has learned that 2D NMR spectra need a minimum of 16 scans but normally much more - comes again from gradient techniques used in the field of MRI (magnetic resonance imaging). In a “normal” 2D experiment the spins of our sample that are equally distributed over the sample volume in the NMR tube are all excited at the same time and an identical signal is recorded for nuclei of the same type from all parts of the sample. If we could have a method that allowed exciting the spins in different portions of the sample separately, we could introduce a space-selective excitation by one scan and perhaps produce a series of different, space-selective evolution times t_1 . A spatially resolved acquisition followed by Fourier transformation would then provide the basis for the particular 2D spectrum, where the necessary t_1 experiments are all excited by a single scan instead of being collected as a result of n scans. Of course, signal enhancement by spectral accumulation would still be necessary for weak resonances.

The recipe for performing the technique described above is known in MRI as echo-planar imaging (EPI), where it was developed by P. Mansfield and his group for slice selection in MRI experiments. For our purpose it consists of applying a z -gradient G_z to the sample and performing sequential excitation of the spins by using a train of frequency-shifted RF pulses G_e . Equal time-shifts and frequency offsets produce spin ensembles with different t_1 values. To remove offset effects, each excitation pulse $+G_e$ is followed by a reversed pulse $-G_e$, thus producing gradient echoes. Spatially discriminating t_2 acquisition followed by Fourier transformation with respect to t_2 and t_1 yields the 2D spectrum in one scan and an experiment time of less than 1 s [8].

Of course, alternative methods for reducing the time necessary for multidimensional NMR spectra have been developed and tested, for example, Hadamard spectroscopy, which uses soft pulses for simultaneous selective excitation and does not need phase cycles and quadrature detection. The interested reader will find more about these aspects in the monograph edited by Morris and Emsley listed below.

References

1. Günther, H. and Schmitt, P. (1985) *Kontakte (Merck)*, 2, 3.
2. Günther, H. and Moskau, D. (1986) *Kontakte (Merck)*, 2, 41.

3. Benn, R. and Günther, H. (1983) *Angew. Chem.*, **95**, 381; *Angew. Chem., Int. Ed. Engl.*, **22**, 350–380.
4. Bax, A. and Freeman, R. (1981) *J. Magn. Reson.*, **44**, 542.
5. Moskau, D. and Günther, H. (1987) *Angew. Chem.*, **99**, 151; *Angew. Chem., Int. Ed. Engl.*, **26**, 1212–1220.
6. Hausmann, H. (1991) PhD thesis, University of Siegen.
7. Schmalz, D. (1989) PhD thesis, University of Siegen.
8. Frydman, L., Lupulescu, A. and Scherf, T. (2003) *J. Amer. Chem. Soc.*, **125**, 9204; (b) Gal, M., Frydman, L., in Morris, G.A. and Emsley, J.W.(eds) (2010) *Multidimensional NMR Methods for the Solution State*, Wiley, Chichester UK, p. 43.
- Brey, W.S. (ed) (1988) *Pulse Methods in 1D and 2D Liquid-Phase NMR*, Academic Press, New York, 561 pp.
- Ernst, R.R., Bodenhausen, G., and Wokaun, A. (1987) *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*, Clarendon Press, Oxford, UK, 610 pp.

Application Oriented

- Sanders, J.K.M. and Hunter, B.K. (1987) *Modern NMR Spectroscopy – A Guide for Chemists*, Oxford University Press, Oxford, UK, 308 pp.
- Friebolin, H. (2010) *Basic One- and Two-Dimensional NMR Spectroscopy*, Wiley-VCH Verlag, Weinheim, 449 pp.
- Akitt, J.W. and Mann, B.E. (2000) *NMR and Chemistry*, 4th ed., Stanley Thornes, Cheltenham, UK, 400 pp.

Textbooks and Monographs

Methods Oriented

- Claridge, T.D.W. (1999) *High-Resolution NMR Techniques in Organic Chemistry*, Elsevier, Amsterdam, 382 pp.
- Keeler, J. (2005) *Understanding NMR Spectroscopy*, Wiley & Sons, Ltd., Chichester, UK, 459 pp.
- Levitt, M.H. (2009) *Spin Dynamics*, 2nd ed. Wiley, Chichester, UK, 714 pp.
- Freeman, R. (1997) *Spin Choreography*, Spectrum Academic Publishers, Oxford, UK, 391 pp.
- Morris, G.A. and Emsley, J.W. (eds) (2010) *Multidimensional NMR Methods for the Solution State*, Wiley & Sons, Ltd., Chichester, UK, 564 pp.
- Braun, S., Kalinowski, H.-O., and Berger, S. (2008) *200 and More Basic NMR Experiments*, Wiley-VCH Verlag, Weinheim, Germany.
- Martin, G.E. and Zektzer, A.S. (1988) *Two Dimensional NMR Methods for Establishing Molecular Connectivity – A Chemist's Guide to Experiment Selection, Performance, and Interpretation*, VCH Publishers, New York, 508 pp.
- Croasmun, W.R. and Carlson, R.M.K. (eds) (1994) *Two-Dimensional NMR Spectroscopy, Methods in Stereochemical Analysis*, VCH Publishers, Weinheim, **9**, 2nd ed, 511 pp.

Review articles

- Williams, K.R. and King R.W. (1990) The Fourier transform in chemistry–NMR: Part 3. Multipulse experiments. *J. Chem. Educ.*, **67**, A93; Williams, K.R. and King, R.W. (1990) The Fourier transform in chemistry–NMR: Part 4. Two-dimensional methods. *J. Chem. Educ.*, **67**, A125.
- Hull, W.E. (1994) Experimental aspects of two-dimensional NMR, in *Two-Dimensional NMR Spectroscopy, Methods in Stereochemical Analysis*, 2nd edn, Vol. 9 (eds W.R. Croasmun and R.M.K. Carlson), VCH Publishers, New York, p. 67.
- Gray, G.A. (1994) Introduction to two-dimensional NMR-methods, in *Two-Dimensional NMR Spectroscopy, Methods in Stereochemical Analysis*, 2nd edn, Vol. 9 (eds W.R. Croasmun and R.M.K. Carlson), VCH Publishers, New York, p. 1.
- Kessler, H., Gehrke, M., and Griesinger, C. (1988) Two-dimensional NMR spectroscopy: background and overview of the experiments. *Angew. Chem.*, **100**, 507; *Angew. Chem., Int. Ed. Engl.*, **27**, 490.
- Morris, G.A. (1986) Modern NMR Techniques for Structure Elucidation. *Magn. Reson. Chem.*, **24**, 371.

- Turner, D.L. (1984) Multiple Pulse NMR in Liquids. *Prog. Nucl. Magn. Reson. Spectrosc.*, **16**, 311; Turner, D.L. (1985) *Prog. Nucl. Magn. Reson. Spectrosc.*, **17**, 281.
- Sørensen, O.W., Eich, G.W., Levitt, M.H., Bodenhausen, G., and Ernst, R.R. (1984) Product operator formalism for the description of NMR pulse experiments. *Prog. Nucl. Magn. Reson. Spectrosc.*, **16**, 163.
- Benn, R. and Günther, H. (1983) Modern pulse methods in high resolution NMR spectroscopy. *Angew. Chem.*, **95** (381); *Angew. Chem., Int. Ed. Engl.*, **22**, 350.
- Pelczer, I. and Szalma, S. (1991) Multidimensional NMR and data processing. *Chem. Rev.*, **91**, 1507.
- Freeman, R. (1991) Selective excitation in high-resolution NMR. *Chem. Rev.*, **91**, 1397.
- Berger, S. (1997) NMR techniques employing selective radiofrequency pulses in combination with pulsed field gradients. *Prog. Nucl. Magn. Reson. Spectrosc.*, **30**, 137.
- Buddrus, J. (1996) INADEQUATE Experiment, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 4, (eds. in chief D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester, UK, p. 2491.
- Buddrus, J. and Lambert, J. (2002) Connectivities in molecules by INADEQUATE: recent developments. *Magn. Reson. Chem.*, **40**, 3.

cuu duong than cong . com

10

More 1D and 2D NMR Experiments: the Nuclear Overhauser Effect – Polarization Transfer – Spin Lock Experiments – 3D NMR

10.1

The Overhauser Effect

Different phenomena are considered in connection with the notion of the *Overhauser effect*. In each case a variation of signal intensity observed during double resonance experiments is involved, but different mechanisms may be responsible for the observed effect. Most important for chemical applications is the nuclear Overhauser effect (NOE), which allows signal enhancement for low- γ nuclei and serves for the determination of inter-proton distances. It is an indispensable aid in structural analysis, in particular for problems of stereochemistry, and in its two-dimensional form, known as *NOESY*, it has become the basis for structural determinations of biological macromolecules.

10.1.1

Original Overhauser Effect

In the case of the original Overhauser effect, discovered by A.W. Overhauser in 1953, for a system that consists of a nuclear spin I and an electron spin S , an increase in the intensity of the nuclear resonance signal is observed if the electron resonance is simultaneously saturated with an RF field of frequency ν_S . This experiment may be performed on a paramagnetic solution of sodium in liquid ammonia by observing the proton resonance under conditions that saturate the electron resonance.

The resulting intensity increase of the nuclear resonance lines can be rationalized by reference to the *Solomon diagram* shown in Figure 10.1 (p. 342) where the eigenstates of a two-spin system IS in a magnetic field are represented. Altogether, there exist four states of different energy and for their arrangement the different sign of the nuclear and electron spin is important. Transitions for the nucleus or the electron can be stimulated by an RF field of the frequency ν_I or ν_S , respectively. Let us consider the probability, W , for the particular relaxation transitions that are responsible for the maintenance of the Boltzmann distribution. The quantities W_1 and $W_{1'}$ correspond to the probability for longitudinal relaxation of nuclear and

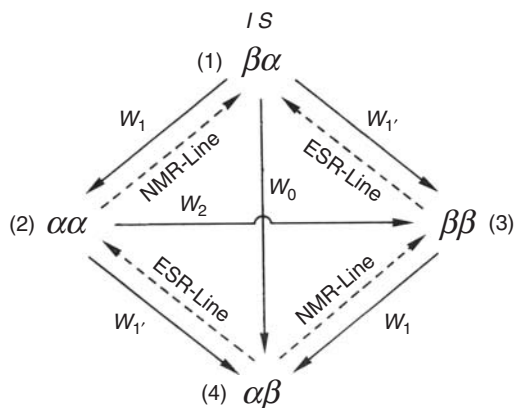


Figure 10.1 Solomon diagram for a two-spin system IS composed of a nuclear spin I and an electron spin S .

electron spins, respectively. In addition there are also the transition probabilities W_2 and W_0 for cases in which nuclear and electron spins flip simultaneously. W_2 and W_0 are of significance only when there is a spin–spin interaction between the spins I and S . If the electron resonance, that is, the transitions $(3) \rightarrow (1)$ and $(4) \rightarrow (2)$, is saturated by an oscillating field B with the frequency ν_S , then the Boltzmann distribution between the states (3) and (1) as well as between (4) and (2) will be disturbed, that is, the populations of (1) and (2) will become too high while those of (3) and (4) will become too low. This perturbation can be counteracted by an increased number of relaxation transitions, that is, through an increase in W_0 , since in this fashion the state (1) is depopulated and the population of state (4) is raised. For the NMR signals, on the other hand, that is, for the transitions $(4) \rightarrow (3)$ and $(2) \rightarrow (1)$, this leads to an intensity enhancement because the net effect of the process is the overpopulation of state (2) and the depopulation of state (3) since the spins are carried along the route $(3) \rightarrow (1) \rightarrow (4) \rightarrow (2)$. The result is a *polarization* of the nuclear spin distribution and the experiment is known as dynamic nuclear polarization (DNP).

For the preceding experiment it is important that the relation $W_0 \gg W_2$ is satisfied. An electron spin thus can flip only when a nucleus simultaneously changes its spin orientation in the opposite direction. In this case the relaxation is produced predominantly through a time-dependent *scalar* spin–spin coupling. In the previously mentioned solution of sodium in liquid ammonia the unpaired electrons are solvated by ammonia molecules. A fast exchange of these molecules between the solvation shell of different paramagnetic centers has the result that the proton–electron coupling vanishes. It maintains its effectiveness, however, as a relaxation mechanism.

Let us consider once more the situation we have just described but now with reference to the magnitude of the energies that are exchanged with the lattice in the relaxation process. For every quantum mechanical system that is characterized

by two energy levels E_p and E_q an equilibrium is established so that the number of transitions $E_p \rightarrow E_q$ is equal to the number of transitions $E_q \rightarrow E_p$. It then follows for the eigenstates (1) and (4) of the spin system **IS** that:

$$N_\alpha n_\beta W_{\alpha\beta \rightarrow \beta\alpha} = N_\beta n_\alpha W_{\beta\alpha \rightarrow \alpha\beta} \quad (10.1)$$

where N_α and N_β signify the populations of the nuclei and n_α and n_β that of the electrons. $W_{\alpha\beta \rightarrow \beta\alpha}$ and $W_{\beta\alpha \rightarrow \alpha\beta}$ denote the transition probabilities. According to the Boltzmann law we have:

$$\frac{N_\beta n_\alpha}{N_\alpha n_\beta} = \frac{W_{\alpha\beta \rightarrow \beta\alpha}}{W_{\beta\alpha \rightarrow \alpha\beta}} = \exp\left(\frac{-\Delta E}{kT}\right) = \exp[-h(\nu_S + \nu_I)/kT] \quad (10.2)$$

If the electron resonance is saturated then $n_\alpha = n_\beta$ and:

$$\frac{N_\beta}{N_\alpha} = \exp[-h(\nu_S + \nu_I)/kT] \quad (10.3)$$

Because $h\nu_S \gg h\nu_I$, the nuclear spin distribution that normally obeys the expression:

$$\frac{N_\beta}{N_\alpha} = \exp(-h\nu_I/kT) \quad (10.4)$$

is now determined by the very much larger energy difference $h\nu_S$.

10.1.2

Nuclear Overhauser Effect (NOE)

If we carry on this train of thought to a spin system that consists of two *nuclear* spins, we arrive at the so-called *nuclear Overhauser effect (NOE)*. For this case the Solomon diagram must be modified, since now both spins have the same sign and the sequence of the states is changed (Figure 10.2). Besides the longitudinal

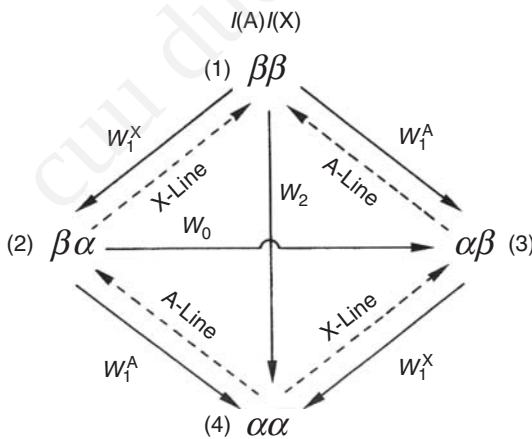


Figure 10.2 Solomon diagram for a two-spin system composed of two *nuclear* spins.

relaxation probabilities W_1 for the A and the X nucleus, respectively, cross relaxation probabilities W_2 for the double quantum transition and W_0 for the zero quantum transition are now of importance. Both are a consequence of *dipolar* spin–spin interactions between A and X.

If the resonance of one nucleus, for example, A in Figure 10.2, is irradiated, an increase in the intensity of the X resonance occurs if $W_0 \ll W_2$. Spin population is then transported from state (3) to state (2) via states (1) and (4). Taking the population of states (1) and (4) in a first approximation as constant, state (3) is depopulated and state (2) is overpopulated. The Boltzmann distribution for the X lines thus requires signal enhancement. Since the frequencies of W_0 transitions are of the order of hertz or kilohertz, while the W_2 frequencies are in the megahertz range, the condition $W_0 \ll W_2$ is always satisfied for mobile liquids or solutions of low molecular weight compounds that have a low viscosity.

Quantitative treatment of the phenomenon leads to the so-called *Solomon equation*, an expression for the increase in the z -magnetization of nucleus X, $M_z(X)$, relative to the equilibrium magnetization, $M_0(X)$:

$$\frac{M_z(X)}{M_0(X)} = 1 + \frac{\gamma_A}{\gamma_X} \left(\frac{W_2 - W_0}{2W_1(X) + W_2 + W_0} \right) \quad (10.5)$$

If a pure dipole–dipole interaction exists between the two nuclei, W_2 , W_1 , and W_0 are in the ratio of $1 : \frac{1}{4} : \frac{1}{6}$ and Eq. (10.5) reduces to:

$$\frac{M_z(X)}{M_0(X)} = 1 + \frac{\gamma_A}{2\gamma_X} \quad (10.6)$$

For the homonuclear case ($\gamma_A = \gamma_X$) a signal enhancement of 50% results. This is, for example, the maximum NOE between protons ($A = X$). For ^{13}C of a ^1H , ^{13}C spin pair the effect is four times as large (200%) if the ^1H resonance is irradiated, because $\gamma(^1\text{H})/\gamma(^{13}\text{C}) \approx 4$. The nomenclature for such experiments is $^{13}\text{C}\{^1\text{H}\}$, with the irradiated nucleus in brackets. The ratio $\gamma_A/2\gamma_X$ of Eq. (10.6) is known as *nuclear Overhauser enhancement*, η . Figure 10.3 shows an example of a heteronuclear NOE.

Accordingly, the NOE is an important tool for improving the sensitivity of NMR measurements of less sensitive nuclei, that is, nuclei with small γ -factors. This is standard practice in ^{13}C NMR spectroscopy, for example, where ^1H broadband decoupling is applied (cf. p. 276). Problems arise, however, if the X nucleus has a negative gyromagnetic ratio, such as for instance ^{15}N or ^{29}Si . The nuclear Overhauser enhancement $\gamma_A/2\gamma_X$ is then negative and the observed X signal will be inverted. Much less favorable conditions are met if competing relaxation mechanisms lead to a reduction of the nuclear Overhauser enhancement. In the limit $\gamma_A/2\gamma_X \approx -1$, the X signal can even be eliminated [see Eq. (10.6)]. A decrease of the NOE is always to be expected if other than dipolar relaxation mechanisms are present.

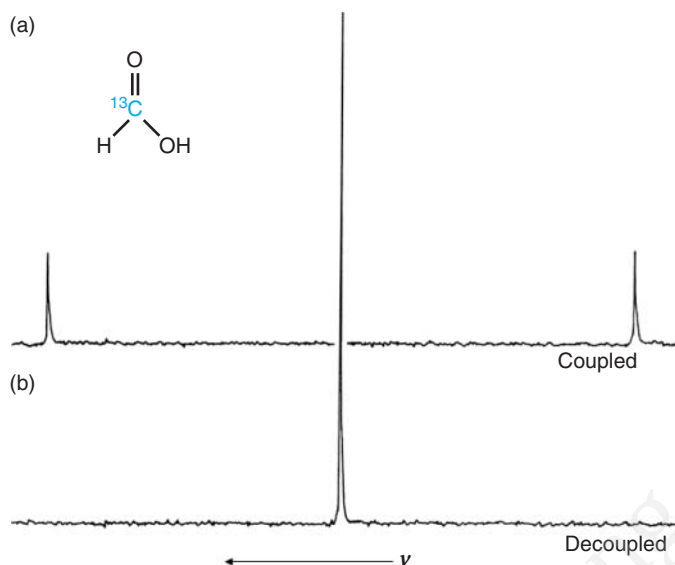


Figure 10.3 ^{13}C NMR spectrum of formic acid ^1H coupled (a) and ^1H decoupled (b); the enhancement η for the ^{13}C signal is close to the maximum of 1.98. In cases as that shown, an additional intensity increase comes from the collapse of multiplets caused by spin–spin coupling [1] (With permission; Copyright Professor R.K. Harris, University of Durham).

10.1.3

One-Dimensional Homonuclear NOE Experiments

10.1.3.1 NOE Measurements of Relative Distances between Protons

It is important to remember that the NOE is governed by dipolar relaxation processes and does not involve scalar spin–spin coupling between the nuclei A and X. The cross relaxation probability is proportional to the factor $1/r^6$ and depends therefore on the distance between the nuclei of interest. For fast molecular motion in liquids the following relation, already presented in Chapter 8 (p. 242) for the dipolar relaxation rate constant R_1 , holds:

$$R_1^{DD} \propto \gamma_C^2 \gamma_H^2 r_{\text{CH}}^{-6} \tau_c \quad (10.7)$$

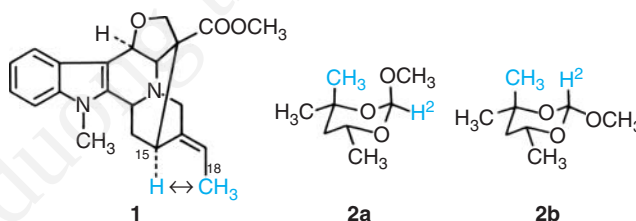
where τ_c is the correlation time for molecular reorientation (cf. p. 240). The practical importance of homonuclear NOE experiments for the measurement of relative distances between protons is based on this relation. Besides the use of NOE effects for signal enhancement, this is the largest area of application for this technique. NOE measurements are consequently valuable aids in structural research and conformational analysis when it is necessary to decide which of two nuclei, A or B, is closer in space to a third nucleus C within the same molecule. Problems of this type are encountered in connection with *cis–trans* isomerism about double bonds and in the conformational analysis of alicyclic compounds.

Experimentally, one measures spectra by irradiating the resonance at ν_C with a secondary field from the ^1H decoupler or transmitter ($\gamma B_2 \approx 10$ Hz for about 10 s), thereby monitoring the intensity of the resonances at ν_A and ν_B . The larger intensity increase is observed for the pair of nuclei that has the smaller distance r , that is, one uses the simplified relation:

$$\eta_{AC}/\eta_{BC} = (r_{BC}/r_{AC})^6 \quad (10.8)$$

This procedure is valid, if for both pairs of nuclei, AC and BC, the same correlation time applies and no NOE exists between A and B. With rigid molecules, the first condition is always met.

Thus it was possible by means of nuclear Overhauser experiments to assign unequivocally the resonances of the methyl groups in dimethylformamide (cf. p. 501 and Figure 1.5, p. 4). Only when the methyl signal at lower field is irradiated is an intensity increase observed for the signal of the formyl proton. This absorption is thus identified as that of the methyl group that stands *trans* to the carbonyl group. In other examples the configuration of the ethylidene side-chain of the alkaloid dehydrovoachalotine (**1**) was established and it could be decided whether 2-methoxy-4,4,6-trimethyl-1,3-dioxane exists in the *cis*- or the *trans*-form (**2a** or **2b**, respectively). For **1** an intensity increase of 26% was observed for the signal of 15-H when the resonance of the methyl group at C18 was irradiated. For the dioxanes the irradiation of one of the methyl groups at the 4-position in **2b** led to a 12% increase in intensity of the signal for H^2 while no such effect was observed in the case of **2a**. We come back to the aspect of distance measurements in Section 10.1.4.



10.1.3.2 NOE Difference Spectroscopy

A useful technique for the estimation of *relative* proton distances by nuclear Overhauser measurements is NOE difference spectroscopy. With this technique, the time signal $S(t_2)$ is accumulated for experiments that are alternatively run with and without irradiation at the ^1H resonance of interest. The data are stored in two different blocks of the computer memory and the difference is obtained before or after Fourier transformation. The Overhauser enhancement remains as the *NOE difference spectrum* (Figure 10.4, p. 347). This form of NOE spectroscopy is very sensitive and allows the detection of small intensity differences (as low as about 3%), because the signals from experiments with and without irradiation are recorded practically under identical conditions. To achieve this, the experiment without irradiation at the proton signal of interest is performed as an off-resonance

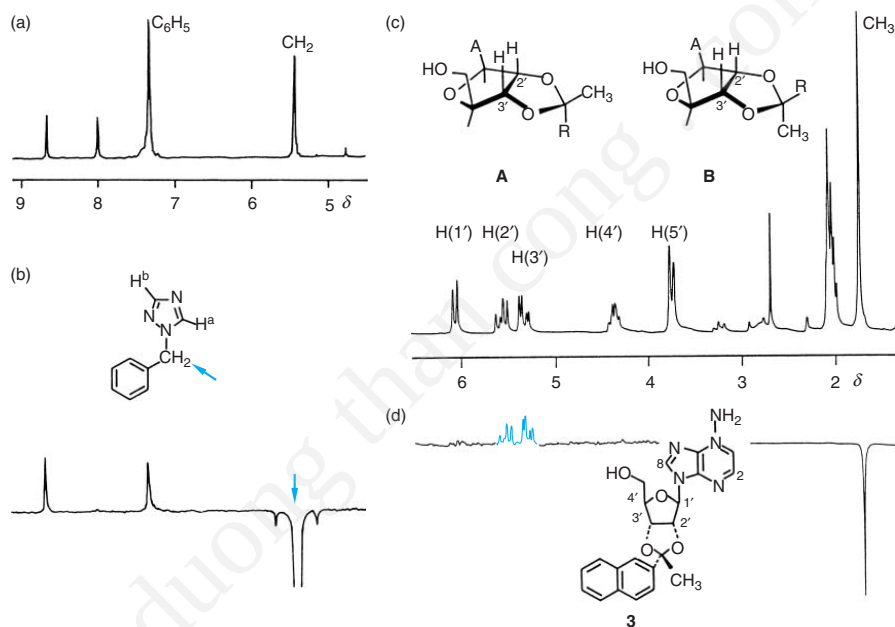


Figure 10.4 80 MHz ^1H NMR spectrum (a) and NOE-difference spectrum (b) of 1-benzyl-1,2,4-triazole for the assignment of the ^1H resonances in the triazole ring [2]. The inverted CH_2 -signal results from the difference between experiments with on-resonance and off-resonance ^1H irradiation; the high-frequency signal at δ 8.7 is identified as H^a . (c) 80 MHz ^1H NMR spectrum and NOE difference spectrum (d) of the ketal from adenosine and 2-acetylnaphthalene (**3**) in the aliphatic region. The signal of the methyl group was irradiated in order to distinguish both configurations A and B. An NOE effect is found for $\text{H}(2')$ and $\text{H}(3')$. Consequently, configuration A with an *exo*- CH_3 group exists. H. Uzar, personal communication.

experiment with the B_2 field positioned outside the spectral window or at the TMS signal.

For NOE measurements we can differentiate between those that use *CW* (continuous wave) irradiation at nucleus A while detecting nucleus X on the one hand and measurements where the X nucleus is detected *after* A nucleus irradiation on the other.

In the first case, for example, NOE experiments for signal enhancement in a heteronuclear AX system like ^1H , ^{13}C , we have a *steady state* experiment. This means that during irradiation of the A resonance a stationary state is reached with respect to the competition between perturbation and re-establishment of the Boltzmann distribution in the spin system. The distance dependence of the cross relaxation probability $W_2 - W_0$ determines the magnitude of the effect and the stronger the perturbation, the stronger also is the driving force to restore the original spin populations and thus the increase in intensity of the X transitions.

In contrast, the spectrum of the X nucleus may be excited by the pulse *after* the irradiation time, t_{NOE} , for the A nucleus during which the Overhauser effect was built up. In the detection time, t_2 , a *transient* NOE is then measured and the relation $\eta_{\text{exp}} < \eta_{\text{max}}$ is valid.

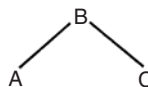
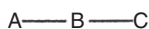
Furthermore, an alternative to the sequence (pre-irradiation(t_{NOE}), 90°_x , FID) is a selective experiment (180°_{sel} ----- t_M ----- 90°_x , FID) where the NOE selectively builds up in the mixing time t_M through cross-relaxation between the pre-selected nucleus and its neighbors and only signals arising from NOE effects with this nucleus are detected. The sequence is known as *1D NOESY* and is an anticipation of the 2D method discussed in the Section 10.1.4. An improved version that uses gradients (DPFGSE-NOE) is also available.

It should be understood that the *intramolecular* NOE is quenched by all influences that allow relaxation via mechanisms other than *intramolecular* dipole-dipole interactions. In particular, *intermolecular* dipole-dipole interactions that contribute to T_{idd}^{-1} must be minimized. The sample solutions should thus be free of oxygen and possibly degassed, and the solvents of choice are those that have only a few magnetic nuclei, such as CS_2 or CCl_4 . In addition, the concentration of the compound under investigation should not be too high.

10.1.4

Complications during NOE Measurements

Several complications during practical applications of NOE measurements result from the fact that in the molecules studied not only isolated two-spin systems are present but in general a certain proton has a large number of different neighbors. For the simple case of three nuclei A, B, and C, for example, a linear and an angular geometry are possible:



In the first case, after A irradiation one finds an intensity increase for nucleus B that is, however, smaller than expected. For the nucleus C, on the other hand, the intensity may have decreased. Such a finding is the result of an indirect NOE effect that is a consequence of dipolar cross relaxation between B and C. A perturbation of the Boltzmann population at B is, therefore, restored not only through an increasing number of B transitions but also through a contribution from nucleus C. In the energy level diagram for the partial spin system BC the population differences of the B nucleus are increased as a consequence of A irradiation. This means, on the other hand, that the population differences for the C nucleus and consequently the intensity of the C resonance decreases. If a fourth nucleus D is present, the effect changes sign again and becomes positive. Indirect NOE effects of this type are generally known as *spin diffusion*. This effect was already seen in the very first application of an NOE experiment for deriving a stereochemical assignment [3] where the methyl groups of 1,1-dimethylacrylic acid could be distinguished by irradiation at positions 1, 2, or 3:

		NOE (%) at H(1)
①	→ <chem>CC(C)=C</chem> H(1)	1: +17
②	→ <chem>CC(C)=C</chem> COOH	2: -4
③	→ Off-resonance	3: 0

A change of the geometry in the direction of an angular arrangement, on the other hand, can give rise to a direct NOE effect between A and C. It has a positive sign and will thus be diminished or even nullified through the negative indirect effect A–C. Consequently, even in the case of relatively short nuclear distances, an NOE effect may not be observed.

A further factor that may complicate NOE measurements is scalar spin–spin coupling. NOE theory for strongly coupled spin systems is, as expected, complex and beyond the level of our introduction. In the case of weakly coupled spin systems, which are met in most cases studied today with high magnetic fields, NOE measurements may fail if selective population transfer (SPT), a phenomenon based on scalar spin–spin coupling and to be discussed in the next section, is present. This is particularly true if irradiation is applied to spin multiplets and special precautions have to be taken in such cases to evaluate the results.

Finally, with large molecules the dependence of the NOE on the product of resonance frequency, ω , and correlation time, τ_c , is important. NOE effects may completely vanish or become negative (Figure 10.5, p. 350). Such situations are found for macromolecules or small molecules in viscous solvents. Equations (10.5) and (10.6) are, therefore, valid only under the condition $\omega\tau_c \ll 1$, which is always true for small molecules ($MG < 500$) in isotropic solutions of low viscosity (*extreme narrowing condition*). In the negative region of the NOE effect we have for the cross relaxation $W_0 > W_2$, because during slow molecular motions frequencies in the kHz region dominate the relaxation process. According to Figure 10.2, upon A irradiation the spin population is now transported from state (4) to state

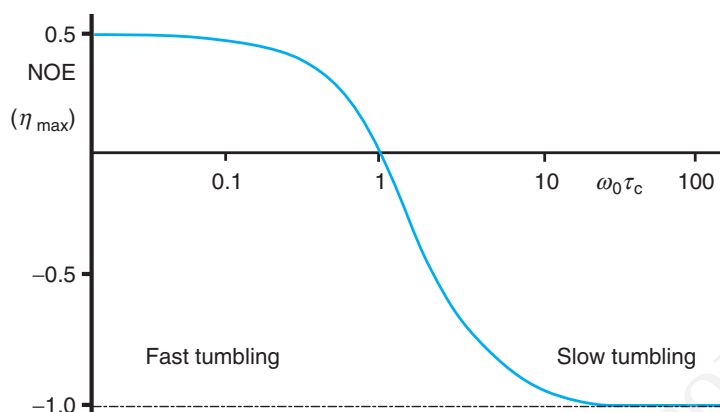


Figure 10.5 Dependence of the homonuclear NOE between protons on the product of Larmor angular frequency, ω_0 , and molecular correlation time, τ_c .

(1) via states (2) and (3), which results in a depopulation of state (4) and an overpopulation of state (1). Consequently, the X lines have an inverse Boltzmann distribution and yield negative (emission) signals. With large molecules it is, furthermore, impossible to assume a unique molecular correlation time, τ_c , since intramolecular dynamic processes must be added and the motion of individual parts of the molecule are not necessarily correlated. In addition, large molecules seldom behave isotropically.

10.1.5

Two-Dimensional Homonuclear Overhauser Spectroscopy (NOESY)

The pulse sequence:

$$90_x^\circ \text{-----} t_1 \text{-----} 90_x^\circ \text{-----} t_M \text{-----} 90_x^\circ, \text{FID}(t_2) \quad (10.9)$$

is used to record two-dimensional homonuclear Overhauser (NOESY) spectra. The exchange of magnetization during the mixing time, t_M , is based on dipolar cross relaxation. This experiment does not rely on irradiation of certain spins as discussed above in Sections 10.1.2–10.1.4 but uses the dipolar coupling between nuclei that are close in space. The magnetization transfer is completely analogous to the mechanism of spin–lattice relaxation we discussed in Chapter 8 (p. 239 ff). As with COSY (correlated spectroscopy) spectra, NOESY spectra display diagonal signals and off-diagonal cross peaks that yield correlation information and allow distance measurements.

The mechanism of the NOESY experiment can be explained on the basis of a classical Bloch vector picture (Figure 10.6). The first 90_x° pulse produces transverse magnetizations $M_y(A)$ and $M_y(X)$ that develop during the evolution time t_1 according to their Larmor frequencies (Figure 10.6a,b). At the end of the evolution

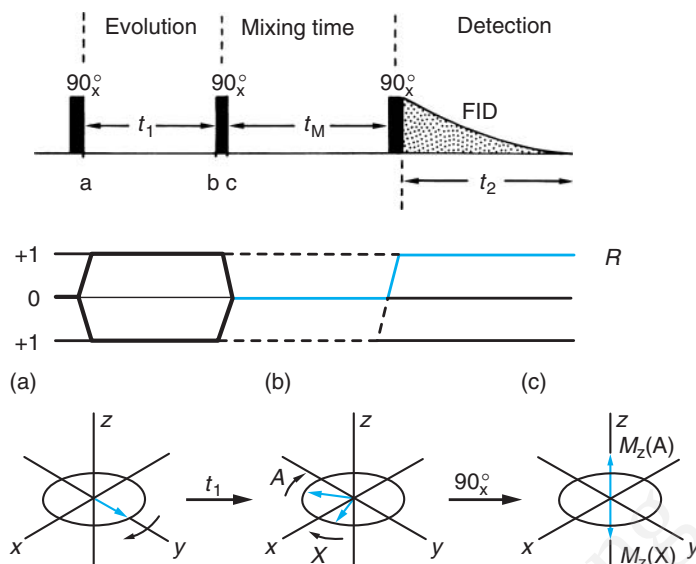


Figure 10.6 (a), (b) Pulse sequence for two-dimensional $^1\text{H},^1\text{H}$ NOESY spectroscopy (NOESY) with coherence transfer pathways and vector diagram; only the z-components of $M(A)$ and $M(X)$ are shown in (c); in the gradient-enhanced version (gs-NOESY) the phase cycle is replaced by a z-gradient during t_M that destroys all transverse magnetization components except zero-quantum coherences, which have to be eliminated by different methods (see below).

time all resonance signals of the particular spectrum have different phases, in other words they are labeled with their Larmor frequency. The second 90°_x pulse produces longitudinal z-magnetization that has, depending on the vector orientation, positive or negative sign and different magnitude (Figure 10.6c). During the mixing time t_M that follows the magnetization transfer is induced by dipolar cross relaxation. The amplitude of the transverse magnetization produced by the third 90°_x pulse and detected in t_2 depends, therefore, on the evolution time t_1 as well as on the efficiency of the magnetization transfer. The transfer rate during the mixing time t_M , which is of the order of 1–2 s, is a function of the Overhauser enhancement and also of the magnitude of the z-magnetization that is present at $t_M = 0$ (Figure 10.6c). As a consequence, magnetization transfer is t_1 -dependent and the signals in a series of t_1 -experiments are amplitude-modulated, which leads to cross peaks in the 2D spectrum. NOESY spectra have the same structure as COSY spectra: the 1D spectrum appears on the diagonal, the cross peaks as off-diagonal elements yield the desired information about spin correlations (Figure 10.6).

For larger molecules, NOESY spectra are a valuable tool for the assignment of partial spectra. Figure 10.7 (p. 352) shows such an application with the ^1H NMR spectrum of the dication of benzo[b]biphenylene (4). In the ^1H NMR spectrum of this compound one observes a singlet at δ 9.85 and two four-spin systems of

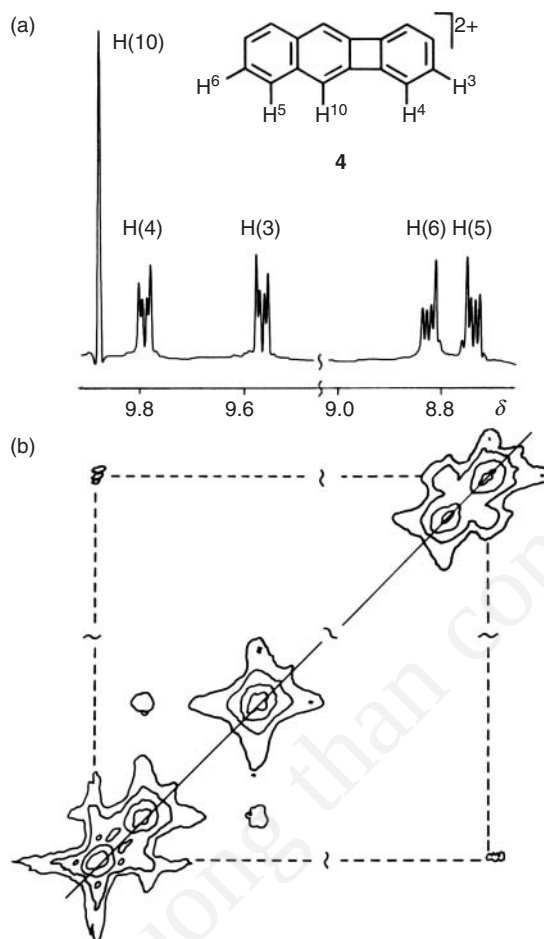


Figure 10.7 (a), (b) ^1H -2D NOESY spectrum of benzo[*b*]biphenyl dication (**4**) in SbF_6 at -30°C ; please note that the intensity of the cross peaks is much smaller than that of the diagonal peaks. A NOESY cross peak between H(10) and H(4) at the larger distance was, therefore, not observed under the experimental conditions used [4].

the AA'XX' and AA'BB' type, H(1)-H(4) and H(5)-H(8), respectively. The NOESY spectrum yields cross peaks between the singlet and the low-frequency part of the AA'BB' system. Because the singlet can be assigned unambiguously to the protons H(9,10), the BB'-part belongs to H(5,8) and both four-spin systems are thus identified. The assignment within the high-frequency AA'XX' system was established by other methods.

Within the product operator formalism (Chapter 9) the NOESY experiment for an AX system without scalar spin-spin coupling can be described by the following

equations:

$$\hat{I}_z(A) + \hat{I}_z(X) \xrightarrow{1^{\text{st}} 90^\circ [\hat{I}_x(A) + \hat{I}_x(X)]} \hat{I}_y(A) + \hat{I}_y(X) \quad (10.10a)$$

$$\xrightarrow{\omega_A t_1 \hat{I}_z(A) + \omega_X t_1 \hat{I}_z(X)} \hat{I}_y(A) \cos \omega_A t_1 + \hat{I}_x(A) \sin \omega_A t_1 + \hat{I}_y(X) \cos \omega_X t_1 + \hat{I}_x(X) \sin \omega_X t_1 \quad (10.10b)$$

$$\xrightarrow{2^{\text{nd}} 90^\circ [\hat{I}_x(A) + \hat{I}_x(X)]} -\hat{I}_z(A) \cos \omega_A t_1 + \hat{I}_x(A) \sin \omega_A t_1 - \hat{I}_z(X) \cos \omega_X t_1 + \hat{I}_x(X) \sin \omega_X t_1 \quad (10.10c)$$

As is expected on the basis of the pulse sequence shown in Eq. (10.9), Eqs (10.10b) and (10.10c) also contain terms that have been derived for the COSY sequence (p. 317 ff.) During the mixing time t_M the NOE leads to an exchange of the new z -magnetization:

$$\hat{I}_z(A) \cos \omega_A t_1 \rightleftharpoons \hat{I}_z(X) \cos \omega_X t_1 \quad (10.10)$$

Consequently, part of the magnetization that precesses during t_1 with ω_A will be modulated during t_2 with $\cos \omega_X t_2$ and vice versa. This leads to cross peaks at ω_A, ω_X and ω_X, ω_A . The transverse magnetization $\hat{I}_X$ present at the beginning of the mixing time is partly lost through transverse relaxation and will be eliminated through the phase cycle that selects only those coherences that have order zero during the mixing time (Figure 10.6).

COSY signals that are produced in most NOESY experiments because of the presence of geminal, vicinal, or long-range $^1\text{H}, ^1\text{H}$ -couplings must be eliminated through the phase cycle. Zero-quantum coherences (ZQCs), which because of their coherence order pass this filter, are eliminated through the introduction of a 180° pulse during the mixing time t_M . Alternatively, the statistical variation of t_M by about 20% serves the same purpose, since NOESY signals increase steadily, while signals from ZQCs have a sine oscillation during t_M and, therefore, cancel.

The large number of the various unwanted transverse magnetization components present during the mixing time requires for the success of the phase cycle several transients for one t_1 increment that lengthens the measuring time. A more elegant procedure is therefore possible through the use of a field gradient during the mixing time that defocuses irreversibly all transverse magnetization components while the z -magnetization is not affected. This experiment is known as *gs-NOESY*.

As we shall see later (Chapter 13), the pulse sequence in Eq. (10.9) can also be used to detect *chemical exchange*, where nuclei periodically change their Larmor frequency as a consequence of a reversible molecular dynamic processes like, for example, hindered rotation or ring inversion. The magnetization transfer during the mixing time is then induced by the dynamic process. In situations where both exchange and NOE effects operate, chemical exchange can be slowed down by

lowering the temperature. Pure NOE effects can then be observed in the region of slow exchange where the rate constant of the dynamic process, k , is smaller than $\sim 2 \times \delta\nu$, with $\delta\nu$ as the frequency difference (in hertz) between the two sites of different Larmor frequency (Chapter 13). Such a case is shown in Figure 10.8 with the 2D-NOESY spectrum of [6]paracyclophane-8,9-dimethyldicarboxylate (**5**) in the methylene proton region measured at -60°C . At that temperature the ring inversion is slow enough for only NOE effects to be observed. Interactions via the short distances between the geminal protons of the CH_2 -groups dominate, and their closeness in space is recognized by cross peaks. Interestingly, NOE effects between the protons of the methylene chain and the protons of the aromatic ring can also be detected. Because of the larger $^1\text{H}, ^1\text{H}$ distances involved, the corresponding cross peaks are considerably less intensive and appear in the contour plot only at a relatively low intensity level that already shows a lot of noise.

An alternative and more generally applicable method to distinguish NOE and chemical exchange is to record phase-sensitive spectra. Here we observe for the “normal” positive NOE effect diagonal and cross peaks with opposite sign, while

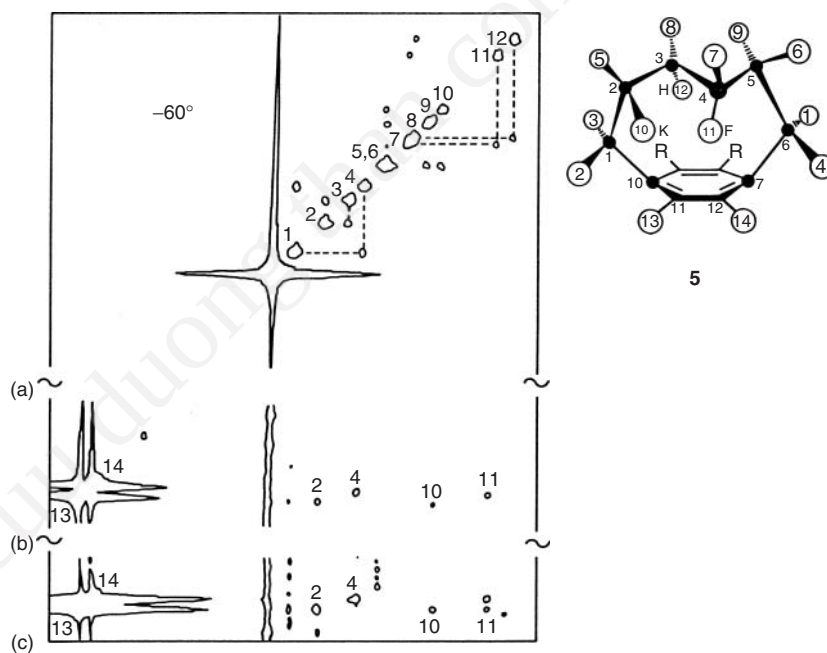


Figure 10.8 400 MHz 2D $^1\text{H}, ^1\text{H}$ NOESY spectrum of [6]paracyclophane-8,9-dimethyldicarboxylate (**5**) at -60°C with cross peaks of different intensity. The contour diagram (a) shows strong geminal NOE effects for all CH_2 groups (only 1/4, 7/11, and 8/12 are marked). The less intensive cross peaks between the various

CH_2 protons on one hand and the aromatic protons H(13) and H(14) on the other hand, which are characteristic for the conformation of the methylene chain, are found in (b) and (c), which were recorded at lower intensity levels; in (c) even cross peak 13/11 is observed [5].

for exchange spectra the same sign is found. However, negative NOE effects for macromolecules also yield the same sign for diagonal and cross peaks. In such cases the ROESY (rotating frame NOESY) experiment, discussed below in Section 10.3.2.3, can be used to differentiate between both effects. For ROESY spectra, the sign of both types of signals is always opposite (see Table 12, p. 671).

NOESY spectroscopy is today indispensable for the conformational analysis of biomolecules. It has paved the way for three-dimensional structure determination in solution because, in addition to correlations based on spin–spin coupling via the network of the chemical bonds, direct information about distances in space can be obtained. With a known reference distance r_r , for example, 178 pm for the H–H distance of a geminal methylene group, the distance of interest, r_i , can be derived from the proportionality of the cross peak intensities I :

$$I_r/I_i = r_r^{-6}/r_i^{-6} \quad (10.12)$$

Provided short mixing times in the pulse sequence prevent spin diffusion, one determines the intensity ratio in the linear regime of the build-up rates of the cross peaks measured through a variation of the mixing time in several 2D experiments. Alternatively, cross peak intensities can be compared to the reference value and classified as strong, medium, or weak. Based on experience, distances of the order of 0.25, 0.35, or 0.5 nm can then be assigned to certain proton pairs with an error of about 10%. The analysis of such NOE data for large molecules (MG up to 20 000) that consist of several hundred cross peaks can only be attempted with data processing, and powerful programs have been developed for this purpose. We come back to this topic in Chapter 15.

10.1.6

Two-Dimensional Heteronuclear Overhauser Spectroscopy (HOESY)

Adding another frequency channel to the pulse sequence of Eq. (10.9) leads to the two-dimensional version of a heteronuclear Overhauser experiment known by the acronym HOESY (heteronuclear Overhauser effect spectroscopy). This was first demonstrated for the ^1H , ^{13}C spin pair but has subsequently found important application in the field of organolithium compounds for ^1H , ^6Li spin pairs. As Figure 10.9 shows for a ^1H , X system, the sequence starts with a 90°_x (^1H) pulse and the evolution time t_1 . Transverse ^1H magnetization, $M_{x,y}(^1\text{H})$, is thus labeled

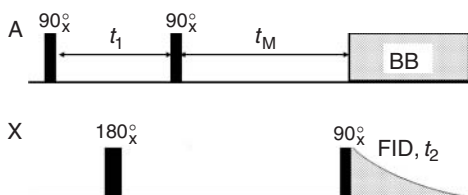


Figure 10.9 Pulse sequence for the two-dimensional heteronuclear Overhauser experiment (HOESY); A = ^1H .

with the ^1H Larmor frequencies. A 180°_x pulse after $t_1/2$ at the X channel produces negative X magnetization, $-M_z(X)$, and decouples X from A. The second 90°_x (^1H) pulse leads again to ^1H z -magnetization and ^1H ,X cross relaxation during the mixing time t_M starts. The read pulse at the X channel yields the X signal amplitude-modulated by the ^1H Larmor frequencies.

The ^1H , ^6Li HOESY experiment profits from the fact that ^6Li relaxation is dominated by dipolar interactions. Since the ^1H , ^6Li scalar coupling constants are usually much smaller than 1 Hz and hardly detected in the 1D ^6Li spectra the 180° X-pulse in the HOESY sequence can even be omitted. An example of a ^1H , ^6Li HOESY spectrum is shown in Figure 10.10 and we shall find out more about this experiment in Chapter 12.

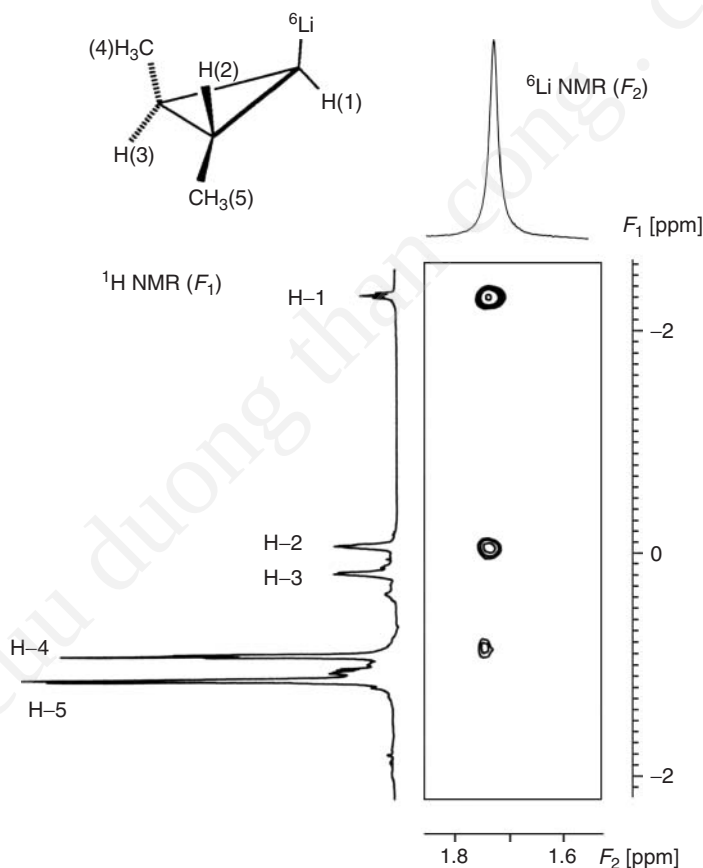


Figure 10.10 ^1H , ^6Li HOESY spectrum of *trans*-2,3-dimethylcyclopropyl-lithium at 179 K, 0.2 M in $[\text{D}_{10}]\text{diethyl ether}/[\text{D}_8]\text{THF}$ with the assignment of the CH_3 - and CH -signals; spectral window 2801 Hz (F_1), 121.3 Hz (F_2), mixing time 1.8 s, relaxation delay 2.5 s, experiment time 3.6 h; note the signal intensity decrease with increasing Li-H distance [6].

10.2

Polarization Transfer Experiments

While the *homonuclear* Overhauser effect between protons with the possibility of deriving ^1H , ^1H distances is an important tool in the field of stereochemistry, the main aspect of *heteronuclear* NOE effects is the sensitivity gain for insensitive nuclei with small γ -factors [see Eq. (10.6)]. The general importance of the latter aspect for NMR spectroscopy – but also the complications that arise during NOE experiments with nuclei that have negative γ -factors – has promoted the search for alternative ways of signal enhancement. The principle of these techniques is known as *polarization transfer* or *polarization inversion*. Contrary to the NOE, these methods rely on scalar spin–spin coupling and do not suffer from negative γ -factors. They can replace NOE measurements in all cases, where a scalar spin–spin interaction between the nuclei of interest exists.

10.2.1

SPI Experiment

For a two-spin AX system of a sensitive and an insensitive nucleus, for example, ^1H , ^{13}C or ^1H , ^{15}N , the equilibrium population of the energy levels and consequently the relative intensities of the A and X lines are governed by the Boltzmann law. The population difference between two states E_p and E_q is then determined by the gyromagnetic ratio of the particular nucleus that changes its spin-state during the transition $E_p \rightarrow E_q$. For states that are connected by the transitions of the sensitive nucleus (A, large γ), a larger population difference results than for those that belong to the transitions of the insensitive nucleus (X, small γ) (Figure 10.11). With $E = \pm \frac{1}{2} \gamma \hbar B_0$ (cf. p. 15) and $\frac{1}{2} \hbar B_0 = p$, we obtain for the energy of the states $\alpha\alpha$, $\alpha\beta$, $\beta\alpha$, and $\beta\beta$ of a two-spin system:

$$\begin{aligned} E_{\beta\beta} &= (\gamma_A + \gamma_X)p \\ E_{\beta\alpha} &= (\gamma_A - \gamma_X)p \\ E_{\alpha\beta} &= -(\gamma_A - \gamma_X)p \\ E_{\alpha\alpha} &= -(\gamma_A + \gamma_X)p \end{aligned} \quad (10.13)$$

and in the case of a ^1H , ^{13}C pair because $\gamma(^1\text{H}) : \gamma(^{13}\text{C}) \approx 4 : 1$ the relative population numbers are 5, 3, -3 , and -5 (Figure 10.11a) result (please note that the population is inversely proportional to the energy of the spin state). The relative intensities of the NMR lines are directly proportional to the corresponding differences, that is, $I(^{13}\text{C}) : I(^1\text{H}) = 4 : 16$ or $1 : 4$. The different natural abundance of the A and the X nucleus is not considered here.

A *selective population inversion (SPI)* for an A line, for example, A1, that interchanges the populations of the connected spin states, then leads to the energy level diagram of Figure 10.11b. It shows for the X lines increased absorption (X2) or emission (X1) and the relative intensities $+10$ and -6 or $+5$ and -3 , respectively. The total intensity found before for the sensitive nucleus (16 or 8 if divided by 2)

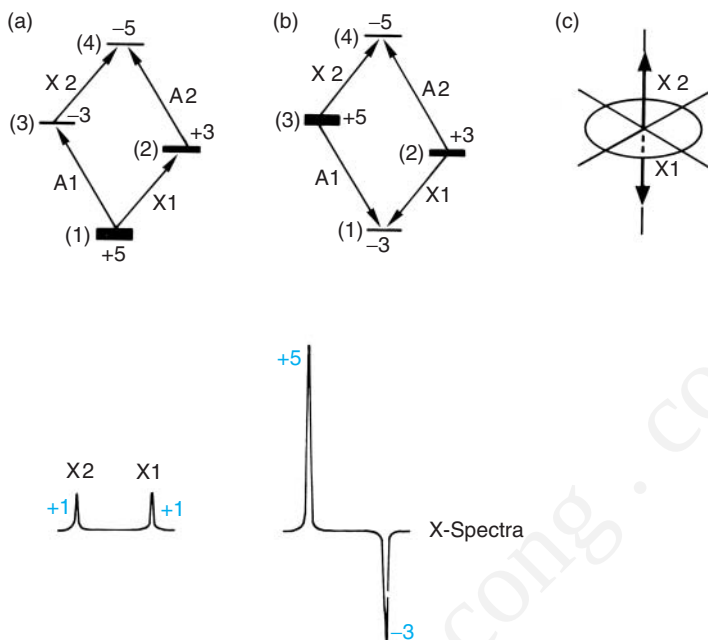


Figure 10.11 Perturbation of the Boltzmann distribution in an AX spin system through a selective 180° pulse on the line A1 of the sensitive A nucleus; (c) vector diagram for the X magnetization after population inversion.

is now observed for the absolute intensity of the lines of the insensitive nucleus. This phenomenon is called *polarization transfer*. The intensity increase achieved for the X nucleus corresponds to the ratio γ_A/γ_X . It is fully developed for the absorption line X2 ($I = 1 + \gamma_A/\gamma_X$). For the emission line X1, on the other hand, one obtains $I = 1 - \gamma_A/\gamma_X$, which still leads to an improved signal-to-noise ratio because generally $\gamma_A/\gamma_X \gg 1$. Note that, contrary to the NOE [Eq. (10.6)], the results are independent of the sign of γ_X . For negative γ_X values the emission and absorption lines are just interchanged. On the other hand, one must remember that the experiment does not yield a net effect, because the integrated intensity, $I(X1) + I(X2)$, is unchanged and with ^1H decoupling during ^{13}C detection an X line of the relative intensity 2 is observed.

Experimentally, population inversion can be achieved by a selective 180° pulse on one of the A lines. In practice this is done most simply for a $^1\text{H}, ^{13}\text{C}$ pair with the proton decoupler, which is adjusted in the CW mode at the frequency of one of the ^1H lines, that is, one of the ^{13}C satellite lines in the ^1H spectrum. If complete population inversion is not achieved, one speaks of SPT (selective population transfer). Figure 10.12 shows the experimental result for the $^1\text{H}, ^{13}\text{C}$ spin system of chloroform, which was the first published example.

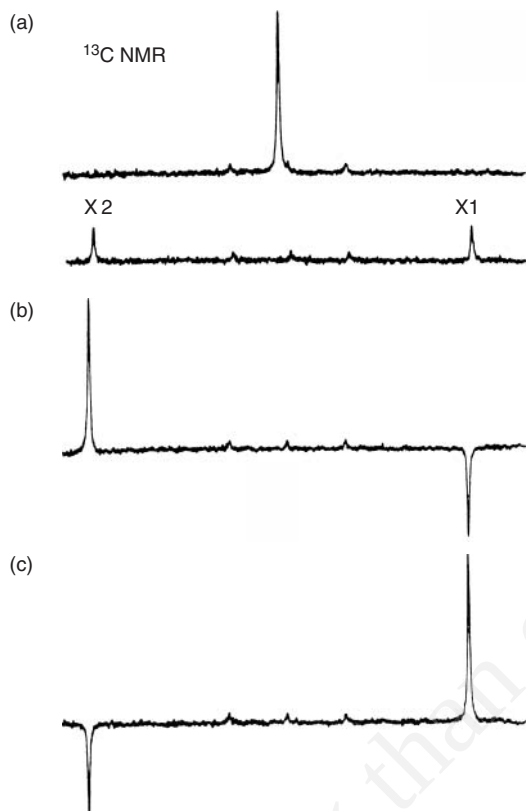


Figure 10.12 SPI experiment for the ^1H , ^{13}C spin pair of chloroform: (a) ^1H decoupled and ^1H coupled ^{13}C NMR signal; (b) ^{13}C spectrum after inversion of the ^1H signal A1 (low-frequency ^{13}C satellite; population inversion

according to Figure 10.11b); (c) spectrum after inversion of the ^1H signal A2 [high-frequency ^{13}C satellite; the low-intensity triplet close to $\delta(^{13}\text{C})$ is due to $^{13}\text{CDCl}_3$] [7].

Exercise 10.1

Describe the results for a 180° pulse on line A2.

The SPI experiment can be helpful for signal assignments as well as for the measurement of insensitive nuclei like ^{13}C , ^{15}N , or ^{29}Si , where ^1H , ^{19}F , or ^{31}P can serve as sensitive A nuclei. The intensity increase that is obtained for a first-order AX spin system of spin $\frac{1}{2}$ nuclei can be judged from a comparison with Pascal's triangle, which describes the normal intensity behavior of first-order spin multiplets (Figure 10.13, p. 360). An important limitation of the SPI method, however, lies in the fact that only one line can be inverted at a time and sensitivity enhancement is limited to a particular A,X spin pair. For structures with several insensitive nuclei of interest the experiment has to be repeated for each X nucleus.

(a)	n	(b)
	0	1
1	1	-3 5
1 2 1	2	-7 2 9
1 3 3 1	3	-11 -9 15 13
1 4 6 4 1	4	-15 -28 6 36 17
1 5 10 10 5 1	5	-19 -55 -30 -50 65 21
1 6 15 20 15 6 1	6	-23 -90 -105 20 135 102 25

Figure 10.13 Number of signals and their relative intensities for the X multiplet of an A_nX group ($A = {}^1\text{H}$) at normal Boltzmann distribution (a) and after selective population inversion for one A line (b).

10.2.2

INEPT Pulse Sequence

With respect to practical applications of polarization transfer experiments for the measurement of insensitive X nuclei important progress was made after it was recognized that polarization transfer can be achieved also non-selectively through a suitable pulse sequence. For this purpose the INEPT sequence (insensitive nuclei enhanced by polarization transfer), shown in Figure 10.14, was constructed. It is illustrated by a series of vector diagrams in Figure 10.14a–e.

Basic elements of the INEPT sequence are the modulation of transverse magnetization of the sensitive nucleus (A) by scalar coupling to the insensitive nucleus (X) and the simultaneous application of two 180°_X pulses in the A and X region. The vector arrangement reached for the doublet components of the A resonance after the evolution time $2\Delta = 1/2J$ can be transformed by a 90°_Y pulse into an arrangement typical for a spin system with selectively inverted Boltzmann distribution. As shown above, in the energy level diagram this corresponds to a population inversion over one A line and leads to X line polarization (Figure 10.14e).

The most important aspect of the INEPT method is the fact that it allows a much larger intensity increase for insensitive nuclei than the NOE. Furthermore, negative γ -factors are no disadvantage because polarization transfer is governed by the ratio γ_A/γ_X , while nuclear Overhauser enhancement is determined by the sum $1 + \gamma_A/2\gamma_X$ [Eq. (10.6), p. 344]. In addition, cumulative effects can arise during polarization transfer experiments in the case of degenerate lines. The theoretical enhancement factors for both methods, which, quite naturally, are only approximated in practice, are collected in Table 10.1. The signals of quaternary carbons and other nuclei without ${}^1\text{H}$ coupling are suppressed.

Typical for simple INEPT spectra without ${}^1\text{H}$ -decoupling is the zero intensity of the central line of an uneven multiplet as well as the inversion of half of the multiplet lines (NH : $-1, +1$; NH_2 : $-1, 0, +1$; NH_3 : $-1, -1, +1, +1$). This results from the phase cycle used, which eliminates the original X magnetization. Only magnetization generated by polarization transfer is detected. The integrated total intensity of an INEPT multiplet is, therefore, zero (compare the net effect in the SPI experiment). ${}^1\text{H}$ decoupling can be used if the X signals are positively phased

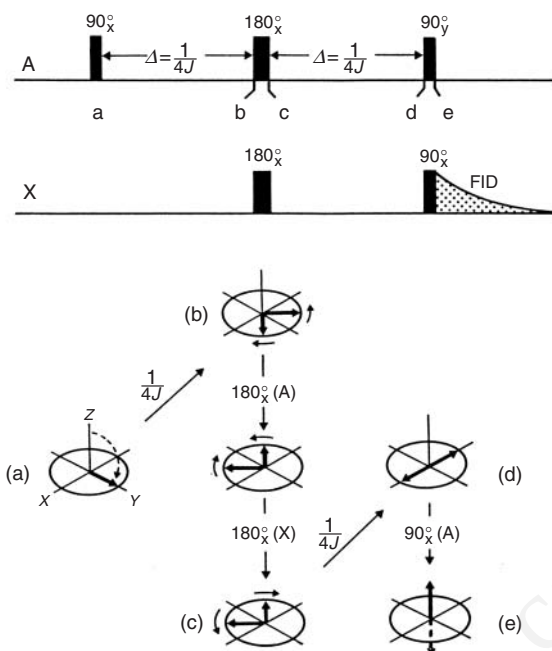


Figure 10.14 Pulse sequence of the INEPT method for an AX system (e.g., A = ^1H , ^{19}F , or ^{31}P ; X = ^{13}C , ^{15}N , or ^{29}Si). The vector diagram shows only the A magnetization in the rotating frame ($\nu_0 = \nu_A$). After 90° excitation (a) the transverse magnetization of the nucleus A is modulated by spin–spin coupling to the less sensitive nucleus X. After the time $\Delta = 1/4J$ a phase difference of 90° exists between both doublet vectors (b). A 180° pulse in the A as well as in the X frequency region leads to the vector diagram (c) so that after the second period Δ state (d) is

reached. A 90° pulse inverts the magnetization of one proton line (e). This corresponds to selective population inversion. The polarization of the spin system is detected by a 90° pulse in the frequency region of the less sensitive nucleus, the signals of which show emission or enhanced absorption. Pure absorption is achieved by an additional spin echo sequence, Δ_2 , for a doublet ($1/4J \dots 180^\circ(\text{A}, \text{X}) \dots 1/4J$) (INEPT⁺). The X resonance can then be detected as a positively polarized doublet or, with simultaneous ^1H decoupling during the detection period, as a singlet (refocused INEPT).

Table 10.1 Enhancement factors $\eta_{\text{NOE}} (= \gamma_A/2\gamma_X)$ and $\eta_{\text{INEPT}} (= |\gamma_A/\gamma_X|)$ for nuclear Overhauser and INEPT experiments, respectively, with A = $\{^1\text{H}\}$ in X $\{^1\text{H}\}$ pairs.

X	^{11}B	^{13}C	^{15}N	^{29}Si	^{57}Fe	^{103}Rh	^{109}Ag	^{119}Sn	^{183}W
η_{NOE}^a	1.56	1.99	−4.93	−2.52	15.41	−15.80	−10.68	−1.33	11.86
η_{INEPT}^b	3.12	3.98	9.86	5.03	30.82	31.59	21.37	2.67	23.71

^aNote that the observed intensity is equal to $1 + \eta_{\text{NOE}}$ [Eq. (10.6)].

^bFor ^{19}F or ^{31}P as polarization source (A nucleus) the data for η_{NOE} and η_{INEPT} are reduced by the factor 0.941 [$(\gamma(^{19}\text{F})/\gamma(^1\text{H}))$] and 0.405 [$(\gamma(^{31}\text{P})/\gamma(^1\text{H}))$], respectively.

by an additional spin echo sequence, Δ_2 . This sequence is called *INEPT*⁺. Without ^1H decoupling, multiplets with positive phases for all lines are then observed, while ^1H decoupling leads to a singlet. However, for AX, A_2X , and A_3X spin systems (e.g., CH, CH_2 , and CH_3 groups) different echo times Δ_2 have to be used. This paves the way for signal selection and assignment, an aspect treated in more detail in Chapter 11 (Figure 11.8 p. 387). On the other hand, echo time variation can be avoided if just before X-signal detection a 90°_x “purging” pulse on the A channel is applied that eliminates unwanted magnetization arising from the multiplet structures by transformation into non-observable multiple-quantum coherence. In general, however, prolongation of the pulse sequence leads to a reduction in signal intensity due to relaxation effects. Therefore, the simple pulse sequence without refocusing and without A decoupling, as shown in Figure 10.14, is often the best choice to measure insensitive nuclei.

Figure 10.15 shows an application of INEPT spectroscopy with the ^{15}N NMR signals of diphenylamine (**6**). The ^1H -coupled doublet (Figure 10.15a) with a splitting of 89 Hz is shown in Figure 10.15b as a negative NOE-enhanced signal

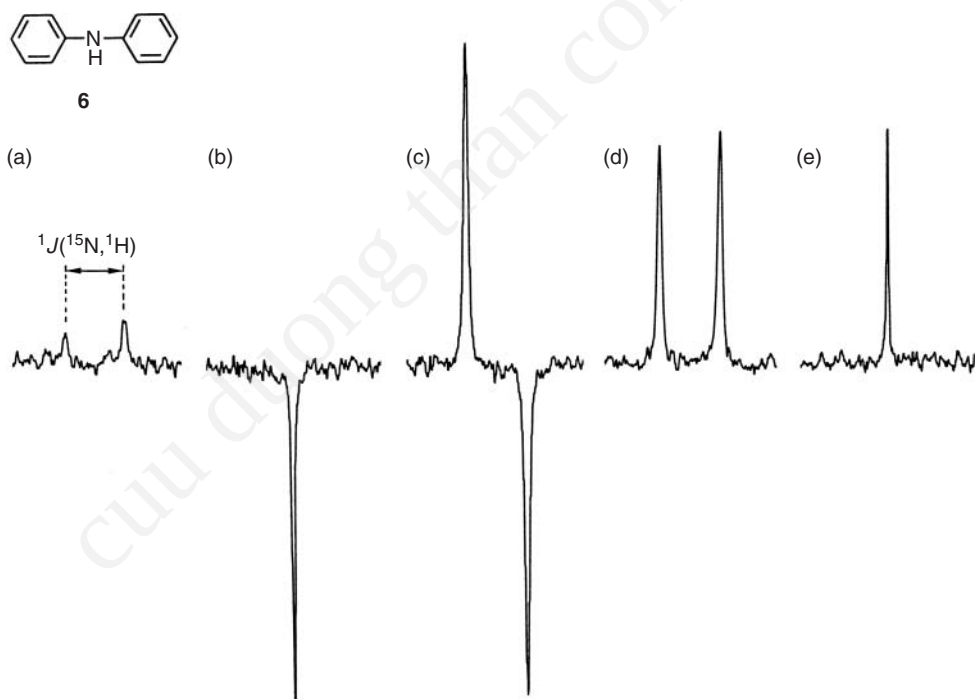


Figure 10.15 ^{15}N NMR signal (40.53 MHz) in diphenylamine (**6**): (a) without NOE effect; (b) with NOE effect through ^1H decoupling; (c) INEPT signal; (d) INEPT signal after applying a spin echo sequence $\Delta_2 = (1/4J \dots 180^\circ_x(A,X) \dots 1/4J)$; (e) as (d), however, refocused with ^1H decoupling; the coupling constant $^1J(^{15}\text{N}, ^1\text{H})$ amounts to 89 Hz; note that relative to (b) the intensity of the signal is now reduced.

in a $^{15}\text{N}\{^1\text{H}\}$ experiment. The INEPT signal shown in Figure 10.15c is positively phased in (d) and then ^1H -decoupled in (e), where the diminished intensity results from ^{15}N relaxation effects and the negative NOE (Table 10.1). An example from heterocyclic chemistry is given in Chapter 12 (p. 441).

As an exercise in product operator calculation we describe the INEPT sequence for a doublet as follows:

$$\hat{I}_z(^1\text{H}) \xrightarrow{90^\circ \hat{I}_z(^1\text{H})} \hat{I}_y(^1\text{H}) \xrightarrow{\pi J 2\Delta \ 2 \hat{I}_z(^1\text{H}) \hat{I}_z(^{13}\text{C})} 2\hat{I}_x(^1\text{H})\hat{I}_z(^{13}\text{C}) \quad (10.14)$$

We start with ^1H z-magnetization that is transformed into transverse y-magnetization by the first 90°_x pulse and evolves under the influence of $^{13}\text{C}, ^1\text{H}$ coupling during the delay 2Δ into anti-phase ^1H magnetization. This follows Eq. (9.23b) (p. 315), where the first term vanishes because the time interval t_1 is in our case fixed to $2\Delta = 1/2J$ and thus $\cos(\pi J 2\Delta) = 0$. Furthermore, for the sine term we have $\sin(\pi J 2\Delta) = 1$. As seen in Figure 10.14, the 180° pulse on both nuclei, ^1H and ^{13}C , does not affect the evolution. The final pulse pair $[\hat{I}_y(^1\text{H})\hat{I}_x(^{13}\text{C})]$ transforms anti-phase ^1H magnetization into anti-phase ^{13}C magnetization:

$$2\hat{I}_x(^1\text{H})\hat{I}_z(^{13}\text{C}) \xrightarrow{90^\circ \hat{I}_y(^1\text{H}) \hat{I}_x(^{13}\text{C})} 2\hat{I}_z(^1\text{H})\hat{I}_y(^{13}\text{C}) \quad (10.15)$$

This yields after Fourier transformation an anti-phase doublet. Since the original ^{13}C magnetization had a relative intensity of $\gamma(^{13}\text{C})/\gamma(^1\text{H}) = \frac{1}{4}$ the intensity increase is equal to $\gamma(^1\text{H})/\gamma(^{13}\text{C}) = 4$.

The ^{13}C magnetization present at the beginning is transformed into the term $-\hat{I}_z(^{13}\text{C})$ by the $180^\circ(^{13}\text{C})$ pulse and into $-\hat{I}_y(^{13}\text{C})$ by the final $90^\circ_x(^{13}\text{C})$ pulse. It is eliminated by a two-step phase cycle where the phase of the last 90° ^1H pulse alternates between $+\gamma$ and $-\gamma$. Subtraction of both spectra cancels the original ^{13}C magnetization and retains the polarization transfer component.

An additional factor for the success of a polarization transfer experiment is the short relaxation time of the sensitive nucleus. Since nuclei like ^1H or ^{19}F relax considerably faster than, for example, ^{13}C , the repetition rate for data accumulation can be much higher than for direct measurements of the insensitive nucleus. This shortens the time necessary to obtain spectra of insensitive nuclei, in the case of ^{15}N NMR measurements by a factor of 2–3. Successful INEPT experiments have also been performed for different metal nuclei. In these cases protons (for ^{103}Rh and ^{109}Ag) but also ^{31}P nuclei (for ^{57}Fe , ^{103}Rh , and ^{183}W) have been used as polarization sources. Also of great importance are $^{29}\text{Si}\{^1\text{H}\}$ and $^{119}\text{Sn}\{^1\text{H}\}$ experiments. Complications arise if strongly coupled ^1H spin systems are present. The complex relaxation behavior then leads very often to a failure of the INEPT experiment.

Finally, we mention an additional experiment, known as *reverse*, *inverse*, or *indirect INEPT*. Here the labels A and X for the two frequency channels in Figure 10.14 have to be interchanged. The sequence starts then with the dilute nucleus and the sensitive nucleus is detected. This has the advantage that only A signals coupled to X are observed. In the case of $^{13}\text{C}, ^1\text{H}$ pair detection, the signals of protons bound to ^{12}C are suppressed. This sequence is often used for less abundant metal nuclei

Table 10.2 Sensitivity of different coherence transfer experiments for the detection of insensitive nuclei [8].

Experiment	Sensitivity
1D experiment on X nucleus ($\gamma_{\text{exc}} = \gamma_{\text{obs}}$)	$S/N_1 \propto \gamma_X^{5/2} \times F$, with $F = [1 - e^{-t_R/T_1(X)}]$
INEPT [$S/N_1 \times (\gamma_A/\gamma_X)$; $A_{\text{exc}}, X_{\text{obs}}$]	$S/N_1 \propto \gamma_A \times \gamma_X^{3/2} \times F$, with $F = [1 - e^{-t_R/T_1(A)}]$
Reverse INEPT ($X_{\text{exc}}, A_{\text{obs}}$)	$S/N_{\text{RI}} \propto \gamma_X \times \gamma_A^{3/2} \times F$, with $F = [1 - e^{-t_R/T_1(X)}]$

where otherwise large ^1H signals from the abundant spins pose problems for the observation of the satellites due to A,X coupling.

For the sensitivity of the different experiments, defined by the signal-to-noise ratio, S/N , theory yields the following results [8]: the signal of the observed nucleus is proportional to the equilibrium magnetization of the excited nucleus and thus to its gyromagnetic ratio γ_{exc} ; it is further proportional to the signal strength of the observed nucleus, which is proportional to γ_{obs}^3 [see Eq. (2.13), p. 26]. For the detector noise one has from experimental experience a third factor equal to $(\gamma_{\text{obs}})^{1/2}$. This yields $S/N \propto \gamma_{\text{exc}} \times \gamma_{\text{obs}}^{3/2}$. In addition, a saturation factor $F = [1 - e^{-t_R/T_1(\text{exc})}]$ that takes care of the recovery of the excited magnetization and that contains an exponential term with the ratios of repetition time t_R used in spectral accumulation and the relaxation time T_1 of the excited nucleus has to be added. We then have the results shown in Table 10.2. They yield for a $^{15}\text{N}, ^1\text{H}$ pair the relation 1:10:30 for the S/N ratios of the three experiments and for ^{13}C 1:3:8.

Of course, these are somewhat idealized results and other factors, such as, for example, distribution of the intensity over various multiplets, dynamic range problems due to large background signals, and short T_2 values, can significantly reduce the sensitivity. The factor F approaches 1 if $t_R \gg T_1$. This means that short relaxation times are favorable for signal accumulation, as already mentioned above for the INEPT experiment where $T_1(A)$ is important. For reverse INEPT, t_R has to increase for slowly relaxing nuclei in order to avoid intensity losses.

Another important polarization transfer sequence is the DEPT experiment (distortionless enhancement by polarization transfer) that is used for spectral editing of ^{13}C signals. It will be discussed in detail in Chapter 11 (p. 387).

10.3

Rotating Frame Experiments

10.3.1

Spin Lock and Hartmann–Hahn Condition

During all one- and two-dimensional experiments discussed so far the static magnetic field B_0 pointed along the z-direction of the laboratory as well as of the rotating frame of reference. In the following we shall describe experimental techniques where the direction of the static field in the rotating frame, at least for

a short period of time, is changed. These techniques are based on a famous idea introduced by S.R. Hartmann and E.L. Hahn in the area of solid state NMR that has also found in recent years new applications in high-resolution NMR of liquids.

The object of the *Hartmann–Hahn experiment* was to improve the detection of an insensitive nucleus X of low natural abundance, for example, ^{13}C , by magnetization transfer from a sensitive nucleus A of high natural abundance, for example, ^1H . The strategy developed for this purpose can be understood best if we introduce the concept of spin temperature. Following Eq. (2.11) (p. 19), the temperature T_s of a spin system depends on the population ratio N_β/N_α . An ensemble of sensitive nuclei with high population excess in the ground state has, therefore, a low spin temperature, while an ensemble of insensitive nuclei with only a small population excess has a high spin temperature. This differentiation is possible since the spins are only weakly coupled to their surroundings, the lattice, while strong coupling exists within the spin system due to dipolar interactions (long T_1 and short T_2 times). For ^1H and ^{13}C spins the relation $\gamma(^1\text{H})/\gamma(^{13}\text{C}) \approx 4$ leads to a ratio $T_s(^{13}\text{C}) : T_s(^1\text{H}) \approx 4 : 1$.

If we succeed in establishing a thermal contact between the “cold” and the “hot” spin reservoir, the ensemble of the insensitive nuclei should be cooled at the expense of the ensemble of the sensitive nuclei. The consequence would be a higher population difference for the X nuclei and, therefore, a more sensitive X resonance. How can thermal contact be achieved? Energy exchange between spins proceeds for *homonuclear* spin systems in solids by a flip-flop mechanism. As discussed in Chapter 8 (p. 244), spin–spin interaction leads to an exchange of energy quanta γB_0 , and a change of spin orientation for one nucleus is accompanied by the opposite change for its neighbor. For *heteronuclear* AX spin systems we have, however:

$$\gamma(\text{A})B_0 \neq \gamma(\text{X})B_0 \quad (10.16)$$

and since all parameters in relation [Eq. (10.16)] are fixed, there is no possibility of overcoming this inequality and achieving magnetization transfer.

In the rotating coordinate system, however, a different situation arises. Here we are able to meet the condition:

$$\gamma(\text{A})B_1(\text{A}) = \gamma(\text{X})B_1(\text{X}) \quad (10.17)$$

by adjusting the B_1 amplitudes of the ^1H and ^{13}C transmitters. In the case discussed above the equation:

$$\gamma(^1\text{H})B_1(^1\text{H}) = \gamma(^{13}\text{C})B_1(^{13}\text{C}) \quad (10.18)$$

results, which is known as the *Hartmann–Hahn condition*. Now, energy can be exchanged by cross polarization (CP) between both spin reservoirs.

In practice, the experiment with two transmitter and receiver channels starts with a 90_x ^1H pulse that is immediately followed by a shift of the B_1 field from the x - to the y -axis of the rotating frame (Figure 10.16, p. 366). Thus, B_1 is parallel to the magnetization vector $\mathbf{M}$ and the protons behave in this new field as before in the B_0 field: they precess with their new Larmor frequency $\omega(^1\text{H}) = \gamma(^1\text{H})B_1$

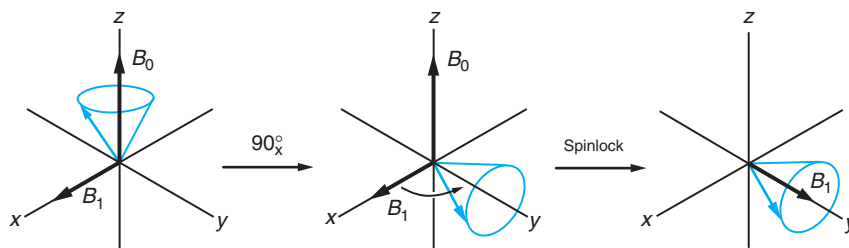


Figure 10.16 Illustration of the Hartmann–Hahn spin lock experiment.

around the y -axis, in other words they are locked in the y -direction of the rotating frame. This state of the ^1H spins is called *spin lock*.

We then spin-lock the ^{13}C magnetization with a continuous B_1 field and adjust the *amplitude* of this field to meet Eq. (10.18). The result is that the transverse magnetizations of both nuclei, ^1H and ^{13}C , oscillate with the same frequency around their own B_1 field. In addition, their z -components oscillate with identical frequencies and a *heteronuclear flip-flop mechanism* is possible: energy transfer from the hot to the cold spin reservoir takes place. To achieve this, the spin lock time must be of the order of the proton spin–lattice relaxation time. The maximum intensity gain for the insensitive nucleus is $\gamma(\text{A})/\gamma(\text{X})$, which in the case of the $^1\text{H}, ^{13}\text{C}$ spin pair is 4:1. In addition, the experiment has the advantage that the repetition rate for signal accumulation is governed by the faster proton relaxation and can be much higher than in direct ^{13}C measurements.

10.3.2

Spin Lock Experiments in Solution

10.3.2.1 Homonuclear Hartmann–Hahn or TOCSY Experiments

The Hartmann–Hahn or CP experiment (Figure 10.17a) plays an important part in solid state NMR spectroscopy (cf. Chapter 13). In liquids, because of the fast molecular motion, dipolar couplings vanish and we have $T_1 \approx T_2$. Thus, the conditions for the original spin lock experiment are not met. Nevertheless, it proved possible to perform spin lock experiments also in liquids with homonuclear as well as with heteronuclear spin systems. Magnetization transfer is then based on *scalar* spin–spin coupling. Such techniques can be used for homo- and heteronuclear shift correlation experiments. They are known by the acronyms HOHAHA (*homonuclear Hartmann–Hahn*) and HEHAHA (*heteronuclear Hartmann–Hahn*), but also as homo- or hetero TOCSY (*total correlation spectroscopy*) experiments.

These methods have in common that during a *spin lock* or *mixing time* the Zeeman contributions to the Hamilton operator, in other words the interactions with the static external magnetic field B_0 and thus the chemical shifts, are practically eliminated and scalar coupling between nuclei dominates. In the case of TOCSY spectroscopy, the mixing operator for complete isotropic coupling has the

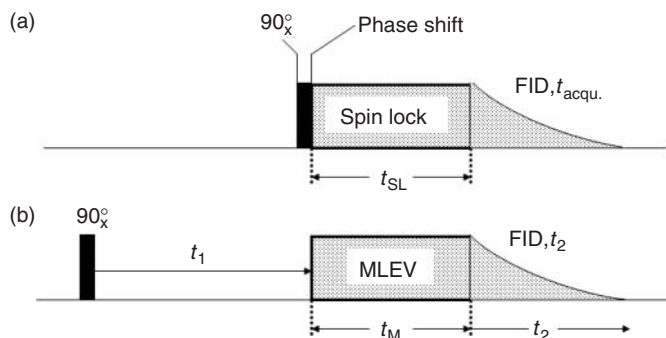


Figure 10.17 Pulse sequence for the CP experiment in solid state NMR (a) and for the two-dimensional homonuclear TOCSY experiment in liquids with mixing time t_M (b).

form:

$$\mathcal{H}_M \equiv \mathcal{H}_J = \sum_{i < j} \sum 2\pi J_{ij} \mathbf{I}(i) \mathbf{I}(j) \quad (10.19)$$

and describes a state of isotropic mixing that is experimentally accessible through the application of multipulse decoupling sequences of the MLEV type discussed earlier (p. 277). During the spin lock or mixing time (t_{SL} or t_M) the series of 180° pulses eliminates the chemical shifts but does not affect the scalar coupling. This situation resembles that of the spin echo experiment. The spins are thus in the *strong coupling* regime and magnetization transfer takes place (Hartmann–Hahn mixing or isotropic mixing). It reaches a maximum after a time interval equal to $1/2J$. Notably, the transfer proceeds beyond the next directly coupled nuclei to remote nuclei and finally progresses through the complete scalar coupled network of nuclei in the particular molecule. Two-dimensional homonuclear correlation spectra can be produced if the evolution time t_1 precedes the spin lock or mixing time (Figure 10.17b).

As a comparison with the COSY sequence (Figure 9.12, p. 296) shows, the second 90°_x pulse is now replaced by the spin lock or mixing time. Here magnetization transfer takes place that is governed by the length of these delays. Short times (20–50 ms) yield primarily cross peaks of strongly coupled protons, while longer spin lock times (100–300 ms) allow magnetization transfer to remote protons of the spin system. For an AMX system magnetization is then transferred from the A to the M nucleus and from there to the X nucleus. So-called *relayed spectra* result that show cross peaks from protons that are separated by more than three bonds. An advantage of the TOCSY experiment compared to the COSY experiment must be seen in the fact that the magnetization transfer leads to a net effect and all signals appear nearly in pure absorption. This differs also from the results of the INEPT experiments discussed above. It is, therefore, possible to record phase sensitive 2D spectra and the danger of signal elimination is removed. Figure 10.18 (p. 368) shows a two-dimensional ^1H , ^1H shift correlation on the basis of the TOCSY sequence.

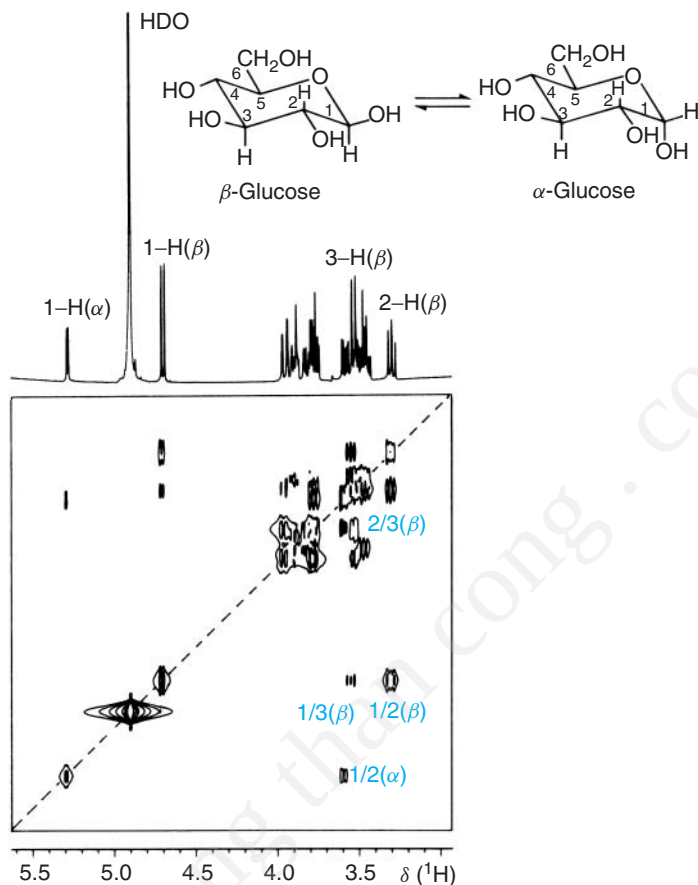


Figure 10.18 2D TOCSY ^1H NMR spectrum of a mixture of α - and β -D-glucose in D_2O with application of the MLEV sequence (spin lock time 30 ms, measuring time 1.5 h); at 4.9 ppm the signal of HDO. The vicinal correlations of the anomeric protons are clearly recognized, as well as the relay signal for 1-H/3-H of β -D-glucose. The low-frequency portion, with its numerous cross and relay peaks, can be analyzed only by use of various filter functions. Relay peaks may be suppressed by using shorter spin lock times.

10.3.2.2 One-Dimensional Selective TOCSY Spectroscopy

As already mentioned earlier, two-dimensional experiments require a considerable investment of measuring time. Methods that are less demanding in this respect are, therefore, still attractive and a number of one-dimensional variants of several 2D experiments have been proposed as alternative NMR techniques. Among them are experiments with selective excitation that are most useful in those cases where a few 1D experiments are sufficient to complete the information already obtained from another source.

From the group of selective techniques we introduce here the 1D TOCSY experiment, which has great potential for applications in structural research. It can be used to advantage in all cases where in a complicated spectrum the signal of a single proton H_i is observed separately and can be used as starting point of the magnetization transfer process. Such a situation exists, for example, for the anomeric protons in carbohydrates. The 1D TOCSY experiment consequently plays an important role in spectral analysis of oligosaccharides and oligonucleotides.

The 1D TOCSY experiment can be performed using difference spectroscopy. In the first sequence a selective 180° GAUSS pulse inverts the magnetization of the proton H_i selected as starting point of the magnetization transfer. Transfer to other protons occurs during the mixing time t_M that follows directly after the 90°_x excitation pulse because the 1D experiment has no evolution time. In the second sequence the 180° pulse is used off-resonance. The difference $S1 - S2$ thus contains only signals that have received a magnetization transfer:

$$\begin{aligned} S1 &: 180^\circ_x(\text{sel, on-resonance}), 90^\circ_x, t_M, \text{FID} \\ S2 &: 180^\circ_x(\text{sel, off-resonance}), 90^\circ_x, t_M, \text{FID} \end{aligned} \quad (10.20)$$

As an alternative to Eq. (10.20), the sequence $\langle 90^\circ_{\text{sel}}, t_M, \text{FID} \rangle$ can be used. Through the length of the mixing time the magnetization transfer is adjustable with respect to the connectivities in the spin system (close or remote), similarly to the 2D experiment. If the spin lock time is sufficiently long, one can produce partial spectra of individual spin systems that are superimposed in the normal 1D spectrum. Figure 10.19 (p. 370) shows an example.

The magnetization progress in a 1D TOCSY experiment through the molecular network is also shown nicely for $[D_5]$ pyridine by deuterium NMR with 1D ^2H TOCSY experiments of different spin lock times (Figure 10.20, p. 370). A special point of interest in this case is the fact that the homonuclear $^2\text{H}, ^2\text{H}$ coupling constants that are responsible for the magnetization transfer through the spin system are too small to be detected by line splittings in the normal 1D ^2H spectrum. Addition of a z -filter and so-called trim pulses improves the performance of the experiment but this technical aspect will not be discussed further.

10.3.2.3 ROESY Experiment

As discussed in Section 10.2.2, the change of sign observed for the NOE in connection with a decrease of the molecular correlation time τ_c is a disadvantage for practical applications. It is, therefore, of general interest that NOE measurements can also be performed in the rotating frame and that under these conditions nuclear Overhauser factors are always positive. The limit for nuclear Overhauser enhancement in the rotating frame is 67.5% (Figure 10.21, p. 371). Such experiments are known by the name *ROESY* (rotating frame NOESY). They have gained considerable importance for the study of large molecules, in particular biological macromolecules.

The pulse sequence for the 2D ROESY experiment is identical to the TOCSY sequence in Figure 10.17b with the difference that during the mixing time a

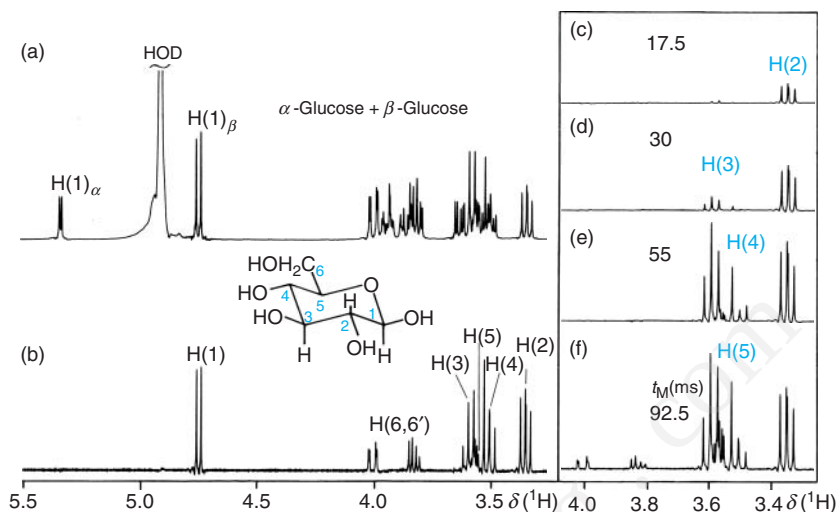


Figure 10.19 1D TOCSY ^1H NMR spectra of a mixture of α - and β -D-glucose; the sample was used also for Figure 10.18. (a) 400 MHz 1D spectrum; (b) 1D TOCSY spectroscopy with $t_M = 130$ ms and excitation of 1-H_β yields the partial spectrum of the β -D-glucose; (c)–(f) 1D TOCSY spectra of β -D-glucose with 1-H_β as starting point and increasing spin lock time allow the signal assignment: signals of neighboring protons appear with increasing mixing

time according to their distance from 1-H_β . The measuring times for each spectrum were 16 min. The partial spectrum of α -D-glucose with 1-H_α as starting point of the magnetization transfer process was not observed under the conditions used since, because of mutarotation, magnetization was transferred by chemical exchange onto the signals of β -D-glucose. Transfer in the opposite direction is negligible because of $k_{\beta \rightarrow \alpha} < k_{\alpha \rightarrow \beta}$.

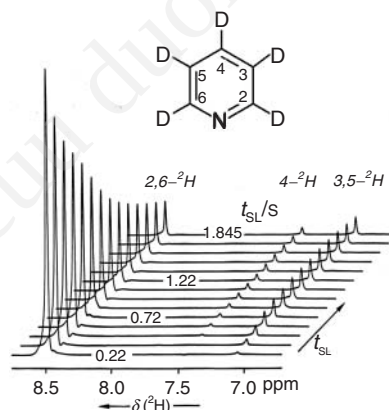


Figure 10.20 $[\text{D}_5]\text{pyridine}$ 1D ^2H TOCSY spectra with different spin lock times; the 90°_{sel} excitation pulse was set on the resonance of $2,6\text{-}^2\text{H}$; magnetization shows up at $3,5\text{-}^2\text{H}$ first and later at $4\text{-}^2\text{H}$; after a mixing or spin lock time t_{SL} of 1.85 s the transfer is complete.

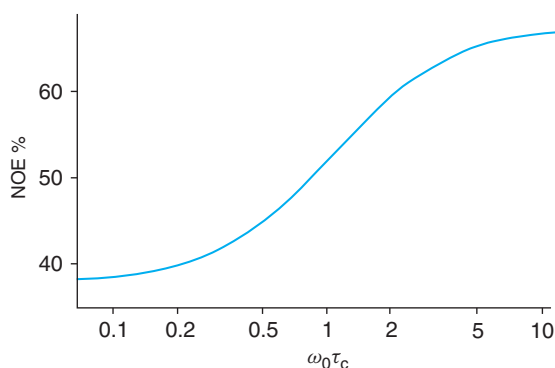


Figure 10.21 Dependence of the ROESY effect for homonuclear two-spin systems on the product of resonance frequency, ω_0 , and molecular correlation time, τ_c .

considerably weaker amplitude for the multipulse radiation is used than during the TOCSY experiment. Magnetization transfer proceeds via dipolar interactions and the situation can be described as transverse NOE spectroscopy. Direct ROESY cross peaks are negative and it is immediately clear that in such an experiment complications can arise through the positive TOCSY signals that are either detected in addition to the ROESY signals or, because of their different phase, can lead to an elimination of ROESY signals. In the first case a differentiation is possible by using phase sensitive spectra, because only TOCSY signals have the same (positive) phase as the diagonal signals. Compared to NOESY spectra, ROESY experiments have the advantage that spin diffusion is less pronounced. However, double transfer processes of the type TOCSY-ROESY or ROESY-TOCSY can lead to further signals that have different phase behavior. The analysis of 2D ROESY spectra may thus sometimes be difficult.

In the one-dimensional version of the ROESY experiments two pulse sequences are used alternately: (i) $\langle 90_x^\circ, \text{spin lock, FID} \rangle$ and (ii) $\langle 180_{\text{sel}}^\circ, 90_x^\circ, \text{spin lock, FID} \rangle$. The selective 180° pulse in the second sequence starts the cross relaxation process, the difference (ii) – (i) yields the ROE effects. With respect to the measuring time, the same advantages apply as discussed above for the 1D TOCSY experiment. Figure 10.22 (p. 372) shows an application of 1D ROESY difference spectroscopy.

10.4

Multidimensional NMR Experiments

A consistent extension of the principle of two-dimensional NMR spectroscopy has led to the introduction of three-dimensional (3D) and even four-dimensional (4D) NMR – generally speaking multidimensional experimental techniques that are valuable tools for the analysis of complicated spectra of biological macromolecules (peptides, proteins, nucleic acids) where signal overlap renders the interpretation

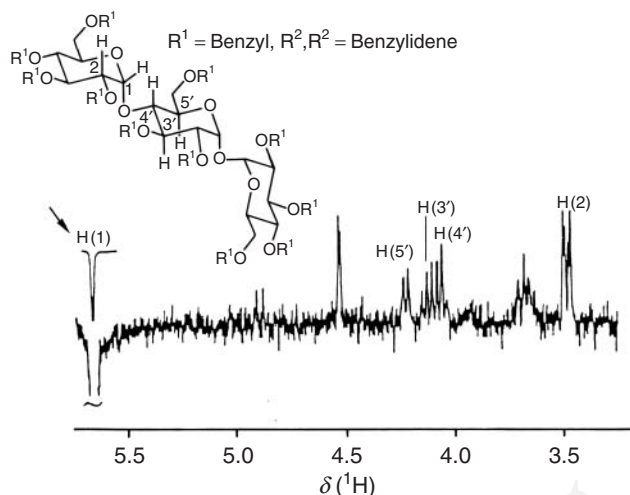


Figure 10.22 1D ROESY difference spectrum of a trisaccharide; the ROESY signals for the protons of neighboring hexose units yield information about the ring connections (note that rotation around the glycoside bond is possible) [9].

difficult. The basic philosophy behind such experiments will be illustrated in this section with a short description of 3D experiments.

Through the introduction of a second evolution time in a known 2D pulse sequence, during which the spin system develops under the action of a different Hamilton operator, it is possible to generate a 3D spectrum after a threefold Fourier transformation of the experimental data. The resulting signals are characterized by three different frequency parameters in the frequency space F_1, F_2, F_3 :

$$90^\circ, t_1, t_2, t_3 \rightarrow S(t_1, t_2, t_3) \xrightarrow{1.FT} S(F_1, t_2, t_3) \xrightarrow{2.FT} S(F_1, F_2, t_3) \xrightarrow{3.FT} S(F_1, F_2, F_3) \quad (10.21)$$

How this improves spectral analysis is best seen in the schematic diagram of Figure 10.23, where overlapping cross-peaks from a 2D experiment are separated in a third frequency axis.

To illustrate the principle of multidimensional NMR we use the simple example of a heteronuclear J -resolved three-dimensional ^{13}C spectrum for a CHD group. The three frequency parameters of interest that are to be separated are the spin-spin coupling constants $^1J(^{13}\text{C}, ^1\text{H})$ and $^1J(^{13}\text{C}, ^2\text{H})$ and the chemical shift of the ^{13}C nucleus, $\delta(^{13}\text{C})$. Consequently, a J, J, δ -spectrum results. The procedure is described in Figure 10.24.

Let us focus first on the “simple” heteronuclear 2D J, δ -spectrum. As with the homonuclear case (see Figure 9.8, p. 290), a spin echo experiment is performed, this time on the ^{13}C channel. During the first half of the evolution time t_1 a t_1 -dependent phase error develops as shown in Figure 9.7c (p. 288) after the first τ -delay. $^{13}\text{C}, ^1\text{H}$

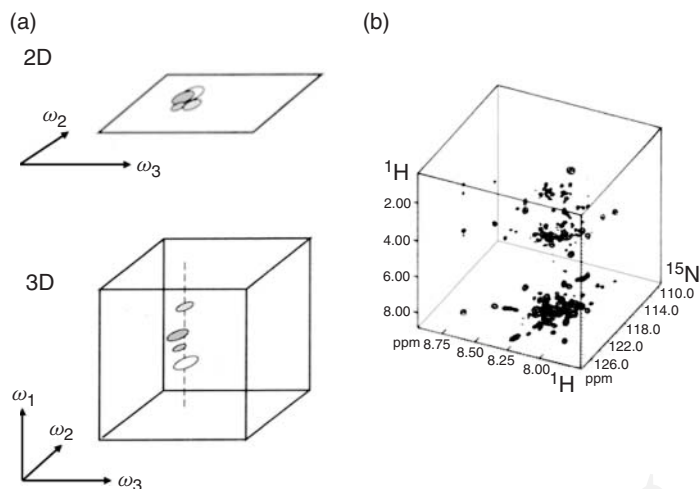


Figure 10.23 (a) Principle of 3D NMR: overlapping cross-peaks are resolved along a third frequency axis [10]; (b) a 3D data set with three frequency axes: ^1H , ^1H , and ^{15}N .

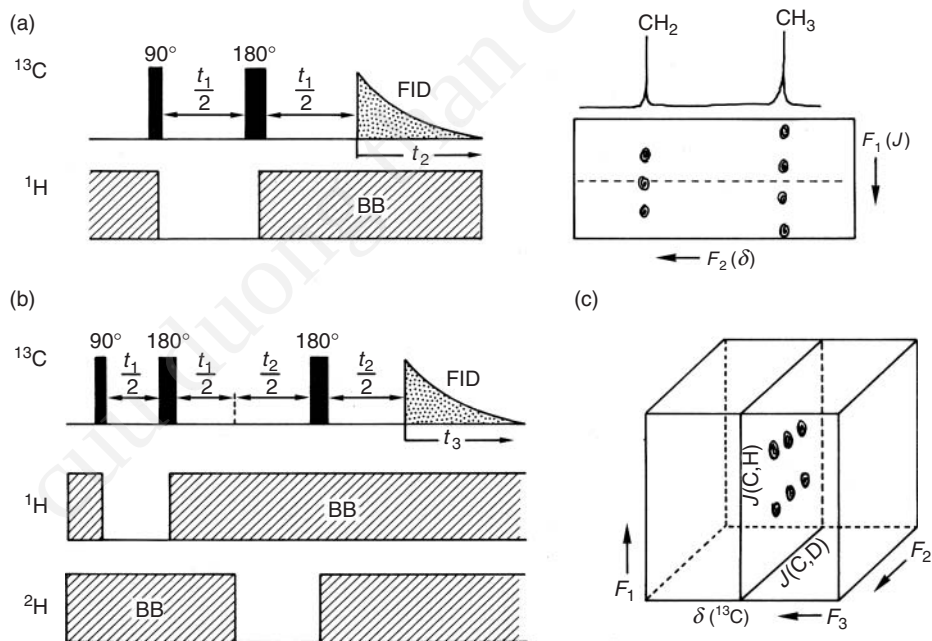


Figure 10.24 (a) Pulse sequence for the heteronuclear 2D J, δ - ^{13}C spectrum and contour diagram for a CH_2 and CH_3 group (schematically); (b) pulse sequence for heteronuclear 3D- JJ, δ - ^{13}C spectrum; (c) results for a CHD group in the frequency space F_1, F_2, F_3 : doublet splitting by $J(^{13}\text{C}, ^1\text{H})$ in F_1 , triplet splitting by $J(^{13}\text{C}, ^2\text{H})$ in F_2 , chemical shift $\delta(^{13}\text{C})$ in F_3 ; BB = broadband decoupling.

coupling must be eliminated during the second half of the evolution time, since otherwise no signal modulation during t_1 would result. The experiment, therefore, uses gated ^1H -decoupling and the ^{13}C signal detected in t_2 is amplitude modulated because the evolution of the coupling varies with the variation of $t_1/2$. The effect of the ^{13}C Larmor frequencies during t_1 is eliminated by the 180° pulse and F_1 contains only the ^{13}C , ^1H coupling constants, while F_2 contains the chemical shifts, $\delta(^{13}\text{C})$. Because ^{13}C , ^1H coupling is “on” only during $t_1/2$, the spin–spin splittings are reduced by 50%. We come back to this experiment in Chapter 11 with an example.

For the proposed 3D JJ,δ -spectrum one can now proceed according to Figure 10.24b. ^{13}C magnetization is modulated during t_1 and t_2 with the ^1H - and ^2H -decoupler on, respectively. After the first Fourier transformation with respect to t_3 , which is now the detection time, one obtains the 2D spectra shown in Figure 10.25. Here the high field ^{13}C signal of the CHD group clearly shows the modulation of its signal amplitude with respect to the time axes t_2 and t_1 . The high frequency signal comes from a $^{13}\text{CH}_2$ group and, as expected, shows amplitude modulation only with respect to t_1 (compare the decoupler sequence of Figure 10.24b). After complete Fourier transformation with respect to all three times domains one expects, finally, six points in the F_1, F_2, F_3 frequency space that are shown schematically in Figure 10.24c.

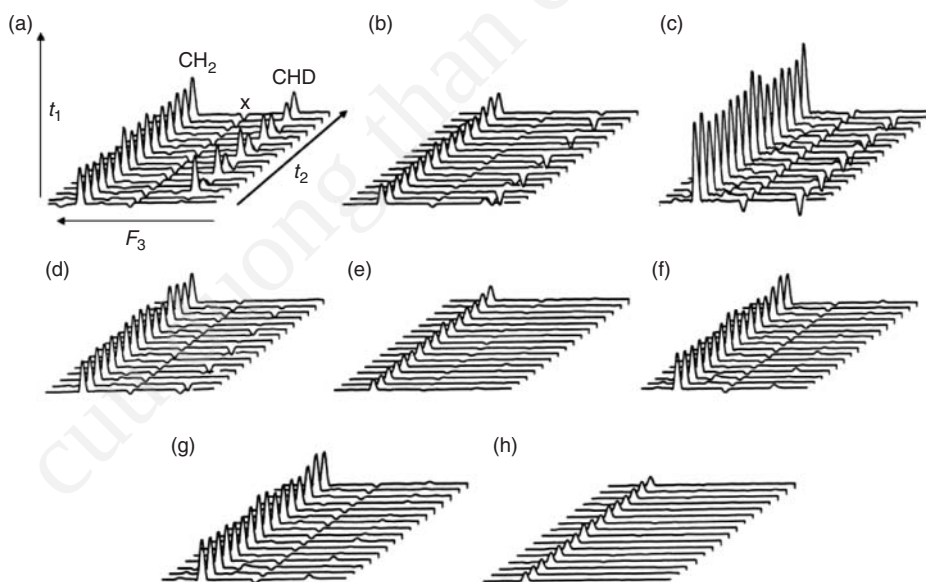


Figure 10.25 (a)–(h) Results of a 3D JJ,δ - ^{13}C experiment for a mixture of diphenylmethane and $[\text{D}_1]$ diphenylmethane after single Fourier transformation; aliphatic region with resonances of the CH_2 and CHD group (x is an artifact of the pulse transmitter). Shown are the pseudo-2D spectra $S(t_1, t_2, F_3)$ that are obtained

after Fourier transformation with respect to t_3 for various t_1 and t_2 values. As expected, only the ^{13}C signal of the CHD group shows modulation in t_2 and t_1 . The signal of the CH_2 group shows amplitude modulation only in the t_1 -dimension [11].

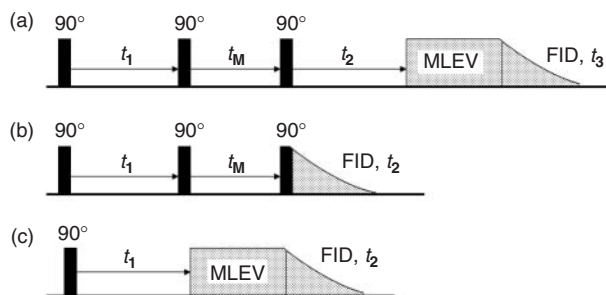


Figure 10.26 (a) Pulse sequence for a 3D NOESY-TOCSY experiment, constructed from a 2D NOESY experiment (b) and a TOCSY experiment with MLEV mixing sequence (c).

In a homonuclear, pure ^1H 3D sequence, for example, a NOESY experiment can be combined with a TOCSY experiment (Figure 10.26). We have then two mixing times, t_M and MLEV, and three evolution times t_1 , t_2 , and t_3 . The magnetization obtained by Fourier transformation with respect to t_3 is then modulated with the NOE developed during t_M and engraved in the t_1 domain and the isotropic coupling active during the MLEV sequence and stored in t_2 . Subsequent Fourier transformation with respect to t_2 and t_1 yields the corresponding frequencies. They give rise to frequency domains F_1/F_2 , F_1/F_3 , and F_2/F_3 that contain different types of magnetizations. In F_1/F_2 we have magnetization from TOCSY transfers with chemical shift modulation in t_1 and isotropic mixing in t_2 , F_2/F_3 contains only NOE-type magnetization, and F_1/F_3 contains magnetization that was transferred from a proton H_a to H_b during the first mixing period and back to H_a during the second mixing period (back-transfer). A cross peak with coordinates f_1/f_3 then indicates that the two protons are not only near in space but are also scalar coupled. Combinations of homo- and hetero-2D experiments, like that shown in Figure 10.23b, will also be cited in Chapter 15.

Evidently, these types of experiments need long measuring times since *two* evolution times, t_1 and t_2 , must now be incremented independently. With a minimum of 16 t_1 and t_2 values $16^2 = 256$ experiments are already necessary. Three-dimensional experiments that require high digital resolution thus need measuring times of more than one day. Time-saving experiments have become available through the development of semi-selective RF pulses that excite only a small portion of the NMR spectrum and powerful data processing systems as well as highly stable instrument hardware have paved the way for growing use of 3D experiments that combine several 2D experiments, for example, homo- and heteronuclear shift correlations as well as NOESY pulse sequences to analyze complicated spectra with strong signal overlap. From the practical point of view, 3D shift correlation experiments are especially important. 3D NMR spectroscopy has thus become an attractive and successful technique for special applications, mainly in the field of biopolymers, notwithstanding the long measuring times. Methods such as those discussed in Section 9.9 are thus of general interest.

References

1. Harris, R.K. (1986) *Nuclear Magnetic Resonance Spectroscopy*, Longman, Harlow, p. 108.
2. Holzer, W. (1991) *Tetrahedron*, **47**, 9783.
3. Anet, F.A.L. and Bourn, A.J.R. (1965) *J. Am. Chem. Soc.*, **87**, 5250.
4. Andres, W. (1991) PhD thesis, University of Siegen.
5. Günther, H., Schmitt, P., Fischer, H., Tochtermann, W., Liebe, J., and Wolf, C. (1985) *Helv. Chim. Acta*, **68**, 801.
6. Fox, T. (1993) PhD thesis, University of Siegen.
7. Pachler, K.G.R. and Wessels, P.L. (1973) *J. Magn. Reson.*, **12**, 337.
8. Ernst, R.R., Bodenhausen, G. and Wokaun, A. (1987) in *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*, Clarendon Press, Oxford, p. 468 ff.
9. Wessel, H.P., Englert, G., and Stangier, P. (1991) *Helv. Chim. Acta*, **74**, 682.
10. Boelens, R. and Kaptein, R. (2010) in *Multidimensional NMR Methods for the Solution State* (eds Morris, G.A. and Emsley, J.W.), Wiley-VCH Verlag, Weinheim, Germany p. 315.
11. Wesener, J.R. (1985) PhD thesis, University of Siegen.

Textbooks

Those listed in Chapter 9 and in addition:

Neuhaus, D. and Williamson, M. (1989) *The Nuclear Overhauser Effect in Structural and Conformational Analysis*, VCH Publishers, Weinheim, p. 522 pp.

Review articles

Those listed in Chapter 9 and in addition:

Sanders, J.K.M. and Merish, J.D. (1983) Nuclear magnetic double resonance; the use of difference spectroscopy. *Prog. Nucl. Magn. Reson. Spectrosc.*, **15**, 353.

Bachers, G.E. and Schaefer, T. (1971) Applications of the intramolecular nuclear Overhauser effect in structural organic chemistry. *Chem. Rev.*, **71**, 617.

Kennwell, P.D. (1970) Applications of the nuclear Overhauser effect in organic chemistry. *J. Chem. Educ.*, **47**, 278.

Muhandiram, R. and Kay, L.E. (1996) *Three-Dimensional HMQC-NOESY, NOESY-HMQC, & NOESY-HSQC in Encyclopedia of Nuclear Magnetic Resonance*, Vol. 7, (eds in chief D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester, UK, p. 4733.

11

Carbon-13 Nuclear Magnetic Resonance Spectroscopy

After having treated in the preceding chapters the principles of Fourier-transform nuclear magnetic resonance (FT NMR) and the experimental aspects and applications primarily of homonuclear two-dimensional techniques, the present chapter will be devoted to the NMR of carbon-13, perhaps the most popular heteronucleus. This also serves to introduce heteronuclear 2D experiments, such as, for example, ^1H , ^{13}C chemical shift correlations.

The element carbon consists of the stable isotopes ^{12}C and ^{13}C with 98.9% and 1.1% natural abundance, respectively. Only the ^{13}C nucleus has a magnetic moment and as a *u,g* nuclide the spin $I = \frac{1}{2}$ while the nucleus of the major isotope ^{12}C is non-magnetic. Nuclear magnetic resonance spectroscopy of carbon, which quite naturally is of great interest for all branches of chemistry, is, therefore limited to the investigation of carbon-13.

The magnetic moment of ^{13}C is four-times smaller than that of the proton (see Table 2.1 on page 26) and the spectrometer frequency for ^{13}C is therefore only 25% of that used in ^1H NMR. Furthermore, the low natural abundance renders ^{13}C detection more difficult and ^{13}C NMR spectroscopy is thus by far less sensitive than ^1H NMR. If one defines, – as already outlined in Chapter 2, p. 26 – the receptivity of a nucleus X for the NMR experiment at constant B_0 field relative to the receptivity of the proton (P), $R^P(\text{X})$, according to:

$$R^P(\text{X}) = \frac{\gamma_X^3 N_X I_X (I_X + 1)}{\gamma_P^3 N_P I_P (I_P + 1)} \quad (11.1)$$

where γ is the magnetogyric ratio, N the natural abundance, and I the spin quantum number of the nuclei in question, one obtains with the appropriate data $R^P(^{13}\text{C}) = 1 : 5700 = 1.75 \times 10^{-4}$. Several experimental developments were thus necessary to counterbalance this disadvantage and to pave the way for a broad application of ^{13}C NMR spectroscopy. On the other hand, it must be remembered that the low natural abundance of ^{13}C also has an advantage: ^{13}C NMR spectra are easily analyzed because homonuclear ^{13}C , ^{13}C spin–spin coupling constants are practically absent (their probability is 1.1% of 1.1% = 0.01 %) and, disregarding the ^{13}C satellites (cf. p. 77, 226), the ^1H NMR spectra of organic molecules are not disturbed by heteronuclear ^{13}C , ^1H coupling. Furthermore, ^{13}C spectra consist only of singlet lines if the protons are decoupled.

11.1

Historical Development and the Most Important Areas of Application

The history of ^{13}C NMR spectroscopy can be divided into three stages. During the pioneering stage, that is, in the 1960s, when only low-field CW spectrometers with iron magnets and without field frequency stabilization were available, spectra had to be recorded with high sweep rates to avoid saturation effects (rapid passage method). Carbon-13 labeled material and large volume sample cells (diameter up to 15 mm), were applied to improve the low signal-to-noise ratio, a consequence of the low natural abundance and the low sensitivity of ^{13}C .

The second period of ^{13}C NMR spectroscopy started as *data accumulation* and *proton broadband decoupling* were introduced. Digital memory units could be used for the accumulation of spectra after the spectrometer was equipped with a field frequency lock and ^1H -decoupling led to a twofold intensity gain: on the one hand through the collapse of multiplet structures and on the other through the nuclear Overhauser effect (Chapter 10). This is illustrated in Figure 11.1 with spectra obtained for pyridine under different experimental conditions.

The next and, without doubt, by far the most important steps for improvement of the signal-to-noise ratio were the introduction of superconducting magnets,

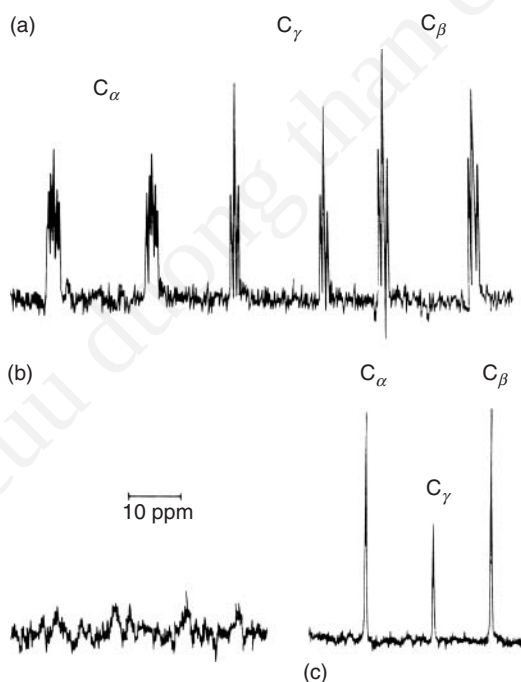


Figure 11.1 ^{13}C spectra of pyridine: (a) CW spectrum at 22.63 MHz after 64 accumulations of 320 s acquisition time each [1]; (b) result of a frequency sweep experiment at 15 MHz; (c) as (b), however, with proton decoupling [2].

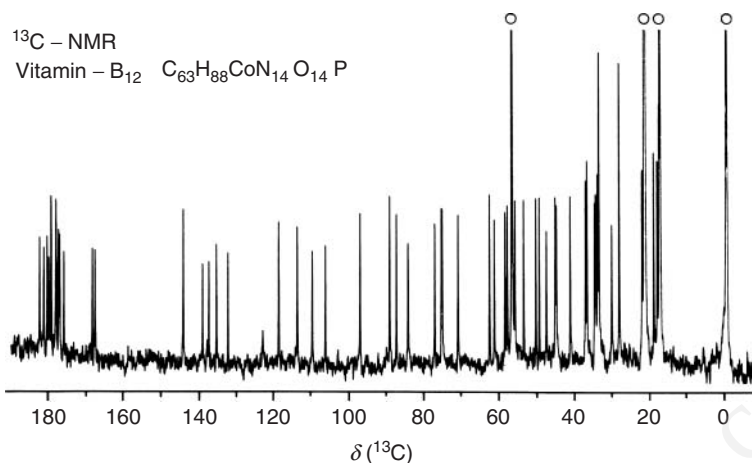


Figure 11.2 100 MHz ^{13}C FT NMR spectrum of vitamin B₁₂ with ^1H -decoupling; (O) signals of the reference compound trimethylsilylpropane sulfonate (TS).

which provided stronger magnetic fields, and *pulse Fourier transform spectroscopy*. The possibility of accumulating a large number of spectra in a relatively short time yielded the basis for routine applications of ^{13}C NMR spectroscopy. Spectra could now be recorded for smaller samples and within a reasonable experiment time. Today, even large molecules can be measured under conditions not very different from those of routine ^1H NMR, as Figure 11.2 demonstrates with the ^{13}C NMR spectrum of vitamin B₁₂.

Unsurprisingly, ^{13}C NMR spectroscopy has since then developed rapidly into a routine method for chemical structure determinations. If one remembers that the organic chemist is interested primarily in the molecular carbon skeleton, evidently a ^{13}C spectrum then yields structural information much more directly than a proton spectrum. In particular, quaternary carbons, such as those of many functional groups ($\text{C}\equiv\text{N}$, $\text{C}\equiv\text{O}$, $\text{C}\equiv\text{NR}$, etc.), are now detectable. The amount of structural NMR data has thus increased enormously. Furthermore, the large ^{13}C chemical shift range (approximately 250 ppm) and the small line width of the ^{13}C signals (0.5 Hz or less) effectively increases spectral resolution. Carbon-13 NMR is thus the method of choice for structural investigations of complex organic molecules such as natural products and synthetic as well as biological oligomers and macromolecules. In the field of steroids, to cite only one example, intensive investigations led to a situation where individual molecules can be recognized by their characteristic ^{13}C NMR finger prints (Figure 11.3).

In this context it is important to emphasize that – despite the enormous progress that has been made – ^{13}C NMR spectroscopy has by no means replaced proton NMR spectroscopy, which is still the most widely used spectroscopic technique. Both methods are, rather, complementary in a very effective way. In practice, the combination of ^1H and ^{13}C NMR data forms the basis for any structural investigation in organic and organometallic chemistry and yields in most cases sufficient

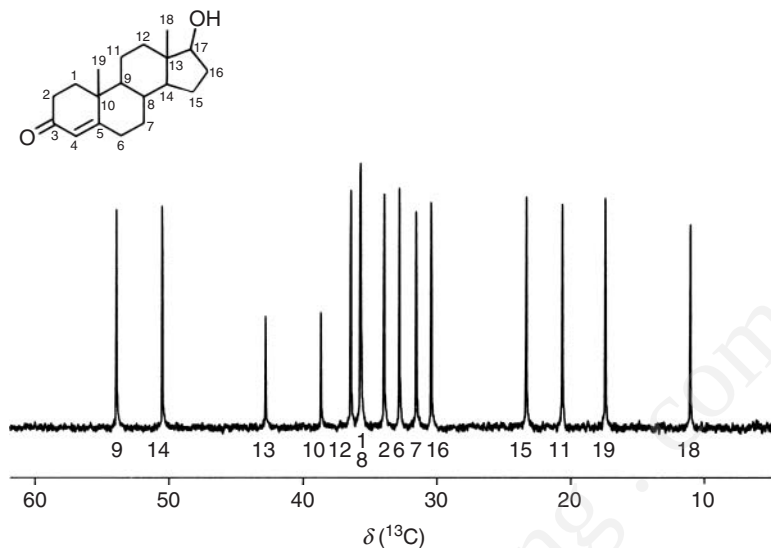


Figure 11.3 50 MHz ^{13}C NMR spectrum of the steroid testosterone in the aliphatic carbon region with ^1H -decoupling; the resonances of C3, C4, and C5 at higher frequencies are not shown.

information to solve the problem under study, especially if mass spectroscopic data are also available. Nevertheless, there are several general aspects of ^{13}C NMR spectroscopy that require special consideration and that will now be discussed.

The large chemical shift range renders ^{13}C attractive as a probe for the study of *dynamic processes*. Under the conditions of proton decoupling, in most cases simple exchange systems $\text{A} \rightleftharpoons \text{B}$ between two sites A and B are present that are readily analyzed. Furthermore, the dynamic process very often leads to more than one two-sites exchange system and thus allows separate line shape analyses that increase the precision of the results. In the slow exchange regime ^{13}C exchange spectroscopy (EXSY) is an important addition to the methods of dynamic nuclear magnetic resonance (DNMR). We come back to this point and to other aspects of ^{13}C DNMR spectroscopy in more detail in Chapter 13.

Another application of significance is ^{13}C labeling. The elucidations of reaction mechanisms in organic chemistry or biochemistry that previously were based exclusively on the use of the radioactive isotope ^{14}C can now be accomplished with the help of ^{13}C NMR spectroscopy. As before, synthesis of the labeled compound is unavoidable, but one is spared the often difficult and not always unequivocal degradation of the isolated reaction products since, when using ^{13}C resonance spectroscopy, the position of the carbon atom in question can be determined easily. In most applications ^{13}C enrichment is employed, but ^{13}C depletion, that is, ^{12}C labeling, has also been recognized as a useful technique. In some cases, even ^{13}C double labeling may be of advantage, because then ^{13}C , ^{13}C spin-spin coupling constants can be used for the analysis. Such experiments are of interest

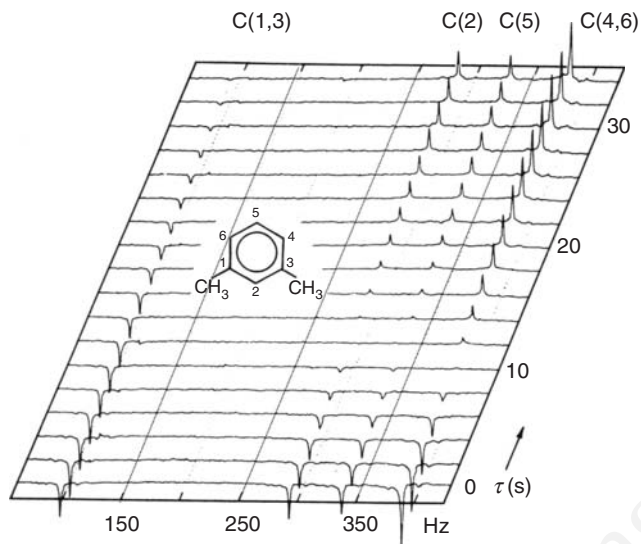


Figure 11.4 Determination of the longitudinal relaxation time, T_1 , of the ^{13}C nuclei in the benzene ring of *m*-xylene. For each spectrum the sequence $180-\tau-90^\circ$ was used and τ (in seconds) was increased in 2 s intervals; the following T_1 values (s) have been determined: C(1,3), 52 ± 5 ; C(4,6), 16.5 ± 2 ; C(2), 19 ± 2 ; and C(5), 20 ± 2 [3].

for mechanistic studies where one wants to prove if a certain C–C bond has been cleaved during the reaction of interest. Only in situations that require the highest sensitivity is labeling with radiocarbon (^{14}C) still superior to ^{13}C NMR.

Finally, beside *chemical shifts* and *coupling constants* (^{13}C , ^{13}C , ^{13}C , ^1H , ^{13}C , X where X = ^{19}F , ^{31}P , etc.) a third ^{13}C NMR parameter is of importance, namely, the ^{13}C *spin–lattice relaxation time*. Through FT NMR, T_1 measurements are facilitated and can be carried out almost routinely. Such an experiment using the inversion-recovery technique (cf. p. 247) is shown in Figure 11.4. Since nuclear relaxation rate constants R_1 ($= 1/T_1$) depend on various molecular properties – in the case of dipolar relaxation mainly on molecular dynamics – these parameters are important sources of information on molecular motion. In general, however, their interpretation is less straightforward than is usually the case with chemical shifts or coupling constants and must be based on physical models for the dynamic processes that are studied; T_1 data are thus less important for structural research than chemical shifts and coupling constants.

11.2

Experimental Aspects of Carbon-13 Nuclear Magnetic Resonance Spectroscopy

The experimental aspects of FT NMR have been dealt with in some detail in Chapters 9 and 10, and the general features discussed there equally well apply to ^{13}C FT NMR. Spectra are obtained with the ^{13}C NMR signal of tetramethylsilane

(TMS) as internal reference and a heteronuclear lock system, usually employing the ^2H resonance of the solvent CDCl_3 . ^1H broadband decoupling and spectral accumulation are used routinely and, thus, chemical shift determinations take a matter of minutes, as the line frequencies are printed out directly by the NMR software. Even if the maximum nuclear Overhauser effect is usually not observed in practice because other relaxation mechanisms may successfully compete with dipolar relaxation, the signal-to-noise ratio is high enough to run ^{13}C NMR spectra of milligram samples if high-field instruments (7.2 T or more) are available. However, a few facts that originate from ^1H decoupling need special comment. First, the elimination of line splittings prevents measurements of ^{13}C , ^1H coupling constants, and valuable experimental information is thus lost. Second, the nuclear Overhauser effect leads to intensity distortions and the integration of these spectra becomes questionable. Finally, the assignment of the NMR signals to specific carbon atoms of the particular structure is by no means obvious.

11.2.1

Gated Decoupling

To deal with these shortcomings, special experimental techniques are available. The application of a method known as *gated decoupling* successfully handles spin–spin coupling and intensity distortions. It is based on the fact that different time scales are characteristic for the decoupling experiment and the nuclear Overhauser effect (NOE). Whereas the latter is governed by spin–lattice relaxation and thus evolves and decays within seconds, decoupling sets in or vanishes almost immediately after the B_2 field has been switched on or off. This difference can be used to advantage in two experimental sequences illustrated in Figure 11.5. In the first (Figure 11.5a), the decoupler is gated such that it is on during the delay time between different pulses and switched off during data acquisition. As a result, the spectra are not decoupled, but at the same time most of the Overhauser enhancement is retained; ^{13}C , ^1H coupling constants – mostly those over one bond – can thus be measured without the need to sacrifice the NOE completely.

If, on the other hand, correct integrals are of interest, the second sequence of experiments (Figure 11.5b) is applied. Here, the decoupler is switched on during data acquisition, but switched off during the remaining time before the next pulse. ^{13}C , ^1H spin–spin coupling is thus eliminated without producing nuclear Overhauser enhancement, primarily because the integrals depend on the initial value of the time domain function. In addition, or alternatively, so-called shiftless relaxation reagents – an area treated in detail in Chapter 14 – can be used to eliminate an unwanted NOE. Because of their paramagnetic moment, these compounds, for example, chromium acetylacetonate $[\text{Cr}(\text{acac})_3]$, provide an effective mechanism for ^{13}C spin lattice relaxation that suppresses dipolar relaxation that is the basis for the NOE (cf. p. 344). It is important, however, to ascertain that the addition of the paramagnetic substance does not affect the ^{13}C chemical shifts.

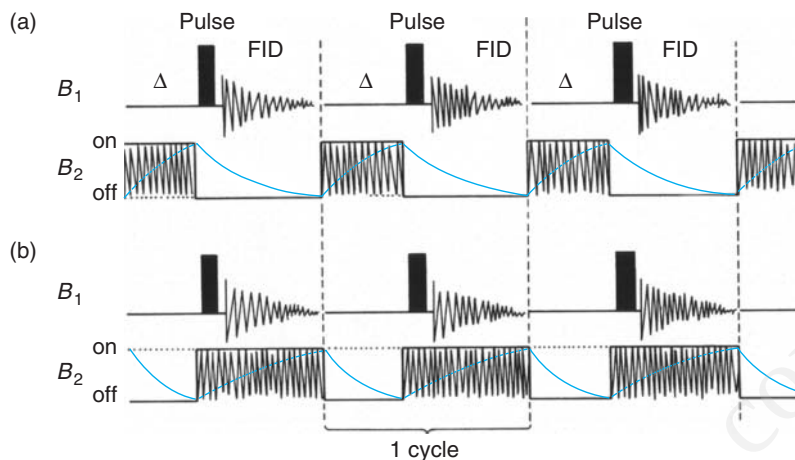


Figure 11.5 Pulse sequences for gated decoupling experiments: (a) the decoupler is switched off during data acquisition; part of the NOE enhancement is retained, ^{13}C spectra are ^1H -coupled; (b) the decoupler is switched on during data acquisition; the NOE is suppressed, ^{13}C spectra are decoupled. The red trace signifies NOE.

11.2.2

Assignment Techniques

Independent methods for the correct assignment of ^{13}C signals to the molecular structure under study were from the start of prime interest to NMR spectroscopists. Many of the older procedures – like off-resonance ^1H -decoupling (see p. 277) – have been replaced in the meantime by modern one- and two-dimensional techniques. The most important experiments used today will be discussed in the following sections. In this respect, two aspects have to be distinguished: On the one hand, we have methods for *spectral editing* or *multiplicity selection* that allow the resonances of quaternary, methine, methylene, and methyl carbons to be distinguished. This was achieved previously by off-resonance ^1H -decoupling. On the other hand, in a second stage, ^{13}C signals must be assigned to certain structural elements of the molecule, which calls for additional experimental procedures.

11.2.2.1 Multiplicity Selection with the Heteronuclear Spin Echo Experiment (SEFT, APT)

Soon after the concept of evolution time was introduced, it was recognized that it can also be used to develop new one-dimensional measuring techniques. On the basis of the heteronuclear spin echo experiment, for example, an assignment technique for ^{13}C signals was established that allows us to differentiate between the resonances of quaternary carbons, (C_q), and carbons of CH , CH_2 , and CH_3 groups. It is known as a SEFT (spin echo Fourier transform) spectroscopy experiment or, slightly modified, as APT (attached proton test) experiment and was an attractive alternative to the traditional method of off-resonance ^1H decoupling. Today,

polarization transfer methods (Section 11.2.2.2) have replaced the SEFT or APT technique for multiplicity selection, but it seems worthwhile describing the older techniques in some detail because the underlying principle is of general importance.

As described on p. 288, during the heteronuclear spin echo experiment for AX spin systems, the A and the X magnetization, respectively, fan out in the x, y -plane due to scalar coupling. For AX, A_2X , and A_3X systems ($A = {}^1\text{H}$, $X = {}^{13}\text{C}$) of CH , CH_2 , and CH_3 groups, characteristic vector orientations result after a certain evolution time. This fact can be used for signal selection if ${}^{13}\text{C}, {}^1\text{H}$ coupling is removed during the detection time by ${}^1\text{H}$ -decoupling. Switching on the decoupler at the end of the evolution time conserves the particular vector orientation. Because of their large values (~ 125 Hz for aliphatic, ~ 160 Hz for olefinic, and ~ 250 Hz for acetylenic C,H bonds, see Section 11.4) this experiment is dominated by the one-bond coupling constants and the effect of the geminal and vicinal couplings, which are considerably smaller, can be neglected.

Figure 11.6a shows the time development of ${}^{13}\text{C}$ magnetization and signal intensity, $I({}^{13}\text{C})$, during the delay τ under the action of $J({}^{13}\text{C}, {}^1\text{H})$. For ${}^1\text{H}$ -coupled ${}^{13}\text{C}$ nuclei it is governed by Eqs (11.2–11.4):

$$\text{CH} : I = I_0 \cos(\pi J \tau) \quad (11.2)$$

$$\text{CH}_2 : I = I_0 \cos^2(\pi J \tau) \quad (11.3)$$

$$\text{CH}_3 : I = I_0 \cos^3(\pi J \tau) \quad (11.4)$$

Two τ values are of practical interest: $\tau = 1/2J$ leads to an elimination of all ${}^1\text{H}$ -coupled resonances, and $\tau = 1/J$ leads to phase selection with positive signals for C_q and CH_2 resonances and negative signals for CH and CH_3 resonances. The corresponding vector pictures are shown in Figure 11.6b and the pulse sequence of the SEFT experiment is given in Figure 11.6c. The $180_x({}^{13}\text{C})$ pulse of the spin echo experiment eliminates the effects of chemical shifts and transverse relaxation and the ${}^1\text{H}$ -decoupler determines the evolution of ${}^{13}\text{C}$ magnetization. The following τ values can be derived from the known magnitude of typical one-bond ${}^{13}\text{C}, {}^1\text{H}$ coupling constants:

C–H bond	J (Hz)	$(1/J)$ (ms)	$(1/2J)$ (ms)
–C–H	~ 125	8	4
=C–H	~ 160	6.25	3.13
$\equiv\text{C}$ –H	~ 250	4	2

The experiment is not critical with respect to smaller variation within each group. These delays also apply to various other experiments described in this chapter.

A practical application of this experiment is given in Figure 11.7 with a spectrum of 4-*tert*-butylcyclohexanone. The proton decoupled ${}^{13}\text{C}$ NMR spectrum of this compound (Figure 11.7b) shows five signals, two of which are nearly degenerate.

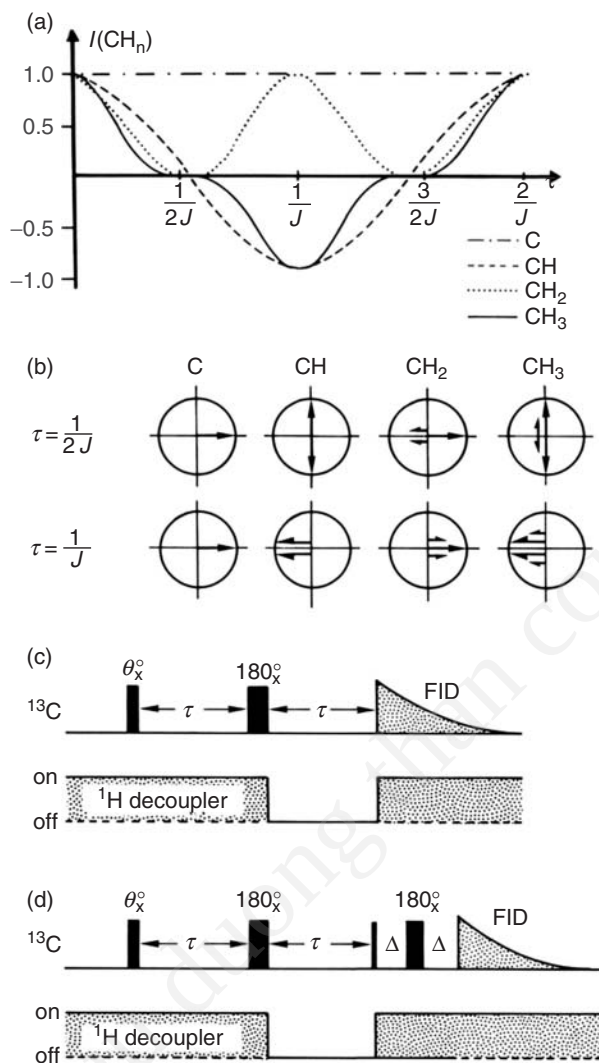


Figure 11.6 (a) Time dependence of the ^{13}C magnetization for CH , CH_2 , and CH_3 groups modulated by scalar ^{13}C , ^1H coupling; relaxation effects are neglected and the magnetization of quaternary carbons is not changed; (b) vector

orientation for the evolution delays $\tau = 1/2J$ and $1/J$; (c) pulse sequence of the SEFT experiment; (d) the APT sequence, pulse angle $\theta_x < 90^\circ$, $\Delta \approx 1$ ms.

The traditional off-resonance ^1H -decoupling experiment (Figure 11.7a) yields unambiguous results for the methine resonance, $\text{C}(4)$, for one CH_2 resonance and for the signal of the quaternary carbon. However, for the closely spaced signals at lowest frequency strong overlap prevents an assignment. The SEFT experiment, first run with $\tau = 1/2J$, confirms the resonance of the quaternary

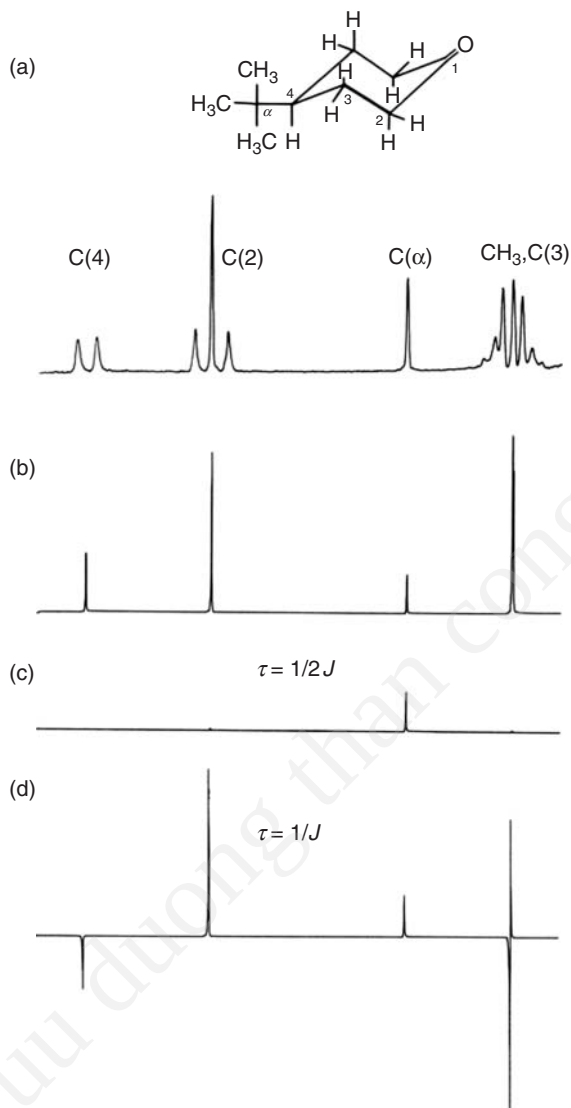


Figure 11.7 Signal assignment for the ^{13}C NMR spectrum of 4-*tert*-butylcyclohexanone; (a) *off-resonance* ^1H -decoupling; (b) ^1H broadband decoupling; (c) SEFT experiment with $\tau = 1/2J$; (d) SEFT experiment with $\tau = 1/J$; for aliphatic C,H bonds we have $J \sim 125$ Hz (cf. Section 11.4) and τ delays of 4 and 8 ms, respectively, were used.

carbon (Figure 11.7c). A second experiment with an evolution time of $\tau = 1/J$ (Figure 1d) then shows additional signals for C(4) (negative phase), C(2) (positive phase), and at high field there are clearly two signals, one with negative and one with positive phase. Accordingly, these two resonances must belong to a CH₃ and a CH₂ group, respectively.

Because 90° pulses require relatively long relaxation delays, the performance of the SEFT experiment can be improved by the APT experiment, mentioned above, where smaller excitation pulse angles are used. It is then necessary, however, to align the remaining ^{13}C z -magnetization again along the $+z$ -axis by a short spin echo sequence after the evolution time and before signal detection (Figure 11.6d).

Exercise 11.1

Verify the effect of the additional spin echo sequence in the APT experiment with the help of vector diagrams.

Additional SEFT or APT experiments with evolution delays around $1/2J$ are necessary to distinguish between resonances of CH and CH_2 groups. This is one of the reasons why polarization transfer experiments have replaced the spin echo techniques for ^{13}C assignments.

11.2.2.2 Polarization Transfer Experiments

With the development of the polarization transfer pulse sequences INEPT and DEPT (distortionless enhancement by polarization transfer) new methods for ^{13}C assignment became available that have the additional advantage of signal enhancement. As shown in Figure 11.8, the evolution of the magnetization of CH, CH_2 , and CH_3 carbons during the refocusing spin echo period of the INEPT sequence, Δ_2 (p. 361), differs and the maxima are observed at different Δ_2 values, a fact that can be used for signal selection. For example, a value of $1/2J(^{13}\text{C},^1\text{H})$ allows us to detect the magnetization of CH groups, while that of CH_2 and CH_3

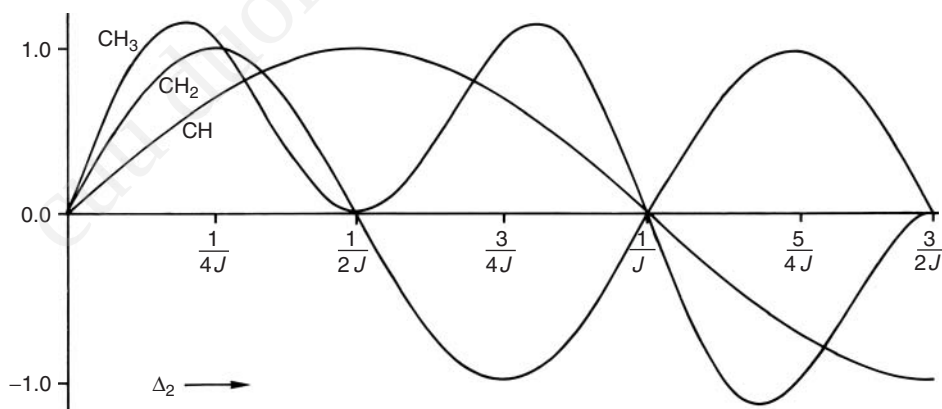


Figure 11.8 Time dependence of ^{13}C magnetization modulated by $^{13}\text{C},^1\text{H}$ coupling in the refocusing period Δ_2 of the INEPT sequence (p. 361) for CH, CH_2 , and CH_3 groups; for refocusing of the respective multiplets, the appropriate Δ_2 delays are $1/2J$ for the doublet, $1/4J$ for the triplet, and $3/4J$ for the quartet.

groups is eliminated. On the other hand, a Δ_2 value of $3/4J(^{13}\text{C}, ^1\text{H})$ yields positive signals for resonances of CH and CH_3 groups and negative signals for CH_2 groups.

Today, in practical applications of polarization transfer experiments for resonance assignments the DEPT sequence, shown in Figure 11.9, is usually preferred. It yields, after three $1/2J$ delays, multiplets with uniform phase and with the application of ^1H -decoupling yields singlet signals for all types of ^{13}C resonances. The pulse angle θ of the last A pulse can be optimized for individual groups to allow signal selection.

Within the product operator formalism the DEPT sequence, applied to a CH fragment and neglecting the 180° pulses, yields the following expressions:

$$\begin{aligned}
 \hat{I}_z(^1\text{H}) &\xrightarrow{90^\circ \hat{I}_x(^1\text{H})} \hat{I}_y(^1\text{H}) \xrightarrow{1/2J} 2\hat{I}_x(^1\text{H})\hat{I}_z(^{13}\text{C}) \\
 &\xrightarrow{90^\circ \hat{I}_x(^{13}\text{C})} 2\hat{I}_x(^1\text{H})\hat{I}_y(^{13}\text{C}) \xrightarrow{1/2J} 2\hat{I}_x(^1\text{H})\hat{I}_y(^{13}\text{C}) \\
 &\xrightarrow{90^\circ \hat{I}_y(^1\text{H})} 2\hat{I}_z(^1\text{H})\hat{I}_y(^{13}\text{C}) \xrightarrow{1/2J} \hat{I}_x(^{13}\text{C})
 \end{aligned} \quad (11.5)$$

The most important aspects are the development of pure anti-phase ^1H magnetization in the first $1/2J$ delay, the transformation of this magnetization into heteronuclear double-quantum magnetization by the $90^\circ(^{13}\text{C})$ pulse, and the transformation of this magnetization into anti-phase ^{13}C magnetization that is refocused in the final $1/2J$ delay. The central $1/2J$ delay results from the necessity to perform in the ^1H as well as in the ^{13}C domain a spin echo sequence to remove relaxation and chemical shift effects. During this delay the double quantum operator $2\hat{I}_x(^1\text{H})\hat{I}_y(^{13}\text{C})$ is invariant with respect to scalar coupling (cf. p. 316).

On the basis of Figure 11.8, Eqs (11.6–11.8) can be derived for the refocusing of ^{13}C magnetization and the editing of subspectra for CH, CH_2 , and CH_3 resonances. If we define an angle θ by $\theta = \pi J\Delta_2$ we obtain for the last pulse of the DEPT sequence with $\Delta_2 = 1/4J$ an angle $\theta(1) = \pi/4$ or 45° [subspectrum S(1)], with $\Delta_2 = 1/2J$ an angle $\theta(2) = \pi/2$ or 90° [subspectrum S(2)], and finally with $\Delta_2 = 3/4J$ an angle $\theta(3) = 3\pi/4$ or 135° [subspectrum S(3)]. The subspectrum S(1) then contains all CH, CH_2 , and CH_3 signals, subspectrum S(2) only the CH signals, and subspectrum S(3) positive signals for CH and CH_3 groups and negative signals for CH_2 groups. Linear combinations are formulated for the selection, where the

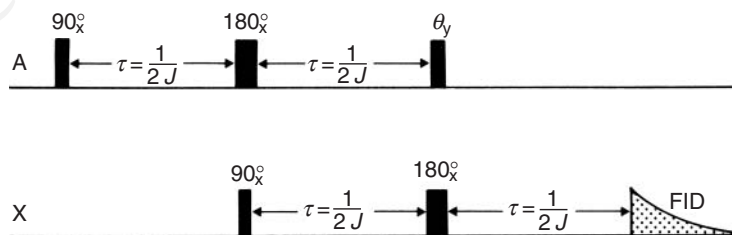


Figure 11.9 DEPT pulse sequence; A = ^1H , X = ^{13}C ; the angle of the last pulse, θ_y , can be varied.

intensity differences must be taken into account:

$$S(\text{CH}) = 2 \times S(2) \quad (11.6)$$

$$S(\text{CH}_2) = S(1) - S(3) \quad (11.7)$$

$$S(\text{CH}_3) = S(1) + S(3) - 1.414 S(2) \quad (11.8)$$

Signals that are not part of these spectra can be assigned to quaternary carbons.

Figure 11.10a shows DEPT-editing of a ^{13}C spectrum. If in a simplified version $\theta_y = 135^\circ$ is used, only the subspectrum $S(3)$ (Figure 11.10b) is obtained. In summary we can state that the assignment techniques described in Sections 11.2.2.1 and 11.2.2.2 have the advantage that ^1H decoupled ^{13}C signals are detected and the information about the multiplicity is transformed into phase information. The assignment can thus be performed under the highest spectral dispersion. In addition, the intensity enhancement by NOE effects or polarization transfer is conserved. Because of the J -dependence of the evolution time, however, in many cases two different experiments are necessary since, as described above, the $^1J(^{13}\text{C}, ^1\text{H})$ values for sp , sp^2 , and sp^3 carbons differ considerably.

Exercise 11.2

Verify the signal assignment given in Figure 11.3 (p. 380) with the help of the DEPT spectrum shown in Figure 11.10b.

11.2.2.3 Heteronuclear Two-Dimensional ^1H , ^{13}C Chemical Shift Correlation

While the methods described so far allow an assignment of ^{13}C signals with respect to their multiplicity and thus yield information about the number of attached protons, further experiments are necessary to derive an assignment to individual positions in a chemical structure. In this respect, two-dimensional heteronuclear ^1H , ^{13}C chemical shift correlations are of major importance. As in the case of homonuclear shift correlations or COSY spectroscopy, discussed in detail in Chapter 9, resonance frequencies of scalar coupled nuclei, in this case ^1H and ^{13}C , are correlated and cross peaks with the coordinates $\delta(^1\text{H})$, $\delta(^{13}\text{C})$ are obtained. Most of these correlations are based on heteronuclear ^{13}C , ^1H coupling constants over one bond. Those nuclei that show cross peaks are, therefore, direct neighbors in the particular molecule and the resonance assignment of the proton spectrum can be transferred directly to the ^{13}C spectrum and vice versa. In addition, correlations based on ^{13}C , ^1H long-range couplings can be used that often yield information that is crucial for the final solution of a structural problem.

Three different pulse sequences, shown in Figure 11.11a–c, are available today for *two-dimensional heteronuclear shift correlations* between a sensitive A nucleus (^1H , ^{19}F , and ^{31}P) and an insensitive X nucleus (^{13}C , ^{15}N):

- the long known polarization transfer experiment HETCOR (*heteronuclear shift correlation*) experiment (Figure 11.11a),
- the HMQC (*heteronuclear multiple quantum correlation*) experiment that involves heteronuclear multiple quantum phenomena (Figure 11.11b),

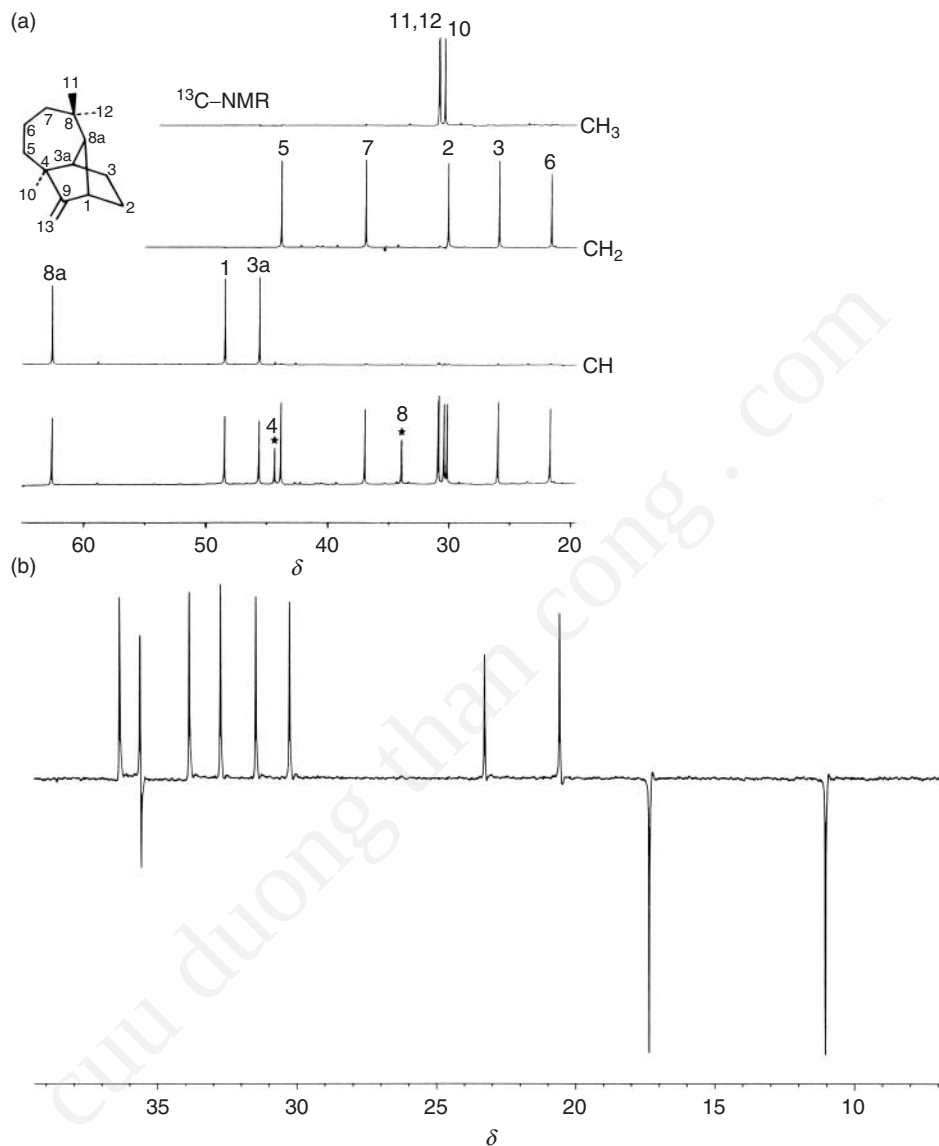


Figure 11.10 (a) Multiplicity selection with the DEPT sequence for the 100 MHz ^{13}C NMR spectrum of the terpene longifolene (aliphatic region); $1/2J = 3.8$ ms; the signals of quaternary carbons are labeled with a star [4]; (b)

simplified DEPT spectrum with $\theta_y = 135^\circ$ for the aliphatic region of the ^{13}C NMR spectrum of testosterone (for the normal 1D spectrum see Figure 11.3, p. 380).

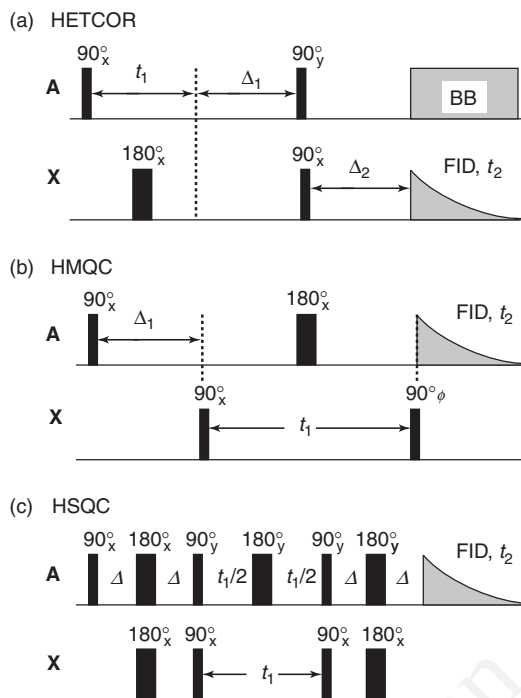


Figure 11.11 Pulse sequences for heteronuclear chemical shift correlations: (a) HETCOR: A→X polarization transfer method with X detection; the delay Δ_1 amounts to $1/2J(A,X)$ and yields anti-phase A-magnetization to be transformed into anti-phase X-magnetization; Δ_2 is the delay responsible for refocusing of the anti-phase X magnetization. For the $^1\text{H}, ^{13}\text{C}$ experiment, the F_1 domain contains the ^1H frequencies, while the F_2 domain contains the ^{13}C frequencies; ^1H broadband decoupling eliminates $J(^{13}\text{C}, ^1\text{H})$ also in F_2 ; (b) HMQC:

“inverse” correlation with A detection and X chemical shift evolution of double quantum coherence without X decoupling; for the $^1\text{H}, ^{13}\text{C}$ experiment the F_1 domain contains ^{13}C frequencies, while the ^1H frequencies appear on the F_2 frequency axis; the delay Δ_1 amounts to $1/2J(A,X)$; (c) HSQC: INEPT magnetization transfer A→X, X evolution time t_1 with A decoupling by a 180° pulse, and reverse INEPT transfer X→A; as in Figure 10.14 (p. 361) the delay Δ is equal to $1/4J(A,X)$.

- the HSQC (heteronuclear single quantum correlation) experiment that makes use of magnetization transfer by INEPT and reverse INEPT pulse schemes (Figure 11.11c).

In the HETCOR experiment, magnetization is transferred from the sensitive A nucleus, generally from the proton, to the insensitive X nucleus, for example, ^{13}C or ^{15}N . This magnetization transfer generates the cross peaks in the two-dimensional spectrum. The signals of the insensitive X nucleus are detected. In the HMQC experiment heteronuclear multiple quantum coherence is produced that develops during the evolution time and is finally transferred into detectable A magnetization.

The sensitive A nucleus is used for signal detection and this method is known as *reverse or inverse shift correlation*. The HSQC experiment starts with an INEPT transfer from A to X, followed by the evolution period t_1 , during which the A nuclei are decoupled from the X nuclei by the 180°_X pulse. An inverse INEPT transfer from X to A yields the A signals in F_2 and the X signals in F_1 . In all three sequences (a)–(c) the 180°_X pulse during the evolution time t_1 decouples A from X and removes this coupling from the F_1 domain. Two examples of ^{13}C , ^1H shift correlations with the HETCOR and HMQC technique, respectively, are shown in Figure 11.12.

Furthermore, in all sequences it is possible to apply a refocusing period, after which decoupling can be used. This is rather simple for the HETCOR experiment, since here the protons must be decoupled. For the other pulse sequences, ^{13}C or generally X nucleus composite pulse decoupling is used. An additional problem exists because in fact the satellites of the X nucleus in the spectrum of the sensitive A nucleus are detected. To avoid signal overlap the main signals of the A nucleus that originate from molecules that do not contain a magnetically active X nuclide have to be eliminated by the phase cycle. If elimination is not complete, the spectra contain strong t_1 noise. In the case of X nucleus, decoupling the X satellites may then coincide with the noise signals and their detection becomes difficult. For this reason X nucleus decoupling is rarely used in practice, which has the additional advantage that the ^{13}C , ^1H spin–spin coupling constants can also be obtained from the 2D spectrum. One must remember, however, that the A nucleus (^1H) doublets are recorded in anti-phase and signal elimination may result in the case of small couplings, an important point for the long-range correlation experiment (see below).

Exercise 11.3

Develop the product operator treatment for the pulse sequences shown in Figure 11.11 for a CH fragment up to signal detection.

Because of A nucleus detection the HMQC and the HSQC experiment are more sensitive than experiments based on polarization transfer. Further sensitivity improvements are achieved if “inverse” probe heads are employed, where the inner coil, which is more sensitive because of the larger filling factor, is used for A detection. The outer coil is then tuned to the X frequency. The theoretical factor of $(\gamma_A/\gamma_X)^{5/2}$ for sensitivity enhancement is not observed in practice, however, because of competing mechanisms that lead to signal losses. In any case, the success of such experiments depends on the careful adjustment of pulse angles and delays during the pulse sequence and on stable spectrometer hardware. Further improvements have been achieved by the introduction of a so-called BIRD sequence (see p. 329) that greatly reduces the signals of the isotopomers with non-magnetic X nuclides.

For ^{13}C NMR, where anti-phase A magnetization develops during the delay Δ_1 , the detection of one-bond or long-range correlations can be controlled in sequences Figure 11.11a,b because of the different magnitude of these spin–spin interactions.

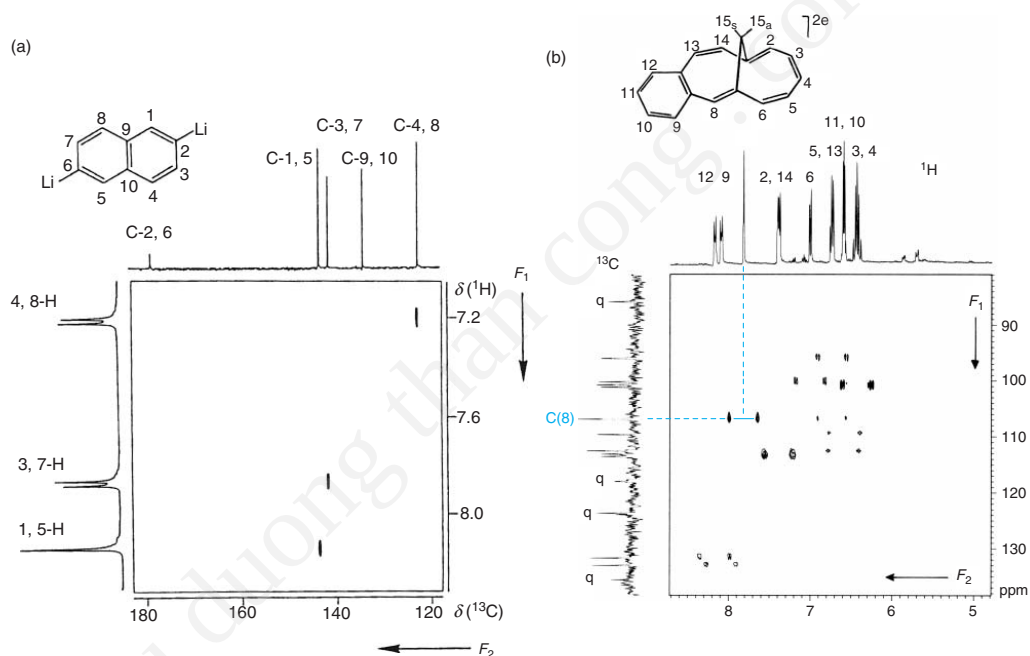


Figure 11.12 (a) 100/400 MHz ^{13}C , ^1H HETCOR spectrum (pulse sequence a, Figure 11.11) of 2,7-dilithionaphthalene in THF based on $^1J(^{13}\text{C}, ^1\text{H})$; spectral windows 6.6 kHz (F_2) and 500 Hz (F_1); 32 t_1 increments, 40 scans each; relaxation delay 2 s; experiment time 40 min. (b) 400/100 MHz ^1H , ^{13}C chemical shift correlation via heteronuclear multiple quantum coherences (HMQC experiment, pulse sequence b, Figure 11.11) for the dianion of benzo[*c*]-1,7-methano[12]annulene with $\Delta_1 = 3.57$ ms for $^1J(^{13}\text{C}, ^1\text{H}) = 140$ Hz; the cross peaks correspond to the ^{13}C satellites in the ^1H spectrum that show the $^1J(^{13}\text{C}, ^1\text{H})$ couplings. H.-E. Mons and H. Günther, unpublished data.

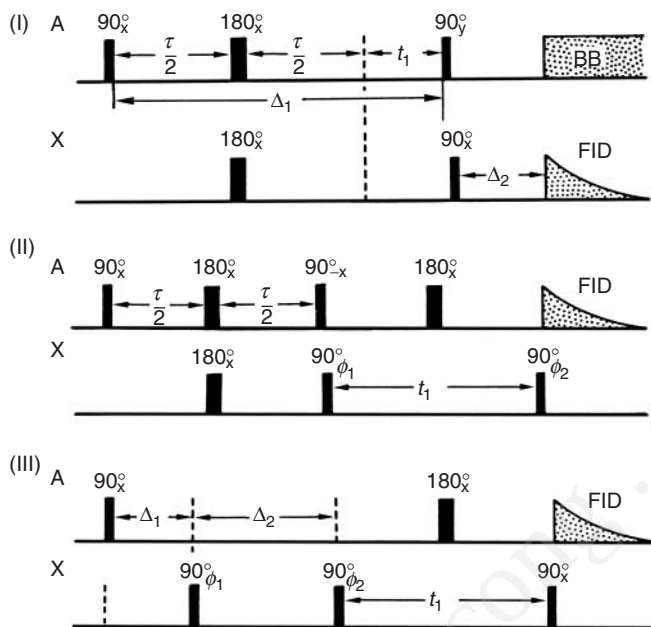


Figure 11.13 Modified pulse sequences for heteronuclear shift correlations: (I) HETCOR COLOC sequence for correlations via long-range couplings; (II) HMQC experiment with improved elimination of single quantum A signals; $\tau = 1/2J$; (III) HMBC sequence.

For $^1J(^{13}\text{C}, ^1\text{H})$ with values between 125 and 170 Hz, a delay of 3.3 ms is a good compromise in practice. For long-range couplings that are of the order of 3–12 Hz, the Δ_1 values are around 25 ms. For the Δ_2 delay a value of 2 ms secures the detection of all correlations via one-bond couplings (CH, CH_2 , and CH_3 groups). In the case of long-range couplings these values are again considerably larger (20–50 ms). In all sequences the repetition rate is governed by the relatively short longitudinal ^1H relaxation time. The relaxation delay can thus be much shorter than for one-dimensional ^{13}C experiments. Because of the interchange of the F_1 and F_2 frequency axes, one difference, however, exists: with Figure 11.11a higher resolution can be obtained for the ^{13}C frequency axis than with the other two sequences.

The general importance of heteronuclear shift correlations has initiated intensive research for improvements with respect to sensitivity and selectivity. From the various modifications that have been proposed we briefly refer to three pulse sequences that have found widespread applications. They are summarized in Figure 11.13.

A variant for A,X shift correlations based on long-range couplings, known as the COLOC sequence (correlation via long-range couplings), is shown in diagram (I). It is a polarization transfer experiment like the sequence in Figure 11.11a, but now the evolution time t_1 for the development of anti-phase A magnetization is incorporated into the Δ_1 delay that is flanked by the two 90° pulses. Because this

delay is unchanged during t_1 incrementation, the experiment is called a “constant time experiment” (cf. p. 329). Incrementation of the evolution time t_1 is achieved by moving the $180^\circ(\text{A}, \text{X})$ pulse pair through the Δ_1 interval. The time τ thus varies in a series of experiments. Because of the $180^\circ(\text{A})$ pulse that refocuses chemical shift effects at the time τ , the evolution of A magnetization that yields the frequency labeling necessary for a shift correlation is restricted to the time $\Delta_1 - \tau$. This is the true t_1 period in this experiment. From the couplings, heteronucleus A,X coupling develops during the whole Δ_1 interval, while homonuclear A coupling is eliminated from the F_1 domain. The result is a shorter pulse sequence with improved detection for fast relaxing cross peak magnetizations and with ω_1 decoupling.

Sequences II and III are variants of the HMQC experiment (sequence in Figure 11.11b). The BIRD pulse sandwich (p. 329) introduced in sequence II greatly improves the suppression of single quantum A magnetization from molecules with magnetically inactive X nuclei, for example, ^1H – ^{13}C in ^1H , ^{13}C experiments. The 180° pulse refocuses chemical shift evolution and the τ -delay is tuned for the heteronuclear coupling so that at the end of this period coupled A magnetization is in anti-phase [$\hat{I}_x(\text{A})\hat{I}_z(\text{X})$] while uncoupled A magnetization – homonuclear A couplings neglected – points still along the y-axis [$\hat{I}_y(\text{A})$]. The 90°_{-x} pulse transforms this magnetization to $\hat{I}_z(\text{A})$, while $\hat{I}_x(\text{A})\hat{I}_z(\text{X})$ is unaffected and proceeds to detection as in the sequence in Figure 11.11b. The homonuclear A couplings can be neglected because the heteronuclear A,X couplings are generally larger by a factor of 10 and dominate the evolution of transverse magnetization. Figure 11.14 (p. 396) shows the improvement achieved with sequence II with an example from a ^2H , ^{13}C correlation experiment with ^2H detection for $[\text{D}_5]\text{pyridine}$.

Finally, sequence III was introduced as an “inverse” COLOC experiment. Here, the delays Δ_1 and Δ_2 are tuned to one-bond and long-range heteronuclear A,X couplings, respectively. The first 90° pulse pair, separated by the delay $\Delta_1 = 1/2^1J(\text{A}, \text{X})$, serves as a low-pass filter (cf. p. 330) that eliminates one-bond correlations. The second $90^\circ(\text{X})$ pulse then creates, after the appreciably longer delay Δ_2 (≈ 60 ms), the desired multiple quantum coherences based on long-range couplings. Before detection, a refocusing delay Δ_2 may be introduced to avoid signal elimination due to the initial anti-phase character of the A-magnetization in the case of small couplings. It is then possible to decouple the X nucleus (^{13}C) by, for example, a composite pulse sequence. While for the HETCOR sequence the refocusing delay Δ_2 is a compromise with respect to the optimal values necessary for different $^{13}\text{C}, ^1\text{H}_n$ groups (see p. 384), a unique value $1/2J(^{13}\text{C}, ^1\text{H})$ serves in sequence III because X coupling to the A nuclei involves only one ^{13}C spin. The sequence goes by the acronym HMBC (*heteronuclear shift correlations via multiple bond connectivities*) and is today most effectively performed using gradient enhanced spectroscopy, which improves significantly the elimination of t_1 -noise from the residual signals of molecules with non-magnetic X nuclei. This is demonstrated in Figure 11.15 (p. 397) with a $^{13}\text{C}, ^1\text{H}$ correlation experiment for 3-fluorophenanthrene that also shows the coherence selection by linear field gradients.

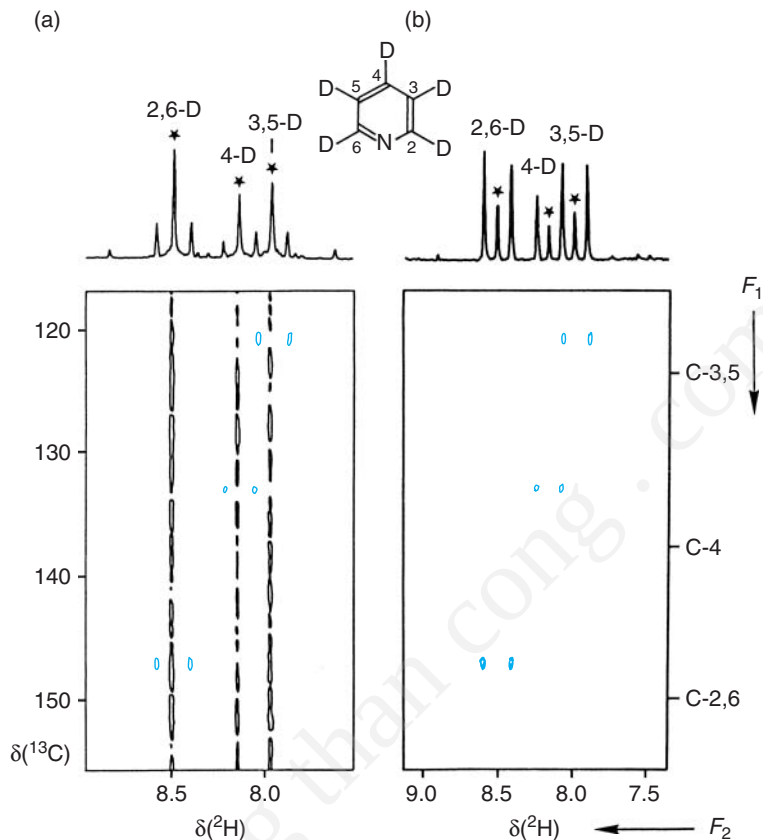


Figure 11.14 Two-dimensional ^2H -detected HMQC $^{13}\text{C}, ^2\text{H}$ shift correlations for $[\text{D}_5]\text{pyridine}$ without (a) and with (b) additional BIRD pulse (sequence II in Figure 11.13). In (b), the $\tau/2$ delay $[= 1/4 J(^{13}\text{C}, ^2\text{H})]$ was set to 10 ms, corresponding to $^1J(^{13}\text{C}, ^2\text{H}) = 25$ Hz. The starred signals are residual ^2H resonances of $^{12}\text{C}-^2\text{H}$ units. The cross peaks (small lighter peaks) are split by $^{13}\text{C}, ^2\text{H}$ spin-spin coupling [5].

We conclude our introduction to the field of heteronuclear shift correlations with a description of four examples of $^{13}\text{C}, ^1\text{H}$ chemical shift correlations in order to illustrate their application.

Figure 11.16 (p. 398) demonstrates how the methyl resonances in the ^{13}C NMR spectra of angelica and tiglic acid – acyl residues that appear quite frequently in natural products – can be assigned. Electron density considerations and stereochemical aspects are not sufficient to derive an unambiguous decision. The situation is different in the ^1H NMR spectrum where only the protons at C(4) have a large vicinal $^1\text{H}, ^1\text{H}$ coupling to the olefinic proton H(3). The doublet of quartets in the ^1H spectrum [^4J coupling between H(4) and H(5)] can, therefore, be safely assigned to H(4). The cross peaks in the HETCOR 2D $^1\text{H}, ^{13}\text{C}$ shift correlation experiment then yield the ^{13}C assignment, which shows that the order of $\delta(4)$

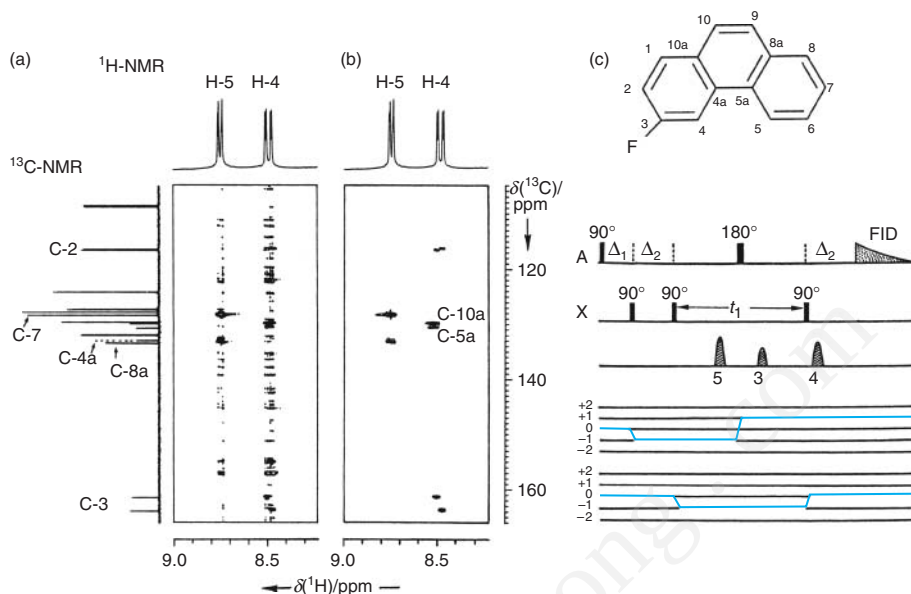


Figure 11.15 100/400 MHz ^{13}C , ^1H HMBC correlation for 3-fluorophenanthrene: (a) with sequence II (Figure 11.13); (b) with sequence III (Figure 11.13) modified for coherence selection by linear B_0 field gradients as shown in (c) with $A = ^1\text{H}$ and $X = ^{13}\text{C}$. According to the coherence pathways shown and the resulting coherence orders, the desired ^1H magnetization evolves during the first $t_1/2$ interval as heteronuclear double quantum coherence with the sum $[(\omega(^1\text{H}) + \omega(^{13}\text{C}))]$. After the $180^\circ(^1\text{H})$ pulse, in the second $t_1/2$ interval, we have $[\omega(^1\text{H}) - \omega(^{13}\text{C})]$ (zero quantum

coherence) and finally during detection single quantum ^1H magnetization, $\omega(^1\text{H})$. If we now consider the ratio $\gamma(^1\text{H}) : \gamma(^{13}\text{C}) \approx 4 : 1$, the gradient pulses ΔG_1 , ΔG_2 , and ΔG_3 shown in (c) must have the amplitudes 5, 3, and 4 in order to refocus the desired ^1H magnetization (see eq. (9.40), p. 328) $[5 \times (-)(4 + 1) + 3 \times (4 - 1) + 4 \times 4 = 0]$. For the undesired t_1 -noise from the ^{12}C molecules we have, during the same intervals, $(-4 \times 5) + (4 \times 3) + (4 \times 4) = 8$ that leads to elimination. In both experiments, the delays Δ_1 and Δ_2 were set to 3 and 47 ms, respectively [6].

and $\delta(5)$ in both compounds is different. While $\delta(4)$ is fairly constant, C(5) is considerably shielded in tiglic acid ($\Delta\delta = -9.3$ ppm), apparently a consequence of steric interactions with the larger groups in geminal and vicinal positions.

Because of the larger spectral dispersion of ^{13}C , a strongly overlapping ^1H spectrum can often be assigned by a ^1H , ^{13}C shift correlation. However, the opposite case can also be found. Both aspects are illustrated in Figure 11.17 (p. 399). Thus, the signals of the methylene protons from individual CH_2 groups in the spectrum of the paracyclophane **1** are identified via their cross peaks with the same carbon resonance (Figure 11.17a). On the other hand, the nicely resolved ^1H NMR spectrum of bis-dehydrobenzo[20]annulene, which is easily analyzed on the basis of coupling constants and ring current effects, can be used to assign the closely spaced ^{13}C signals in the frequency region between 126.0 and 127.5 ppm (Figure 11.17b).

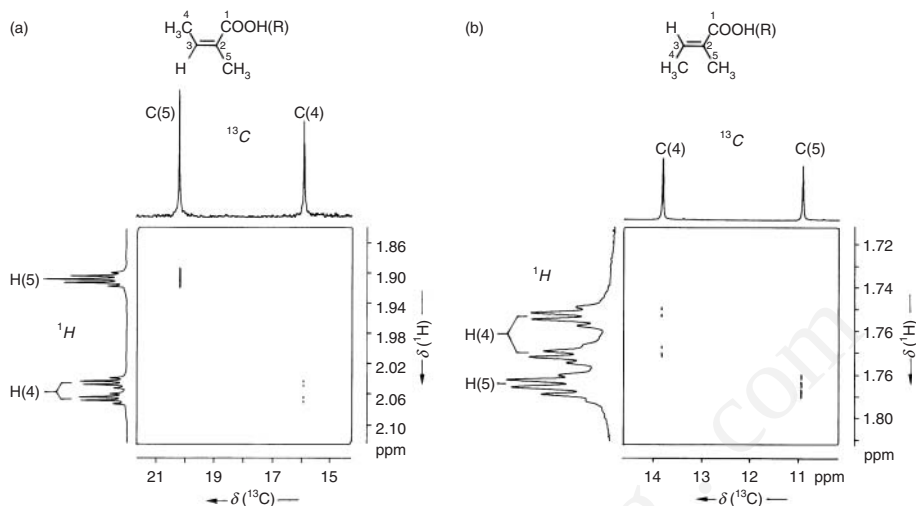


Figure 11.16 400/100 MHz 2D ^1H , ^{13}C chemical shift correlation for angelic (a) and tiglic acid (b) on the basis of the HETCOR pulse sequence (Figure 11.11, p. 391) [7].

11.2.2.4 The ^{13}C , ^{13}C INADEQUATE Experiment

In Chapter 9 we discussed the 2D INADEQUATE experiment, a homonuclear chemical shift correlation on the basis of double-quantum magnetization. This experiment was originally developed for ^{13}C NMR spectroscopy and was first executed as a one-dimensional experiment. The idea was to measure ^{13}C , ^{13}C coupling constants more easily. The experimental determination of these parameters suffers from the low natural abundance of carbon-13, which leads to only 0.01 % probability of finding two neighboring ^{13}C nuclei in the same molecule that means in only one molecule in 10,000. If enough sensitivity is available, satellites can then be observed in the ^1H -decoupled ^{13}C NMR spectrum of these isotopomers that accompany the 200-times more intensive main signal S_0 due to molecules with only one ^{13}C . These satellite signals belong to the lines of AX spin systems of ^{13}C , ^{13}C spin pairs and can be detected best for directly bonded nuclei where the couplings are of the order of 35–90 Hz, depending on carbon hybridization (cf. Section 11.4.1.1). For smaller coupling constants (geminal or vicinal spin pairs) the satellites are mostly superimposed with the main signal S_0 .

In this context, the one-dimensional INADEQUATE sequence, shown in Figure 11.18 (p. 400), is of great interest because it largely eliminates the strong main signal S_0 . Its success depends on the phase cycle that selects the double-quantum coherence of the ^{13}C , ^{13}C AX systems while the single-quantum magnetization of molecules with only one ^{13}C nucleus is suppressed. Spectra such as that shown in Figure 11.19 (p. 400) are then obtained. The technique of gradient enhanced coherence selection greatly facilitates this signal selection process and is especially useful if smaller coupling constants of geminal or vicinal spin pairs are to be measured. The delay $\tau = 1/4J$ has to be optimized for the couplings of

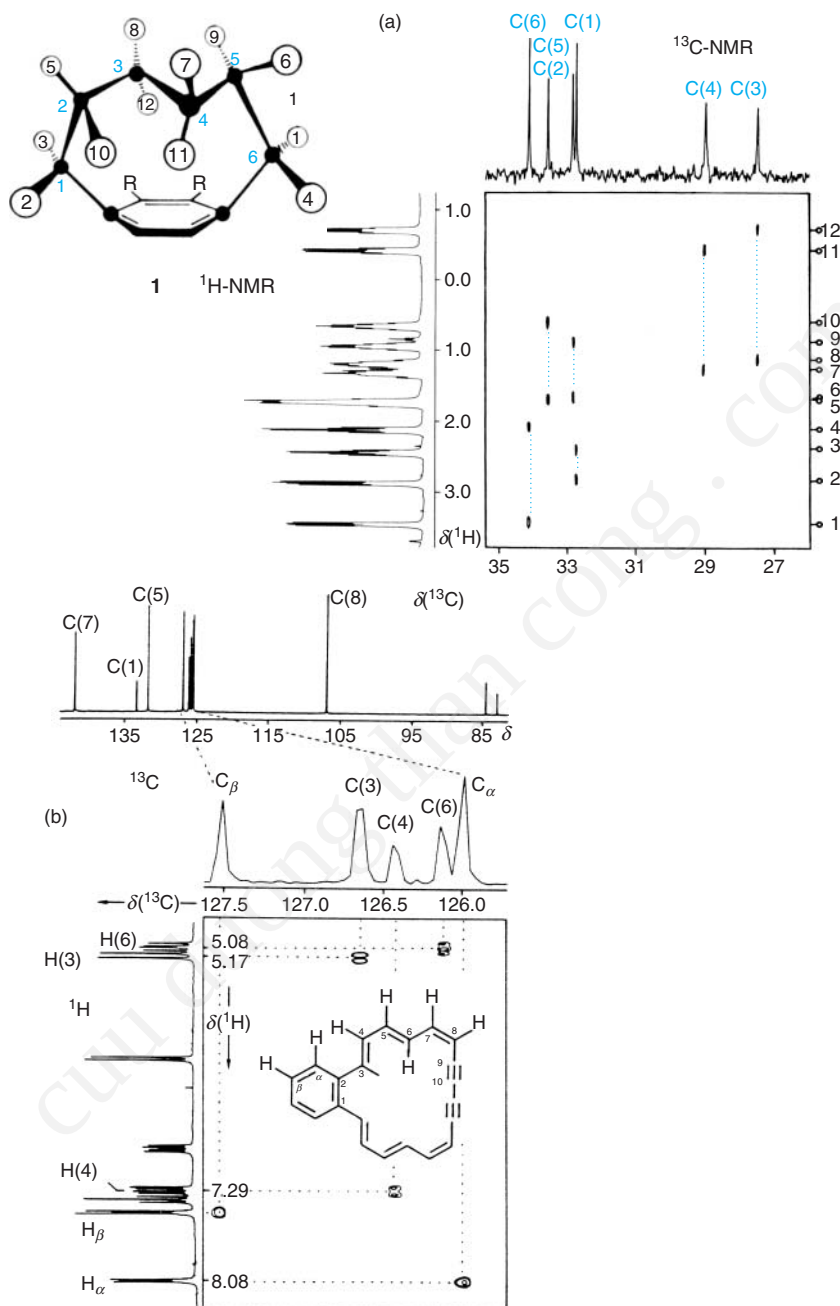


Figure 11.17 Two-dimensional ^1H , ^{13}C shift correlation for the paracyclophane **1** (a) and bis-dehydrobenzo[20]annulene (b); from [8] and [9], respectively.

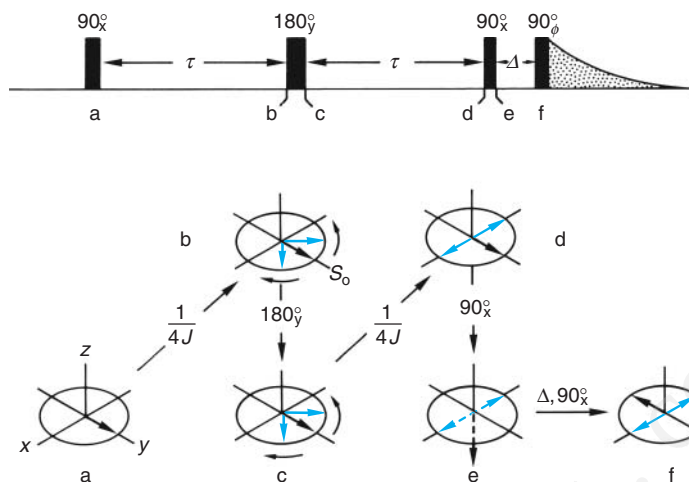


Figure 11.18 Pulse sequence of the 1D INADEQUATE experiment for the detection of ^{13}C , ^{13}C spin-spin coupling constants. The experiment is performed with ^1H broad band decoupling. In both $\tau = 1/4J$ delays anti-phase ^{13}C magnetization develops (a–d) that is transformed into homonuclear double quantum coherence by the second 90° pulse (e, vectors shown as broken lines). Please note that the 180° pulse is non-selective. After a short delay (about $10\ \mu\text{s}$) the last 90°

pulse of variable phase θ produces detectable anti-phase single-quantum magnetization. The phase program or the application of gradient pulses selects magnetization components that proceeded via the coherence pathway of coherence order $p = 2$. The magnetization S_0 (black vector) of molecules with only one ^{13}C nucleus follows the coherence pathway with coherence order $p = 1$ and shows different phase behavior (cf. Exercise 11.4).

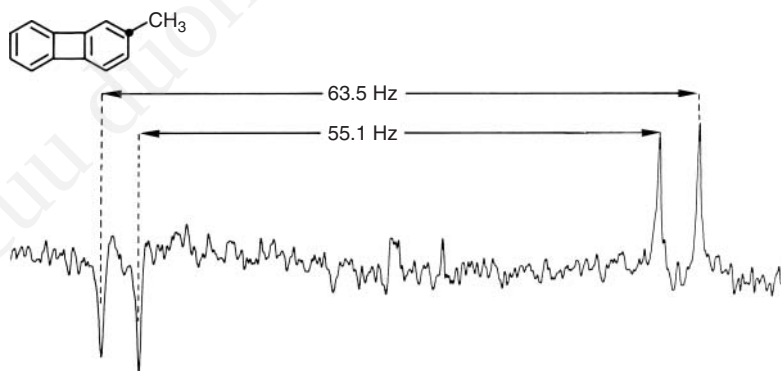


Figure 11.19 One-dimensional INADEQUATE experiment for the measurement of the ^{13}C , ^{13}C coupling constants of the methylated β -carbon of 2-methylbiphenylene. With a delay $\tau = 1/4J = 4.5\ \text{ms}$ ($\hat{=} J = 55.6\ \text{Hz}$) the couplings to C1 and C3 have been detected. A

separate measurement for the CH_3 signal yields $^1J(\text{C2}, \text{CH}_3) = 44.2\ \text{Hz}$; note the anti-phase of the ^{13}C signals (cf. Figure 11.18f) and the good suppression of the S_0 signal in the center of the spectrum [10].

interest according to their structural dependence; however, deviations of up to 10% can be tolerated.

Exercise 11.4

Draw a coherence level diagram for the one-dimensional INADEQUATE sequence (Figure 11.19) and propose (i) a phase cycle and (ii) the introduction of gradient pulses that allow the selective detection of ^{13}C , ^{13}C spin systems.

An interesting and powerful extension of the 1D INADEQUATE experiment was introduced by adding the evolution time t_1 that leads to a second frequency dimension and thus a 2D experiment. This pulse sequence, already introduced with Eq. (9.42) (p. 332), and extensively discussed there, is used here for ^{13}C observation with ^1H broadband decoupling. During the evolution time homonuclear ^{13}C double-quantum coherence develops and the individual ^{13}C , ^{13}C AX systems of neighboring carbon atoms in the molecule are separated along the F_1 frequency axis on the basis of their different double quantum frequencies $\nu_{\text{DQ}} = \nu_{\text{A}} + \nu_{\text{X}} - 2\nu_0$. The goal of this experiment is not the determination of ^{13}C , ^{13}C coupling constants but, rather, analysis of the carbon skeleton of a molecular structure. Neighboring carbons are detected via their $^1J(^{13}\text{C}, ^{13}\text{C})$ coupling and this leads to a resonance assignment that is directly connected to the carbon chain in the molecule. The 2D INADEQUATE experiment would certainly be the method of choice for the analysis of complex molecular structures if its low sensitivity (see above) could be overcome. Nevertheless, many liquids and highly concentrated solutions of compounds with good solubility have been successfully studied.

In several cases even fairly large molecules have been investigated by the 2D INADEQUATE technique. The experiment is of special interest for systems with a greater number of identical partial structures. Strong overlap of the signals of these structural elements then results for the ^{13}C NMR spectrum and the assignment becomes difficult. Such conditions are met, for example, with nucleic acids and related compounds with their repeating ribose or deoxyribose units. This is demonstrated with the example of NAD (2), where a sufficiently concentrated solution can be prepared in D_2O (Figure 11.20) (p. 402).

In the solid, 2D INADEQUATE experiments have even been performed successfully for ^{29}Si , ^{29}Si pairs in order to investigate the structure of zeolites. We come back to this topic in Chapter 12.

11.2.2.5 Heteronuclear J, δ Spectroscopy

In the preceding section we have shown how ^{13}C , ^{13}C coupling constants can be measured with the INADEQUATE experiment. To determine ^{13}C , ^1H coupling constants, on the other hand, apart from the analysis of ^1H -coupled ^{13}C spectra, we can make use of heteronuclear J, δ or J -resolved spectroscopy, an experiment related to the homonuclear spin echo spectroscopy described in detail in Chapter 9 and briefly mentioned in connection with the 3D experiment on page 372, where Figure 10.24a also shows the pulse sequence for the X channel, here ^{13}C , that

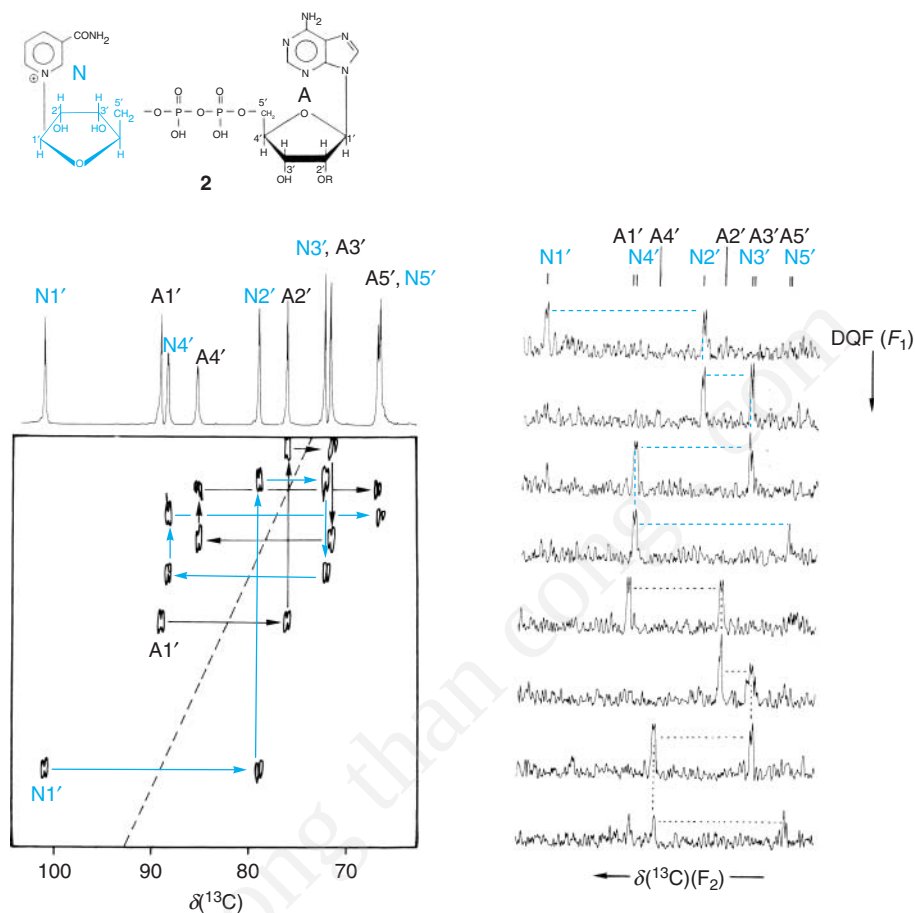


Figure 11.20 Result of a 2D INADEQUATE experiment for assignment of the ribose ^{13}C NMR signals of nicotinamide adenine dinucleotide (NAD, **2**): (a) contour plot with the assignment of the ribose spectra and (b) F_1 traces of the two-dimensional data matrix. For each double-quantum frequency the corresponding AX system is observed [11].

is accompanied by gated ^1H decoupling. As mentioned there, because $^{13}\text{C}, ^1\text{H}$ coupling is active only during $t_1/2$, the spin–spin splittings are reduced by 50%. Figure 11.21 shows another example of a $^{13}\text{C}, ^1\text{H}$ J, δ spectrum.

An alternative sequence for heteronuclear 2D J, δ spectroscopy, known as the *spin-flip method*, does not use ^1H decoupling during $t_1/2$, but instead a 180° proton pulse at $t_1/2$. The $^{13}\text{C}, ^1\text{H}$ coupling is thus active over the whole evolution time and the complete J data are found in F_1 . In addition, a sequence with a selective instead of the non-selective 180° ^1H pulse can be used to measure $^{13}\text{C}, ^1\text{H}$ long-range coupling constants as described in the following section.

The ^{13}C J, δ as well as the INADEQUATE experiments discussed above suffer from the low natural abundance of ^{13}C pairs, which leads to long experiment times.

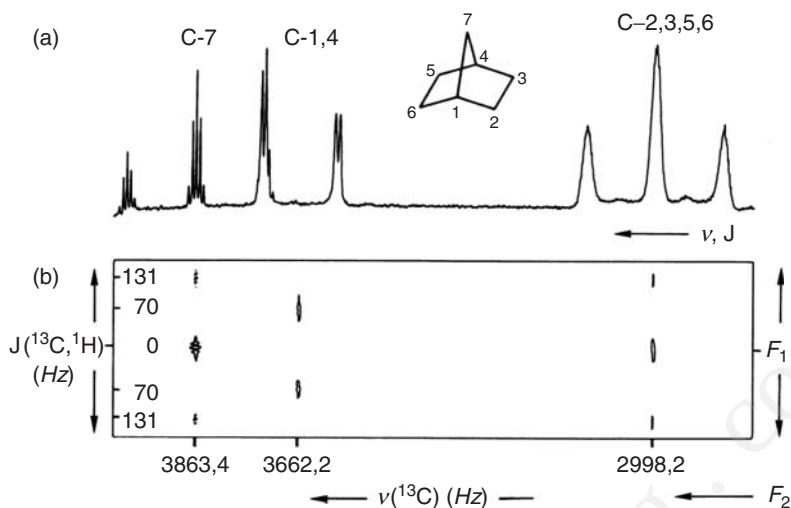


Figure 11.21 2D $^{13}\text{C}, ^1\text{H}$ J, δ spectrum of norbornane at 100.6 MHz: (a) 1D ^{13}C spectrum and (b) contour plot of the 2D spectrum; the J data in F_1 have been doubled; measuring time 7.3 h [12] (with kind permission of Springer Science+Business Media).

The use of relaxation reagents (Chapter 14) to allow shorter relaxation delays is thus recommended.

Exercise 11.5

Verify with reference to Figure 9.7 that in the spin-flip method the heteronuclear coupling is indeed active over the full t_1 period.

11.2.2.6 Assignment Techniques with Selective Excitation

As with other two-dimensional techniques, those described in the preceding section for the assignment of ^{13}C resonances have the disadvantage of long measuring times, in the case of the INADEQUATE method even more so because of the low natural abundance of ^{13}C . As in ^1H NMR resonance, alternative one-dimensional experiments are therefore of interest if selective excitation is feasible. Such experiments rely on the DANTE sequence or on GAUSS pulses (Chapter 8, p. 260). They are especially useful if several pieces of information on the molecular structure are already known and only a few assignments are in question. A complete 2D experiment would then duplicate much of the data and the expense in instrument time would not be justified. Three examples illustrate this idea.

With a selective INEPT sequence, for instance, where a GAUSS pulse at a certain ^1H resonance ν_i is used for the 90° (^1H) pulse, ^{13}C nuclei adjacent to H_i can be detected and assigned. As in the case of the selective ^1H -decoupling experiment one has to irradiate both ^{13}C satellites in the ^1H spectrum and the selectivity achieved depends on the relative magnitude of the $^{13}\text{C}, ^1\text{H}$ coupling constants involved.

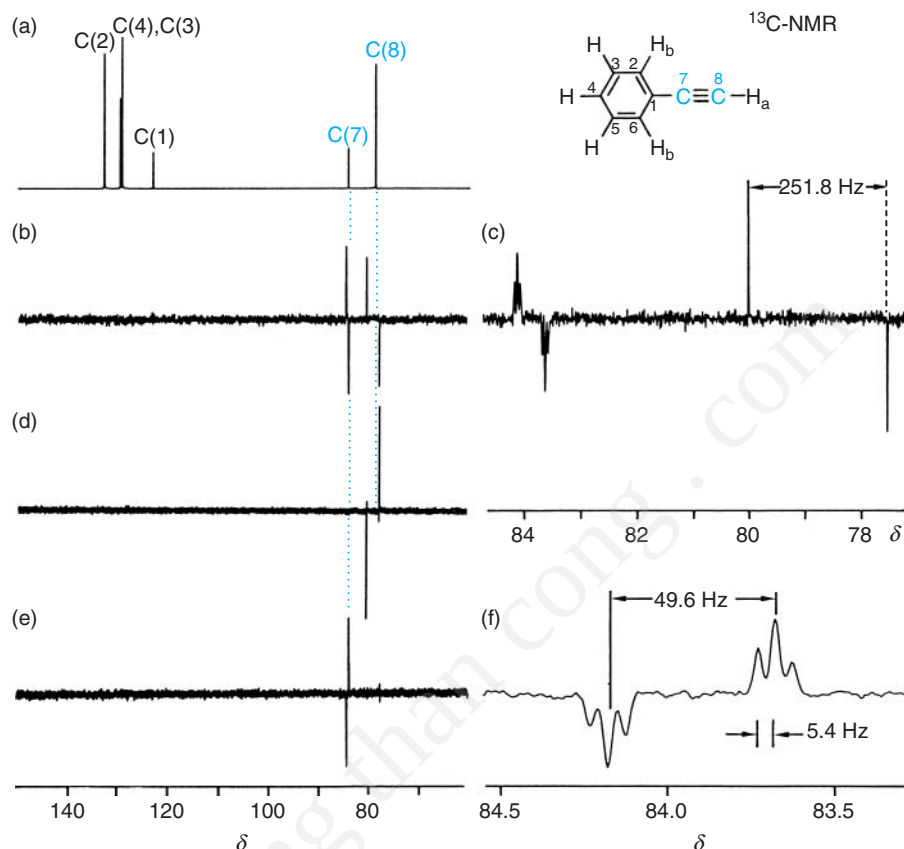


Figure 11.22 Selective INEPT experiments in the spectrum of phenyl acetylene: (a) 100 MHz $^{13}\text{C}\{^1\text{H}\}$ spectrum of phenyl acetylene (10% in acetone- d_6) and (b) INEPT experiment with selective 90_y (^1H) pulse at the H_a resonance; the delay $1/4J(^{13}\text{C}, ^1\text{H})$ of the INEPT sequence was optimized with 1 ms for the ^1J coupling $\text{C}(8), \text{H}_a$, which amounts to 252 Hz. Since the ^2J coupling between $\text{C}(7)$ and H_a in phenylacetylene is unusually large (49.6 Hz), a polarization transfer is also observed for $\text{C}(7)$. Both carbons at the triple bond can, therefore, be distinguished if

the coupling pattern of their signals is compared [see spectra (c) and (f)]. For the more distant carbons of the benzene ring the relation $^nJ \ll ^1J$ is valid and these signals are not detected. (c) Signals of $\text{C}(7)$ and $\text{C}(8)$ from spectrum (b) enlarged; one also observes the vicinal coupling between $\text{C}(7)$ and H_b ; (d), (e) INEPT experiments with selective 90_x (^{13}C) read pulse at the $\text{C}(8)$ and $\text{C}(7)$ resonance and optimized INEPT delay (1 and 5 ms), respectively; (f) spectrum (e) enlarged.

Because of the rule $^1J \gg ^nJ$ ($n > 1$) it is generally sufficient in order to distinguish next neighbors from remote neighbors (Figure 11.22).

A selective 2D heteronuclear J, δ experiment with the spin-flip technique is useful for the measurement of $^{13}\text{C}, ^1\text{H}$ long-range coupling constants. One takes advantage of the fact that $^2J(^{13}\text{C}, ^1\text{H})$ and $^3J(^{13}\text{C}, ^1\text{H})$ coupling constants are an order of magnitude smaller than the $^{13}\text{C}, ^1\text{H}$ coupling constants over one bond

(see Section 11.4). The respective ^{13}C satellites in the ^1H spectrum are thus close to the main signal S_0 of the isotopomer with only one ^{13}C and well separated from the satellites of the large ^1J couplings. One proton signal is then selected for an adjusted 180° ^1H GAUSS pulse, leading to the detection of the respective ^{13}C coupling constants in t_2 . All ^{13}C couplings of the other protons are refocused at the end of the evolution time.

Furthermore, instead of a 2D INADEQUATE experiment, a selective 1D INADEQUATE experiment can be constructed if in the pulse sequence shown in Figure 11.19 the fourth 90° pulse is replaced by a selective GAUSS pulse. Detectable anti-phase magnetization is then produced only for the selectively excited ^{13}C nucleus and its direct neighbors and one observes only AX systems where these nuclei participate. The acronym SELINQUATE (*selective INADEQUATE*) was coined for this experiment.

11.2.2.7 Alternative Assignment Techniques

Aside from the methods described so far, which were exclusively of spectroscopic origin, other techniques exist that rely on arguments based on chemical structure. Here we mention first ^{13}C , ^1H spin–spin coupling constants, discussed in more detail later in this chapter. The structural dependence of these parameters often yields unequivocal assignments. For example, methine and methylene groups in three-membered rings are immediately recognized by their large ^{13}C , ^1H couplings over one bond that are much larger than the corresponding couplings in open-chain compounds. In three-membered rings we find values around 160 Hz, while for strainless ring systems like cyclohexane or aliphatic chains values around 125 are observed.

In many cases ^1H -coupled ^{13}C spectra yield first-order multiplets and such a straightforward application of coupling information for assignment purposes is

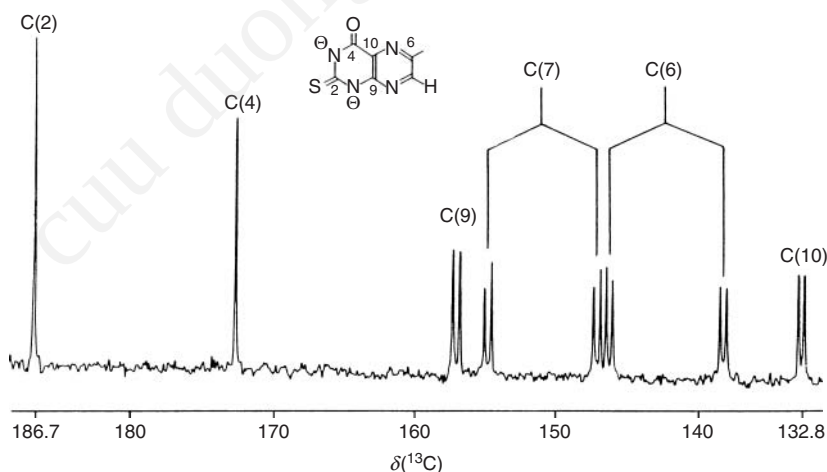


Figure 11.23 First-order splittings due to ^{13}C , ^1H spin–spin coupling in the ^{13}C NMR spectrum of 2-thio-4-oxotetrahydropteridine dianion [13].

illustrated with the spectrum of the 2-thio-4-oxotetrahydropteridine dianion shown in Figure 11.23 (p. 405). Here three pairs of carbon atoms can be distinguished by the multiplicity of their ^{13}C NMR signals: quaternary carbons C(2) and C(4) show no splitting, carbons C(9) and C(10) show vicinal coupling to H(7) and H(6), respectively, whereas C(6) and C(7) show line splitting due to $^1J(^{13}\text{C}, ^1\text{H})$ and $^2J(^{13}\text{C}, ^1\text{H})$ (doublets of doublets). Of course, the assignment within each pair of carbons must be based on independent arguments from different sources.

Among chemical methods used for the assignment of ^{13}C NMR signals there are shifts induced by the addition of shift reagents, by changing the pH of the solution causing protonation or deprotonation, or by solvent effects. Finally, if a simple and unequivocal route to specific deuteration is available, ^2H labeling yields the desired information. Owing to $^{13}\text{C}, ^2\text{H}$ coupling, 1 : 1 : 1 triplet structures are observed for the carbon resonances, most pronounced for the directly substituted carbon [remember, however, that $J(^{13}\text{C}, ^2\text{H}) = J(^{13}\text{C}, ^1\text{H})/6.5$, as discussed on p. 229]. In addition, characteristic isotope effects on chemical shifts are observed and these are also of diagnostic value. The method is best explained by using an example. For the olefinic carbons of 1,6-indane oxide **3** one observes two singlets at δ 126.3 and δ 128.3. Figure 11.24 shows the olefinic ^{13}C resonances of **3** deuterated specifically in position 4. From the triplet observed in the low-frequency absorption it is immediately clear that this resonance belongs to C3 and C4. We note that $\delta(3)$ and $\delta(4)$ are different owing to the isotope effect that shifts $\delta(4)$ to lower frequency

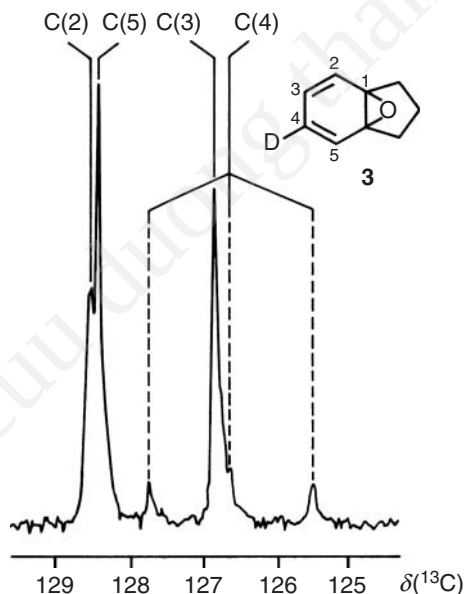
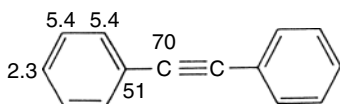


Figure 11.24 ^1H -decoupled ^{13}C NMR spectrum of 1,6-indane oxide specifically deuterated at C4 (**3**) for assignment of the ^{13}C resonances; the deuterium-induced isotope shifts $\Delta\delta$ amount to -0.1 and -0.3 ppm for C3 and C4, respectively, and to $+0.01$ and -0.14 ppm for C(2) and C(5), respectively [14].

by 0.3 ppm as compared with the shift in the non-deuterated compound. For $\delta(3)$, two bonds away, this effect is much smaller (0.1 ppm). The isotope effect also discriminates between the resonances of C2 and C5, with the former at higher frequency broadened owing to an unresolved $^3J(^{13}\text{C}, ^2\text{H})$ coupling.

Deuterium-induced isotope shifts of ^{13}C resonances are observed when -OH groups are replaced by -OD groups under conditions of low exchange rates, usually in DMSO as solvent. They were found useful for the assignment of hydroxy-bearing carbons in carbohydrates. Two-bond (β -) as well as three-bond (γ -) effects are employed and the method was later termed “SIMPLE NMR.” The topic of NMR isotope effects and its usefulness in organic chemistry will be discussed in more detail in Chapter 15.

Finally, for complicated structures such as those of natural products, T_1 measurements are sometimes used to assign different ^{13}C resonances. As was briefly mentioned in Chapter 8 (p. 242), ^{13}C spin-lattice relaxation rates in organic molecules show a r^{-6} dependence on C,H distances, and relaxation times T_1 for the quaternary carbon atoms are therefore considerably longer than those for carbon atoms substituted by hydrogen. An example is given with the data of diphenylacetylene (T_1 in seconds). We come back to this point in Section 11.5.



11.3 Carbon-13 Chemical Shifts

The chemical shifts of ^{13}C resonances in organic molecules span a range of about 250 ppm, including extreme values to low and high frequency (tetraiodomethane and carbocations, respectively) of even 650 ppm. A general survey is presented in Figure 11.25, and Table 11.1 contains a more detailed collection.

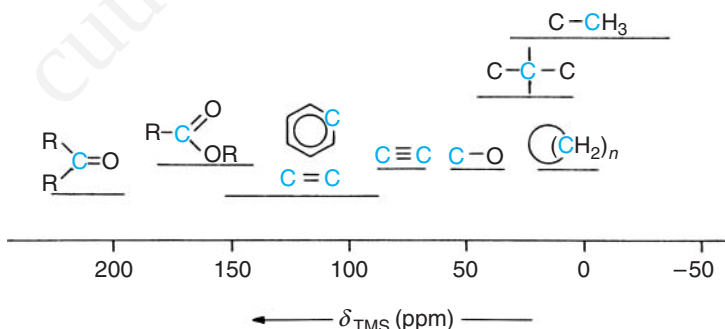
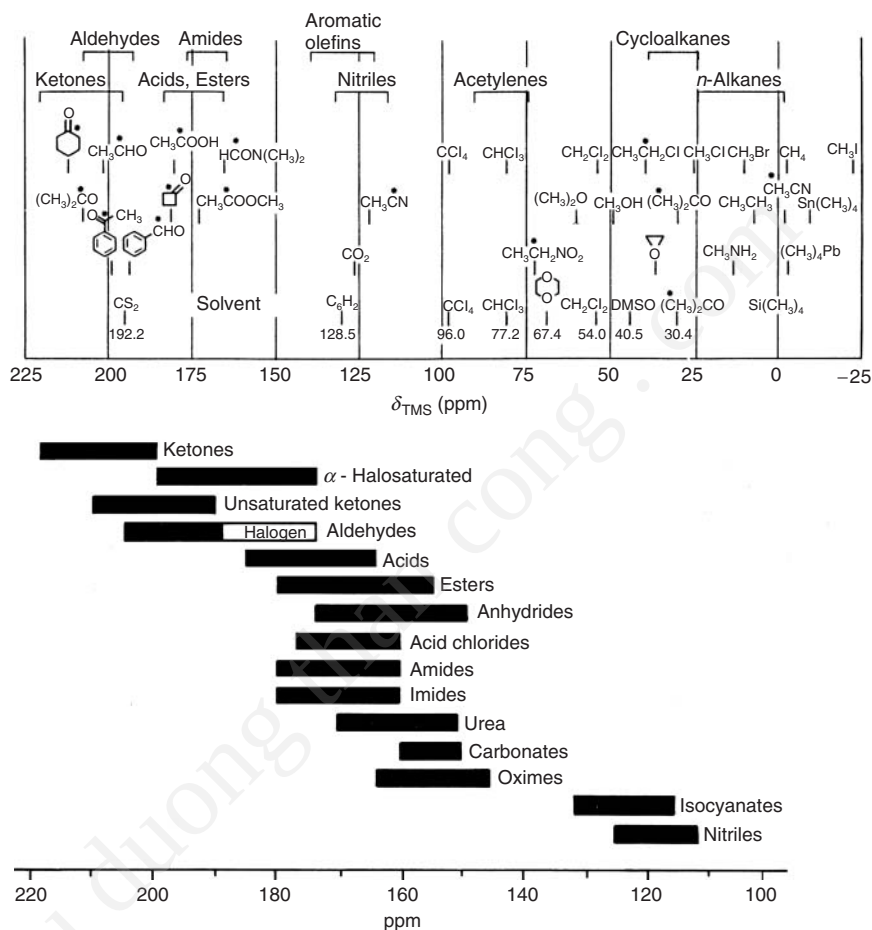


Figure 11.25 δ -scale of ^{13}C resonances in organic compounds.

Table 11.1 ^{13}C resonances in selected organic compounds (a) and in functional groups [15] and [16], respectively.

As in ^1H NMR, the δ -scale for carbon-13 can be divided into subregions for the resonances of aliphatic, olefinic, and acetylenic carbon atoms. Carbonyl carbon atoms are the most strongly deshielded and their resonances form a separate region at highest frequency. In earlier work carbon disulfide served simultaneously as reference compound and solvent, but later the ^{13}C resonance of TMS was introduced and is today accepted as internal reference. This has the advantage that most ^{13}C δ -values are positive, as are the $\delta(^1\text{H})$ values. A collection of ^{13}C chemical shifts from organic compounds, and a table of ^{13}C resonances of important solvents is included in the Appendix (p. 659 ff).

11.3.1

Theoretical Models

For discussion of the correlation between $\delta(^{13}\text{C})$ and the molecular structure we remember Eq. (3.6) (p. 32) where the shielding constant σ is given as the sum of three terms. These are the local diamagnetic and paramagnetic contributions and the effect of neighboring groups:

$$\sigma = \sigma_d + \sigma_p + \sigma' \quad (11.9)$$

As for other heavy nuclei (cf. Chapter 12), ^{13}C chemical shifts are determined mainly by variation of σ_p and, to a lesser extent, by σ_d . Neighboring group effects that are well known in ^1H NMR are only of minor importance.

Substituent-induced changes of σ_d for a particular carbon atom C_i , $\Delta\sigma_d^i$, can be assessed in a semiempirical manner through an equation similar to the Lamb formula for the free atom:

$$\Delta\sigma_d^i = \frac{\mu_0}{4\pi} \frac{e^2}{3m_e} \sum_{j \neq i} Z_j R_{ij}^{-1} \quad (11.10)$$

where Z_j is the atomic number of the neighboring atom j , R_{ij} is the internuclear distance, and the other terms are well-known constants. This contribution is of particular importance in the case of heavy atoms, where increased shielding is observed with increasing atomic number. For the halogens, this effect is most pronounced for iodo substitution and has become known as the *heavy atom effect* (Figure 11.26).

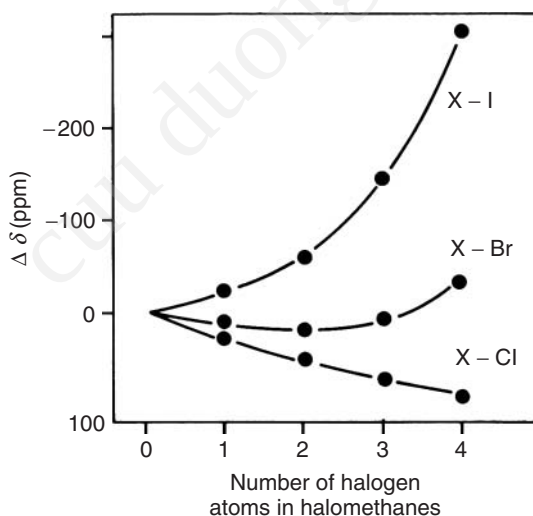


Figure 11.26 Effect of halogens on ^{13}C shielding [17].

For the paramagnetic contribution, early theoretical considerations by N.F. Ramsay, A. Saika, and C.P. Slichter led to the expression:

$$\sigma_p^i \approx -\frac{1}{\Delta E} \left(\frac{1}{r_i^3} \right)_{2p_z} \sum_{j \neq i} Q_{ij} \quad (11.11)$$

where ΔE is a mean electronic excitation energy, r_i is the average radius of the carbon $2p_z$ orbital, and Q_{ij} is a bond order term that originates from the presence of π -bonds.

As it turns out, structural changes usually affect all of the individual contributions to σ_p and only in a few cases does a predominant influence of one component justify a separate treatment. Nevertheless, Eq. (11.11) can still be used as a guide for the interpretation of several prominent features observed for carbon shielding, since it allows discussion of experimental data in terms of chemical significance. It has to be pointed out again, however, that the calculation of chemical shifts – and equally that of spin–spin coupling constants – has made considerable progress in recent years and advanced quantum chemical procedures are available today for this purpose. One of the most successful approaches is provided by the IGLO method and such data have already been used for structure determinations. Detailed discussion of these developments, however, is beyond the scope of the present text and the interested reader is referred to the literature listed at the end of this chapter.

Returning to the discussion of Eq. (11.11), we note that with respect to the ΔE dependence of σ_p , except for $\pi \rightarrow \pi^*$ excitations that are excluded owing to symmetry considerations, all other transitions ($\sigma \rightarrow \pi^*$, $\pi \rightarrow \sigma^*$, $\sigma \rightarrow \sigma^*$, $n \rightarrow \pi^*$, and $n \rightarrow \sigma^*$) are important, with the largest contribution usually arising from the transition of lowest energy.

The increasing shift of ^{13}C resonances in the series alkanes – alkenes – carbonyl compounds is thus not unexpected. For the last group of compounds, a linear correlation between the wavelength of the $n \rightarrow \pi^*$ transition and the chemical shift of the carbonyl resonance has even been found. The bond order term superimposes additional changes that are most pronounced for the central carbon of allene and the ^{13}C resonances of alkynes.

	$\text{H}_3\text{C}-\text{CH}_3$	$\text{H}_2\text{C}=\text{CH}_2$	$\text{H}_2\text{C}=\text{C}=\text{CH}_2$	$\text{HC}\equiv\text{CH}$
δ/ppm	5.9	123.3	74.8 213.5	71.9

For the latter, theory yields $\sum_{j \neq i} Q_{ij} = 0$ as in alkanes, whereas for allene $\sum_{j \neq i} Q_{ij} = 0.8$.

Perhaps the most important contribution to σ_p of ^{13}C , at least the one that is most frequently supported by experimental observation, is the $(r_i^{-3})_{2p_z}$ term, which can be related to the charge density. Partial negative charge thus leads to an increase in r_i (orbital expansion) and consequently to a diminution in σ_p , and increased shielding results. For partial positive charge, the opposite reasoning holds, orbital contraction producing a deshielding effect. This charge dependence of ^{13}C NMR chemical shifts was recognized in the early stages of the technique and led to the development of an empirical relation between the changes of the shielding

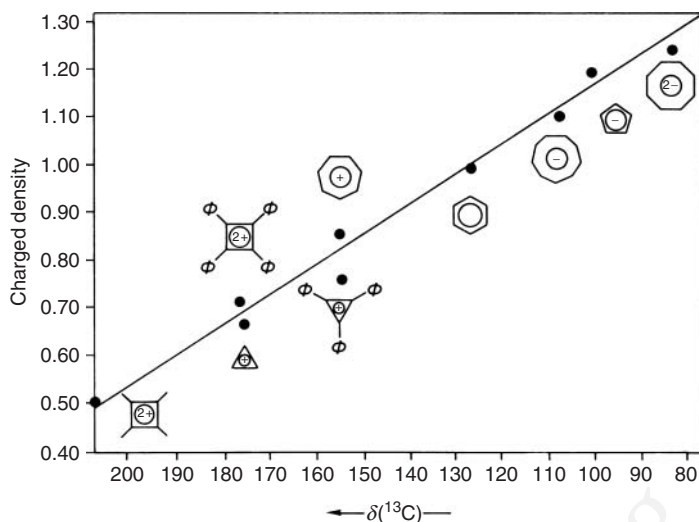


Figure 11.27 Correlation of ^{13}C chemical shifts and π -electron densities in aromatic systems [18].

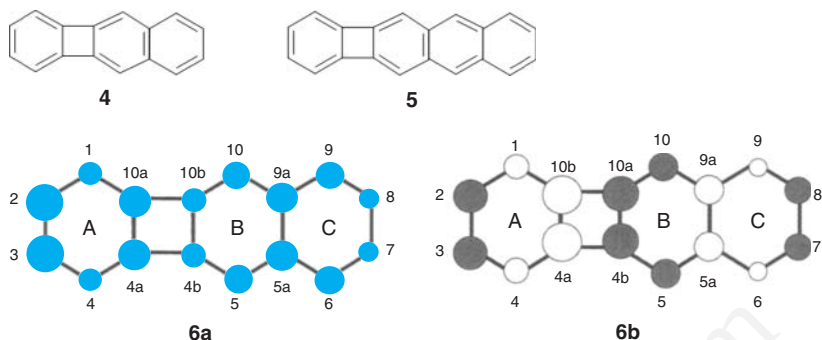
constant, $\Delta\sigma$, and the corresponding π -charge density changes, $\Delta\rho$. It is based on the ^{13}C resonance of benzene and of aromatic ions and relative to benzene with $\rho = 1.0$ and $\Delta\rho_i = \rho_i - 1.0$ one finds:

$$\Delta\sigma_i = K_C \Delta\rho_i \quad \text{or} \quad \Delta\delta_i = -K_C \Delta\rho_i \quad (11.12)$$

with $K_C = 160$ ppm. Figure 11.27 gives an extended diagram of this correlation.

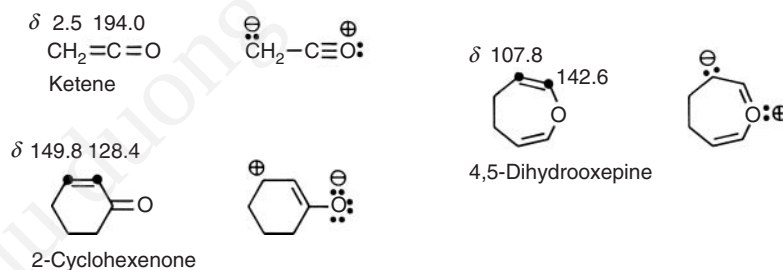
Equation (11.12) is analogous to the similar correlation derived for protons [Eq. (5.2), p. 89]. Note, however, that the origin of the two correlations is different, since in the case of protons changes in the local diamagnetic term are responsible.

A great variety of data have been subjected to regression analysis based on Eq. (11.12) and consequently various proportionality constants K_C have been derived. This is not so surprising if we remember the mutual dependence of the different terms in Eq. (11.11). In addition, different methods of calculating the charge density changes – pure π -electron calculations as well as those including σ -electrons – have been applied. Numerical calculations for estimating $\Delta\delta$ or $\Delta\rho$ using such a simple equation as Eq. (11.12) with a particular proportionality constant are therefore restricted to certain classes of compounds. Generally, Eq. (11.12) yields good results for ions of benzenoid hydrocarbons. For the dication of benzo[*b*]biphenylene (4) and the dianion of naphtha[2,3-*b*]biphenylene (5), for example, the sum of the $\Delta\delta(^{13}\text{C})$ values amounts to +322 and –320 ppm, respectively, which is in excellent agreement with the two positive charges in 4^{2+} and the two negative charges in 5^{2-} . A comparison of the $\Delta\delta(^{13}\text{C})$ values (high-frequency shifts) given for 4^{2+} as red dots in 6a and the Hückel-MO coefficients for the highest bonding π -orbital where the two electrons are removed by oxidation (6b) also shows general agreement.

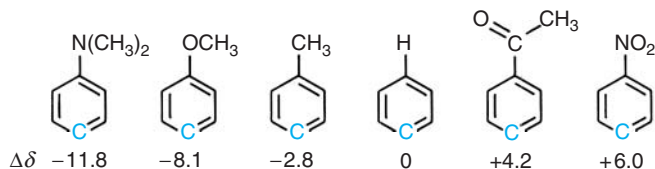


Nevertheless, large variations for K_C in Eq. (11.12) have been observed for charged systems that sustain significant paramagnetic ring current effects in ^1H NMR. In these compounds we have a small energy gap, ΔE , between ground and excited states (see p. 106). This is also responsible, according to Eq. (11.11), for an increase of σ_p that cancels partly the shielding due to the negative charge in dianions; K_C is thus reduced and even values below 100 ppm have been found. On the other hand, in case of oxidation to paratropic dications, charge and ΔE effect operate in the same direction (deshielding) and K_C can be much larger than 160 ppm. In the case of **4** and **5** discussed above the ΔE term is unimportant because oxidation as well as reduction leads to a diatropic system.

The charge density dependence of ^{13}C resonances also forms the basis of the fact that resonance structures are often helpful in rationalizing ^{13}C chemical shifts. The following examples serve to illustrate this point:



Furthermore, the mesomeric effect of substituents in aromatic systems shows itself through the changes induced for the ^{13}C resonance, as the data for the *para*-carbon of several substituted benzenes show:



In the *ortho*-position, additional steric effects may operate.

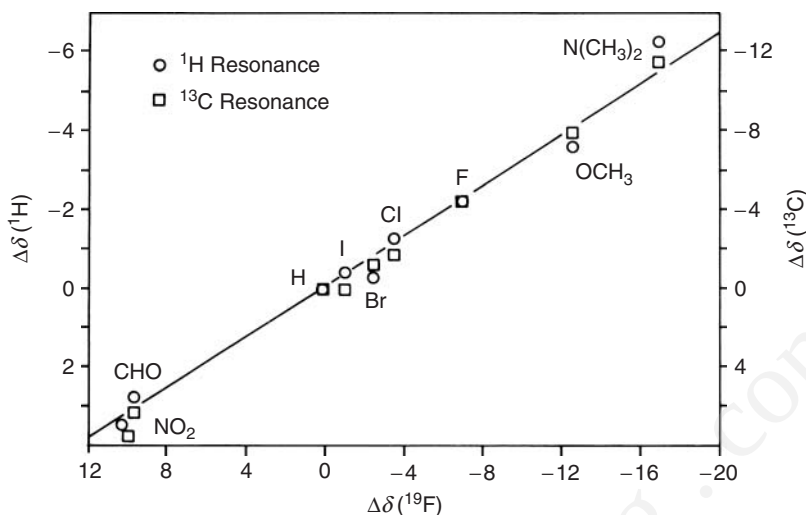


Figure 11.28 Correlation between the resonance frequencies of ^1H and ^{13}C in the *para*-position to substituents in mono-substituted benzenes and the ^{19}F resonance frequencies of the correspondingly *para*-substituted fluorobenzenes; δ values in ppm relative to benzene [19].

Unsurprisingly, since charge density/chemical shift correlations also exist for protons and ^{19}F nuclei, the chemical shifts of the resonance frequencies of all three nuclei are in many cases linearly related to one another. This is clearly illustrated for the ^1H and ^{13}C resonances at the *para* position of monosubstituted benzenes and the ^{19}F resonances in *para*-substituted fluorobenzenes in Figure 11.28.

Another observation related to the charge density effect is the finding that alternating and non-alternating π -electron systems are well distinguished by their ^{13}C NMR spectra. Since the latter have a non-uniform charge density distribution, their ^{13}C NMR spectra show a significant spread, covering a much larger shift range than that of alternating systems. An example is presented in Figure 11.29 (p. 414).

Finally, large shifts for the ^{13}C resonance are observed in the case of protonation or deprotonation, and the study of carbanions and carbocations especially has profited a great deal from the development of ^{13}C NMR. As an illustration of the protonation dependence of ^{13}C chemical shifts, Figure 11.30 (p. 414) shows the pH dependence of the ^{13}C resonance of pyridine, where the transition from the free amine to the pyridinium ion is accompanied by large chemical shifts.

Interestingly, only the shifts of C4 and C3,5 are in accord with expectation (high frequency shift due to the inductive effect of the positive charge, see Exercise 5.5, p. 116), whereas the shielding observed for the α -carbon atoms C2,6 does not conform. It can be rationalized, however, if we remember that protonation of the nitrogen will change the electron transition at the nitrogen from an $n \rightarrow \pi^*$ to a $\sigma \rightarrow \pi^*$ type and thus increase ΔE . If this effect dominates, σ_p will decrease, and shielding results for the directly bonded carbons, as is indeed observed.

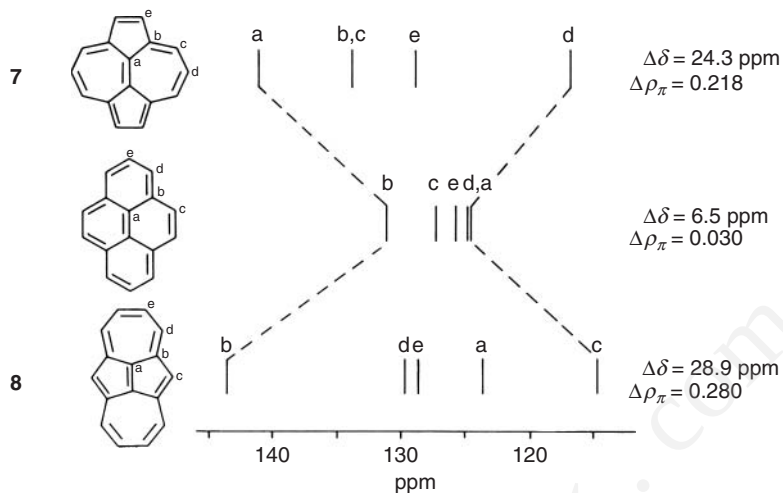


Figure 11.29 Ranges of ^{13}C chemical shifts, $\Delta\delta$, and of π -charge density differences, $\Delta\rho_\pi$, in pyrene and the two isomeric non-alternating hydrocarbons dicyclopentaheptalene (7) and dicycloheptapentalene (8); $\Delta\rho_\pi$ was obtained from CNDO/2 calculations [20].

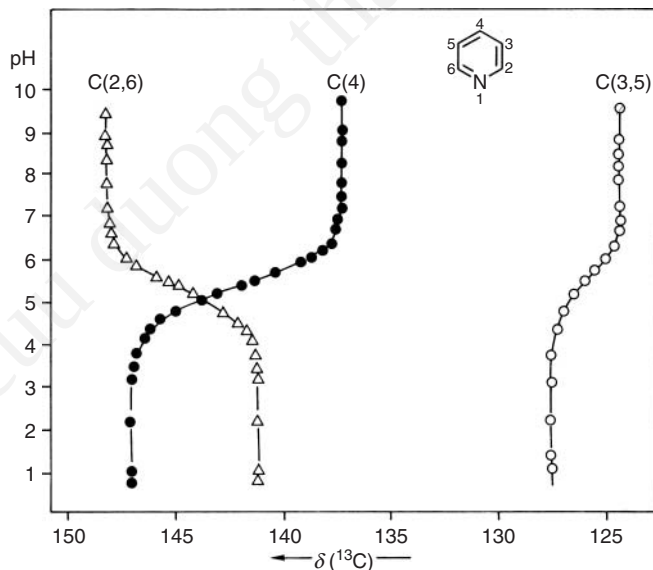


Figure 11.30 pH dependence of ^{13}C resonances of pyridine [21].

Table 11.2 ^{13}C resonances of carbocations (δ_{TMS}).

	$^{13}\text{C}^{\oplus}$	$^{13}\text{CH}_3$
$(\text{CH}_3)_3\text{C}^{\oplus}$	328	47
$(\text{CH}_3)_2\text{CH}^{\oplus}$	318	60
$(\text{CH}_3)_2\text{C}^{\oplus}\text{C}_2\text{H}_5$	332	43
$(\text{CH}_3)_2\text{C}^{\oplus}$ 	280	27
$\text{C}_6\text{H}_5\text{C}^{\oplus}(\text{CH}_3)_2$	254	—
$(\text{C}_6\text{H}_5)_2\text{C}^{\oplus}\text{CH}_3$	198	—
$(\text{C}_6\text{H}_5)_3\text{C}^{\oplus}$	211	—

Particularly drastic shifts toward high frequency are encountered, as expected, for the ^{13}C resonance frequencies of *carbocations*. Using ^{13}C resonance spectroscopy, the distribution of the positive charge over neighboring carbon atoms in these systems can also be studied.

As the data in Table 11.2. show, the ^{13}C resonance frequencies of the central carbon atoms in systems with cation-stabilizing substituents such as cyclopropyl and phenyl groups are paramagnetically shifted far less than those of the positively charged carbon atoms in the simple alkyl cations, since in the former cases the charge is distributed over the substituents. The apparently anomalous paramagnetic shift in going from the dimethylphenyl to the triphenylmethyl carbenium is caused by the steric hindrance of the phenyl groups in the triphenylmethyl system. The phenyl groups in this system cannot assume a coplanar arrangement and as a consequence the conjugative delocalization of the positive charge to the substituents is reduced.

With ^{13}C NMR it can also be demonstrated that fast rearrangements take place in a series of carbocations. For example, it has been shown that the isopropyl cation (**9**) labeled with 50% ^{13}C at position 2 undergoes a rearrangement with a half-life of 1 h at -60°C that distributes the label equally among all three carbons. This rearrangement probably takes place via a protonated cyclopropane (**10**):

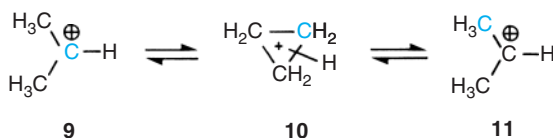
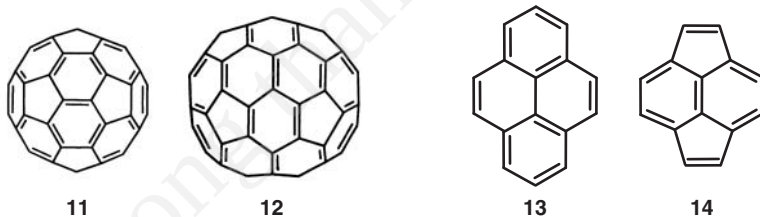


Table 11.3 ^{13}C NMR data of some higher fullerenes [22].

Fullerene	C_{70}	C_{76}	$\text{C}_{78}(\text{C}_{2v})^a$	$\text{C}_{78}(\text{D}_3)^a$	C_{84}
Number of ^{13}C NMR signals	5	19	21	13	31
Range of ^{13}C NMR signals (ppm)	130.8–150.8	129.6–150.0	132.3–147.6	132.2–149.5	133.8–144.6
Center of gravity (ppm)	145.0	142.7	141.9	141.1	140.3

^aStructural isomers of different symmetry.

A new field for ^{13}C NMR investigations started with the discovery of the *fullerenes*, which are spherical all-carbon compounds like the soccer ball-shaped C_{60} (**11**) and the rugby-ball-shaped C_{70} (**12**), which are, alongside diamond and graphite, new modifications of the element carbon. They are constructed of unsaturated five- and six-membered rings. Because of its high symmetry, the icosahedral C_{60} with 12 five- and 20 six-membered rings (point group I_h , chemical nomenclature [3, 4]-fullerene-60- I_h) only yields one ^{13}C signal at 143.2 ppm in the region typical for sp^2 -hybridized carbons. Higher fullerenes with lower symmetry give rise to much more signals (Table 11.3).



For the spectral assignment in these cases the 2D INADEQUATE experiment was of great help and thanks detailed investigations typical regions in the structures can be correlated with certain chemical shift ranges. For example, it could be shown that in C_{70} ([3, 4]-fullerene-70- D_{5h}) the most shielded signal at 130.8 ppm originates from ten carbon atoms at the intersections of three hexagons, a sub-structure with a pyrene-type environment (**13**). At higher frequencies, between 137 and 150 ppm, ^{13}C signals are found that resemble the ^{13}C resonances in pyracylene (**14**).

The spherical structure of the fullerenes soon raised the question of the properties of their π -electron system and the concept of *spherical aromaticity* or *3D aromaticity* attracted new interest. This topic was introduced earlier to describe the special properties of boron hydrides. Because protons are absent, the usual probe for diatropic and paratropic features is not available in the fullerenes and information on these properties has to come from theoretical calculations. In this respect the nucleus-independent chemical shift (NICS) values (p. 111) are useful. For C_{60} two different calculations yielded values of -8.0 and -2.8 ppm, while for C_{70} values of -23.1 and -27.2 ppm were obtained (note that the negative sign means shielding).

Apparently, the diatropic character of C_{70} exceeds that of C_{60} , and, as subsequently found, that of all other known fullerenes. In agreement with these results was the observation that the exaltation of the diamagnetic susceptibility, Λ , of C_{60} is essentially zero. Later it was found that this unspectacular magnetic behavior arises because the fairly large diamagnetism of the hexagons is quenched by paratropic pentagons. For C_{70} the cancelation of these two contributions is incomplete and an overall diatropic behavior results that also leads to a large diamagnetic susceptibility exaltation.

Experimental verification of this result comes from fullerenes with an encapsulated ^3He atom (encapsulation indicated by the sign @). After their successful isolation it was expected that it should be possible to trap atoms inside the cage and this was achieved by heating the fullerene under high pressure (2700 bar) in the presence of noble gases. In this way the NMR active helium-3 atom with spin $I = \frac{1}{2}$ was incorporated. Shielding shifts for ^3He of -6.3 and -28.8 ppm for $\text{He}@C_{60}$ and $\text{He}@C_{70}$ were found, respectively, indicating modest diatropicity for C_{60} and strong diatropicity for C_{70} , in excellent agreement with the theoretical results and the measured Λ data. Furthermore, helium shielding (~ -5 ppm) was also observed for the fully hydrogenated $\text{He}@C_{60}\text{H}_{60}$ and $\text{He}@C_{70}\text{H}_{70}$, an indication that diamagnetic shielding may also arise from the σ -framework of these molecules.

Later, fullerene anions (fullerides) were prepared and endohedral ^3H NMR of the closed-shell hexa-anions $\text{He}@C_{60}^{6-}$ and $\text{He}@C_{70}^{6-}$ yielded large shielding ($\Delta\delta -48.7$) and modest deshielding ($\Delta\delta +8.3$) for ^3He , respectively. Thus, the diatropicity of C_{60} is raised and that of C_{70} is decreased in these systems. Their carbon resonances are also affected, but shielding as well as deshielding is observed. The latter, for example, 14 ppm for C_{60}^{6-} , is unexpected for a charged system and may result from a local diamagnetic ring current effect on carbons attached to the particular ring. This would be analogous to the proton deshielding in benzene, which is certainly exceptional for carbon.

Further synthetic efforts yielded, via a [3+2]cycloaddition of diazomethane to a double bond and subsequent thermolysis or photolysis, respectively, methano-bridged isomers where the protons function as “spies” or “observers” for the magnetic properties of certain partial structures of the fullerene or, after reduction, of the fulleride.

Concluding this section, a short discussion of the σ' term in Eq. (11.9) seems appropriate. As far as diamagnetic anisotropy effects are concerned, changes in $\Delta\sigma$ depend only on $\Delta\chi$ and the relevant geometry. Induced shifts are therefore of the same order as in ^1H NMR (usually less than 1 ppm). In ^{13}C NMR they are masked completely by the much larger changes due to σ_p and σ_d . In particular the ring current effect is practically absent for ^{13}C resonances, as is suggested by the fact that a common region for olefinic and aromatic carbons exists on the $\delta(^{13}\text{C})$ scale. Only in carefully selected cases has it been found that variations in $\delta(^{13}\text{C})$ can be attributed to the shielding effects of cyclic π -electron systems (see above). The detection of ring current effects is therefore as before a feature within the domain of ^1H NMR.

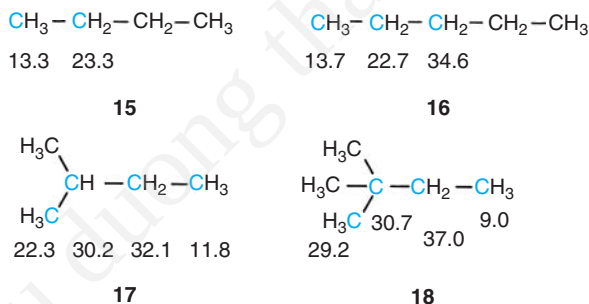
In contrast, in several cases, for example, carboxylate ions and protonated amines, it has been shown that the electric field effect contributes significantly to carbon shielding. Of course, changes in $\Delta\sigma$ due to the polarization of bonds are ultimately a consequence of changes in σ_d and σ_p , and a qualitative estimate of the electric field effect through classical equations such as Eq. (5.17) (p. 115) merely constitutes a different approach to the same phenomenon. Similarly, the van der Waals effect, which is probably related to the γ -effect discussed below, may be treated by bond polarization models.

11.3.2

Empirical Correlations

Since the early days of ^{13}C NMR several empirical chemical shift/molecular structure relations have been developed that are most useful for the analysis of ^{13}C spectra. Some of them may be rationalized using the concepts discussed in the last section, but they may also be taken as empirical correlations based on experimental observations.

Best known are the substituent effects observed in alkanes, where replacement of a hydrogen atom by a methyl group leads to deshielding of 9–10 ppm for the α - and β -carbon and to shielding of 2.5 ppm for the γ -carbon. Comparing the data for pentane (16) and the branched hydrocarbons 17 and 18 with those of butane (15) as a reference, these effects are clearly documented:



They are fairly constant for the whole series, and an empirical additivity rule may be used to predict the chemical shift for carbons in alkane chains:

$$\delta(\text{C}_i) = B + \sum_j n_j A_j \quad (11.13)$$

Here B is a constant almost equal to the chemical shift of methane ($\delta -2.3$ ppm), A_j is the chemical shift increment for α -, β -, or γ -substituents, and n_j is the number of substituents present at the particular position. By regression analysis it was determined that $A_\alpha = +9.1$, $A_\beta = +9.4$, $A_\gamma = -2.5$, and $B = -2.6$ ppm. More elaborate equations with correction terms S_{kl} for branching have been proposed.

Table 11.4 Shift increments (ppm) for methyl substitution in cyclohexane.

	Axial CH ₃	Equatorial CH ₃
α -effect	+1.4	+6.0
β -effect	+5.4	-9.0
γ -effect	-6.4	0

Exercise 11.6

Predict the $\delta(^{13}\text{C})$ values of 3-methylheptane with the help of Eq. (11.13) and the data from Table 11.4.

Similarly, methyl substitution in cycloalkanes leads to typical shift increments that differ from those in open-chain compounds. For cyclohexane (δ 27.6 ppm) the parameters shown below have been found for axial and equatorial substitution.

Differentiation between axial and equatorial substituents is important for conformational analysis and the stereochemistry of different conformers can be assessed through their ^{13}C data. The two cyclohexanes **19a,b**, where the different α -effect clearly characterizes the axial and the equatorial isomers, respectively, are illustrative.



For alkenes, the chemical shift of the olefinic carbon C_A may be predicted using the increments below with the ethylene value (123.2 ppm) as reference. Of interest is the different sign of the β -effect (increments for C_β and $\text{C}_{\beta'}$, respectively).

$$\Delta\delta: \begin{array}{cc} -0.4 & +6.8 & +7.7 & -6.5 & -1.6 & +1.1 \\ \text{C}_\alpha & -\text{C}_\beta & -\text{C}_\alpha & -\text{C}_\text{A} & =\text{C} & -\text{C}_\alpha & -\text{C}_{\beta'} & -\text{C}_{\gamma'} \end{array}$$

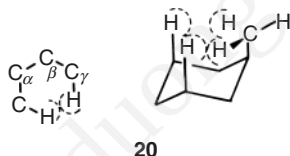
Of course, such schemes can be extended to other substituents and various additivity rules for different classes of compounds may be found in the literature. For obvious reasons we cannot treat them in detail here and will conclude our discussion with a short summary in Table 11.5. Additional ^{13}C chemical shifts are collected in the Appendix.

One of the most frequently discussed empirical observations for ^{13}C chemical shifts is the γ -effect, that is, the shielding observed for a carbon atom if substituents are introduced at the γ -position (see above for the A_γ values for alkanes). It is not restricted to alkyl groups in alkanes, and it has been observed for other substituents as well and in structures such as cyclohexanes, bicyclic systems, and olefins. As the

Table 11.5 Substituent-induced chemical shifts for ^{13}C resonances in alkanes, alkenes, and benzenes; $\Delta\delta$ values in ppm [23].

Substituent	Alkanes			Alkenes		Benzenes			
	α	β	γ	α	β	<i>ipso</i>	<i>ortho</i>	<i>meta</i>	<i>para</i>
F	70.1	7.8	-6.8	24.9	-34.3	35.1	-14.3	0.9	-4.4
Cl	31.0	10.0	-5.1	2.6	-6.1	6.4	0.2	1.0	-2.0
Br	18.9	10.0	-3.8	-7.9	-1.4	-5.4	3.3	2.2	-1.0
I	-7.2	10.9	-1.5	-38.1	7.0	-32.3	9.9	2.6	-0.4
OR	49.0	10.1	-6.2	29.4	-38.9	30.2	-14.7	0.9	-8.1
OCOCH ₃	52.0	6.5	-6.0	18.2	-27.1	23	-6	1	-2.3
NR ₂	28.3	-10.3	-5.1	—	—	22.4	-15.7	0.8	-10.8
NO ₂	61.6	3.1	-4.6	22.3	-0.9	19.6	-5.3	0.8	6.0
CN	3.1	2.4	-3.3	-15	+15	-16.0	3.5	0.7	4.3
COOH	20.1	2.0	-2.8	4.2	8.9	2.4	1.6	-0.1	4.8
CHO	29.9	-0.6	-2.7	13.6	13.2	9.0	1.2	1.2	6.0
CH=CH ₂	21.5	6.9	-2.1	14.8	-5.8	7.6	-1.8	-1.8	-3.5
C $\equiv$ CH	4.4	5.6	-3.4	—	—	-6.1	3.8	0.4	-0.2
C ₆ H ₅	22.1	9.3	-2.6	12.5	-10.0	13.0	-1.1	0.5	-1.0
CH ₃	9.1	9.4	-2.5	12.9	-7.4	9.3	0.6	0	-3.5

examples chosen in Table 11.6. demonstrate, upfield shifts are observed in all cases where the stereochemistry leads to van der Waals interactions of the type indicated by diagram 20.



Finally, we mention again that deuterium-induced isotope shifts for ^{13}C resonances can be observed if hydrogen in a molecule is replaced by deuterium. These data correlate with several other parameters, like scalar coupling constants, Hammett σ_p constants, or structural features like dihedral angles. We have already alluded to the usefulness of ^{13}C isotope shifts for assignment purposes and we come back to the topic of isotope shifts in more detail in Chapter 15.

11.4

Carbon-13 Spin-Spin Coupling Constants

There are three important groups of spin-spin interactions in ^{13}C NMR: ^{13}C , ^{13}C , ^{13}C , ^1H , and ^{13}C , X coupling constants, where X is another NMR-active element,

Table 11.6 The γ -effect in ^{13}C NMR (δ_{TMS} in ppm).

preferably of high natural abundance. Interestingly, the experimental approaches used in determining these constants differ considerably.

If we turn first to the homonuclear ^{13}C , ^{13}C coupling constants we refer to our discussion in connection with the introduction of the INADEQUATE experiment (Section 11.2.2.4, p. 398). $^1J(^{13}\text{C}, ^{13}\text{C})$ data can now be measured by the 1D as well as the 2D version for situations where AX- or AB-type spectra are found. Pulse sequences tailored for the detection of the smaller geminal and vicinal coupling constants are also available. Furthermore, for symmetrical HCCH units, such as one finds in systems of the type XHCCHX, the “mixed” ^1H , ^{13}C INADEQUATE experiment for the AA'XX' of the isotopomer with two ^{13}C atoms was used to determine the $^1J(^{13}\text{C}, ^{13}\text{C})$ coupling. With ^{13}C labeling, on the other hand, one can determine $^nJ(^{13}\text{C}, ^{13}\text{C})$ data from the satellites of the ^1H -decoupled ^{13}C signals in the non-labeled positions.

Secondly, in the field of heteronuclear couplings, there is an extensive body of experimental data concerning ^{13}C , ^1H coupling constants, mostly those over one bond. As mentioned in Chapter 4, these have been obtained from the ^{13}C satellites in ^1H NMR spectra, which have the advantage of measuring the nucleus with the larger γ -factor, and more recently from ^{13}C NMR spectra. In this case, however, the spin systems observed are quite often of higher order and exact determination of coupling constants – especially those over more than one bond – involves complete analysis of the ^1H -coupled ^{13}C spectrum. The gated decoupling technique described in Section 11.2 is used to advantage here.

Finally, ^{13}C , X coupling constants with nuclei of high natural abundance, like X = ^{19}F , ^{31}P , etc., are most easily measured from the ^1H -decoupled ^{13}C spectra of the appropriate compounds.

11.4.1

Carbon-13 Coupling Constants and Chemical Structure11.4.1.1 ^{13}C , ^{13}C Coupling Constants

From the data collected in Table 11.7, it becomes clear that ^{13}C , ^{13}C coupling constants over *one bond* are sensitive to the nature of the carbon–carbon bond involved.

For hydrocarbons, a dependence on the *s*-character product for the carbon orbitals ϕ_i and ϕ_j forming the $\text{C}_i\text{--C}_j$ sigma bond has been observed:

$$^1J(^{13}\text{C}, ^{13}\text{C}) = 550 s(i)s(j) \quad (11.14)$$

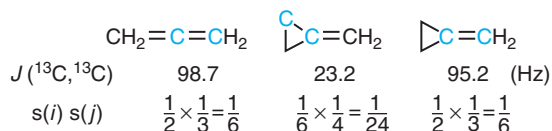
The basis of such a correlation is the assumption that only one of the various mechanisms that contribute to spin–spin coupling, the so-called *Fermi contact term*, dominates. This term depends on the electron density at the nucleus – hence the name “contact term” – and consequently only on the *s*-orbitals involved. For ethane, ethylene, and acetylene we have 25, 33, and 50% *s*-character for the carbon hybrids forming the C–C bond. With the *s*-character products $\frac{1}{4} \times \frac{1}{4}$, $\frac{1}{3} \times \frac{1}{3}$, and $\frac{1}{2} \times \frac{1}{2}$, Eq. (11.14) yields 34.4, 61.1, and 137.5 Hz, respectively, for the respective $^1J(^{13}\text{C}, ^{13}\text{C})$ data. Except for acetylene, good agreement with the experimental values, given in Table 11.7 is found.

The usefulness of Eq. (11.14) in understanding the magnitude of one-bond ^{13}C , ^{13}C couplings is further illustrated with experimental results for three-membered rings. Here, the Walsh model for cyclopropane is used to derive the *s*-character of the particular hybrid orbitals of the carbons. In this model three sp^2 -hybridized carbons are arranged in such a way that three sp^2 hybrids overlap in the center of the three-membered ring and the *p*-orbitals overlap in the plane. The remaining sp^2 orbitals are used for the two C–H bonds. They are oriented by 60° above and below the ring plane. The *s*-character of the sp^2 hybrid directed to the center of the ring amounts to $\frac{1}{3}$, which is equally distributed between the two C–C bonds and thus contributes $\frac{1}{6}$ *s*-character for each bond. The *s*-character product for a C–C bond is thus $\frac{1}{6} \times \frac{1}{6} = \frac{1}{36}$ and for the coupling we have $550/36 = 15.3$ Hz, which is close to the experimental value of 12.4 Hz. Other examples

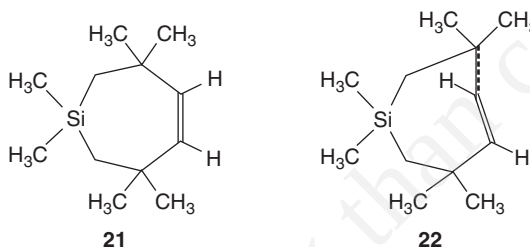
Table 11.7 ^{13}C , ^{13}C spin–spin coupling constants (hertz).

$\text{H}_3\text{C--CH}_3$	34.6		X = CH ₃	36.9
$\text{H}_2\text{C=CH}_2$	67.6		= NH ₂	37.1
$\text{HC}\equiv\text{CH}$	171.5		= OH	39.5
$\text{C}_6\text{H}_5\text{--H}_2\text{C--CH}_3$	34		= Cl	40.0
$\text{C}_6\text{H}_5\text{--HC=CH}_2$	70		= Br	40.2
$\text{C}_6\text{H}_5\text{--C(=O)--CH}_3$	43		X Y	
$\text{H}_3\text{C--C}\equiv\text{N}$	57.3		H H	12.4
			Br H	13.3
			I H	12.9
			Cl Cl	12.2

for this simple model are allene and *exo*-methylene cyclopropane (please note that here one carbon is sp -hybridized):



For cyclic acetylenes one observed a decrease of the $^1J(^{13}\text{C}, ^{13}\text{C})$ data across the triple bond as the $\text{C}-\text{C}\equiv\text{C}$ bond angles deviate from 180° . An interesting observation was reported for the two cyclic silyl compounds *cis*- and *trans*-silacycloheptene **21** and **22**, respectively. The $^1J(^{13}\text{C}\equiv^{13}\text{C})$ coupling constants showed an identical value of 71 Hz in both systems that is in the normal range, despite the fact that in **22** the double bond is – according to X-ray measurements – strongly twisted with a torsional angle of only 131° instead of 180° . The finding was taken as indication that the coupling is transmitted exclusively through the overlapping carbon sp^2 hybrids and a contribution from the π -orbitals is negligible. This fits into the picture of the dominance of the Fermi contact term given above [24].



In contrast to the strong variation of the $^1J(^{13}\text{C}, ^{13}\text{C})$ data with bond order or bond length of the $\text{C}-\text{C}$ bond involved, seen in Table 11.7, substituent effects for couplings across $\text{C}-\text{C}$ single bonds are generally less pronounced. A large increase in the double bond coupling was, however, observed for substitution by chlorine or fluorine, even leading to a value of 172 Hz for $\text{F}_2\text{C}=\text{CFCl}$ [25].

The $^{13}\text{C}, ^{13}\text{C}$ coupling constants over more than one bond are smaller than 20 Hz, mostly smaller than 10 Hz. The vicinal interactions, which are around 5 Hz and even less, are of interest for stereochemical assignments. Here, a dihedral angle dependence similar to the Karplus curve for $^1\text{H}, ^1\text{H}$ coupling constants [Eq. (5.21), p. 129] has been found for ^{13}C labeled bicyclic systems with various dihedral angles [26]:

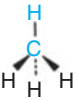
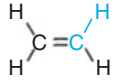
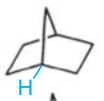
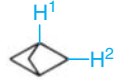
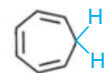
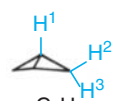
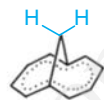
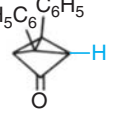
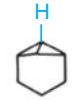
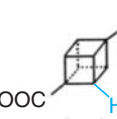
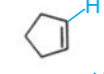
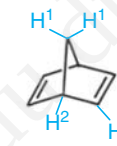
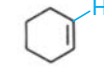
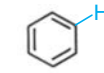
$$^3J(^{13}\text{C}, ^{13}\text{C}) = 1.67 + 0.18 \cos \phi + 2.24 \cos 2\phi \quad (11.15)$$

Noteworthy is the exception from the double bond rule $^3J_{\text{trans}} > ^3J_{\text{cis}}$ with $J(0^\circ) = 4.1$ and $J(180^\circ) = 3.7$ Hz.

11.4.1.2 $^{13}\text{C}, ^1\text{H}$ Coupling Constants

For $^{13}\text{C}, ^1\text{H}$ coupling constants, the structure dependence of the $^1J(^{13}\text{C}, ^1\text{H})$ data, shown with several examples in Table 11.8 has been of considerable interest to

Table 11.8 $^{13}\text{C}, ^1\text{H}$ coupling constants over one bond.

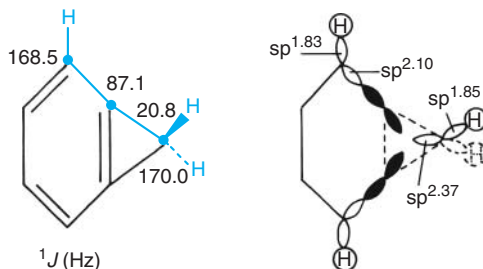
	125		157	$\text{HC}\equiv\text{CH}$	250
	134		142		
	161		178.5		
	(1) 164 (2) 144		131		
	(1) 202 (2) 170 (3) 152		142		
	190		220		
	200		170		
	160		162		
	(1) 135.5 (2) 146 (3) 172.5		158		
			159		
		CH_3Cl	151		
		CH_2Cl_2	178		
		CHCl_3	215		

chemists. In this case too an s -character dependence was found and for hydrocarbons the following empirical relation has been derived:

$$^1J(^{13}\text{C}, ^1\text{H}) = 500 s(i) \quad (11.16)$$

By analogy with Eq. (11.14) [note that in the present case $s(j) = 1$ for the proton $1s$ orbital], it relates the coupling to the fractional s -character $s(i)$ of the C,H bond involved. Since the s -character in turn is related through the equation $s(i) = 1/(1 + \alpha)$ to the hybridization parameter α of the carbon orbital sp^α , one can obtain information concerning the hybridization of a particular

carbon atom through $^1J(^{13}\text{C}, ^1\text{H})$ measurements. Thus, for the highly strained hydrocarbon benzocyclopropene, the combination of data derived from $^1J(^{13}\text{C}, ^{13}\text{C})$ and $^1J(^{13}\text{C}, ^1\text{H})$ couplings yields the hybridization diagram shown below.



In particular, the remarkable *ring size dependence* of $^1J(^{13}\text{C}, ^1\text{H})$ in cycloalkanes is of interest and lends the coupling constant diagnostic value. Three-membered rings may, therefore, be identified through their large $^1J(^{13}\text{C}, ^1\text{H})$ values. For cyclopropane, the value of 161 Hz, typical for an sp^2 CH bond, is in accord with the Walsh model for the bonding situation in the three-membered ring. From Eq. (11.15) it follows that 32% *s*-character is contained in each C,H bond orbital, leading to $\text{sp}^{2.1}$ hybrids. For the C–C bonds on the other hand high *p*-character (82%) results.

Attempts have also been made to draw conclusions from the $^{13}\text{C}, ^1\text{H}$ coupling constants concerning the bond angle in the CH_2 group under consideration. However, this parameter is a better probe for the inter-orbital angle, and it must be remembered that this angle often deviates significantly from the structural angle between the internuclear axes. Also of importance is the fact that, in addition to hybridization changes, several other factors determine the magnitude of the $^{13}\text{C}, ^1\text{H}$ coupling constant. In particular, electronegative substituents can give rise to significant variations, as is seen in the values for the chloromethanes given in Table 11.8. Presumably, changes in the effective nuclear charge of carbon are responsible for these findings. In these cases the simple correlation with the hybridization of the carbon bond orbitals breaks down. Charge effects are also observed for ions of aromatic π -systems, where partial positive charges lead to an increase and partial negative charges to a decrease of the corresponding $^1J(^{13}\text{C}, ^1\text{H})$ values. For tropylium ion one finds 166.8 Hz while benzene has a value of 158.4 Hz. An increase of $^1J(^{13}\text{C}, ^1\text{H})$ is also observed for complexation of a π -system by a transition metal carbonyl group like $\text{Cr}(\text{CO})_3$.

Geminal and *vicinal* $^{13}\text{C}, ^1\text{H}$ coupling constants are much smaller than the couplings over one bond. Generally, values between 1 and 12 Hz are observed. Their determination from the ^{13}C satellites in ^1H NMR spectra is thus more difficult because the signals of interest are closer to the large main signal of the ^{12}C molecules. In addition, the exact analysis of complicated spin systems is usually required.

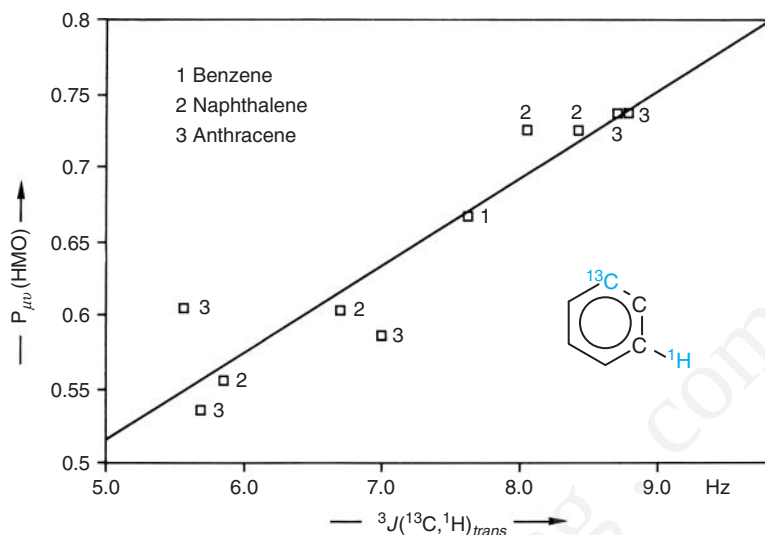


Figure 11.31 Relation between vicinal transoid $^{13}\text{C}, ^1\text{H}$ spin-spin coupling constants and HMO π -bond order of the central C-C bond in the ^{13}C -C-C- ^1H fragment of benzenoid aromatics. H. Günther and P. Schmitt, unpublished work.

Exercise 11.7

Use the $^{13}\text{C}, ^{13}\text{C}$ coupling constants measured for methylene cyclopropane (p. 423) and $^1J(\text{C}, \text{H})_{\text{ring}} = 161.5$, $^1J(\text{C}, \text{H})_{\text{db}} = 160.8$ Hz) and derive with the help of Eqs (11.14) and (11.15), on the basis of the Walsh model for three-membered ring, a hybridization diagram for this hydrocarbon.

With respect to structure determinations the vicinal coupling constants are of greatest interest. Like the $^3J(^1\text{H}, ^1\text{H})$ data, they depend on bond lengths, valence angles, and dihedral angles. For benzenoid aromatics, a correlation between $^3J(^{13}\text{C}, ^1\text{H})_{\text{trans}}$ and the bond length R_{CC} (in nm) or the Hückel MO π -bond order P_{μ} of the central C-C bond in the particular ^{13}C -C-C- ^1H fragment, respectively, was found (Figure 11.31). The linear relations have the form:

$$^3J(^{13}\text{C}, ^1\text{H}) = -404.7 R_{\text{CC}} + 63.69 \quad (11.17)$$

$$^3J(^{13}\text{C}, ^1\text{H}) = 14.77 P_{\mu} - 2.32 \quad (11.18)$$

The dihedral angle dependence of the $^3J(^{13}\text{C}, ^1\text{H})$ data is of interest for conformational analysis, for example, in the case of nucleotides or carbohydrates. Equations that are analogous to the well-known Karplus equation for vicinal $^1\text{H}, ^1\text{H}$ coupling constants (p. 129) have been derived experimentally as well as from theoretical calculations. Those based on experimental data vary to some extent depending on

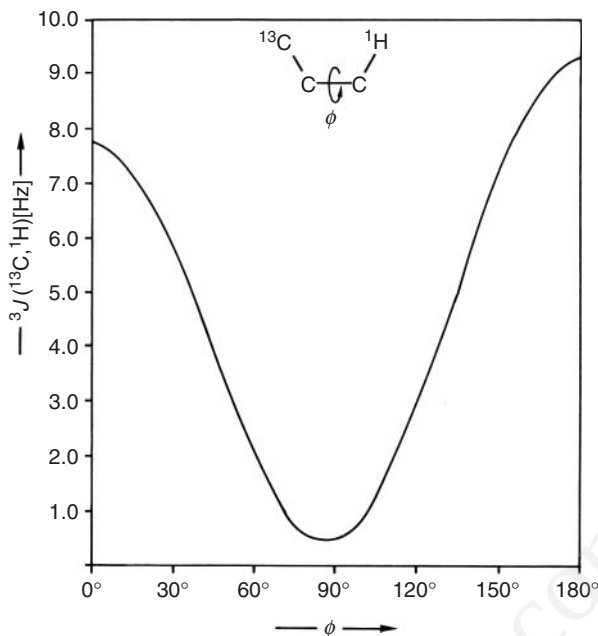


Figure 11.32 Dihedral angle (ϕ) dependence (Karplus curve) for vicinal $^{13}\text{C}, ^1\text{H}$ spin-spin coupling constants in aliphatic hydrocarbons; one finds $^3J(0^\circ) = 7.7$, $^3J(60^\circ) = 2.0$, $^3J(90^\circ) = 0.5$, $^3J(120^\circ) = 2.9$, and $^3J(180^\circ) = 9.4$ Hz [27].

the class of compounds that was used to establish these relations. For aliphatic hydrocarbons we have:

$$^3J(^{13}\text{C}, ^1\text{H}) = 4.50 - 0.87 \cos \phi + 4.03 \cos 2\phi \quad (11.19)$$

as shown in graphical form in Figure 11.32. As in the case of the vicinal $^1\text{H}, ^1\text{H}$ coupling one finds the minimum at $\phi = 90^\circ$ and $^3J(0^\circ) < ^3J(180^\circ)$; for olefins $^3J_{\text{trans}} > ^3J_{\text{cis}}$ holds. Similar relations have been derived from measurements of carbohydrates and nucleotides.

11.4.1.3 $^{13}\text{C}, \text{X}$ Coupling Constants

Quite a number of magnetic X nuclei lead to line splittings in the ^1H -decoupled ^{13}C NMR spectra of inorganic, organic, or organometallic molecules, and, depending on the natural abundance of X, give rise to multiplet structures or satellite lines. In organic chemistry, for instance, numerous $^{13}\text{C}, ^{19}\text{F}$, $^{13}\text{C}, ^{31}\text{P}$, or $^{13}\text{C}, ^{15}\text{N}$ coupling constants have been measured that yield interesting structural information. In organometallics, couplings like $J(^{13}\text{C}, ^6\text{Li})$, $J(^{13}\text{C}, ^{109}\text{Sn})$, or $J(^{13}\text{C}, ^{199}\text{Hg})$, to name only a few, are observed. For a detailed account of these data the reader is referred to monographs on ^{13}C NMR. We note, however, that the one-bond spin-spin interactions between ^{13}C and ^{19}F nuclei are larger than those between ^{13}C and protons. They vary between 170 and 400 Hz and have a negative sign. The sign of

the $^{13}\text{C}, ^1\text{H}$ coupling constants, in contrast, is positive, so that the signs of the other spin–spin interactions can often be correlated with the sign of $^{13}\text{C}, ^1\text{H}$ coupling constants and thereby be determined.

11.5

Carbon-13 Spin–Lattice Relaxation Rates

Spin–lattice relaxation rates for nuclei in organic molecules are readily determined by Fourier-transform spectroscopy using inversion-recovery experiments or similar pulse techniques. We discussed these types of experiments in Chapter 8 and an application for ^{13}C was illustrated in Figure 11.9. It is therefore of interest to consider briefly what information can be derived from such measurements, and how the spin–lattice relaxation rate is related to phenomena of chemical interest.

As outlined in Chapter 8, spin–lattice relaxation originates from fluctuating magnetic fields that provide an RF frequency suitable for an NMR transition. There are several sources of such fluctuating fields, and therefore several mechanisms contribute to the relaxation. Of primary interest to us is the dipolar relaxation mechanism, where the fluctuating field results from a modulation of a dipolar spin–spin coupling. The local field induced at a nucleus by a neighboring magnetic dipole is given by Eq. (2.12) and its time dependence arises in intramolecular cases through changes in the angle θ , and in intermolecular cases through changes in both θ and the internuclear distance r .

For ^{13}C it turns out that protons bonded to carbon most effectively contribute to the dipolar relaxation of the latter, with the modulation of the coupling being provided by the molecular motion in the liquid phase. Following theoretical considerations, the dipolar relaxation rate, $(1/T_1)^{\text{DD}} = R_1^{\text{DD}}$, can be related to the distance r between the nuclei and the correlation time, τ_c , through the equation (11.20) which was already introduced in Chapter 8 (p. 242):

$$R_1^{\text{DD}} = \left(\frac{\mu_0}{4\pi}\right)^2 \hbar^2 N \gamma_{\text{C}}^2 \gamma_{\text{H}}^2 r_{\text{CH}}^{-6} \tau_c \quad (11.20)$$

where N is the number of directly bonded protons. As outlined there, the correlation time (τ_c) characterizes the reorientation of a molecule in a liquid and for non-viscous solutions of samples with a molecular weight below about 500 it is of the order of 10^{-10} s.

Equation (11.20) thus yields the basis for obtaining information on intramolecular distances and molecular dynamics in the liquid state. To interpret the experimental results correctly, the extent to which other factors contribute to the observed relaxation rate must be determined. This is most conveniently carried out by measuring the nuclear Overhauser enhancement factor, η_i , for the particular carbon resonance, since the NOE itself depends on dipolar relaxation. As was pointed out in Chapter 10, for pure dipolar relaxation the NOE has a maximum value of $\eta = \gamma_{\text{H}}/2\gamma_{\text{C}} = 1.988$. The fractional dipolar relaxation rate is thus given by:

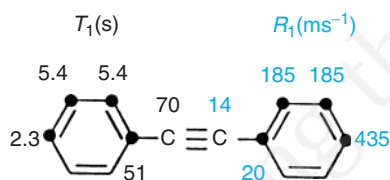
$$\text{Dipolar relaxation} = \frac{\eta_i}{1.988} \times 100 (\%) \quad (11.21)$$

and:

$$R_1^{\text{DD}} = R_1^{\text{obs.}} \times \frac{\eta_i}{1.988} \times 100 \quad (11.22)$$

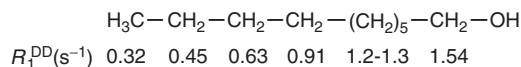
The distance dependence of R_1^{DD} forms the basis for the use of T_1 measurements for assignment purposes, which was mentioned on page 407. It yields considerably different T_1 values for quaternary carbon atoms on one side and protonated carbon atoms of CH -, CH_2 -, and CH_3 -groups on the other, with ranges of 20–100 and 1–20 s, respectively. The long T_1 values of quaternary carbons are responsible for the systematic diminution of their signal intensity observed during routine measurements. Only if long relaxation delays or relaxation reagents are used can ^{13}C spectra with correct intensity distributions be expected.

The molecular motion influences R_1^{DD} through the correlation time (τ_c). For rigid, isotropically tumbling systems, such as adamantane, the motion can be described as a single τ_c and R_1^{DD} is a function of r or the number of protons present. Thus, for adamantane $R_1^{\text{DD}}(\text{CH}) = 49 \text{ ms}^{-1}$ and $R_1^{\text{DD}}(\text{CH}_2) = 88 \text{ ms}^{-1}$. For anisotropic motion, on the other hand, different correlation times result for different CH bonds. This is seen from the relaxation rates for the *ortho*- and *meta*-carbon atoms of diphenylacetylene on the one hand (185 ms^{-1}) and the *para*-carbon atom on the other (435 ms^{-1}). The latter is faster because $\tau_c(\text{para}) > \tau_c(\text{ortho}, \text{meta})$ owing to the preferential rotation of the molecule around its long axis.



With R_1^{DD} as a probe for molecular dynamics an interesting topic, namely, segmental motion, that is, localized motion along an aliphatic chain, can be investigated. Since T_1 values can be measured for carbon atoms and protons, a body of experimental data sufficient to describe certain aspects of the dynamic behavior of chain-like molecules is available.

Thus, for 1-decanol, for example, the following ^{13}C - R_1^{DD} values were found:



Their increasing magnitude toward the OH group indicates an increase in the effective correlation time and reduced motion due to hydrogen bonding. Quantitative treatment of such results is by no means straightforward, since sophisticated models are needed to separate the effects of segmental motion from those of overall molecular motion. Nevertheless, rotational barriers of methyl groups in the order of 12 kJ mol^{-1} have frequently been determined.

References

1. Bruker Analytische Messtechnik GmbH *Spectral Catalogue*, Karlsruhe.
2. Joel-Kontron Co. Technical Bulletin, Joel-Kontron Co., Munich.
3. Bremser, W., Hill, H.P.W., and Freeman, R. (1971) *Messtechnik*, **78**, 14.
4. Joseph-Nathan, P., Santillan, R.L., Schmitt, P., and Günther, H. (1984) *Org. Magn. Reson.*, **22**, 450.
5. Frankmölle, W. (1990) Ph.D. thesis, University of Siegen
6. Fircks, G.V. (1995) PhD thesis. University of Siegen.
7. Joseph-Nathan, P., Wesener, J.R., and Günther, H. (1984) *Org. Magn. Reson.*, **22**, 190.
8. Günther, H., Schmitt, P., Fischer, H., Tochtermann, W., Liebe, J., and Wolff, C. (1985) *Helv. Chim. Acta*, **68**, 801.
9. Schmitt, P. and Günther, H. (1983) *Angew. Chem.*, **95**, 509; *Angew. Chem., Int. Ed. Engl.*, **22**, 499.
10. Schmitt, P. (1983) PhD thesis, University of Siegen.
11. Bast, P. (1988) PhD thesis, University of Siegen.
12. Günther, H. and Schmitt, P. (1984) *Naturwissenschaften*, **71**, 342.
13. Ewers, U. (1973) PhD thesis, University of Cologne.
14. Günther, H. and Jikeli, G. (1973) *Chem. Ber.*, **106**, 1863.
15. Bremser, W. (1973) *Chem. Z.*, **97**, 248.
16. Levy, G.C., Lichter, R.C., and Nelson, G.L. (1980) *Carbon-13 NMR Spectroscopy*, 2nd edn, Wiley Interscience, New York.
17. Stothers, J.B. (1972) *Carbon-13 NMR Spectroscopy*, Academic Press, New York.
18. Olah, G.A. and Mateescu, G.P. (1970) *J. Am. Chem. Soc.*, **92**, 1430.
19. Spiesecke, H. and Schneider, W.G. (1961) *J. Chem. Phys.*, **35**, 731.
20. Günther, H. and Schmickler, H. (1975) *Pure Appl. Chem.*, **44**, 807.
21. Breitmaier, E. and Spohn, K.H. (1973) *Tetrahedron*, **29**, 1045.
22. Diederich, F. and Whetten, R.L. (1992) *Acc. Chem. Res.*, **25**, 119.
23. Clerc, J.T., Pretsch, E., and Sternhell, S. (1973) *¹³C-Kernresonanzspektroskopie*, Akademische Verlagsges, Frankfurt.
24. Berger, S., Krebs, A., Thölke, B., and Siehl, H.-U. (2000) *Magn. Reson. Chem.*, **38**, 566.
25. Kamińska-Trela, K., Biedrzycka, Z., and Dabrowski, A. (1991) *Magn. Reson. Chem.*, **29**, 1216.
26. Berger, S. (1980) *Org. Magn. Reson.*, **14**, 65.
27. Aydın, R. and Günther, H. (1990) *Magn. Reson. Chem.*, **28**, 448.

Textbooks and Monographs

- Kalinowski, H.-O., Berger, S., and Braun, S. (1988) *Carbon-13 NMR Spectroscopy*, John Wiley & Sons, Ltd, Chichester, 792 pp.
- Wehrli, F.W., Marchand, A.P., and Wirthlin, T. (1988) *Interpretation of Carbon-13 NMR Spectra*, John Wiley & Sons, Ltd, Chichester, 484 pp.
- Breitmaier, E. and Voelter, W. (1987) *¹³C-NMR Spectroscopy*, Monographs in Modern Chemistry, Vol. 5, VCH Publishers, Weinheim, 334 pp.
- Levy, G.C., Lichter, R.C., and Nelson, G.L. (1980) *Carbon-13 NMR Spectroscopy*, 2nd edn, Wiley Interscience, New York, 338 pp.
- Stothers, J.B. (1972) *Carbon-13 NMR Spectroscopy*, Academic Press, New York, 559 pp.
- Levy, G.C. (ed) (1974 ff.) *Topics in Carbon-13 NMR-Spectroscopy*, Wiley, New York, Vol. 1–3.

Review articles

- Buddrus, J. (1996) INADEQUATE Experiment, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 4, (eds in-chief D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester, UK, p. 2491.
- Buddrus, J. and Lambert, J. (2002) Connectivities in molecules by INADEQUATE: recent developments, *Magn. Reson. Chem.*, **40**, 3.
- Traficante, D.D. (1996) Relaxation: An Introduction, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 6, (eds in-chief D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester, UK, p. 3988.

12

Selected Heteronuclei

After the discovery of NMR and its applications in chemistry the proton and other sensitive nuclei like fluorine-19 and phosphorus-31 dominated NMR spectroscopy in chemical research. Further nuclei from the Periodic Table were used rarely or could not be measured at all. This situation changed with the introduction of the Fourier-transform technique and the improvements in NMR sensitivity by the construction of high-field superconducting magnets. In addition, considerable progress was made by the use of the nuclear Overhauser effect (NOE) and the development of polarization transfer experiments (INEPT, DEPT) as well as shift correlations with “inverse” detection (HMQC, HSQC). Thus, many of the so-called heteronuclei – with respect to proton and carbon-13 also labeled “other” nuclei and a large number of them furnished with a quadrupole moment – became more and more accessible and interest in these additional probes for molecular structure and reactivity increased. Aside from progress made for solution NMR of these nuclei, solid state NMR measurements, which have a long tradition in physics, are also now easier to perform for this group through cross-polarization (CP) and magic-angle spinning (MAS). Thus, as well as the common nuclei like ^{13}C , ^{15}N , ^{19}F or ^{31}P , many metals can be observed in solid compounds and NMR is now also a valuable tool in materials science. This aspect will be discussed in more detail in Chapter 14.

After having treated the spectral parameters of ^1H and ^{13}C as well as the standard NMR pulse experiments, we shall now describe in the following the most important aspects associated with a number of heteronuclei that are frequently used for NMR investigations in organic, organometallic, bio-organic, and inorganic chemistry where the complete arsenal of 1D and 2D NMR techniques are applied. Of course, only a general survey of measuring techniques and NMR parameters can be given, especially for nuclei like nitrogen-15, fluorine-19, or phosphorus-31 that have over many years been studied intensively, resulting in a huge amount of experimental data. Our selection includes non-metals (^{11}B , ^{15}N , ^{17}O , ^{19}F , ^{29}Si , ^{31}P), main group metals (^6Li , ^{27}Al , ^{119}Sn) and several transition metals. The limits we necessarily had to accept do not imply that nuclei not mentioned are unimportant. This chapter, rather, aims to stimulate interest in NMR of heteronuclei and more detailed information must be obtained from the monographs and review articles cited at the end of the chapter.

Table 12.1 Classification of nuclei according to natural abundance and magnetic strength.

Magnetic strength ^a	Natural abundance		
	High (>90%)	Medium	Low (<10%)
1. Nuclei with spin $I = \frac{1}{2}$			
S	¹ H, ¹⁹ F, ³¹ P	²⁰⁵ Tl	³ He
M	—	¹¹³ Cd, ¹²⁹ Xe, ¹⁷¹ Yb, ¹⁹⁵ Pt, ¹⁹⁹ Hg, ²⁰⁷ Pb	¹³ C, ¹⁵ N, ²⁹ Si, ⁷⁷ Se, ¹¹⁹ Sn, ¹²⁵ Te
W	⁸⁹ Y, ¹⁰³ Rh, ¹⁶⁹ Tm	¹⁰⁹ Ag, ¹⁸³ W	⁵⁷ Fe, ¹⁸⁷ Os
2. Quadrupolar nuclei with spin $I > \frac{1}{2}$			
S	⁷ Li	—	—
M	⁹ Be, ²³ Na, ²⁷ Al, ⁴⁵ Sc, ⁵¹ V, ⁵⁵ Mn, ⁵⁹ Co, ⁷⁵ As, ⁹³ Nb, ¹¹⁵ In, ¹²⁷ I, ¹³³ Cs, ¹⁸¹ Tl, ²⁰⁹ Bi	¹¹ B, ³⁵ Cl, ⁶³ Cu, ⁶⁵ Cu, ⁷¹ Ga, ⁸¹ Br, ⁸⁷ Rb, ¹²¹ Sb, ¹³⁷ Ba, ¹³⁹ La, ¹⁸⁷ Re	² H, ⁶ Li, ¹⁷ O, ²¹ Ne
W	¹⁴ N, ³⁹ K	²⁵ Mg, ³⁷ Cl, ⁸³ Kr, ⁹⁵ Mo, ¹³¹ Xe, ¹⁸⁹ Os, ²⁰¹ Hg	³³ S, ⁴³ Ca, ⁴⁷ Ti, ⁴⁹ Ti, ⁵³ Cr, ⁶⁷ Zn, ⁷³ Ge, ⁸⁷ Sr

Adapted from Reference [1].

^aMagnetic strength: S = strong, M = medium, and W = weak.

A few general remarks that apply to NMR of heteronuclei should be made at the beginning, especially with respect to the properties of quadrupolar nuclei. Table 12.1 shows a classification of those magnetic nuclei of the Periodic Table that are suitable for NMR measurements. They are arranged according to their natural abundance and their magnetic strength and separated into spin $\frac{1}{2}$ and quadrupolar nuclei. With regard to our selection (given in Table 12.1 in red), most favorable are obviously ¹⁹F and ³¹P, but due to fast signal averaging with the FT method the less abundant nuclei ¹⁵N, ²⁹Si, and ¹¹⁹Sn are also in easy reach, as we have already seen for ¹³C. The more abundant transition metal nuclides ¹¹³Cd, ¹⁹⁵Pt, and ¹⁹⁹Hg also belong to this group, while NMR of the spin $\frac{1}{2}$ nuclei ¹⁸³W, ⁵⁷Fe, and ¹⁸⁷Os proves to be more difficult because of the small magnetic moment involved. The quadrupolar nuclei ⁷Li and ²⁷Al are well accessible because of their high natural abundance and ⁶Li because of easy practicable isotope enrichment.

As we see from Table 12.1, the majority of magnetic nuclei has a nuclear quadrupole moment, Q , and quadrupolar nuclei are most abundant in the groups of the metals and transition metals. The important point is that the nuclear quadrupole moment is responsible for a very effective *relaxation mechanism* that may complicate the observation of NMR signals because of large line widths, thus causing difficulties in measuring exact chemical shifts and detecting coupling constants. As already mentioned in Chapter 8 (p. 243), the interaction of the quadrupole moment with the electric field gradient at the nucleus, which originates

from the surrounding electron distribution, leads to an efficient energy transfer via molecular rotation. Both the longitudinal and the spin–spin relaxation time for the quadrupolar nucleus, T_{1q} and T_{2q} , respectively, are related to the quadrupole moment and the rotational correlation time, τ_c , through Eq. (12.1):

$$T_{1q}^{-1} = T_{2q}^{-1} = \frac{3\pi^2}{10} \frac{(2I+3)}{I^2(2I-1)} \chi^2 \left(1 + \frac{1}{3}\eta^2\right) \tau_c \quad (12.1)$$

where χ is the nuclear quadrupole coupling constant¹⁾ and η the asymmetry parameter of the electric field gradient. For χ we have:

$$\chi = e^2 q_{zz} Q / h \quad (12.2)$$

where e is the electronic charge, q_{zz} is the largest component of the electric field gradient, and h is Planck's constant. The asymmetry parameter η lies between 0 and 1, $0 < \eta < 1$, and is given by:

$$\eta = (q_{yy} - q_{xx})/q_{zz} \text{ or } (\chi_{yy} - \chi_{xx})/\chi_{zz} \quad (12.3)$$

The *line width* for a Lorentzian NMR signal, $\Delta_{1/2}$, depends on T_2 ($\Delta_{1/2} = 1/\pi T_2$, cf. p. 246) and is then given by:

$$\Delta_{1/2} = \frac{3\pi}{10} \frac{(2I+3)}{I^2(2I-1)} \chi^2 \left(1 + \frac{1}{3}\eta^2\right) \tau_c \quad (12.4)$$

Its variation found experimentally for the different nuclei results from the variation of Q ; for individual compounds with the same nuclide the variation of q_{zz} is mainly responsible. A small quadrupole moment (^2H , ^6Li) leads to relatively small line widths, as does a symmetric electron distribution. For the ^{14}N NMR signal, for example, one finds line widths of about 5 Hz for $\text{N}(\text{CH}_3)_4$ and about 1300 Hz for aniline. For ^{35}Cl the difference is even larger: about 10 Hz for the chloride ion and about 10 kHz for CCl_4 !

For constant electric field gradient a line width factor, W_f , which shows the influence of the spin I , can be extracted from Eq. (12.4):

$$W_f = \frac{(2I+3)Q^2}{I^2(2I-1)} \quad (12.5)$$

Owing to the factor I^2 in the denominator, higher spins tend to give sharper signals.

Turning to the *chemical shift*, we already know from ^{13}C NMR that the chemical shift scales of nuclei heavier than the proton are quite large. They may extend over several hundred and even several thousand parts per million. This leads to another relaxation mechanism that is important for metal nuclei that have a large chemical shift range, such as, for instance, platinum-195 (~7500 ppm) or rhodium-103 (~12 000 ppm). It is based on the chemical shift anisotropy (CSA), $\Delta\sigma$, which affects the line shapes of solid state NMR spectra directly (cf. Chapter 14) but the line shapes observed in the liquid state indirectly, where it provides a very efficient

1) Please note that χ is also the symbol for the magnetic susceptibility; some authors prefer therefore the abbreviation QCC for the quadrupole coupling; however, it is clear from the text which physical property is meant.

mechanism for nuclear relaxation, the so-called CSA mechanism. The situation is similar to that for dipole–dipole coupling. For the spin–lattice relaxation time of a nucleus X_i in a magnetic field B_0 governed by $\Delta\sigma$ we have:

$$\frac{1}{T_{1, \text{CSA}}} = \frac{\mu_0 \gamma_i^2 B_0^2 \Delta\sigma^2 \tau_c}{30\pi} \quad (12.6)$$

with τ_c as the correlation time for molecular tumbling and μ_0 as the permeability of free space. Obviously, this mechanism is very effective at high magnetic fields.

Existing experimental data show that *chemical shift ranges* tend to increase with the atomic number Z across a given row of the Periodic Table and down a given group. As discussed earlier for carbon-13 (p. 410 ff.), the significant contribution to the shielding of heavier nuclei comes from the paramagnetic term, σ_p , in the general equation for the shielding constant, σ . The average excitation energy, ΔE , for electronic transitions stimulated by the magnetic field and the extension of the electron cloud around the nucleus, characterized by a radius r_i for the atomic orbital or the orbital coefficient at the nucleus of interest, are important parameters. Since σ_p is proportional to ΔE^{-1} and r^{-3} , large excitation energies and extensions of the electron cloud will diminish σ_p and lead to shielding, and vice versa, and the proportionality shown in Eq. (11.11) allows us to rationalize observed experimental trends. For example, changes in the excitation energy, ΔE , of magnetic–dipole allowed electronic transitions are in many cases responsible for large resonance shifts to higher or lower frequency.

Not only the chemical shifts but also the scalar coupling constants of heteronuclei are generally much larger than those of ^1H NMR. However, nuclides with a quadrupole moment often have broad resonance signals that prevent the detection of spin–spin coupling. Difficulties for measuring scalar coupling constants arise also for some heavy spin $\frac{1}{2}$ nuclides like ^{199}Hg that have very short relaxation times because of the existence of a large chemical shift anisotropy and CSA relaxation [see Eq. (12.6)] that leads in fact to decoupling.

A further point with heteronuclei is that the NMR parameters are more sensitive to solvent, concentration, and temperature than those of ^1H or ^{13}C and finding an ideal reference compound is often difficult. Various standards have been employed, and to compare results of different measurements conversion factors for the reference signal must be used. To avoid reactions and solvent shifts, external standards can be used, but this requires susceptibility corrections. It is therefore more practical to adjust the spectrometer to a reference frequency and calibrate the spectrum relative to the spectrometer frequency.

For this purpose an alternative method for chemical shift measurements was introduced to avoid the problems discussed above. With modern FT spectrometers all Larmor frequencies can now be scaled to be appropriate for a standard applied field B_0 , and the proton resonance frequency of TMS (tetramethylsilane) at 100 MHz was selected as a universal reference. The Greek letter $\mathcal{E}$ is used for frequencies on this scale that is defined by Eq. (12.7):

$$\mathcal{E}_X(\%) = 100(\nu_X^{\text{obs}}/\nu_{\text{TMS}}^{\text{obs}}) \quad (12.7)$$

Values of $\mathcal{E}$ are given in Table 12.2 and in Table 12.19 (Section 12.3) below for the nuclei treated in the present chapter.

The chemical shifts δ on this universal scale are then determined by the following procedure:

- 1) Record a proton spectrum of TMS, either separately or with the sample of interest;
- 2) measure the absolute frequency of TMS;
- 3) take $\mathcal{E}_X$ for the particular nucleus from the literature and determine the zero-point of the parts per million scale for the spectrum to be measured by $\mathcal{E}_X \times \nu_{\text{TMS}}^{\text{obs}}/100 \text{ MHz}$.

If, for some reason, a different reference should be used, its $\mathcal{E}_X^{\text{R}}$ value has to be obtained separately and used as zero-point. The frequency differences for the individual signals, $\nu_i^{\text{obs}} - \mathcal{E}_X^{\text{R}}$ are then converted into parts per million.

Exercise 12.1

On a spectrometer with $B_0 = 3.523 \text{ T}$ a ^{19}F resonance is measured at 141.141 323 MHz; what is the chemical shift relative to TMS in parts per million?

Because in our context the chemical shift is the most important NMR parameter, Figure 12.1 gives, for comparison, a survey of *chemical shift scales* for the common non-metallic heteronuclei together with the reference generally used (at 0 ppm) and some compounds typical for the different subregions. The important physical NMR parameters of the nuclides to be discussed in Section 12.1 (semimetals and non-metals, with the exception of hydrogen and carbon) and Section 12.2 (four main group metals) are collected in Table 12.2. Transition metals and their properties are treated in Section 12.3.

12.1

Semimetals and Non-metals with the Exception of Hydrogen and Carbon

12.1.1

Boron-11

Of the two NMR active boron isotopes ^{10}B and ^{11}B , the latter has the higher natural abundance and sensitivity and is thus preferred for NMR studies. It also shows the greater spectral dispersion in hertz/parts per million. Owing to its quadrupole moment, ^{11}B spin–lattice relaxation times are quite short, typically 10^{-2} – 10^{-3} s , except for highly symmetric environments, but line broadening effects are generally not severe and direct measurements of ^{11}B spectra using FT NMR are possible. However, small spin–spin coupling constants ($<10 \text{ Hz}$) are often difficult or impossible to resolve.

Table 12.2 Nuclear properties of important heteronuclei.^a

Nucleus	<i>I</i>	Natural abundance (%)	μ/μ_N	γ (10^7 rad s^{-1} T $^{-1}$)	Q (barn = 10^{-28} m ^{2})	ν (MHz at 2.3548 T) = $\bar{\nu}$ (%)	Reference compound	R^H	R^C	W_F (10^{-59} m ^{4})
1. Semimetals and non-metals										
^{11}B	$\frac{3}{2}$	80.1	3.4710	8.5847	4.1×10^{-2}	32.083 974	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	0.132	7.77×10^2	2.2
^{15}N	$\frac{1}{2}$	0.368	-0.4905	-2.7126	—	10.136 767	MeNO_2	3.84×10^{-6}	2.25×10^{-2}	—
^{17}O	$\frac{5}{2}$	0.038	-2.2408	-3.6281	-2.6×10^{-2}	13.556 457	D_2O	1.11×10^{-5}	6.50×10^{-2}	0.21
^{19}F	$\frac{1}{2}$	100	4.5533	25.1815	—	94.094 011	CCl_3F	0.834	4.90×10^3	—
^{29}Si	$\frac{1}{2}$	4.683	-0.9618	-5.3190	—	19.867 187	Me_4Si	3.68×10^{-4}	2.16	—
^{31}P	$\frac{1}{2}$	100	1.9510	10.8394	—	40.480 742	H_3PO_4	6.65×10^{-2}	3.91×10^2	—
2. Main group metals										
^6Li	1	7.59	1.1626	3.9372	-8.08×10^{-4}	14.716 086	LiCl	6.45×10^{-4}	3.79	3.3×10^{-3}
^7Li	$\frac{3}{2}$	92.41	4.2041	10.3977	-4.01×10^{-2}	38.863 797	LiCl	0.271	1.54×10^3	2.1
^{27}Al	$\frac{5}{2}$	100.0	4.3087	6.9763	14.66×10^{-2}	26.056 859	$\text{Al}(\text{NO}_2)_3$	0.207	1.22×10^3	6.9
^{119}Sn	$\frac{1}{2}$	8.59	1.8139	-10.0317	—	37.290 632	Me_4Sn	4.53×10^{-3}	26.6	—

^a *I* = spin quantum number; μ = magnetic moment in units of μ_N^b , the Bohr magneton; γ = magnetogyric ratio; ν = resonance frequency at 2.358 T (^1H = 100 00 MHz), $\bar{\nu}$ (%), for definition see (p. 434 ff); R^H = receptivity relative to proton; R^C = receptivity relative to carbon-13; W_F = linewidth factor; for some nuclides additional NMR active isotopes exist, but in the present context they are of minor importance and thus are neglected.
^b $\mu_N = eh/4\pi m_p c = 5.0505 \times 10^{-27}$ JT $^{-1}$.
Data adapted from Reference [2].

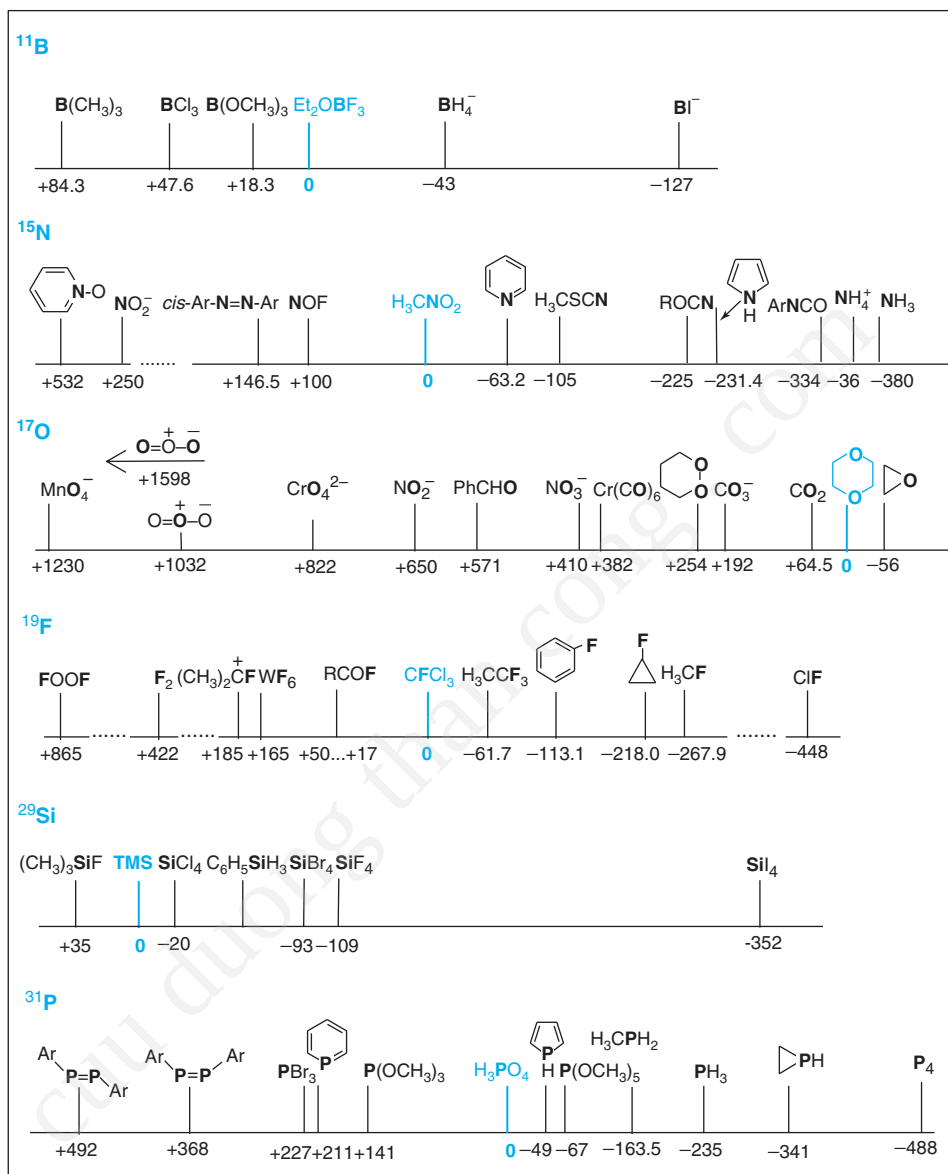


Figure 12.1 Chemical shift scales of heteronuclei; δ -values in parts per million.

12.1.1.1 Referencing and Chemical Shifts

The range for $\delta(^{11}\text{B})$ of trigonally coordinated boron compounds extends over about 100 ppm from about -10 to +90 ppm relative to the signal of $(\text{C}_2\text{H}_5)_2\text{OBF}_3$ that is used as an external reference (Figure 12.2) while ^{11}B in tetrahedrally coordinated compounds shows negative δ -values. The data do not reflect the electronegativity

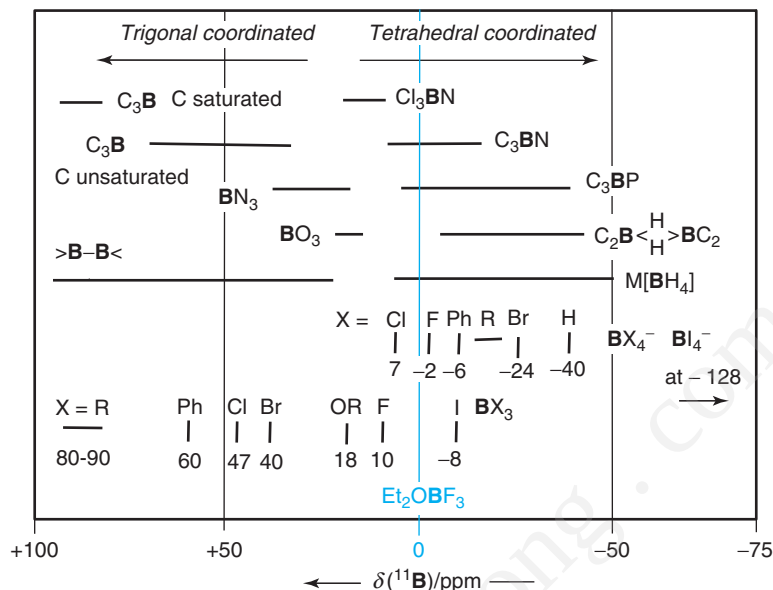


Figure 12.2 ^{11}B chemical shift diagram for simple boron compounds. Data from Reference [3].

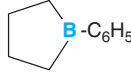
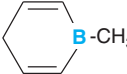
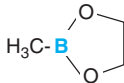
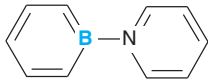
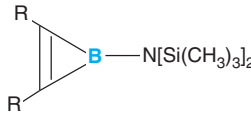
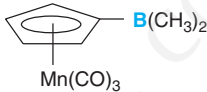
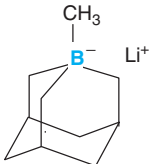
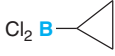
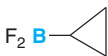
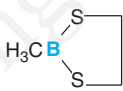
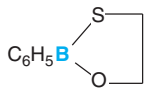
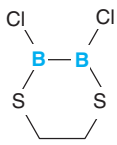
of the substituents in a simple way because they are dominated mostly by the paramagnetic contribution, σ_p , to the shielding constant σ . For both species, trigonal and tetrahedral, linear correlations between ^{11}B shifts and ^{13}C shifts in isoelectronic carbon compounds were found. Several simple, mostly trigonal boron compounds and their chemical shifts, are collected in Table 12.3.

12.1.1.2 Polyhedral Boranes

Only carbon and silicon exhibit more hydrides than boron. Unusual bonding situations for the boron–boron and boron–hydrogen bonds lead to a great structural versatility that is not easily analyzed. For example, four different structures are formed by ten boron atoms and a varying number of hydrogens: B_{10}H_8 , $\text{B}_{10}\text{H}_{12}$, $\text{B}_{10}\text{H}_{14}$, and $\text{B}_{10}\text{H}_{16}$. Double bonds are not involved and boron uses B–B–B or B–H–B three-center bonds to form cage structures. Chemical shifts for ^{11}B or ^1H are thus not easy to assign, especially since not all coupling constants are resolved, and shift–structure correlations are restricted to certain families of cage structures. NMR studies in this field profit most from the introduction of two-dimensional methods like $^{11}\text{B}, ^{11}\text{B}$ and $^1\text{H}, ^{11}\text{B}$ COSY spectra as well as $^{11}\text{B}, ^1\text{H}$ HETCOR experiments. Figure 12.3 (p. 440) shows an example of a $^{11}\text{B}, ^{11}\text{B}$ COSY spectrum.

Homo- and heteronuclear coupling constants are divided into *endo*- (within the cage structure) and *exo*- (with outer substituents) couplings. Values for $^1J(^{11}\text{B}, ^1\text{H})_{\text{exo}}$ are in the range of 120–170 Hz and are thus well resolved. $^1J(^{11}\text{B}, ^1\text{H})_{\text{endo}}$ is often much smaller than 50 Hz and is usually not resolved, for example, in case of the B–H–B three-center bonds.

Table 12.3 $\delta(^{11}\text{B})$ values for selected boron compounds (ppm relative to Et_2OBF_3).

$(\text{H}_3\text{C})_3\text{B}$	$(\text{H}_3\text{C})_2\text{B}-\text{F}$	59.0	-I	79.1	$-\text{NH}_2$	47.1	
86.0	-Cl	77.2	$-\text{OCH}_3$	53.0	$-\text{CH}=\text{CH}_2$	74.5	
	-Br	78.8	$-\text{SCH}_3$	73.6	$-\text{C}\equiv\text{C}-\text{CH}_3$	71.7	
		92.5		52.8		34.2	
		33.9	25.0		72.0		
$(\text{H}_3\text{C})_2\text{B}$ 	81.8		-20.3	BF_3	10.0	BCl_3	38.7
Cl_2B 	59.4			BCl_3	46.5	BI_3	-7.9
F_2B 	28.3					$\text{B}(\text{OCH}_3)_3$	18.3
						$\text{B}[\text{N}(\text{CH}_3)_2]_3$	27.3
$(\text{C}_6\text{H}_5)\text{B}(\text{C}\equiv\text{C}-\text{CH}_3)_2$		40.0	69.6		47.7		67.8
$(\text{H}_3\text{C})_2\text{O}(\text{BH}_3)$	H_3NBH_3	$\text{Li}[\text{BH}_4]$	$[\text{BX}_4]^-$ X = F	0.1... -2.3	Br	-23... -26	
2.5	-20.1	-3.8	Cl	4 ... 8	I	-128	

Data from Reference [4].

12.1.2

Nitrogen-15

Among group-5 elements of the Periodic Table nitrogen is by far the most important for organic and bioorganic chemistry. Of its two nuclides, ^{14}N and ^{15}N , ^{14}N was preferred in the earlier years because of its high natural abundance, but its broad

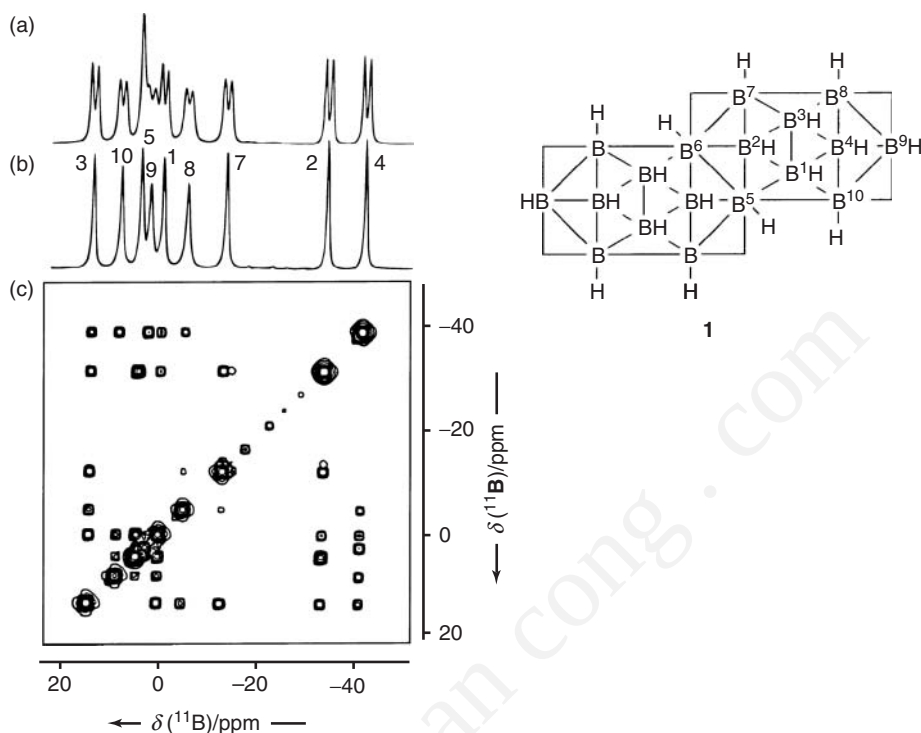


Figure 12.3 ^{11}B , ^{11}B COSY spectra of anti- $\text{B}_{18}\text{H}_{22}$ (**1**) at 128 MHz: (a) ^{11}B spectrum with ^1H coupling; (b) the same with ^1H decoupling and assignment; (c) ^{11}B , ^{11}B COSY spectrum [5].

resonance lines – a consequence of its large quadrupole moment – made chemical shift measurements very inaccurate. In contrast, the time for the spin $\frac{1}{2}$ nucleus ^{15}N came with FT NMR combined with proton decoupling. The negative Overhauser factor, close to -5.0 (cf. p. 361), however, leads to signal inversion and a “normal” spectrum is observed only after a 180° phase shift. In unfortunate situations an Overhauser enhancement of only -1.0 would lead to signal loss. Thus, the INEPT experiment (described in detail in Chapter 10, p. 360 ff.), with a much larger enhancement factor of nearly -10 , soon became the method of choice for ^{15}N NMR.

The INEPT sequence for ^{15}N NMR works with one- or two-bond ^{15}N , ^1H coupling constants that are of the order 90 and 10 Hz, respectively, and that have to be used in two separate experiments. An example is shown in Figure 12.4, where the ^{15}N signals of pteridine were recorded via $^2J(^{15}\text{N}, ^1\text{H})$. Alternatively, the DEPT sequence (p. 387) can be used and inverse detection via ^1H NMR (HMQC or HSQC, cf. p. 389 ff.) further increases the sensitivity in cases where appropriate ^{15}N , ^1H coupling is available. Thus, the measurement of ^{15}N NMR spectra has developed into a standard experiment, especially since in critical cases, such as for biopolymers, isotopic enrichment is used.

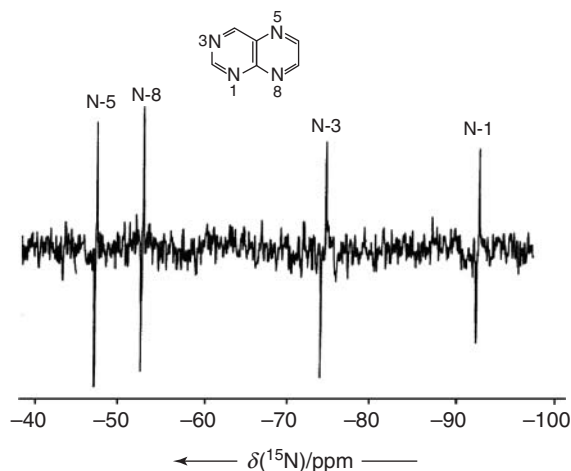


Figure 12.4 ^{15}N INEPT NMR spectrum of pteridine, 0.1 M in $[\text{D}_6]\text{DMSO}$; measuring frequency 40.53 MHz, 9059 transients, spectral width 6024 Hz, digital resolution 0.43 Hz, signal-to-noise ratio 5.6: 1, measuring time 13.5 h. The $1/4J$ delay of the INEPT sequence (p. 360) was 19.23 ms, which corresponds to an average of 13 Hz for the geminal $^{15}\text{N}, ^1\text{H}$ coupling. The signals are found at -46.9 , -52.4 , -74.1 , and

-92.5 ppm relative to external $\text{CD}_3^{15}\text{NO}_3$. The coupling constants measured from the anti-phase doublet splittings are $^2J(1,2) = 14.6$, $^2J(2,3) = ^2J(3,4) = 12.5$, $^2J(5,6) = 11.2$, and $^2J(8,7) = 10.8$ Hz. The center line of the N3 triplet has zero intensity in the INEPT experiment [6] (Copyright 1984; with kind permission of Springer Science+Business Media).

12.1.2.1 Referencing and Chemical Shifts

The reference compound for ^{15}N NMR is $[\text{D}_3]\text{nitromethane}$, CD_3NO_2 , where the CD_3 group serves as lock signal. It has to be used as external reference or by fixing the spectrometer frequency to its resonance that appears at high frequency. Most δ -values for ^{15}N are therefore negative. Various other standards used earlier can be transformed into the nitromethane scale with the help of the data collected in Table 12.4.

Table 12.4 Reference compounds for ^{15}N NMR [7].

Compound	Medium	δ -Value
CH_3NO_2	Neat	0.0
NH_3	Fluid at 25°C	-380.2
NH_4NO_3	Saturated in H_2O	$-359.5/-3.9^a$
NH_4Cl	Saturated in H_2O	-352.9
HNO_3	Concentration 15.7 mol l^{-1}	-31.3
HNO_3	1 M in D_2O	-6.2

^aThe ^{15}N of the NO_3 group.

The ^{15}N chemical shift scale is about two times larger than that of ^{13}C . Figure 12.5 gives an overview with approximate regions for different structural elements. Table 12.5 and the following text supplement this information with rounded-off δ -values for selected nitrogen compounds of different structure.

As in carbon-13 NMR, *saturated systems* yield signals at low frequency and substitution by electronegative elements shifts these resonances into the positive

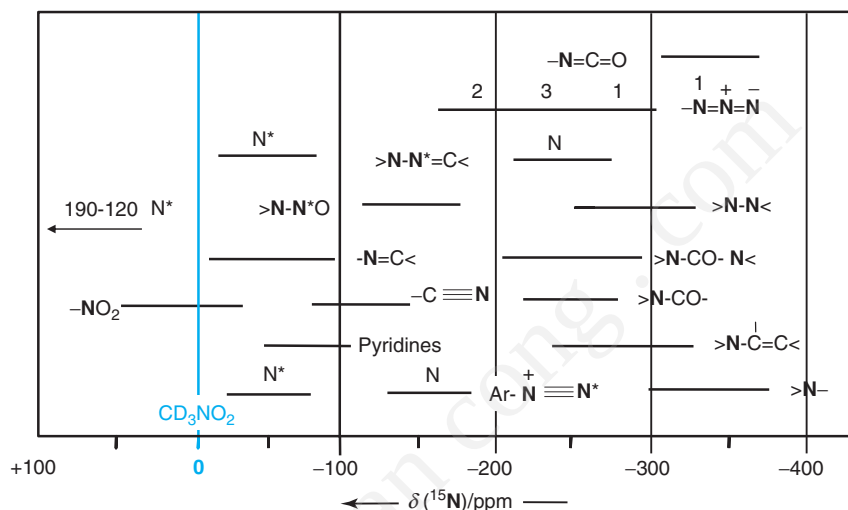
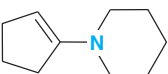
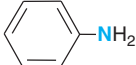
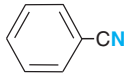
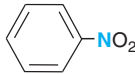
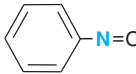


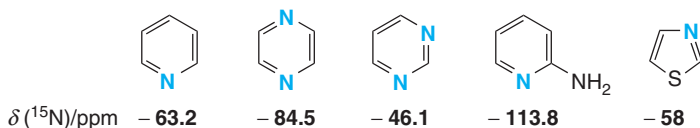
Figure 12.5 ^{15}N chemical shift diagram for organic compounds. Data from Reference [7].

Table 12.5 $\delta(^{15}\text{N})$ values for selected nitrogen compounds (ppm relative to CH_3NO_2).

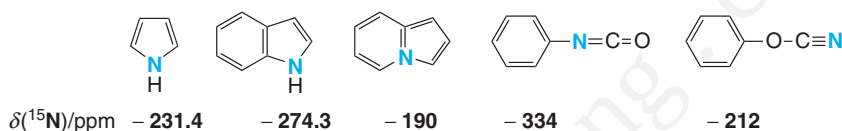
CH_3NH_2 -377	$(\text{CH}_3)_2\text{NH}$ -370	$(\text{CH}_3)_3\text{N}$ -363	 -353	 -343
 -340	 -313	 -320	$\text{H}_2\text{N}-\text{NH}_2$ -335	
CH_3-CN -137	 -122	 -10	 532	
$\text{H}_3\text{C}-\text{CH}(\text{NH}_2)\text{COOH}$ -331	H_3CCONH_2 -270	$\text{HCONHC}_6\text{H}_5$ -242	$(\text{H}_3\text{C})_2\text{N}-\text{N}=\text{O}$ -147 156	

Data from Reference [7].

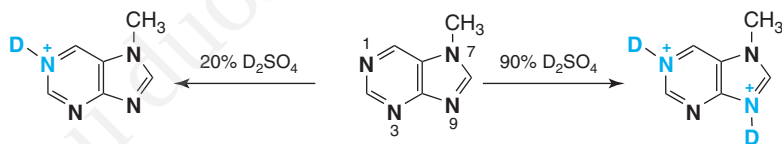
region of the δ -scale at higher frequency. Nitro group resonances are thus found around 0 ppm and extreme δ -values of over +100 ppm are observed for the nitroso nitrogen in nitrosamines; nitrile resonances are found near -100 ppm and nitrogens in aromatic amines are expected in the region of -50 to -120 ppm:



In enamine structures the ^{15}N resonance is again shielded, and even more in isocyanates (δ -values are more negative than -300 ppm); the latter can easily be distinguished from cyanate resonances, which are found around -200 ppm:



Owing to its free electron pair, nitrogen is subject to coordination with solvents and acids and the ^{15}N chemical shifts are solvent dependent. Especially, protonation leads to large shifts and allows the investigation of protonation sequences in nitrogen heterocycles. As an example Figure 12.6 (p. 444) shows the chemical shift changes observed for 7-methylpurine by changing the solvent from D_2O to various concentrations of D_2SO_4 . The *shielding* of N1 in 20% D_2SO_4 indicates addition of a deuteron in the six-membered ring and that of N9 in 90% D_2SO_4 a second addition in the five-membered ring:



This contrasts with the *deshielding* of the carbon-13 resonance in carbenium ions and may be caused by an increase of σ_d and/or a decrease of σ_p [larger ΔE -term in Eq. 11.11 (p. 410) due to replacement of $n \rightarrow \pi^*$, σ^* by $\sigma \rightarrow \pi^*$, σ^* transitions]. Furthermore, coordination with metal salts leads to ^{15}N association shifts that indicate the position and magnitude of the interaction. An example is shown in Figure 12.7 (p. 444).

Dynamic processes like ring inversion or hindered rotation can also be detected in compounds with appropriate nitrogen substitution and the NH tautomerism that is observed in many nitrogen heterocycles was studied by proton as well as ^{15}N NMR. At room temperature it averages the chemical shift of the sp^2 - and sp^3 -bonded nitrogen:

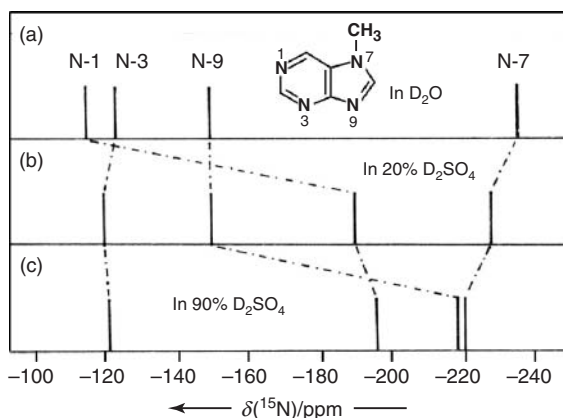


Figure 12.6 (a)–(c) ^{15}N NMR detection of the “protonation” sequence in 7-methylpurine, external reference $\text{CD}_3^{15}\text{NO}_3$; the shielding shifts for the deuterated nitrogens are $\Delta\delta(^{15}\text{N}1) = 74.8$ and $\Delta\delta(^{15}\text{N}9) = 68.2$ ppm [8].

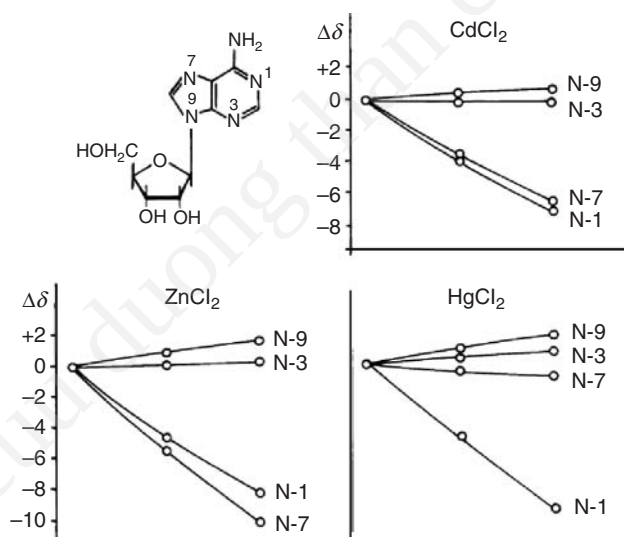
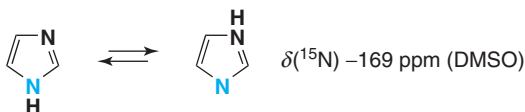


Figure 12.7 ^{15}N NMR study of the interaction between adenosine and various metal salts in DMSO; the shifts $\Delta\delta$ (ppm) show the changes in shielding relative to the ^{15}N resonances in the free nucleoside at 0.5 and 1.0 mol equivalent of metal salt. While for CdCl_2 and ZnCl_2 shielding of N1 and N7 is observed, HgCl_2 affects

primarily only N1. Small deshielding effects, indicating withdrawal of charge, are found in all cases for N9, while N3, which resides in the stable conformation of adenosine above the ribose ring, seems to be sterically shielded against attack [6] (Copyright 1984; with kind permission of Springer Science+Business Media).

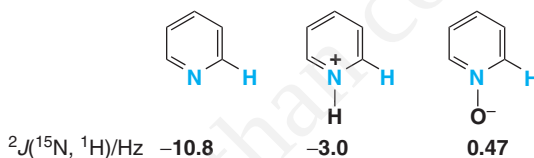


12.1.2.2 Spin-Spin Coupling

From the various nitrogen *coupling constants* the one-bond $^{15}\text{N}, ^1\text{H}$ couplings are those with the largest magnitude. Because of the negative γ -factor of ^{15}N they are of negative sign. They reach from -61 Hz for NH_3 to -98 Hz in octaethylporphyrin and their magnitude increases at positively charged nitrogens. As for $^{13}\text{C}, ^1\text{H}$ coupling constants a correlation with the s -character of the X-H bond was found:

$$s(i)(\%) = 0.43 |^1J(^{15}\text{N}, ^1\text{H})| - 6.00 \quad (12.8)$$

Geminal $^{15}\text{N}, ^1\text{H}$ couplings are one magnitude smaller, in heterocycles around -10 Hz . For N-CH_3 groups they drop to about -1.5 Hz , which has the consequence that INEPT spectra have to be optimized for the detection of N-CH_3 or $=\text{N-CH=}$ resonances. These couplings are also sensitive to nitrogen protonation or substitution, as the following observations show:



The usefulness of a *Karplus-type* relation between vicinal coupling constants and dihedral angles has also been established for $^3J(^{15}\text{N}, ^1\text{H})$ values, especially in peptides and proteins. This aspect will be discussed in more detail in Chapter 15. *Long-range* $^{15}\text{N}, ^1\text{H}$ couplings are generally smaller than 3 Hz , but quite a number of $^{15}\text{N}, \text{X}$ couplings with $\text{X} = ^{13}\text{C}, ^{15}\text{N}, ^{29}\text{Si}$, or ^{31}P have been observed.

12.1.3

Oxygen-17

Because of its very low natural abundance (0.037%), a nuclear spin of $I = \frac{5}{2}$, and a relatively large quadrupole moment, oxygen-17, the only magnetic oxygen isotope, is a difficult nucleus for routine NMR investigations. Isotopic enrichment of ^{17}O has thus quite often been used for NMR studies if synthetic routes for $^{16}\text{O}/^{17}\text{O}$ exchange with ^{17}O enriched water are available. Nevertheless, its broad occurrence makes it an interesting probe for various aspects of chemical and biochemical structure and the results of ^{17}O NMR often pay for the extra experimental effort that has to be invested. Of course, FT NMR has allowed an increasing number of studies and an extended knowledge of ^{17}O chemical shifts in functional groups has been accumulated (Figure 12.8, p. 446). The short relaxation times lead to broad resonance lines (up to about 300 Hz , and in special cases of fast relaxing nuclei

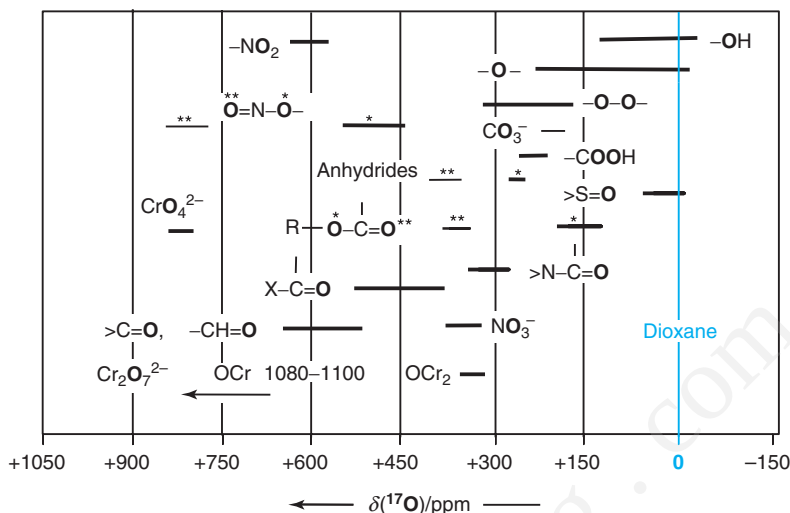


Figure 12.8 ^{17}O chemical shift diagram for functional groups. Data from Reference [9].

in viscous solutions even up to 1 kHz), but spectral accumulation is facilitated by high pulse repetition rates that are possible because of the short relaxation times. Large numbers of transients (100 000 or more) can thus be acquired.

The low resonance frequency (54.248 MHz for ^{17}O at a 400 MHz spectrometer) and low natural abundance quite often result in so-called *acoustic ringing* and a strong distortion of the base line. This lasts for about 100 μs and originates from mechanical vibrations of the probe head. It can be removed by skipping the first 100 data points or so of the FID using a pre-acquisition delay – at the cost, however, of phase distortions – or simply by a left shift of the FID. These techniques also eliminate broad solvent lines with short T_2 . A better solution results from the use of the *ring down elimination* (RIDE) pulse sequence (Figure 12.9). This technique is also employed for NMR of other quadrupole nuclei, such as sulfur-33.

Exercise 12.2

Draw vector diagrams for the RIDE sequence. Please note that the magnetization is relaxed at the end of each acquisition period pointing along the positive z-axis.

12.1.3.1 Referencing and Chemical Shifts

The ^{17}O chemical shift scale extends over about 700 ppm for the most prominent organic compounds (Figure 12.9), but larger values are found for some transition metal complexes or oxo- and polyoxo anions of molybdenum, vanadium, and other transition metals (>700 ppm). Dioxane, which has nearly the same $\delta(^{17}\text{O})$ value as H_2O , is recommended as external reference, using susceptibility corrections. As in the case of ^{15}N , a prominent area of ^{17}O NMR studies is the pH dependence of

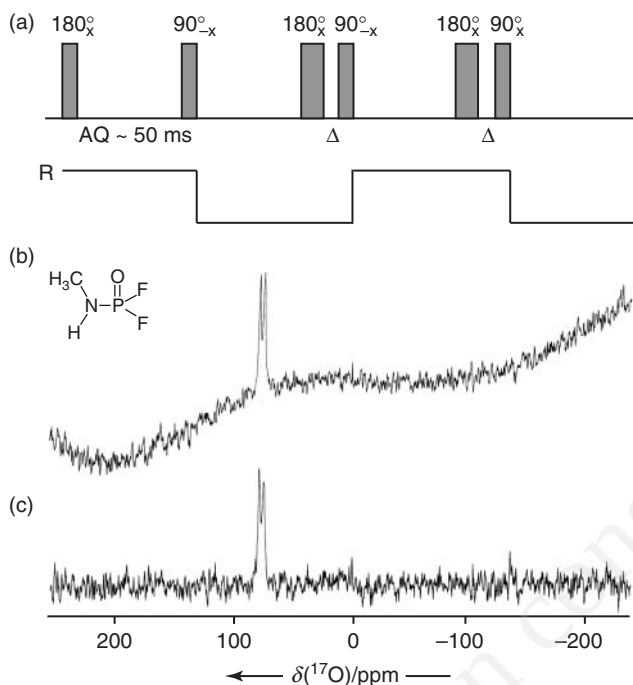


Figure 12.9 RIDE technique for the elimination of effects from acoustic ringing: (a) pulse sequence; the phase cycle for the receiver eliminates the signal of the artifact that is always positive; AQ: acquisition period; R: receiver phase; Δ : short delay for switching the pulse phase; (b) normal ^{17}O spectrum of *N*-methyl-difluorophosphonic acid amide, $\text{H}_3\text{CNHP}(\text{O})\text{F}_2$; (c) the same spectrum measured with the RIDE sequence [$J(\text{P},\text{O}) = 156.3$ Hz] [9] (With permission from G. Thieme Verlag, Stuttgart. Copyright 1992.)

the ^{17}O resonance. In addition, ^{17}O isotope shifts induced by deuterium have been used in the elucidation of biological pathways. *Spin-spin coupling* is difficult to measure and has only been observed for $^{17}\text{O},\text{X}$ interactions – practically exclusively over one bond – and in cases with relatively long relaxation times. Values range from 16 Hz ($^{13}\text{C}^{17}\text{O}$) through 79 Hz ($^1\text{H}_2^{17}\text{O}$) to 424 Hz ($^{19}\text{F}_2^{17}\text{O}_2$).

12.1.4

Fluorine-19

With 100% natural abundance and a γ -factor nearly as large as that of the proton and therefore close in resonance frequency, the ^{19}F nucleus was one of the early nuclei to be investigated by NMR, even if less important than the proton because of the more restricted number of fluorine compounds. Nevertheless, many molecules containing fluorine are found in organic and inorganic chemistry and some are used as probes in systems with biological importance, leading to a general interest in ^{19}F NMR.

12.1.4.1 Referencing and Chemical Shifts

Chemically inert trichlorofluoromethane, CFCl_3 , with its resonance signal at high frequency is used as internal reference compound. The *chemical shift* scale of ^{19}F is large and extends over nearly 2500 ppm as the data of small, predominantly inorganic fluorides collected in Table 12.6 show. The signals of organic fluorine compounds are found in a smaller range of about 350 ppm, mostly at negative δ -values (Figure 12.10). Reference compounds other than CFCl_3 are frequently used and chemical shift data have to be converted (CF_3COOH -76.6 ppm; C_6F_6 -163 ppm). Because ^{19}F resonances are more strongly influenced by solvent effects than those of ^1H , experimental errors of 5 ppm or more are not unusual.

As in other cases, the large range of $\delta(^{19}\text{F})$ values is again a consequence of the dominance of the paramagnetic contribution to the shielding constant. Diamagnetic contributions are very small ($\sim 1\%$) and neighboring group effects,

Table 12.6 $\delta(^{19}\text{F})$ values of selected fluorides (ppm relative to CFCl_3).

Compound	δ (ppm)	Compound	δ (ppm)	Compound	δ (ppm)
CH_2F_2	-1436	SbF_5	-108	IF_7	170
ClF	-420	AsF_5	-66	ClF_5	247; 412
MoF_6	-278	TeF_6	-57	XeF_2	258
CH_3F	-272	CF_2Cl_2	-8	ReF_7	345
SiF_4	-164	CFBr_3	7	XeF_4	438
C_6F_6	-163	SeF_6	55	XeF_6	550
BF_3	-131	WF_6	166	PtF_6	966

Data from Reference [3b, 9].

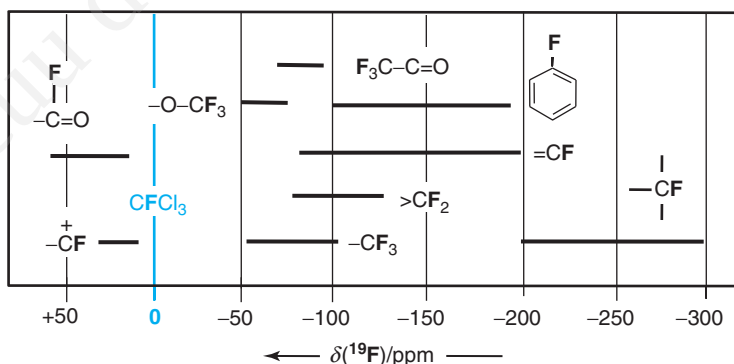


Figure 12.10 ^{19}F chemical shift diagram for organic fluorine compounds. Data from Reference [9].

like ring current effects or local magnetic anisotropies, play virtually no role. The extensive ^{19}F shifts can cause experimental problems for FT measurements at high fields provided by superconducting magnets because the pulse power may not be sufficient to excite all parts of the spectrum equally. Separate measurements for small regions are then necessary.

The ^{19}F NMR spectra of organic fluorine compounds are thus characterized not only by large chemical shifts but also by strong spin–spin interactions of the ^{19}F , ^{19}F and ^{19}F , ^1H type. This leads frequently to a considerable number of signals. The partial ^{19}F NMR spectra of 1*H*,1*H*,4*H*-heptafluorobutane and 4*H*-heptafluorobut-1-ene, shown in Figure 12.11, serve as a good demonstration of this effect. Many ^{19}F NMR spectra can be analyzed by first-order rules, especially if high-field instruments are used.

Turning to the structural dependence of $\delta(^{19}\text{F})$ in organic fluorine compounds we find in Figure 12.10 for *saturated* systems a definite gradation in the series CF_3 , CF_2 , CF with $\delta(^{19}\text{F})$ for the tertiary compound at lowest frequency. Increasing substitution by fluorine obviously reduces the ionic character of the C–F bond and therefore the F^- character at the ^{19}F nucleus. Notably, in the selection given in Table 12.7 (p. 451), in contrast to ^1H NMR, the ^{19}F chemical shifts for fluorine at *saturated* and *unsaturated* carbon, that is, the ^{19}F shifts in *aliphatic* and *aromatic* or *olefinic* fluorine compounds, overlap extensively (see also Figure 12.10, p. 448). The ^{19}F resonances of fluorocarocations are strongly deshielded.

Similar to ^1H NMR of hydrogen halides there is a correlation of $\delta(^{19}\text{F})$ with the electronegativity E of neighboring atoms that shows deshielding (high-frequency shifts) with increasing electronegativity:

	BF_3	CF_4	NF_3	SiF_4	PF_3	ClF_3
$\delta(^{19}\text{F})$ (ppm)	–129	–64	–142	–164	–34	83
E	2.0	2.5	3.0	1.8	2.1	3.0

On the other hand, and contrary to $\delta(^1\text{H})$ in methyl halides, halogen substituents at a CF_3 group lead to the opposite trend: shielding (low-frequency shifts) with increasing electronegativity:

	$\text{CF}_3\text{--I}$	$\text{CF}_3\text{--Br}$	$\text{CF}_3\text{--Cl}$	$\text{CF}_3\text{--F}$
$\delta(^{19}\text{F})$ (ppm)	–5	–21	–33	–64
E	2.5	2.8	3.0	4.0

This may result from a reduced paramagnetic contribution to $\delta(^{19}\text{F})$ in the order $\text{I} < \text{Br} < \text{Cl} < \text{F}$, where electron excitation becomes more difficult and the ΔE

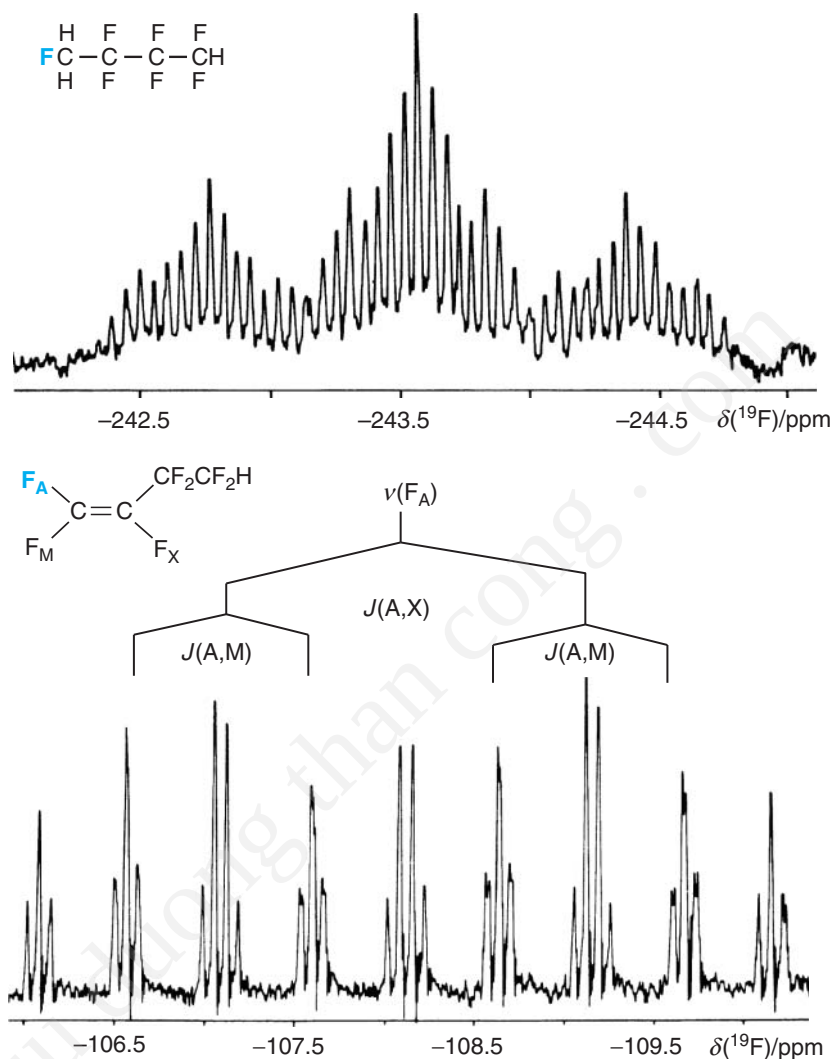
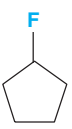
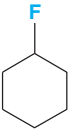
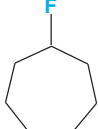
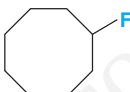
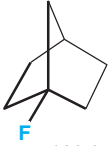
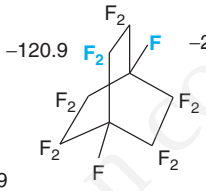
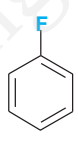
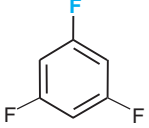
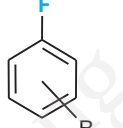
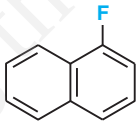
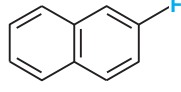
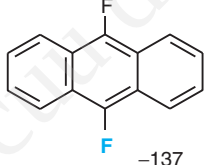
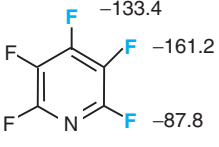
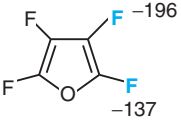


Figure 12.11 Sections from the ^{19}F spectra of 1H,1H,4H-heptafluorobutane and 4H-heptafluorobut-1-ene: ^{19}F resonance of (a) the CH_2F group and (b) F_A . Line splittings not assigned arise from further coupling to CF_2 groups (a, b) and ^1H (b) [10].

contribution to σ_p increases. For protons, on the other hand, the charge density effect dominates.

The deshielding of ^{19}F in the CF_3 groups of perfluoroneopentane as compared to perfluoro-*t*-butyl fluoride can be explained by the effect of steric crowding. The same applies to the series of *o*-halofluorobenzenes with F, Cl, Br, and I as neighboring groups with increasing van-der-Waals radii, r_vdW (p. 452).

Table 12.7 $\delta(^{19}\text{F})$ values of selected organic fluorine compounds (ppm relative to CFCl_3).

CH_3F	-268	Perfluorocyclopropane	-151
$\text{CH}_3\text{CH}_2\text{F}$	-211	Perfluorocyclobutane	} ~-133
$\text{C}_6\text{H}_5\text{CH}_2\text{F}$	-207	- pentane	
		- hexane	
	-218.0		-160.2
	-170.5		-174.2
			-164.9
			-160.2
	-182.0		-158.9
			-120.9
			-113.1
	-107.6		-106 ... -139
			-123.5
			-114.8
	-137		-133.4
			-161.2
			-87.8
$(\text{C}_6\text{H}_5)_2\text{CF}_2$	-88.5	$\text{C}_6\text{H}_5\text{CF}_2\text{Cl}$	-49.4
$(\text{C}_6\text{H}_5)_2\text{C}^+\text{F}$	+11.5	$\text{C}_6\text{H}_5\text{C}^+\text{F}_2$	+12.0
			-196
			-137

Data from Reference [9, 10].

For the ^{19}F resonances in *aromatic* fluorine compounds, linear correlations with Hammett σ -substituent constants, separated after Taft into contributions from inductive and resonance effects ($\sigma = \sigma_I + \sigma_R$), exist for fluorine at the *meta*- and *para*-position:

$$\delta(^{19}\text{F})_m = -(5.83 \pm 0.26)\sigma_I + 0.2 \quad (12.9)$$

$$\delta(^{19}\text{F})_p = -5.83\sigma_I - (18.80 \pm 0.81)\sigma_R + 0.8 \quad (12.10)$$

These equations also hold for 3,4- and 3,5-disubstituted systems and can be used to predict ^{19}F chemical shifts. In case of *ortho* substituents additional steric effects must be considered.

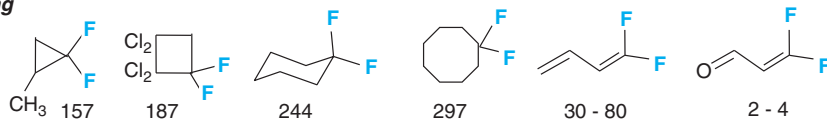
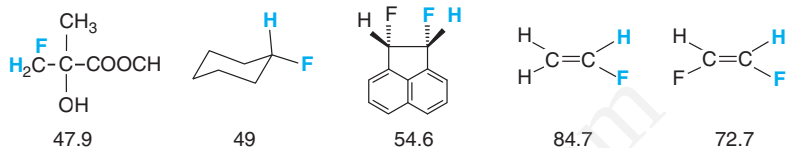
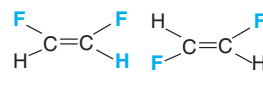
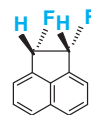
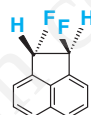
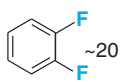
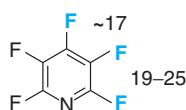
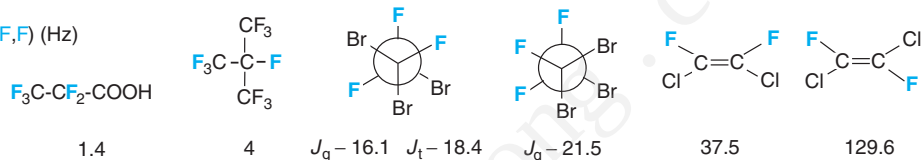
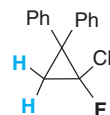
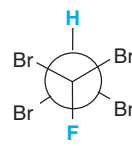
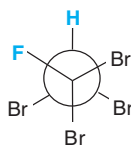
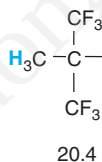
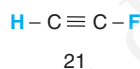
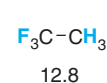
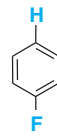
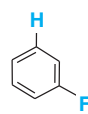
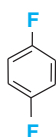
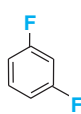
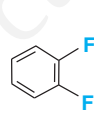
Finally, the large ^{19}F chemical shifts allow one to differentiate between OH groups of different type if esterification with trifluoroacetic acid is used because the shifts of the resulting trifluoroacetate residues vary sufficiently.

12.1.4.2 Spin-Spin Coupling

Just as the ^{19}F chemical shifts are larger than those of the proton, the scalar *spin-spin interactions* of fluorine nuclei are also larger than the corresponding interactions between protons. This is true for one-bond $\text{X}, ^{19}\text{F}$ ($\text{X} = ^1\text{H}, ^{13}\text{C}, ^{15}\text{N}$, etc.), and $^{19}\text{F}, ^{19}\text{F}$ couplings. Table 12.8 presents a general survey of geminal, vicinal, and long-range $^{19}\text{F}, ^{19}\text{F}$ and $^1\text{H}, ^{19}\text{F}$ coupling constants in organic compounds. Only in a few cases is the experimentally determined sign of the spin-spin interaction given.

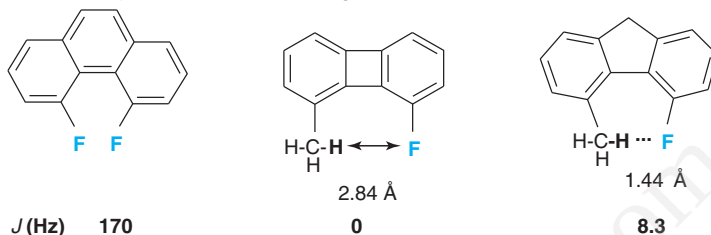
In organic compounds, the largest values for *homonuclear* ^{19}F couplings are observed for geminal interactions. These coupling constants may be as large as 300 Hz and they have a positive sign. In open-chain systems they are larger than in cyclopropanes, and here, in turn, they are larger than in olefinic CF_2 groups. Vicinal coupling constants span a wide range and may have either positive or negative signs. The rule $J_{\text{trans}} > J_{\text{cis}}$ at the double bond also holds for $^{19}\text{F}, ^{19}\text{F}$ and $^1\text{H}, ^{19}\text{F}$ couplings. In perfluoro aromatics, the ranges of magnitudes for *ortho*, *meta*, and *para* couplings overlap and for all three coupling pathways values between 5 and 20 Hz are found. Evidently, structural assignments cannot always be made in these cases on the basis of $^{19}\text{F}, ^{19}\text{F}$ or $^1\text{H}, ^{19}\text{F}$ couplings alone.

Representative values for $^1\text{H}, ^{19}\text{F}$ coupling constants are also shown in Table 12.8. The geminal interactions in these cases are smaller in magnitude (about 50 ± 10 Hz) than the $^{19}\text{F}, ^{19}\text{F}$ couplings. For vicinal $^1\text{H}, ^{19}\text{F}$ coupling constants various *Karplus-type* relations with the dihedral $\text{H}-\text{C}-\text{C}-\text{F}$ angle have been derived from experimental and theoretical investigations for different classes of compounds.

Table 12.8 ^{19}F , ^{19}F and ^{19}F , ^1H coupling constants in organic compounds (in hertz).**Geminal coupling** $^2J(\text{F},\text{F})$ (Hz) $^2J(\text{H},\text{F})$ (Hz)**Vicinal coupling** $^3J(\text{F},\text{F})$ (Hz) $^3J(\text{H},\text{F})$ (Hz)**Long-range coupling**

Data from Reference [9, 10].

The rules derived for ^1H , ^1H spin–spin interactions cannot be applied in all cases to ^{19}F couplings because here an additional mechanism, through-space coupling (cf. p. 143), often operates. This interaction is not based on the dipolar mechanism, but rather a through-space effect via close contact of non-bonding orbitals. It has been supported by experimental findings also for ^1H , ^{19}F spin–spin interactions:



12.1.5

Silicon-29

From the three isotopes of silicon with atomic numbers 28, 29, and 30 only ^{29}Si has a magnetic moment. It has the lowest natural abundance (4.70%), a spin $I = \frac{1}{2}$ and a negative gyromagnetic ratio γ . Thus, as with ^{15}N , the NOE is negative and may lead to signal loss. In addition, relative long spin–lattice relaxation times of 10 to several hundred seconds make the ^{29}Si nucleus unfavorable for direct measurements. The use of relaxation reagents like $\text{Cr}(\text{acac})_3$ (cf. p. 243) has several drawbacks, including its possible reaction with silicon compounds. ^{29}Si NMR spectra in solution may thus be best obtained using the DEPT or INEPT pulse sequences.

12.1.5.1 Referencing and Chemical Shifts

Quite naturally, TMS is used in ^{29}Si NMR as reference compound. It has however the disadvantage that its resonance appears within the region of other silicon compounds, that is, it is not well separated as it is in ^1H and ^{13}C NMR. The usual practice, therefore, is to calibrate the spectrometer to TMS in a separate experiment, using the spectrometer frequency for the measurement of interest. In solids, ^{29}Si NMR spectra are mostly referenced to the signal of $[(\text{CH}_3)_3\text{SiO}]_4\text{Si}$, a tetrasiloxane abbreviated as M_4Q [$\text{M} = (\text{CH}_3)_3\text{SiO}_{1/2}$ and $\text{Q} = \text{Si}(\text{O}_{1/2})_4$].

On the TMS scale, ^{29}Si chemical shifts in solution span a range from about +70 to –200 ppm (Figure 12.12). Except for the silicate anions, the various regions overlap fairly strongly.

Table 12.9 shows the effect of substituents. Substitution of methyl groups in TMS by halogens or alkoxy groups leads first to deshielding and with three and four substitutions to increased shielding (Figure 12.13, p. 456). This parabola-like or U-shaped behavior is also called *sagging behavior*. It is found for various other substituents and has been observed also in ^{119}Sn NMR (see below). A similar relation was observed between $\delta(^{29}\text{Si})$ and the sum of the substituent electronegativity, ΣE , in $\text{SiR}_1\text{R}_2\text{R}_3\text{R}_4$ compounds with extreme values of –80 and –120 ppm at $\Sigma E \sim 8$ and 16, respectively, and a minimum around +30 ppm and $\Sigma E \sim 11$. Double-bonded silicon is strongly deshielded with δ -values between 50 and 95 ppm. In

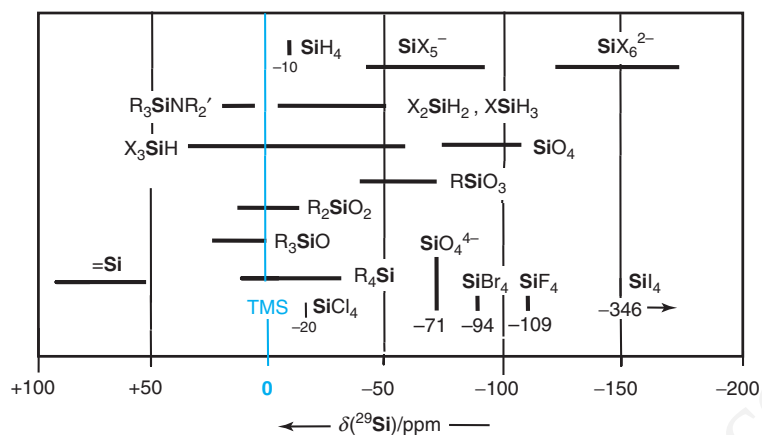


Figure 12.12 ^{29}Si chemical shift diagram. Data from Reference [11].

Table 12.9 $\delta(^{29}\text{Si})$ values of silanes (ppm relative to TMS).

Methylsilanes $(\text{CH}_3)_{4-n}\text{SiX}_n$					
		<i>n</i>			
X		1	2	3	4
F		35.4	8.8	-51.8	-109.0
Cl		30.2	32.2	12.5	-18.5
Br		26.4	19.9	-18.2	-93.6
I		8.7	-33.7	-18.0	-346.2
H		-18.5	-41.5	-65.2	-93.1
OCH ₃		17.2	-2.5	-41.4	-79.2
OC ₂ H ₅		13.5	-6.1	-44.5	-82.6
OC ₆ H ₅		17.2	-6.1	-54.0	-101.1
OC(O)CH ₃		22.3	4.4	-42.7	-74.5
OSi(CH ₃) ₃		6.9	-21.5	-65.0	-105.2
N(CH ₃) ₂		5.9	-1.7	-17.5	-28.1
C ₂ H ₅		1.6	4.6	6.5	8.4
C ₆ H ₅		-5.1	-9.4	-11.9	—
CH=CH ₂		6.8	-13.7	-20.6	-22.5

$\text{Y}_{4-n}\text{SiX}_n$ compounds						
		<i>n</i>				
X	Y	0	1	2	3	4
F	Cl	-18.7	-32.1	-55.0	-81.7	-109.0
F	Br	-93.6	-67.0	-67.4	-82.4	-109.0
F	C ₆ H ₅	—	-4.7	29.1	-72.7	-109.0
H	C ₆ H ₅	—	-21.1	-34.5	61.5	—

Data from Reference [12].

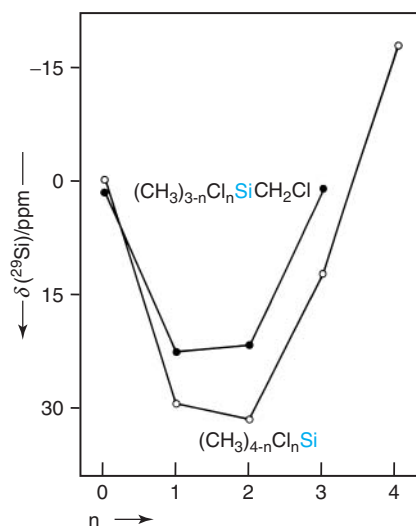


Figure 12.13 Dependence of $\delta(^{29}Si)$ on multiple substitution. (Reprinted from Reference [12]; Copyright 1971. With permission from Elsevier).

contrast, higher coordination numbers (C.N.s) lead to shielding, with low frequency shifts well over -100 ppm. Silylation of hydroxy groups in organic compounds with trimethylsilyl residues is often used to avoid proton exchange for OH or NH groups. In these derivatives the spread of chemical shift is usually only 0.5 ppm for ^1H or 5 ppm for ^{13}C , but it is 40 ppm for ^{29}Si , an advantage that facilitates structural assignments. In cyclic silyl compounds, ^{29}Si in three-membered rings is less shielded than in larger rings, contrary to ^1H and ^{13}C NMR; $\delta(^{29}Si)$ values are about -9 and -22 ppm, respectively. Data for a few other compounds are collected in Table 12.10.

A large area of applications for ^{29}Si NMR, in solution as well as in the solid, is provided by the chemistry of polysiloxanes and silicates where a great variety of structures exist. The chemical shifts for polysiloxanes span a range between 10 and -110 ppm on the TMS scale, while those of silicates in solution are found between

Table 12.10 $\delta(^{29}Si)$ values for selected silicon compounds (ppm relative to TMS).

SiF_6^{2-}	$PhSiH_3$	$(CH_3)_3SiCNCO$	$(CH_3)_2SiH_2$	$Si(CH=CH_2)_4$
-192	-160	-59	-37	-30
$(CH_3)_3SiCN$	$N(SiH_3)_3$	$H_3SiCNCO$	$(CH_3)_3SiC \equiv CSi(CH_3)_3$	$(CH_3)_3SiHCl_2$
-12	-40	+8	+19	+32
$(CH_3)_2Si-Si(CH_3)_2$	$R_1 = alkyl; R_2 = SiR_3$  			
-22	-87...-106			

Data from References [11, 12].

–80 and –95 ppm. In addition, a huge amount of structural information has been obtained for solid silicates by applying various techniques of solid state NMR and this aspect will be mentioned briefly in Chapter 14.

12.1.5.2 Spin-Spin Coupling

As for other nuclei with low natural abundance, homonuclear coupling and coupling to rare spins (^{15}N , ^{13}C) is seen in ^{29}Si NMR spectra only by satellite signals (Figure 12.14) or after isotopic substitution. On the other hand, abundant NMR active isotopes with spin $\frac{1}{2}$ give rise to the well-known splitting patterns.

Table 12.11 (p. 458) presents a survey of the ranges observed for one-bond ^{29}Si coupling constants with various elements. The largest values are observed for couplings with hydrogen, fluorine, and phosphorus. Homonuclear ^{29}Si ^1J values can also be quite large. The geminal and vicinal couplings are in most cases one order of magnitude smaller, except for $^2J(^{29}\text{Si}, ^{19}\text{F})$ values, which have a range of 17–91 Hz.

The domination of the Fermi contact term for ^1J couplings leads to empirical linear correlations with the s-character, $s(i)$, of the corresponding Si bond orbital similar to the equations found for ^{13}C couplings, with, however, a dependence on the square of $s(i)$:

$$^1J(^{29}\text{Si}, ^1\text{H}) = 725s(i)^2 + 15.9 \quad (12.11)$$

$$^1J(^{29}\text{Si}, ^{13}\text{C}) = 555.4s(i)_\text{C}^2 \times s(i)_{\text{Si}}^2 + 18.2 \quad (12.12)$$

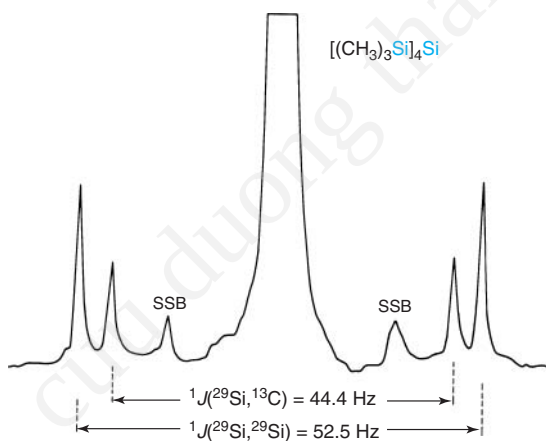


Figure 12.14 ^{29}Si resonance of the $(\text{CH}_3)_3\text{Si}$ group of tetrakis(trimethylsilyl)silane showing satellites due to one-bond $^{29}\text{Si}, ^{13}\text{C}$ and $^{29}\text{Si}, ^{29}\text{Si}$ coupling (SSB, spinning sidebands). From J.D. Cargioli and E.A. Williams, unpublished, cited in Reference [12]. (Reprinted from Reference [12]; Copyright 1971. With permission from Elsevier).

Exercise 12.3

Explain the relative signal heights of $\sim 3:4$ for the ^{13}C and ^{29}Si satellites.

Table 12.11 Ranges of selected one-bond ^{29}Si spin–spin coupling constants.

Type	Sign	Value (Hz)
$^1J(^{29}\text{Si}, ^1\text{H})$	–	75–420
$^1J(^{29}\text{Si}, ^{19}\text{F})$	+	108–488
$^1J(^{29}\text{Si}, ^{31}\text{P})$	+	16–256
$^1J(^{29}\text{Si}, ^{13}\text{C})$	–	37–113
$^1J(^{29}\text{Si}, ^{29}\text{Si})$		23–186

Data from Reference [11b].

12.1.6

Phosphorus-31

The spin $I = \frac{1}{2}$ nucleus ^{31}P has a natural abundance of 100% and high NMR sensitivity. No wonder then that ^{31}P NMR spectroscopy has as long a history as proton and fluorine-19 NMR. A huge number of investigations in solution and – after the introduction of MAS also in the solid phase – have established the usefulness of ^{31}P NMR in organic, organometallic, and inorganic chemistry, and the variety of structures is enormous. As one reviewer put it “the wealth of information is both blessing and an embarrassment to the worker in ^{31}P NMR” [13]. Accordingly, we limit our introduction to a few of the most important aspects.

12.1.6.1 Referencing and Chemical Shifts

^{31}P NMR spectra are usually referenced to external H_3PO_4 (85%) and the *chemical shift range* extends from about –500 to 600 ppm. Nevertheless, most compounds yield signals between –100 and +150 ppm and the situation with respect to the range of chemical shifts is thus similar as that for carbon-13 (Figure 12.15).

The great structural variety for phosphorus compounds originates from the fact that aside from P–X bonds ($\text{X} = \text{C}, \text{N}, \text{O}, \text{S}, \text{F}, \text{Cl}, \text{Br}$, etc.) phosphorus forms P–P bonds that give rise to cyclic and polycyclic compounds. In addition there are many compounds with phosphorus–metal bonds. Furthermore, we find P=P double bonds and double bonds with carbon, nitrogen, oxygen, and sulfur. Even triple bonds with carbon are observed and in general the coordination number (C.N.) of phosphorus, which varies from 1 to 6 with 3 and 4 as the most common, is an important factor. Approximate shift regions for most compounds (in ppm) are:

C.N. 2: 0 to 350,

C.N. 3: –200 to +250 [extreme values are –461 for P_4 and +245 for $\text{PF}_3(\text{CH}_3)_3$],

C.N. 4: –50 to +100 (extreme values are –315 for SPBrI_2 and +143 for $[\text{PF}(\text{CH}_3)_3]^+$),

C.N. 5: –100 to 0,

C.N. 6: –200 to –100.

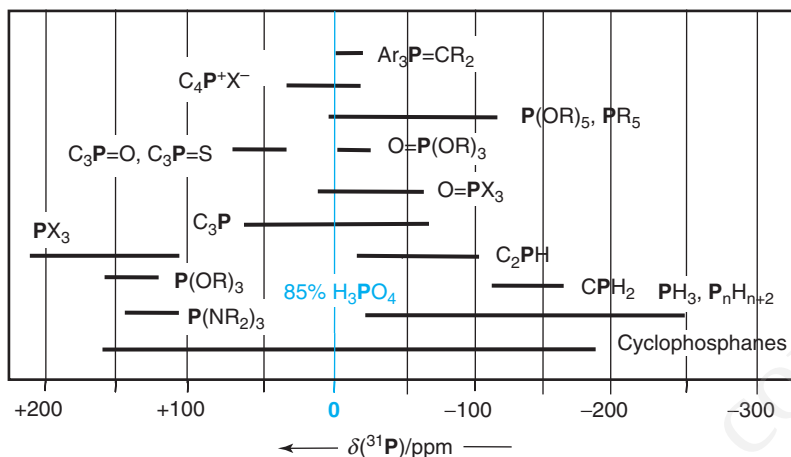


Figure 12.15 ^{31}P chemical shift diagram for phosphorus compounds. Data from Reference [14a].

The effect of the coordination number (C.N.) on $\delta(^{31}\text{P})$ is seen in Table 12.12, and Table 12.13 (p. 460) surveys the chemical shift ranges for different bonding situations. Tables 12.14 and 12.15 (p. 461) summarize the effect of charge and structure and of the C.N. Coordination with metal carbonyls $\text{M}(\text{CO})_5$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) and platinum dichloride (*cis*- PtCl_2L_2) shifts the resonances of the respective phosphorus ligands to higher frequency towards or into the positive δ -range. Simple correlations of $\delta(^{31}\text{P})$ with the electronegativity of substituents are lacking.

Phosphorus ligands are important constituents of transition metal complexes used for homogeneous catalysis. Complexation with phosphorus ligands leads to coordination shifts for the metal resonances that vary with the type of the metal fragment and the type of the phosphorus ligand. For phosphines that are relevant to applications in homogeneous catalysis ^{31}P resonances of the trivalent phosphorus ligands cover a range from about -50 to 200 ppm, with subregions depending on the type of $\text{P}-\text{X}$ bonds present ($\text{X} = \text{C}, \text{O}, \text{N}$; Figure 12.16, p. 460).

Table 12.12 Effect of the coordination number on ^{31}P chemical shifts.

Y	PY_3	PY_4^+	PY_5	PY_6^-
F	+97	—	−80	−145
Cl	+219	+87	−80	−295
Br	+227	—	−101	—
OC_2H_5	+139	−2.7	−71	—
C_6H_5	−6	+21	−89	−181
H	−238	−105	—	—

Data from Reference [13].

Table 12.13 ^{31}P chemical shift ranges for different bonding situations (ppm relative to H_3PO_4). Data from Reference [14b].

$\text{P}\equiv$	+100 ... -70		+140 ... -90
$\text{P}=\text{C}$	+950 ... -360		+220 ... -240
	+220 ... -290		+10 ... -80
$\text{P}=\text{C}=\text{C}$	+300 ... +40		80 ... -290

^{31}P NMR greatly assisted studies of phosphanes, cyclophosphanes, and polycyclophosphanes by 1D and 2D experiments because spectra are in many cases complicated by homonuclear ^{31}P , ^{31}P coupling as well as by heteronuclear ^{31}P , ^1H coupling. Quite often, low-temperature studies yielded information about the conformation. The results for diphosphanes showed the staggered conformations, gauche and trans, to be more stable than the eclipsed form:

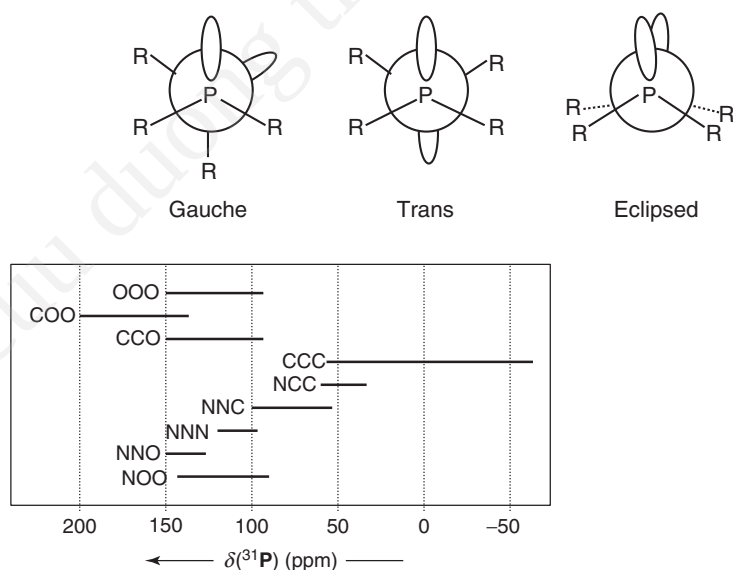
**Figure 12.16** Approximate chemical shift ranges for ^{31}P resonances of phosphines important for homogeneous catalysis. After Reference [15].

Table 12.14 Effect of charge and structure on ^{31}P chemical shifts (ppm).

P(OH)_4^+ −2.7	$\text{P(OCH}_3)_4^+$ +1.4	$\text{P(OC}_6\text{H}_5)_4^+$ −18	$\text{OP(OCH}_3)_3^+$ −2.4	$\text{OP(OC}_6\text{H}_5)_3^+$ −18
PH_3 −238	$\text{P(CH}_3)_3$ −62.2	$\text{P(C}_2\text{H}_5)_3$ −19.2	$\text{P(C}_6\text{H}_5)_5$ −5.4	$\text{P}(t\text{-C}_4\text{H}_9)_3$ +61.9
PH_4^+ −101	$\text{P(CH}_3)_3\text{H}^+$ −3.2	$\text{P(C}_2\text{H}_5)_3\text{H}^+$ +22.5	$\text{P(C}_6\text{H}_5)_5\text{H}^+$ +6.8	$\text{P}(t\text{-C}_4\text{H}_9)_3\text{H}^+$ +58.3
$\text{PO(SCH}_3)_3$ +66	$\text{PO(CH}_3)_3$ +36.2	POCl_3 +1.9	POClBr_2 −64.8	POBr_3 −103
$\text{PS(SCH}_3)_3$ +98	$\text{PO(CH}_3)_3$ +59.1	PSCl_3 +28.8	PSClBr_2 −61.4	POBr_3 −112

Data from Reference [13].

Table 12.15 Typical $\delta(^{31}\text{P})$ values (ppm) for three- and four-coordinated compounds.

Y	Br	Cl	OCH_3	SCH_3	$\text{N(CH}_3)_2$	F	NCS	$t\text{-(C}_4\text{H}_9)$	CF_3
PY_3	+227	+219	+141	+125	+122	+97	+86	+63	−2.6
POY_3	−103	+2	−2.4	+66	+23	−36	−62	−41	+2.3
PSY_3	−112	+29	+73	+98	+82	−35.5	−10	—	—
	C_6H_5	CH_3	$\text{C}\equiv\text{CH}$	C_6F_5	CN	H	Si CH_3	I	
PY_3	−6	−62	−91	−77	−136	−238	−330	+178	
POY_3	+25	+36	−56	−8	—	—	—	—	
PSY_3	+40	+59	—	−9	—	—	—	—	

Data from Reference [13].

For cyclic polyphosphanes an interesting correlation between $\delta(^{31}\text{P})$ and the internal P–P–P angle was found (Figure 12.17, p. 462).

12.1.6.2 Spin–Spin Coupling

Aside from ^{31}P , ^{31}P couplings, phosphorus-31 *spin–spin coupling* to other NMR active nuclei complicates ^{31}P NMR spectra. Depending on the natural abundance of the coupling partner, the extra lines range from intensive signals to satellite spectra. Splittings are usually large, for $^1J(^{31}\text{P}, ^{31}\text{P})$ about 100–300 Hz, and for $^2J(^{31}\text{P}, ^{31}\text{P})$ one order of magnitude smaller. An interesting and unique record is provided by ^{31}P , ^{199}Hg couplings over one bond that are as large as 17 000 Hz! In general, one-bond couplings to transition metals, for example, platinum, are >1 kHz and those to heavy nuclei like ^{77}Se or ^{125}Te are several hundred hertz, and often more than 1 or even 2 kHz. Of special interest are ^{31}P couplings with

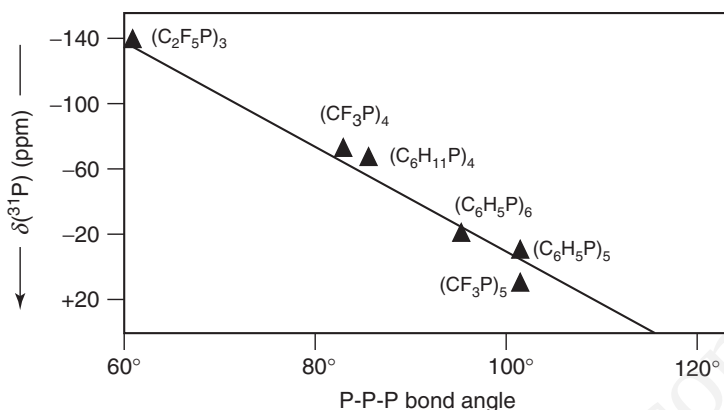


Figure 12.17 Dependence of $\delta(^{31}\text{P})$ for cyclic polyphosphanes on the *endo*-cyclic P-P-P bond angle [14a, 16].

transition metals like vanadium, cobalt, nickel, rhodium, tungsten, and platinum because of the important catalytic properties of phosphorus complexes of these metals or their carbonyl derivatives.

One-bond ^{31}P , ^{13}C couplings in organophosphorus compounds are often negative and range from about -40 to 150 Hz. Geminal interactions are not very much smaller, in some cases close to 40 Hz. For vicinal ^{31}P , ^{13}C couplings several *Karplus-type* curves have been empirically established for different classes of compounds.

Since the phosphate group is an essential building block in molecules with biological importance, such as adenosine diphosphate (ADP) and adenosine triphosphate (ATP) or the nucleic acids RNA and DNA, ^{31}P NMR is of great value for studies in biochemistry and biology. Other important biological or medical applications of ^{31}P NMR are the so-called *in vivo* experiments, where by monitoring the ^{31}P resonance of ADP or other prominent biomolecules the metabolism in living tissue or cell cultures can be studied. These aspects will be treated briefly in Chapter 15.

12.2

Main Group Metals

12.2.1

Lithium-6,7

Two lithium nuclides – ^6Li and ^7Li – are available for structural investigations by NMR spectroscopy (Tables 12.1 and 12.2). Both are quadrupolar nuclei but the quadrupole moment of ^6Li with spin 1 is the smallest known for all NMR active nuclei and ^6Li has been called humorously an “honorary spin $\frac{1}{2}$ nucleus.” The line width factor of ^6Li is smaller than that of ^7Li by 3 orders of magnitude. Thus, ^6Li is the nucleus of choice for high-resolution NMR studies because the low natural abundance can be counteracted through isotopic enrichment. The quadrupole

moment of ^7Li with spin $\frac{3}{2}$ leads to line broadening, even in solution, and ^7Li is used mainly for solid state studies, despite its better chemical shift resolution that is a consequence of its higher resonance frequency. For solid state NMR studies the larger quadrupole coupling constant of ^7Li can be an advantage.

Relaxation of the lithium nuclides is dominated by the quadrupolar mechanism for ^7Li but to a lesser extent for ^6Li , where a relatively large contribution from the dipolar mechanism exists. This is the basis for ^6Li nuclear Overhauser enhancements. The T_1 values for ^7Li are of the order of seconds, for ^6Li even tens of seconds. For the relaxation rate constants we have $R_{1q} \approx R_{2q}$ for ^7Li but $R_2 > R_1$ for ^6Li . For both nuclei, however, chemical exchange processes are quite common and the strongest contribution to R_2 will then originate from this source.

12.2.1.1 Referencing and Chemical Shifts

External references with 1.0 or 0.1 M solutions of lithium salts (LiCl , LiBr , LiClO_4) in H_2O or organic solvents like tetrahydrofuran are usually employed for high-resolution $^{6,7}\text{Li}$ NMR spectra. The *chemical shift* scale is rather small – about 2 ppm – and the δ -values are of limited value for structural investigations of aggregates (see Figure 12.18, p. 465). A different situation is found in π -complexes with cyclic conjugation, where ^6Li chemical shifts are affected by diamagnetic (shielding) or paramagnetic (deshielding) ring current effects. Table 12.16 (p. 464) gives representative δ -values.

Organolithium compounds, which play an important role in synthetic organic chemistry, are air- and moisture-sensitive, and their solutions, mostly in deuterated etherial solvents like $[\text{D}_{10}]$ diethyl ether or $[\text{D}_8]$ tetrahydrofuran, have to be handled under dry argon atmosphere. NMR tubes are thus dried and filled on the vacuum line and finally sealed. Alkyl and aryl lithium compounds form dimers, tetramers, or even higher aggregates in solution (Figure 12.18). At room temperature fast *inter*- and *intra*-aggregate exchange exists that averages the molecular environment of the lithium atoms and thus the $^{6,7}\text{Li}$ chemical shifts and coupling constants. Structural studies require, therefore, low-temperature measurements, usually below -50°C . The desired information then comes mainly from one-bond $^{6,7}\text{Li}, \text{X}$ coupling constants ($\text{X} = ^{13}\text{C}$, ^{15}N , ^{29}Si , ^{31}P) measured in the slow exchange limit of the NMR time scale. Homonuclear $^6\text{Li}, ^6\text{Li}$ as well as heteronuclear $^6\text{Li}, ^1\text{H}$ couplings are very small – usually less than 1 Hz – and hard to resolve. The success of ^6Li NMR investigations therefore rests mainly on the measurement of $^1J(^6\text{Li}, ^{13}\text{C})$ values and in addition on the use of many two-dimensional methods like shift correlations and heteronuclear Overhauser effect spectroscopy (HOESY) experiments that we introduced in Chapter 10 (p. 355). Cross relaxation between ^1H and ^6Li can be measured for several $^1\text{H}, ^6\text{Li}$ spin pairs with only one 2D experiment. Cross peaks are also observed between ^6Li and the protons of solvent molecules or of coordinated ligands.

12.2.1.2 Spin-Spin Coupling

Heteronuclear $^6\text{Li}, ^{13}\text{C}$ couplings over one bond are best measured from spin multiplets in ^{13}C spectra or from ^{13}C satellites in ^6Li spectra. Owing to the higher

Table 12.16 ^6Li chemical shifts of selected organolithium compounds.

Compound	Aggregation	$\delta(^6\text{Li})$ (ppm) ^a	Solvent
CH_3Li	—	1.32	Ether
$\text{C}_2\text{H}_5\text{Li}$	—	1.71	Cyclopentane
		1.00	Benzene
		0.6	Ether
$n\text{-C}_4\text{H}_9\text{Li}$	—	1.85	Cyclopentane
$(\text{CH}_3)_2\text{CHLi}$	—	1.17	Cyclopentane
$(\text{CH}_3)_3\text{Li}$	—	0.40	Toluene
		0.89	Cyclopentane
$\text{C}_6\text{H}_5\text{Li}$	—	1.2	Ether
$\text{C}_6\text{H}_5\text{Li}$	Dimer	1.52 ^b	Ether (−102°C)
	Tetramer	2.26	—
$\text{C}_6\text{H}_5\text{Li/TMEDA}$ (tetramethylethylenediamine)	Monomer	2.07 ^b	Ether (−111°C)
		2.32	—
Lithium salts of cyclic π -systems	n^c	$\delta(^6\text{Li})$ (ppm) ^a	Solvent
$[\text{Li}(\text{THF})_4][\text{LiOEP}]^d$	18	−16.5 ^e	$\text{C}_6\text{D}_6/\text{TMEDA}$
$[\text{Li}(\text{THF})_4][\text{LiOEP}]$	18	−11.55 ^f	DMSO
$[\text{CP-Li}^+-\text{CP}][\text{P}(\text{C}_6\text{H}_5)_4]^+$	6 + 6	−11.05	THF ^e
Cyclooctatetraene dianion	10	−8.55	—
Cyclopentadienide (CP)	6	−8.37	—
Biphenylene dianion	14	−6.10	—
Azulene dianion	12	+2.05	—
15,16-Dimethyldihydropyren dianion	16	+3.15	—
1,2,4,5-Tetrakis(trimethylsilyl) benzenide	8	+10.7	—

^aAt 25°C, relative to external 3 M aqueous LiBr.^bRelative to external 0.1 M LiBr in THF.^cNumber of π -electrons.^dOEP = octaethylporphyrin.^eRelative to external 0.3 M LiCl in MeOH.^fThis and all systems below in THF relative to external aqueous 1 M LiCl.

gyromagnetic ratio of lithium-7, ^7Li , X coupling constants are larger by a factor of $\gamma(^7\text{Li})/\gamma(^6\text{Li}) = 2.64$ than ^6Li , X coupling constants, but this advantage is very often annihilated by ^7Li quadrupole effects such as line broadening and partial decoupling. This applies in particular to the low-temperature measurements that are necessary to slow down the dynamic processes. In addition, one- or two-dimensional ^6Li , $^{13}\text{C}\{^1\text{H}\}$ HMQC experiments can be used, and examples of which are shown in Figures 12.19 and 12.20 (p. 466). The 1D version of the 2D HMQC experiment (Figure 12.19) can often be utilized to advantage because of the appreciable time saving that arises from the absence of an evolution time t_1 and the incrementation thereof.

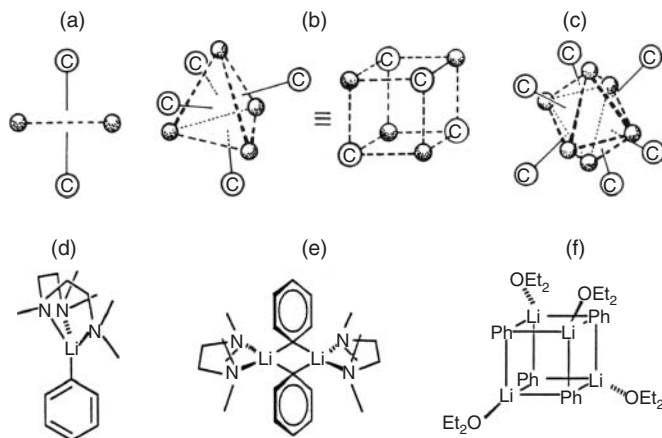


Figure 12.18 Schematic representation of organolithium aggregates: (a) dimer; (b) tetramer; (c) hexamer; shaded circles represent lithium atoms, circled carbons organic ligands; the negatively charged lithium atoms form polyhedra where the organic ligands occupy positions on polyhedron planes

with multiple bonding to the metal; (d)–(f) aggregates of phenyllithium: (d) monomer, stabilized by PMDTA (pentamethyldiethylenetriamine); (e) dimer, stabilized by TMEDA (tetramethylethylenediamine); (f) tetramer, stabilized by diethyl ether.

Exercise 12.4

Discuss the pulse sequence of Figure 12.19 with the help of vector pictures and the product operator formalism. Compare it also with the 2D experiment of Figure 11.11b (p. 391).

An empirical rule, Eq. (12.7) relates $^1J(^{6,7}\text{Li}, ^{13}\text{C})$ to n , the number of equivalently coupled lithium nuclei:

$$^1J(^{6,7}\text{Li}, ^{13}\text{C})_{\text{obs.}} \approx 17/n \text{ (Hz)} \quad \text{or} \quad ^1J(^7\text{Li}, ^{13}\text{C})_{\text{obs.}} \approx 45/n \text{ (Hz)} \quad (12.13)$$

Surprisingly, these relations are valid irrespective of the carbon hybridization. This was explained by results from *ab initio* calculations that showed that the product of the *s*-character and the covalent bond order is approximately constant for C–Li bonds in methyllithium, lithioethene, and lithioacetylene.

Static aggregates are characterized by coupling to next neighbors, while in *fluxional* aggregates remote nuclei are also involved (Figure 12.21, p. 467). Equation (12.13) leads to $^1J(^{6,7}\text{Li}, ^{13}\text{C})$ coupling constants of about 17 Hz for monomers, 8.5 Hz for dimers, and 5.7 Hz for tetramers and hexamers and drops to 4.3 and 2.8 Hz, respectively, for fluxional systems. $^1J(^{6,7}\text{Li}, ^{13}\text{C})$ has a positive sign, but coupling over more than one bond has not been observed and $^{6,7}\text{Li}, ^{13}\text{C}$ coupling is not found for

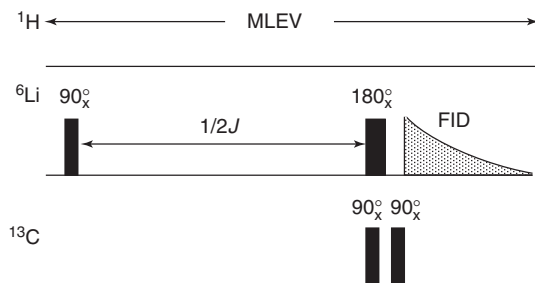


Figure 12.19 Pulse sequence of the one-dimensional HMQC experiment for the detection ^{13}C satellites in ^6Li spectra.

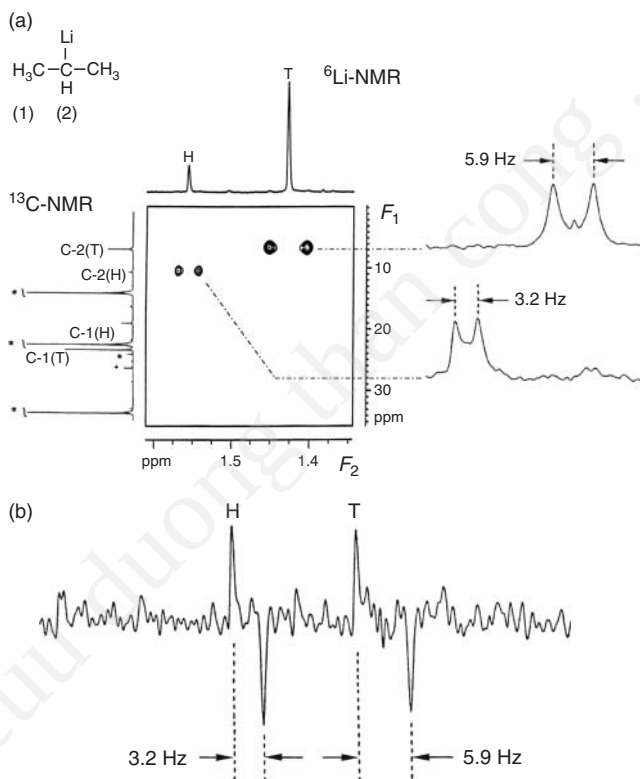


Figure 12.20 (a) Two-dimensional ^6Li detected $58.88/100.13$ $^{13}\text{C}, ^6\text{Li}\{^1\text{H}\}$ HMQC spectrum (magnitude mode) of isopropyllithium (1.4 M in pentane at -53°C) measured with the pulse sequence shown in Figure 11.11b (p. 391); experiment time 7 h; external projections 1D ^6Li (F_2) and ^{13}C (F_1) spectra; * solvent signals. External reference 0.1 M LiBr in THF; F_1 traces at 6.3 and 10.2 ppm show

the one-bond $^{13}\text{C}, ^6\text{Li}$ coupling for the tetramer (T) and hexamer (H), respectively. (b) Carbon-13 satellites due to scalar coupling $^1J(^{13}\text{C}, ^6\text{Li})$ in the ^6Li spectrum of the tetramer (T) and hexamer (H) of isopropyllithium; ^6Li detected $^{13}\text{C}, ^6\text{Li}\{^1\text{H}\}$ 1D-HMQC experiment (pulse sequence of Figure 12.19); experiment time 0.6 h [17].

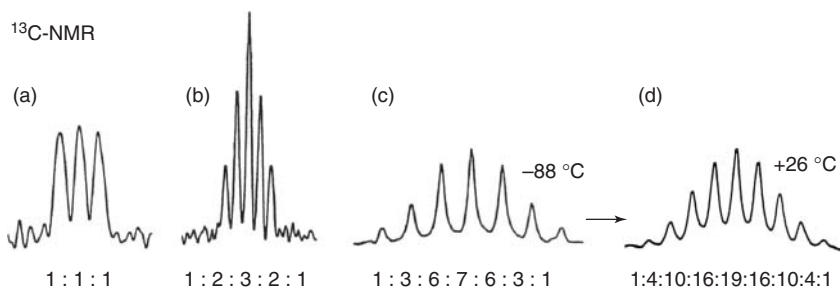


Figure 12.21 ^{13}C multiplets and their relative intensity distribution caused by scalar coupling to ^6Li : (a) monomer of phenyllithium; (b) dimer of *n*-butyllithium; (c) tetramer of *t*-butyllithium at -88°C ; (d) the signal of *t*-butyllithium at 26°C ; the coupling constants for (a)–(d) are 14.8, 7.9, 5.4, and 4.1 Hz, respectively. Please note that $I(^6\text{Li}) = 1$ and the multiplicity is given

by $2nI + 1$ with $n = 1$ for the monomer, $n = 2$ for the dimer, $n = 3$ for the static tetramer at low temperature, and $n = 4$ for the fluxional tetramer at RT. The signal intensities are obtained from the Pascal triangle for $I = 1$ (^6Li) or $I = \frac{3}{2}$ (^7Li), respectively (Appendix, p. 664) [17, 18] (in part reprinted with permission from [18]. Copyright 1986, American Chemical Society.)

organolithium compounds with π -bound lithium in π -complexes and for solvent separated ion pairs (SSIPs).

A relation similar to Eq. (12.13) exists for one-bond ^6Li , ^{15}N coupling constants:

$$^1J(^6\text{Li}, ^{15}\text{N})_{\text{obs.}} \sim 7/n \text{ (Hz)} \quad \text{or} \quad ^1J(^6\text{Li}, ^{15}\text{N})_{\text{obs.}} \sim 18.5/n \text{ (Hz)} \quad (12.14)$$

The small homonuclear ^6Li , ^6Li coupling constants (<1 Hz) are not resolved, but can be detected by ^6Li , ^6Li long-range COSY as well as ^6Li , ^6Li 1D INADEQUATE experiments (Figure 12.22, p. 468). It is then possible to decide if two ^6Li signals originate from the same or from two different aggregates. Larger coupling constants (up to 10 Hz) were found for ^6Li , ^1H interactions in lithium hydrido complexes.

Finally, we mention that numerous dynamic NMR studies using temperature-dependent line shape changes in ^{13}C or $^6/7\text{Li}$ spectra have been performed in order to measure the thermodynamic (ΔG°) and kinetic ($\Delta H^\ddagger$, $\Delta S^\ddagger$) parameters of the exchange processes associated with organolithium compounds. They may lead to coalescence phenomena of $^6/7\text{Li}$ signals or to changes in $^6/7\text{Li}$ coupled ^{13}C multiplets. Again, the use of ^6Li is of advantage. The reader can find an example in Chapter 13 (p. 553).

In *solids*, the quadrupolar coupling constant, χ , of ^7Li – which is in the kilohertz range – has emerged as a useful parameter for structural investigations. Its magnitude mirrors the symmetry around the ^7Li nuclei in question with small values for symmetric arrangements, as in solvent-separated ion pairs (SSIPs), and large values (>100 kHz) in contact ion pairs (CIPs). Both static and MAS powder spectra can be used to obtain the desired information (cf. Chapter 14). Solid state ^7Li NMR has also been employed extensively for the study of inorganic solids like glasses and other materials.

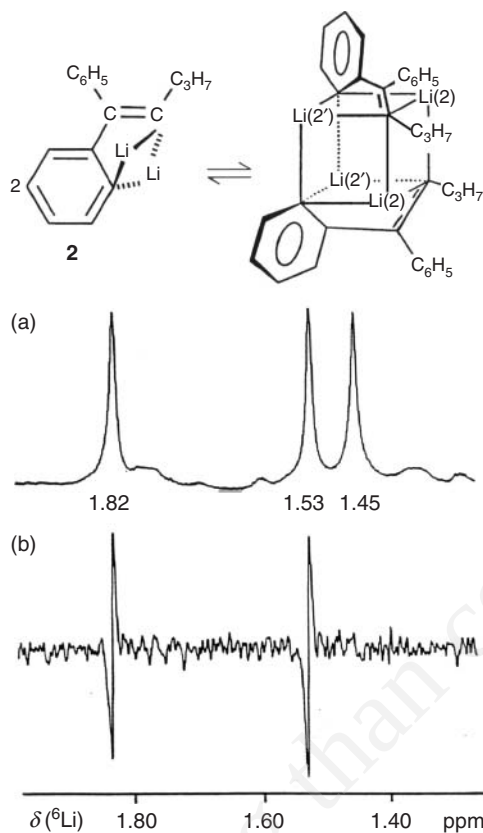


Figure 12.22 (a) 58.88 MHz ^6Li NMR spectrum of the dimer and monomer of (*E*)-2-lithio-1-(2-lithiophenyl)-1-phenylpent-1-ene (**2**); (b) ^6Li , ^6Li 1D INADEQUATE spectrum of the same sample, which identifies the coupled signals at 1.82 and 1.53 ppm (relative to external 0.1 M LiBr in THF) as the two non-equivalent lithium signals of the dimer and the signal at 1.45 ppm as that of the monomer [19].

12.2.2

Aluminum-27

The quadrupolar nuclide aluminum-27 with spin $I = \frac{5}{2}$ is another “100% nucleus” with relatively high sensitivity. However, the quadrupole moment is rather large – nearly four times that of lithium-7. Consequently, large line widths are found for ^{27}Al NMR spectra in solution, generally several hundred hertz, except for situations where we have cubic symmetry around the central aluminum atom. Furthermore, line widths and chemical shifts are temperature and concentration dependent. Aluminum is a key element for the solid state chemistry of aluminosilicates and porous materials like zeolites and a large area of ^{27}Al NMR is dedicated to solid state studies. Considerable progress in this field has come about through

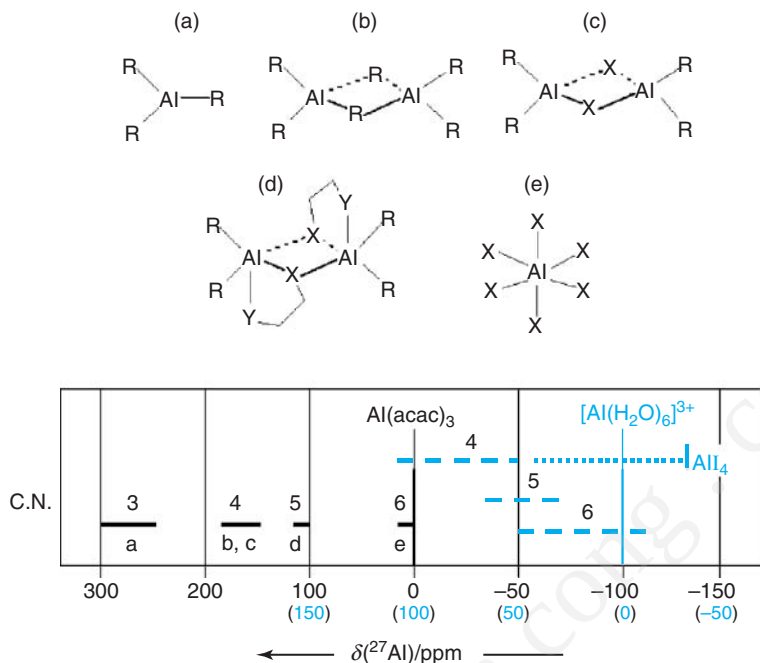


Figure 12.23 Approximate chemical shift ranges for ^{27}Al NMR of organoaluminum compounds (a–e) and inorganic salt solutions (bottom scale; lines to the right of 0); C.N. = coordination number. Data from References [20, 21]

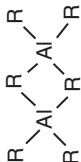
the development of multiple quantum experiments combined with magic angle spinning (MQMAS) that separate the resonance signals into two dimensions, improve the line shape and facilitate the assignment (see review article Al-27 (c) on page 499).

12.2.2.1 Referencing and Chemical Shifts

The *chemical shifts* for ^{27}Al cover in solution a range of about 300 ppm. They are separated in different regions by the aluminum C.N. This is true for inorganic samples, mostly aluminum salts dissolved in water, and organoaluminum compounds that resonate at higher frequencies (Figure 12.23). For aqueous solutions $[\text{Al}(\text{H}_2\text{O})_6]^{3+}$, which gives a signal at relatively low frequency, is used as external reference and most $\delta(^{27}\text{Al})$ values are positive. For strongly basic solutions $[\text{Al}(\text{OH})_4]^-$ serves as an alternative standard. The shift difference between both standards amounts to 80 ppm, with $[\text{Al}(\text{OH})_4]^-$ at higher frequency. Samples prepared with D_2O also provide the lock signal, the small isotope shift of about 0.25 ppm that results can usually be neglected considering the broad signals. For organoaluminum compounds dissolved in organic solvents, such as THF, $\text{Al}(\text{acac})_3$ is a suitable reference compound.

Several selected aluminum compounds are collected in Table 12.17 with their δ -values, line width, and with the solvent used.

Table 12.17 $\delta(^{27}\text{Al})$ -values for selected aluminum compounds and complexes (parts per million relative to $\text{Al}(\text{acac})_3$ and to $\text{Al}(\text{H}_2\text{O})_4$ otherwise^a).

Compound	DA ^b	Solvent	δ (²⁷ Al) (ppm)	Δ _{1/2} (Hz)	Compound	Solvent	δ (²⁷ Al) (ppm)	Δ _{1/2} (Hz)
(<i>i</i> -Bu) ₃ Al	1	[D ₈]toluene	276	6 300 ^a	AlBr ₄ [−]	CH ₃ CN	80	35
(<i>t</i> -Bu) ₃ Al	1	[D ₈]toluene	255	6 100 ^a	AlI ₄ [−]	—	—	—
	—	—	—	Al(OH) ₄ [−]	KOH/H ₂ O	80	60–100	
	—	—	—	—	AlCl ₃	CH ₃ OH	10	50
R = CH ₃	2, C	Neat	156	450 ^a	AlI ₂ Cl ₂	CH ₂ Cl ₂	59	57
R = C ₂ H ₅	2, C	[D ₈]toluene	153	850 ^a	Al ₂ I ₆	(C ₂ H ₅) ₂ O	39	90
	2, C	Cyclohexane	174	1 000 ^a	AlI ₃ Cl	CH ₂ Cl ₂	22	46
R = cyclopropyl (H ₃ C) ₂ AlCl (H ₃ C) ₂ AlH (H ₃ C) ₂ AlOCH ₃ R = Cl	2, C	[D ₈]toluene	154	2 550 ^a	AlI ₃ Br	CH ₂ Cl ₂	8	—
	2, Cl	[D ₈]toluene	143	2 750 ^a	[Al(H ₂ O) ₄ (SO ₄) ₂]	H ₂ O, H ₂ SO ₄	−7	80
	3, H	[D ₈]toluene	180	2 150 ^a	Al(POCl ₃) ₃ ³⁺	POCl ₃	−21	55–77
	3, O	[D ₈]toluene	159	2 500 ^a	Al(CH ₃ CN) ₆ ³⁺	CH ₃ CN	−34	73
	—	(C ₂ H ₅) ₂ O	152	1 400 ^a	Al(C ₆ H ₅ CN) ₆ ³⁺	C ₆ H ₅ CN	−46	100
R = Br	—	(C ₂ H ₅) ₂ O	105	126	—	—	—	—
AlH ₄ [−]	—	Toluene	91	300	—	—	—	—
AlH ₄ [−]	—	(C ₂ H ₅) ₂ O	96	100	—	—	—	—
	—	(C ₂ H ₅) ₂ O (saturated)	100	420	—	—	—	—

^aData from References [20, 21].

^bDegree of aggregation and bridge atom.

Few *spin–spin coupling* constants of ^{27}Al to other nuclei have been measured, which is not surprising considering the broad lines usually observed in the ^{27}Al spectra and the disappearance of line splitting in the spectra of neighboring nuclei due to fast quadrupolar relaxation of ^{27}Al . In AlH_4^- values of 170–173 Hz were found for ^1J , and one-bond couplings to carbon are of the order of 70–100 Hz. Couplings to nitrogen-14 are around 40 Hz, but those to phosphorus are quite large with well over 200 Hz.

12.2.3

Tin-119

From the magnetically active isotopes ^{115}Sn , ^{117}Sn , and ^{119}Sn , all with spin $I = \frac{1}{2}$, ^{119}Sn is used almost always in NMR because it has the highest natural abundance (8.58%). The chemistry of tin is very rich in applications in many areas such as organic synthesis and catalysis and NMR is thus important as an analytical tool, and also in structural studies of tin coordination compounds. Here, the C.N. or the pattern of substitution is of interest.

Direct observation or polarization transfer methods like INEPT, reverse INEPT or HMQC are employed to measure ^{119}Sn NMR spectra. High sensitivity is obtained if ^{119}Sn is measured with the two-dimensional proton-detected HMQC or HMBC experiments described in Chapter 11. The factor for sensitivity gain here is $11.6 = [\gamma(^1\text{H})/\gamma(^{119}\text{Sn})]^{5/2}$ as compared to the reverse INEPT factor of $4.4 = [\gamma(^1\text{H})/\gamma(^{119}\text{Sn})]^{3/2}$ or the simple INEPT factor $2.6 = \gamma(^1\text{H})/\gamma(^{119}\text{Sn})$.

In the ^1H NMR spectra of organotin compounds, aside from the ^{119}Sn satellites, satellites due to ^{117}Sn with a slightly smaller natural abundance (7.61%) are also observed. Since the $^{119}\text{Sn},\text{X}$ coupling constants are larger than the $^{117}\text{Sn},\text{X}$ coupling constants [$\gamma(^{119}\text{Sn}) > \gamma(^{117}\text{Sn})$] the correct assignment is straightforward. With high sensitivity even ^{115}Sn satellites can be detected (Figure 12.24).

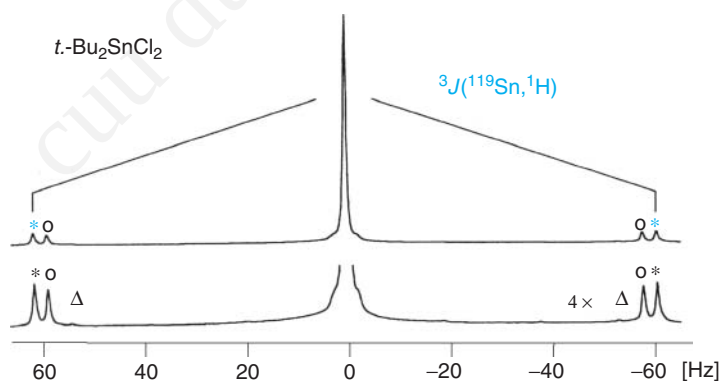


Figure 12.24 ^1H NMR spectrum of $t\text{-Bu}_2\text{SnCl}_2$ in DMSO with satellites from $^3J(^{119}\text{Sn}, ^1\text{H})$ (*), $^3J(^{117}\text{Sn}, ^1\text{H})$ (o), and $^3J(^{115}\text{Sn}, ^1\text{H})$ (Δ) [22].

12.2.3.1 Referencing and Chemical Shifts

The chemical shifts of ^{119}Sn are scattered over a range of about 600 ppm, from about -400 to $+200$ ppm relative to the reference compound tetramethyltin, $\text{Sn}(\text{CH}_3)_4$ (Figure 12.25). Extreme values are observed for SnI_4 (-1701 ppm) or negatively charged complexes like $\text{Sn}(\text{OH})_6^{2-}$ (-591 ppm), SnCl_6^{2-} (-732 ppm), and SnBr_6^{2-} (-2064 ppm).

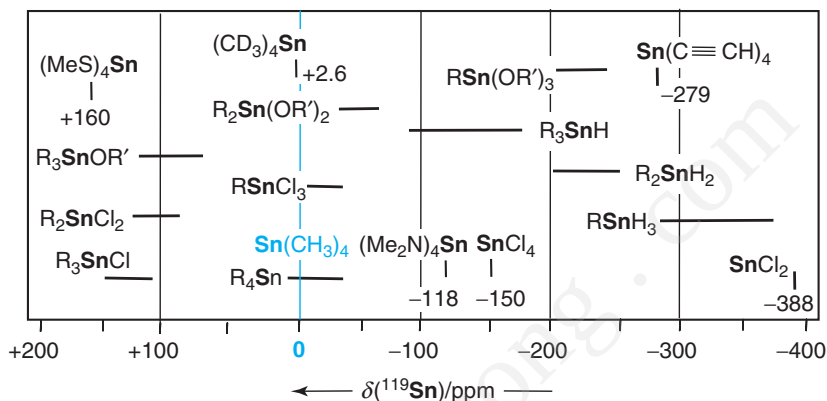
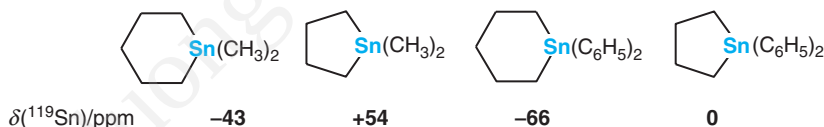


Figure 12.25 ^{119}Sn chemical shift diagram. Data from Reference [23].

Various structural features have been found to influence the ^{119}Sn chemical shift, which is dominated by the paramagnetic term. Electron-withdrawing substituents lead to high frequency shifts as do smaller C–Sn–C bond angles in cyclic compounds [24]:



The C.N. is also an important factor, where increased shielding is observed with an increase of C.N. (similar to silicon and lead) from 4 to 5 or 6 with about 150 ppm for each step and an extra shift of about 100 ppm in the case of C.N. = 7. Therefore, the tin chemical shift varies considerably for various coordination schemes in donor solvents like dimethyl sulfoxide. Interestingly, as for $\delta(^{29}\text{Si})$, plots of $\delta(^{119}\text{Sn})$ against the number of substituents in a series of $\text{R}_{4-n}\text{SnX}_n$ compounds often show an U-type characteristic or “sagging behavior” with the minimum shielding at or near C.N. = 2. Finally, we mention that secondary deuterium-induced isotope shifts for ^{119}Sn can be used successfully for structural investigations where, for example, $\text{Sn} \dots \text{O}-\text{H}$ coordination is detected through the two-bond isotope shift of about 50 ppb in the deuterated segment $\text{Sn} \dots \text{O}-\text{D}$. Table 12.18 shows a survey of ^{119}Sn chemical shifts for selected compounds.

The entries in the first two rows of compounds indicate shielding by steric crowding, an effect known in ^{13}C NMR as the γ -effect (p. 419). In the case of

Table 12.18 $\delta(^{119}\text{Sn})$ values for selected tin compounds (ppm relative to $\text{Sn}(\text{CH}_3)_4 = 0.0$)^a.

$\text{Sn}(\text{C}_2\text{H}_5)_4$ +1.4	$\text{Sn}(\text{C}_3\text{H}_7)_4$ −16.8	$\text{Sn}(i\text{-C}_3\text{H}_7)_4$ −43.9	$\text{Sn}(\text{C}_4\text{H}_9)_4$ −6.6	
$(\text{H}_3\text{C})_3\text{Sn}(\text{C}_6\text{H}_5)$ −30	$(\text{H}_3\text{C})_2\text{Sn}(\text{C}_6\text{H}_5)_2$ −60	$\text{H}_3\text{CSn}(\text{C}_6\text{H}_5)_3$ −98	$\text{Sn}(\text{C}_6\text{H}_5)_4$ −137	$(\text{C}_6\text{H}_5)_3\text{SnOH}$ −86
$(\text{H}_3\text{C})_3\text{SnCH}_2\text{Cl}$ +4	$(\text{H}_3\text{C})_3\text{SnCHCl}_2$ +33	$(\text{H}_3\text{C})_3\text{SnCCl}_3$ +85	$(\text{H}_3\text{C})_3\text{SnCBr}_3$ +101	$\text{H}_3\text{CSn}(\text{OC}_2\text{H}_5)_3$ −434
SnH_4 −9.9	SnCl_4 −150	SnBr_4 −638	SnI_4 −1701	—
$(\text{H}_3\text{C})\text{SnCl}_3$ +6.3	$(\text{H}_3\text{C})_2\text{SnCl}_2$ +137	$(\text{H}_3\text{C})_3\text{SnCl}$ +154 to +166 ^b	$(\text{H}_3\text{C})_3\text{SnOH}$ +118	—
SnH_4 −9.9	$(\text{H}_3\text{C})\text{SnH}_3$ −346	$(\text{H}_3\text{C})_2\text{SnH}_2$ −224.6	$(\text{H}_3\text{C})_3\text{SnH}$ −104.5	—
$(\text{H}_3\text{C})_3\text{SnN}(\text{CH}_3)_2$ +75	$(\text{H}_3\text{C})_3\text{SnP}(\text{C}_6\text{H}_5)_2$ −2.3	$(\text{H}_3\text{C})_3\text{Sn}(\text{SCH}_3)_3$ +167	$\text{Sn}(\text{SCH}_3)_4$ +160	$\text{Sn}(\text{SeCH}_3)_4$ −80.5

^aData from Reference [23a, b].^bSolvent dependent.

substitution by phenyl groups charge density changes at the metal may also be responsible. The third row shows deshielding, possibly by inductive interactions ($-I$ effect). The fourth row demonstrates a *heavy atom effect* with increased shielding, again known from carbon NMR (p. 409). A dramatic shielding shift is observed in the third row by replacing $-\text{CBr}_3$ by three $-\text{OC}_2\text{H}_5$ groups ($\Delta\delta = -535$ ppm).

12.2.3.2 Spin–Spin Coupling

Scalar coupling of ^{119}Sn to abundant X nuclei like ^1H , ^{19}F , or ^{31}P is easily measured from the X spectra; however, the number of coupled X nuclei may be seen most clearly in the ^{119}Sn spectra. In addition, $^{119}\text{Sn}, ^1\text{H}$ couplings show up through the satellites in 2D ^1H detected experiments. More difficulties arise when coupling to rare spin $\frac{1}{2}$ nuclei is to be measured. This applies to $^{119}\text{Sn}, ^{13}\text{C}$ coupling but especially to $^{119}\text{Sn}, ^{15}\text{N}$ couplings. While the former can generally be detected via the ^{119}Sn satellites in ^{13}C spectra, special techniques have to be employed for measuring $^{119}\text{Sn}, ^{15}\text{N}$ couplings because of the low natural abundance of ^{15}N (0.35%).

One-bond coupling constants of ^{119}Sn are fairly large, often from several hundred hertz for ^{13}C or ^{31}P to more than 1000 Hz for ^1H , ^{19}F , and heavy nuclei like ^{195}Pt or ^{199}Hg . $^1J(^{119}\text{Sn}, ^{13}\text{C})$ values that have a negative sign and increase in magnitude in tetraorganotin derivatives if carbon hybridization changes from sp^3 to sp^2 to sp [25]:

	$\text{Sn}(\text{C}_2\text{H}_5)_4$	$\text{Sn}(\text{CH}_3)_4$	$\text{Sn}(\text{CH}=\text{CH}_2)_4$	$\text{Sn}(\text{C}_6\text{H}_5)_4$	$\text{Sn}(\text{C}\equiv\text{CH})_4$
$^3J(^{119}\text{Sn}, ^1\text{H})/\text{Hz}$	−330.0	−336.6	−519.8	−530.8	−1 176.2

For organotin(IV) compounds there is also an increase with the C.N. Homonuclear $^{119}\text{Sn}, ^{119}\text{Sn}$ couplings vary strongly with structure and range from 1350 to

even 16 000 Hz. Geminal couplings of tin are in general of smaller magnitude, with the exception of $^2J(^{119}\text{Sn}, ^{119}\text{Sn})$ values, which cover a range of 20 kHz! *Karplus-type* relations have been found for vicinal ^{119}Sn couplings to ^1H and ^{13}C and even for the homonuclear case. Some solid state NMR results for tin compounds are discussed in Section 14.4.

12.3

Transition Metals

All of the 30 transition metals of the Periodic Table have at least one NMR-active isotope, but their NMR properties are sufficiently different, rendering some of the nuclides, such as for example, ^{77}Ir or ^{177}Hf , even today as most difficult to study. In addition, many of the other nuclei were out of reach when only CW (continuous wave) techniques were available, but this situation changed after the introduction of Fourier-transform NMR and the development of polarization transfer experiments like INEPT and HMQC. In addition, much progress has been made in the calculation of transition metal chemical shifts.

Today we can divide transition metal nuclides into four groups according to the NMR techniques necessary for their detection:

Group 1: nuclei of spin $\frac{1}{2}$ with large γ and short T_1 – like ^{113}Cd , ^{195}Pt , or ^{199}Hg – can be measured with standard pulse techniques;

group 2: quadrupolar nuclei with spin $I > \frac{1}{2}$, small γ , and long T_1 – like ^{57}Fe , ^{103}Rh , ^{109}Ag , ^{183}W , or ^{187}Os – are studied at strong B_0 fields and/or by polarization transfer from ^1H or ^{31}P with INEPT or HMQC;

group 3: quadrupolar nuclei (spin $I > \frac{1}{2}$) with small quadrupole moment Q and short T_2 – like ^{47}Ti , ^{51}V , ^{53}Cr , ^{63}Cu , ^{91}Zr , ^{95}Mo , or ^{99}Ru – can again be measured by standard pulse techniques;

group 4: quadrupolar nuclei (spin $I > \frac{1}{2}$) with large quadrupole moment Q and very short T_2 – like ^{55}Mn , ^{59}Co , ^{61}Ni , or ^{105}Pd – can also be measured by standard pulse techniques but strong B_0 fields have to be used.

The nuclides ^{51}V , ^{55}Mn , ^{59}Co , and ^{103}Rh have the advantage of very high natural abundance (99.76% for ^{51}V and 100% for the others). The nuclear properties of the nuclei we selected are collected in Table 12.19.

Especially, the HMQC experiment – which has also the interesting feature that in an AMX spin system, e. g. $A = ^1\text{H}$, $M = ^{31}\text{P}$, with a 'passive' spin X, e. g. ^{103}Rh , the tilt of the cross peaks allows to determine the relative signs of the coupling constants $J(\text{AX})$ and $J(\text{MX})$ (cf. p. 305) – was applied successfully for nuclei of group 2, quite often with ^{31}P as sensitive nucleus. With these developments not only important structural information about transition metal compounds was gathered but also the chemical shift of many of these nuclei was found to correlate linearly with thermodynamic data such as complex stability constants or kinetic data for quite a number of reactions like ligand displacements or catalytic activities.

Based on a literature screening for the year 2010 three groups of nuclides could be distinguished from the rest simply by the number of articles dealing with NMR

Table 12.19 Nuclear properties of some chemically important transition metal nuclei.^a

Nucleus	<i>I</i>	Natural abundance (%)	μ/μ_N	γ (10^7 rad s^{-1} T $^{-1}$)	Q (barn = 10^{-28} m ^{2})	ν (MHz at 2.358 T) = $\mathcal{E}$ (%)	R^H	R^C	W_f (10^{-59} m ^{4})
^{51}V	$\frac{7}{2}$	99.750	5.838	7.0455	-5.2×10^{-2}	26.302 948	0.383	2.25×10^3	0.37
^{55}Mn	$\frac{5}{2}$	100.0	4.104	6.6453	0.33	24.789 216	0.179	1.05×10^3	35
^{57}Fe	$\frac{1}{2}$	2.119	0.1570	0.8681	—	3.237 778	7.24×10^{-3}	4.25×10^{-3}	—
^{59}Co	$\frac{7}{2}$	100.0	5.247	6.332	0.42	23.727 074	0.278	1.64×10^3	24
^{63}Cu	$\frac{3}{2}$	69.17	2.8755	7.1118	-0.22	26.515 473	6.50×10^{-3}	3.82×10^2	65
^{95}Mo	$\frac{5}{2}$	15.92	-1.082	-1.751	-0.015	6.516 926	5.21×10^{-4}	3.06	0.15
^{103}Rh	$\frac{1}{2}$	100	-0.1522	-0.8468	—	3.186 447	3.17×10^{-5}	0.186	—
$^{113}\text{Cd}^b$	$\frac{1}{2}$	12.22	-1.0779	-5.9609	—	22.193 175	1.35×10^{-3}	7.94	—
^{183}W	$\frac{1}{2}$	14.31	0.2040	1.1282	—	4.166 387	1.07×10^{-5}	6.31×10^{-2}	—
^{187}Os	$\frac{1}{2}$	1.96	0.1120	0.6193	—	2.282 331	2.43×10^{-7}	1.43×10^{-3}	—
^{195}Pt	$\frac{1}{2}$	33.832	1.0557	5.8385	—	21.496 784	3.51×10^{-3}	20.7	—
^{199}Hg	$\frac{1}{2}$	16.87	0.8762	4.8458	—	17.910 822	10^{-3}	5.89	—

^a*I* = spin quantum number; μ = magnetic moment in units of μ_N , the Bohr magneton; γ = magnetogyric ratio; ν = resonance frequency at 2.358 T (^1H = 100.00 MHz), $\mathcal{E}$ (%), for definition see (p. 434); R^H = receptivity relative to the proton; R^C = receptivity relative to carbon-13; W_f = linewidth factor; for some nuclides additional NMR active isotopes exist, but in the present context they are of minor importance and thus are neglected.

^bLong-lived radioactive isotope.
Data adapted from Reference [2].

spectra of these elements. Two nuclides, ^{51}V and ^{195}Pt , stand out with citation numbers over 2700. The next group with 1000–2000 citations consists of ^{59}Co , ^{63}Cu , ^{103}Rh , ^{113}Cd , while ^{57}Fe , ^{55}Mn , ^{95}Mo , ^{183}W , and ^{199}Hg form another group with citation numbers between 500 and 1000. Less than 200 papers dealing with ^{187}Os NMR were found. These numbers are mainly governed by the chemical interest that these elements presently find and the importance of NMR spectroscopy for the elucidation of their chemistry. Furthermore, to a certain extent the natural abundance of their NMR active isotopes and the easiness with which they are detected are reflected. The citations include solution as well as solid state measurements that will not be treated here, but some of these investigations shall be discussed in Chapter 14. Among the selected nuclei, whose important NMR properties are collected in Table 12.19, are six with spin $I = \frac{1}{2}$ (^{57}Fe , ^{103}Rh , ^{113}Cd , ^{183}W , ^{187}Os , ^{195}Pt , ^{199}Hg) while the others with spin $I > \frac{1}{2}$ have a quadrupole moment (^{51}V , ^{55}Mn , ^{59}Co , ^{63}Cu , ^{95}Mo). Considering only the resonance frequencies ν_0 at 2.345 T, we have nuclei with $\nu_0 > 17$ MHz (^{199}Hg , ^{195}Pt , ^{113}Cd , ^{59}Co , ^{55}Mn , ^{51}V , ^{63}Cu) that are more sensitive than the rest with $\nu_0 < 6.5$ MHz (^{95}Mo , ^{183}W , ^{57}Fe , ^{103}Rh , ^{187}Os).

In the following, we do not follow the order of the Periodic Table but limit our introduction to the nuclides presented above. A summary of the chemical shift ranges and the referencing methods used is given in Table 12.21 (p. 478). The chemical shift extends in most cases over several kilohertz and is dominated by the paramagnetic term in the Ramsey equation (cf. p. 410). For the relaxation of spin $\frac{1}{2}$ nuclei the CSA and/or spin rotation mechanisms are important, while nuclei with spin $> \frac{1}{2}$ relax via the quadrupole mechanism.

In the remaining text several important aspects relevant for NMR applications in the field of these nuclides are described briefly, and the literature consulted for this purpose is listed at the end of this chapter.

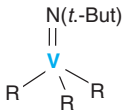
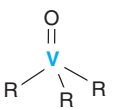
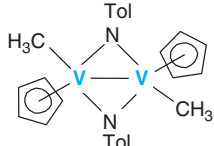
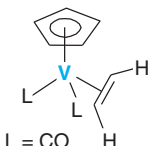
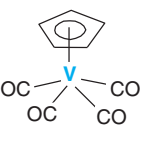
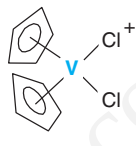
12.3.1

Vanadium-51

Vanadium-51 has a spin $I = \frac{7}{2}$ and a high detection sensitivity ($R^P = 0.38$) because of nearly 100% natural abundance. The small quadrupole moment assures sufficiently narrow lines even for compounds with low symmetry; however, line splittings due to scalar coupling are less common. The ^{51}V nucleus has attracted much interest in solution and, in particular, solid state NMR because of the catalytic properties of vanadium compounds, and 1D as well as 2D methods have been applied. Numerous organovanadium compounds of great structural variety are known and the *chemical shift* range spans almost 5000 ppm. Table 12.20 shows a few selected structures and their $\delta(^{51}\text{V})$ values.

Generally, the chemical shift does not correlate with the oxidation number and structural determinations based on ^{51}V chemical shifts alone are difficult to make and require additional information from NMR data of ligand nuclei or other sources. In addition, ^{51}V chemical shifts are often temperature-sensitive. The factors that influence the ^{51}V shielding are considered to be complex. The main influence

Table 12.20 $\delta(^{51}\text{V})$ values of selected structures of vanadium complexes (ppm relative to $^{51}\text{VOCl}_3$).

	$\delta(^{51}\text{V})$		$\delta(^{51}\text{V})$
3 x R_1	+879	3 x R_1	+1205
2 x R_1, R_2	+293	2 x R_1, R_2	+627
$R_1, 2 \times R_2$	-324	$R_1, 2 \times R_2$	-47
$R_1 = \text{CH}_2\text{-}t\text{-But}$	-751	$R_1 = \text{CH}_2\text{-SiMe}_3$	-723
$R_2 = \text{O-}t\text{-But}$		$R_2 = \text{O-SiPh}_3$	
			
$\delta(^{51}\text{V})$: +674			
			
$L = \text{CO}$			
$\delta(^{51}\text{V})$: -598			
			
$\delta(^{51}\text{V})$: -1534			
			
$\delta(^{51}\text{V})$: -135			

Data from Reference [26].

comes from the paramagnetic term in the familiar Ramsey equation (cf. p. 410):

$$\sigma_p^i \simeq (\Delta E^{-1})_{av} \langle r_i^{-3} \rangle_{3d} c_{\text{LCAO}}^2 \quad (12.15)$$

where ΔE is the electronic excitation energy – the HOMO–LUMO gap – and r_i is now the effective radius of the 3d valence shell and c_{LCAO} the valence d-electron LCAO (*linear* combination of atomic orbitals) coefficient. Correlations with the ΔE term, as well as with the expansion of the d-electron cloud, that is, the $\langle r_i^{-3} \rangle_{3d}$ term, have been found. Donor ligands of the σ/π type, which are “weak” ligands in low-valent complexes of oxidation states V(III), and V(–I), for example, carbonylvanadates with V(–I), increase σ_p^i because they lower ΔE ; ^{51}V resonances are thus deshielded and $\delta(^{51}\text{V})$ becomes less negative because the signal of the reference compound VOCl_3 appears at high frequency. “Strong” ligands like carbonyl, phosphites, and phosphines are effective π -acceptors and they have the opposite effect, that is, ΔE increases and consequently ^{51}V is shielded and $\delta(^{51}\text{V})$ becomes more negative. The series of pentacarbonyl vanadate complexes $[\text{V}(\text{CO})_5\text{L}]^-$ of oxidation state –I with different ligands demonstrates these effects:

L^a	THF	$\text{NH}(\text{Et})_2$	NCMe	$\text{P}(t\text{-But})_3$	PMe_3	CNCy^b	$\text{P}(\text{OMe})_3$	PF_3
$\delta(^{51}\text{V})$ (ppm)	–1367	–1498	–1601	–1833	–1875	–1901	–1928	–1961

^a L =ligand^bCyclohexyl

For high vanadium oxidation states (+IV for dinuclear complexes because mononuclear complexes are paramagnetic, +V; vanadates, thio-, peroxy-, and hetero-vanadates) σ/π type ligands are “weak” and induce shielding. On the other hand, polarizable groups such as the halogens or sulfur, selenium, and tellurium

Table 12.21 Approximate chemical shift ranges and referencing for selected transition metals as they appear in the text.^a

	Chemical shift ranges (ppm)	Referencing
Vanadium-51	–2000 to +2000 –1000 to –1600 for Cp-V(CO)₄ complexes +400 to –2000 for Cp-V(L)_x complexes 0 to +2400 for dinuclear complexes and organo-vanadium compounds with sandwiching ligands	⁵¹VOCl₃ neat or in C₆D₆ $\bar{\epsilon}$ = 26.302 948 MHz
Platinum-195	15 000, temperature-sensitive Pt(IV) halides ≈ 12 500 ppm [PtX₃L][–] ≈ –1500 to –5800 [PtX₂L₂][–] ≈ –1700 to –5500 [PtXL₂L][–] ≈ –4200 to –5100 For X = Cl, Br, I, and ligands L = N, P, As, Sb, S, Se, Te 19 300 between [Co(H₂O)₆]³⁺ (high frequency) and [Co(PF₃)₄][–] (low frequency)	[PtCl_x]^{2–} (x = 4, 6) or [PtCN₆]^{2–} in D₂O $\bar{\epsilon}$ = 21.496 784 MHz for Na₂PtCl₆ — External [Co(CN)₆]^{3–} conversion factors for this standard (in ppm) are +7120 for [Co(en⁺)₃]³⁺, +12 500 for Co(acac)₃, and 8150 for [Co(NH₃)₆]³⁺ $\bar{\epsilon}$ = 23.727 074 MHz for the hexacyano complex in D₂O 0.56 M. External [Cu(CH₃CN)₄]¹⁺X (X = BF₄[–], PF₆[–], or ClO₄[–]) in CH₃CN, usually 0.1 mmol l^{–1}; line width about 400 Hz $\bar{\epsilon}$ = 26.515 473 MHz
Copper-63	Cu complexes –434 to +500 ppm Cu carbonyl clusters around –2410 ppm Complexes with phosphine ligands 70–90 ppm, Those with phosphate ligands 150–250 ppm	Rh(acac)₃ $\bar{\epsilon}$ = 3.186 447 MHz saturated in CDCl₃. Cd[ClO₄]₂ Cd(CH₃)₂ $\bar{\epsilon}$ = 22.193 175 MHz for neat Cd(CH₃)₂. Fe(CO)₅ $\bar{\epsilon}$ = 3.237 778 MHz in C₆D₆.
Rhodium-103	+500 to –2000	
Cadmium-113	–50 to +500 for cadmium salts and complexes 0 to –385 for organocadmium compounds	
Iron-57	–600 to +2100 for iron in compounds with iron in the formal oxidation state 2 or 0; iron porphyrins ~8200; cytochrome c 11 197	

Manganese-55	~3000 about 0 ppm for Mn(IV), -1000 to -1500 for Mn(II), and -1700 to -3000 for Mn(-I)	KMnO ₄ in HD ₂ O at the extreme high frequency end; solvent dependent (18 ppm for hexamethylphosphoramide, 10 ppm for acetone) $\mathcal{E} = 24.789\ 216\ \text{MHz}$
Molybdenum-95	-3000 to +4200; overlapping domains for the different oxidation states: Mo(0) $\approx$ -860 to -2130 for the carbonyl derivatives, -1585 to +2270 for the other species Mo(I) $\approx$ -1856 to +182 Mo(II) $\approx$ -2100 to +315 (monomers); +3200 to +4150 (dimers) Mo(III) $\approx$ +2400 to +3700 (dimers) Mo(IV) $\approx$ +990 to +3180 Mo(V) $\approx$ -93 to +586 (dimers) Mo(VI) $\approx$ -620 to +3200	2 M [MoO ₄] ²⁻ in aqueous alkaline at pH 11 $\mathcal{E} = 6.516\ 926\ \text{MHz}$
Tungsten-183	6500 -2500 to -3500 W(CO) ₆ [P, S, N] _n -2750 to -3000 CpW(CO) ₃ X -3500 to -4000 CpW(CO) ₃ R -3000 to -3500 CpW(CO) ₂ (L)PR ₂ -500 to -1750 W(F) _{6-n} (OR) _n	— WF ₆ or [WO ₄] ²⁻ at -1120 ppm (for better comparison with ⁹⁵ Mo shift data); recommended 1 M Na ₂ [WO ₄] in D ₂ O at pH 9 $\mathcal{E} = 4.166\ 387\ \text{MHz}$ for Na ₂ WO ₄
Mercury-199	5000; +1700 for [Hg(SiR ₃) ₄] ²⁻ to -3500 for [HgI ₄] ²⁻	External neat Hg(CH ₃) ₂ , solvent-dependent. Caution! Very hazardous! Alternatively Hg(ClO ₄) ₂ 0.1 M in 0.1 M HClO ₄ $\delta = -2255\ \text{ppm}$ relative to Hg(CH ₃) ₂ as external reference $\mathcal{E} = 17.910\ 822\ \text{MHz}$ for neat Hg(CH ₃) ₂ . OsO ₄ in CCl ₄ , 0.98 M $\mathcal{E} = 2.282\ 331\ \text{MHz}$
Osmium-187	750	

^aFor the explanation of the $\mathcal{E}$ frequencies see p. 434.

substituents lead to deshielding. The series of complexes of type $\text{CpV}(\text{N-}t\text{-But})\text{X}_2$ serves to illustrate this:

X	O- <i>t</i> -But	NH- <i>t</i> -But	SPh	Cl	Br	SePh	I	CH ₃
$\delta(^{51}\text{V})$ (ppm)	-904	-894	-475	-457	-329	-304	-110	-25

Finally, one-bond *coupling constants* in organovanadium compounds are small for ^1H (~ 20 Hz), about 100 Hz for ^{13}C , and >100 Hz for heavier nuclei like ^{19}F or ^{31}P . A coupling of 900 Hz has been observed with ^{119}Sn .

12.3.2

Platinum-195

Platinum-195, the only NMR active isotope of platinum, is a nuclide with favorable NMR properties. With a spin of $I = \frac{1}{2}$ and a natural abundance of 33.8% direct measurements were even possible with the CW method and ^{195}Pt satellites in ^1H NMR spectra gave early information about ^{195}Pt , ^1H coupling constants. The rich chemistry of platinum, which forms complexes in four different oxidation states [Pt(0), Pt(II), Pt(III), Pt(IV)], renders ^{195}Pt NMR the technique of choice for structural studies in this field. Today, ^{195}Pt NMR spectra are also recorded by indirect detection via ^1H , and 2D methods like HMQC and HMBC are in use. In addition, ^{31}P functions as the high γ nucleus for polarization transfer. Spin–lattice relaxation times T_1 of ^{195}Pt are short, which allows rapid data acquisition, but T_2 values are also short, leading to broad lines, and satellites due to ^{195}Pt , X coupling are often broadened especially at high B_0 fields. The spin-rotation mechanism (cf. p. 243) dominates the ^{195}Pt relaxation in small, highly symmetric complexes like $[\text{PtCl}_4]^{2-}$. Normally, line widths are of the order of 25 Hz. The CSA mechanism (cf. p. 434) is important for ^{195}Pt because of the large chemical shift range $\Delta\sigma$ ($R_1^{\text{CSA}} = \frac{2}{15}\gamma^2 B_0^2 [\Delta\sigma]^2 \tau_c$). As R_1^{CSA} increases with B_0^2 and the correlation time for reorientation, τ_c , line broadening results and line splittings due to scalar couplings are often washed out. Increasing the temperature may resolve the spin–spin coupling by lowering τ_c , as the example in Figure 12.27 (p. 481) shows.

The largest sub-range for ^{195}Pt *chemical shifts* exists for Pt(IV) complexes, but the regions for the different oxidation states overlap (Figure 12.26). From the numerous data reported in the literature trends for ^{195}Pt shifts in Pt(II) complexes induced by

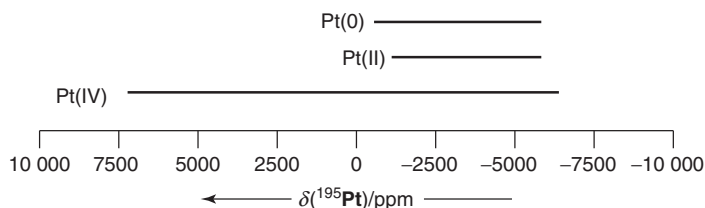


Figure 12.26 Approximate ranges of $\delta(^{195}\text{Pt})$ for different Pt oxidation states relative to $[\text{Pt}(\text{CN})_6]^{2-}$ in D_2O . After Reference [28].

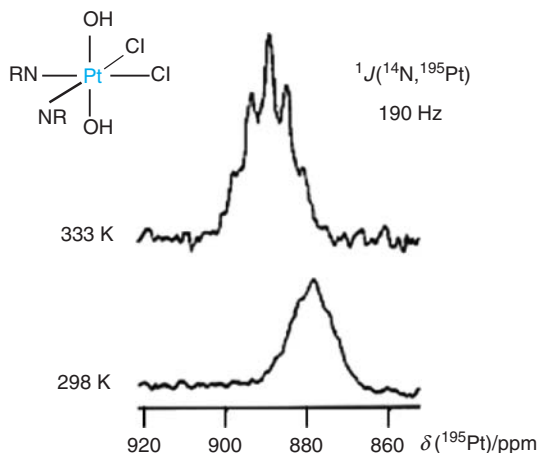
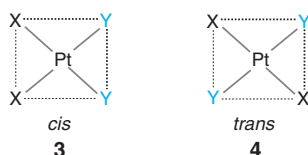


Figure 12.27 ^1H -decoupled ^{195}Pt NMR spectra of *cis,cis,trans*-[Pt(isopropylamine) $_2$ Cl $_2$ (OH) $_2$] with resolved ^{195}Pt , ^{14}N coupling at higher temperature (Reprinted with permission from [27]. Copyright 1983 American Chemical Society).

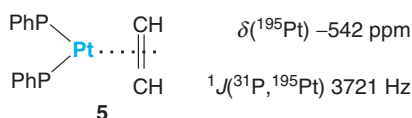
various ligands like halogens, amines, phosphanes, and nitrogen heterocycles are well established, with overlapping shift ranges of -1500 to -5800 (Figure 12.26). The $\delta(^{195}\text{Pt})$ data (in ppm) given below demonstrate the sensitivity of ^{195}Pt chemical shifts ($\delta(^{195}\text{Pt})$ in ppm) for ligand exchange:

<i>cis</i> -[Pt(NH ₃) ₂ (H ₂ O) ₂] -1593	<i>cis</i> -[Pt(NH ₃) ₂ (NO) ₂] -2214	<i>cis</i> -[Pt(NH ₃) ₂ (SCN) ₂] -3016	
[PtCl ₃ (SnCl ₃)] ²⁻ -2748	<i>cis</i> -[PtCl ₂ (SnCl ₃) ₂] ²⁻ -4202	[PtCl(SnCl ₃) ₃] ²⁻ -4829	[Pt(SnCl ₃) ₄] ²⁻ -5615

Since Pt(II) complexes of the type [PtX $_2$ Y $_2$] have a square-planar structure the substituents can occupy *cis*- or *trans*-positions (3 and 4, respectively):



For complexes with X = I and various substituents as Y, the respective $\delta(^{195}\text{Pt})$ values differ by about 30–80 ppm, with stronger shielding for $\delta(^{195}\text{Pt})_{\text{cis}}$. The *cis*-complex also shows the larger geminal ^{195}Pt , ^1H , and ^{195}Pt , ^{13}C coupling constants if Y is an amino substituent. Similar results hold for complexes with X = Cl. Typical data for platinum phosphane complexes with different olefin ligands are shown in formula 5.



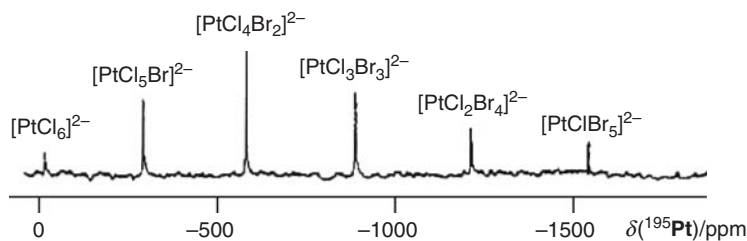


Figure 12.28 Replacement of Cl by Br in a 1 M solution of $\text{Na}_2[\text{PtCl}_6]$ and NaBr in D_2O (Reproduced in part from References [28, 29] with permission of The Royal Society of Chemistry).

Platinum(IV) halides show a large range of chemical shifts that span approximately 12 500 ppm:

	$[\text{PtF}_6]^{2-}$	$[\text{PtCl}_6]^{2-}$	$[\text{PtBr}_6]^{2-}$	$[\text{PtI}_6]^{2-}$
$\delta(^{195}\text{Pt})$ (ppm)	7326	0	-1860	-5120

and an example for the shielding of ^{195}Pt by successive replacement of Cl by Br in $[\text{PtCl}_6]^{2-}$ is shown in Figure 12.28. Similar results hold for Pt(II) complexes.

12.3.2.1 Spin-Spin Coupling

Spin-spin coupling between ^{195}Pt and other nuclei is quite common and yields valuable structural information about the geometry of the complexes (e.g., cis or trans) and the extent of Pt–ligand interaction. It has been observed for ^1H , ^{13}C , ^{15}N , ^{19}F , and ^{31}P , in many cases, as already mentioned above, via the ^{195}Pt satellites in the X-nucleus spectrum. One-bond couplings with X-nuclei can vary over several orders of magnitude, as exemplified by $^1J(^{195}\text{Pt}, ^1\text{H}) \approx 1$ kHz, $^1J(^{195}\text{Pt}, ^{31}\text{P}) \approx 2$ kHz, $^1J(^{195}\text{Pt}, ^{119}\text{Sn}) \approx 20$ kHz, and $^1J(^{195}\text{Pt}, ^{105}\text{Tl}) \approx 57$ kHz. Homonuclear $^1J(^{195}\text{Pt}, ^{195}\text{Pt})$ couplings have been reported for binuclear Pt(II) and Pt(IV) complexes with values between 600 and 7000 Hz.

12.3.3

Cobalt-59

According to its NMR sensitivity, cobalt-59 belongs with 100% natural abundance to the six most easily detected nuclei. However, with a spin of $I = \frac{7}{2}$ it has a quadrupole moment that may lead to line broadening. The situation is thus similar to ^{51}V NMR. Because of the relatively high symmetry around ^{59}Co in octahedral Co(III) complexes that exist for most cobalt compounds, the line width problem is not stringent for chemical shift measurements and many data for ^{59}Co have been collected. With nearly 20 000 ppm the ^{59}Co chemical shift scale is the largest from all nuclides of the Periodic Table, as the following data show:

	$\text{Co}(\text{H}_2\text{O})_6^{3+}$	$\text{Co}(\text{NH}_3)_6^{3+}$	$\text{Co}(\text{CN})_6^{3-}$	$\text{Co}(\text{CO})_4^-$	$\text{Co}(\text{PF}_3)_3^-$
$\delta(^{59}\text{Co})$ (ppm)	15100	8150	0	-3200	-4200

$\delta(^{59}\text{Co})$ is thus very sensitive for small structural changes and in addition sensitive to solvent and temperature. Because of the large shift range a secondary standard, for example, $\text{Co}(\text{acac})_3$ (cf. Figure 12.29) is often necessary but can be avoided if the $\mathcal{E}$ scale is used. An overview of the chemical shift scale for cobalt complexes is given in Figure 12.29, while Figure 12.30 displays $\delta(^{59}\text{Co})$ data for cobalt olefin complexes.

Resonances for $\text{Co}(\text{III})$ complexes are found at low frequency between 2000 and -1300 ppm, those for other oxidation states (I, 0, -I) are more shielded.

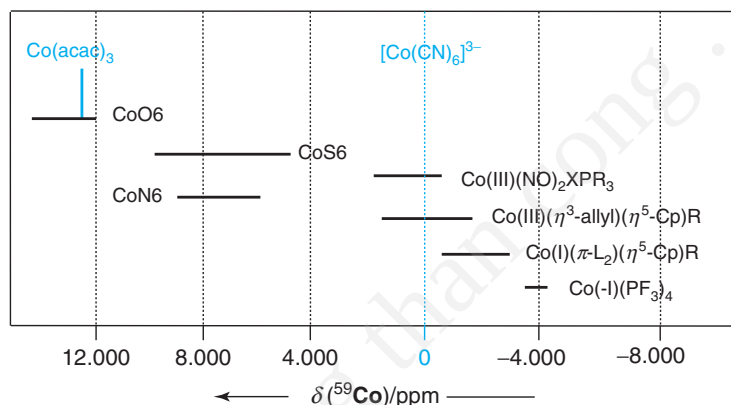


Figure 12.29 ^{59}Co chemical shift diagram for different cobalt complexes; CoO_6 , CoN_6 , and CoS_6 are compounds with sixfold cobalt coordination to O-, N-, and S-ligands. After Reference [20].

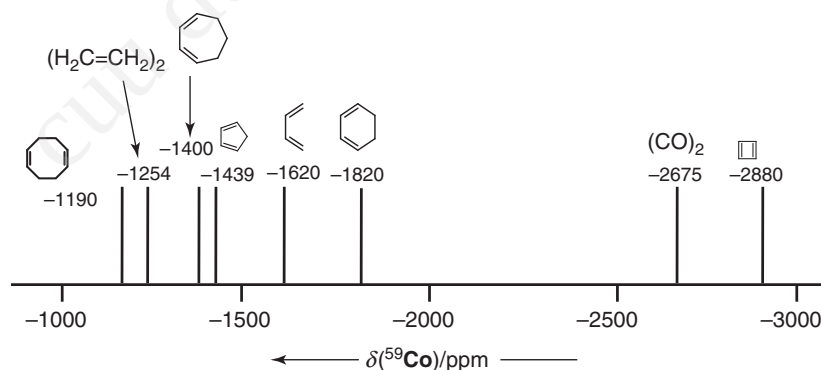


Figure 12.30 ^{59}Co chemical shift diagram for $[\text{CpCo}(\pi\text{-L}_2)]$ complexes with different dienes relative to external $[\text{Co}(\text{CN})_6]^{3-}$. After Reference [20].

A linear correlation between transition energy, ΔE , of the lowest d–d excitation in the visible UV region and $\delta(^{59}\text{Co})$ was found for octahedral Co(III) complexes pointing to the importance of the paramagnetic shielding term for ^{59}Co . Also of interest is the observation that $\delta(^{59}\text{Co})$ correlates linearly with the catalytic activity of cyclopentadienyl-cyclohexadiene cobalt complexes, $(\text{R-Cp})\text{Co}(\text{COD})$, in the cyclization reaction of alkynes and nitriles to form pyridines. This finding stimulated further investigations of the correlation between homogeneous catalysis and metal NMR.

For *coupling constant* measurements the ^{59}Co line width poses problems and not many are known. For the same reason few relaxation time measurements have been performed.

12.3.4

Copper-63

There are two copper nuclides, ^{63}Cu and ^{65}Cu , both of spin $I = \frac{3}{2}$ and suitable for NMR with similar properties. Owing to the higher natural abundance (69.1%) ^{63}Cu is preferred for NMR measurements. The investigation of copper complexes is somewhat limited because only those of Cu(I) are diamagnetic. Owing to the quadrupole moment of ^{63}Cu , smaller line widths are only observed for complexes with high symmetry.

The ^{63}Cu *chemical shifts* of copper compounds – generally measured relative to external $[\text{Cu}(\text{CH}_3\text{CN})_4]^+\text{X}$ ($\text{X} = \text{BF}_4^-, \text{PF}_6^-, \text{or } \text{ClO}_4^-$) in CH_3CN – are found mostly between 700 and -400 ppm. Smaller regions exist for complexes with phosphine ligands (70–90 ppm) and for those with phosphites (150–250 ppm). Ligands with arsenic, antimony, or tellurium have shielding effects and shift the $\delta(^{63}\text{Cu})$ -values into the negative region (about -40 to -250 ppm). Frequently, exchange of ligands leads to line broadening, in the case of mixed complexes like $[\text{Cu}(\text{CN})_3\text{L}]^{2-}$ with $\text{L} = \text{halogenide}, \text{SCN}^-, \text{NH}_3$, or $(\text{NH}_2)_2\text{CO}$ with $\Delta_{1/2}$ between 85 Hz and even 5 kHz. A few data, given in Table 12.22, may serve to illustrate the findings described.

Owing to the line width problem, the measurement of *coupling constants* is difficult. Several $^1J(^{63}\text{Cu}, ^{31}\text{P})$ data were found with values between 750 and 1220 Hz. ^{63}Cu solid state NMR studies of copper-based materials have proved useful and

Table 12.22 $\delta(^{63}\text{Cu})$ values for selected copper compounds (ppm relative to $[\text{Cu}(\text{CH}_3\text{CN})_4]^+$)^a.

Complex: $[\text{Cu}(\text{C}_6\text{H}_5\text{NC})_4][\text{ClO}_4]$ $[\text{Cu}(\text{PMe}_2\text{Ph})_4][\text{ClO}_4]$ $[\text{Cu}(\text{AsMe}_2\text{Ph})_4][\text{PF}_6]$ $[\text{Cu}(\text{SbPh}_3)_4][\text{PF}_6]$				
$\delta(^{63}\text{Cu})$	549	247	–17	–245
$\Delta_{1/2}$ (Hz)	300	2750	1500	160
Solvent	$\text{C}_6\text{H}_5\text{NC}$	CH_3CN	$\text{CH}_2\text{Cl}_2/\text{CD}_2\text{Cl}_2$	$\text{CH}_2\text{Cl}_2/\text{CD}_2\text{Cl}_2$

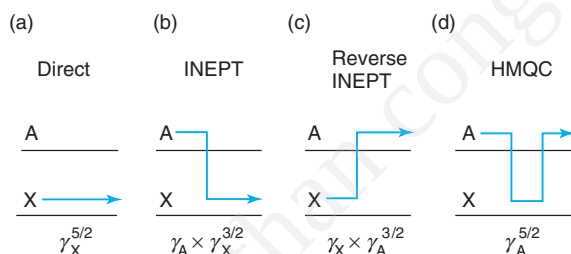
^aData from Reference [30]

the investigation of high-temperature superconducting cuprates like $\text{YBa}_2\text{Cu}_4\text{O}_8$ is presently an active research topic.

12.3.5

Rhodium-103

As with cobalt-59, rhodium-103 is a 100% natural abundance nucleus but has the disadvantage of a low gyromagnetic ratio. A breakthrough for rhodium came with FT NMR and the advances in detection methods by polarization transfer and indirect observation via sensitive nuclei like ^1H or ^{31}P that require, however, scalar $^{103}\text{Rh}, \text{X}$ coupling constants to protons or phosphorus as sensitive partners. We recall the relations for the different detection techniques with the short-hand notation shown in the following diagram, where the dependence of the signal-to-noise ratio on the γ factors is given below each graph:



For the final result a saturation factor $(1 + e^{t_R/T_1})$ with t_R as the repetition time in the case of spectral accumulation and T_1 the spin–lattice relaxation time of the excited (a, b) or observed (c, d) nucleus has to be considered (Chapter 10, p. 364). The signal enhancements expected from NOE ($\eta_{\text{NOE}} = \gamma_A/2\gamma_X$) and – relative to situation (a) above – from INEPT (γ_A/γ_X), reverse INEPT $[(\gamma_A/\gamma_X)^{3/2}]$, and HMQC $[(\gamma_A/\gamma_X)^{5/2}]$ are collected for several nuclei of interest in Table 12.23. Since NOE enhancement does not require scalar coupling, as the other techniques do, it may be helpful in cases where spin–spin coupling is missing. However, the

Table 12.23 Intensity enhancement factors for NOE, polarization transfer, and inverse detection experiments for $^1\text{H}, \text{X}$ spin pairs of selected X nuclei.

X =	^{13}C	^{57}Fe	^{95}Mo	^{103}Rh	^{183}W	^{187}Os
NOE	1.99	15.41	−7.64	−15.80	11.86	21.60
INEPT	3.98	30.8	15.3	31.6	23.7	43.2
Inverse INEPT	7.93	171	59.7	178	115	284
HMQC	31.5	5272	912	5610	2738	12 264

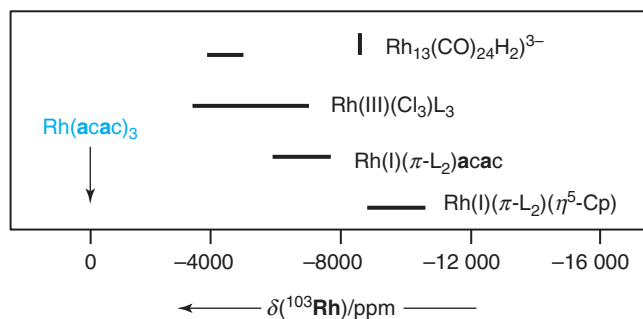


Figure 12.31 ^{103}Rh chemical shift diagram for various rhodium complexes. After Reference [20].

NOE is based on dipolar interactions and will be diminished if other relaxation pathways are available. Since metal nuclei relaxation is dominated by the CSA mechanism the enhancement achieved in these cases is often negligible. Furthermore, for nuclei with negative γ -values, small negative signal “enhancements” may lead in fact to an intensity decrease (cf. Chapter 10, p. 344).

As Table 12.23 (p. 485) shows, a considerable enhancement factor of 31.59 results for ^{103}Rh NMR by INEPT experiments with protons. For indirect detection via ^1H we have an additional enhancement of $[\gamma(^1\text{H})/\gamma(^{103}\text{Rh})]^{3/2} = 177.6$ and the largest sensitivity advantage is obtained by the inverse 2D experiment HMQC. Of course, if coupling or nearby protons are absent, simple FT experiments with relaxation reagents and the accumulation of a large number of scans have to be used, especially since the NOE is mostly not an alternative (see above).

A survey of rhodium-103 *chemical shifts* is shown in Figure 12.31, while Figure 12.32 gives information about the smaller range for complexes with organic ligands, which is also smaller than that for the corresponding cobalt-59 complexes by about 500 ppm (cf. Figure 12.30, p. 484).

Interesting correlations between $\delta(^{103}\text{Rh})$ and structural as well as kinetic and thermodynamic properties of rhodium complexes have been found. For systems of

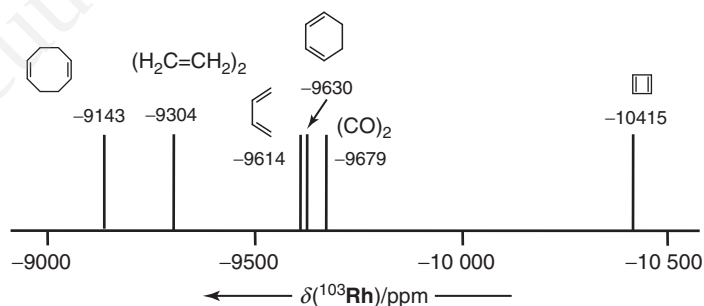


Figure 12.32 ^{103}Rh chemical shift diagram for rhodium complexes of the $[\text{CpRh}(\pi\text{-L})_2]$ type with organic ligands. After Reference [20]

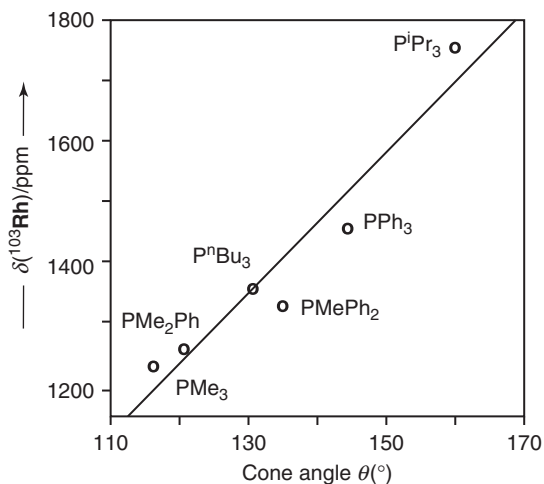
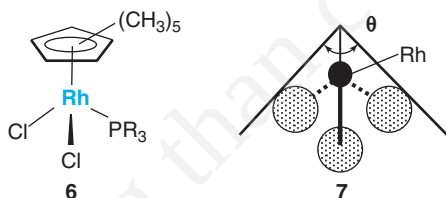
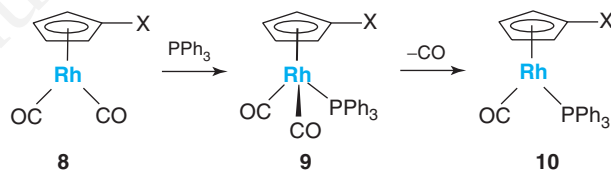


Figure 12.33 Correlation between $\delta(^{103}\text{Rh})$ and the Tolman angle θ in $\text{RhCp}^*\text{Cl}_2(\text{PR}_3)$ complexes (**6**) [31].

type **6** the structural angle θ , known as the *Tolman angle* and defined in **7**, correlates linearly with the ^{103}Rh chemical shift (Figure 12.33).



In another investigation, a linear relation between the reaction rate for the replacement of CO by triphenylphosphine in half-sandwich complexes shown in **8–10** and the ^{103}Rh chemical shift demonstrates the catalytic activity of rhodium complexes (Figure 12.34, p. 488). Other examples have been described and have established rhodium NMR as an important tool for studies of homogeneous catalysis.



Coupling constants between ^{103}Rh and ^{13}C in complexes with organic ligands cover a range between ~ 5 and nearly ~ 100 Hz. A negative sign was observed through 2D cross peak distortions in HMQC spectra for coupling to ^1H , ^{19}F , and ^{31}P , while the homonuclear ^{103}Rh , ^{103}Rh coupling and that to ^{15}N , ^{119}Sn , ^{125}Te were found positive.

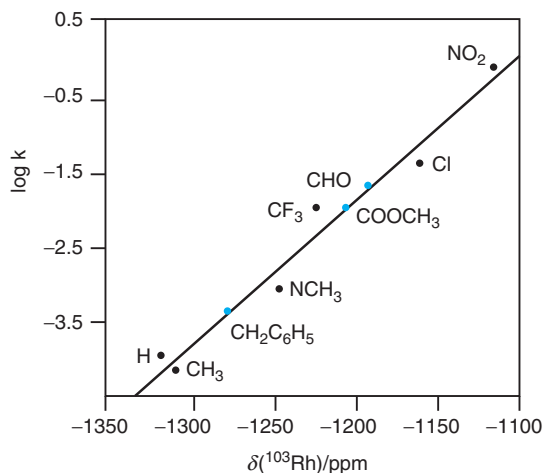


Figure 12.34 Correlation of ^{103}Rh chemical shifts of substituted $(\text{X})\text{CpRh}(\text{CO})_2$ complexes with the rate constant of carbonyl displacement reaction with $\text{P}(\text{C}_6\text{H}_5)_3$. (Reproduced with permission from [32]; Copyright 1992 American Chemical Society).

12.3.6

Cadmium-113

The nuclide cadmium-113 of the two cadmium isotopes with spin $I = \frac{1}{2}$, ^{111}Cd and ^{113}Cd , has a slightly larger magnetic moment. Both nuclides have a natural abundance of about 12.5% but the nuclide ^{113}Cd is used nearly exclusively for NMR measurements because of its higher sensitivity. Cadmium complexes are labile in aqueous solution and samples often contain more than one species. Organic complexes are measured mostly in benzene as solvent. A few typical *chemical shift* values for organic and inorganic complexes are collected in Table 12.24.

Table 12.24 Typical cadmium chemical shifts $\delta(^{113}\text{Cd})$ in ppm for organic^a and inorganic^b complexes^c.

$\text{H}_3\text{C-Cd-C}_2\text{H}_5$ -50	$\text{Cd}(\text{C}_2\text{H}_5)_2$ -94	$\text{Cd}(n\text{-C}_3\text{H}_7)_2$ -48; 20% in CH_2Cl_2	$\text{Cd}(n\text{-C}_3\text{H}_7)_2$ -139; neat	$\text{Cd}(i\text{-C}_3\text{H}_7)_2$ -207
$\text{Cd}(\text{C}_6\text{H}_5)_2$ -314	$\text{H}_3\text{C-Cd-OCH}_3$ -323	$\text{H}_3\text{C-Cd-OC}_6\text{H}_5$ -383	$\text{H}_3\text{C-Cd-S}(i\text{-C}_3\text{H}_7)$ -31	$\text{H}_3\text{C-Cd-S}(t\text{-C}_4\text{H}_9)$ -44
CdCl_2 +98 in D_2O	CdCl_2 +265 in 12 M HCl	CdBr_2 +109 in D_2O	CdBr_2 +167 in 9 M HBr	CdI_2 +55
$\text{Cd}[\text{SO}_4]$ -5	$\text{Cd}[\text{NO}_3]_2$ -49	$\text{Cd}[\text{SCN}]_2$ 60	$\text{Cd}[(\text{CN}_4)]^{2-}$ 510	$\text{Cd}[\text{Mn}(\text{CO})_5]_2$ 552 in CH_3OH

^aRelative to $\text{Cd}(\text{CH}_3)_2$ in benzene if not stated otherwise.

^bRelative to $\text{Cd}[\text{ClO}_4]_2$ in D_2O or H_2O if not stated otherwise.

^cData from Reference [33].

In the first row of compounds we see again a shielding effect in complexes with steric crowding, but also a solvent effect. The second row shows that oxygen is a shielding ligand, while sulfur is deshielding. The halogens in the third row show no definite trend, but strong deshielding in acidic media. Finally, tetra-coordinated and metal-substituted cadmium is strongly deshielded with the resonances at the highest frequencies.

Cadmium NMR has more recently found important applications in studies of metalloproteins where cadmium as a surrogate probe can replace zinc or calcium, which are much more difficult nuclei for NMR measurements. A metalloprotein whose metal center is coordinated through sulfur atoms of thiolate groups alone yields highly deshielded ^{113}Cd resonances between 600 and 700 ppm, whereas Cd(II) ions coordinated exclusively via the carbonyl oxygens give rise to signals between 0 and -125 ppm. This difference in shielding parallels the entries in the second row of compounds in Table 12.24. Furthermore, the measurement of $^{113}\text{Cd}, ^1\text{H}$ coupling constants via 2D spectroscopy has given valuable information about metal–ligand connectivities and the structure at the metallocenter. In dialkyl cadmium complexes $^2J(^{113}\text{Cd}, ^1\text{H})$ amounts to about 50 Hz, while ^3J values are larger. For cadmium alkoxides a $^1J(^{113}\text{Cd}, ^{13}\text{C})$ of about 500 Hz was found while for $^1J(^{113}\text{Cd}, ^{31}\text{P})$ in cadmium phosphanes values of 1200 to nearly 1400 have been observed.

12.3.7

Iron-57

From the last group of nuclei, ^{57}Fe , ^{55}Mn , ^{95}Mo , ^{183}W , ^{187}Os , and ^{199}Hg , iron-57 was – aside from ^{187}Os – the most difficult nucleus to measure. Its detection sensitivity relative to ^{13}C is only 0.004 and its natural abundance is not more than 2.2%. Its spin $I = \frac{1}{2}$, normally an advantage, has the negative effect that its resonance is easily saturated due to the high power necessary for detection and the lack of effective quadrupolar relaxation. The breakthrough for iron NMR – as for rhodium and other nuclei with low sensitivity – came with FT NMR and the advanced detection methods such as polarization transfer and indirect 2D experiments via sensitive nuclei like ^1H or ^{31}P that require, however, scalar $^{57}\text{Fe}, \text{X}$ coupling. Considerable enhancement factors for NOE and INEPT experiments with protons result for ^{57}Fe [$\eta_{\text{NOE}} = 15.4$, $\eta_{\text{INEPT}} = 30.8$ (Table 12.22)]. For indirect detection via ^1H we even have an enhancement of $[\gamma(^1\text{H})/\gamma(^{57}\text{Fe})]^{5/2}$, nearly 5300. Today, ^{57}Fe can be considered as an NMR friendly nucleus that yields important structural information for iron compounds and their use in homogeneous catalysis.

Figure 12.35 (p. 490) shows the results of a standard FT NMR experiments for $^{57}\text{Fe}(\text{CO})_5$ at 12.96 MHz with a “search” spectrum measured with high power, a large sweep range, and unknown length for the 90° pulse (Figure 12.35a), the same with optimized parameters (Figure 12.35b), and the spectrum of a mixture of ferrocene and tricarbonyl(butadiene)iron (Figure 12.35c). For these direct measurements of insensitive nuclei several points have to be considered:

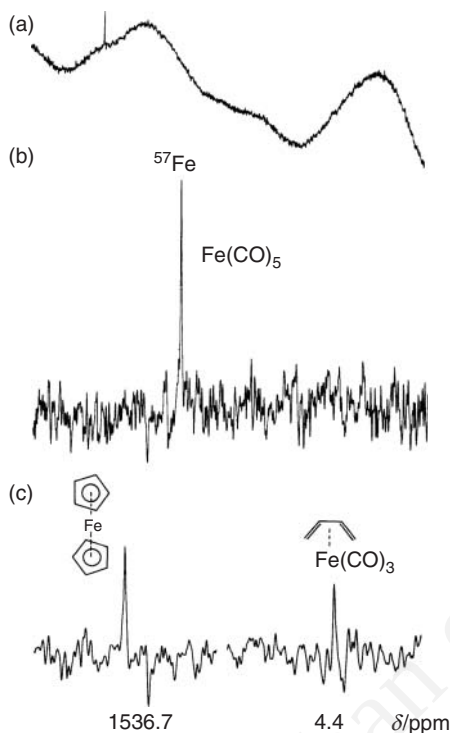


Figure 12.35 ^{57}Fe NMR spectroscopy at 12.96 MHz: (a) “search” spectrum, 77 000 transients, measuring time 11 h; (b) optimized parameters [$t_p(90^\circ) = 74 \mu\text{s}$], measuring time 1 h 14 min, signal-to-noise ratio 6.4:1; (c) spectrum of a mixture of ferrocene and tricarbonyl(butadiene)iron, 1 M in benzene, reference $\text{Fe}(\text{CO})_5$ [6] (Copyright 1984; with kind permission of Springer Science+Business Media).

- 1) Measurements are greatly facilitated if the pulse width t_p of the 90° pulse is known at least approximately. In some cases it is possible to obtain a good guess by determining the pulse length for a more sensitive nuclide with a similar NMR frequency.
- 2) As for most of the insensitive nuclei, spin–lattice relaxation is dominated by the CSA mechanism where T_1 is inverse proportional to B_0^2 (cf. Eq. 12.6, p. 434); high B_0 fields should thus be used in order to reduce T_1 which allows high repetition rates.
- 3) The large chemical shift ranges of transition metal nuclide require short pulses. At a B_0 field of 9.4 T, for example, 10 000 ppm correspond for ^{57}Fe to ca. 129 kHz and the pulse should be less than $3.9 \mu\text{s}$, otherwise the observed signal may be folded.
- 4) The temperature dependence of metal chemical shifts requires temperature control during long-time measurements.

As shown in Figure 12.36, the ^{57}Fe chemical shifts [general reference external $\text{Fe}(\text{CO})_5$] for compounds with a formal iron oxidation state +2 are scattered over

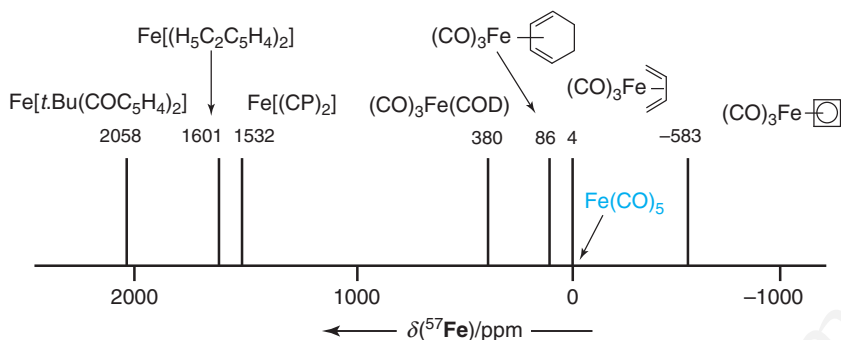


Figure 12.36 ^{57}Fe chemical shift diagram for various iron compounds. After Reference [20].

about 3000 ppm. Iron porphyrin complexes show resonances around 8200 ppm, cytochrome *c* even at 11 200 ppm. As for rhodium, several linear correlations between $\delta(^{57}\text{Fe})$ and the rate for reactions of iron complexes were established, for example, insertion of CO into iron–ligand bonds or ligand exchange.

12.3.8

Manganese-55

In contrast to ^{57}Fe , manganese-55 is an easy nucleus to measure, even without signal averaging, and its 100% natural abundance yields a favorable signal-to-noise ratio. Nevertheless, with a spin $I = \frac{5}{2}$ it has a large quadrupole moment, the magnitude of which is approximately twice that of ^{51}V . Therefore, ^{55}Mn NMR suffers from large line widths. Values between 1 and 21.5 kHz have been reported. Because of the tetrahedral symmetry around the ^{55}Mn nucleus, the line width of the reference compound KMnO_4 , with the only observed resonance for a Mn(VII) oxidation state at the extreme high-frequency end of the *chemical shift* scale, is of the order of only 10 Hz. ^{55}Mn shielding has mostly been measured for carbonylmanganese compounds and differs for systems with different oxidation states of the metal. Diamagnetic compounds correspond to oxidation states of +I, 0, and –I. A few selected shift values observed in THF as solvent are summarized below [33]:

	$\text{ClMn}(\text{CO})_5$	$\text{CpMn}(\text{CO})_3$	$\text{CH}_3\text{Mn}(\text{CO})_5$	$\text{HMn}(\text{CO})_5$	$\text{HMn}(\text{PF}_3)_5$
$\delta(^{55}\text{Mn})$ (ppm)	–1004	–2225	–2265	–2630	–2953
$\Delta_{1/2}$ (Hz)	331	10 039	3040	4347	10 785

In $\text{XMn}(\text{CO})_3$ compounds the shielding increases in the order $\text{X} = \text{Cl} < \text{Br} < \text{I}$ (–1004, –1160, –1485), similar to the situation met for ^{13}C and other nuclei. In systems of the type $\text{LMn}(\text{CO})_3$, the polarity of the L–Mn bond is reflected in the ^{55}Mn shielding with low-frequency shifts for high electron density around the metal. Changes in electron density that result in changes of bond polarity along the

z -axis of these compounds with C_{4v} symmetry cause perturbations of manganese 3d-electrons that in turn change the orbital angular momentum factor in σ_p .

Because of the large line widths generally observed, line splittings due to *spin-spin coupling* to other nuclei are rare. Exceptions are phosphine and phosphite complexes that show couplings of over hundred hertz. One-bond ^{55}Mn , ^{13}C coupling constants between 35 and 190 Hz were found to increase with the metal-carbon bond order.

12.3.9

Molybdenum-95

Two magnetically active nuclides, ^{95}Mo and ^{97}Mo , are known for molybdenum, both with spin $I = \frac{5}{2}$ but with an unusual difference in their quadrupole moment (-0.022 versus 0.255 barn). That of molybdenum-95 is the smaller one and this nucleus is generally preferred for NMR studies.

Molybdenum has a rich chemistry with compounds of oxidation states Mo(0) to Mo(VI). Those with Mo(III) and Mo(VI) are paramagnetic and only the diamagnetic dimers can be studied. The *chemical shift* range of ^{95}Mo resonances that are measured relative to the reference line of $[\text{MoO}_4]^{2-}$ extends over more than 7000 ppm. Subregions for the different oxidation states overlap and most of the data have been collected for Mo(VI), Mo(II), and Mo(0) complexes. The line widths of the ^{95}Mo signals are not exceedingly large with upper values of 250 Hz, but many are less than 50 Hz. For Mo(arene)(CO)₃ complexes the small line width of 6 Hz allowed detection of the chemical shift induced by substituents in the second coordination sphere, thus demonstrating the sensitivity of metal NMR to minor structural changes [34]:

$\text{RMo}(\text{CO})_3$; R =	Mesityl	<i>m</i> -Xylyl	<i>p</i> -Xylyl	<i>o</i> -Xylyl	Tolyl
$\delta(^{95}\text{Mo})$ (ppm)	-1907	-1971	-1979	-1988	-2034

Numerous one-bond ^{95}Mo , ^{31}P *coupling constants* with values between 117 and 290 Hz, especially for Mo(0) complexes, have been determined. Couplings with ^1H (~ 15 Hz) or ^{13}C (~ 70 Hz) are less frequently observed.

12.3.10

Tungsten-183

Despite the favorable fact that tungsten-183 has a spin $I = \frac{1}{2}$ and a fairly high natural abundance of 14.3%, the low γ -factor makes ^{183}W NMR difficult. Early workers used the INDOR (inter-nuclear *double resonance*) technique for indirect detection via sensitive nuclei like ^1H , ^{19}F , or ^{31}P , but with the advent of FT the use of modern pulse methods has become possible and interest in ^{183}W NMR to study tungsten compounds has increased markedly. Especially, 2D experiments as applied to ^{183}W have helped to establish the complex structure, for example, of

polyoxotungstates (Figure 12.37). Nevertheless, relatively long relaxation times that require many scans to reach a reasonable signal-to-noise ratio are a drawback.

Because the chemistry of tungsten is similar to that of molybdenum, many parallel studies of ^{95}Mo and ^{183}W have been carried out. ^{183}W has a chemical shift range that exceeds 6000 ppm. A smaller subregion between -4000 and -2500 ppm is observed for organotungsten compounds, but the individual ranges overlap (Table 12.20). A few compounds from different regions of the chemical shift scale are selected with their resonances relative to WF_6 in Table 12.25. Today, $[\text{WO}_4]^{2-}$ that is easier to handle than WF_6 , is the recommended reference (see Table 12.20).

One-bond coupling constants of ^{183}W in several tungsten hydrides range from 20 to 80 Hz (those with ^{13}C vary between 125 and 200 Hz).

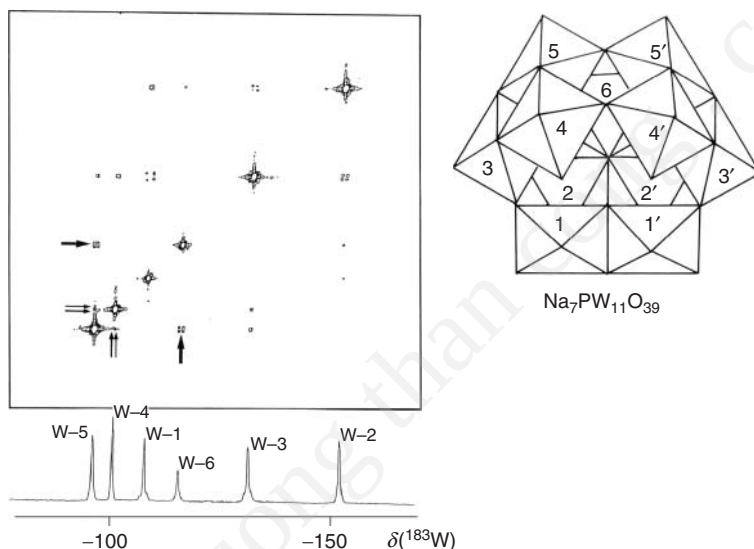


Figure 12.37 ^{183}W , ^{183}W COSY spectrum of the tungsten cluster $\text{Na}_7\text{PW}_{11}\text{O}_{39}$; the cross-peaks result from geminal ^{183}W couplings in the ^{183}W -O- ^{183}W fragments (isotope abundance 2%) (Reprinted with permission from [35]. Copyright 1983 American Chemical Society).

Table 12.25 $\delta(^{183}\text{W})$ values for selected tungsten compounds (ppm relative to WF_6).

$\delta(^{183}\text{W})$	$t\text{-WF}_4\text{O(OMe)}_2$	$\text{WF}_5(\text{OPh})$	$\text{WF}_5(\text{OMe})$	WF_6	$\text{W(CO)}_3\text{CpCl}$
Solvent	Neat	C_6F_6	C_6F_6	Neat	CDCl_3
$\delta(^{183}\text{W})$	$\text{W(CO)}_3\text{CpBr}$	$\text{W(CO)}_3\text{CpI}$	$\text{W(CO)}_5(\text{PMePh}_2)$	$\text{W(CO)}_3\text{CpH}$	WCp_2H_2
Solvent	CDCl_3	CDCl_3	CDCl_3	CDCl_3	CDCl_3

Data from Reference [33].

12.3.11

Mercury-199

The element mercury has two isotopes with non-zero nuclear spins, ^{199}Hg with $I = \frac{1}{2}$ and ^{201}Hg with $I = \frac{5}{2}$ and a quadrupole moment. Unsurprisingly then, mercury-199 is the nucleus of choice for chemical applications of mercury NMR. Because of the short relaxation times of ^{199}Hg (<0.1 s), caused by the CSA mechanism (cf. p. 434), high repetition rates can be used for direct FT measurements. For the same reason, polarization transfer methods like INEPT or DEPT are not very efficient and at strong magnetic fields coupling to other nuclei might vanish. Figure 12.38 shows results obtained for the ^1H and ^{13}C spectra of bis(trimethylsilyl)mercury at two different field strengths of B_0 , 1.88 and 9.4 T, that demonstrate the field dependence of the CSA mechanism. Satellites due to ^{199}Hg , ^1H and ^{199}Hg , ^{13}C coupling are strongly broadened at 9.4 Tesla. Similar results are obtained for bis(*t*-butyl)mercury and the spin–lattice relaxation times T_1 (ms) measured for both compounds at three different B_0 fields demonstrate the acceleration of the relaxation rate, as shown below.

	B_0 (T)		
	1.88 (80) ^a	6.35 (270)	9.40 (400)
T_1 (ms) bis(trimethylsilyl)mercury	460	45.4	21.5
T_1 (ms) bis(<i>t</i> -butyl)mercury	1280	136	63.5

^a ^1H frequency in megahertz in parenthesis.

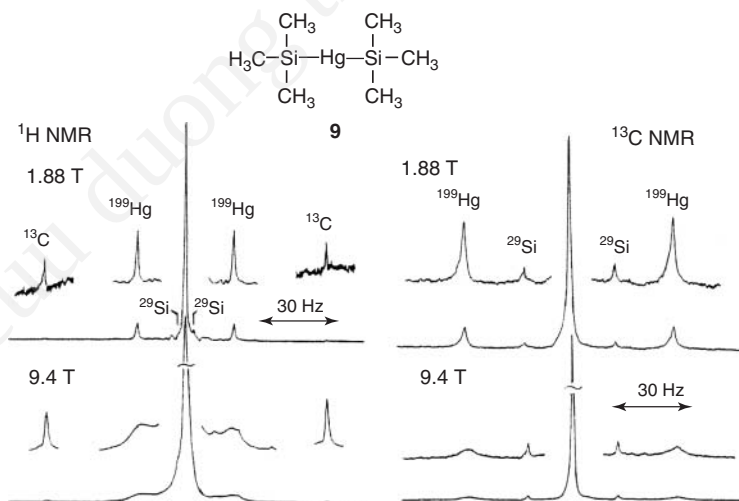


Figure 12.38 ^1H and ^{13}C NMR spectra of bis(trimethylsilyl)mercury (9) at 1.88 and 9.4 T. The following coupling constants were measured at 1.88 T from the respective satellites: $^1J(^{13}\text{C}, ^1\text{H}) = 119.6$, $^2J(^{29}\text{Si}, ^1\text{H}) = 6.6$, $^3J(^{199}\text{Hg}, ^1\text{H}) = 40.7$, $^1J(^{13}\text{C}, ^{29}\text{Si}) = 40.1$, and $^1J(^{13}\text{C}, ^{199}\text{Hg}) = 92.1$ Hz [36].

The *chemical shift* of the reference compound $\text{Hg}(\text{CH}_3)_2$ (caution! highly poisonous) is strongly solvent dependent, as the following data [ppm relative to neat $\text{Hg}(\text{CH}_3)_2$] shows:

Solvent	DMSO	Pyridine	Acetonitrile	THF	Benzene	CH_2Cl_2	Hexane
$\delta(^{199}\text{Hg})$ (ppm)	−108	−94	−78	−76	−50	−46	+5

Such a strong solvent dependence is also found for ^{199}Hg resonances of other compounds and is a general feature of ^{199}Hg NMR. All shift data given below are relative to neat $\text{Hg}(\text{CH}_3)_2$. In addition to the solvent dependence, ligand exchange is fairly easy in aqueous solution and this may have a severe line broadening effect on the ^{199}Hg resonance. Furthermore, it is not always clear what species is measured. For mercury halides one observes a heavy-atom effect with shielding in the order $\text{Cl} < \text{Br} < \text{I}$ with $\delta(^{199}\text{Hg})$ values (1.0 M DMSO) of −1499 for HgCl_2 , −2067 for HgBr_2 , and −3131 ppm for HgI_2 . Other mercury salts and complexes show resonances between about −400 ppm, for example, $\text{HgCl}_2[\text{P}(n\text{-But.})_3]_2$ −404, and −2400 ppm, for example, $\text{Hg}(\text{OCOCH}_3)_3$ −2389 ppm. The introduction of iodine always shifts the resonance to lower frequency. Some trends for ^{199}Hg shielding in diorganomercury compounds have been extracted from the literature [37]. For alkyl mercury compounds one finds a strong β -effect that yields shielding:

	$(\text{Me})_2\text{Hg}$	$(\text{Et})_2\text{Hg}$	$(i\text{-Pr})_2\text{Hg}$	$(t\text{-But})_2\text{Hg}$
$\delta(^{199}\text{Hg})/(\text{C}_6\text{H}_6)$ (ppm)	−50	−294	−595	−828

The opposite trend is observed in silyl-substituted systems, where the introduction of methyl groups yields deshielding:

	$(\text{H}_3\text{Si})_2\text{Hg}$	$(\text{Me}_3\text{Si})\text{Hg}(\text{SiH}_3)$	$(\text{Me}_3\text{Si})_2\text{Hg}$
$\delta(^{199}\text{Hg})/(\text{C}_6\text{H}_6)$ (ppm)	+196	+327	+456

Shielding is again observed upon substitution by electronegative groups like chlorine, which may lead to an increase of the energy for electronic excitations, ΔE , at the mercury atom that in turn reduces the paramagnetic contribution to the shielding constant:

	$(\text{Me}_3\text{Si})_2\text{Hg}$	$(\text{Me}_2\text{ClSi})_2\text{Hg}$	$(\text{MeCl}_2\text{Si})_2\text{Hg}$	$(\text{Cl}_3\text{Si})_2\text{Hg}$
$\delta(^{199}\text{Hg})/(\text{C}_6\text{D}_6/\text{C}_6\text{F}_6)$ (ppm)	+499	−315	−658	−1001

Of interest is that the γ -effect that yields shielding for many nuclei has the opposite trend for $\delta(^{199}\text{Hg})$ because van-der-Waals effects (see p. 116) are absent due to the linear bonding situation at mercury ($-\text{Hg}-$):

	$(\text{CH}_3\text{CH}_2)_2\text{Hg}$	$(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{Hg}$	$[(\text{CH}_3)_3\text{CCH}_2]_2\text{Hg}$
$\delta(^{199}\text{Hg})$ (ppm)	−294	−240	−149

Scalar coupling of ^{199}Hg to various X nuclei has been observed and one-bond couplings are usually large: for ^{13}C and ^{29}Si from about 500 to nearly 4000 Hz and for ^{31}P from 140 to even more than 17 kHz! Systematic correlations with structure

are, therefore, difficult to make. Geminal and vicinal couplings are an order of magnitude smaller.

12.3.12

Osmium-187

Osmium-187, a nuclide of the group of difficult nuclei with spin $\frac{1}{2}$ but low γ -factors like ^{54}Fe or ^{103}Rh , also has a very low natural abundance of less than 2% and is in fact the nucleus with the lowest receptivity. The other osmium nuclide, ^{189}Os , with higher natural abundance (16.1%) is not an attractive alternative because of its spin $I = \frac{5}{2}$ and large quadrupole moment (0.856 barn). Nevertheless, the detection techniques available today have successfully overcome the obstacles of ^{187}Os NMR and several studies have reported osmium *chemical shifts*. For (*p*-cymene) $\text{Os}(\text{Cl}_2)\text{PR}_3$ complexes it was possible to observe a linear relation between $\delta(^{187}\text{Os})$ and the Tolman steric parameter θ (cf. Figure 12.33 for ^{103}Rh) of complexes with differently substituted phosphane groups PR_3 . The ^{187}Os shifts observed span a range of 700 ppm, from -2300 to -1600 relative to the resonance of OsO_4 and, like $\delta(^{95}\text{Mo})$, $\delta(^{187}\text{Os})$ is sensitive to changes of substituents in the second coordination sphere of osmium arene complexes: $(\text{C}_6\text{H}_5\text{R}^1)\text{Os}(\text{Cl}_2)\text{PR}_3$ ($\text{R}^1 = \text{H}$, -2431 ppm; $\text{R}^1 = t\text{-butyl}$, -2268 ppm).

References

1. Harris, R.K. in *NMR and the Periodic Table* (eds R.K. Harris and E. Mann), Academic Press, New York, p. 16.
2. Harris, R.K., Becker, E.D., Cabral de Menezes, S.M., Goodfellow, R., and Granger, P. (2002) *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 9, (eds in chief D.M. Grant and R.K. Harris), John Wiley & Sons, Ltd, Chichester, p. 5.
3. (a) Reed, D. (1996) in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 2 (eds in chief D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester, p. 1002. (b) Mann, B.E. (1978) in *NMR and the Periodic Table* (eds R.K. Harris and E. Mann), Academic Press, New York, p. 87 ff.
4. Wrackmeyer, B. (1988) *Annu. Rep. NMR Spectrosc.*, **20**, 61. (b) Mann, B.E. (1978) in *NMR and the Periodic Table* (eds in chief R.K. Harris and E. Mann), Academic Press, New York, p. 91.
5. Fontaine, X.-L.R., Greenwood, N.N., Kennedy, J.D., and McKinnon, P. (1988) *J. Chem. Soc., Dalton Trans.*, 1785.
6. Günther, H. and Schmitt, P. (1984) *NMR in den 80er Jahren*, Naturwissenschaften **71**, 342.
7. Berger, S., Braun, S., and Kalinowski, H.-O. (1992) in *NMR-Spektroskopie von Nichtmetallen*, Vol. 2, G. Thieme Verlag, Stuttgart; English edn, Wiley-VCH Verlag GmbH, Weinheim.
8. Schumacher, M. and Günther, H. (1983) *Chem. Ber.*, **116**, 2001.
9. Berger, S., Braun, S., and Kalinowski, H.-O. (1992) in *NMR-Spektroskopie von Nichtmetallen*, Vol. 1, G. Thieme Verlag, Stuttgart; English edn, Wiley-VCH Verlag GmbH, Weinheim.
10. Mooney, E.F. (1970) *An Introduction to ^{19}F NMR Spectroscopy*, Heyden-Sadtler, London.
11. (a) Harris, R.K., Kennedy, J.D., and McFarlane, W. (1978) in *NMR and the Periodic Table* (eds in chief R.K. Harris and E. Mann), Academic Press, New York, p. 310. (b) Marsmann, H.C. (1996) *Encyclopedia of Nuclear Magnetic Resonance* (eds in chief D.M. Grant and R.K.

- Harris), vol. 7, John Wiley & Sons, Ltd, Chichester, p. 4386.
12. Schraml, J. and Bellama, J.M. (1976) in *Determination of Organic Structure by Physical Methods*, Vol. 6 (eds F.C. Nachod, J.J. Zuckerman, and E.W. Randall), Academic Press, New York, pp. 203–269.
 13. Dixon, K.R. (1987) in *Multinuclear NMR* (ed J. Mason), Plenum Press, New York, p. 369.
 14. (a) Berger, S., Braun, S., and Kalinowski, H.-O. (1992) in *NMR-Spektroskopie von Nichtmetallen*, Vol. 3 G. Thieme Verlag, Stuttgart; English edn, Wiley-VCH Verlag GmbH, Weinheim. (b) Karaghiosoff, K. (1996) in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 6 (eds in chief, D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester.
 15. Baumann, W. (2008) NMR spectroscopic methods, in *Phosphorus Ligands in Asymmetric Catalysis* (ed A. Boerner), Wiley-VCH Verlag GmbH, Weinheim, pp. 1407–1432.
 16. (a) Smith, L.R. and Mills, J.L. (1976) *J. Am. Chem. Soc.*, **98**, 3852. (b) Baudler, M., Carlsohn, B., Böhm, B., and Reuschenbasch, G. (1976) *Z. Naturforsch., Teil B*, **31**, 558.
 17. Günther, H. (1996) in *Advanced Applications of NMR to Organometallic Chemistry* (eds M. Gielen, R. Willem, and B. Wrackmeyer), Wiley-VCH Verlag GmbH, Weinheim, p. 247.
 18. Thomas, R.D., Clarke, M.T., Jensen, R.M., and Young, T.C. (1986) *Organometallics*, **5**, 1851.
 19. Eppers, O., Fox, T., and Günther, H. (1992) *Helv. Chim. Acta*, **75**, 883.
 20. Benn, R. and Ruffínska, A. (1986) *Angew. Chem.*, **98**, 851; *Angew. Chem., Int. Ed. Engl.*, **25**, 861.
 21. Akitt, F.W. (1988) *Progr. Nucl. Magn. Reson. Spectros.*, **21**, 1.
 22. Kayser, F., Biesemans, M., Gielen, M., and Willem, R. (1996) in *Advanced Applications of NMR to Organometallic Chemistry* (eds M. Gielen, R. Willem, and B. Wrackmeyer), Wiley-VCH Verlag GmbH, Weinheim, p. 45.
 23. a) Harris, R.K., Kennedy, J.D., and McFarlane, W. (1978) in *NMR and the Periodic Table* (eds R.K. Harris and E. Mann), Academic Press, New York, p. 342. b) Kennedy, J.D. and McFarlane, W. (1987) in *Multinuclear NMR* (ed J. Mason), Plenum Press, New York, p. 305.
 24. Davis, A.G., Tse, M.W., Kennedy, J.D., Pyne, G.S., McFarlane, W., Ladd, M.F.C., and Povey, D.C. (1981) *J. Chem. Soc., Perkin Trans. 2*, 369 and references cited therein.
 25. Kersch, S., Sebald, A., and Wrackmeyer, B. (1985) *Magn. Reson. Chem.*, **23**, 514.
 26. Rehder, H. (2008) Vanadium NMR of organovanadium complexes. *Coord. Chem. Rev.*, **252**, 2209.
 27. Ismail, I.M. and Sadler, P.J. (1983) in *Platinum, Gold, and Other Metal Chemotherapeutic Agents*, ACS Symposium Series, Vol. 209 (ed S.J. Lippard), American Chemical Society, Washington D.C., p. 171.
 28. Still, B.M., Kumar, P.G.A., Aldrich-Wright, J.R., and Price, W.S. (2007) ^{195}Pt NMR – theory and application. *Chem. Soc. Rev.*, **36**, 665–686.
 29. McDonald, F.M. and Sadler, P.J. (1986) in *Biochemical Mechanisms of Platinum Antitumour Drugs* (eds D.C.H. McBrien and T.F. Slater) Association for International Cancer Research and Symposia, IRL Press, Oxford, p. 361.
 30. Malito, J. (1999) *Annu. Rep. NMR Spectrosc.*, **38**, 265.
 31. Tedesco, V. and Philipsborn, W.v. (1996) *Magn. Reson. Chem.*, **34**, 373.
 32. Koller, M. and von Philipsborn, W. (1992) *Organometallics*, **11**, 467.
 33. Garth Kidd, R. and Goodfellow, R.J. (1978) in *NMR and the Periodic Table* (eds R.K. Harris and E. Mann), Academic Press, New York, p. 195.
 34. Rehder, D. (1987), in Mason, J. (ed) *Multinuclear NMR*, Plenum Press, New York, p. 479.
 35. Brevard, C. (1983) *J. Am. Chem. Soc.*, **105**, 7059.
 36. Benn, R., Günther, H., Maercker, A., Menger, V., and Schmitt, P. (1982) *Angew. Chem.*, **94**, 314. 1982) *Angew. Chem., Int. Ed. Engl.*, **21**, 295.
 37. Wrackmeyer, B. and Contreras, R. (1992) *Annu. Rep. NMR Spectrosc.*, **32**, 267.

Textbooks

- Atkitt, J.W. and Mann, B.E. (2000) *NMR and Chemistry: An Introduction to Modern NMR Spectroscopy*, 4th edn, Stanley-Thornes, Cheltenham, 400 pp.
- Iggo, J. (2003) *NMR Spectroscopy in Inorganic Chemistry*, Oxford University Press, 88 pp.
- Levy, G.C. and Lichter, R.L. (1979) *Nitrogen-15 NMR-Spectroscopy*, Wiley-VCH Verlag GmbH, Weinheim, 221 pp.
- Pregosin, P.S. (2012) *NMR in Organometallic Chemistry*, Wiley-VCH Verlag GmbH, Weinheim, 392 pp.

Monographs

- Mason, J. (ed) (1987) *Multinuclear NMR*, Plenum Press, New York, 639 pp.
- Harris, R.K. and Mann, E. (eds) (1978) *NMR and the Periodic Table*, Academic Press, New York, 459 pp.
- Brevard, C. and Granger, P. (1981) *Handbook of High Resolution Multinuclear NMR*, John Wiley & Sons, Inc., New York, 229 pp.
- Berger, S., Braun, S., and Kalinowski, H.-O. (1992) in *NMR-Spektroskopie von Nichtmetallen*, Vol. 1–4 G. Thieme Verlag, Stuttgart; English edn, Wiley-VCH Verlag GmbH, Weinheim.
- Martin, G.J., Martin, M.L., and Gouesnard, J.-P. (1981) *¹⁵N-NMR Spectroscopy*, in *NMR-Basic Principles and Progress*, Vol. 18, Springer, Berlin, 382 pp.
- Gielen, M., Willem, R., and Wrackmeyer, B. (eds) (1996) *Advanced Applications of NMR to Organometallic Chemistry*, Wiley-VCH Verlag GmbH, Weinheim, 376 pp.
- Pregosin, P.S. (1991) *Transition Metal Nuclear Magnetic Resonance*, Elsevier, Amsterdam.
- Lambert, J.B. and Siegel, F.G. (eds) (1983) *The Multinuclear Approach to NMR Spectroscopy*, Riedel, Dordrecht.
- Laszlo, P. (ed) (1983) *NMR of Newly Accessible Nuclei*, Vol. 1 and 2, Academic Press, New York.

General Review Articles

- Iggo, J.A., Liu, J., and Overend, G. (2009) The indirect detection of metal nuclei by correlation spectroscopy (HSQC and HMQC). *Annu. Rep. NMR Spectrosc.*, **65**, 179.
- Bühl, M. (2009) DFT computations of transition-metal chemical shifts. *Annu. Rep. NMR Spectrosc.*, **65**, 77.
- von Philipsborn, W. (1999) Probing organometallic structure and reactivity by transition metal NMR spectroscopy. *Chem. Soc. Rev.*, **28**, 95.
- Gudat, D. (1999) Application of heteronuclear X,Y. Correlation spectroscopy in organometallic and organoelement chemistry. *Annu. Rep. NMR Spectrosc.*, **38**, 139.
- Mann, B.E. (1996) Organometallic compounds, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 5 (eds in chief D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester, p. 3400.
- Granger, P. (1996) Quadrupolar transition metal and lanthanide nuclei, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 6 (eds in chief D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester, p. 3889.
- Wrackmeyer, B. (1994) NMR-Spektroskopie von Metallkernen in Lösung. *Chius.*, **28**(6), 309–320.
- Mann, B.E. (1991) The Cinderella nuclei. *Annu. Rep. NMR Spectrosc.*, **23**, 141.
- Buchanan, G.W. (1989) Application of ¹⁵N NMR spectroscopy to the study of molecular structure, stereochemistry and binding phenomena. *Tetrahedron*, **45**, 581.
- Benn, R. and Ruffńska, A. (1986) High resolution metal nuclei NMR spectroscopy of organometallic compounds. *Angew. Chem.* **98**, 851; *Angew. Chem., Int. Ed. Engl.*, **25**, 861.

Selected Review Articles dealing with Individual Nuclei not cited Above

- Li-6,7: Günther, H. (1996) High resolution ^{6,7}Li NMR of organolithium compounds, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 5 (eds in

- chief D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester, p. 2807. Grutzner, J.B. (2002) Application of NMR in carbanion chemistry, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 9, (eds in chief D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester, p. 481.
- B-11: Hermanik, S. (1992) Boron-11 NMR spectra of boranes, main-group heteroboranes, and substituted derivatives. *Chem. Rev.*, **92**, 325.
- N-15: (a) von Philipsborn, W. and Müller, R. (1986) ^{15}N -NMR-Spektroskopie - neue Methoden und ihre Anwendung. *Angew. Chem.*, **98**, 381; *Angew. Chem. Int. Ed.* **28**, 383; (b) Marek, R., Lycka, A., Kolehmainen, E., Sievanen, E., and Tousek, J. (2007) ^{15}N NMR spectroscopy in structural analysis: an update (2001–2005). *Curr. Org. Chem.*, **11**, 1154.
- Al-27: (a) Akitt, J.W. (1988) *Prog. Nucl. Magn. Reson. Spectrosc.*, **21**, 1. (b) Öhmann, L.-O. and Edlund, U. (1996) Aluminum-27 NMR of Solutions, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 5 (eds in chief D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester, p. 742. (c) Amoureux, J.-P. and Pruski, M. (1996) Advances in MQMAS NMR, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 9 (eds in chief D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester, p. 226.
- Si-29: (a) Wrackmeyer, B. (2006) Applications of ^{29}Si NMR parameters. *Annu. Rep. NMR Spectrosc.*, **57**, 1. (b) Schraml, J. (2001) ^{29}Si NMR experiments in solutions of organosilicon compounds, in *Chemistry of Organic Silicon Compounds* (eds Z. Rappoport and Y. Apeloig), Wiley-VCH Verlag GmbH, Weinheim. (c) Engelhardt, G. (1996) in *Encyclopedia of Nuclear Magnetic Resonance* (eds in chief D.M. Grant and R.K. Harris) John Wiley & Sons, Ltd, Chichester, pp. 4398–4407.
- V-51: Rehder, D., Polenova, T., and Bühl, M. (2007) Vanadium-51 NMR. *Annu. Rep. NMR Spectrosc.*, **62**, 49.
- Co-59: Chan, J.C.C. and Au-Yeung, S.C.F. (2000) Cobalt-59 NMR spectroscopy. *Annu. Rep. NMR Spectrosc.*, **41**, 1.
- Cu-63: (a) Malito, J. (1999) Copper-63 NMR-spectroscopy. *Annu. Rep. NMR Spectrosc.*, **38**, 265. (b) Szymanska, I. (2006) ^{63}Cu and ^{31}P nuclear magnetic resonance for characterization of Cu(I) complexes with P-donor ligands. *Pol. J. Chem.*, **80**, 1095.
- Mo-95: Malito, J. (1996) Molybdenum-95 NMR spectroscopy. *Annu. Rep. NMR Spectrosc.*, **33**, 151.
- Rh-103: (b) Carlton, L. (2008) Rhodium-103 NMR. *Annu. Rep. NMR Spectrosc.*, **63**, 49.
- Sn-119: (a) Wrackmeyer, B. (1996) Indirect nuclear ^{119}Sn -X spin-spin coupling, in *Advanced Applications of NMR to Organometallic Chemistry* (eds M. Gielen, R. Willem, and B. Wrackmeyer), Wiley-VCH Verlag GmbH, Weinheim, p. 87. (b) Wrackmeyer, B. (1999) Application of ^{119}Sn NMR parameters. *Annu. Rep. NMR Spectrosc.*, **38**, 203.

cuu duong than cong . com

13

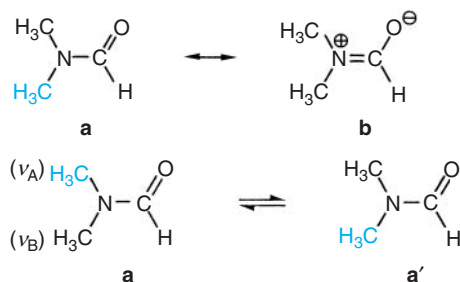
Influence of Dynamic Effects on Nuclear Magnetic Resonance Spectra

As mentioned in the introduction and in the previous chapters, nuclear magnetic resonance (NMR) spectroscopy can be applied to study temperature-dependent reversible processes like conformational changes or valence tautomerism because the line shape of NMR signals is sensitive to these phenomena if they affect the NMR parameters chemical shift or spin–spin coupling. The NMR spectra of many compounds therefore change with temperature. In the following the physical basis of this phenomenon, known as *chemical exchange* or *dynamic nuclear magnetic resonance (DNMR)*, is discussed and applications in chemistry are illustrated with reference to specific examples. Again, proton NMR will dominate, but the methods that we describe apply equally well to other nuclei like lithium-6, carbon-13, fluorine-19, or phosphorus-31, to name only a few.

13.1

Exchange of Protons between Positions with Different Larmor Frequencies

Let us consider at the outset the classical example of *N,N*-dimethylformamide (**a**). The C–N bond between the carbonyl group and the nitrogen atom in this compound has significant double bond character, as is represented by the contribution of structure (**b**) to the resonance hybrid. In the lowest energy planar conformation the protons of the two methyl groups are in different chemical environments and have accordingly different resonance frequencies, ν_A and ν_B . Internal rotation around the N–CO bond leads to an intramolecular exchange of the methyl groups (**a**) $\rightleftharpoons$ (**a'**); however, because of the high energy barrier to rotation (about 88 kJ mol^{−1}



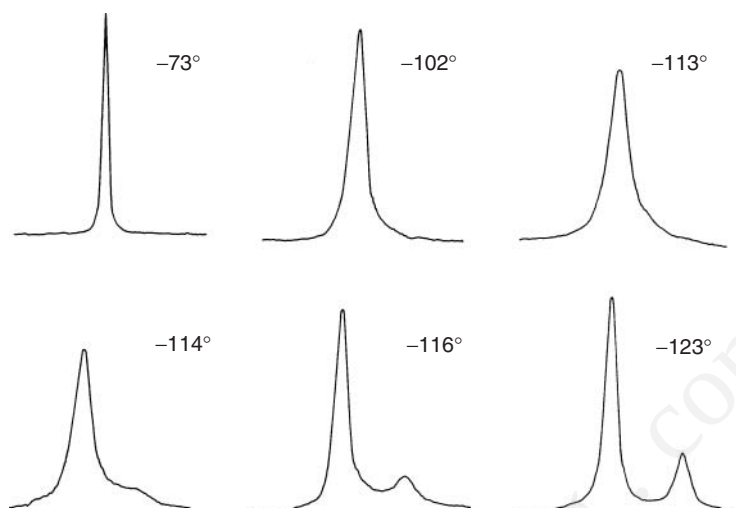
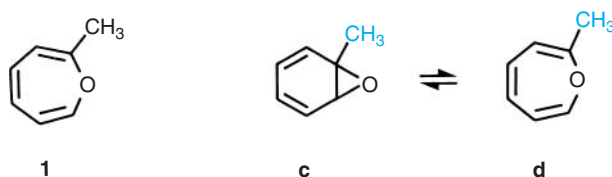


Figure 13.1 ^1H NMR absorption of the methyl protons in 2-methyloxepine (**1**) as a function of temperature ($^{\circ}\text{C}$).

or 21 kcal mol^{-1}) the exchange frequency at room temperature is small and the residence time of the methyl groups in positions *cis*- or *trans*- to the carbonyl group is thus relatively long. Consequently, two separate resonance signals are observed (see Figure 1.5, p. 4).

If the temperature is raised these signals broaden and finally, at temperatures above 120°C , coalesce to a single line. Apparently, at the elevated temperatures the ability to differentiate between the *cis*- and the *trans*-methyl groups is lost.

A similar temperature-dependent phenomenon is observed for the proton resonance signals of 2-methyloxepine (**1**). If we record the absorption of the methyl group the change in the NMR spectrum as a function of temperature is clearly established (Figure 13.1). This variation with temperature can be rationalized on the basis of the valence isomerization between 2-methylbenzene oxide and 2-methyloxepine (**c** $\rightleftharpoons$ **d**), which is fast at room temperature and causes a periodic change to the chemical environment and thus in the Larmor frequency of the methyl protons. Here, where the energy barrier is only about 30 kJ mol^{-1} (7 kcal mol^{-1}), the methyl resonances for the two isomers can be observed only at very low temperature. Furthermore, one finds an intensity difference for these signals since both isomers are of different energy and therefore are present in different concentrations.



A further important type of temperature-dependent variation is illustrated in the spectrum of methanol (Figure 13.2). At -65°C the splitting pattern expected for the AX_3 system of H_3COH is observed. At elevated temperatures the lines broaden and the splittings caused by spin–spin coupling finally vanish until, at 37°C , sharp signals, however without splitting, are again observed. In addition to the loss of spin–spin splitting we note that the chemical shift difference is temperature dependent.

The common cause of the effects described above is the very small energy difference that exists between magnetic sites of different Larmor frequency. To measure such small differences, the *life-time*, τ , of the nuclei in each site must be sufficiently long. According to the uncertainty principle, the lower limit for τ is given by:

$$\tau\delta\nu \approx 1/2\pi \quad (13.1)$$

where $\delta\nu = \Delta E/h$ is the frequency difference $\nu_{\text{A}} - \nu_{\text{B}}$ involved. If τ becomes too small, a time-averaged spectrum is observed.

For dimethylformamide, Eq. (13.1) is violated if the frequency of internal rotation increases with temperature causing the life-time of the methyl protons in positions of different Larmor frequency to decrease. The same is true for the interconversion of the valence tautomers 2-methylbenzene oxide and 2-methyloxepine, where fast reaction rates at room temperature shorten the life-time below the recognizable limit. Similarly, for methanol, the observation of spin–spin splitting corresponds to a detection of very small energy differences. The OH proton is bound to OCH_3 residues that have different total spin $(+\frac{3}{2}, +\frac{1}{2}, -\frac{1}{2}, -\frac{3}{2})$ and different effective Larmor frequencies result. To resolve the corresponding energy differences the

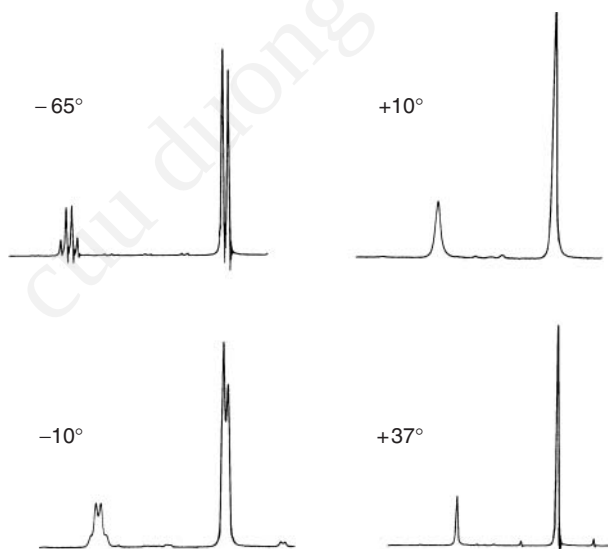


Figure 13.2 ^1H NMR spectrum of methanol as a function of temperature ($^{\circ}\text{C}$).

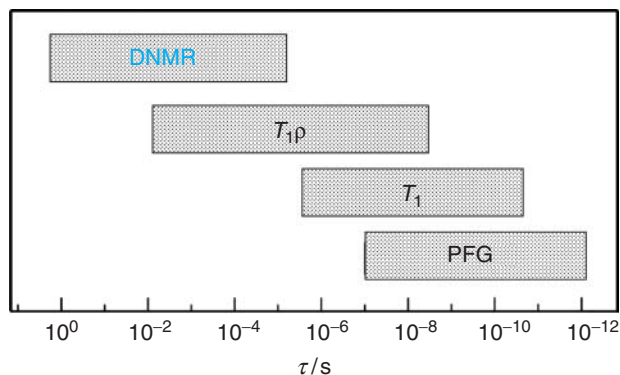


Figure 13.3 Typical regions for NMR methods and correlation times, τ , for dynamic processes.

life-time of the OH proton at each site must satisfy Eq. (13.1) and the intermolecular exchange through hydrogen bonds must be slow. Otherwise, the differentiation between individual signals disappears and only a time-averaged spectrum is recorded.

The ability of the NMR spectrometer to detect such phenomena has an obvious analogy in its likeness to a camera loaded with a film of low sensitivity. To obtain a sharp picture we need a long exposure time and therefore our object, the nucleus in question, must have a relatively long residence time in a given environment. In comparison, infrared and ultraviolet spectroscopies operate substantially faster and time averages of spectral parameters are usually not observed. This difference is explained in the fact that the individual bands in these spectra represent distinct energies. Thus a difference of 10 cm^{-1} in wave numbers is equivalent to an energy difference, ΔE , of 119.7 J mol^{-1} ($28.6 \text{ cal mol}^{-1}$) while a difference of 100 Hz at 600 MHz corresponds to a value of only about $4 \times 10^{-6} \text{ J mol}^{-1}$ ($10^{-6} \text{ cal mol}^{-1}$).

For completeness we mention that aside from the NMR line shape other spectral parameters like relaxation times (T_1 , $T_{1\rho}$) are sensitive probes for molecular dynamics. Including methods of pulsed field gradients the correlation times τ ($= 1/k$) for dynamic processes that can be studied by NMR span a range of several orders of magnitude (Figure 13.3). The experiments in the regime of DNMR that we discuss in the present chapter are generally characterized by correlation times longer than about 10^{-4} s , which corresponds to reaction rates smaller than about $10\,000 \text{ s}^{-1}$.

13.1.1

Quantitative Description of Dynamic Nuclear Magnetic Resonance

To establish a quantitative description concerning the correlation between the line shape of the NMR spectrum on the one hand and the mechanism and kinetics of dynamic processes of the type described above on the other, we must find a

relationship between the life-time of the protons in positions A and B and the line shape of the NMR signal. This is possible on the basis of the Bloch equations that describe the shape of the resonance signal as a function of frequency, ν , and transverse relaxation time, T_2 . Since, as noted on page 246, chemical exchange processes represent an effective mechanism for transverse relaxation, their influence on the NMR line shape is a function of T_2 .

For the present case – a dynamic process that causes a change of Larmor frequencies $\nu_A \rightleftharpoons \nu_B$ – the Bloch equations that in their usual form allow only the calculation of NMR signals at ν_A or ν_B must be modified. In addition to the normal relaxation effects, time-dependent changes of the magnetization at each site are caused by the chemical equilibrium:



Thus, the x, y -magnetization at site A, M_A , is increased through arriving nuclei by an amount proportional to $k_B M_B$. On the other hand, because of the departing nuclei, it suffers a loss proportional to $k_A M_A$. An analogous situation develops at site B. The explicit consideration of these terms on the basis of the classical Bloch theory for the NMR experiment then leads to equations that allow the calculation of the NMR line shape for chemical exchange. Several software packages for this purpose are available, as described in more detail in the Appendix (p. 671).

For the average life-times τ_A and τ_B the relationships in Eq. (13.3) also hold:

$$\tau_A = \tau/p_B = 1/k_A \quad \text{and} \quad \tau_B = \tau/p_A = 1/k_B \quad (13.3)$$

In Figure 13.4 (p. 506) the results of a calculation of the NMR line shape for different τ values according to Eq. (A.22) (p. 669), is represented for a typical case of an exchange process with a chemical shift difference $\delta\nu = \nu_A - \nu_B = 30$ Hz, equal populations at site A and B ($p_A = p_B = 0.5$), and a natural line width $\Delta_{1/2}$ of 1.0 Hz. For large τ values separate signals at ν_A and ν_B are observed. This area is called the region of *slow exchange*. At the *coalescence point* the two signals merge into a broad band and in the region of *fast exchange* the spectrum becomes a singlet with a normal line width that is recorded at a frequency $(\nu_A + \nu_B)/2$. In the presence of fast exchange, each NMR parameter $\tilde{P}$ is an average value according to:

$$\tilde{P} = p_A P_A + p_B P_B \quad (13.4)$$

where P_A and P_B are the parameters in question at positions A and B, respectively.

In general, for n positions:

$$P_{\text{obs}} = \sum_i p_i P_i (i = 1, 2, n) \quad (13.5)$$

13.1.2

Relationships to Reaction Kinetics

The significance of line shape calculations must be seen in the fact that they set up the possibility of determining rate constants if a reversible chemical reaction is

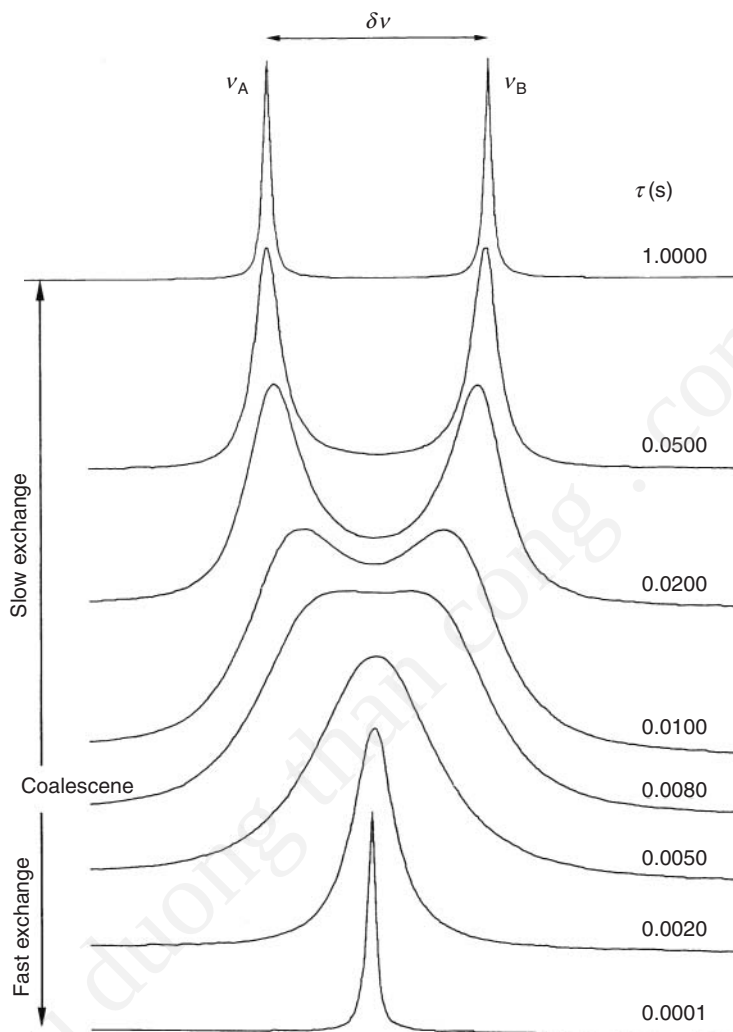


Figure 13.4 Theoretical nuclear magnetic resonance spectra for an exchange process $A \rightleftharpoons B$ as a function of the parameter τ ; chemical shift difference $\delta\nu = 30$ Hz; populations p_A and p_B of sites A and B, respectively, 0.5; $\Delta_{1/2}$, half width of the NMR signal without exchange broadening 1.0 Hz.

accompanied by a change in the Larmor frequency of one or more nuclei. The order of magnitude of the rate constants, k , that can be measured using this technique generally lies between 10 and 10^5 s⁻¹. The dynamic processes of interest are first-order reactions that are characterized by energy barriers of between 20 and 100 kJ mol⁻¹ (5–25 kcal mol⁻¹). In general, the kinetics of these processes are too fast to be determined using classical methods. As we shall show, especially in Section 13.2, our knowledge of the internal dynamics of molecules has been expanded

tremendously by means of NMR spectroscopy. Most of these processes and others that we shall discuss are different from the chemical reaction in the usual sense where the irreversible conversion of a reactant into a product through the agency of some reagent occurs. They can rather be classified in a broad sense as structural changes brought about by thermal energy, such as conformational transformations, inversions of configuration, and valence isomerizations. The results obtained are therefore of interest both to chemistry and molecular physics.

In the application of NMR spectroscopy for the determination of reaction rates one compares the experimental spectrum measured at a specific temperature with a series of theoretical spectra calculated for different values of τ , that is, for different rate constants. By matching the calculated spectra with the observed ones the correct value of k can be found. This procedure is not feasible without the use of a computer and can then even be performed iteratively by changing one or more of the line shape parameters. Use is also made of plotting the results of the calculation in the scale of the experimental spectrum. This yields spectra such as those shown in Figure 13.4.

In the specific case of a kinetic investigation the NMR spectrum of the spin system of interest is measured over a temperature range as wide as possible. In the region of slow exchange, where the spectrum is no longer sensitive to the dynamic process, the values of $\delta\nu$ and $\Delta\nu_{1/2}$, the frequency difference of interest and the natural line width of the resonance lines, are determined. The knowledge of these parameters is essential for any line shape calculation. One then makes the assumption that these values are temperature independent and uses them for calculations at higher temperature. The rate constants determined by the comparison of theoretical with experimental spectra for a series of different temperatures are then substituted into the Arrhenius equation [Eq. (13.6)]. An Arrhenius plot yields the *Arrhenius activation energy*, E_a , and the frequency factor, A , for the reaction under investigation. Thereby, it is assumed that both quantities are temperature independent. Also of general interest are the activation parameters of transition state theory, the enthalpy of activation, $\Delta H^\ddagger$, and the entropy of activation, $\Delta S^\ddagger$, which can be calculated by using Eqs (13.7) and (13.8), respectively:

$$\ln k = -\frac{E_a}{RT} + \ln A \quad (13.6)$$

$$\Delta H^\ddagger = E_a - RT \quad (13.7)$$

$$\Delta S^\ddagger = R \left[\ln \left(\frac{hA}{\kappa k_B T} \right) - 1 \right] \quad (13.8)$$

where T is the absolute temperature (K), R is the universal gas constant (8.31 J K^{-1}), k_B is the Boltzmann constant ($1.3805 \times 10^{-23} \text{ J K}^{-1}$), h is Planck's constant ($6.6256 \times 10^{-34} \text{ J s}$), and κ is the so-called transmission coefficient that is usually set equal to 1. This means that every transition state is going on to the product.

From the relation:

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger \quad (13.9)$$

the free energy of activation at a specific temperature can also be obtained. E_a , $\Delta H^\ddagger$, and $\Delta G^\ddagger$ are measured in kJ mol^{-1} and $\Delta S^\ddagger$ in $\text{J K}^{-1} \text{mol}^{-1}$.

Another possibility for evaluation of the free energy of activation is based on the well-known Eyring equation:

$$k = \kappa \frac{k_B T}{h} \exp(-\Delta G^\ddagger/RT) \quad (13.10)$$

or:

$$\Delta G^\ddagger = RT[23.76 - \ln(k/T)] \quad (13.11)$$

or:

$$\ln(k/T) = 23.76 - (\Delta H^\ddagger/RT) + (\Delta S^\ddagger/R) \quad (13.12)$$

Here one plots $\ln(k/T)$ against $1/T$. A straight line is obtained, with a slope of $-\Delta H^\ddagger/R$ and an intercept of $(23.76 + \Delta S^\ddagger/R)$. From these, the free activation parameters can be calculated. Unlike the data obtained through the use of Eqs (13.7) and (13.8), the activation parameters calculated using the Eyring equation are independent of temperature and these should be used in comparisons of the energy profiles of analogous reactions.

If the components of the equilibrium are not of equal energy, the temperature dependence of the equilibrium constants, K , in the region of slow exchange must be determined by integration of the appropriate signals. One then calculates the enthalpy and the entropy differences according to van't Hoff:

$$\ln K = -\Delta G^\circ/RT = -\Delta H^\circ/RT + \Delta S^\circ/R \quad (13.13)$$

In the calculation of the spectra the molar fractions of the components of the equilibrium must be considered. If they are very different, that is, if there is a large free energy difference between the two systems, the coalescence of the two resonance signals often is not well defined. The exchange process is then apparent only from a transient line broadening of the resonance signal of that component that is present in excess.

Finally, we should point out that spin echo experiments (see p. 248) also have been used to investigate dynamic processes on the basis that the amplitude of the echo is related to transverse relaxation. The shortening of T_2 by means of chemical exchange is not important in this connection if the residence time of the nuclei in positions with different Larmor frequencies is large compared with the delay time, τ , between pulses. However, for fast reactions or larger pulse intervals the amplitude of the echo decreases more rapidly than in the case of unperturbed transverse relaxation. If one determines this additional decrease as a function of τ one can calculate the rate constant at the temperature at which the experiment is run. The method has the advantage that it is applicable over a large temperature range and is not affected by spin-spin interactions. However, so far it has found only a few applications.

13.1.3

Approximate Solutions and Sources of Error

The relatively complex form of Eq. (A.22), page 669, and the reluctance to use a complete line shape analysis have made popular several approximate solutions. The best known of these is the relation:

$$k_{\text{coal.}} = \pi \delta \nu / \sqrt{2} = 2.22 \delta \nu \quad (13.14)$$

which gives the rate constant at the coalescence temperature, T_c (K), for the exchange between two equally populated sites ($p_A = p_B$). This enables one to use the Eyring equation to make a quick evaluation of the energy barrier for the process at this temperature. Making the appropriate substitution, one obtains:

$$\Delta G^\ddagger = RT_c [22.96 + \ln(T_c / \delta \nu)] (\text{J mol}^{-1}) \quad (13.15)$$

According to Eq. (13.14) separate signals at ν_A and ν_B are observed for $k/\delta \nu < 2.22$. If, on the other hand, $k/\delta \nu > 2.22$ an average signal is recorded at $(\nu_A + \nu_B)/2$. It must be emphasized that the value of the energy barrier thus obtained is temperature dependent because of the entropy term ($\Delta G^\ddagger = \Delta H^\ddagger - T \Delta S^\ddagger$).

Since, in general, the coalescence temperature is different for different dynamic processes, a comparison of the $\Delta G^\ddagger$ values is reasonable only if the entropy of activation for each of the processes under consideration is zero. To the extent that it is experimentally feasible, complete line shape calculations for a kinetic measurement over a larger temperature range is always preferable. Of course, this requires a greater expenditure of time and effort.

Furthermore, attempts have been made to use characteristic variations of the line shape such as the separation of the maxima before the coalescence or the ratio of the intensities in the maximum or minimum for a simpler evaluation of k values. These approaches are, however, subject to systematic errors so that the results obtained are less reliable. More suitable is the use of the additional line broadening caused by the exchange, the so-called *exchange broadening*, Δ_e . This can be obtained from the observed line width, Δ_{obs} , by subtracting the natural line width, $\Delta_{1/2}$, and the broadening due to inhomogeneity, Δ_I :

$$\Delta_e = \Delta_{\text{obs}} - \Delta_{1/2} - \Delta_I \quad (13.16)$$

The following equations for approximate values of the rate constant can then be written:

Slow exchange (for the signal in position A):

$$\frac{1}{\tau_A} = k_A = \pi \Delta_e \quad (13.17)$$

Fast exchange (for the average signal):

$$\frac{1}{\tau_A} = k_A = 4\pi p_A p_B^2 \delta \nu^2 / \Delta_e \quad (13.18a)$$

and for $p_A = p_B = 1/2$ we have

$$\frac{1}{\tau_A} = \pi \delta \nu^2 / 2 \Delta_e \quad (13.18b)$$

Applications of Eqs (13.17) and (13.18a,b) are, however, limited to relatively narrow ranges that lie at the lower and upper ends of the temperature interval for which a variation in the line shape is observed.

In addition to the uncertainty that arises from an incorrect calculation of the line shape, the NMR method for determining rate constants is susceptible to a series of *systematic errors* that sometimes cannot be eliminated. Especially critical are those cases in which the parameter $\delta \nu$ amounts to only a few hertz. The variation in the line shape then falls within a very narrow temperature region and is therefore not as well defined as it is in the case of more widely separated signals. Therefore, high magnetic fields that increase the $\delta \nu$ value are of advantage. As Eq. (13.14) demonstrates, at the coalescence point the rate constant k is proportional to the relative chemical shift $\delta \nu$ between the Larmor frequencies in question. Fast reactions, that is, those with large rate constants and low activation energies, can thus be investigated in a more easily accessible temperature range if it is possible to increase $\delta \nu$, thereby increasing k_{coal} . and, therefore, the coalescence temperature. If possible, one may take advantage of the larger chemical shifts of carbon-13 or other heteronuclei to study the process of interest.

Ring inversion of the thiepine dioxide derivative **2** offers an example of the effect of higher B_0 fields. Here, the presence of diastereotopic methyl groups indicating the non-planarity of the compound was detected at -150°C only with a 250-MHz spectrometer (Figure 13.5). Since the rate constant was the same in all three

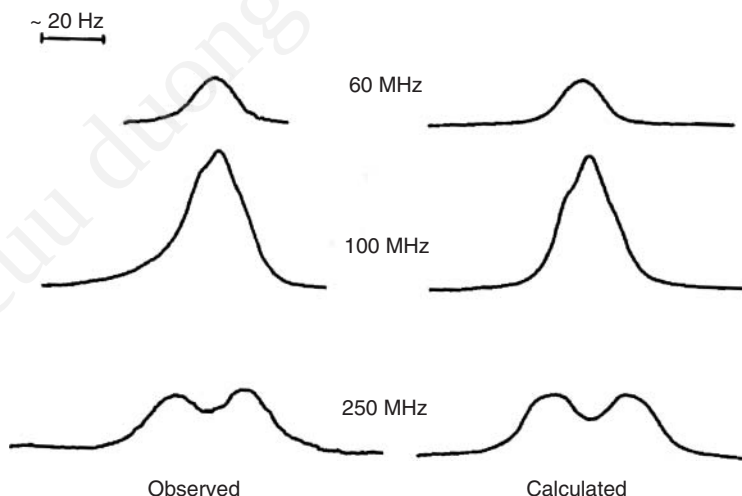
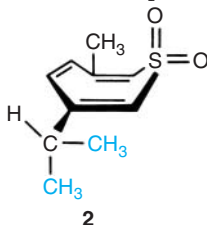


Figure 13.5 Absorption of the methyl protons of the thiepine dioxide (**2**) at -150°C and different spectrometer frequencies [1]; according to Eq. (13.14), increasing $\delta \nu$ requires an increase of k_{coal} , which means a higher coalescence temperature and line splitting appears.

experiments, because they were run at the same temperature, it is the increase in $\delta\nu$ that is responsible for the observed line separation.



The occasional temperature dependence of the parameters $\delta\nu$ and Δ_{obs} mentioned above is also a source of error in DNMR experiments. In polar solvents and in systems with heteroatoms and polar substituents one can count on association through hydrogen bonding to cause a temperature-dependent variation of the shift difference. If possible, the temperature dependence of $\delta\nu$ and Δ_{obs} should therefore be determined in the region of slow exchange in order to allow extrapolations to higher temperature where fast exchange occurs. Attempts can also be made to obtain $\delta\nu$ and Δ_{obs} together with the k value for the specific temperature directly from the line shape. To do this one matches the experimental spectrum with calculated spectra obtained by iterative variation of all three parameters.

Also to be considered is the fact that all effects that cause an additional line broadening, such as partial saturation of the resonance line or field inhomogeneity, simulate too high a value of k in the region of slow exchange and too low a value of k in the region of fast exchange. As a result the calculated activation energy is too low. Through the observation of signals of protons that are not involved in the exchange process, for example, the signal of the internal standard, these errors can, to some extent, be eliminated. One must be aware, however, that the relaxation times and thus the natural line widths of signals from different substances and even of those arising from different protons within the same molecule are not necessarily equal. In many cases further complications arise through spin-spin splittings that make a correct interpretation difficult. Generally, then, one must consider very carefully which factors may affect the results and how errors can be avoided. By means of careful choice of experimental technique, errors in the activation energy can usually be limited to about 2 kJ mol^{-1} ($0.5 \text{ kcal mol}^{-1}$) and can be even less than that in favorable cases. In several systems with relatively high energy barriers, measurements using both the methods of classical kinetics and of NMR spectroscopy have been possible and satisfactory agreement between the results was obtained.

Between 1956 and 1969 the values determined for the energy of activation for the internal rotation of dimethylformamide cited at the outset of this chapter rose from $29 \pm 12 \text{ kJ mol}^{-1}$ ($7 \pm 3 \text{ kcal mol}^{-1}$) to $118 \pm 8 \text{ kJ mol}^{-1}$ ($28.2 \pm 2 \text{ kcal mol}^{-1}$). The increase in the magnitude of the value and its precision over the years illustrates the achievements of research in improving experimental techniques and our understanding of the sources of possible errors. Not only the small shift difference between the methyl proton signals (10 Hz at 60 MHz) but also the polar

structure of the molecule and the long-range coupling with the formyl proton make this system a difficult “test case” for the NMR method. Today, the accepted values for the energy of activation, E_a , and the frequency factor, A , determined with the neat liquid are $85.8 \pm 0.8 \text{ kJ mol}^{-1}$ ($20.5 \pm 0.2 \text{ kcal mol}^{-1}$) and $5 \pm 3 \times 10^{12}$, respectively.

Finally, with the progress made for carbon-13 NMR and for other nuclei with low natural abundance, the investigation of dynamic processes employing these nuclei came into reach. As already discussed in Chapter 11, the large chemical shift for ^{13}C is attractive as well as the simple exchange systems between two uncoupled sites ($A \rightleftharpoons B$) that are found in most cases and that yield under the conditions of proton decoupling singlet spectra that are readily analyzed. Some examples will be presented in the following sections. Furthermore, very often several two-site exchange systems are observed that allow separate line shape analyses for the same compound, which increases the precision of the results.

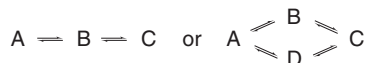
It must be remembered, however, that the line shape changes depend on the frequency difference between the nuclei in question measured in hertz. Because of its smaller magnetogyric ratio [$\gamma(^{13}\text{C}) : \gamma(^1\text{H}) = 1 : 4$], ^{13}C is thus not as effective as one could expect on the basis of the chemical shift scale in ppm. Nevertheless, because of the generally greater sensitivity of ^{13}C shielding constants to structural variations, the $\delta\nu$ values in ^{13}C NMR are usually larger by a factor of 10 than the corresponding chemical shift differences in the proton spectrum. On the other hand, a drawback of dynamic ^{13}C NMR must be seen in the fact that in many cases the coalescence region – where the line width reaches its maximum and is most sensitive for the dynamic process – is not feasible for measurements because of the low ^{13}C sensitivity, especially since the requirement of constant temperature sets limits to the accumulation time in Fouriertransform NMR. On the other hand, this disadvantage if compared to ^1H NMR is somewhat diminished by the fact that the slope of the graphs in the Arrhenius or Eyring diagrams is predominantly determined by the data points from the fast and the slow exchange regime at the upper and lower end. Exchange spectroscopy (EXSY) – a two-dimensional experiment to be introduced in Section 13.1.6 below – is a valuable addition to the methods of DNMR for measurements in the slow exchange limit in general and especially also for ^{13}C applications. It extends the temperature range that is accessible by the line shape calculations to lower values. In conclusion, as in other branches of NMR spectroscopy, ^{13}C NMR widens the area of applications but by no means substitutes ^1H NMR.

13.1.4

More Complex Exchange Phenomena

Equation (A22) (p. 669) holds, as should be emphasized again, only for the simplest case of an exchange process, namely, for the periodic change of the Larmor frequency of a nucleus between two values ν_A and ν_B in the absence of scalar spin–spin coupling. In practice, however, dynamic processes that involve different modes of exchange are frequently encountered. For example, the exchange between

more than two Larmor frequencies can occur if equilibria of the following type are involved:



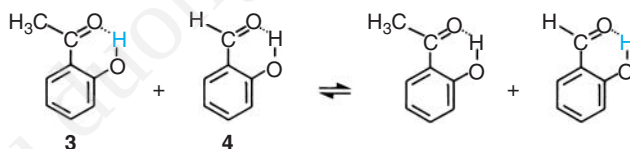
In addition, processes are known that lead to the magnetic equivalence of specific nuclei, that is, they cause the transition from an AB to an A_2 system. Furthermore, all *intermolecular* exchange processes that lead to the collapse of spin–spin multiplets cannot be investigated by means of Eq. (A.22).

Specific examples of these processes will be discussed in Section 13.2 but the underlying theory is beyond the scope of our introduction. Despite this, we do not wish to forego the demonstration of possible applications of variable-temperature NMR spectroscopy. In this context we must emphasize the importance of analyzing the dynamic process in question carefully so that the correct theoretical method can be chosen for interpretation of the experimental data. The power of modern data processing and software packages (see Appendix, p. 671) then allows, even in the case of relatively complicated exchange processes, calculation of the complete line shape of the spectrum.

13.1.5

Application of Inversion-Recovery Experiments to the Determination of Rate Constants

In the presence of a chemical exchange process of the type $A \rightleftharpoons B$, as has been discussed in detail in the preceding section, the rate constant, k , in the region of slow exchange can be determined by a different FT NMR method if separate signals for the resonances at ν_A and ν_B are observed, as in the hydrogen exchange between 2-hydroxy-acetophenone (3) and salicylaldehyde (4):



By selective inversion of the signal at ν_A , using a selective 180° GAUSS pulse, the spin distribution of the A nucleus is perturbed. This perturbation is now transmitted through the reaction $A \rightarrow B$ to the resonance signal at ν_B , assuming that the longitudinal relaxation time T_{1A} is not too short relative to the reaction rate. As in the inversion-recovery experiment for T_1 determinations (cf. p. 247), the spectrum is then measured after a certain delay time with a 90° pulse. During the delay, magnetization transfer by a chemical exchange operates. By varying the delay time, the rate constants k can be calculated from the time dependence of the ratio $M_z^A(t)/M_z^A(t \rightarrow \infty)$ on the basis of the following arguments: the life-time τ_{1A} of a spin state in the position A depends on the longitudinal relaxation time T_{1A} in this position and the rate constant k_A . We can, therefore, write:

$$1/\tau_A = 1/T_{1A} + 1/\tau_A \quad (13.19)$$

For the new equilibrium magnetization it holds that:

$$M_z^A(t \rightarrow \infty) = M_0^A(\tau_{1A}/T_{1A}) \quad (13.20)$$

while previously (we shall omit the derivation here) $M_z(t)$ was expressed as:

$$M_z^A(t) = M_0^A[C \exp(-t/\tau_{1A}) + \tau_{1A}/T_{1A}] \quad (13.21)$$

With Eq. (13.20) it follows that:

$$M_z^A(t) = M_0^A C \exp(-t/\tau_{1A}) + M_z^A(t \rightarrow \infty) \quad (13.22)$$

and:

$$M_z^A(t) - M_z^A(t \rightarrow \infty) = M_0^A C \exp(-t/\tau_{1A}) \quad (13.23)$$

or:

$$\ln[M_z^A(t) - M_z^A(t \rightarrow \infty)] = -t/\tau_{1A} + \text{const.} \quad (13.24)$$

Therefore, if one plots the observable $\ln[M_z^A(t) - M_z^A(t \rightarrow \infty)]$ against the time, t , one can obtain τ_{1A} as the slope of the line and with Eqs (13.20) and (13.19) the desired value of τ_A since the ratio $M_z^A(t \rightarrow \infty)/M_0^A$ can be determined experimentally. One proceeds analogously for the determination of τ_B by irradiating the signal at site A if the two sites A and B are unequally populated.

The experiment just described represents a useful extension of the application of NMR spectroscopy to the measurement of rate constants. It is applicable in the region of slow exchange where the line shape of the spectrum is insensitive to the dynamic process being investigated. It also represents an elegant method of identifying nuclei that are involved in chemical exchange or for analyzing qualitatively the dynamic behavior of a molecule. Its analogon in CW (continuous wave) NMR spectroscopy was a double resonance experiment where one of the exchanging sites was irradiated by a B_2 field while the intensity of the other site was monitored. It was successfully applied, for example, in detecting the conformational flexibility of [18]annulene at room temperature. Irradiating the resonance of the “internal” protons led to a distinct decrease in the intensity of the “external” protons (cf. p. 531), thereby establishing chemical exchange between these positions.

13.1.6

Two-Dimensional Exchange Spectroscopy (EXSY)

2D NMR provides another powerful method to study dynamic processes in the slow exchange region: *two-dimensional exchange spectroscopy (EXSY)*. With the pulse sequence:

$$90_x^\circ \text{-----} t_1 \text{-----} 90_x^\circ \text{-----} t_M \text{-----} 90_x^\circ, \text{FID}(t_2) \quad (13.25)$$

which we introduced in Chapter 10 for 2D NOESY spectroscopy, cross peaks are observed for dynamic systems in the region of slow exchange between the resonances of those nuclei that are exchanging their Larmor frequencies. Again, the classical Bloch vector pictures shown in Figure 10.6, page 351, apply; however,

during the mixing time t_M that follows the evolution period t_1 , the dynamic process now induces magnetization transfer. The amplitude of the transverse magnetization produced by the third 90_x° pulse and detected in t_2 depends therefore on the evolution time t_1 as well as on the efficiency of the magnetization transfer. The transfer rate during the mixing time t_M , which is of the order of 1–2 s, is a function of the rate constants of the particular dynamic process, and also of the magnitude of the z -magnetization that is present at $t_M = 0$. As a consequence, magnetization transfer is t_1 dependent and the signals of exchanging nuclei are amplitude modulated, which leads to cross peaks in the 2D spectrum. In the phase-sensitive experiments diagonal and cross peaks of EXSY spectra have the same sign, contrary to the situation found for the NOESY experiment [cf. Table 12, p. 671].

The application of an ^1H EXSY experiment is demonstrated in Figure 13.6 with the 2D exchange spectrum for the methyl resonances of 2,3-dimethylanthraquinone-9-cyanimine (5). Here, the inversion process at the CN double bond leads to equilibrium between two isomers 5a and 5b:

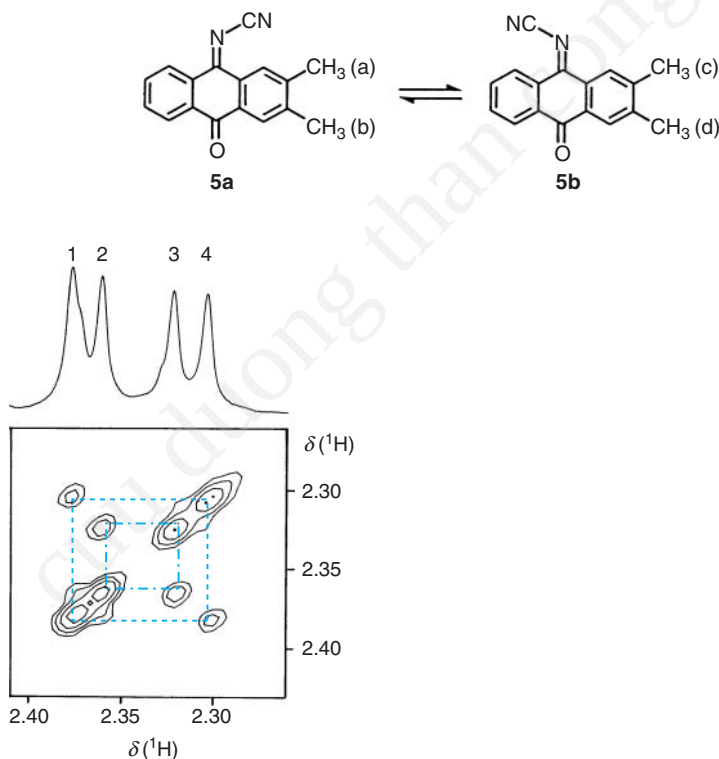


Figure 13.6 2D ^1H exchange spectrum (EXSY spectrum) of 2,3-dimethylanthraquinone-9-cyanimine (5) in CD_2Cl_2 at -33°C ; $t_M = 1$ s, measuring time 6.3 h (δ -values in ppm). Assuming $\Delta\nu_{a,c} > \Delta\nu_{b,d}$, the observed exchange process $1 \rightleftharpoons 4$ and $2 \rightleftharpoons 3$ allows the assignments $1 = a$, $2 = b$, $3 = c$, and $4 = d$. H. Günther and H.E. Mons, unpublished results.

Consequently, in the region of slow exchange four different environments result for the methyl groups a–d, which can, however, exchange their Larmor frequencies only pair-wise. The 2D exchange spectrum measured at -33°C (Figure 13.6) yields the information that magnetization is transferred between signals 1 and 4 as well as 2 and 3. Accordingly, in the region of fast exchange at room temperature one observes only one signal, since the average signals $(1 + 4)/2$ and $(2 + 3)/2$ are superimposed.

The pattern of the cross peaks observed in the 2D exchange spectrum is characteristic for the mechanism of the exchange process. Further applications of this experiment will be discussed in Sections 13.2.3 and 13.2.4. It is also important to point out that the volume intensity of the cross peaks yields information about the rate constants of the various transfer processes. For the simple case of slow exchange between two equally populates sites ($p_A = p_B$) and in the absence of scalar spin–spin coupling the rate constants can be calculated from the intensity ratio of diagonal to cross peaks, I_D and I_C , respectively, and the mixing time t_M according to Eq. (13.26):

$$I_D/I_C = (1 - kt_M)/kt_M \quad \text{or} \quad k = 1/[t_M(I_D/I_C + 1)] \quad (13.26)$$

2D-EXSY spectroscopy has, therefore, great potential for the investigation of dynamic processes in solution. In many cases rate constants measured by line shape analysis can be supplemented by EXSY data obtained in the slow exchange regime at lower temperatures. In addition to two-dimensional ^1H EXSY, ^{13}C EXSY has become important. For ^{13}C nuclei, because of their low natural abundance, application of the pulse sequence Eq. (13.25) does not lead to cross peaks that arise from homonuclear Overhauser effects. Therefore, the results are usually less ambiguous than for 2D ^1H EXSY. An application of this experiment is described in Section 13.2.4. Also, quite a number of X,X EXSY spectra ($X = ^7\text{Li}$, ^{11}B , ^{29}Si , ^{31}P , ^{195}Pt , etc.) have been used to unravel the mechanisms and determine the thermodynamic data of chemical exchange phenomena. As an example, Figure 13.7 shows the ^{11}B , ^{11}B EXSY spectrum that was used to study halogen Cl, Br exchange in boron halides.

13.1.7

Measurements of First-Order Rate Constants by Integration

Our survey would be incomplete without mentioning that NMR spectroscopy can also be employed in following slow irreversible reactions. The integration of individual signals is employed to trace the course of a transformation $A \rightarrow B$, monitoring the changes in concentrations of A or B as a function of time. In this way the concentration ratio $[A]/[B]$ can be calculated directly or, by using an internal standard of known concentration, the increase in $[B]$ or the decrease in $[A]$ can be determined. As an example, the course of the conversion of the dichlorocarbene adduct of cyclo-octatetraene (**6**) into the 1,2-dihydroindene derivative (**7**) is illustrated in Figure 13.8 (p. 518). As the spectra show, the resonance signals at δ 4.8 and δ 3.7 assigned to H_a , H_b , and H_c in **7** appear as the reaction progresses. At the

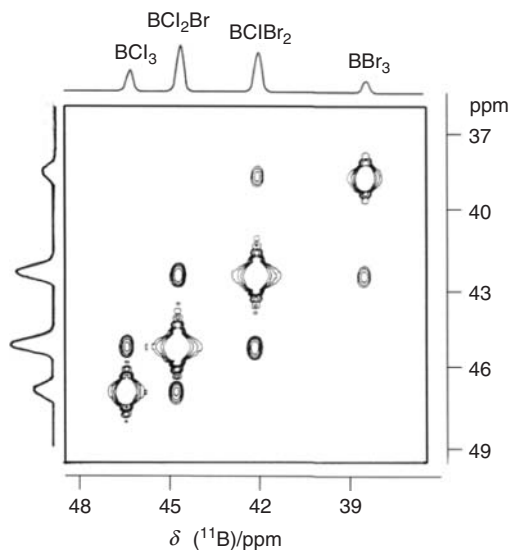
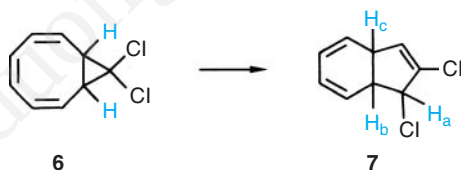


Figure 13.7 ^{11}B EXSY spectrum of a $\sim 1:1$ mixture of BCl_3 and BBr_3 at 400 K [2].

same time, the relative intensity of the singlet at δ 2.4, which is due to the tertiary protons of **6**, decreases. The reaction was run in NMR tubes in a thermostat at 80°C and after each hour a tube was removed and the reaction quenched at -70°C . The ratio [6] : [7] could then be determined by integration of the NMR spectrum. Its dependence on the reaction time led to a rate constant of $k(80^\circ\text{C}) = 6 \times 10^{-5} \text{ s}^{-1}$ for the transformation in acetonitrile as solvent and thence by use of Eq. (13.11) to a free energy of activation of $115.4 \text{ kJ mol}^{-1}$ ($27.6 \text{ kcal mol}^{-1}$).



13.2 Internal Dynamics of Organic Molecules

As stated earlier, we want to deal in this section with the *conformational mobility* of organic molecules and with *valence isomerizations*. The examples chosen should give an indication of the multitude of phenomena that can be studied by means of NMR spectroscopy. Thus, we shall be more concerned with the description of experimental observations and their qualitative significance than with quantitative aspects. Nevertheless, we shall mention the calculated activation parameters (E_a , $\Delta H^\ddagger$, $\Delta S^\ddagger$, and $\Delta G^\ddagger$;) to provide the reader with a feeling for the energy requirements of the individual processes, which without exception are *intramolecular*.

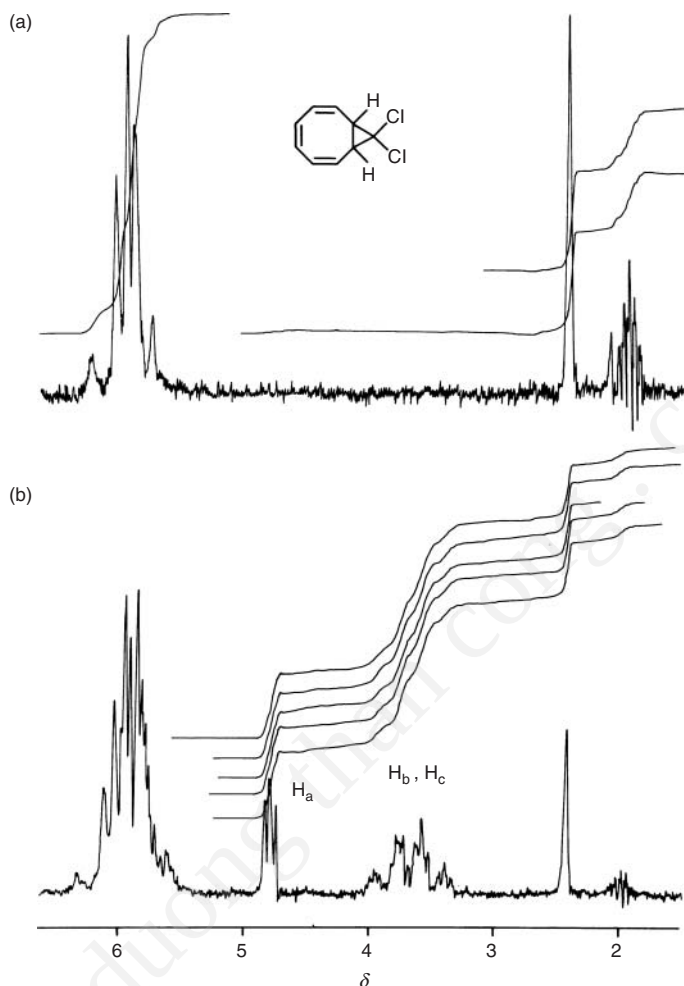


Figure 13.8 ^1H NMR spectra of the rearrangement **6** $\rightarrow$ **7** in acetonitrile- d_3 : (a) starting material; (b) reaction mixture after heating for 6 h at 80°C .

13.2.1

Hindrance to Internal Rotation

13.2.1.1 Bonds with Partial Double Bond Character

As with dimethylformamide, other molecules having a group with the general structure:

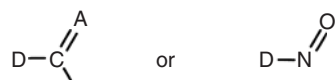
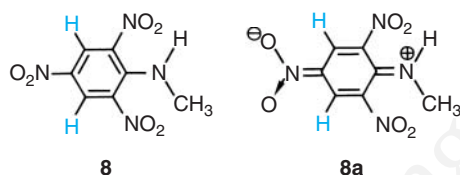


exhibit hindered rotation around the D–C or the D–N bond. In these compounds D is an electron-donating group, such as nitrogen or an aromatic π -system, and A is an

electron acceptor such as oxygen or sulfur. Temperature-variable NMR spectra are therefore observed for thioamides, carbamates, furfuraldehyde, and benzaldehyde, and with protonated ketones as well as with nitrosamines and nitrites in which the oxygen serves as the electron donor. Table 13.1 gives the activation parameters for a few compounds that have been measured by means of NMR spectroscopy.

In several systems the dynamic process causes two protons to change from an AB system into an A₂ system. One such case is encountered in *N*-methyl-2,4,6-trinitroaniline (**8**) where, because of the three nitro substituents, the benzene nucleus acts as an electron acceptor. As the resonance structure **8a** suggests, one conformation in which the N–CH₃ bond lies in the plane of the aromatic nucleus is favored by resonance stabilization.



The asymmetric substitution of the amino nitrogen leads to the low temperature AB system observed for the two aromatic protons since, because of the steric interaction with the methyl group, one of the two *ortho*-nitro groups probably has

Table 13.1 Examples of hindered rotation with activation energies in kJ mol⁻¹.

	$E_a \sim 105$		$\Delta G_{298}^\ddagger$ 57
	$\Delta G_{270}^\ddagger$ 67		E_a 96
	$\Delta G_{146}^\ddagger$ 33		$\Delta H^\ddagger$ 62
	$\vec{E}_a$ 50 $\vec{E}_a$ 46		$E_a \sim 42$

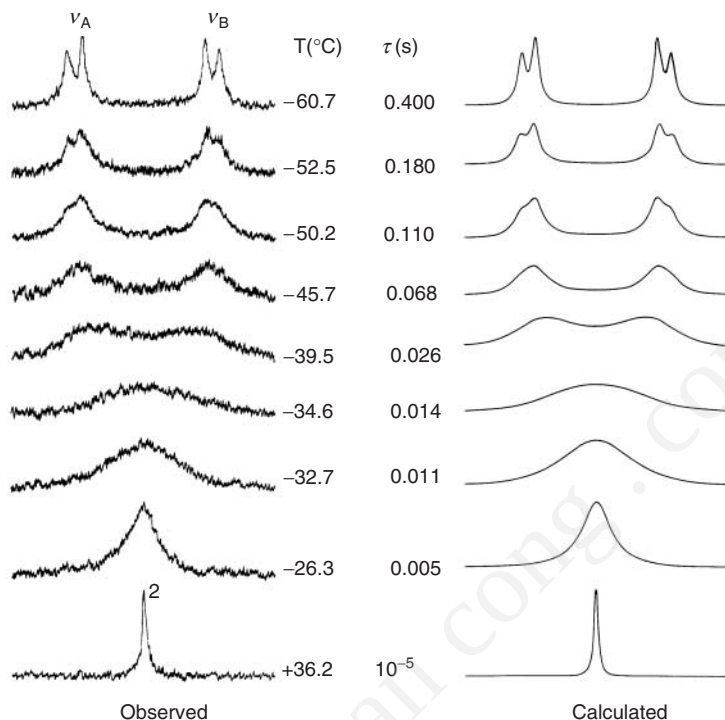


Figure 13.9 Experimental and calculated spectra of the aromatic protons of *N*-methyl-2,4,6-trinitroaniline (8) as a function of temperature [3].

its plane perpendicular to the plane of the benzene nucleus. With the more rapid rotation of the methylamino group at higher temperatures the two protons become equivalent and the spectrum degenerates to an A_2 system (Figure 13.9). It is worth discussing this example in more detail because, neither Eq. A22, page 669 nor the approximate methods derived from it can be used to interpret the NMR line shape. If we describe the two nuclei as we have done before through the product functions $\alpha\alpha$, $\alpha\beta$, $\beta\alpha$, and $\beta\beta$, the exchange process leads to the result that the $\alpha(1)\beta(2)$ state is transformed into the $\beta(1)\alpha(2)$ state. The functions $\alpha\beta$ and $\beta\alpha$ are now acceptable only when there is no interaction between the two nuclei. This is, however, not the case, since the two nuclei couple with one another. The line shape must therefore be derived on the basis of quantum mechanical theory, a procedure we cannot discuss in detail here. Let it merely be noted that even for this case an explicit expression for the shape of the spectrum as a function of the exchange rate can be obtained, by means of which the theoretical spectra shown in Figure 13.9 were calculated. The following relation can be used as an approximation at the coalescence point so that the rate constant at the coalescence temperature can be obtained rather easily:

$$k_{\text{coal.}} = \pi \sqrt{(\nu_A - \nu_B)^2 + 6J_{AB}^2} / \sqrt{2}$$

13.2.1.2 Substituted Ethanes

It has long been known that the rotation around the carbon–carbon bond in ethane is hindered. The first evidence for this came from the finding that the entropy of the compound was lower than that expected on the basis of theoretical calculations assuming free rotation. The molecule must therefore surmount an energy barrier in the conversion of the staggered conformation (a) into its rotational isomer (a'). The transition state for such a process can be represented by the eclipsed conformation (b).

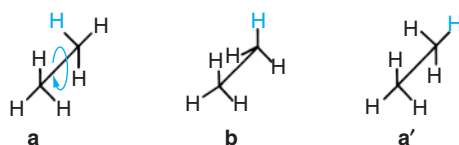


Figure 13.10 shows the energy profile for a full rotation as a function of the torsional angle ϕ ; the height of the barrier as measured by microwave spectroscopy is about 12 kJ mol^{-1} ($3.0 \text{ kcal mol}^{-1}$). This hindrance to rotation has its origin in electronic repulsions, as shown by MO (molecular orbital) calculations. It is also known that the replacement of one or more hydrogen atoms by groups with larger steric requirements increases the height of the barrier, and on this basis one can conclude that steric interactions play a dominant role in restricting rotation in substituted ethanes.

With respect to this problem it is of considerable significance that additional experimental data have been obtained by using NMR spectroscopy. Thus, data concerning the stable conformations of substituted ethanes were gathered from vicinal coupling constants and their dihedral angle dependence (p. 129). Furthermore, the barrier to rotation in a series of systems has been measured by analyzing the temperature dependence of the spectra. For these investigations ^{19}F NMR spectroscopy

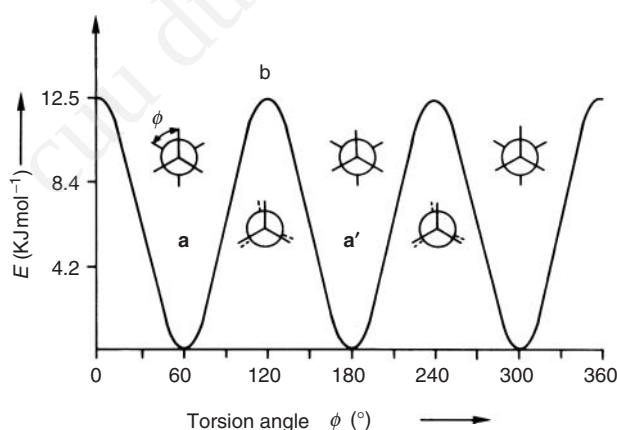


Figure 13.10 Energy profile for rotation around the carbon–carbon bond in ethane.

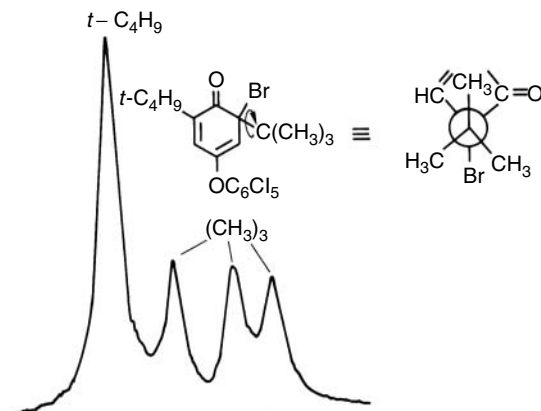
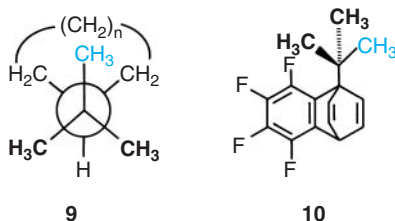


Figure 13.11 Proton absorption of the chemically non-equivalent methyl groups of the *t*-butyl group in 6-bromo-4-pentachlorophenoxy-2,6-di-*t*-butylcyclohex-2,4-dien-1-one at -90°C and 220 MHz [4]. Spin–spin coupling between the methyl protons, because of its small value, leads only to a line broadening.

was used almost exclusively because here large chemical shift differences $\delta\nu$ are more easily observed.

Of interest in the present context is that in several cases the hindrance to rotation of a tertiary butyl group is so large that at low temperatures the methyl groups become non-equivalent. An example is shown with the low-temperature spectrum of a highly substituted cyclohexadienone in Figure 13.11.

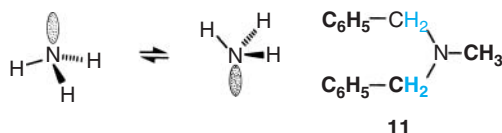
Furthermore, in the case of butylcycloheptane, for example, and also in other *t*-butyl-substituted cycloalkanes, a 2 : 1 doublet is observed for the *t*-butyl protons. This observation is consistent with the staggered conformation **9** in which only two methyl groups are equivalent. The barrier to rotation at the coalescence point (-126°C) has been determined to be 31.0 kJ mol^{-1} (7.4 kcal mol^{-1}). It was found further that this barrier is a function of the cycloalkane ring size and reaches a maximum of 32.6 kJ mol^{-1} (7.8 kcal mol^{-1}) in *t*-butylcyclo-octane. Compound **10**, even at room temperature, exhibits a doublet with an intensity ratio of 2 : 1 for the methyl resonances and fine structure arising from direct (through-space) fluorine–hydrogen coupling. At 134°C the signals coalesce and a barrier to rotation of 77.4 kJ mol^{-1} ($18.5\text{ kcal mol}^{-1}$) has been found.



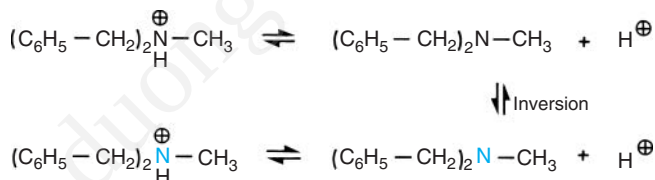
13.2.2

Inversion of Configuration

As was shown above, because of its lone pair of electrons, a nitrogen atom plays a very important role in molecules that exhibit hindrance to internal rotation. Another phenomenon that can be closely studied by means DNMR is the inversion of configuration, which has been well established in the case of ammonia by microwave spectroscopy. It is also known as *pyramidal atomic inversion*:



That inversion occurs in dibenzylmethylamine (**11**) has been elegantly demonstrated by using NMR spectroscopy and, without resorting to low-temperature measurements, the activation energy for inversion at room temperature has been determined. According to our explanations in Chapter 7 we would expect the methylene protons in **11** to give rise to an AB system due to their diastereomeric environment. However, because of rapid nitrogen inversion at room temperature, the signals degenerate into a singlet. On the other hand, if the measurement is carried out in acidic solution with a pH less than 2.0 the amine exists in the protonated form and the inversion process is slowed down. The CH₂ protons in the salt are diastereotopic and give rise to an AB system. Under these conditions the equilibrium below, where the color change indicates an inversion of nitrogen, can be formulated.

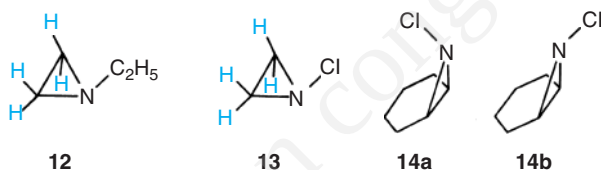


The inversion, therefore, can take place only in the amine and its rate depends on the concentration of the free amine and thus on the pH of the solution. The protonation and deprotonation of the amine is also a rapid equilibrium reaction during which the configuration of the amine does not change. The fact that spin-spin coupling of the N-H proton with the protons of the N-methyl group vanishes at lower acid concentrations (pH 2.0) before the methylene protons become enantiotopic provides experimental evidence for this additional process. A further increase in the pH then causes the methylene protons to become magnetically equivalent. The expression for the rate constant, k' , that characterizes the exchange of the methylene protons and that can be derived from the line shapes of the NMR spectra measured at different pH values is:

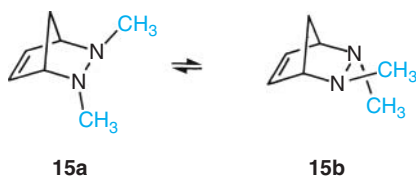
$$k' = k_{\text{inv}}[\text{Amine}]/([\text{Amine} + \text{Salt}])$$

The ratio of the concentrations at different pH can be calculated from the known pK_a of the amine. The rate constant for inversion is then obtained graphically by plotting k' against the concentration ratio. This gives $k_{\text{inv.}} = (2 \pm 1) \times 10^5 \text{ s}^{-1}$, which corresponds to a $\Delta G^\ddagger$ value of about 42 kJ mol^{-1} (10 kcal mol^{-1}). In a later study diastereotopic methylene protons in dibenzylamine were observed directly at -155°C .

In cyclic amines nitrogen inversion has also been detected. For example, the AA'BB' system of the ring protons in *N*-ethylaziridine (**12**) coalesces to a singlet at $108 \pm 5^\circ\text{C}$. The energy barrier for this process is about 81 kJ mol^{-1} ($19.4 \text{ kcal mol}^{-1}$). In the case of *N*-chloroaziridine (**13**) the coalescence temperature lies above the temperature at which the sample decomposes ($>180^\circ\text{C}$); the barrier to inversion must therefore be fairly high. This barrier-raising effect of chlorine substitution – which results from the higher p-character in the C–Cl bond due to the $-I$ -effect of the halogen and a stabilizing effect of the pyramidal ground state structure – led in the case of 7-chloro-7-azabicyclo[4.1.0]heptane to the actual separation of the diastereomeric invertomers **14a** and **14b**.



In cyclic diazines, such as 2,3-diazabicyclo[2.2.1]hept-5-ene (**15**), evidence for a consecutive inversion of the two nitrogen atoms has been obtained. The equilibrium **15a** $\rightleftharpoons$ **15b** is characterized by a barrier of $\Delta G^\ddagger_{264} = 60.7 \text{ kJ mol}^{-1}$ ($14.5 \text{ kcal mol}^{-1}$). Figure 13.12 shows the time-averaged spectrum recorded at 57°C and the superposition of the identical spectra of the two enantiomers obtained at -39°C . Clearly, at the lower temperature the molecule has lost the C_s symmetry that was effective on the NMR time scale at 57°C . While the AB system of the bridge protons ($\delta 1.7$ and $\delta 2.1$) remains unaffected, as expected, separate absorptions are observed for the methyl protons ($\delta \approx 2.5$) and also for the bridgehead and the olefinic protons ($\delta \approx 4.0$ and 6.5 , respectively). Of further interest is the fact that the vicinal and allylic coupling constants between olefinic and bridgehead protons differ as a result of the different configurations of the two nitrogen atoms.



In the diaziridine **16**, an analogous inversion process requires more than 96 kJ mol^{-1} (23 kcal mol^{-1}). This increase in energy barrier obviously results from the change in ring size since in the three-membered ring the planar transition state for inversion is expected to be of higher energy than in larger ring systems because of the smaller internal C–N–C bond angle.

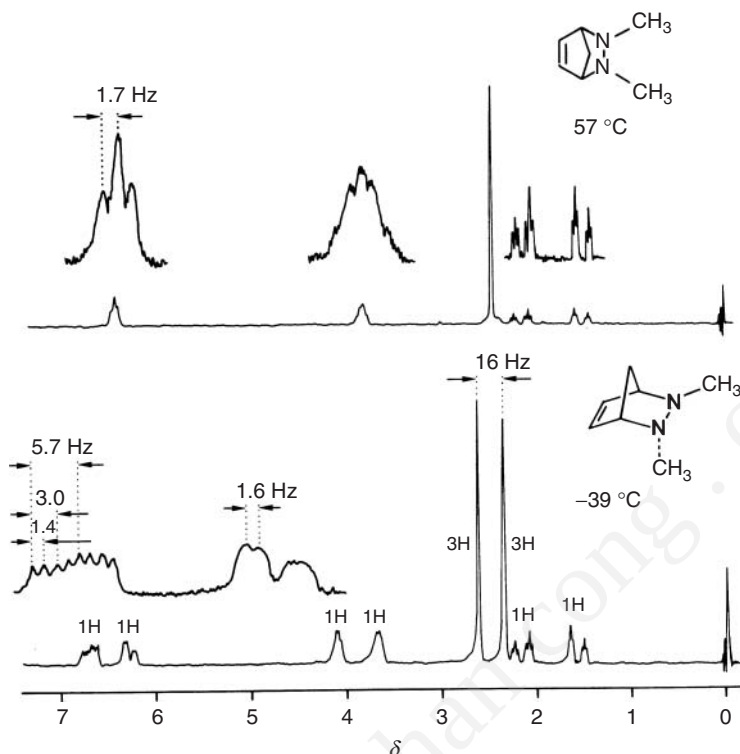
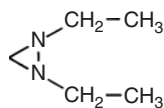
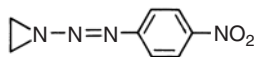


Figure 13.12 Temperature dependence of the ^1H NMR spectrum of 2,3-diazabicyclo[2.2.1]hept-5-ene (**15**) [5].

On the other hand, the inversion barrier decreases if substituents on the nitrogen lead to a flattening of the pyramidal configuration ($\text{sp}^3 \rightarrow \text{sp}^2$) through electronic interactions with the nitrogen lone pair. Consequently, in compound **17** a value for $\Delta G^\ddagger_{231}$ of only 49.8 kJ mol^{-1} ($11.9 \text{ kcal mol}^{-1}$) is observed.



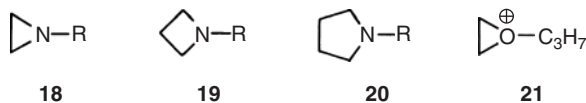
16



17

Relative to *inversion* and *hindered rotation* associated with the nitrogen atom, it is interesting that in cyclic systems the ring size influences the energy barrier for the two processes differently. The activation energy for inversion in the series **18–20** ($\text{R} = \text{Cl}$ or CH_3) becomes smaller as a result of reduced destabilization in the transition state while the barrier to rotation in the same series with $\text{R} = \text{COOR}$ increases. Here the ground state is stabilized in the larger ring systems because

the conjugative interaction is favored by an increase in the C–N–C bond angle that allows a change in nitrogen hybridization from sp^3 toward sp^2 .



Trialkyloxonium salts are isoelectronic with amines and inversions of configuration at the oxygen atom have also been detected in compounds of this type. For example, the isopropyloxonium ion of ethylene oxide (**21**) exhibits a singlet for the methylene protons of the ring at 40°C that at -70°C becomes an AA'BB' multiplet. Similar inversion processes have been observed in phosphorous and arsenic compounds.

13.2.3

Ring Inversion

The classical example, the inversion of the cyclohexane ring that stands for similar inversion processes in a large number of saturated six-membered heterocyclic rings, has been investigated extensively. The observed activation parameters are $\Delta H^\ddagger = 45.2 \pm 0.4 \text{ kJ mol}^{-1}$ ($10.8 \pm 0.1 \text{ kcal mol}^{-1}$) and $\Delta S^\ddagger = 11.71 \pm 2.1 \text{ J K}^{-1} \text{ mol}^{-1}$ ($2.8 \pm 0.5 \text{ cal K}^{-1} \text{ mol}^{-1}$). They characterize the transition of the chair conformation (**a**) into a high-energy conformation such as the boat or the twist boat (**c**, **b**) and finally into the equivalent chair conformation (**a'**). The energy profile has the form illustrated in Figure 13.13. The transitions between the twist boat and the boat conformers are effected without encountering angle deformation simply by rotation around carbon–carbon single bonds. Such conformational transitions that are generally distinguished by low energy barriers are called *pseudo rotations*.

The transmission coefficient, κ , for the reaction (**a**) $\rightarrow$ (**a'**) must be assumed to be 0.5 since the probabilities that an individual molecule is transformed from

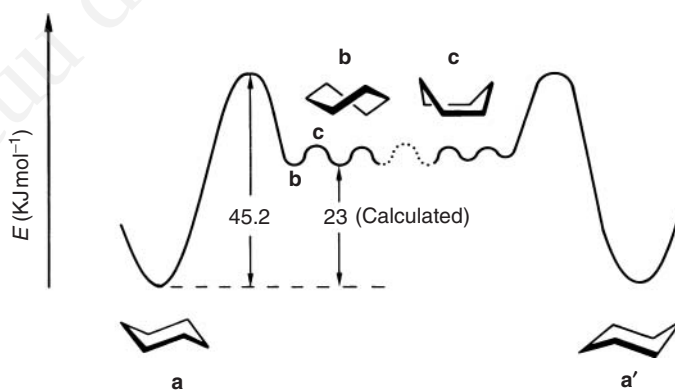


Figure 13.13 Energy profile for the ring inversion of cyclohexane.

conformation (b) or (c) to (a) or to (a') are identical. In other words, the rate constants k_{ab} and k_{ac} must be twice as large as $k_{aa'}$.

For an experimental investigation of the ring inversion process, one takes advantage of the different chemical shifts of the cyclohexane protons in the axial and equatorial positions (cf. p. 96). Especially simple spectra are obtained for $[D_{11}]$ cyclohexane if one eliminates the spin-spin interaction between the proton and the deuterium atoms by heteronuclear decoupling. Figure 13.14 shows the result of such an experiment. In substituted cyclohexanes corresponding ring inversion processes have also been detected. Table 13.2 gives the results for several monosubstituted cyclohexanes obtained by means of NMR experiments at about -80°C . At this temperature all systems are in the region of slow exchange and the equilibrium constant can be determined by integration of the separate resonance signals for the axial and equatorial methine protons (cf. Figure 13.15a for bromocyclohexane). From the equation $\Delta G^{\circ} = RT \ln K$ the difference in free energy of the two conformations, known as the *A value* of the substituent, is

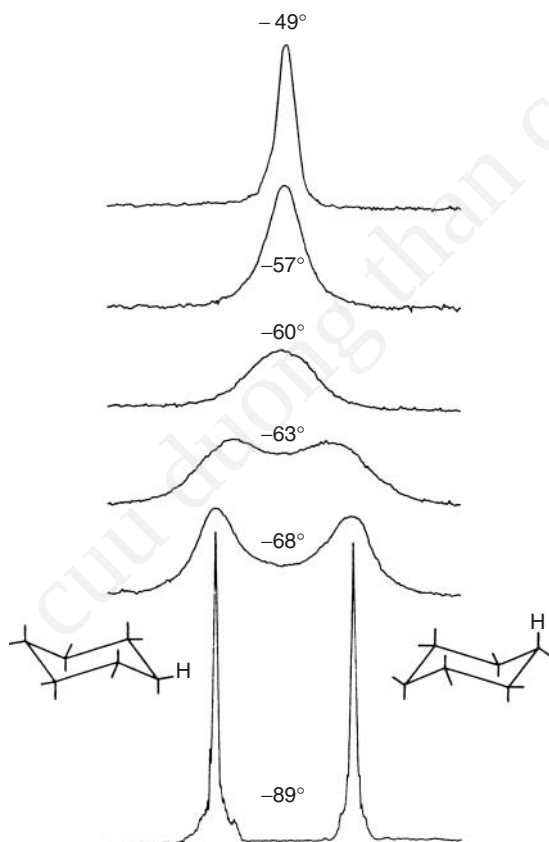
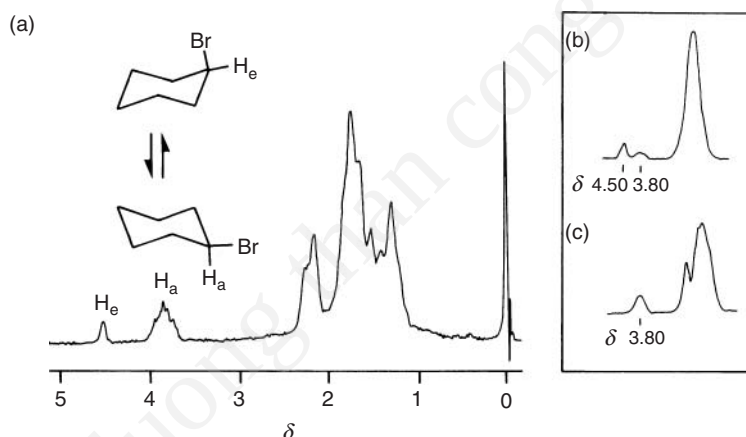


Figure 13.14 ^1H NMR spectrum of $[D_{11}]$ cyclohexane with ^2H decoupling as a function of temperature [6].

Table 13.2 Conformational free energies of different substituents on cyclohexane [7].

Substituent	A value (kJ mol ⁻¹)	A value (kcal mol ⁻¹)	Temperature (°C)	Equilibrium constant
CN	1.00	0.24	-79	1.88
F	1.15	0.28	-86	2.10
I	1.96	0.47	-80	3.39
Br	1.99	0.48	-81	3.48
Cl	2.21	0.53	-81	3.99
OCD ₃	2.29	0.55	-82	4.23
SCD ₃	4.48	1.07	-79	16.1
CH ₃	7.1	1.7		
C ₂ H ₅	7.5	1.8		
<i>i</i> -C ₃ H ₇	8.8	2.1		
C(CH ₃) ₃	21	5		

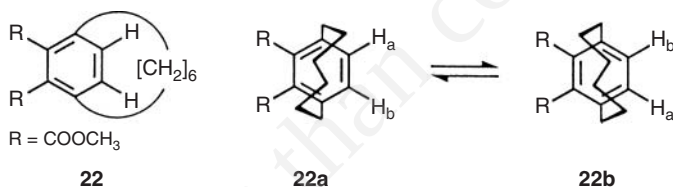
**Figure 13.15** ¹H NMR spectra of monosubstituted cyclohexanes: (a) equilibrium mixture of axial and equatorial bromocyclohexane at -100°C [8]; (b) mixture of axial and equatorial chlorocyclohexane at -150°C [9]; (c) pure equatorial chlorocyclohexane at -150°C [9].

obtained. It is positive if the substituent favors the equatorial position. Also included in Table 13.2 are A values for alkyl groups that were determined by other methods. Interestingly, the A values for the halogens do not follow the order of increasing van der Waals radii (F, 0.135; Cl, 0.180; Br, 0.195; and I, 0.215 nm). Increased carbon-halogen bond length and polarizability reduce non-bonded interactions in the cases of axially disposed iodine and bromine atoms. However, the -OCD₃ and the -SCD₃ and also the alkyl groups exhibit the expected gradation in A values.

From the data for chlorocyclohexane it can be estimated that at -150°C the half-life of each isomer should be several hours. By fractional crystallization in an NMR tube it was actually possible at this temperature to prepare a solution that contained

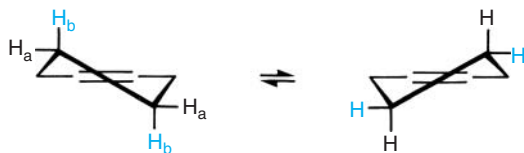
only the isomer with equatorial chlorine. As the NMR spectrum of this solution (Figure 13.15c) indicates, when compared with that of an incompletely separated mixture (Figure 13.15b), the enrichment of the equatorial isomer was essentially complete. This represented the first preparative separation of conformational isomers of monosubstituted cyclohexanes.

For larger cycloalkanes, dynamic processes can also be analyzed by NMR spectroscopy albeit, owing to the greater mobility of these ring systems, the barriers are often below the limit of detection. A relatively simple process of ring inversion has been found for the methylene chain in the paracyclophane **22**, which we introduced in Chapter 10 with its NOESY spectrum (p. 354). Formally, a ten-membered ring is involved; however, the partial structure of the aromatic ring reduces the flexibility and thereby the number of the possible dynamic processes. As a consequence, the intramolecular motion is confined to the inversion process of the methylene chain, $22a \rightleftharpoons 22b$. The kinetics of this process can be traced most easily by the line shape changes of the AB spectrum of the aromatic protons, which degenerates in the region of fast exchange to an A_2 system (Figure 13.16a, p. 530). The Eyring diagram (Figure 13.16b) yields activation parameters of $\Delta H^\ddagger = 43.1 \text{ kJ mol}^{-1}$ ($10.3 \text{ kcal mol}^{-1}$), $\Delta S^\ddagger = -51 \text{ J K}^{-1} \text{ mol}^{-1}$ ($12.2 \text{ cal K}^{-1} \text{ mol}^{-1}$), and $\Delta G^\ddagger(298) = 58.6 \text{ kJ mol}^{-1}$ ($14.0 \text{ kcal mol}^{-1}$).



We have cited this example also because the 2D EXSY spectrum in the slow exchange region yields clear cut results with respect to the conformational changes that occur in the CH_2 chain. As seen in Figure 13.16c, NOESY cross peaks are absent and new cross peaks are now observed between those methylene protons that become identical if a rotation of the $\text{C}(3)\text{--C}(4)$ group around the fixed positions $\text{C}(2)$ and $\text{C}(5)$ is assumed: 7/12; 8/11; 5/9; 6/10; 1/3; 2/4 while in the NOESY spectrum the geminal interactions were detected. The assignment of the ^1H NMR spectrum that forms the basis of this analysis was established before by 2D methods.

Of the many dynamic processes involving cyclic olefins that have been studied we shall describe only two. In cyclohexene, ring inversion has the effect of making the methylene protons H_a and H_b equivalent:



The activation energy for this interconversion is 22.6 kJ mol^{-1} ($5.4 \text{ kcal mol}^{-1}$). It is similar to that for cycloheptatriene [25 kJ mol^{-1} (6 kcal mol^{-1})], which according

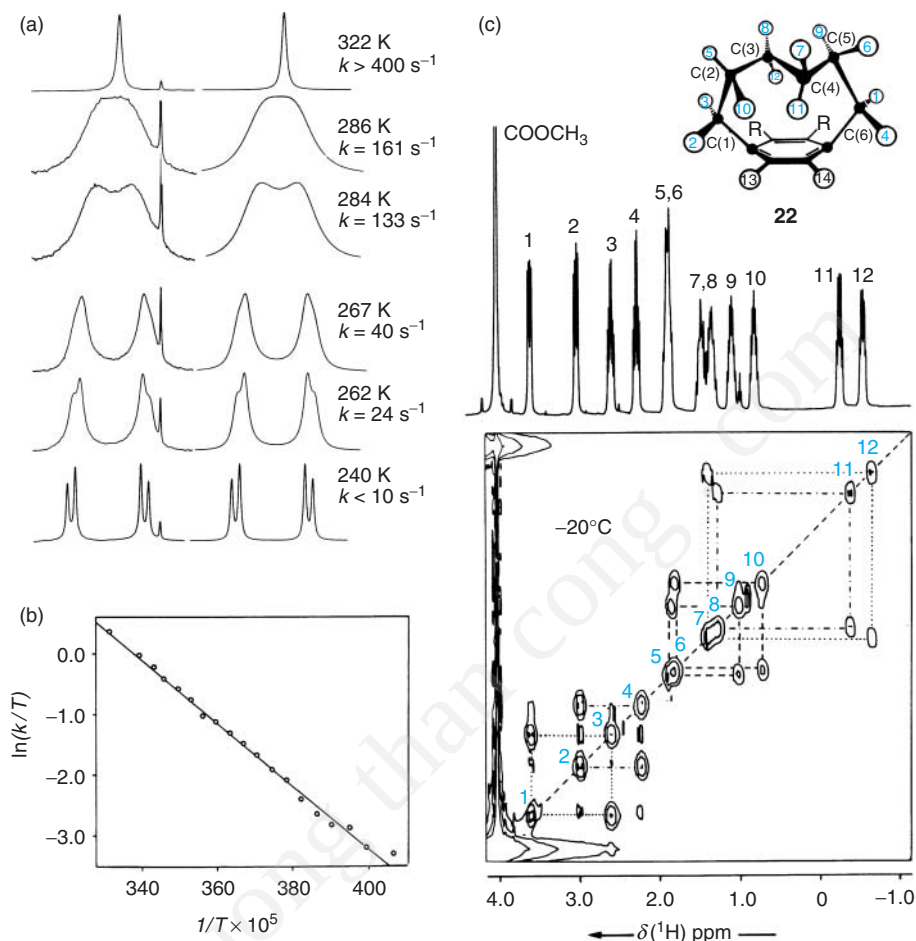
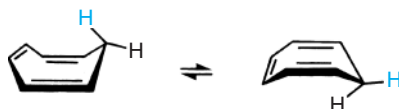


Figure 13.16 Ring inversion in [6]paracyclophane-8,9-dimethylcarboxylate (**22**); (a) line shape changes of the AB spectrum of the aromatic protons H^{13} and H^{14} ; experimental (left) and calculated (right); (b) Eyring diagram; (c) 400 MHz ^1H 2D-exchange spectrum at -20°C recorded with the pulse sequence in Eq. (13.25); mixing time $t_M = 1$ s; note the different cross peaks compared to the NOESY spectrum on page 354. [10].

to electron-diffraction measurements exists in a tub conformation. At -150°C the non-equivalence of the methylene protons (**5**, p. 99) can be detected while at room temperature both protons are equivalent because of the fast equilibrium below:



Interesting conformational equilibria have also been observed and quantitatively investigated in the case of certain annulenes. Two examples may be cited here.

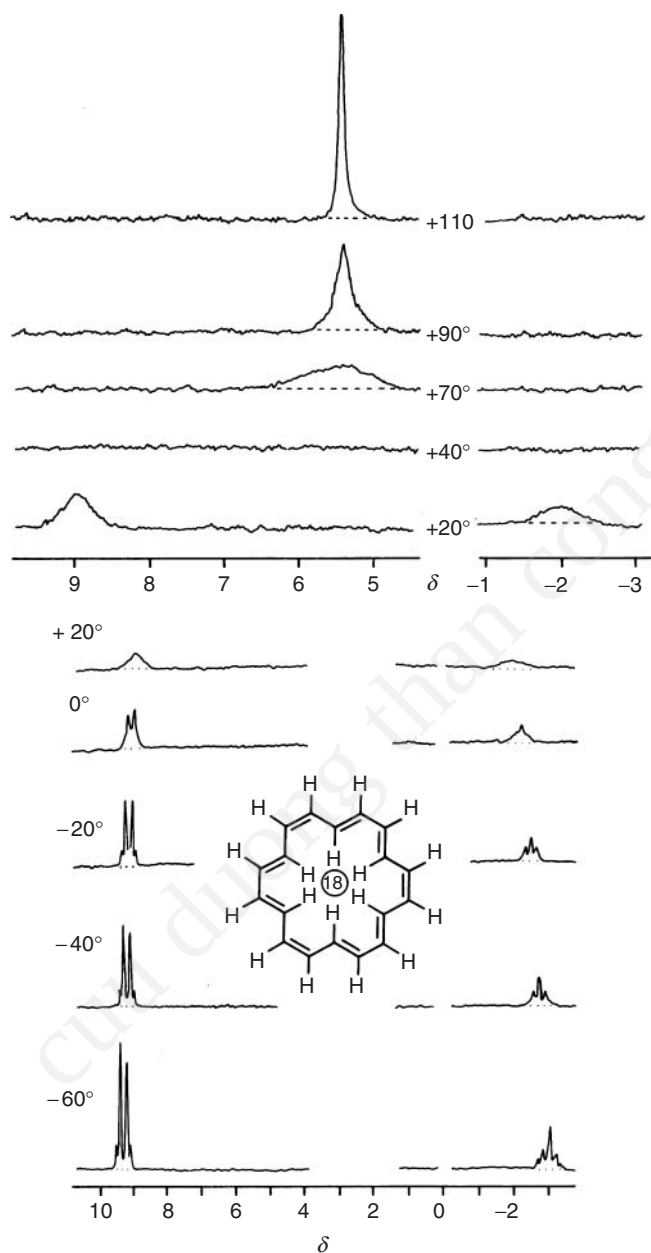
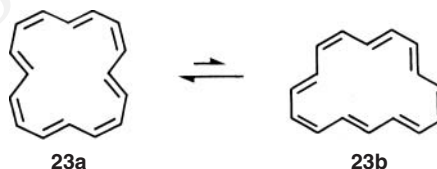


Figure 13.17 Temperature dependence of the ^1H NMR spectrum of [18]annulene [11].

Figure 13.17 (p. 531) shows the temperature-dependent spectra of [18]annulene. The spectrum measured at -60°C corresponds to expectations for a planar diatropic $(4n+2)\pi$ system since resonances are found at $\delta -3.0$ for the six internally directed protons and at $\delta 9.3$ for the 12 externally directed protons. Increasing the temperature leads to line broadening and finally a coalescence at 40°C that is indicative of an exchange of internal and external protons. The signal at $\delta 5.4$ recorded at 100°C lies, as expected, near the statistical average of $\delta 5.2$. The exchange process is effected in this case by rotations around carbon–carbon bonds, a phenomenon that is normally not expected in an aromatic molecule. However, in [18]annulene it is possible because the size of the ring confers unusual flexibility on the carbon skeleton. Interestingly, in this connection, the first NMR measurements on [18]annulenes led to puzzling results since, because of line broadening due to exchange at normal temperatures around 30°C , no “satisfactory” spectrum could be recorded and the possibility of conformational transformations was not even suspected at that time.

Complicated conformational transformations and bond isomerizations have been elucidated in the case of [16]annulene. At -30°C the spectrum of this compound consists of a singlet of $\delta 6.74$. Detailed analysis of the temperature-dependent line shape down to -130°C leads to the following conclusions:

1. [16]Annulene exists in two conformations, **(23a)** and **(23b)**, that are in fast reversible equilibrium. At -60°C the equilibrium constant is $K = (p_A/p_B) = 2.9$.
2. Each conformation possesses an internal mobility such that, in connection with a simultaneous double-bond shift, all protons can successively assume the 4 or 16 magnetically different positions, respectively, in the two structures. Isomer **(23a)** thereby passes through 8 and isomer **(23b)** through 32 identical conformations that are differentiated only by the exchange of certain protons:



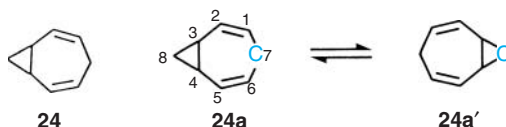
Noteworthy in this case is the fact that the existence of conformation **(23b)** was demonstrated by the finding that the experimental spectra could not be matched with spectra obtained by line shape calculations without assuming a contribution of **(23b)** to the equilibrium.

13.2.4

Valence Tautomerism and Bond Shifts

A fascinating area of organic chemistry, the development of which would be difficult to imagine without NMR spectroscopy, is that of fast, reversible *valence tautomerism* or *valence isomerization*. Such a process was first observed by means of

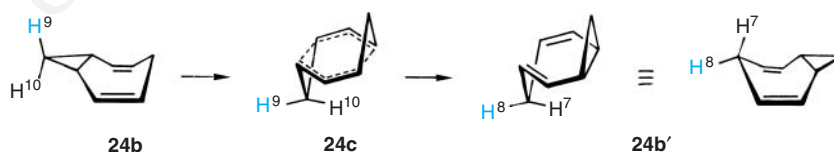
NMR spectroscopy in the case of 3,4-homotropilidene (**24**). The reaction involves a degenerate Cope rearrangement in that the cyclopropane bond between C3 and C4 migrates to the position between C1 and C6 via a 3,3-sigmatropic shift:



Since the starting material and the product are identical with respect to their chemical and physical properties, this kind of rearrangement has been termed an identity or “invisible” reaction. The equilibrium $(24a) \rightleftharpoons (24a')$ is likewise called *isodynamic*. Through NMR, however, a process such as this becomes “visible” and thus experimentally detectable, since the spectrum allows us to identify the chemical environment of an individual nucleus in the molecule and to trace possible changes in its environment. Thus, during the rearrangement, C7 proceeds from an allylic to a cyclopropyl position. Similarly, the other atoms, with the exception of those in positions 2 and 5, experience an exchange of their environments and since this change occurs very rapidly at room temperature homotropilidene is called a *fluxional molecule*.

As can be seen immediately, NMR spectroscopy is the method of choice for the detection of such valence tautomerism since the spectrum is sensitive to a change in the Larmor frequency of the nuclei in question. The transition $(a) \rightleftharpoons (a')$ manifests itself in the region of fast exchange through the chemical equivalence of the protons in positions 7 and 8 as well as those in positions 1, 3, and 4, 6. The spectrum of the “frozen” structure can be observed after line broadening in the region of slow exchange at temperatures below -30°C .

For the rearrangement mechanism, 2D EXSY spectroscopy yields important information. According to the results of investigations using different techniques, among them analysis of the ^1H NMR spectrum, 3,4-homotropilidene (**24**) exists in the ground state in a *transoid* boat conformation **24b**. If the Cope rearrangement were to proceed through the corresponding *transoid* transition state **24c** to the isomer **24b'** the exchange of the methylene protons should follow the scheme $\text{H}^9 \rightleftharpoons \text{H}^8$ and $\text{H}^{10} \rightleftharpoons \text{H}^7$:



The 2D-EXSY spectrum (Figure 13.18), however, shows cross peaks between the protons H^9 and H^7 as well as between H^{10} and H^8 . Consequently, the rearrangement takes place via the *cisoid* transition state (**24e**). The valence tautomerism to (**24b'**) thus proceeds by a conformational change via (**24d**), (**24e**), and (**24d'**):

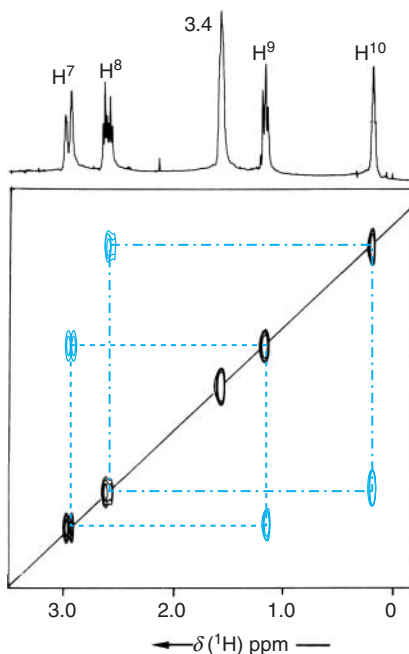
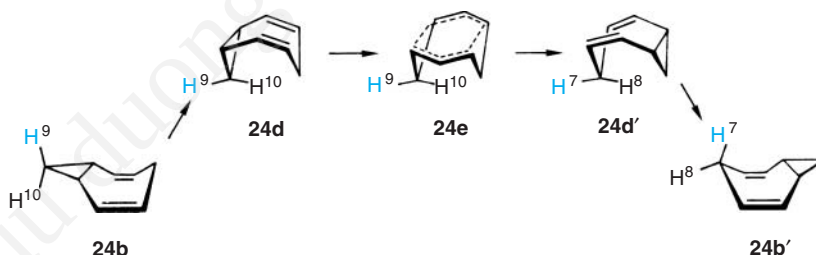


Figure 13.18 400 MHz ^1H 2D-EXSY spectrum of 3,4-homotropilidene (**24**) in the region of slow exchange at -7°C (aliphatic region). The cross peaks between the resonances of the cyclopropane protons H^3 , H^4 and the olefinic protons H^1 , H^6 are not shown. The 1D spectrum was recorded at -30°C .



This result is also in agreement with a stereochemical analysis of this concerted reaction based on MO considerations.

The subsequent development of the idea of degenerate Cope rearrangements led to the conception of bullvalene (**25**), the synthesis and NMR spectrum of which created much interest. In this compound each of the three cyclopropane bonds may be broken and a series of valence isomerizations of the type described above leads to a network of thousands of interconverting structures with permutations for all CH groups. Consequently, at 80°C the equivalence of all protons is evidenced by a singlet in the NMR spectrum (Figure 13.19). On lowering the temperature one observes line broadening and, finally, at -80°C a spectrum that is consistent

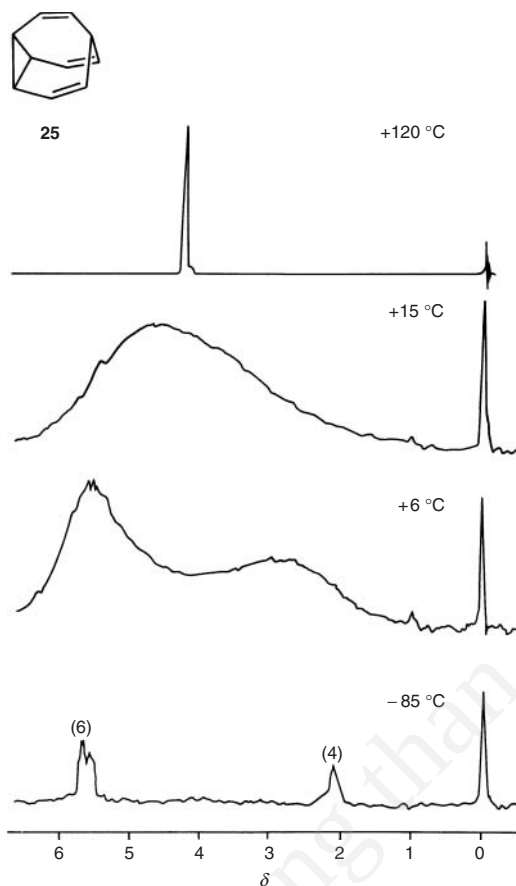


Figure 13.19 Temperature dependence of the ^1H NMR spectrum of bullvalene (**25**) [12].

with the frozen structure **25** (the resonances of the cyclopropane protons and the tertiary proton are by chance superimposed). An activation energy E_a of 49 kJ mol^{-1} ($11.8 \text{ kcal mol}^{-1}$) has been derived for the process responsible for the averaging of all proton chemical shifts from the analysis of the temperature-dependent line shape.

Later, the bullvalene valence tautomerism was again studied, this time, however, by dynamic ^{13}C NMR at 22.6 MHz in the slow and fast exchange limit, where the temperature ranged from -59 to -28°C and from 86 to 128°C , respectively. As with the protons in ^1H NMR, all carbons become equivalent in the ^{13}C NMR spectrum above room temperature and a single line at $\delta_{\text{TMS}} = 86 \text{ ppm}$ is observed at 128°C . Lowering the temperature leads after strong line broadening to the slow-exchange spectrum shown in Figure 13.20a (p. 536). Calculated spectra for various k values were compared with the experimental ones to yield the Arrhenius and Eyring activation parameters. Please note that from the resonances of the olefinic carbons C_c and C_b , the high-frequency resonance shows at -37°C a stronger exchange broadening. It may thus be assigned to C_c because with one rearrangement all

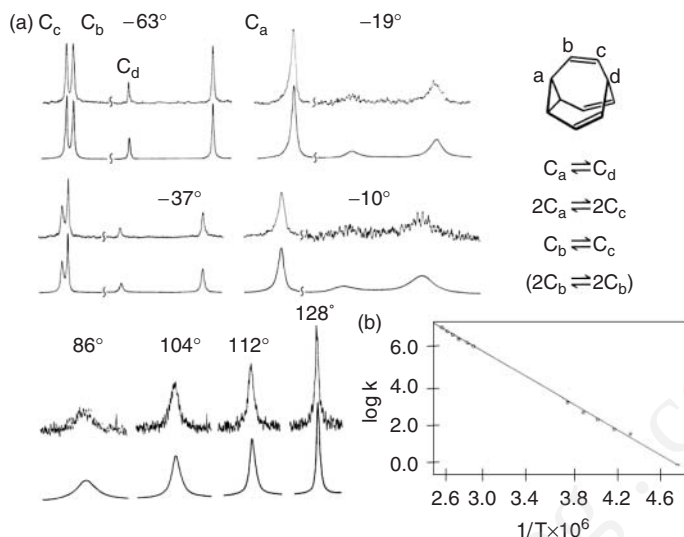


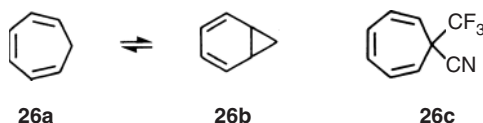
Figure 13.20 ^{13}C NMR spectrum of bullvalene (25) at -63°C and exchange pattern due to the degenerate Cope rearrangement: (a) Comparison of experimental (above) and calculated (below) temperature-dependent spectra in the slow and fast exchange limit. Here we have chemical exchange between four sites with different populations and a method more advanced than that described in Section 13.1.1 for the calculation of the exchange broadened spectra, due to Anderson, Kubo, and Sack [13a–c],

was used. The activation parameters found were $E_a = 58.2 \text{ kJ mol}^{-1}$ ($13.9 \text{ kcal mol}^{-1}$); $\log A = 14.0$; $\Delta H^\ddagger = 55.6 \text{ kJ mol}^{-1}$ ($13.3 \text{ kcal mol}^{-1}$), $\Delta S^\ddagger = -14.2 \text{ J K}^{-1} \text{ mol}^{-1}$ ($3.4 \text{ cal K}^{-1} \text{ mol}^{-1}$). This yields with Eq. (13.6) at room temperature (298 K) a $\Delta G^\ddagger$ of 51.5 kJ mol^{-1} ($12.3 \text{ kcal mol}^{-1}$) and a rate constant k of $6.5 \times 10^3 \text{ s}^{-1}$; (b) Arrhenius plot of the rate constants (Reprinted from Reference [14]; Copyright 1974. With permission from Elsevier).

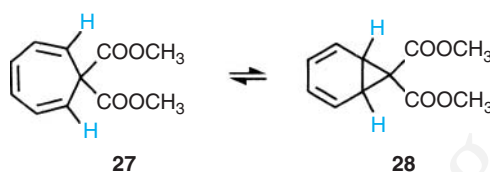
three carbons of this type change their environment whereas only one carbon of type C_b is affected.

This example also shows that, as described before (p. 512), due to sensitivity reasons, ^{13}C spectra in the coalescence region are difficult to observe and often cannot be used for analysis. Consequently, the determination of k -values in this region is impossible and a large gap results in the Arrhenius plot (Figure 13.20b). In the present case the line width in the coalescence region extends over nearly 3 kHz.

A classical problem of organic chemistry is the question of whether cycloheptatriene (26a) participates in a fast and reversible equilibrium with its valence tautomer norcaradiene (26b). By using NMR spectroscopy it has been possible to detect norcaradiene $\rightleftharpoons$ cycloheptatriene equilibria in a series of derivatives. The case involving 7-cyano-7-trifluoromethylcycloheptatriene (26c) was the first example.



Exact data for one such reaction have been determined for dicarbomethoxycycloheptatriene (**27**), the low-temperature spectrum of which is shown in Figure 13.21. Signals of the α -protons at C1,6 of both isomers can clearly be seen as the doublet at δ 5.72 (**27**, $J_{\alpha\beta} = 9.5$ Hz, large vicinal cis-coupling across the double bond to the β -protons at C2,5) and the broadened singlet at δ 2.86 (**28**, small coupling because of a dihedral angle of about 60°). Three signals can be assigned to the protons of the ester methyl groups. Those of lower intensity (δ 3.74 and 3.50) arise from the *exo*- and *endo*-carbomethoxy groups in norcaradiene **28** and the more intense singlet (δ 3.64) has been assigned to the equivalent methyl groups in **27**. At room temperature a time-averaged spectrum is observed.



Since the components of the equilibrium $27 \rightleftharpoons 28$ are not of equal energy, the temperature dependence of the equilibrium constant had to be determined by integration of the α -proton signals in the region of slow exchange. The enthalpy of the norcaradiene was found to be $673 \pm 21 \text{ J mol}^{-1}$ ($161 \pm 5 \text{ cal mol}^{-1}$) lower than that of the cycloheptatriene, while an entropy difference of $11.9 \pm 0.1 \text{ J K}^{-1} \text{ mol}^{-1}$ ($2.85 \pm 0.03 \text{ cal K}^{-1} \text{ mol}^{-1}$) favored the triene. The entropy factor is thus responsible for the fact that at room temperature the free energy of the triene is less than that of the norcaradiene: $\Delta G^\ddagger_{298} = -2.89 \text{ kJ mol}^{-1}$ ($-0.69 \text{ kcal mol}^{-1}$). A line shape analysis leads to values of $29.4 \pm 0.6 \text{ kJ mol}^{-1}$ ($7.02 \pm 0.15 \text{ kcal mol}^{-1}$) for the Arrhenius activation energy E_a and $10^{11.9 \pm 0.2}$ for the frequency factor A of the reaction $28 \rightarrow 27$.

In case of the heterocycle oxepine (**30**) an equilibrium with the isomeric benzene oxide (**29**) has been detected for the parent compound. Here the bicyclic structure

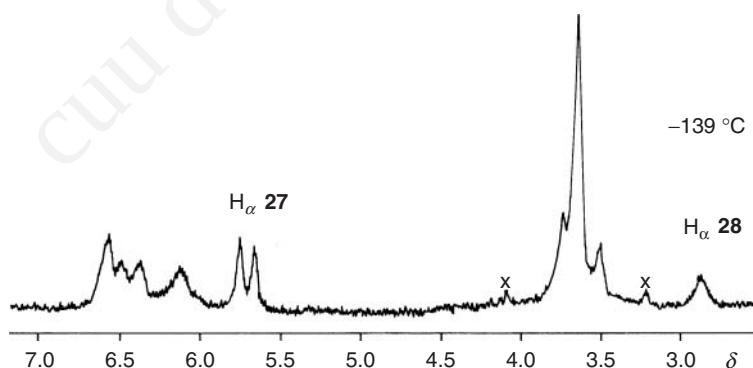
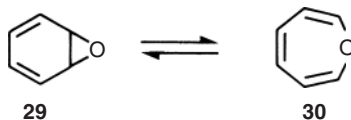


Figure 13.21 ^1H NMR spectrum of the fluxional system $27 \rightleftharpoons 28$ in the region of slow exchange [15]. The letter x identifies the spinning side bands.

is about 7.1 kJ mol^{-1} ($1.7 \text{ kcal mol}^{-1}$) more stable while the entropy of the oxepine is about $42 \text{ J K}^{-1} \text{ mol}^{-1}$ ($10 \text{ cal K}^{-1} \text{ mol}^{-1}$) larger. The activation energies, E_a , for the forward and reverse reactions ($29 \rightleftharpoons 30$) are 38.1 kJ mol^{-1} ($9.1 \text{ kcal mol}^{-1}$) and 30.1 kJ mol^{-1} ($7.2 \text{ kcal mol}^{-1}$), respectively.



Another interesting variation of valence tautomerism is the phenomenon of *double bond* or π -bond shift that has already been mentioned in the case of [16]annulene. Such a process was first detected in a very elegant manner for cyclo-octatetraene via observation of the ^{13}C satellites in the ^1H NMR spectrum caused by a ^{13}C - ^1H group. At low temperature (-55°C) one observes a doublet for each satellite with a coupling of 11.8 Hz , typical for a cis-coupling at a double bond. The coupling to the other neighboring proton over the single bond is not resolved due to an unfavorable dihedral angle in the tub conformation of the hydrocarbon. At elevated temperature the lines broaden and the doublet splitting is replaced by a broad absorption that contains the time-averaged couplings to both protons. These spectral changes document the double bond shift.

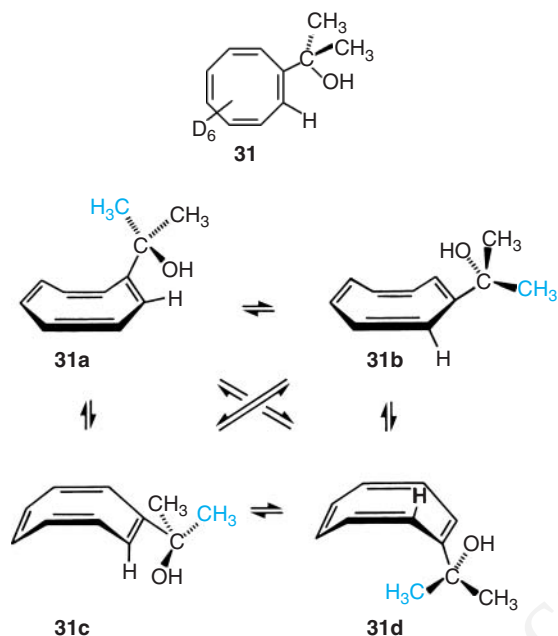
However, the situation is complicated by the fact that in addition to the bond shift a ring inversion occurs. It has been possible to analyze both processes separately by using 1-(dimethylhydroxymethyl)-2,3,4,5,6,7-hexadeutero-cyclo-octatetraene (**31**) (Scheme 13.1).

In this compound two pairs of structural isomers [(**31a**)/(**31b**) and (**31c**)/(**31d**)] and two pairs of conformational isomers [(**31a**)/(**31c**) and (**31b**)/(**31d**)] are in equilibrium with one another as a result of the following processes:

- 1) ring inversion: (**31a**) $\rightleftharpoons$ (**31c**) and (**31b**) $\rightleftharpoons$ (**31d**);
- 2) double bond shift: (**31a**) $\rightleftharpoons$ (**31b**) and (**31c**) $\rightleftharpoons$ (**31d**);
- 3) double bond shift with ring inversion: (**31a**) $\rightleftharpoons$ (**31d**) and (**31b**) $\rightleftharpoons$ (**31c**).

At -35°C all of the transformations are sufficiently slow and the resonance of the olefinic proton appears as two equally intense singlets at $\delta 5.80$ and $\delta 5.76$ that can be assigned to the isomers (**31a**) and (**31c**) and (**31b**) and (**31d**), respectively. As one would expect, because of the chirality of the non-planar olefinic system, two signals, separated by about 0.05 ppm , are observed for the methyl protons.

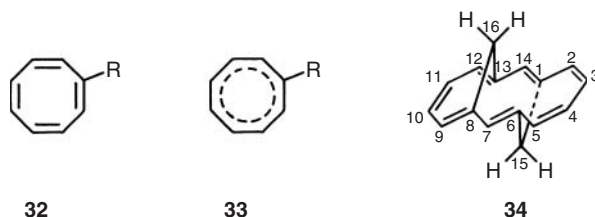
At higher temperature the signals of the methyl protons and also those of the olefinic proton degenerate to singlets. The coalescence temperatures for the changes are -2 and 41°C , respectively. This difference shows that the transition from diastereotopic to enantiotopic methyl groups is achieved only through a ring inversion that confers an effective plane of symmetry on the molecule on the NMR time scale. At higher temperatures the double bond isomerization accounts for the time averaging of the environment of the olefinic proton and the processes (**31a**) $\rightleftharpoons$ (**31b**) and (**31c**) $\rightleftharpoons$ (**31d**) now also contribute to the magnetic equivalence of the methyl protons.



Scheme 13.1

These observations lead to the conclusion that a lower activation energy is necessary for the ring inversion than is required for the double isomerization, especially since the parameter $\delta\nu$ is smaller for the exchange (31a) $\rightleftharpoons$ (31b) or (31c) $\rightleftharpoons$ (31d) than for (31a) $\rightleftharpoons$ (31c) and (31b) $\rightleftharpoons$ (31d). If the free energy of activation for both processes were the same, the coalescence of the olefinic proton signals would have been observed first because, according to Eq. (13.14), a smaller $\delta\nu$ value requires a smaller k value and hence a lower temperature for coalescence.

Quantitative evaluation of $\Delta G^\ddagger$ at -2°C leads to a value of 61.5 kJ mol^{-1} ($14.7 \text{ kcal mol}^{-1}$) for ring inversion and 71.5 kJ mol^{-1} ($17.1 \text{ kcal mol}^{-1}$) for double bond isomerization. Assuming for both processes a planar transition state characterized in one case by **32** and in the other by **33** it can be concluded that the structure **33** with a delocalized $4n$ π -system is destabilized by about 8 kJ mol^{-1} (2 kcal mol^{-1}) with respect to the olefinic structure **32** with localized double bonds; planar cyclo-octatetraene would therefore be *antiaromatic* [16].



As we touched on briefly above, in the area of dynamic effects 2D ^{13}C EXSY experiments have become important. For ^{13}C nuclei, because of their low natural abundance, application of the pulse sequence (13.25) (p. 514) does not lead to cross peaks that arise from homonuclear Overhauser effects. Therefore, the results are usually less ambiguous than for 2D ^1H EXSY. An example of a 2D ^{13}C exchange spectrum is shown in Figure 13.22, where the double bond shift in *n*-butyl-cyclo-octatetraene is detected.

Interestingly, with respect to the observations made for cyclo-octatetraene, 1,6:8,13-anti-bismethano-[14]annulene (34) – already introduced on page 110 as structure **24a** – has localized double bonds and shows a double bond shift. The important point is that here, for the first time, we encounter such a process in a $(4n + 2)$ π -system that formally satisfies with 14 π -electrons the Hückel rule for aromatic systems where the π -electrons are expected to be delocalized. Of course, this rule also assumes the coplanar arrangement of the carbon atoms

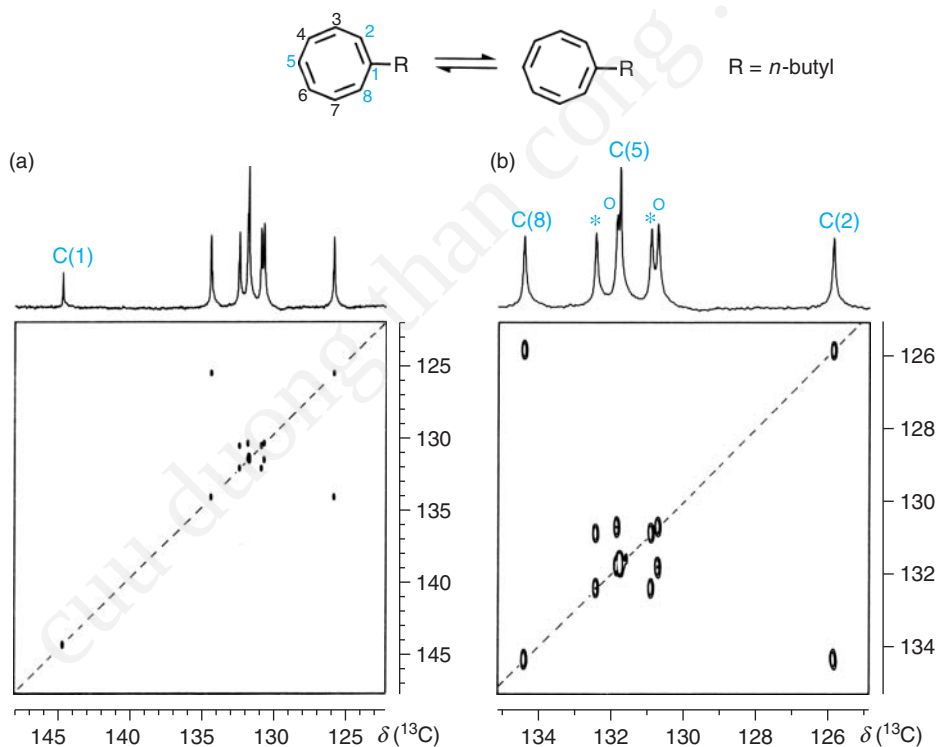


Figure 13.22 Detection of the double bond shift in *n*-butyl-cyclo-octatetraene by 2D ^{13}C exchange spectroscopy at room temperature; (a) total spectral range; as expected, the quaternary carbon C(1) shows no cross peaks because it does not participate in the exchange process and (b) the same is true for

C(5) that gives rise to a sharp singlet in the low-frequency region; the signals of C(2) and C(8) are connected by cross peaks; the remaining signals belong to C4,6 and C3,7, but have not been assigned. H. Günther and H. Hausmann, unpublished.

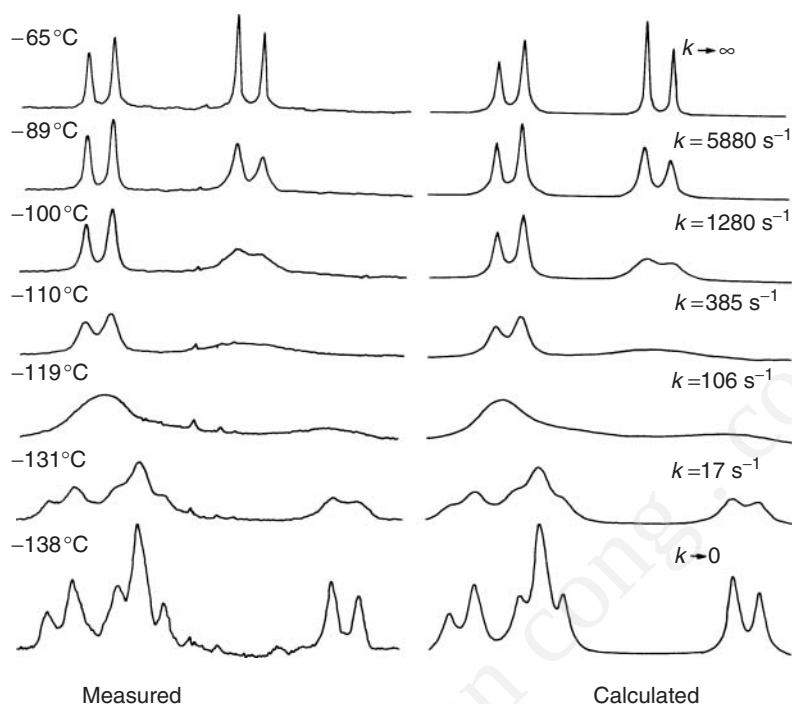
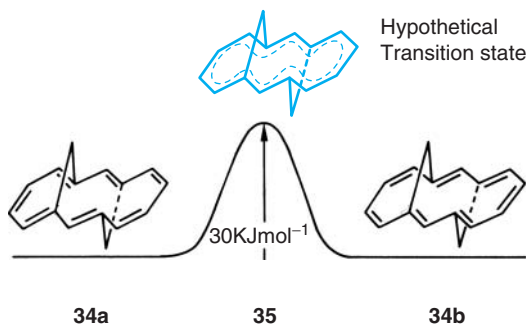


Figure 13.23 Temperature dependence of the absorption of the methylene protons in 1,6;8,13-anti-bismethano[14]annulene [17]. Since the molecule in the region of fast exchange effectively possesses C_{2h} symmetry, only one AB system is observed. At -138°C the methylene groups are no longer equivalent and one finds, because of the localized double bonds, two AB systems that are partially superimposed [$\delta(^1\text{H})$ -values see page 110].

of the molecular perimeter. As discussed before (p. 110) in the case of **34** this requirement obviously is not fully met. The ^1H NMR spectrum of **34** – at 25°C one AB system at δ 1.88, 2.48 and two singlets for the ring protons at δ 6.20 and 6.33 (4:1) – is temperature dependent and after line broadening and decoalescence two overlapping AB systems for the protons of the methylene bridges are observed that document structure **34** with alternating single and double bonds (Figure 13.23). Line shape changes for the olefinic protons are less characteristic, except for the singlet of the central protons in position 7 and 14 that is temperature independent because the position of these nuclei is on the symmetry plane for the dynamic process. The rate constants for the π -bond shift $\mathbf{34a} \rightleftharpoons \mathbf{34b}$ can be derived from the temperature-dependent variation of the methylene proton resonances. Figure 13.23 shows several typical experimental and calculated spectra for different temperatures. The activation energy E_a and the frequency factor A were calculated to be 30 kJ mol^{-1} ($7.1 \text{ kcal mol}^{-1}$) and $10^{12.2}$, respectively. If one assumes, as we did in the case of cyclo-octatetraene, the delocalized structure **35** to be the transition state, one obtains the following energy profile:

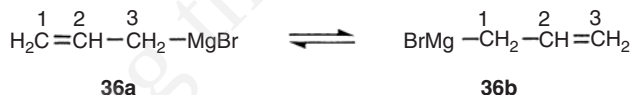


The resonance energy of the 14π system would then be overcome by the strain resulting in a planar ring. The reaction can, of course, be formulated alternatively by electrocyclic processes.

13.2.5

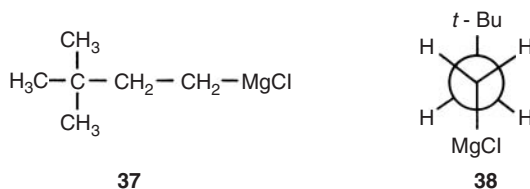
Dynamic Processes in Organometallic Compounds and Carbocations

Considerable progress in developing an understanding of the structure of Grignard reagents has been made through the application of NMR techniques. For example, the ^1H NMR spectrum of allylmagnesium bromide (**36**) consists of a quintuplet at δ 6.2 and a doublet at δ 2.5 in an intensity ratio of 1 : 4, indicating the presence of an AX_4 system. This observation is consistent with a rapid equilibrium involving the two isomers **36a** and **36b**:



For 3,3-dimethylbutylmagnesium chloride (**37**) the spectrum has been observed to be temperature dependent. At -53°C an $\text{AA}'\text{XX}'$ system is obtained while at 32°C one observes a spectrum of the A_2X_2 type (Figure 13.24).

For a simplified explanation we assume that at low temperature the compound exists predominantly in the *trans* conformation **38**:



The observation of an $\text{AA}'\text{XX}'$ system is consistent with this conclusion. The transition to an A_2X_2 system means then that at high temperatures the parameter L becomes zero. This indicates that for the spin-spin interaction between the A and the X protons only one coupling constant exists. The protons A and A' and X and X' must therefore be magnetically equivalent, that is, they should exchange magnetic sites with one another. The most plausible mechanism for such an exchange is the

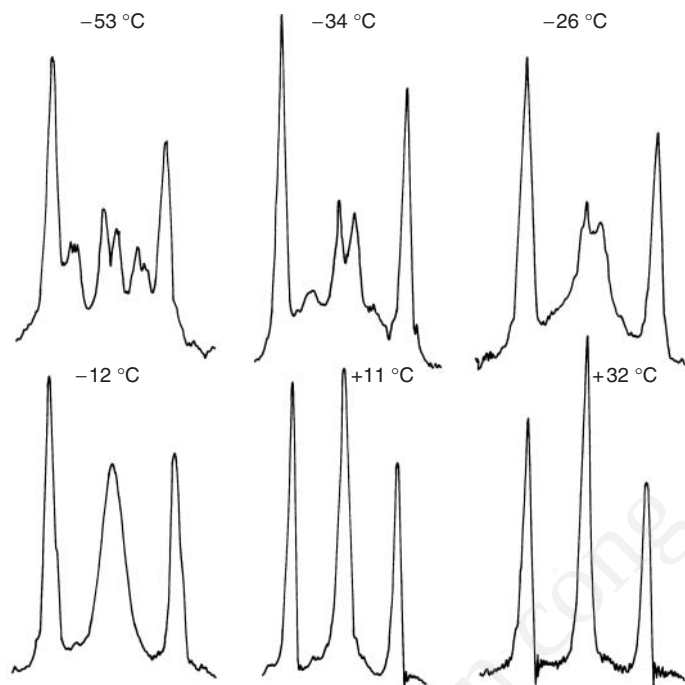
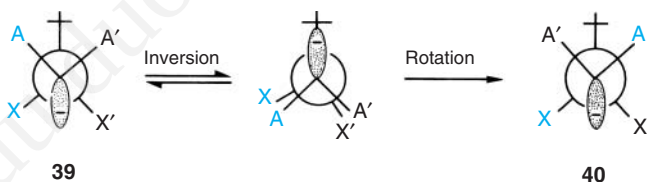
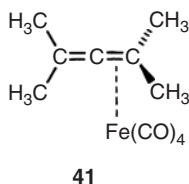


Figure 13.24 Temperature-dependent variations in the ^1H NMR spectrum of 3,3-dimethylbutylmagnesium chloride; AA' portion [18].

inversion of the carbanion ($39 \rightleftharpoons 40$), which is isoelectronic with an amine. The activation energy for this process was determined from the temperature-dependent line shape of the spectrum to be $48 \pm 8 \text{ kJ mol}^{-1}$ ($11 \pm 2 \text{ kcal mol}^{-1}$).



In metal carbonyl complexes of olefins interesting exchange phenomena involving the metal carbonyl moieties have been observed. Thus, the $\text{Fe}(\text{CO})_4$ complex of tetramethylallene (**41**) at room temperature exhibits only a singlet (Figure 13.25).



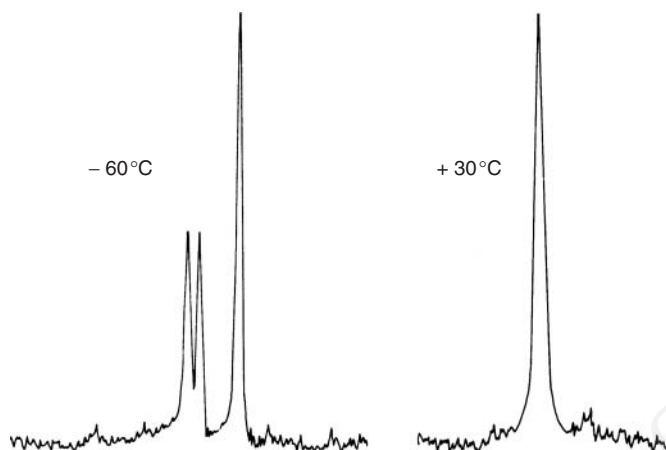
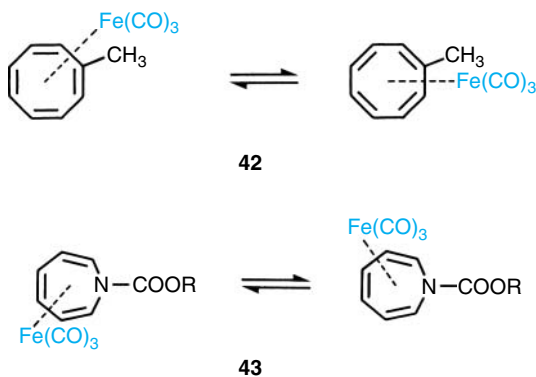


Figure 13.25 ^1H NMR spectra of the $\text{Fe}(\text{CO})_4$ complex of tetramethylallene (**41**) at different temperatures [19].

At -60°C , however, the spectrum consists of three signals with an intensity ratio of 1 : 1 : 2, as would be required for a “frozen” structure. An exchange of the $\text{Fe}(\text{CO})_4$ group between the two double bonds is therefore responsible for the simple room temperature spectrum. The intramolecular nature of this tautomerism has been confirmed by the fact that in the fast-exchange region signals for uncomplexed excess tetramethylallene can be observed separately.

Analogous processes have also been reported in cyclic olefins. Thus with the methylcyclo-octatetraene(tricarbonyl)iron (**42**) and the *N*-carbomethoxyazepine (tricarbonyl)iron (**43**) the indicated equilibria with free energies of activation of 33 kJ mol^{-1} (8 kcal mol^{-1}) and 65 kJ mol^{-1} ($15.5 \text{ kcal mol}^{-1}$), respectively, have been observed. In **42** the exchange of the tricarbonyliron group is accompanied by a double bond shift that lowers the barrier and that cannot take place in **43**. In **42** the tricarbonyliron group moves to the adjacent C-C bond, while in **43** an additional bond is involved.



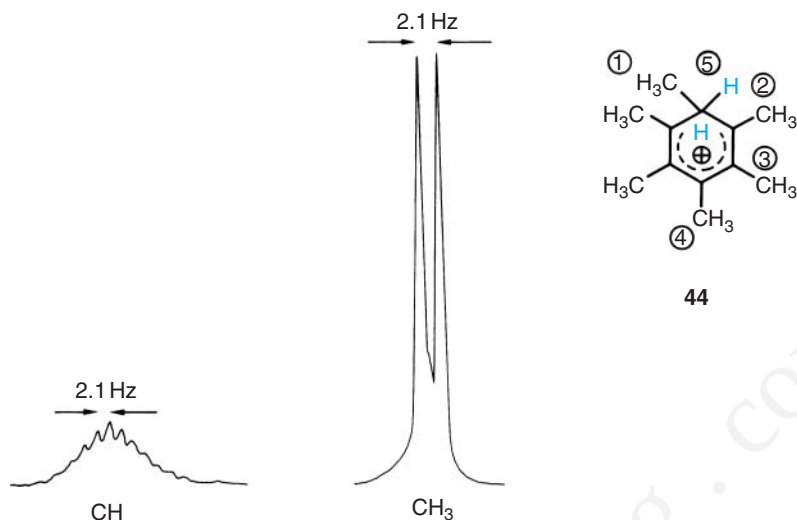


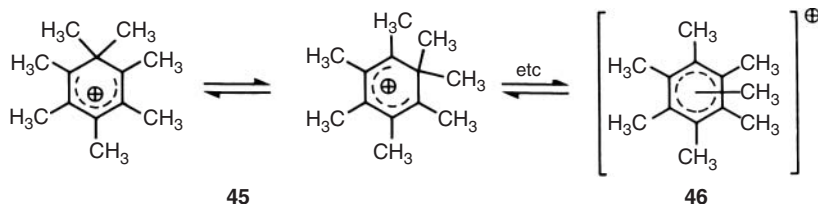
Figure 13.26 ^1H NMR spectrum of protonated hexamethylbenzene (**44**) in the region of rapid exchange [20].

Deeper insight into the mechanisms of proton shifts in carbocations has also developed as the result of applications of NMR spectroscopy. Thus, hexamethylbenzene in hydrofluoric acid forms the σ -complexed cation **44** that is the accepted intermediate in electrophilic aromatic substitution. The ^1H NMR spectrum of this cation at room temperature indicates that there is a rapid migration of the added proton around the ring (Figure 13.26). One observes a doublet ($J = 2.1$ Hz) for the methyl resonances and a multiplet for the tertiary proton that – as a result of its rapid exchange – is effectively coupled to all of the 18 methyl protons. Therefore, the observed splitting, according to Eq. (13.27), is an average of the coupling constants observed in the low-temperature spectrum of the “frozen” structure **44**; $J_{15} = 6.8$ Hz, $J_{45} = 3.5$ Hz, $J_{25} = 1$ Hz, and $J_{35} = 0$ Hz:

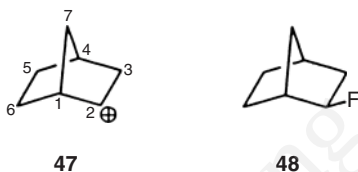
$$J_{\text{obs.}} = (J_{15} + J_{45} + 2J_{25})/6 \quad (13.27)$$

The comparison of experimental and calculated line shapes in the temperature range between -105 and 55°C leads to an activation energy of 55.7 ± 3.3 kJ mol $^{-1}$ (13.3 ± 0.8 kcal mol $^{-1}$) for the proton migration.

In an analogous case, for the heptamethylbenzonium ion even the mechanism of the exchange process can be clarified in this way. The theoretical spectra expected for a series of 1,2-shifts (**45**) and the alternative, a statistical exchange via an intermediate π -complex **46**, were both calculated. Only in the first case did the calculated and the experimental spectra agree.



One problem of carbocation chemistry that has attracted much interest for many years, the structure of the norbornyl cation (47), was also investigated by dynamic NMR:



The ion was prepared from the fluoride 48 in a solution of SbF_5 and SO_2F_2 and exhibited the spectrum displayed in Figure 13.27a. The presence of three signals in the intensity ratio of 4:1:6, which coalesce at higher temperatures to a singlet, allows the conclusion that even at -113°C no “frozen” structure exists. Wagner–Meerwein rearrangements and 2,6-hydride shifts (Scheme 13.2, p. 548) cause the protons in positions 1, 2, and 6 and also those in positions 3, 5, and 7 to become equivalent under these conditions. The proton in position 4 does not participate in this exchange process and the cation possesses C_{3v} symmetry on the NMR time scale. At -113°C the 2,3-hydride shift, however, is slow so that the enthalpy of activation of $45.2 \pm 2.5 \text{ kJ mol}^{-1}$ ($10.8 \pm 0.6 \text{ kcal mol}^{-1}$) derived from the line shape changes of the spectrum at higher temperatures (-100 to $+3^\circ\text{C}$) can be assigned to this process.

If one uses a mixture of SbF_5 , SO_2ClF , and SO_2F_2 it is even possible to record spectra down to -158°C . By further cooling, the signal at highest frequency splits into two singlets of equal intensity. More over, the low-frequency signal develops a shoulder while the signal of the proton in the 4-position remains unchanged throughout. The low-temperature spectrum obtained in this way is best rationalized on the basis of a protonated nortricyclene structure (49), which is a non-classical carbocation with a five-coordinate carbon atom. The bond to C2 and C6 can be described as a three-center bond and the threefold axis of symmetry has been replaced by a symmetry plane. Neither the classical structure 47 nor the assumption that the Wagner–Meerwein rearrangements are still fast even at this low temperature can explain this spectrum. For the second dynamic process an activation energy of $24.7 \pm 0.8 \text{ kJ mol}^{-1}$ ($5.9 \pm 0.2 \text{ kcal mol}^{-1}$) has been derived on the basis of spectral changes from a line shape calculation.

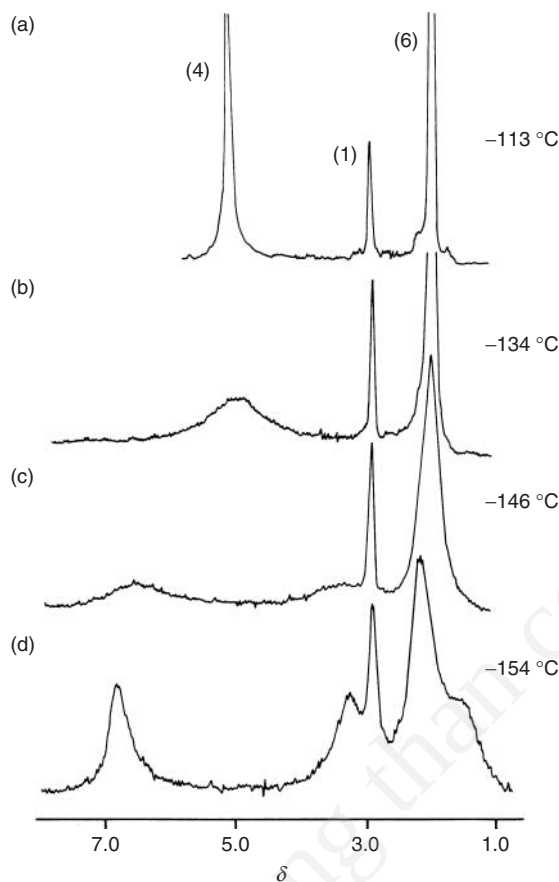
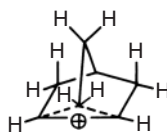
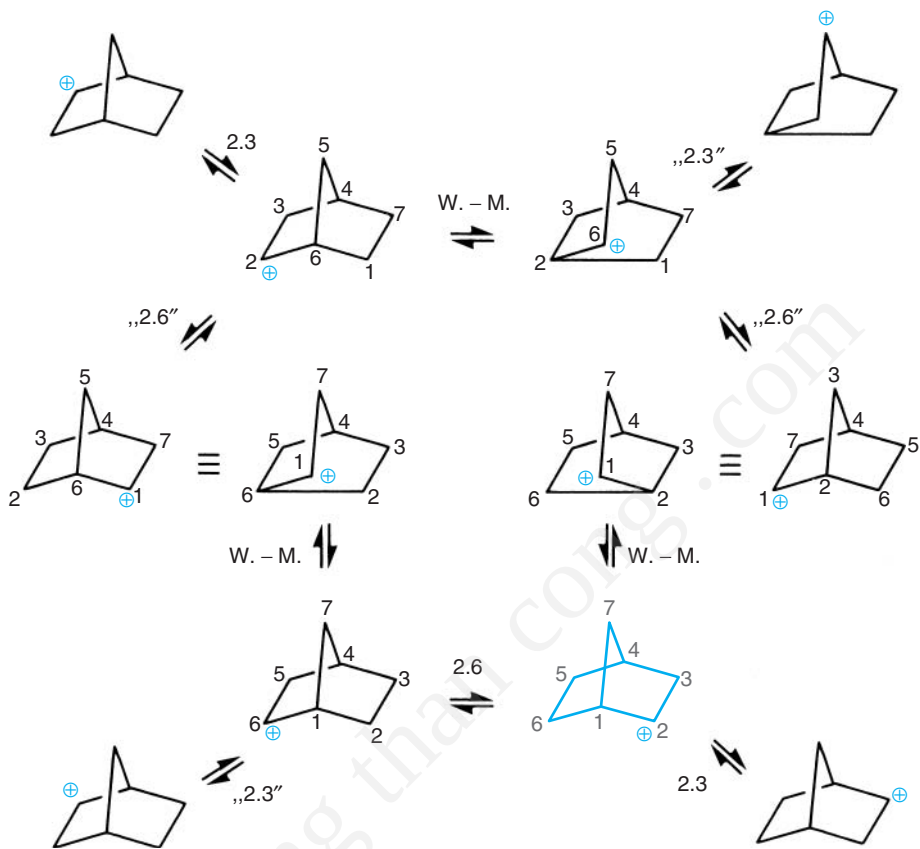


Figure 13.27 (a)–(d) ^1H NMR spectra of the norbornyl cation as a function of temperature; the numbers in parenthesis are relative intensities; the signal at about 3 ppm is due to 4-H [21].



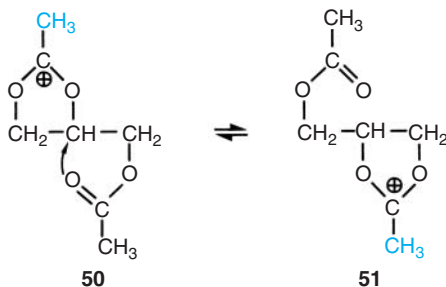
49

Finally, we discuss the rearrangement of acyloxonium salts proceeding as neighboring group participation. In the case of the cation **50** – obtained by treating glycerine triacetate with antimony pentachloride – the NMR spectrum indicates a fast reversible rearrangement into the isomer **51**. At room temperature, with $[\text{D}_3]\text{acetonitrile}$ as solvent, the methyl protons appear as two singlets at δ 3.35 and δ 2.16, the line widths of which increase upon heating. Finally, the two signals

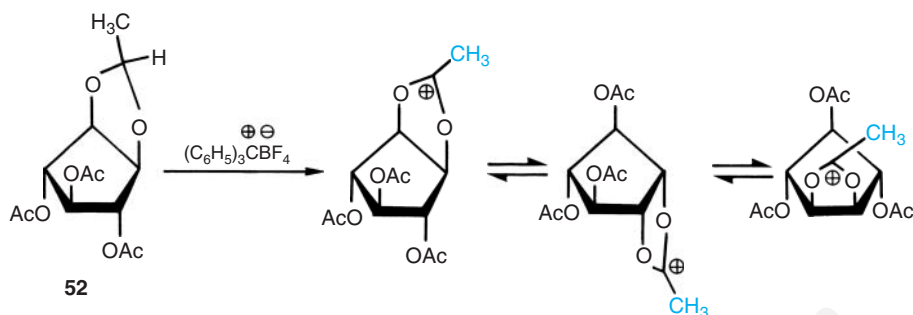


Scheme 13.2 W.-M. = Wagner-Meerwein rearrangement (shift of a C–C bond); 2.3 = hydride shift over one C–C bond; 2.6 = hydride shift over two C–C bonds.

coalesce at 105°C and a value of 78.2 kJ mol⁻¹ (18.7 kcal mol⁻¹) was determined for $\Delta G^\ddagger$.



In cyclic compounds a neighboring group reaction of this kind leads to analogous valence isomerizations and in the case of the cation **52** the participation of all the acetoxy groups in a series of identity reactions can take place.



13.3 Intermolecular Exchange Processes

The exchange processes discussed so far were without exception *intramolecular*. Here, we mention briefly a few exchange phenomena that are characterized by their *intermolecular* nature. These include almost all proton transfer reactions such as those discussed for methanol (p. 503) and other alcohols as well as amines and carboxylic acids. In these cases the collapse of spin–spin multiplets is quite often of diagnostic value. Table 13.3 gives the results of several investigations on alcohols, amines, and related substances. The processes involved are exclusively second-order reactions, in contrast to the first-order reactions treated above.

Of special interest to the chemist are keto–enol equilibria that involve both intermolecular and intramolecular proton transfer and that can also be detected and studied by means of NMR spectroscopy. In the ^1H spectrum of acetylacetone (Figure 13.28, p. 550) one clearly sees the signals of both the keto form [$\delta(\text{CH}_3)$ 2.2, $\delta(\text{CH}_2)$ 3.7] and the enol form [$\delta(\text{CH}_3)$ 2.0, $\delta(=\text{CH})$ 5.7], indicating that the rate

Table 13.3 Intermolecular proton transfer reactions and their second-order rate constants ($\text{l mol}^{-1} \text{s}^{-1}$) as determined using NMR spectroscopy [22].

Reaction	k
$\text{H}_2\text{O} + \text{H}_3\text{O}^+ \rightleftharpoons \text{H}_3\text{O}^+ + \text{H}_2\text{O}$	10^{10}
$\text{H}_2\text{O}_2 + \text{H}_3\text{O}^+ \rightleftharpoons \text{H}_3\text{O}_2^+ + \text{H}_2\text{O}$	2×10^7
$\text{CH}_3\text{OH} + \text{H}^*\text{OH} \rightleftharpoons \text{OCH}_3\text{OH}^* + \text{HOH}$	3
$\text{CH}_3\text{OH} + \text{H}_3\text{O}^+ \rightleftharpoons \text{CH}_3\text{OH}_2^+ + \text{H}_2\text{O}$	10^8
$\text{RSH}_2^+ + \text{R}^*\text{SH} \rightleftharpoons \text{RSH} + \text{R}^*\text{SH}_2^+$	10^2
$\text{RS}^- + \text{R}^*\text{SH} \rightleftharpoons \text{RSH} + \text{R}^*\text{S}^-$	6×10^5
$\text{R}_3\text{NH}^+ + \text{H}_2\text{O} \rightleftharpoons \text{R}_3\text{N} + \text{H}_3\text{O}^+$	10^{-2}
$\text{R}_3\text{NH}^+ + \text{R}_3\text{N} \rightleftharpoons \text{R}_3\text{N} + \text{R}_3\text{NH}^+$	10^8
$\text{R}_2\text{NH} \sim \text{OH}^- \rightleftharpoons \text{R}_2\text{N}^- + \text{HOH}$	5×10^6
$(\text{CH}_3)_3\text{PH}^+ + (\text{CH}_3)_3\text{P} \rightleftharpoons (\text{CH}_3)_3\text{P} + (\text{CH}_3)_3\text{PH}^+$	10^2
$\text{Ph-C}\equiv\text{C-H} + \text{OH}^- \rightleftharpoons \text{Ph-C}\equiv\text{C}^- + \text{H}_2\text{O}$	5×10^2

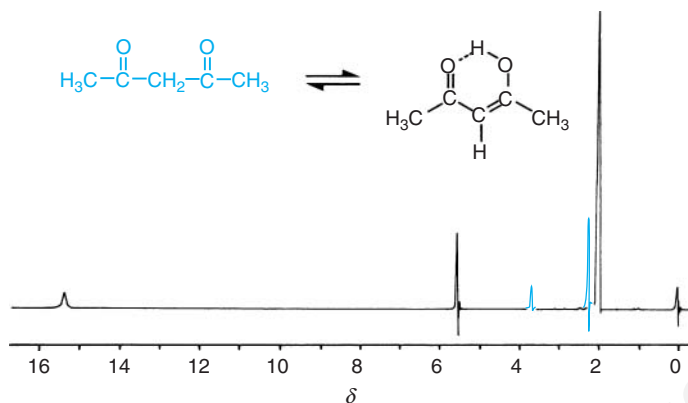
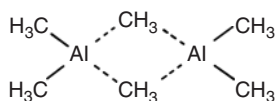


Figure 13.28 ^1H NMR spectrum of acetylacetone at room temperature in carbon tetrachloride.

of the equilibrium reaction is slow on the NMR time scale ($k < 10^{-1}$). With the addition of base or by raising the temperature, the reaction rate increases and line broadening and finally coalescence to a time-averaged spectrum is observed.

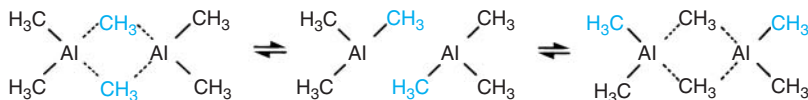
From the relative intensities of the signals it is clear that at room temperature the enol form predominates in the equilibrium mixture. Integration shows that the mixture contains 86% enol and 14% ketone. The strong deshielding of the enol hydroxyl proton is a consequence of intramolecular hydrogen bond formation. The magnetic equivalence of the methyl groups of the enol form, provided it is not accidental, indicates a rapid intramolecular exchange of the hydrogen atoms between the two oxygen functions.

Intermolecular exchange processes are also encountered in organometallic chemistry. Figure 13.29 shows the temperature dependence of the NMR spectrum of trimethylaluminium in toluene. At -55°C two separate signals corresponding to the dimeric structure **53** are observed.



53

These signals can be assigned to the methyl bridges and to the terminal methyl groups. The equivalence of all of the methyl groups at higher temperature can be rationalized on the basis of the following mechanism:



The activation energy for the exchange was determined to be 65.3 kJ mol^{-1} ($15.6 \text{ kcal mol}^{-1}$). The intermolecular course of the process was confirmed by the fact that in the presence of trimethylgallium not only the individual signals of

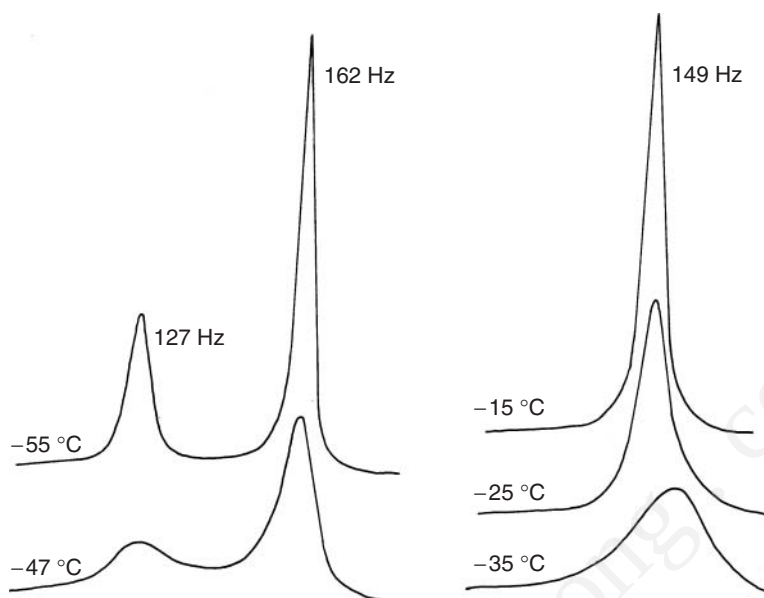


Figure 13.29 Temperature dependence of the ^1H NMR spectrum of trimethylaluminum (in toluene) [23].

the methyl groups of trimethylaluminum and trimethylgallium coalesced but at higher temperatures even the two average signals of these two compounds merged with one another.

In other cases the coupling constants between the proton and the metal of the organometallic compound have been used as an indicator for a dynamic process. For example, cadmium occurs naturally as a mixture of isotopes that consists of ^{111}Cd (13%) and ^{113}Cd (12%) nuclei, each with a spin of $I = \frac{1}{2}$, in addition to ^{112}Cd nuclei with a spin of $I = 0$. In the ^1H NMR spectrum of dimethylcadmium one therefore observes satellites that are caused by spin–spin interaction with the cadmium (Figure 13.30, p. 552). As in the case of the splitting of the hydroxyl proton signal in methanol, this fine structure disappears when individual methyl groups are exchanged between different cadmium atoms. It has been observed experimentally that with increasing temperature the satellites at first broaden and finally disappear under the principal signal of the methyl resonance. The fact that one can still easily observe the ^{13}C satellites after the disappearance of the Cd satellites clearly indicates that the exchange involves entire methyl groups and not individual protons.

Intra- as well as *intermolecular* exchange has been detected for many organolithium compounds and line shape changes can be observed for all nuclei that participate in the particular exchange system (^1H , $^6/7\text{Li}$, ^{13}C , ^{31}P). As has already been described in Chapter 12, organolithium species exist in ethereal solvents nearly exclusively as aggregates, mostly as dimers, tetramers, or hexamers, and quite often various aggregates exist at room temperature in fast, reversible

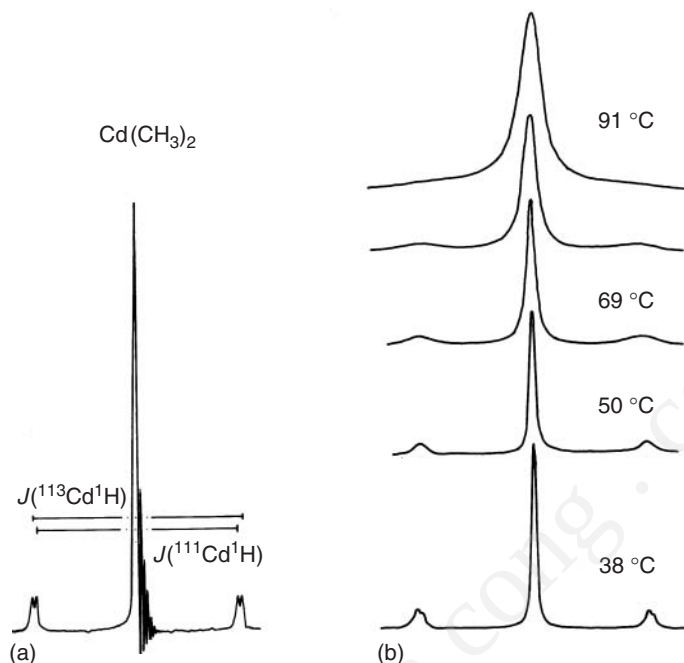


Figure 13.30 (a) ^1H NMR spectrum of dimethylcadmium in toluene [23]; (b) temperature dependence of the ^1H NMR spectrum of pure dimethylcadmium [24].

equilibrium. An example is shown in Figure 13.31 with the temperature variations of the ^6Li NMR spectrum of trans-2,3-dimethyl-cyclopropyllithium (**54**). The signal observed at ca. 2.2 ppm (relative to external 0.1 M LiBr in THF) broadens at lower temperature and splits below 225 K into three signals at 2.22, 2.08, and 2.02 ppm, respectively, in the intensity ratio of 1.0 : 1.23 : 1.15. These were later identified by methods not discussed here as belonging to three different species: a tetramer, a dimer, and a monomer (in the order of the chemical shifts given above).

On the basis of the temperature-dependent line shape changes in the NMR spectra the exchange processes between different aggregates can be analyzed. $^6/7\text{Li}$ spectra (for ^6Li isotope-enriched) are favorable because line splittings due to homonuclear scalar coupling are absent and the number of signals is usually small. However, in this context it is important to realize that *inter-aggregate* exchange is concentration dependent and the NMR analysis only yields pseudo-first-order rate constants.

In some cases, dynamic processes are indicated by line shape changes of lithium-coupled ^{13}C signals and have to be analyzed on the basis of density matrix treatments. An example is given in Figure 13.32 with the ^{13}C signal of dibromomethyl lithium (**55**), labeled with ^6Li (99.5%) and ^{13}C (90%) to facilitate the analysis that yielded a free activation enthalpy $\Delta G^\ddagger(25^\circ)$ of $25.4 + 0.8 \text{ kJ mol}^{-1}$ ($6.16 + 0.2 \text{ kcal mol}^{-1}$). The $^1J(^{13}\text{C}, ^6\text{Li})$ coupling of 16.3 Hz characterizes **55** as monomer and the dynamic process may be described as in Scheme 13.3 with a

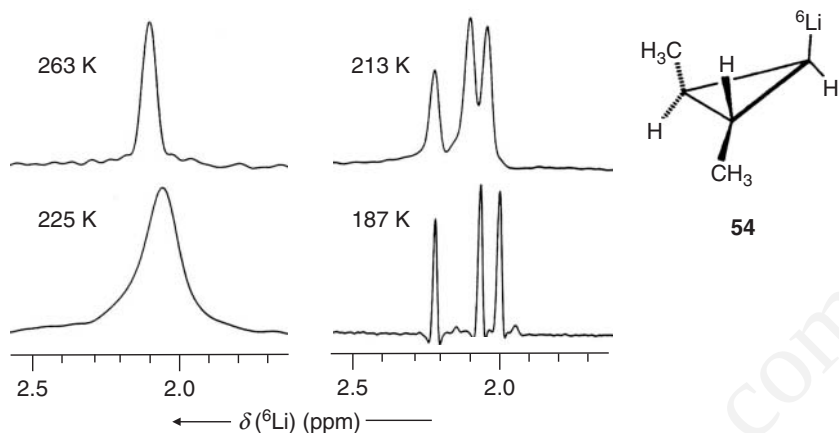


Figure 13.31 Temperature dependence of the 58.88 MHz ^6Li NMR spectrum of *trans*-2,3-dimethylcyclopropyllithium in $[\text{D}_{10}]\text{diethylether}$ [25].

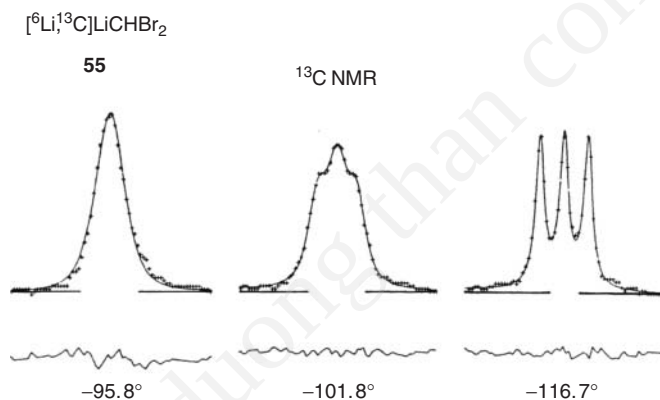
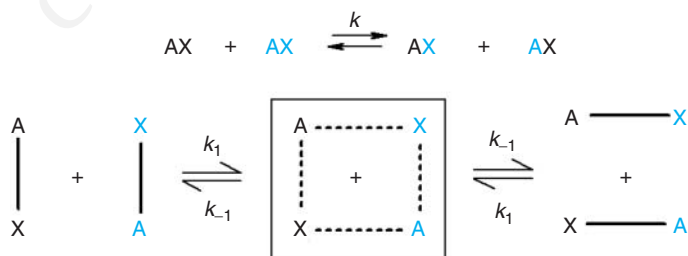


Figure 13.32 Experimental (+) and calculated ^{13}C signals of $[\text{}^6\text{Li}, \text{}^{13}\text{C}]\text{LiCHBr}_2$ (55) in THF at various temperatures ($^\circ\text{C}$); the errors $y_i(\text{calc.}) - y_i(\text{exp.})$ are visualized at the same intensity as the spectra by the noisy lines [26].



Scheme 13.3

dimer as intermediate: Fast exchange scrambles the spin states of the coupled nuclei and the line splitting disappears.

13.4

Line Broadening by Fast Relaxing Neighboring Nuclei

Finally, at this point, we discuss the effect that causes line broadening not by dynamic processes but by the relaxation behavior of neighboring nuclei. In organic compounds this is often caused by nitrogen where nitrogen-14 is the dominant nuclide (natural abundance 99.64%) of this element.

As pointed out earlier (p. 439 ff.), the ^{14}N nucleus has a spin quantum number of $I = 1$ and, as a result of its non-spherical charge distribution, a quadrupole moment that is of significance for its relaxation behavior. Interactions of the quadrupole moment with the electric field gradients of the electron cloud of the molecule in question represent an efficient mechanism by which the ^{14}N nucleus can exchange its energy with the lattice. If relaxation is fast, a coupled proton, for example, “sees” only a time average of the possible spin states $m_I(^{14}\text{N}) = 1, 0, \text{ and } -1$ and the expected splitting into a 1 : 1 : 1 triplet vanishes. This amounts to a “decoupling” of both nuclei.

As a rule the relaxation times of the ^{14}N nuclei in organic compounds are of such a magnitude that they do not lead to a complete disappearance of line splittings. The result is usually a more or less extensive line broadening for the ^1H signals due to scalar $^{14}\text{N}, ^1\text{H}$ interactions over one or two bonds ($^{14}\text{N}-^1\text{H}$, $^{14}\text{N}-\text{C}-^1\text{H}$). Therefore, if one wishes to measure $^{14}\text{N}, ^1\text{H}$ coupling constants the quadrupolar relaxation must be suppressed. This can be achieved by *increasing the temperature* or by making the electronic environment of the ^{14}N nucleus symmetrical. Accordingly, the proton resonance spectrum of the ammonium ion ($^{14}\text{NH}_4^+$) consists of a 1 : 1 : 1 triplet with sharp lines (cf. Exercise 3.11, p. 54). $^{14}\text{N}, ^1\text{H}$ coupling is also observed in isonitriles, from which it can be concluded that the electric field gradient of the electron cloud at the nitrogen in these compounds is small.

On the other hand, the line broadening effect is found in nitrogen metal complexes as demonstrated in Figure 12.27 (p. 481). A modest increase in temperature allows us to measure the $^{195}\text{Pt}, ^{14}\text{N}$ coupling.

If, on the other hand, one wishes to observe $^1\text{H}, ^1\text{H}$ coupling in a molecule such as pyridine without the perturbing line broadening effect of ^{14}N , quadrupolar relaxation must be increased. This can often be accomplished by *lowering the temperature*. Alternatively, heteronuclear double resonance can be used to decouple the ^{14}N nucleus as shown in Figure 8.33 (p. 274). In compounds that are labeled with the spin $\frac{1}{2}$ nucleus ^{15}N the line-broadening effect is, of course, not observed.

The relationships described can further be complicated by the fact that N–H protons participate in exchange processes via hydrogen bond formation. In many cases this also leads, as mentioned on p. 38, to line broadening. Furthermore, the exchange provides an additional mechanism that, as in the case of methanol (p. 503), can lead to a disappearance of $^{14}\text{N}, ^1\text{H}$ or $^1\text{H}, ^1\text{H}$ coupling constants.

Since the rate of proton exchange is increased by raising the temperature or by the addition of catalysts such as H_2O , OH^- , or H_3O^+ the temperature must be decreased for the elimination of these effects. Likewise, by using dimethyl sulfoxide as solvent the proton exchange can be suppressed to the extent that coupling constants of N–H protons can be measured.

Line broadening in ^1H NMR is also observed in the presence of a number of spin- $\frac{1}{2}$ metal nuclei like ^{195}Pt (Figure 13.32) or ^{199}Hg . Here the satellites observed in ^1H spectra due to scalar coupling with these nuclei are broadened or completely eliminated. This originates from the CSA (chemical shift anisotropy) mechanism that dominates the relaxation of these nuclei. Relaxation caused by the CSA mechanism is proportional to B_0^2 and thus especially effective at high magnetic fields. An example for ^{199}Hg was discussed in Chapter 12 (p. 494).

References

1. Anet, F.A.L., Bradley, C.H., Bradley, M.A., Brown, M.A., Mock, W.L., and McCausland, J.H. (1969) *J. Am. Chem. Soc.*, **91**, 7782.
2. Deroose, E.F., Castillo, J., Saulys, D., and Morrison, J. (1991) *J. Magn. Reson.*, **93**, 347.
3. Heidberg, J., Weil, J.A., Janusonis, G.A., and Anderson, J.K. (1964) *J. Chem. Phys.*, **41**, 1033.
4. Kessler, H. (1970) *Angew. Chem.*, **82**, 237; *Angew. Chem., Int. Ed. Engl.*, **9**, 219.
5. Anderson, J.E. and Lehn, J.-M. (1967) *J. Am. Chem. Soc.*, **89**, 81.
6. Bovey, F.A. (1969) *NMR Spectroscopy*, Academic Press, New York.
7. Eliel, E.L., Wilen, S.H., and Mander, L.N. (1994) *Stereochemistry of Organic Compounds*, Wiley, New York, and literature cited therein.
8. (1970) Japan Electron Optics Laboratory News, Vol. 7C, No. 4, p. 8.
9. Jensen, F.R. and Bushweller, C.H. (1969) *J. Am. Chem. Soc.*, **91**, 3223.
10. Günther, H., Schmitt, P., Fischer, H., Tochtermann, W., Liebe, J., and Wolff, C.H. (1985) *Helv. Chim. Acta*, **68**, 801.
11. Sondheimer, F. et al. (1967) *Aromaticity*, The Chemical Society, London.
12. Schröder, G., Oth, J.F.M., and Merenyi, R. (1965) *Angew. Chem.*, **77**, 774.
13. (a) Anderson, P.W. (1954) *J. Phys. Soc. Jpn.*, **9**, 316. (b) Kubo, R. (1954) *J. Phys. Soc. Jpn.*, **9**, 935. (c) Sack, R.A. (1958) *Mol. Phys.*, **1**, 163.
14. Günther, H. and Ulmen, J. (1974) Applications of Carbon-13 Resonance Spectroscopy – XV; The Degenerate Cope-Rearrangement of Bullvalene. *Tetrahedron*, **30**, 3781.
15. Görlitz, M. and Günther, H. (1969) *Tetrahedron*, **24**, 4467.
16. (a) Anet, F.A.L. (1962) *J. Am. Chem. Soc.*, **84**, 671. (b) Anet, F.A.L. Bourn, A.J.R. and Lin, Y.S. (1964) *J. Am. Chem. Soc.*, **86**, 3576.
17. Vogel, E., Haberland, U., and Günther, H. (1970) *Angew. Chem.*, **82**, 510; *Angew. Chem., Int. Ed. Engl.*, **9**, 513.
18. Whitesides, G.M., Witanowski, M., and Roberts, J.D. (1965) *J. Am. Chem. Soc.*, **87**, 2854.
19. Ben-Soshan, R. and Pettit, R. (1967) *J. Am. Chem. Soc.*, **89**, 2231.
20. Mackor, E.L. and McLean, C. (1964) *Pure Appl. Chem.*, **8**, 393.
21. Olah, G.A. and White, A.M. (1969) *J. Am. Chem. Soc.*, **91**, 3957.
22. Loewenstein, A. and Connor, T.M. (1963) *Ber. Bunsenges. Phys. Chem.*, **67**, 280.
23. Ham, N.S. and Mole, T. (1969) *Prog. Nucl. Magn. Reson. Spectrosc.*, **4**, 91.
24. Bremser, W., Winokur, M., and Roberts, J.D. (1970) *J. Am. Chem. Soc.*, **92**, 1080.
25. Fox, T. (1993) PhD thesis, University of Siegen.
26. Heinzer, J., Oth, J.F.M., and Seebach, D. (1985) *Helv. Chim. Acta*, **69**, 1848.

Textbooks

- Sandström, J. (1982) *Dynamic NMR Spectroscopy*, Academic Press, New York.
- Jackman, L.M. and Cotton, F.A. (eds) (1975) *Dynamic Nuclear Magnetic Resonance Spectroscopy*, Academic Press, New York.
- Kaplan, J.I. and Fraenkel, G. (1980) *NMR of Chemically Exchanging Systems*, Academic Press, New York, 165 pp.

Review Articles

- Bain, A.D.. (2008) Chemical exchange. *Ann. Rep. NMR Spectrosc.*, **63**, 23.
- Orrell, K.J.G. (1996) Two-dimensional methods of monitoring chemical exchange, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 8 (eds in chief D.M. Grant and R.K. Harris), John Wiley & Sons, Ltd, Chichester, p. 4850.
- Orrell, K.J.G. (1996) Fluxional motion, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 3 (eds in chief D.M. Grant and R.K. Harris), John Wiley & Sons, Ltd, Chichester, p. 2071.
- Perrin, C.L. and Dwyer, T.J. (1990) Application of two-dimensional NMR to kinetics of chemical exchange. *Chem. Rev.*, **90**, 935.
- Willem, G. (1988) 2D NMR applied to dynamic stereochemical problems. *Prog. Nucl. Magn. Reson. Spectrosc.*, **20**, 1.
- Binsch, G. and Kessler, H. (1980) The kinetic and mechanistic evaluation of NMR spectra. *Angew. Chem.*, **92**, 445; *Angew. Chem., Int. Ed. Engl.*, **19**, 411.
- Johnson, L.S. Jr., and Moreland, C.G. (1973) The calculation of NMR spectra for many-site exchange problems. *J. Chem. Educ.*, **50**, 477.
- Binsch, G. (1968) The study of intramolecular rate processes by dynamic nuclear magnetic resonance, in *Topics in Stereochemistry*, Vol. 3 (eds N.L. Allinger and E.L. Eliel), Interscience Publishers, New York.

14

Nuclear Magnetic Resonance of Partially Oriented Molecules and Solid State NMR

14.1

Nuclear Magnetic Resonance of Partially Oriented Molecules

High-resolution nuclear magnetic resonance of liquids and solutions is generally characterized by small line widths and the spectra are determined by the two parameters *chemical shift* and *scalar spin–spin coupling*. A unique advantage of these NMR spectra and the basis for their immediate and successful acceptance in chemistry is the fact that another NMR parameter, the dipole–dipole coupling between individual nuclear moments – a distance and angle dependent *through-space* interaction – does not lead to additional line splittings because, as was mentioned earlier (Chapter 2, p. 22), it is eliminated by the Brownian motion of the molecules in the liquid phase. It only affects the line width by the mechanism of dipolar relaxation (Chapter 8, p. 239 ff).

The other extreme is found in the NMR of solids – for a long time a domain of physics – where the fixed orientation of the molecules in the magnetic field B_0 gives rise to strong dipole–dipole coupling and very broad NMR signals in the kilohertz range. This will be discussed in more detail in Section 14.2.

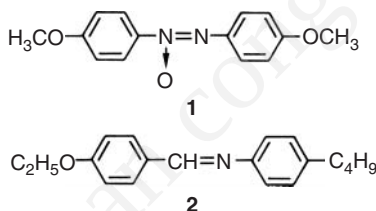
A field intermediate between these two situations is the NMR of partially oriented molecules. Several techniques are available to restrict Brownian motion to the extent that line splittings due to *dipolar* or *direct couplings* – not to be confused with the scalar or indirect coupling constants J that are transmitted through the chemical bonds – become visible. Already a very small degree of orientation in the field B_0 suffices to show this effect. The spectra are then more complicated, but at the same time experimental information about nuclear distances and bond angles in the molecule under study becomes available. Herein lies the interest in this field of NMR.

Several methods have been developed to achieve partial orientation of molecules, ranging from the use of electric fields to the application of biological systems and polymers. Research in this direction was initiated in 1963 when A. Saupe and G. Englert discovered that small molecules like benzene dissolved in a liquid crystal showed unexpected line splittings, an experiment that shall now be described.

14.1.1

Nuclear Magnetic Resonance in Liquid Crystals

Liquid crystals - today essential components of display units (LCDs) - are organic compounds that exhibit, even in the liquid state, in a temperature range of about 20–40 °C above the melting point, an ordered structure resembling in some ways that of a solid. On raising the temperature further, the *clearing point* is reached where the ordered structure is lost and the behavior becomes similar to that of isotropic liquids. The *nematic phases*, a particular group of liquid crystals, show predominantly a parallel arrangement of individual molecules (Figure 14.1) that have a rod-like shape. The anisotropy of their diamagnetic susceptibility leads, in an applied magnetic field (>0.1 T), to a uni-axial orientation. Substances of this class are compounds such as 4,4'-dimethoxyazobenzene (**1**) and *N*-(ethoxybenzylidene)-4-butylaniline (**2**). They are called *thermotropic* and may be used pure or as mixtures.



For NMR it is of significance that a solute molecule dissolved in the nematic phase and submitted to the magnetic field B_0 of the spectrometer will, to a certain degree, assume a preferred orientation within the liquid crystal. Obviously, the position of the solute molecule is not fixed and it can undergo translational and rotational motions. These motions are, however, not completely free as in a normal isotropic liquid, but restricted by the surrounding structure of the liquid crystal. The degree of ordering that results for the solute in the time average is relatively low, typically less than 1%, but it is sufficient to show dipole–dipole coupling

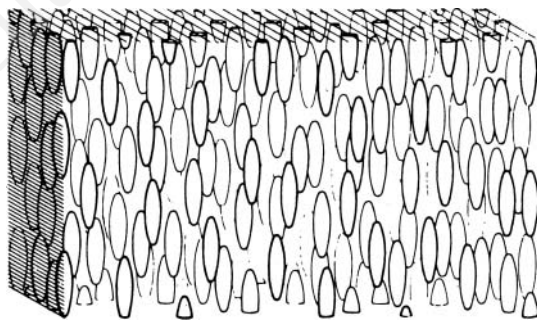


Figure 14.1 Structure of a nematic phase.

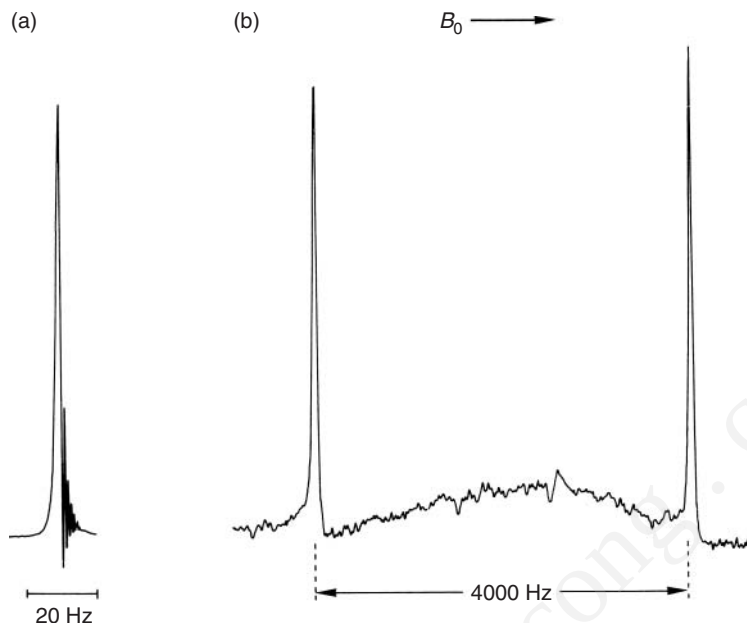


Figure 14.2 ^1H NMR spectrum of methylene chloride in (a) isotropic and (b) anisotropic environments. The nematic phase was provided by compound **2**; the spectrum was measured at 54 °C.

between protons and other magnetic nuclei if the NMR spectrum of a compound is measured in such an anisotropic environment. Because of diffusion of the solute molecules through the solvent these dipolar couplings are strictly *intramolecular* and *intermolecular* interactions are absent. The latter are encountered only in true solids.

The dipolar interaction between the nuclear spins leads then to an additional line splitting in the spectrum. This is shown in Figure 14.2 for a simple case, the A_2 system of the protons of methylene chloride, CH_2Cl_2 . In isotropic liquids we would obtain a singlet, but here, using compound **2** as solvent, a doublet with a splitting of 4000 Hz is observed that contains not only the dipolar coupling D_{ij} but also the much smaller indirect coupling J_{ij} . The line width of the NMR signals is still of the order of 1 Hz because the motion of the solute molecule does not deviate appreciably from that in a normal liquid and the relaxation times of nuclei in partially oriented molecules are similar to those obtained in standard solutions.

To understand this finding, let us recall the energy level diagram for the A_2 case (p. 161). By the application of symmetry functions, we obtained an antisymmetric state and three symmetric eigenvalues linked through the degenerate transitions $E_2 \rightarrow E_1$ and $E_4 \rightarrow E_2$ (Figure 14.3a,b). The interaction between two nuclear dipoles μ_1 and μ_2 separated by a distance r_{12} causes the eigenstates of the spin system to

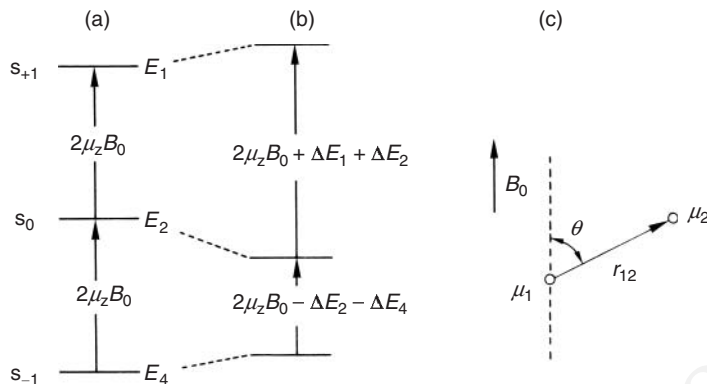


Figure 14.3 (a)–(c) Energy level diagram of an oriented A₂ system.

be either stabilized or destabilized. The energy of the interaction is given by the expression:¹⁾

$$E = \frac{\mu_1 \mu_2}{r_{12}^3} - \frac{3(\mu_1 r_{12})(\mu_2 r_{12})}{r_{12}^5} \quad (14.1)$$

where r_{12} of length r_{12} is the distance vector between the two nuclei as defined in Figure 14.3c. Using the relation [Eq. (2.5)] (page xxx), Eq. (14.1) is transformed into the quantum mechanical Hamiltonian operator [Eq. (14.2)]:

$$H_{12} = \gamma_1 \gamma_2 \hbar^2 \left\{ \frac{\hat{I}_1 \hat{I}_2}{r_{12}^3} - \frac{3(\hat{I}_1 r_{12})(\hat{I}_2 r_{12})}{r_{12}^5} \right\} \quad (14.2)$$

If we apply this operator to the symmetric wave functions $\alpha\alpha$, $(\alpha\beta + \beta\alpha)/\sqrt{2}$, and $\beta\beta$, the detailed calculation, assuming $\mu_1 = \mu_2$ (i.e., for equivalent nuclei), leads to a destabilization of states (1) and (4) by the amount:

$$\Delta E_{1,4} = -\frac{1}{4}\gamma^2 \hbar^2 (3\cos^2\theta - 1)r_{12}^{-3} \quad (14.3)$$

and to a stabilization of state (2) by the amount:

$$\Delta E_2 = \frac{1}{2}\gamma^2 \hbar^2 (3\cos^2\theta - 1)r_{12}^{-3} \quad (14.4)$$

The angle θ , shown in Figure 14.3c, is the angle between the distance vector, r_{12} , and the direction of the external magnetic field, B_0 . Resonance then occurs relative to ν_0 at:

$$\nu = \nu_0 \pm \frac{3}{4}\gamma^2 \frac{\hbar}{4\pi^2} (3\cos^2\theta - 1)r_{12}^{-3} \quad (14.5)$$

or:

$$\nu = \nu_0 \mp \frac{3}{2}D_{12} \quad (14.6)$$

1) For brevity, the factor $\mu_0/4\pi$ is omitted from the present discussion.

if one introduces the general expression:

$$D_{ij} = \frac{-h\gamma^2}{4\pi^2} \frac{1}{2} \left\langle \frac{(3\cos^2\theta - 1)}{r_{ij}^3} \right\rangle \quad (14.7)$$

for the dipolar coupling, D_{ij} , between two protons. The geometrical factor in brackets is taken over intra- and intermolecular motions. If one further defines the degree of orientation of the internuclear distance by the relation:

$$S_{ij} = \frac{1}{2} \langle 3\cos^2\theta - 1 \rangle \quad (14.8)$$

where S_{ij} is the *order parameter*, then:

$$D_{ij} = -\frac{h\gamma^2}{4\pi^2} S_{ij} r_{ij}^{-3} \quad (14.9)$$

The same result is applicable for an *isolated* A_2 system in a solid single crystal where it is not necessary to average over molecular motions. In a solid powder, on the other hand, the fixed orientation of the distance vectors $\mathbf{r}_{ij}$ relative to the magnetic field $\mathbf{B}_0$ is randomly distributed and not time-averaged. The dipolar coupling for each A_2 system then differs because of the different angles θ . Broad lines in the kilohertz range result and D_{ij} is much larger than D_{ij} for an only partially oriented molecule.

As Eq. (14.9) shows, the line splitting depends on the distance, r_{12} , between the two nuclei. If there were a reliable independent method for calculating S_{ij} , one could obtain the internuclear distance from the experimentally determined dipolar couplings. This, however, is not the case, since in A_2 systems only *one* observable relates the *two* unknowns, S_{12} and r_{12} . This results from the fact that the dipolar coupling D_{ij} , in contrast to the scalar coupling J_{ij} , is not a molecular constant and the value of 4000 Hz measured above for the line splitting in methylene chloride depends through the degree of orientation upon temperature, concentration, and the nematic phase used. Therefore, it varies in practice with each new experiment.

NMR spectra of rigid molecules ²⁾ partially oriented in a nematic phase like **1** or **2** are distinguished from spectra measured in isotropic media by their larger spectral width. Since dipolar couplings exceed scalar couplings by a factor of $10-10^3$, these spectra often extend over several kilohertz. In addition, because the orientation parameters are strongly temperature and concentration dependent, the spectral appearance is also very sensitive to these factors and for reliable results strict temperature control is necessary.

Furthermore, a unique feature of the NMR spectra of partially oriented molecules is the fact, already derived above, that spin-spin coupling between magnetically equivalent nuclei becomes measurable. A particularly impressive example of this is seen in the spectrum of partially oriented benzene, which shows more than 50 lines for an A_6 spin system (Figure 14.4)! The high symmetry of the molecule here significantly facilitates spectral analysis that is based on the Hamiltonian operator

2) "Rigid" means that *large amplitude* internal motions are absent; vibrational motions are always present.

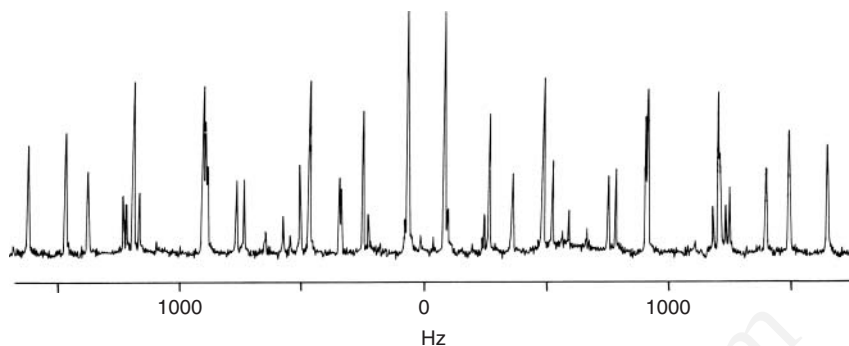


Figure 14.4 ^1H NMR spectrum of partially oriented benzene [1].

introduced in Chapter 6. It contains, in addition to the scalar spin–spin interactions J_{ij} also the dipolar couplings D_{ij} :

$$\begin{aligned} \mathcal{H} = & \sum_i \nu_i \hat{I}_z(i) + \sum_{i < j} \sum (J_{ij} + 2D_{ij}) \hat{I}_z(i) \hat{I}_z(j) \\ & + \sum_{i < j} \sum (J_{ij} - D_{ij}) \hat{I}_x(i) \hat{I}_x(j) + \hat{I}_y(i) \hat{I}_y(j) \end{aligned} \quad (14.10)$$

The resonance frequencies ν_i are different from those in the isotropic phase by an anisotropy contribution to the shielding constant. In the same way, the scalar or indirect coupling constants J_{ij} contain a small anisotropy contribution that is for a pair of protons, however, negligible. In the Hamiltonian matrix J_{ij} is replaced by $J_{ij} + 2D_{ij}$ in the diagonal elements and by $J_{ij} - D_{ij}$ in the off-diagonal elements. In principle, the scalar interactions can also be determined by an analysis based on Eq. (14.10). However, one can simplify the problem if one obtains them from an analysis of the spectrum measured in an isotropic phase. Significantly, by means of the NMR spectra of partially oriented molecules it is possible to determine the absolute signs of the scalar coupling constants if one can predict a preferential orientation of the molecule on the basis of its structure. Finally, it must be emphasized again that the relatively simple form of the Hamiltonian operator arises only because *intermolecular* dipolar interactions can be disregarded as a result of rapid diffusion processes in the liquid crystal. This is not the case in solids.

As mentioned above, the molecules of the nematic phase are also oriented in the magnetic field. They align with their long molecular axis parallel to the direction of $\mathbf{B}_0$. It is of advantage that, because of the relatively high degree of order and the large number of protons, the spectra of the liquid crystals are strongly broadened and practically disappear in the noise. The spectra of the partially oriented guest molecules are thus unperturbed by the liquid crystal solvent. Alternatively, to avoid spectral overlap, deuterium labeling of the nematic phase can be used.

As a consequence of the alignment of the liquid crystal with respect to the external field it was previously not possible to rotate the NMR sample tube during the experiment in conventional iron magnets because rotation around the y -axis

would destroy the orientation of the phase. In superconducting magnets used today, however, the z -axis is parallel to the rotational axis of the NMR tube and sample spinning does not affect the ordering of the crystalline liquid and leads to much narrower NMR signals.

We now ask how the spectra of partially oriented molecules can be used for structure determinations; in other words: How can we obtain the distances r_{ij} and the angles θ_{ij} of the solute? The first task is analysis of the spectrum to obtain the dipolar couplings. Then the knowledge of the order parameters S_{ij} for each distance vector $\mathbf{r}_{ij}$ is necessary in order to calculate the angles θ_{ij} and the distances r_{ij} with the help of Eqs. (14.8) and (14.9). To achieve this, following Saupe, a Cartesian coordinate system (axes ξ , η , and ζ) fixed within the molecule is selected and related to the z -direction of the magnetic field $\mathbf{B}_0$ by the angles α_ξ , α_η , and α_ζ . The average orientation of the molecule can then be described by an *order matrix* or *order tensor*, a symmetrical and traceless 3×3 matrix $\mathbf{S}$ with five independent elements, the so-called *Saupe matrix*. The matrix elements S_{pq} are given by Eq. (14.11):

$$S_{pq} = \frac{1}{2} \left\langle 3 \cos \alpha_p \cos \alpha_q - \delta_{pq} \right\rangle \quad (14.11)$$

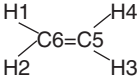
with $p, q = \xi, \eta, \zeta$ and $\delta_{pq} = 1$ for $p = q$ and 0 for $p \neq q$. These matrix elements are in turn related to any axis, which means any distance vector $\mathbf{r}_{ij}$, in the molecular coordinate system. For $\mathbf{r}_{ij}$ forming the angles β_ξ , β_η , and β_ζ with the fixed coordinate system of the molecule we have Eq. (14.12):

$$S_{ij}(r_{ij}) = \sum_{p,q} \cos \beta_p \cos \beta_q \times S_{pq} \quad (14.12)$$

In the next step, order parameters S_{ij}^0 can be calculated on the basis of Eq. (14.9) from – in the general case – at least five measured D_{ij} values for an assumed structure $\mathbf{M}^0$ of the molecule studied. These S_{ij}^0 values are then used to calculate the order matrix $\mathbf{S}^0$ that now allows us to also calculate the remaining dipolar couplings. The difference $D_{ij}^{\text{calc}} - D_{ij}^{\text{exp}}$ is then minimized by an iterative least-squares procedure that yields the final S_{ij} values for the calculation of θ_{ij} and r_{ij} .

On the basis of molecular symmetry, a suitable choice of the fixed coordinate system allows us to reduce the number of independent S -values. With a larger number of dipolar coupling constants one usually has enough information at hand to determine distance *and* orientation for a particular pair of nuclei from the NMR spectrum. Importantly, as Eq. (14.9) shows, only the ratios S_{ij}/r_{ij} are obtained that yield in turn distance ratios r_{ij}/r_{ik} but not absolute atomic distances. These can be derived if one of the r_{ij} values is known through independent information. Considering various sources of experimental errors, a realistic estimated value for the accuracy of the distance determinations is 1 pm. Since bond angles can also be determined, the NMR spectroscopy of partially oriented molecules has developed into an important method of structure determination. Later, it was found that, because NMR parameters are average values over vibrational

Table 14.1 Comparison of structural data for selected molecules determined by liquid crystal NMR and other methods^a.

Compound		Structural data	
		NMR	Electron diffraction
Cyclopropane ^b [2]	$r(\text{CC})$	1.5104	1.5104(15)
	$r(\text{CH})$	1.0807	1.079(30)
	$r(\text{HH})$	1.8245	—
	$\angle\text{HCH}$	115.15°	$115.8 \pm 1.0^\circ$
Cyclobutane ^b [3]	$r(\text{CC})$	(1.548)	1.548(3)
	$r(\text{CH})$	1.171(20)	1.092(10)
	$\angle\text{HCH}$	$108.5 \pm 2^\circ$	110°
	Dihedral angle	28°	35°
Infrared spectroscopy			
Ethylene [4]	r_{14}/r_{12}	1.3232(17)	1.3290(42)
	r_{16}/r_{12}	0.5845(14)	0.5853(08)
	r_{56}/r_{12}	0.7210(17)	0.7206(17)
	$\angle\text{HCH}$	$121^\circ 10.5' \pm 6.6'$	$121^\circ \pm 7.5'$

^aBond length in Å; error of last digit in parentheses.^bIncluding ¹³C satellites.

effects,³⁾ correct structural data are only obtained if this factor is included in the analysis of the NMR results. In addition, molecules may be slightly deformed in the liquid crystal matrix. The latter aspect explains, for example, the observation that even tetrahedral molecules like methane or tetramethylsilane that have a ball-shaped structure, and, therefore, should not show any orientational effect, yield dipolar couplings when dissolved in a liquid crystal.

NMR spectroscopy of molecules dissolved in liquid crystals thus supplements the well-known techniques of microwave spectroscopy as well as electron and X-ray diffraction, especially if line splittings due to the presence of ¹³C nuclei can be included in the analysis, which is most easily done in the case of ¹³C labeled molecules but is also possible through the observation of ¹³C satellites. These data also yield information on the carbon geometry, which is obviously of greater interest than the proton geometry alone. Table 14.1 compares NMR results with those of two other techniques of structural analysis for a few selected molecules. The most important aspect of the NMR method probably is that structural information can be obtained in the liquid state and software for the various steps of a structure investigation – spectral analysis, structure determination, and vibrational corrections – has been developed (see the literature cited at the end of this chapter).

For molecules with internal dynamics, like conformational changes, interpretation of the experimental results is more complicated than described above. Two

- 3) The time scale for vibrational motions is 10^{-12} to 10^{-14} s, for D_{ij}^{-1} it is in the order of 10^{-3} s.

extreme situations can be imagined: If the rate for the dynamic process is fast compared to the rate of reorientation, the solute can be described by an average structure. If, on the other hand, the two rates are similar or the dynamic rate is much slower than the reorientation rate, each structural isomer has to be treated individually.

Finally, we mention that quadrupolar nuclei in partially oriented molecules show, like in the solid (Section 14.2), line splittings due to quadrupolar coupling. We shall come back to this point in the following section.

14.1.2

Other Alignment Methods – Residual Dipolar Couplings

Because dipolar coupling constants are directly related to nuclear distances, their determination was always of great interest for structural studies. Solid state spectra are, however, too complicated to allow a quick and accurate measurement of these parameters. The finding that dipolar couplings can be observed in the spectra of partially oriented molecules in liquid crystal matrices and determined with high precision by spectral analysis was thus an important step forward. However, while the method was successful for rigid molecules of low molecular weight, it fails for larger systems because of the increasing number of protons present and the relatively high degree of orientation that leads to dipolar splittings in the kilohertz range and to unresolved spectra. We have already mentioned that the spectrum of the nematic phase itself disappears in the noise. Furthermore, to study biomolecules like peptides and nucleic acids, measurements in aqueous medium are necessary.

Alternative alignment techniques are, therefore, of general interest. In fact, attempts to achieve alignment of molecules date back several decades, when electric fields were first used to orient molecules that possess large electric dipole moments, such as, for example, *p*-nitroaniline. Later, the increase in the B_0 field strength stimulated studies of the alignment of molecules with an anisotropic diamagnetic susceptibility, $\Delta\chi$. If the degree of alignment is again given by Eq. (14.8), S_{ij} may be evaluated on the basis of the Boltzmann law for the distribution of energies as:

$$S_{ij} = \Delta\chi B_0^2 / 15k_B T \mu_0 \quad (14.13)$$

where k_B is the Boltzmann constant, T the absolute temperature, and μ_0 the permeability of free space. The alignment is thus proportional to the square of the magnetic field and inversely proportional to the temperature. A calculation for benzene ($\Delta\chi = -630 \times 10^{-36} \text{ m}^3$ [SI-system]) yields, for a 600 MHz magnet at 300 K, -1.6×10^{-6} . Relatively large $\Delta\chi$ values and high magnetic fields are thus necessary to observe dipolar splittings.

An interesting development started with the observation that a low degree of orientation can be achieved for biomolecules in aqueous solution that contain discotic phospholipid micelles that just above room temperature change their structure from a gel to a liquid crystal phase. They then form disc-shaped particles,

known as *bicelles* that have diameters of ~ 50 nm and a thickness of about 5 nm. Because the lipids have a diamagnetic anisotropy, they orient in the magnetic field and induce a certain partial alignment also on the solute, for example, a peptide. Consequently, dipolar couplings can be observed in the NMR spectrum of the solute. The important point is that these splittings – today called *residual dipolar couplings* (RDCs) – are small, a few hertz or less, because the degree of alignment is low, of the order of $\sim 10^{-3}$. This yields spectra that are easy to analyze. On the other hand, the alignment of the solute in the aqueous medium is adjustable through changes in the concentration of the liquid crystal phase. Thus, the measurement of proton–proton distances in biopolymers that relied before exclusively on the nuclear Overhauser effect with its r^{-6} dependence are now also possible with the r^{-3} dependence of dipolar couplings and the limit of distance measurements extends from about 5–6 Å (0.5–0.6 nm) to about 10 Å (1 nm). Aside from H–H distances, C–H and N–H distances can be measured, the latter in fully ^{15}N labeled compounds. For sufficiently small alignments, dipolar splittings are restricted to directly connected spins and the RDCs are smaller than the scalar couplings. For a $^{13}\text{C}, ^1\text{H}$ spin pair, for example, which is a first-order AX system, the experimental splitting J_{exp} is given by:

$$J_{\text{exp}} = J_{\text{CH}} + 2D_{\text{CH}} \quad (14.14)$$

[see also Eq. (14.10); only the first coupling term applies]; $J_{\text{exp}}(^{13}\text{C}, ^1\text{H})$ can be measured by HMQC or HSQC experiments (see Chapter 11) with ^{13}C in natural abundance. In the first-order case the splitting increases by alignment if the dipolar coupling D is positive and decreases for negative D values. The J_{CH} data are taken from measurements in the isotropic phase. For ^1H investigations the sign of the dipolar couplings are available for coupled protons, but for non-coupled only the magnitude of D_{ij} is obtained. To obtain nuclear distances r_{ij} and structural angles θ_{ij} the orientation or alignment parameters S_{ij} have to be determined in the same way as outlined above for the structure determination in nematic phases. However, especially for partially oriented small molecules (see below) a slightly different mathematical approach is used with the concept of an alignment tensor $\mathbf{A}$ that is related to the Saupe matrix $\mathbf{S}$ by:

$$\mathbf{S} = \frac{3}{2}\mathbf{A} \quad (14.15)$$

$\mathbf{A}$ is derived as described above for $\mathbf{S}$ from the measured dipolar couplings in an iterative procedure that is based on an assumed structure obtained from X-ray results or by theoretical calculations.

While at the beginning the RCD method was exclusively used for studies of biomolecules, it has later been extended to investigations of organic molecules. Here, problems of assignment, especially those related to stereochemistry, can be solved via dipolar couplings. Investigations of rigid molecules prevail, because, as expected, flexible molecules are difficult to handle due to averaging of NMR parameters as a consequence of dynamic processes. Numerous systems with ability to induce alignments have been tested: polypeptides, cholesteryl derivatives, and even polymer films and special alignment media are available for different

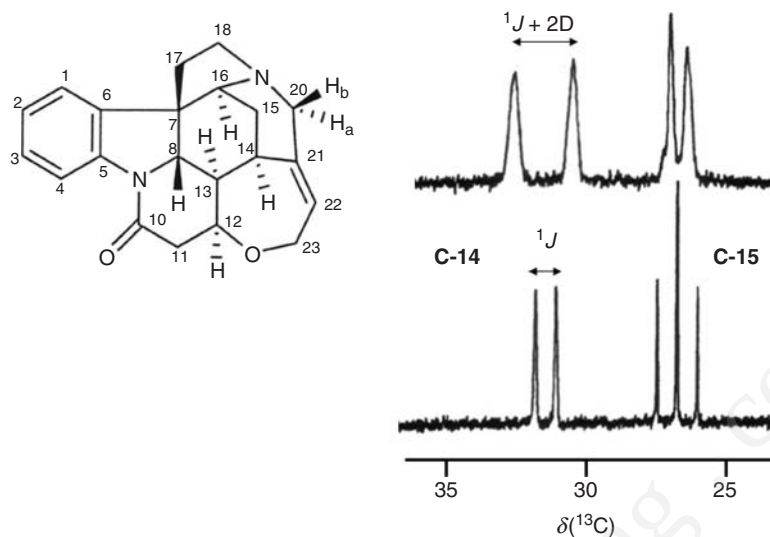


Figure 14.5 Two signals of aliphatic carbons from the ^1H -coupled 176.1 MHz ^{13}C NMR spectrum of strychnine partially aligned in poly- γ -benzyl L-glutamate (PBLG) (top); the signals from the conventional ^{13}C NMR spectrum are shown below. The dipolar coupling $D(^{13}\text{C}, ^1\text{H})$

of 123.8 Hz for C14 can be obtained directly from the line splitting if the scalar coupling is known (Adapted with permission from Reference [5]. Copyright 2003 American Chemical Society).

classes of compounds. For medium-sized molecules like the alkaloid strychnine the polypeptic liquid crystal poly- γ -benzyl L-glutamate (PBLG) was successfully used; Figure 14.5 shows an example with two ^{13}C signals from aliphatic carbons of strychnine. The resonance of C14 shows an enlarged splitting by $2D(^{13}\text{C}, ^1\text{H})$ that can be, according to Eq. (14.14), directly measured. In contrast, the coupling for C15 is not readily available because this resonance is part of a higher order spectrum. By analyzing the complete spectrum the assignment of the diastereotopic protons H_a and H_b at C20 was achieved.

To control results obtained for a certain sample and to obtain assignments unambiguously, measurements at various degrees of alignment are helpful. For changing the alignment, different alignment media or solvents can be used. In addition, temperature changes might be successful. An elegant method is provided by spinning the sample at different angles θ_r relative to the field B_0 (variable angle sample spinning, VASS), a technique related to magic-angle spinning (MAS) that is described below. It was found that at a critical spinning speed – depending on the molecular properties of the liquid crystal, like the diamagnetic susceptibility, χ_M , or the viscosity – the director of the liquid crystal starts to orient parallel to the axis of spinning. All anisotropic NMR parameters are then scaled according to Eq. (14.16) for the measured line splitting J_{eff} where the small anisotropic part of the scalar coupling is neglected:

$$J_{\text{eff}} = J + (3\cos^2\theta_r - 1)2D \quad (14.16)$$

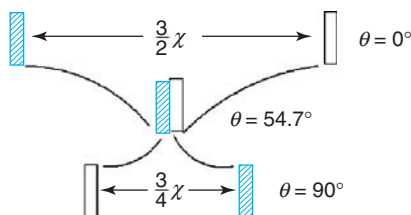


Figure 14.6 Angular dependence of the quadrupole splitting for nuclei with $I = 1$ according to Eq. (14.16); θ is the angle between the direction of the external magnetic field $\mathbf{B}_0$ and the main direction of the electric field gradient [6].

If a molecule contains a *quadrupolar nucleus*, partial orientation leads to a line splitting of its resonance signal if the quadrupolar relaxation is not too fast (*quadrupole splitting*). This is a result of *quadrupole coupling*, an interaction of the nuclear quadrupole moment with the electric field gradient at the nucleus that in turn is determined by the bonding situation of the particular atom (Chapter 12, p. 433). Deuterium with its relatively small quadrupolar moment (Table 2.1, p. 26) and spin $I = 1$ shows this effect quite clearly. Here one usually can assume axial symmetry of the electric field gradient since deuterium appears nearly exclusively in CD bonds. The ^2H NMR signal then splits according to:

$$\Delta\nu_Q = \frac{3e^2qQ}{2h} \frac{1}{2} (3\cos^2\theta - 1) = \frac{3e^2qQ}{2h} S_{ij} \quad (14.17)$$

into a doublet. The tensor e^2qQ/h is the nuclear quadrupolar coupling constant – often also characterized by the Greek letter χ (p. 433) – the product between the electric quadrupole moment, eQ , and the field gradient, eq , at the nucleus (h = Planck's constant). The variation of the doublet splitting with the angle θ between the direction of the external magnetic field $\mathbf{B}_0$ and the main direction of the electric field gradient is shown in Figure 14.6. S_{ij} is the order parameter of Eq. (14.8) above, now for a C–D bond. Equation (14.17) also applies to the solid state (see below).

Use was made of these relations in testing whether enantiomeric molecules can be distinguished after partial orientation in a chiral liquid crystal phase. This was indeed the case when a mixture of enantiomers was dissolved in a cholesteric liquid crystal. The sample was investigated by proton-decoupled ^2H NMR, which has the big advantage that the spectra can be interpreted by inspection and the complex spectra that result from dipolar couplings in ^1H spectra can be avoided. An example with a typical result in a different medium is shown in Figure 14.7, where enantiomeric excess can be measured by integration.

14.2

High-Resolution Solid State Nuclear Magnetic Resonance Spectroscopy

The last section has shown already that *intramolecular* dipolar couplings can complicate the NMR spectra of small molecules. This effect is considerably more

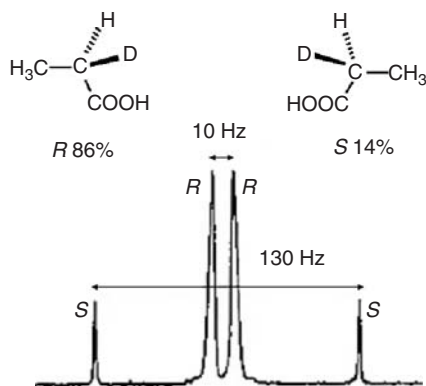


Figure 14.7 38.4 MHz ^1H decoupled ^2H NMR spectrum of a mixture of a (*R*)-enriched mixture (72% ee) of $[\text{D}_1]$ propionic acid dissolved in poly- γ -benzyl L-glutamate (PBLG)/ CH_2Cl_2 [7].

pronounced in solids, where in addition *intermolecular* dipolar couplings are important. Furthermore, transverse relaxation times T_2 are very short in solids and only structureless broad-line spectra with half-widths of several kilohertz are then observed. Direct information about the local environment of the individual nuclei that comes from chemical shifts and scalar and dipolar spin–spin couplings is completely lost (Figure 14.8). In recent years, however, active research and the use of pulse and multidimensional NMR has produced a large number of new experiments for solids that provide new solutions for various applications that were difficult or even impossible before.

One of the most spectacular developments was the progress made in line narrowing by controlling the mechanisms that lead to the enormous line broadening mentioned above. As a result of these efforts a new field of NMR evolved, namely, high-resolution solid state NMR, based on high-power proton decoupling and *magic angle spinning* (MAS).

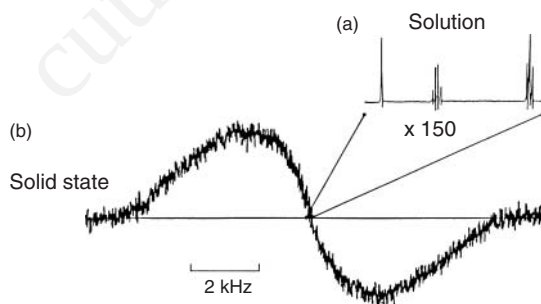


Figure 14.8 ^1H NMR spectrum of ethanol: (a) spectrum of the liquid; (b) spectrum of a solid sample [6].

Thus, solid state NMR spectra with relatively narrow lines (10–50 Hz line width) that again yield chemical shift information can be observed today. Aside from solid state NMR spectroscopy of single crystals, which forms a special area of solid state physics not discussed here, high-resolution NMR of powdered solids has developed in recent years into a powerful tool for structural elucidations in inorganic, organic, and organometallic chemistry. Through chemical shifts and scalar spin–spin couplings that can now also be measured for solids it provides us with information about the bonding situation, symmetry properties, and dynamic behavior of solid state structures. In comparison to structural analysis on the basis of X-rays that requires relatively large single crystals, it is important that NMR spectroscopy can be applied to microcrystalline samples, crystal powders, and even to amorphous materials.

14.2.1

Experimental Techniques of High-Resolution Solid State NMR Spectroscopy

14.2.1.1 Line Narrowing

While in isotropic liquids the NMR spectra are dominated by the Zeeman interaction with the external field B_0 ($\hat{H}_z$), the shielding constant σ ($\hat{H}_{CS}$), and by scalar spin–spin interaction J ($\hat{H}_S$), in solids additional mechanisms operate. Dipole–dipole interactions ($\hat{H}_{DD}$), quadrupolar interactions ($\hat{H}_Q$) as well as the anisotropy of nuclear shielding and scalar coupling are complicating factors that lead to severe line broadening. The Hamilton operator for both domains, the liquid and the solid, is thus defined by the following expressions:

$$\begin{aligned} \text{Solution : } \hat{H} &= \hat{H}_z + \hat{H}_{CS}^{\text{iso}} + \hat{H}_S^{\text{iso}} \\ \text{Solids : } \hat{H} &= \hat{H}_z + \hat{H}_{CS} + \hat{H}_S + \hat{H}_{DD} + \hat{H}_Q \end{aligned} \quad (14.18)$$

The individual terms of these equations are of different importance and the experimental concepts for the observation of highly resolved solid state NMR spectra vary. In this respect the NMR active nuclei behave differently and can be divided into four groups according to the following scheme:

$$\begin{aligned} \text{Nuclei with } I = \frac{1}{2} : & \begin{cases} \text{high natural abundance (e.g., } ^1\text{H, } ^{19}\text{F}); \text{ –Group 1} \\ \text{low natural abundance (e.g., } ^{13}\text{C, } ^{15}\text{N, } ^{29}\text{Si, } ^{31}\text{P}); \text{ –Group 2} \end{cases} \\ \text{Nuclei with } I > \frac{1}{2} : & \begin{cases} \text{integer spin (e.g., } ^2\text{H, } ^6\text{Li}); \text{ –Group 3} \\ \text{half integer spin (e.g., } ^{11}\text{B, } ^{17}\text{O, } ^{27}\text{Al}); \text{ –Group 4} \end{cases} \end{aligned}$$

Most difficult are measurements for nuclei belonging to Group 1 because their high natural abundance leads to strong homonuclear dipolar interactions and homonuclear decoupling is obviously impossible. The nuclei belonging to Groups 3 and 4 are also not without problems due to the presence of quadrupolar interactions. Therefore, mainly experiments with nuclei of Group 2 have been used in pioneering the development of high-resolution solid state NMR spectroscopy with applications in chemistry. The advantage lies in the fact that these nuclei are diluted, either as a result of their low natural abundance (^{13}C , ^{15}N , ^{29}Si) or,

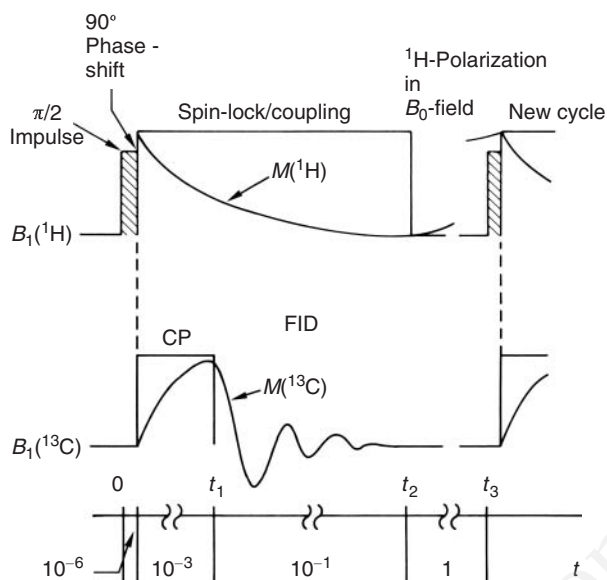


Figure 14.9 Time scale of a $^1\text{H} \rightarrow ^{13}\text{C}$ cross polarization (CP) experiment for solid state NMR spectroscopy [8].

as in the case of ^{31}P , because the chemical structures of interest often contain only one atom of this kind. In the molecular crystals of organic and inorganic compounds these nuclei are then effectively isolated. Homonuclear coupling is absent and heteronuclear interactions can be removed through spin decoupling. For insensitive nuclei there is the additional option of magnetization transfer from abundant protons by cross polarization (CP) in a Hartmann–Hahn experiment (cf. p. 364 ff.). This technique paved the way for high-resolution ^{13}C NMR spectroscopy in solids, which played a leading role in the development of this branch of NMR spectroscopy.

In the standard experiment for recording high-resolution solid state ^{13}C NMR spectra (Figure 14.9), the ^{13}C nuclei are excited by $^1\text{H} \rightarrow ^{13}\text{C}$ CP. During signal detection high power ^1H -decoupling is used. In this way dipolar and scalar heteronuclear spin–spin interactions are eliminated and the signals are broadened solely by the anisotropy of the chemical shift that results from the directional dependence of the shielding constant σ in the $\mathbf{B}_0$ -field; σ is a tensor that can be brought into diagonal form through a suitable coordinate transformation:

$$\sigma = \begin{vmatrix} \sigma_{11} & 0 & 0 \\ 0 & \sigma_{22} & 0 \\ 0 & 0 & \sigma_{33} \end{vmatrix} \quad (14.19)$$

In solids, $\sigma_{11} \neq \sigma_{22} \neq \sigma_{33}$, or for axially symmetric molecules $\sigma_{11} = \sigma_{22} \neq \sigma_{33}$. In liquids the chemical shift is measured as the trace of the symmetric matrix

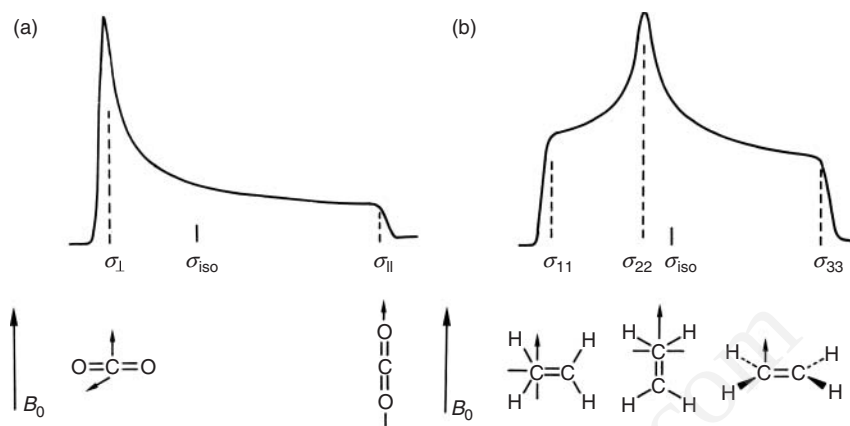


Figure 14.10 ^{13}C resonances for powder spectra of molecules with axial symmetry (a) and without axial symmetry (b); depending on the relative size of the shielding constants, mirror images of the signal shapes shown can also be observed.

shown in Eq. (14.19):

$$\text{tr}\sigma = \frac{1}{3}(\sigma_{11} + \sigma_{22} + \sigma_{33}) \quad (14.20)$$

For powder spectra different σ -values are observed depending on the orientation of the individual microcrystals relative to the field direction. The experimental spectra reflect this distribution by the line shapes shown in Figure 14.10. From these spectra, the anisotropy of the chemical shift can be determined. It gives us information about the electron distribution around the nucleus that is directly related to chemical bonding.

Even if the contributions of dipolar ^1H , ^{13}C coupling to the observed spectrum can be practically eliminated by high-power ^1H decoupling, line widths of several kilohertz are still the rule and, especially, spectra of compounds with several non-equivalent nuclei are difficult to analyze because of strong line overlap. It is only by the application of a further technique that line narrowing is sufficient to observe true *high resolution spectra*: rotation of the sample cell around the magic angle (MAS). In this experiment, the so-called *rotor* – a small capsule about 10 mm long and 4 or 7 mm in diameter made from zirconium oxide or boronitride and filled with the powdered solid – is rotated with a high spinning rate (up to 10 kHz) around an axis that makes the *magic angle* $\theta = 54.7^\circ$ (cf. p. 23) with the axis of the external field B_0 . For axial symmetric groups the time average of the chemical shift anisotropy then vanishes because of the angular term:

$$\langle \sigma_A(t) \rangle \sim \frac{1}{3} (\sigma_{\parallel} - \sigma_{\perp}) (3\cos^2\theta - 1) \quad (14.21)$$

At rotational frequencies of 2–9 kHz it is possible to narrow the resonance lines to such an extent that it is indeed correct to speak of high resolution NMR. Combined with CP we obtain CP/MAS solid state spectra (Figure 14.11).

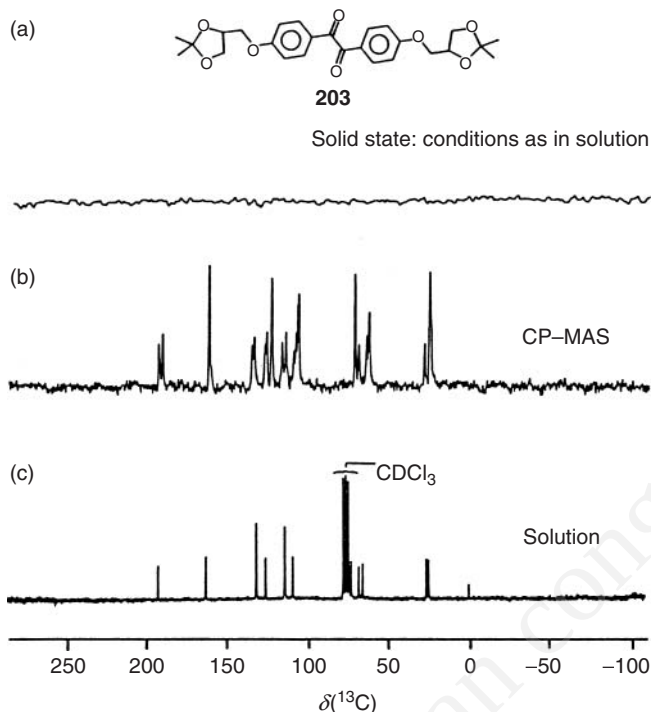


Figure 14.11 ^{13}C NMR spectrum of solid 4,4'-bis[2,3-(dihydroxypropyl)oxy]benzoyl diacetoneide: (a) conditions as in solution; (b) high-resolution CP/MAS solid state spectrum; (c) spectrum of a sample in solution [8].

The effect of sample rotation is shown in Figure 14.12 for the case of a ^{31}P resonance. In practice the rotational frequency accessible is not always sufficient to remove the anisotropy effect completely. Sample rotation then leads to the formation of rotational side bands that vanish only at very high spinning speeds (Figure 14.12a–e). While this effect may complicate the spectra and the line assignment, it also has a positive aspect: one can calculate the anisotropy of the shielding tensor from the position and the intensity distribution of the side bands (Herzfeld–Berger method). Normally, these parameters, which are of interest with respect to the bonding situation of the particular atom, are obtained from single crystal studies, where the sample is measured in various orientations with respect to the B_0 field axis.

Alternatively, rotational sidebands can be suppressed by the pulse sequences TOSS (total suppression of sidebands) or SELTICS (sideband elimination by temporary interruption of the chemical shift). With TOSS, after the 90° pulse or a Hartmann–Hahn contact and prior to the free induction decay (FID), a number of π -pulses with fixed delays adjusted to the rotor period lead to destructive interferences of the sideband magnetization. A drawback is that the relatively long time between excitation and signal detection may lead to relaxation losses. The

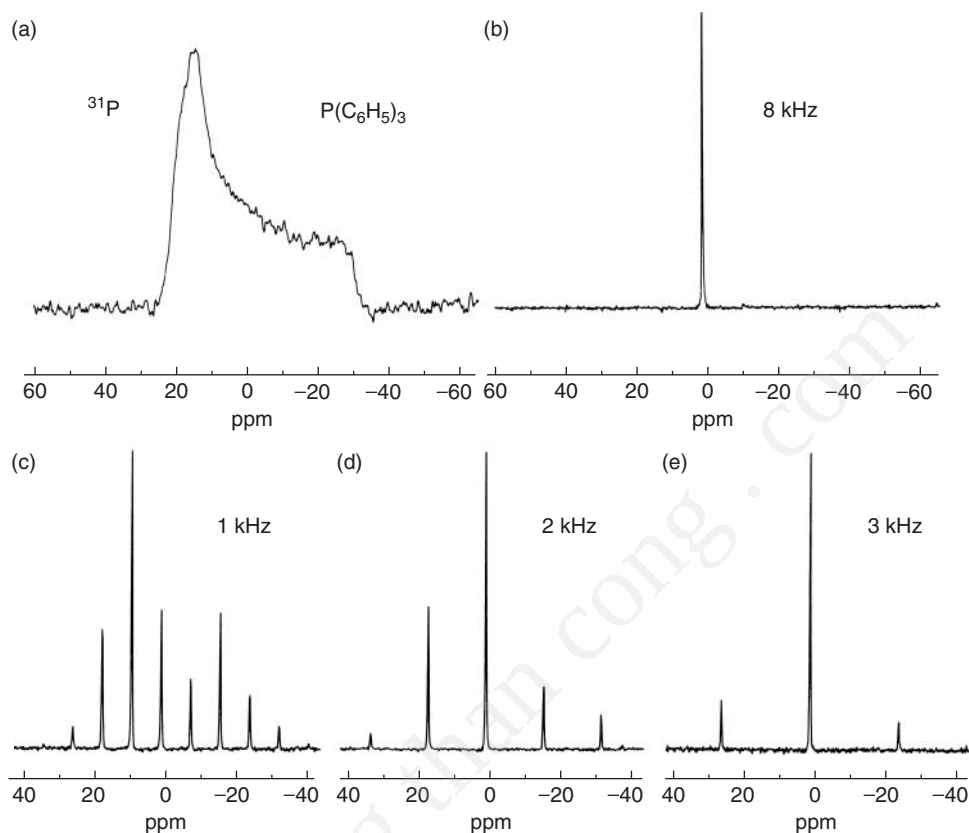


Figure 14.12 ^{31}P resonance of triphenylphosphine in the solid without (a) and with (b) MAS effect; measuring frequency 121.5 MHz; (c)–(e) rotational side bands at different rotational frequencies.

SELTICS sequence also works with four pulses between spin-lock and acquisition to eliminate sideband magnetization, but the excitation/acquisition interval is significantly shorter. Again, the pulse lengths are adapted to the rotor period τ_R (Figure 14.13). An example of the results that can be obtained is shown in Figure 14.14 with the spectra of the amino acid tyrosine hydrochloride. All nine carbon resonances are nicely resolved by the SELTICS experiment.

The CP/MAS technique has been used successfully for the detection of a large number of spin $\frac{1}{2}$ nuclei, for example, ^{29}Si , ^{33}S , ^{77}Se , ^{89}Y , ^{119}Sn , ^{195}Pt , ^{199}Hg , ^{205}Tl , and ^{207}Pb . One can dispose of CP and record only MAS spectra if the sample contains no protons. This applies to ^{29}Si spectra of silicates.

A completely different approach that yields high-resolution solid state spectra was used independently and relatively early on the basis of multipulse sequences. Here the time averaging of dipolar couplings is achieved through a series of RF pulses that is constructed in such a way that the nuclear spins practically rotate around the magic angle (spin-flip narrowing). A typical four-pulse sequence of 90°

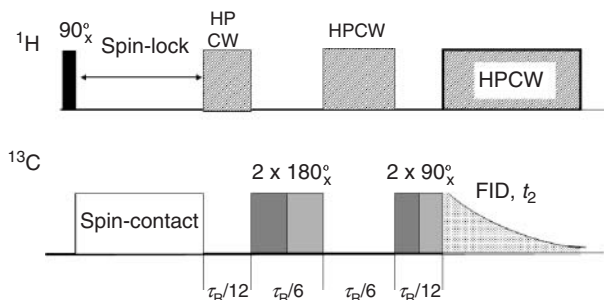


Figure 14.13 SELTICS pulse sequence for sideband suppression in ^{13}C solid state MAS spectra.

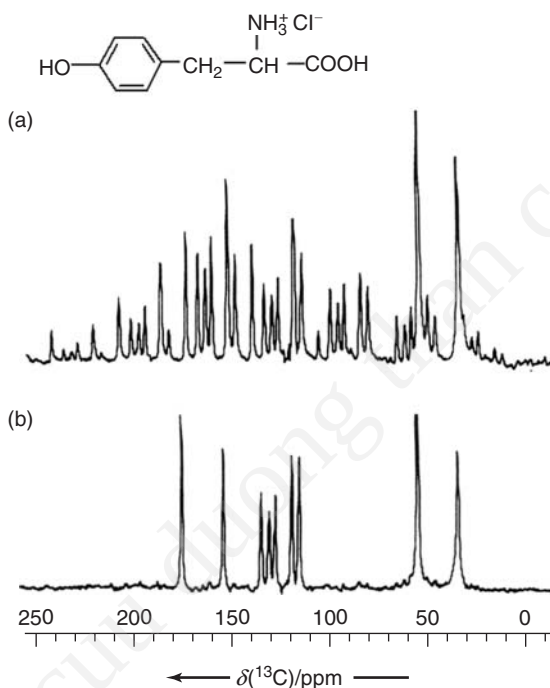


Figure 14.14 ^{13}C MAS spectra of tyrosine hydrochloride; (a) CP-MAS spectrum and (b) the same with the application of the SELTICS sequence (Reprinted from Reference [9], Copyright 1993, with permission from Elsevier).

pulses, known as a WAHUA sequence (after its inventors *Waugh*, *Huber*, and *Haeberlen*, Figure 14.15), has, in the rotating frame, the following form:

$$P1_x - 2\tau - P2_{-x} - \tau - P3_y - 2\tau - P4_{-y} - \tau - \quad (14.22)$$

Since homonuclear dipolar couplings can also be eliminated, the spin-flip method found later interesting applications in connection with the MAS technique for

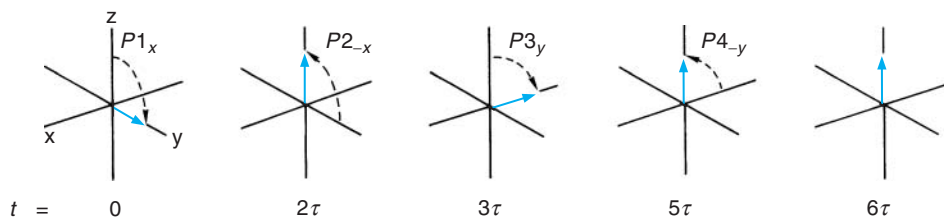


Figure 14.15 WAHUHA pulse sequence for high-resolution solid state NMR spectroscopy.

the measurement of high-resolution ^1H solid state spectra (CRAMPS, combined rotation and multi-pulse NMR spectroscopy) of solids.

14.2.1.2 Assignment Methods

For multiline spectra, as those observed for ^{13}C NMR of organic solids, the problem of assignment exists. Several one- and two-dimensional experiments are available for this purpose and two of them are now discussed. One is used to distinguish the resonances of quaternary carbons and CH_3 groups on the one hand from those of CH and CH_2 groups on the other. The second sequence allows the determination of signal multiplicity and thereby the number of protons bound to the carbon of interest.

As shown in Figure 14.16a, in the first sequence one uses delayed signal detection. During the delay Δ that amounts to 30–100 μs , proton coupling is allowed. Dipolar interactions between neighboring ^1H , ^{13}C spin pairs can then lead to a decay of transverse ^{13}C magnetization and these signals are lost. Quaternary carbons are less affected since the dipolar interactions are strongly reduced with increasing distance between the nuclei (factor r^{-3}). For methyl carbons, dipolar couplings to

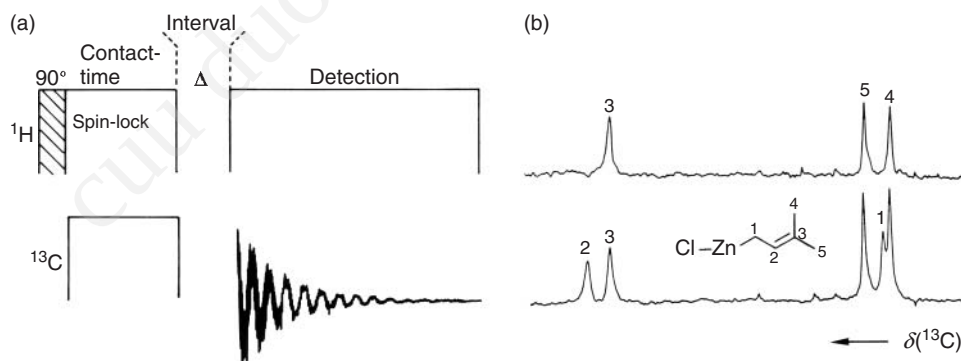


Figure 14.16 (a) Pulse sequence for the assignment of ^{13}C resonances in CP/MAS solid state NMR spectra known as the NQS sequence (non-quaternary carbon suppression); (b) CP/MAS ^{13}C NMR spectrum of allyl zinc

chloride (below) with application of the NQS experiment (above); only the signals of the methyl carbons (4, 5) and that of the quaternary carbon (3) are retained in the NQS spectrum [10]. H. Grondey and R. Benn, unpublished.

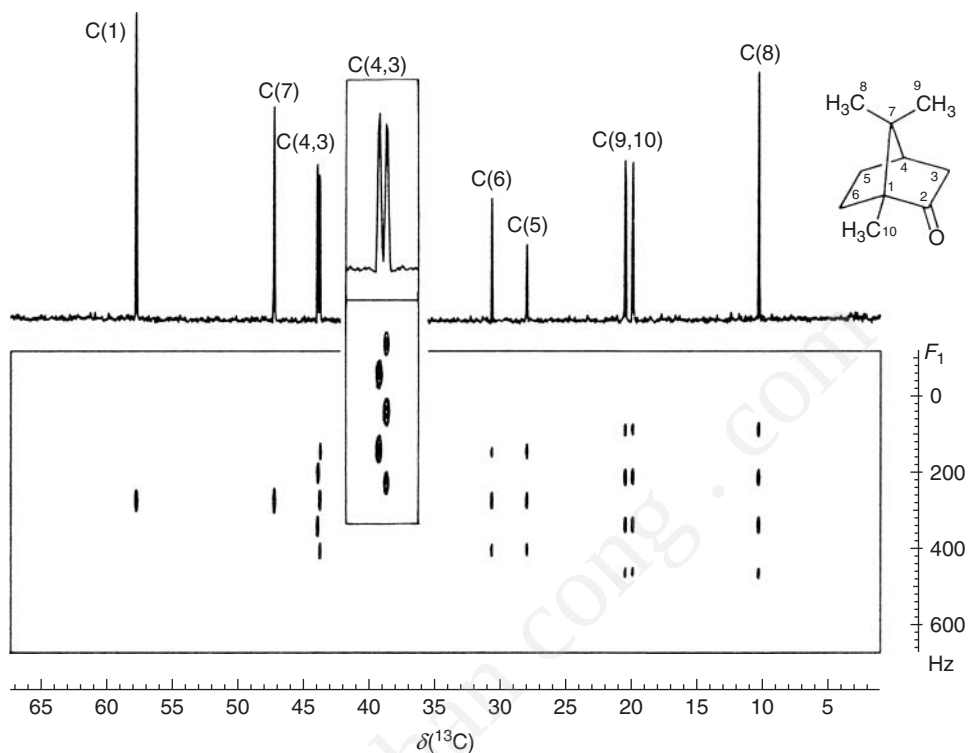


Figure 14.17 High-resolution two-dimensional ^{13}C J, δ -spectrum of solid camphor; contour diagram, measuring frequency 75 MHz; the signal of the carbonyl carbon is not shown. The ^{13}C multiplets due to scalar $^{13}\text{C}, ^1\text{H}$ coupling are clearly shown on the F_1 -axis and differentiation between the resonances of quaternary carbons, CH -, CH_2 -, and CH_3 -groups becomes possible.

protons are eliminated even in the solid because of the high rotational frequency of the methyl groups (energy barriers $< 15 \text{ kJ mol}^{-1}$). Signals of CH_3 carbons are thus also retained. Figure 14.16b documents the application of this technique with an example of an allyl zinc compound.

The second method is based on heteronuclear J, δ -spectroscopy, introduced in Chapters 10 and 11 (cf. p. 372, 401). Scalar spin-spin coupling is allowed only during half of the echo time. In solid state NMR this is achieved through the application of two different ^1H decoupling sequences, multipulse decoupling (elimination of dipolar couplings, see above), and high power ^1H decoupling (elimination of dipolar and scalar coupling). The result of such an experiment is shown in Figure 14.17 for the ^{13}C spectrum of camphor.

14.2.1.3 Quadrupolar Nuclei

With quadrupolar nuclei a complicating factor in solid state NMR is the splitting of the resonance by quadrupolar coupling that, in general, cannot be eliminated

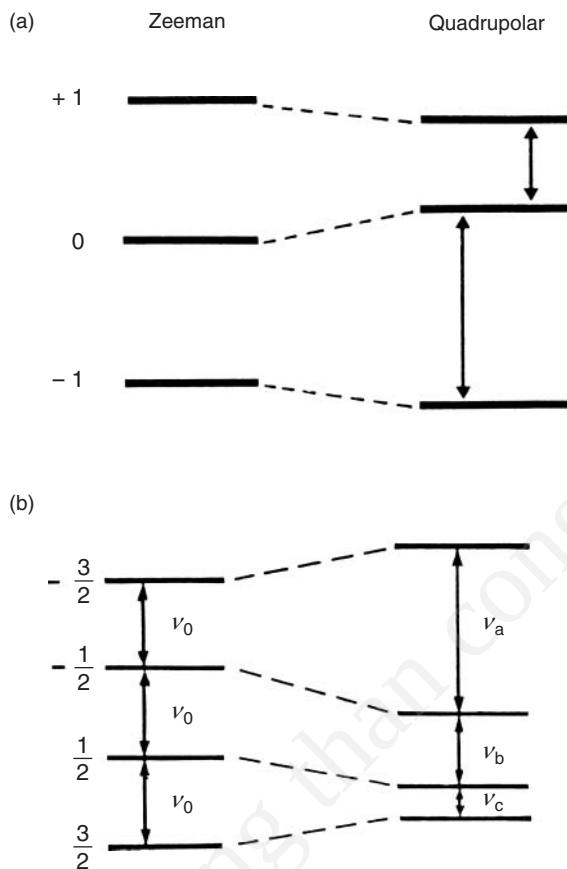


Figure 14.18 Energy level diagram for quadrupolar nuclei in solids: (a) spin $I = 1$ and (b) $I = \frac{3}{2}$.

by MAS because of the large frequencies involved. The changes in the energy level diagram associated with this interaction for nuclei with integer and half-integer spin are shown in Figure 14.18. As one can see, the degeneracy of individual transitions is removed and multiplet structures (doublets, triplets) arise. For some aspects, like MAS, the theoretical treatment for quadrupolar nuclei with half-integer spin ($\frac{3}{2}, \frac{5}{2}, \frac{7}{2}$) differs from those with integer spin (1, 2, 3), but we forego detailed discussion of this point.

A relatively simple situation is met with spin 1 nuclei, of which deuterium, because of its small quadrupolar moment, has been investigated most frequently. As described above [Eq. (14.17)], the ^2H NMR signal of an oriented species splits into a doublet. The angular dependence of the splitting is shown in Figure 14.6.

For deuterons the magnitude of the quadrupole coupling constant, χ , ranges between 170 and 200 kHz, for ^{14}N χ amounts to about 5 MHz and for ^{35}Cl values of up to 80 MHz can be assumed. This leads to digitizing problems (remember the

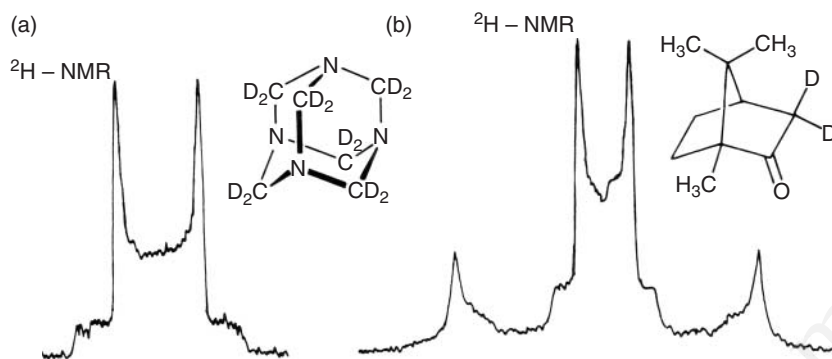


Figure 14.19 Static ^2H solid state NMR spectrum of [12]hexamethylenetetramine with isochronic deuterons (a) and camphor-3- d_2 with anisochronic deuterons (b) [6].

Nyquist theorem!) and only for deuterons is the spectral region accessible with the standard digitizers available.

For crystal powders all orientations of the C–D bonds relative to the field axis are possible and the resulting superposition of the resonances of individual deuterons leads to a typical line shape (Figure 14.19a). For compounds with several anisochronic deuterons such lines are superimposed and the spectra are more complicated (Figure 14.19b).

The line shape of the ^2H solid state resonance is, because of the angular dependence of the quadrupolar coupling, also influenced by dynamic processes in the solid. Through the analysis of such spectra important information can be gained about the dynamic properties of polymer chains. Experiments aimed at a reduction or elimination of the quadrupolar broadening of the ^2H -resonances by application of the MAS technique are not successful because of the large spectral width. In connection with special techniques (data collection synchronized with the rotor speed, excitation of double quantum transitions) resonances of deuterons bound to aromatic and aliphatic carbon have been separated. The small chemical shift range for deuterium and the line broadening due to quadrupolar effects of higher order, however, limits application of these methods to special cases. For quadrupole nuclei with non-integral spin $I > \frac{1}{2}$ there is no quadrupolar first-order line broadening for the transition between the states with $m_I = -\frac{1}{2}$ and $m_I = +\frac{1}{2}$ (Figure 14.14b). Solid state NMR spectra of nuclei like ^{11}B , ^{23}Na , ^{27}Al , and ^{17}O have thus often been measured as broad-line spectra without MAS application. Sample rotation leads to line narrowing; however, the broadening effects of higher order cannot be eliminated. Therefore, these spectra, which are in addition complicated because of the relatively small chemical shift range for these nuclei, are difficult to analyze. Subsequently, a new technique called *double rotation* (DOR) was developed to deal with these problems. One can show that sample rotation around two separate axes that are perpendicular leads to the observation of narrow lines. This sophisticated technique as well as the recently developed multiple quantum MAS (cf. p. 469) constitute a real breakthrough in solid state NMR of quadrupolar nuclei.

Finally, we mention that the usefulness of dipolar couplings in determining nuclear distances, which is sacrificed by using MAS, initiated research to find methods that allow again dipolar couplings to be measured. The result is the REDOR (rotational echo double resonance) experiment, which we shall not, however describe further.

Finally, we remind the reader that in CP solid state NMR an additional relaxation time, $T_{1\rho}$, can be observed for the *relaxation in the rotating frame*. In the Hartmann–Hahn experiment for CP, described in detail already in Chapter 10, (p. 364 ff.), the transverse x -magnetization M_x is phase-shifted to the y -axis and spin-locked in the B_1 field (see Figure 10.16). Relaxation of M_y starts after the spin-lock pulse and the relaxation time, $T_{1\rho}$, can be evaluated from the intensity loss in a series of FIDs recorded at increasing delays τ . This experiment is thus similar to the determination of the spin–lattice relaxation times T_1 described on page 247.

14.2.2

Applications of High-Resolution Solid State NMR Spectroscopy

From the numerous applications of the CP/MAS or MAS technique in structural research only a few typical examples can be discussed in this section. One aspect of general interest is certainly the fact that chemical shift data that are important indicators of the bonding situation in the molecules of interest are now accessible for solids. More direct information about the electronic structure of solids is thus available. In particular, charge density differences or changes can be easily recognized in the NMR spectra. Furthermore, the number of the resonance lines measured is directly connected to molecular symmetry and to the number of equivalent molecules in the unit cell of the crystals.

14.2.2.1 Spin $\frac{1}{2}$ Nuclei

For ^{13}C NMR spectroscopy of rigid molecules one can assume that the structure of a particular compound in solution and in the solid is identical if a comparison between solid state and solution NMR data yield $\Delta\delta$ values that are smaller than 5 ppm. Significant structural alterations are indicated by larger differences. Sometimes solvation effects that are absent in the solid may stabilize a certain structure in solution and spectral differences between liquid and solid state NMR spectra are found. This aspect is shown in Figure 14.20 with the spectra of 2-methylzinc chloride where not only the position but also the number of ^{13}C signals clearly indicates that the solution structure is different from the structure in the solid.

As another spin $\frac{1}{2}$ nucleus ^{119}Sn lacks complications arising from quadrupolar effects and solid state NMR spectra of ^{119}Sn can readily be obtained by the CP/MAS technique. By comparison with NMR data from solutions, the number of non-equivalent resonances observed and chemical shift data yield important information about the solid state structure, in cases where X-ray data are available and even more so when crystals suitable for X-ray work are not obtainable.

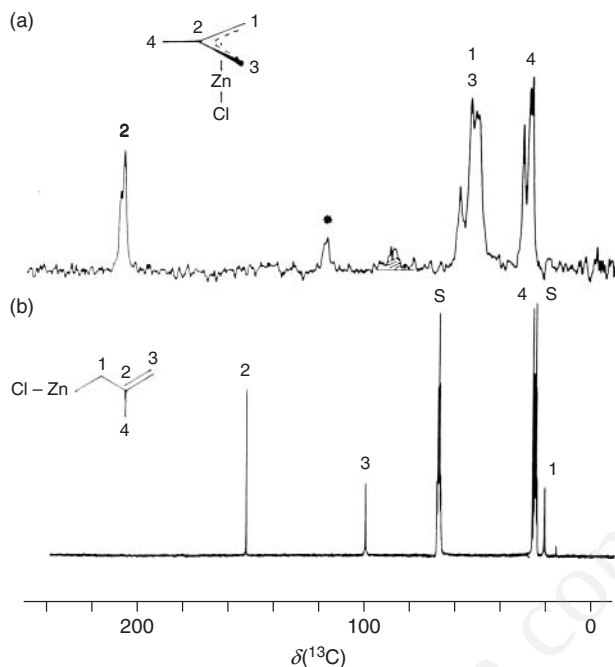


Figure 14.20 50.3 MHz ^{13}C NMR spectra of 2-methylallyl zinc chloride in the solid (CP/MAS) (a) and in THF (tetrahydrofuran) solution (b) and the η^3 - and η^1 -structures derived from these spectra; S = solvent signals [11].

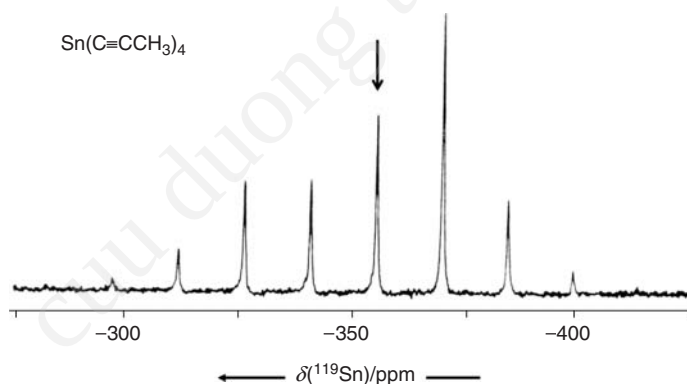


Figure 14.21 111.9 MHz ^{119}Sn CP/MAS spectrum of $\text{Sn}(\text{C}\equiv\text{CCH}_3)_4$ at a rotor frequency of 1.1 kHz; reference $(\text{C}_6\text{H}_{11})_4(^{119}\text{Sn})$; the arrow indicates the isotropic chemical shift [12].

As Figure 14.21 for the tetra-substituted tin compound $\text{Sn}(\text{C}\equiv\text{CCH}_3)_4$ shows, the symmetry of the ^{119}Sn shielding tensor that can be derived from the envelope of the CP/MAS sideband pattern is often helpful in the elucidation of the solid structure. In this case it is typical for non-axial symmetry (cf. Figure 14.10b)

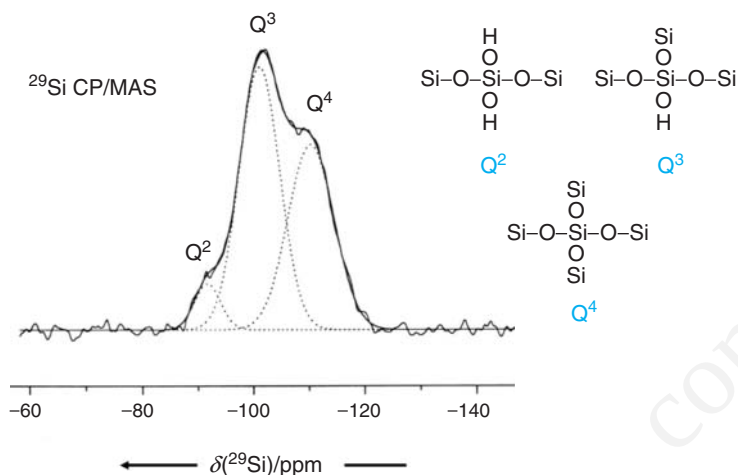


Figure 14.22 59.62 MHz CP/MAS ^{29}Si spectrum of silica-60 after annealing at 500 °C; chemical shifts are -90.4, -101.0, and -110.2 ppm for Q^2 , Q^3 , and Q^4 , respectively, relative to $\text{Me}_3^{29}\text{Si}$ of Q_8M_8 [= $(\text{Me}_3\text{SiOSiO}_{1.5})_8$] at 1.5 ppm [13].

and the highly symmetric point groups T_d for a strict tetrahedral arrangement of the substituents or C_{3v} for a structure with axial symmetry can be excluded. Using additional information from the ^{13}C CP/MAS spectrum, which yielded four resonances for each of the acetylenic carbons as well as four methyl signals, it could be concluded that $\text{Sn}(\text{C}\equiv\text{CCH}_3)_4$ is a completely asymmetric molecule belonging to point group C_1 . In contrast, for the analogous lead compound, $\text{Pb}(\text{C}\equiv\text{CCH}_3)_4$, three acetylenic resonances in an intensity ratio of 1 : 1 : 2 and two methyl signals in an intensity ratio 3 : 1 were found. The point group C_s was suggested for this compound, showing that homologous systems are not necessarily isostructural in the solid state.

A related example is provided by phosphorus(V) chloride, where the structure was in question. Its ^{31}P MAS NMR spectrum yields, relative to aqueous H_3PO_4 , two ^{31}P resonances at +96 and -281 ppm. Considering the large $\Delta\delta$ value of 377 ppm and the known charge density dependence of the ^{31}P resonance, this problem was solved easily in favor of the ionic structure $\text{PCl}_4^+[\text{PCl}_6^-]$.

In the field of inorganic solids and ceramic materials ^{29}Si MAS NMR has long been an important tool for structural studies. Typical building blocks of silicates that contain $\text{Si}-\text{O}^-$ or $\text{Si}-\text{O}-\text{Si}$ groups, abbreviated as Q^n where n stands for the number of $\text{Si}-\text{O}-\text{Si}$ bonds at a certain Si atom, can be distinguished by their chemical shifts. Figure 14.22 shows an example with the spectrum of silica-60, where the chemical shifts of the Q^2 , Q^3 , and Q^4 units have been determined by curve analysis using three Gauss-shaped signals.

During investigations of zeolites and aluminosilicates information not easily available from other sources was obtained and chemical shift ranges could be

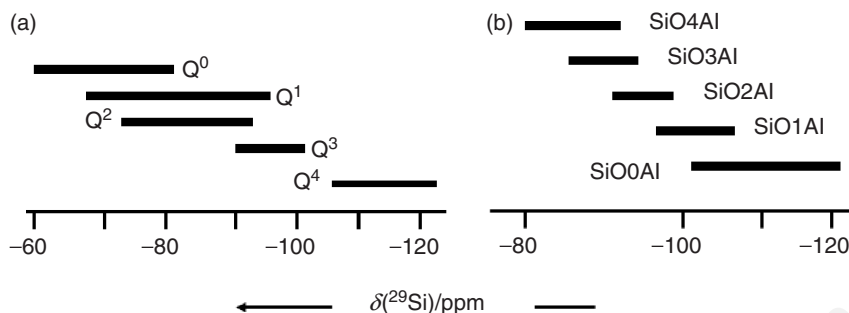


Figure 14.23 ^{29}Si solid state chemical shift ranges for different silicon environments in silicates (a) and aluminosilicates (b).

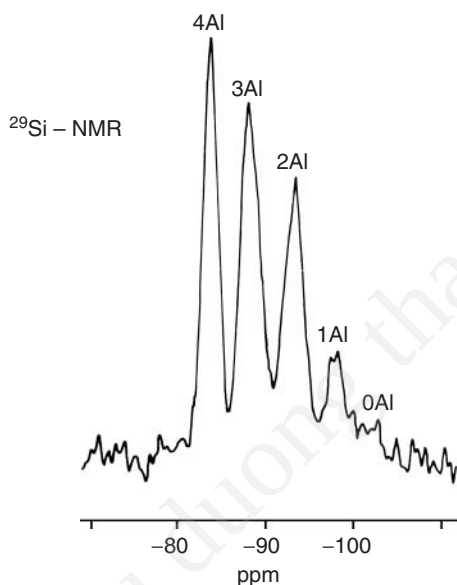


Figure 14.24 ^{29}Si -MAS spectrum of the zeolite analcite with individual signals for different aluminum environments [14].

established (Figure 14.23). There is some overlap but the separation between most chemical shifts is sufficiently large to distinguish ^{29}Si nuclei in different environments. Figure 14.24 shows an example from aluminosilicates with one to four aluminum atoms. Such studies are of particular interest because the X-ray method, where similar diffraction patterns are observed for Si and Al, is difficult to apply to these materials. Furthermore, it is not easy to grow crystals that are sufficiently large for X-ray investigations.

With NMR it has even been possible to reveal ^{29}Si - ^{29}Si connectivities in zeolites, compounds with complicated cage structures and important activity for

Si atoms; the numbers signify different SiO₄ groups. (Reprinted with permission from Reference [15]. Copyright 1991 American Chemical Society).

heterogeneous catalysis, using the 2D INADEQUATE experiment to establish the framework connectivities. Figure 14.25 shows typical results with the spectrum of zeolite ZSM-12, which shows signals arising from homonuclear $^{29}\text{Si}-\text{O}-^{29}\text{Si}$ coupling between structurally distinct Si atoms.

An interesting observation was made when ^{13}C MAS spectra were measured for samples of aromatic compounds absorbed on silica or aluminum oxide of various pore sizes. The large ^{13}C line width usually found for these compounds even under CP/MAS conditions is greatly reduced and even proton spectra can be measured (Figure 14.26). The effect apparently originates from a high molecular mobility of the compounds on the surface or in the pores of the supporting materials.

14.2.2.2 Quadrupolar Nuclei

Alkalides and electriles, **3** and **4**, respectively, are new materials with interesting properties that are prepared from alkaline metals and crown ethers. In these systems, for example, the caesium cations are bound to the crown ether as guest ions, while the caesium anions or even free electrons are highly mobile as counter ions. For the successful preparation of such structures, the experimental conditions must be controlled very accurately. For this purpose high-resolution ^{133}Cs solid state NMR

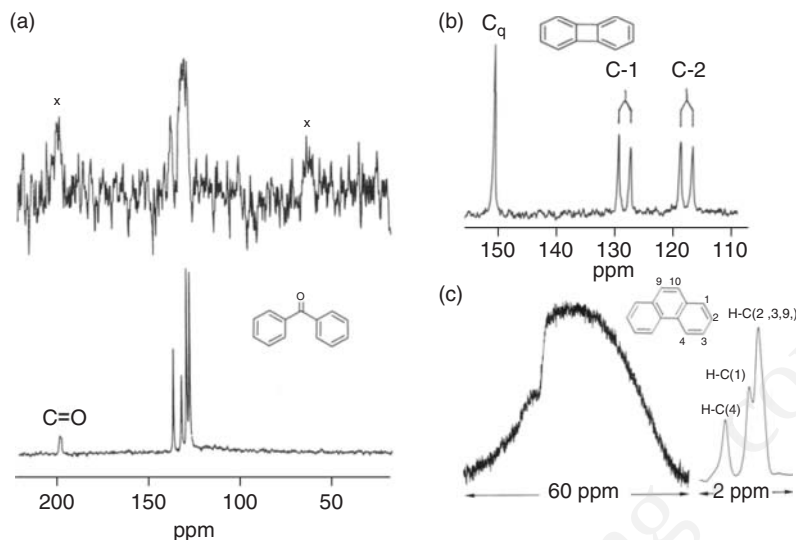
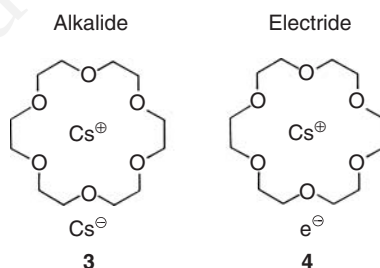


Figure 14.26 (a) 75.5 MHz ^{13}C CP/MAS NMR spectrum of solid benzophenone (above, $\times$ sidebands) and MAS ^{13}C NMR spectrum of benzophenone adsorbed on $\text{Al}_2\text{O}_3\cdot 90$; (b) 75.5 MHz ^{13}C MAS NMR spectrum of biphenylene adsorbed on $\text{Al}_2\text{O}_3\cdot 90$, showing $^{13}\text{C}, ^1\text{H}$ coupling; (c) 300 MHz MAS ^1H NMR spectrum of solid phenanthrene (32 transients, left) and of phenanthrene adsorbed on $\text{Al}_2\text{O}_3\cdot 90$ (8 transients, right) [16].

spectroscopy is well suited because it yields for the two species $\text{Cs}^+(\text{18-crown-6})_2/\text{e}^-$ and $\text{Cs}^+(\text{18-crown-6})_2/\text{Cs}^-$ three well-separated signals (Figure 14.27, p. 586). Newly synthesized products can thus be easily tested with respect to their composition. ^{133}Cs has a natural abundance of 100% and a relatively small quadrupole moment Q of $-4.1 \times 10^{-2}/10^{-28} \text{ m}^2$ and is, despite its high spin ($I = \frac{7}{2}$), a suitable nucleus for these MAS NMR measurements, which can be performed without CP.



Another case of interest is solid state NMR of ^7Li , a nucleus that has a spin $I = \frac{3}{2}$ and a quadrupole moment approximately one order of magnitude larger than that of deuterium [0.04 vs. 0.003 barn; see Tables 2.1 (p. 26) and 12.2 (p. 436)]. ^7Li NMR is employed extensively in the study of inorganic materials and glasses. Its quadrupolar coupling constant, χ , which is in the kilohertz range, has emerged also as a useful parameter for structural investigations of solid organolithium

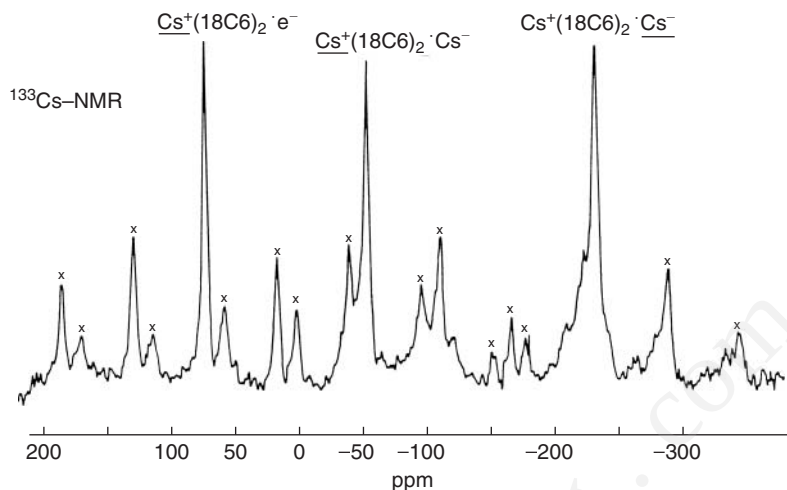
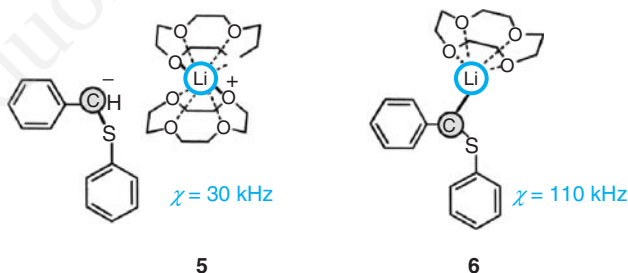


Figure 14.27 ^{133}Cs MAS NMR spectrum of crystalline material from a solution of caesium and 18-crown-6 (2:3) in a polar amine/ether mixture. Rotational side bands are marked (x), the parts per million scale refers to $\text{Cs}^+(\text{H}_2\text{O})$; the line widths are 100–200 Hz [17].

compounds. In these systems one has a favorable situation because usually only one ^7Li nucleus is present and χ can be measured either from the simulation of the sideband pattern in MAS spectra or from a static spectrum that is particular easy to analyze (Figure 14.28).

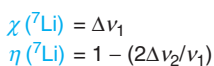
The magnitude of χ , which can have values between 10 and 600 kHz, mirrors the symmetry around the ^7Li nuclei in question with small values (<100 kHz) for symmetric arrangements such as in solvent-separated ion pairs (5) and large values (>100 kHz) in contact ion pairs (6).



The asymmetry parameter, η , of the quadrupolar interaction is characterized through the three principal components of the electric field gradient tensor q_{zz} , q_{xx} , and q_{yy} by the relation:

$$\eta = (q_{xx} - q_{yy})/q_{zz} \quad (14.23)$$

With $q_{zz} > q_{xx}$, and q_{yy} we have $0 \leq \eta \leq 1$. For axial symmetry obviously $\eta = 0$ and η is close to 1 if $q_{xx} \gg q_{yy}$ holds (Figure 14.29).



coupling χ (in kilohertz) and the asymmetry parameter η are calculated as shown in the figure. For **5** one finds $\chi = 325$ kHz, which is typical for a contact ion pair, and $\eta \approx 0$.

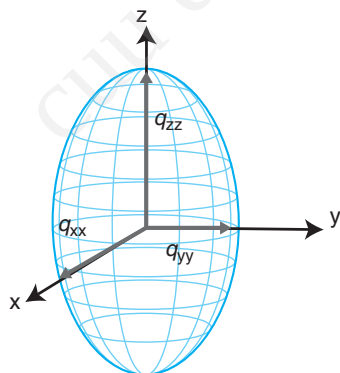


Figure 14.29 Definition of the anisotropy parameter η for quadrupolar nuclei.

14.2.2.3 Dynamic Processes

A unique feature of NMR is its sensitivity for dynamic processes. As was pointed out in Chapter 13, using different techniques, from the well-known line shape calculations to the application of relaxation time measurements, the correlation times of dynamic processes that can be studied span a range of several orders of magnitude. This applies to high-resolution NMR in the liquid phase as well as to investigations of solids by solid state NMR techniques. In fact, processes like internal rotation or ring inversion proceed in solids quite often with barriers that are not very different from those found for these types of internal motion in the liquid state. Thus, for the activation barrier $\Delta G^\ddagger$ of the equatorial $\rightleftharpoons$ axial ring inversion of fluorocyclohexane values of 42.4 and 43.9 kJ mol⁻¹ have been measured in the liquid and the solid, respectively. The packing forces in the molecular crystals of organic compounds are thus similar to the forces that restrict internal molecular motions by solvation in solution. This high mobility even leads to so-called plastic crystals for several compounds that yield high resolution NMR spectra even without particular provisions. Examples are adamantane and P₄S₃. The familiar thermal ellipsoids of individual atoms obtained from X-ray studies of crystals are well-known qualitative indicators of molecular motion in the solid,

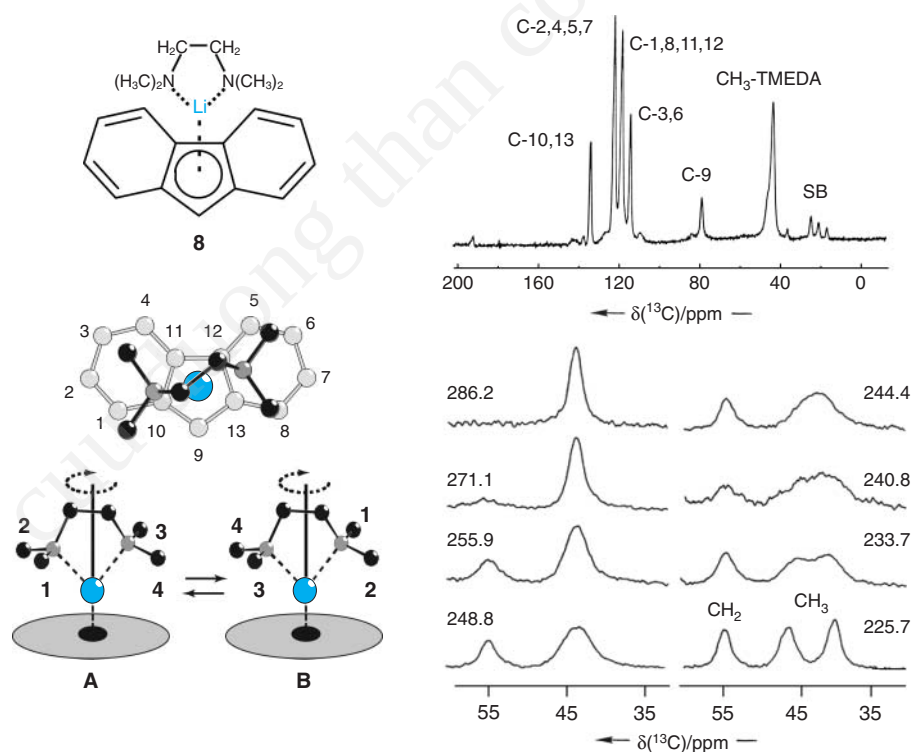


Figure 14.30 Temperature dependence of the ¹³C MAS line shape of the methyl resonances in fluorenyllithium·(TMEDA) (8); temperatures in K [18].

but a more quantitative investigation of such processes became only possible after appropriate solid state NMR techniques were applied.

In many cases the basis for dynamic solid state NMR experiments is the same as in liquids: the dependence of the NMR line shape on the life time of nuclei in positions with different Larmor frequencies. Temperature-dependent spectra then reveal the mechanisms and the activation parameters for conformational changes and other intramolecular processes by line shape analysis. An example is shown in Figure 14.30 with the temperature-dependent ^{13}C MAS spectra of fluorenyllithium (TMEDA) (TMEDA = tetramethylethylenediamine) (8), where rotation of the Li-TMEDA ring by 180° (π flip $A \rightleftharpoons B$) leads to an exchange process for the methyl groups. The N-CH_3 ^{13}C signal at 44.1 ppm broadens and splits at 235 K into two signals separated by 441 Hz. From spectral simulation for 12 different temperatures activation parameters of $\Delta H^\ddagger = 42.7 \pm 0.5 \text{ kJ mol}^{-1}$, $\Delta S^\ddagger = -5.3 \pm 2.1 \text{ e.u.}$, and $\Delta G^\ddagger(298) = 44.3 \text{ kJ mol}^{-1}$ were obtained for the rotational barrier of this dynamic process.

In addition to these frequently used methods of dynamic nuclear magnetic resonance (DNMR), dynamic processes in the solid can also be characterized by 2D exchange spectroscopy (EXSY) spectra and variable-temperature measurements of the relaxation times T_1 and/or $T_{1\rho}$. For an equally populated two-sites exchange system, for example, we have

$$\frac{1}{T_{1\rho}^{\text{ex}}} = \pi^2 \delta\nu^2 \left[\frac{\tau_{\text{ex}}}{1 + \omega_1 \tau_{\text{ex}}^2} \right] \quad (14.24)$$

where $\delta\nu$ is the chemical shift difference in the region of slow exchange, ω_1 the strength of the spin lock field, and $1/\tau_{\text{ex}} = k$ the rate constant. Relaxation time investigations have often been performed in polymer chemistry.

References

1. Saupe, A. (1968) *Angew. Chem., Int. Ed. Engl.*, **80**, 99.
2. Snyder, L.C. and Meiboom, S. (1967) *J. Chem. Phys.*, **47**, 1480.
3. Meiboom, S. and Snyder, L.C. (1968) *Science*, **162**, 1337.
4. Diehl, P., Sykora, S., and Wullschleger, E. (1975) *Mol. Phys.*, **29**, 305.
5. Thiele, C.M. and Berger, S. (2003) *Org. Lett.*, **5**, 705.
6. Fyfe, C.A. (1983) *Solid State NMR for Chemists*, CFC Press, Guelph.
7. Meddour, A., Canet, I., Loewenstein, A., Pechine, J.M., and Courtieu, J. (1994) *J. Am. Chem. Soc.*, **116**, 9652.
8. Yannoni, C.S. (1982) *Acc. Chem. Res.*, **15**, 201.
9. Hong, J. and Harbison, G.S. (1993) *Magic-Angle Spinning Sideband Elimination by Temporary Interruption of the Chemical Shift*, *J. Magn. Reson., Ser. A*, **105**, 128.
10. Grondey, H. (1988) PhD thesis, University of Siegen.
11. Benn, R., Grondey, H., Lehmkuhl, H., Nehl, H., Angermund, K., and Krüger, C. (1987) *Angew. Chem.*, **99**, 1303; *Angew. Chem., Int. Ed. Engl.*, **26**, 1300.
12. Klaus, E. and Sebald, A. (1994) *Magn. Reson. Chem.*, **32**, 679.
13. Oepen, S. (1996) PhD thesis, University of Siegen.
14. Wasylshen, R.E. and Fyfe, C.A. (1982) *Annu. Rep. NMR Spectrosc.*, **12**, 1.

15. Fyfe, C.A., Feng, Y., Grondey, H., Kokotailo, G.T., and Gies, H. (1991) *Chem. Rev.*, **91**, 1525.
16. Ebener, M., Fircks, G.V., and Günther, H. (1991) *Helv. Chim. Acta*, **74**, 1296.
17. Dawes, S.B., Ellaboudy, A.S., and Dye, J.L. (1987) *J. Am. Chem. Soc.*, **109**, 3508.
18. Focke, A., Hausmann, H., Jost, S., and Günther, H. (2012) *Helv. Chim. Acta.*, **95**, 2317.
- Brunner, E. (2001) Residual Dipolar Couplings in Protein NMR. *Concepts Magn. Reson.*, **13**, 238.
- Yan, J. and Zartler, E.R. (2005) Application of residual dipolar couplings in organic compounds. *Magn. Reson. Chem.*, **43**, 53.
- Laws, D.D. Bitter, H.-M.L., and Jerschow, A. (2002) Solid-State NMR Spectroscopic Methods in Chemistry. *Angew. Chem.*, **114**, 3224; *Angew. Chem. Int. Ed.*, **41**, 3096.

Textbooks

- Duer, M.J. (ed) (2002) *Solid State NMR Spectroscopy*, Blackwell Science, Oxford, 567 pp.
- Stejskal, E.O. and Memory, J.D. (1994) *High Resolution NMR in the Solid State*, Oxford University Press, New York, 189 pp.
- Fyfe, C.A. (1983) *Solid State NMR for Chemists*, CFC Press, Guelph, 593 pp.
- Grimmer, A.-R. and Blümich, B. (1994) Introduction to Solid State NMR, *NMR – Basic Princ. Progr.*, **30**, 1.
- Blümich, B. and Spiess, H.W. (1988) Two-dimensional solid state NMR spectroscopy: new possibilities for the investigation of the structure and dynamics of solid polymers. *Angew. Chem.*, **100**, 1716; *Angew. Chem., Int. Ed. Engl.*, **27**, 1655.
- Voelkel, R. (1988) High-resolution solid state ^{13}C NMR spectroscopy of polymers. *Angew. Chem.*, **100**, 1525; *Angew. Chem., Int. Ed. Engl.*, **27**, 1468.

Review Articles

- Diehl, P. (1996) Structure of Rigid Molecules Dissolved in Liquid Crystalline Solvents, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 7 (eds D.M. Grant and R.K. Harris) editors in chief, John Wiley & Sons, Ltd, Chichester, p. 4591.
- Kummerlöwe, G. and Luy, B. (2009) Residual dipolar couplings for the configurational and conformational analysis of organic molecules. *Annu. Rep. NMR Spectrosc.*, **68**, 193.
- Thiele, C.M. (2008) Residual Dipolar Couplings (RDCs) in Organic Structure Determination. *Eur. J. Org. Chem.*, 5673.
- Yannoni, C.S. (1982) High-resolution NMR in solids: the CPMAS experiment. *Acc. Chem. Res.*, **15**, 201.
- Lyerla, J.R., Yannoni, C.S., and Fyfe, C.A. (1982) Chemical applications of variable-temperature CPMAS-NMR spectroscopy in solids. *Acc. Chem. Res.*, **15**, 208.
- Engelhardt, G. (1996) Silicon-29 NMR of Solid Silicates, in *Encyclopedia of Nuclear Magnetic Resonance*, Vol. 7 (eds in chief D.M. Grant and R.K. Harris), John Wiley & Sons, Ltd, Chichester, p. 4398.

15

Selected Topics of Nuclear Magnetic Resonance Spectroscopy

In many laboratories, nuclear magnetic resonance (NMR) spectra are obtained as a daily routine for a large number of samples and the NMR experiment performed with the available instrumentation, mostly for ^1H and ^{13}C spectra, is practically “programmed.” If sample concentrations are similar, the experimental settings need hardly be adjusted and spectra can be obtained in an on-line fashion, especially if an automatic sample changer is installed. With this approach, obviously, only a fraction of the enormous potential behind the method is used, but this limitation is readily accepted since it guarantees a rapid return of information.

On the other hand, throughout the Periodic Table there are magnetic nuclei suitable for NMR experiments and, thus, different probes for the properties of molecules and solids are available. In the last few chapters we have introduced the reader to these exciting possibilities for structural research. Of course, only some of the more important areas of present-day NMR could be treated and many more experimental variations are possible. The physics of spin systems is as fascinating today as it was in earlier times and NMR certainly ranks among the most versatile spectroscopic techniques that we have at our disposal. In the present chapter we introduce briefly several additional topics that are of interest for chemistry and related areas in order to round up our introductory tour of NMR.

15.1

Isotope Effects in Nuclear Magnetic Resonance

In a molecule, for the replacement of an atom ^mX by a heavier isotope $^{m'}\text{X}$ with $m < m'$ one of two effects may be expected:

- 1) a *primary isotope effect*, which means that the properties of interest for ^mX and $^{m'}\text{X}$ differ;
- 2) a *secondary isotope effect* where the properties of interest for neighboring atoms change to a smaller or larger extent depending on their position relative to $^{m'}\text{X}$.

For NMR, a primary isotope effect would be observed if, for example, replacement of a proton by deuterium (^2H versus ^1H) would change the δ -value of the chemical

shift [$\delta(^1\text{H}) \neq \delta(^2\text{H})$]. A secondary isotope effect is observed, if, for example, in a methyl group the substitution of hydrogen by deuterium changes the chemical shift of the carbon-13 resonance.

In the following, we restrict our discussion exclusively to secondary isotope effects, which are also known as *intrinsic isotope effect*. Both NMR parameters, the chemical shift and scalar spin–spin coupling, are affected. The changes in coupling constants are, however, extremely small and difficult to measure and we shall not pursue this aspect further. In contrast, changes in chemical shifts are large enough to be easily detected. Usually, the neighbor next to the heavier isotope that is introduced is affected most and its resonance moves to lower frequency in the majority of cases. For example, deuterium substitution in a molecule of interest results generally in a shielding effect. The isotope shifts induced by deuterium in ^{13}C NMR are of the order of 0.1–0.5 ppm or less. In Chapter 11 we have already seen that deuterium-induced isotope shifts of ^{13}C resonances can be used for signal assignment in ^{13}C NMR spectra (p. 406). The phenomenon has long been known, but information about these effects increased with the introduction of high-field spectrometers that allowed the detection of small changes of chemical shifts with high accuracy.

Isotope shifts are measured as the difference $\Delta = A^m\text{X} - A^{m'}\text{X}$ and designated as ${}^n\Delta A^{(m/m')\text{X}}$, where ΔA stands for the shift of nucleus A in parts per million or, because of the small magnitude, preferably expressed in parts per billion (ppb), m is for the light and m' for the heavy atom X, and n for the number of bonds between A and X. Thus, ${}^1\Delta^{13}\text{C}(^{2/1}\text{H})$ is a deuterium-induced ^{13}C shift over one bond. To minimize errors, measurements are always made on samples that contain both compounds, $A^m\text{X}$ and $A^{m'}\text{X}$, and unequivocal assignment can be made by changing their ratio. Figure 15.1 shows a couple of examples of isotope shifts in NMR spectra.

Isotope shifts in NMR originate from mass-induced changes of vibrational and rotational averaging of nuclear shielding. As mentioned already in Chapter 3, the measured chemical shift is an average over all vibrational and rotational degrees of freedom of the molecule as there are bond extensions and angle deformations, well known from infrared spectroscopy. Based on theoretical studies, two factors affect the magnitudes and sign of isotope shifts: (i) the dynamic factor that results from the small changes induced for the rovibrationally averaged structure of the molecule and (ii) the electronic factor that originates from the sensitivity of the chemical shift to changes in the molecular geometry. For deuterium-induced isotope shifts of ^{13}C the slightly shorter C–D bond as compared to the C–H bond is important. This difference in bond lengths is a consequence of the anharmonicity of the C–H bond potential and the lower zero-point energy of the C–D bond (Figure 15.2).

Experimental work has established several empirical relations between isotope shifts and structure that are generally observed, but exceptions are not unusual:

- 1) As mentioned above, isotope shifts are in most cases shifts to low frequency (higher shielding) and, thus, according to their definition ($\Delta = A^m\text{X} - A^{m'}\text{X}$) positive [$\delta(A^m\text{X}) > \delta(A^{m'}\text{X})$];
- 2) their magnitude decreases with n , the number of bonds between A and $m'\text{X}$;
- 3) their magnitude reflects the chemical shift range of A;

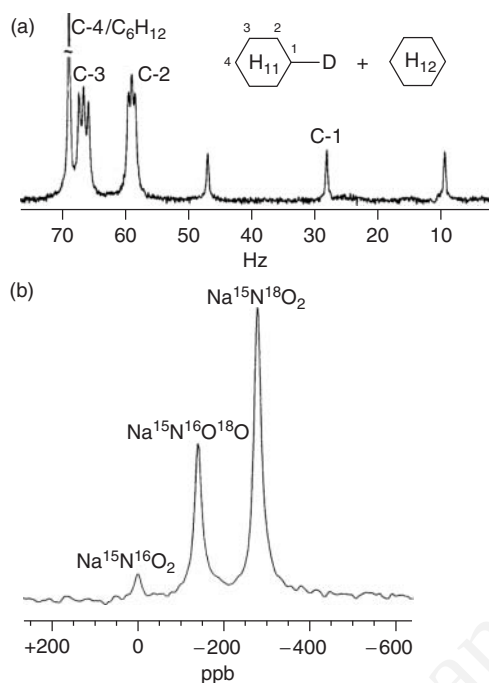


Figure 15.1 Isotope-induced shifts observed by introducing a heavy isotope for a light one: (a) cyclohexane; ${}^n\Delta^{13}\text{C}(^{2/1}\text{H})$ on $\delta(^{13}\text{C})$ measured at 100.61 MHz: C1 ($^1\Delta$) 418.0, C2 ($^2\Delta$) 103.7, C3 ($^3\Delta$) 24.9 ppb. The signal of C4 coincides with that of the reference compound C_6H_{12} . (Reprinted with permission from

Reference [1]; Copyright 1981 American Chemical Society) (b) Sodium nitrate; ${}^n\Delta^{15}\text{N}(^{18/16}\text{O})$ on $\delta(^{15}\text{N})$ measured at 47.6 MHz: low-frequency isotope shifts are 138 ppb per ^{18}O (Reprinted from Reference [2]; Copyright 1990; with kind permission of Springer Science+Business Media).

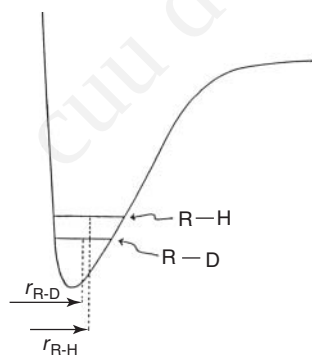


Figure 15.2 Potential curve for the vibrational states of the C–H and C–D bond.

- 4) the larger the fractional mass change, $(m' - m)/m$, the larger is Δ ;
- 5) isotope shifts observed for multi-substitution by $m'X$ are additive.

For deuterium-induced isotope shifts of ^{13}C , which have been extensively investigated, several linear relations with other parameters like spin–spin coupling constants, Hammett σ_p values, and the equilibrium distance, r_e , of the C–H bond have been found. In earlier work, as ^{19}F NMR spectra were easier to measure than ^{13}C NMR spectra, related observation were made for $^n\Delta(^{19}\text{F})$ values. As with the ^{13}C chemical shift increments discussed in Chapter 11, $^1\Delta(^{13}\text{C}(^{2/1}\text{H}))$ data depend linearly on the number of substituents in substituted methanes (Figure 15.3a). Long-range $^n\Delta(^{13}\text{C}(^{2/1}\text{H}))$ isotope shifts over two, three, and even more bonds obey the same rules as formulated above for one-bond effects. They are one or two orders of magnitude smaller than those over one bond, except for carbocations where the hyperconjugative interactions with the empty p-orbital at the positively charged carbon differ for CH_3 and CD_3 groups. In CD_3 -substituted benzenoid aromatics, $^3\Delta(^{13}\text{C}(^{2/1}\text{H}))$ correlates linearly with the π -bond order of the adjacent C–C bond (Figure 15.3b). For $^3\Delta(^{13}\text{C}(^{2/1}\text{H}))$ in saturated compounds, on the other hand, a dihedral angle dependence similar to that of the Karplus curve for vicinal $^1\text{H}, ^1\text{H}$ coupling constants was found (Figure 15.3c).

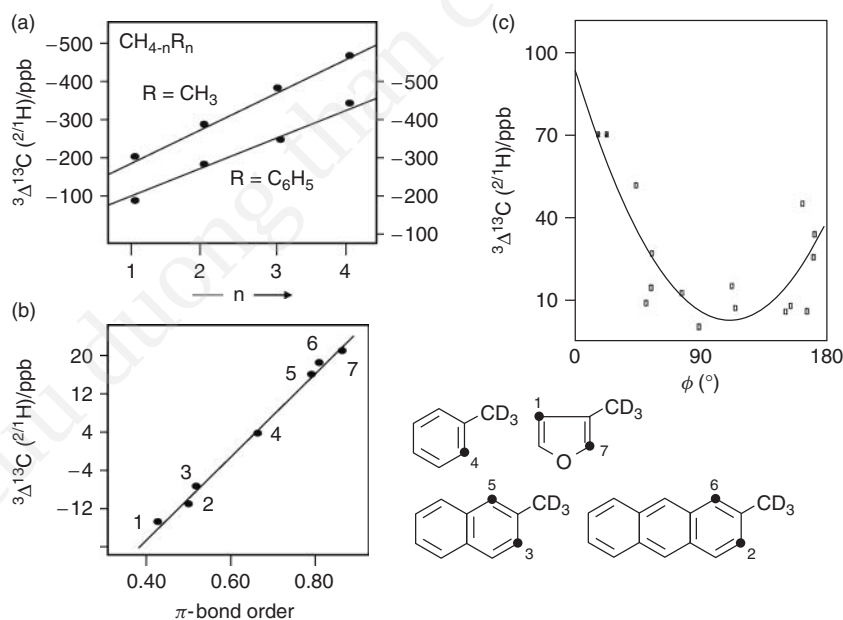
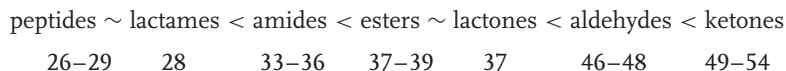


Figure 15.3 (a) Correlation between $^1\Delta(^{13}\text{C}(^{2/1}\text{H}))$ and the number of substituents; (Reprinted with permission from Reference [3]. Copyright 1985 American Chemical Society). (b) relation between $^3\Delta(^{13}\text{C}(^{2/1}\text{H}))$ and the π -bond order of the adjacent C–C bond

in benzenoid aromatics (Reprinted with permission from Reference [4]. Copyright 1983 American Chemical Society); (c) dihedral angle dependence of $^3\Delta(^{13}\text{C}(^{2/1}\text{H}))$ in saturated hydrocarbons [5].

Numerous isotope shifts for ^{13}C and ^{15}N induced by ^{18}O , the heavy oxygen isotope that has, like carbon-12, no spin, have been observed and used for structural and kinetic studies in organic and biochemistry. For example, the one-bond ^{18}O isotope shifts for ^{13}C in carbonyl groups show a significant dependence on the functional group (in parts per billion to lower frequency):



Furthermore, a linear correlation between ^{13}C isotope shifts in $^{13}\text{C}=\text{}^{18}\text{O}$ groups and the ^{13}C chemical shift of the carbonyl carbon was found [6]:

$$^1\Delta^{13}\text{C}(^{18/16}\text{O})[\text{ppb}] = 0.438\delta(^{13}\text{C}=\text{O}) - 41.6 \quad (15.1)$$

^{18}O induced isotope shifts were also successfully used in the field of biosynthetic studies of enzyme mechanisms where they permit direct, semiquantitative localization of the ^{18}O label. The advantage of NMR compared to other techniques, that is, mass spectroscopy, is again the non-destructive nature of the method.

Finally, we mention for completeness that kinetic isotope effects during biochemical transformations can lead to differences in the natural deuterium distribution of biomolecules such as carbohydrates and other plant products that have a different environmental history. This produces fingerprints, specific deuterium distributions in a molecule. For example, in the methyl or methylene group of ethanol one does not observe the statistical value of 0.0156% for the natural abundance of deuterium in both groups but instead higher or lower values and the ratio $^2\text{H}(\text{CH}_3):^2\text{H}(\text{CH}_2)$ data – measured by deuterium NMR – differs from the theoretical ratio 3:2. For example, the ethyl group of ethyl acetate produced from two different ethanol samples – obtained from fermentation of maize (i) and beet-root sugar (ii), respectively – yielded integral ratios for the ^2H signals of the methyl and methylene group of 3.08:1.92 (i) and 2.72:2.16 (ii) instead of 3:2. Thus we have deuterium depletion in the methylene group of sample (i) and in the methyl group of sample (ii) and enrichment in the methyl group of (i) and the methylene group of (ii), and the differences are significant and larger than the experimental error.

The interesting point is that these fingerprints are typical for the environment where the natural product was produced by the plant or for the type of industrial process used for its preparation. This yields valuable information about the history of food products and beverages like wine where the ^2H fingerprint of ethanol is used to locate the source of the sample. The technique is called *SNIF-NMR* (SNIF = site-specific natural isotope fractionation) and plays an important role in food control. In addition, other elements yield isotopic fingerprints and their use in analytical chemistry is well established.

15.1.1

Isotopic Perturbation of Equilibrium

An interesting observation is related to the fact that chemical equilibria are also affected by isotopic substitution, a finding known as *isotopic perturbation of*

equilibrium. For example, in cyclohexane, the introduction of a deuterium atom shifts the equilibrium between the two chair conformations to the side with deuterium in the equatorial position. An equilibrium constant of $K \approx 1.03$ was measured and confirmed by theoretical calculations.

An ingenious application of isotope effects was found in the field of carbocations, where deuteration affects the normally isoenergetic equilibrium. For the 2,3-dimethylbutyl-2-ium ion, for example, a fast hydride shift establishes the equilibrium $I \rightleftharpoons II$ shown in Figure 15.4a. Because of the low barrier of interconversion,

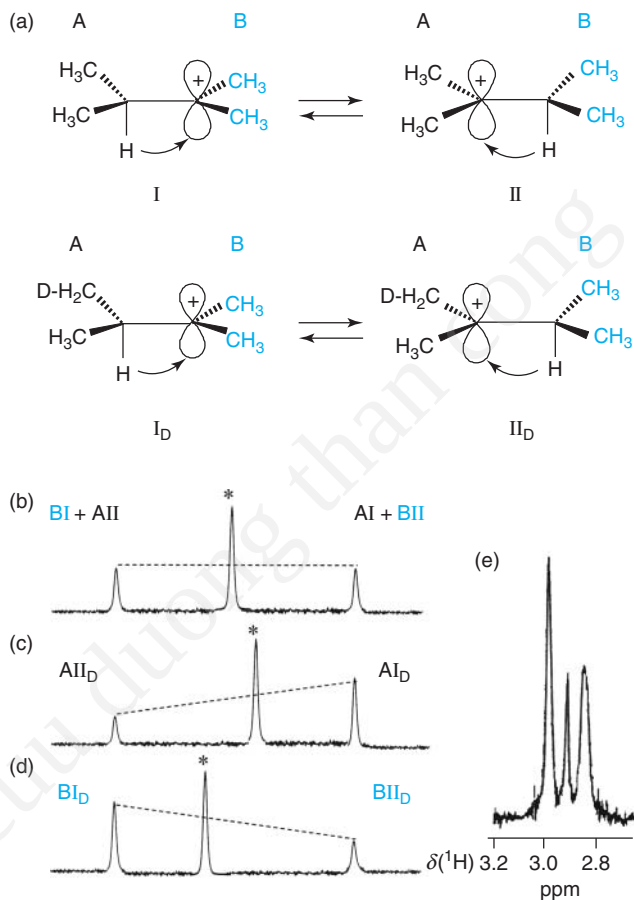


Figure 15.4 Perturbation of equilibrium: the effect of deuteration on a fast equilibrium (a) between isomeric carbenium ions I and II; (b) schematic ¹H NMR spectrum of the non-deuterated system $I \rightleftharpoons II$; with the hypothetical signals of the different methyl groups and the average signal marked (*); (c), (d) the same for the deuterated system $I_D \rightleftharpoons II_D$; (e) experimental

spectrum for the methyl protons of $I_D \rightleftharpoons II_D$ in SbF_5-SO_2ClF at $-56^\circ C$ with decoupling of the methylene proton; the signal at $\delta 2.93$ is due to the starting material, the 3-D-2,3-dimethylbutyl-2-ium ion (Reprinted in part with permission from Reference [7]. Copyright 1971 American Chemical Society).

it is not possible to reach the slow exchange limit with different signals for the methyl groups of type A and B by lowering the temperature. The ^1H NMR spectrum just shows the average signal at $[\nu(\text{I}) + \nu(\text{II})]/2$ (Figure 15.4b). If one methyl group is mono-deuterated, however, the spectrum shown in Figure 15.4e results: two signals are now observed (the sharp center signal at 2.93 ppm is due to starting material). Obviously, the γ -deuterium effect and the β -deuterium effect on the stability of the carbenium ion are different. If I_D is stabilized, an average signal for the methyl groups of type A results that is shifted to lower frequency (shielding) relative to the unperturbed signal (methyl groups of type AI at uncharged carbon are higher populated than those of type AII). In contrast, for the methyl groups of type B again those at isomer I_D are more highly populated but now the average signal for $\text{BI} \rightleftharpoons \text{BII}$ shifts to higher frequency due to the increased carbenium ion contribution (deshielding). The lower intensity of the low-frequency signal in the experimental spectrum (Figure 15.3e) results from the fact that due to the deuteration of one methyl group only five protons are averaged in this case and line-broadening results from unresolved $^1\text{H}, ^2\text{H}$ coupling. This shows that indeed isomer I_D is more stable than isomer II_D ; in other words, the carbenium ion center prefers to be substituted by unlabeled methyl groups that provide stronger hyperconjugation. The equilibrium constant $K = \text{I}_\text{D}/\text{II}_\text{D}$ is given by $(\Delta\nu + \Delta')/(\Delta\nu - \Delta')$ and requires knowledge of $\Delta\nu$, the unknown shift difference in the slow exchange limit. With an estimated value of 210 Hz, taken from another carbenium ion rearrangement, and the measured shift difference Δ' of 13 Hz, a value of $K = 1.132 \pm 0.007$ was obtained and from its temperature dependence a ΔH° of $54 \pm 3 \text{ cal mol}^{-1}$ ($226 \pm 13 \text{ J mol}^{-1}$) in favor of I_D resulted.

15.2

Nuclear Magnetic Resonance Spectroscopy of Paramagnetic Materials

15.2.1

Contact Shifts

In Chapter 8 we alluded to the fact that paramagnetic impurities markedly accelerate the longitudinal relaxation of protons and therefore hinder the measurement of NMR spectra. It follows that materials that themselves are paramagnetic cannot, in general, be investigated by using NMR spectroscopy because two effects are produced by unpaired electrons in a molecule: (i) changes of chemical shifts and (ii) efficient relaxation of the nuclei. The chemical shifts can be as large as several hundred parts per million and the NMR signals are mostly extremely broadened. Compounds of several transition metals in certain oxidation states, for example, $\text{V}(\text{II})$, $\text{Cr}(\text{III})$, $\text{Mn}(\text{II})$, and $\text{Cu}(\text{II})$ or the lanthanide $\text{Gd}(\text{III})$ are well-known examples. NMR investigations of these systems are, therefore, less common.

However, there are cases in which a paramagnetic compound such as a radical anion of an aromatic hydrocarbon ($\text{R}_1^\bullet$) exists in low concentration in the presence of the corresponding diamagnetic species (R_2). Here an intermolecular exchange

of the unpaired electron according to Eq. (15.2) results:



The paramagnetic spin density is then distributed over a large number of molecules with the effect that it is “diamagnetically diluted.” If, in addition, electron spin relaxation is fast, it becomes possible to observe the NMR signals of these systems. The lines are broadened compared to those of pure diamagnetic compounds, but despite this they may be easily measured.

It is significant that the interaction between electron and nuclear spin that manifests itself in electron spin resonance (ESR) spectroscopy as the hyperfine splitting of the ESR signal, here merely leads to a shift of the NMR signal to higher or lower frequency relative to the signal of the same proton in the diamagnetic compound. This effect is known as *contact shift*.

In ESR spectroscopy the hyperfine coupling constant a for the scalar interaction between electron and nuclear spin that leads to the line splitting in the ESR spectrum is given by the relation:

$$a = Q\rho \quad (15.3)$$

where Q is a proportionality factor of about -25 gauss (G) and ρ is the unpaired spin density at the carbon atom under consideration; ρ is a dimensionless quantity and a is thus expressed in gauss. The spin density, ρ_μ , at the center μ of a π -system, for example, can be calculated through the relation $\rho_\mu = c_{\kappa\mu}^2$ from the coefficient $c_{\kappa\mu}$ of the wave function Ψ_κ at the center μ ; Ψ_κ is the molecular orbital (MO) in which the unpaired electron resides. The coefficients in turn can be obtained, for example, by using Hückel MO calculations where the MOs are expressed as linear combinations of the $2p_z$ atomic orbitals at the carbon atoms:

$$\Psi_\kappa = \sum_{\mu=1}^n c_{\kappa\mu} \phi_\mu \quad (15.4)$$

One would now expect that the multiplet structure of the electron resonance in the case of a two-spin system of the AX type, as represented here by the nuclear spin I and the electron spin S , would also lead to a splitting in the NMR spectrum. There are two reasons why this is not the case. The first is the fast spin relaxation of the electrons and the second is the rapid exchange of electrons occurring between radical anions $R^\cdot$ and diamagnetic molecules R in the solution. As in the case of methanol (p. 503), time averaging results and the line splitting vanishes since the electron interacts with a large number of nuclei in different spin states. The average NMR line should then assume the same position as the corresponding resonance signal of the diamagnetic compound. However, as the phenomenon of the contact shift shows, this is not observed. The reason for this lies in the different populations of the two electronic eigenstates. Since the energy difference $h\nu_S$ is substantially larger than the corresponding value $h\nu_I$ in NMR, the low energy level ($m_S = +\frac{1}{2}$) is much more highly populated and contributes with a greater weight ($N_{+1/2} > N_{-1/2}$) to the time average of ν according to:

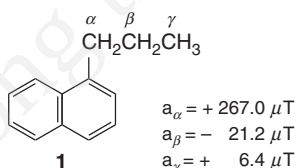
$$\langle \nu \rangle = N_{+\frac{1}{2}} \nu_{+\frac{1}{2}} + N_{-\frac{1}{2}} \nu_{-\frac{1}{2}} \quad (15.5)$$

The magnitude of the contact shift Δ is field dependent and satisfies the expression:

$$\frac{\Delta B}{B_0} = \frac{a \gamma_e^2 \hbar}{4 \gamma_p k_B T} \quad (15.6)$$

where γ_e and γ_p signify the magnetogyric ratio of the electron and the proton, respectively, k_B is the Boltzmann constant and T is the absolute temperature. Moreover, there is a dependence on the concentration of the paramagnetic molecules. As one can see, the equation above allows us to determine the sign of the hyperfine coupling constant, a , information that is not available from the ESR spectrum alone.

As an illustration, Figure 15.5 shows the NMR spectra of 1-propylnaphthalene (**1**) for different concentrations of the corresponding radical anion. It can be seen that the hyperfine coupling constants for the methyl protons and the protons of the β -methylene group have opposite signs since the CH_3 lines are shifted to lower field while the CH_2 lines are shifted to higher field. Moreover, the spectra confirm that the magnitude of the contact shift, as expected according to the equation above, is proportional to the magnitude of the constants a (cf. formula 1). A more detailed consideration of the relaxation processes shows further that the line width is also proportional to the magnitude of a . In addition, it is a function of the factor $1/r^6$, where r is the distance of the nucleus under consideration from the radical center. In our case this is the $2p_z$ orbital of the corresponding carbon atom of the naphthalene ring. The lines of the ring protons and the methylene protons at C_α are therefore especially strongly shifted and broadened so that they can no longer be observed in the spectrum (c). The values of the hyperfine coupling constants determined in this experiment are indicated next to formula 1.



An advantage of using contact shifts of NMR to obtain ESR data is the high *sensitivity*, which enables us to determine very small hyperfine coupling constants that cannot be measured by using ESR spectroscopy directly. In favorable cases it has even been possible to observe the NMR spectra of *radicals* and to determine the ESR hyperfine coupling constants from the magnitude and signs of the contact shifts.

15.2.2

Pseudo-contact Shifts – Shift Reagents

In addition to the mechanism of the interaction between electron and nuclear spins mentioned so far, a second possibility of mutual influence can be detected using NMR spectroscopy. This mechanism, known as *pseudo-contact interaction*, leads to a shift of the NMR line and operates when a strongly anisotropic paramagnetic center is present in the molecule. The unpaired electrons in the valence orbitals of the rare

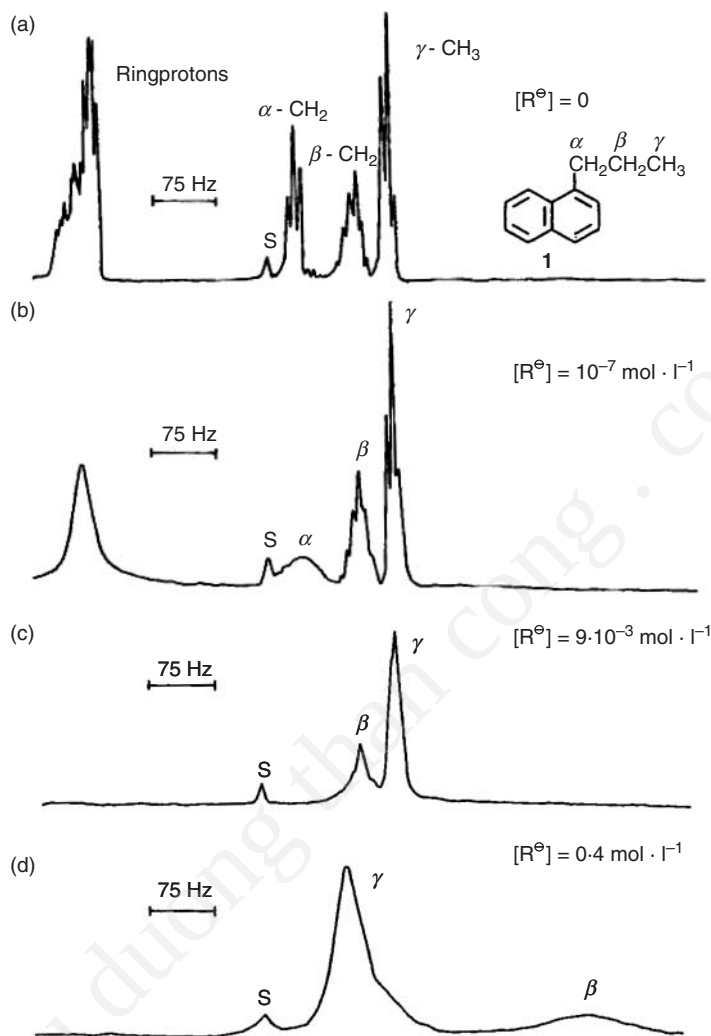
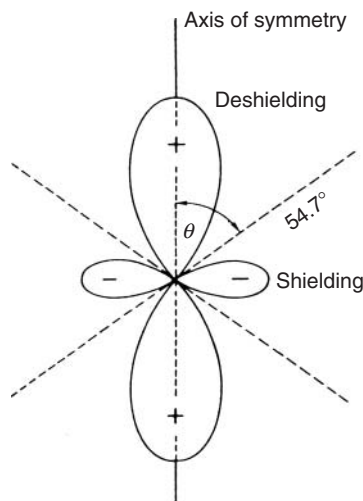
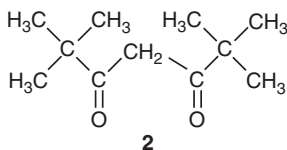


Figure 15.5 ^1H NMR spectrum of 1-propylnaphthalene (1) in the presence of different concentrations of the corresponding radical anion $R^\bullet$ in tetrahydrofuran; the absorption at s is that of incompletely deuterated solvent [8].

earth metals, for example, possess such anisotropic properties. The influence on the proton resonance is the result of a dipolar through-space interaction between the magnetic moments. Its magnitude is proportional to the expression $(3\cos^2\theta - 1)r^{-3}$, where r is the distance between the nucleus under consideration and the site of the paramagnetism and θ is the angle between the effective symmetry axis of the paramagnetic moment and the distance vector, r , to the nucleus. For example, the dipole field of an axially symmetrically paramagnetic center then has the following form:



The pseudo-contact interaction may be observed in both *crystals* and *solutions*. Thus, it has been found that the coordination of hydroxyl or amino groups with europium(III) causes a significant paramagnetic shift of the proton resonances of the corresponding alcohols or amines if one adds the complex formed from Eu(III) and the β -diketone **2** (the tris(dipivaloylmethanato)-Eu(III) complex [Eu(DPM)₃]) to the solution of the sample under investigation. On the basis of the angle factor $(3\cos^2\theta - 1)$, shifts to both lower and higher frequency – known as *LIS* (lanthanide induced shift) – can be observed. Complexes with praseodymium or ytterbium show similar effects. These substances, called *shift reagents*, have found wide application, since they allow complex spectra in which numerous proton resonance signals overlap to be significantly simplified. The effect is in certain ways comparable to that which one attains by the application of strong B_0 fields, that is, with superconducting magnets and was called, facetiously, “a poor man’s high-field NMR.” Especially with saturated compounds, a considerable increase in information is achieved through the use of shift reagents, as is shown in Figure 15.6 for the case of 2-adamantanol. Here the resonances of all the protons and the geminal coupling constants, which have the largest values of all spin–spin interactions in this compound, can be unraveled. Fortunately, the line broadening caused by the paramagnetic moment of lanthanides is relatively small.



The LIS effect originates from complex formation between the shift reagent, where the lanthanide cation still has free coordination sites, and the substrates. The

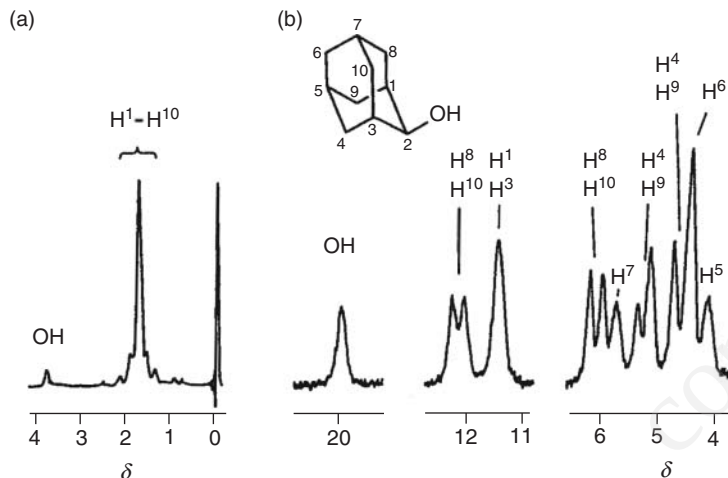
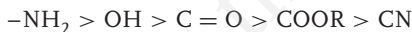


Figure 15.6 ^1H NMR spectrum of 2-adamantanol: (a) normal spectrum and (b) spectrum in the presence of tris(dipivaloylmethanato)europium(III) [9].

observed spectra are the time average for free and complexed substrate. Individual lanthanides differ with respect to the sign of their dipole field. For example, for Eu(III) we find a situation as shown on page 601, while for Pr(III) the signs are reversed. The magnitude of the resulting shift is strongly dependent on the basicity of the complexing group in the substrate and decreases in the following sequence:



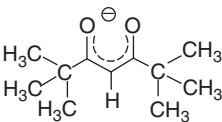
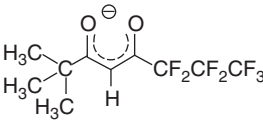
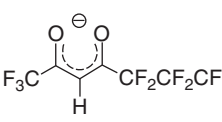
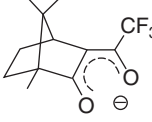
Acidic groups very often lead to decomposition of the lanthanide complex and can, thus, in general not be investigated (see, however, Table 15.1). In addition, owing to the lack of complex formation, the spectra of saturated and unsaturated hydrocarbons cannot be simplified by the application of shift reagents. However, it proved possible to use silver salts as auxiliary reagents to observe LISs for olefinic and aromatic compounds. The proper signals of the groups in the shift reagents are generally not observed because they are shifted in the opposite direction. Furthermore, because of the small concentration of the shift reagent, these signals are of low intensity (see also Table 15.1). For the induced LISs of the NMR signals (^1H or ^{13}C) in the substrate, Δ_i , the following relation holds for axial symmetry:

$$\Delta_i = K(3\cos^2\theta - 1)r^{-3} \quad (15.7)$$

Here K is an empirical constant typical for the complex under consideration. On the basis of the geometrical factor structural data (angles, distances) can be derived from the experimentally observed Δ_i values for various nuclei in the ligand (^1H , ^{13}C), provided that contact and non-axial contributions to the LIS data are absent.

The quantitative analysis of LISs is of considerable interest for conformational analysis. In practice, however, very often a qualitative empirical analysis is already sufficient to solve a stereochemical problem. For example, Figure 15.7 shows

Table 15.1 Most common shift reagents and their properties.

Anion	Cation
 DMP⁻	 FOD⁻
DPM (=dipivalomethanato)	
FOD (=1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octandionato)	
Chiral Legend	
 DFHD⁻	 FACAM⁻
DFHD (=1,1,1,5,5,6,6,7,7-decafluoro-2,4-heptandione)	
FACAM (=3-trifluoroacetyl-D-campherato)	
Properties	
DPM	FOD
good solubility in organic solvents	(+) (+)(+) excellent solubility in organic solvents, high concentration possible, good resolution can be achieved
good complex formation with strong bases	(+) (+) strong complex formation with strong bases
weak complex formation with weak basis	(-) (+) good complex formation even with weak bases
<i>t</i> -butyl signal close to TMS, in most cases at higher field	(+)(+) (-) <i>t</i> -butyl signal can appear in the n.m.r. region of aliphatic protons
substrate conformation weakly influenced	(+) (-) substrate conformation can be strongly changed
unstable against weak acids, phenols, carboxylic acids	(-) (+) stable against weak acids

After Reference [10].

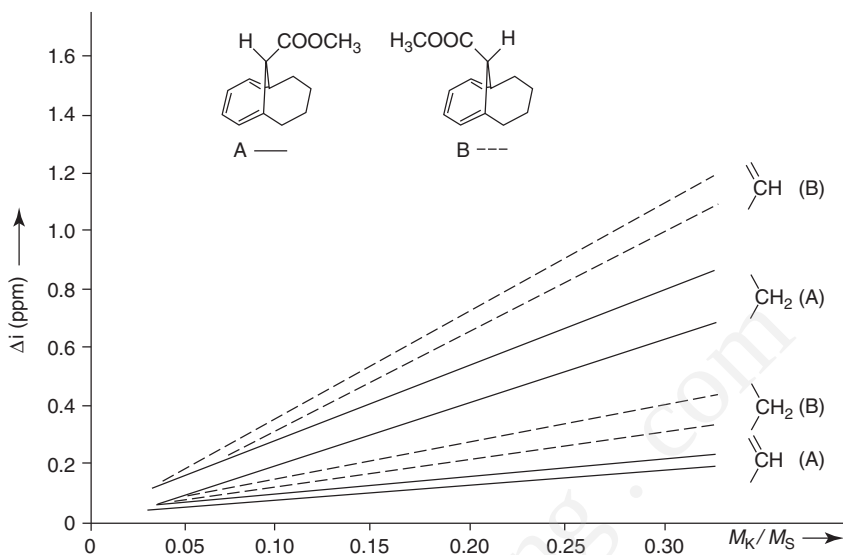


Figure 15.7 $\text{Eu}(\text{FOD})_3$ -induced pseudo-contact shifts in the ^1H NMR spectra of the *exo/endo*-isomers of 11-carbomethoxy-bicyclo[4.4.1]undeca-1,3,5-triene; M_K/M_S = molar ratio $\text{Eu}(\text{FOD})_3$ /substrate [11]; complexation is achieved at the ester group.

the resonance shifts measured for the olefinic and the methylene protons of the *syn*- and *anti*-isomer of 11-carbomethoxy-bicyclo[4.4.1]undeca-1,3,5-triene. They are sufficiently different to allow assignment of the stereochemistry at the bridge carbon. Owing to the different distances of the ester protons on one side and the olefinic and methylene protons on the other we find for isomer A $\Delta(\text{CH}_2) > \Delta(=\text{CH})$ and for B $\Delta(\text{CH}_2) < \Delta(=\text{CH})$.

Lanthanide complexes with chiral ligands are used quite frequently to determine the optical purity of enantiomeric mixtures. As in the case of diastereomers that are formed by solvation with optically active solvents (see p. 217), one observes different NMR signals for diastereomeric complexes of D- and L-species, if a shift reagent with a unique stereochemistry of the ligand is used. Complexes of various lanthanides with different ligands are commercially available. The ligands and cations used most frequently are collected in Table 15.1 with their relevant properties.

15.3

Chemically Induced Dynamic Nuclear Polarization (CIDNP)

Intimately connected with the relaxation effects responsible for the nuclear Overhauser effect (NOE) is a process that has become known as chemically induced dynamic nuclear polarization (CIDNP). Since its discovery it has developed into a powerful technique for the investigation of radical reactions.

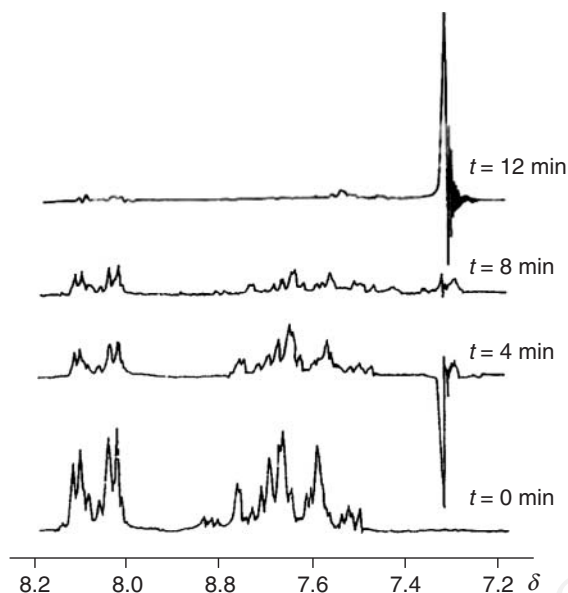


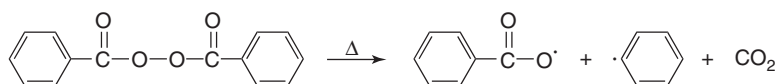
Figure 15.8 100 MHz ^1H NMR spectra during the decomposition of dibenzoyl peroxide in cyclohexanone at 110°C ; the decomposition starts at $t = 0$ [12].

The starting point was the observation that in the thermal decomposition of dibenzoyl peroxide using cyclohexanone as a solvent the resonance signal of the benzene produced temporarily appeared as an emission line (Figure 15.8). It could be ascertained that the resonance line came from of a diamagnetic species that accordingly must have had an inverse spin population. The theory of this phenomenon has been developed to the extent that the effect can be attributed to an intermediate radical pair, $[\text{R}^1\cdot, \cdot\text{R}^2]$, that exists within a solvent cage. Within the electron–nuclear spin system of this radical pair, singlet–triplet transitions lead to a perturbation of the Boltzmann distributions and thereby to a polarization of the nuclear spin system that finally manifests itself in the NMR spectrum of the diamagnetic product through emission or enhanced absorption. The most important aspects of the physical chemistry behind the CIDNP effect will be discussed in the following sections.

15.3.1

Energy Polarization (Net Effect)

On heating, benzoyl peroxide, dissolved in cyclohexanone, decomposes into a benzoyloxy and a phenyl radical by breaking the O–O bond, liberating CO_2 :



The phenyl radicals formed abstract a hydrogen atom from the solvent to yield benzene.

Let us now investigate the primary process more closely and in more general terms. After cleavage of the σ -bond, both radical fragments stay together for a certain time in the solvent cage and the spin orientation of the electrons that were paired in the precursor before this bond was broken corresponded to the singlet state. This radical pair, $[R^1\bullet, \bullet R^2]$, also called a *geminate pair*, is known as a *correlated radical pair*. Because decomposition takes place in the magnetic field B_0 , the singlet state of the radical pair in the moment of its formation by a thermal reaction can be described by a vector model as shown in Figure 15.9a. One electron spin (S_1) is oriented parallel, the other (S_2) anti-parallel with respect to the B_0 field. The phase angle between the spin vectors amounts to 180° and the total spin, therefore, is zero. Because of the interaction between B_0 and S_1 and S_2 , respectively, a precession of the electron spins around the field axis starts, which is completely analogous to the Larmor precession of the nuclear spins discussed in Chapters 2 and 8. Since the radicals $R^1\bullet$ and $\bullet R^2$ of the correlated pair have different structures, the Larmor precession frequencies of the electrons, ω_s , are also different. For ESR, ω_s is related to the Bohr magneton μ_B and the magnitude of the external magnetic field B_0 by Eq. (15.8), where g is a typical constant for a particular radical, the so-called *Landé- or g-factor*:

$$\omega_s = g \frac{\mu_B B_0}{h} \quad (15.8)$$

The difference between the Larmor frequencies for both radicals is thus:

$$\Delta\omega_s = \Delta g \frac{\mu_B B_0}{h} \quad (15.9)$$

With $\Delta g = (g_1 - g_2)$ we have $g_1 > g_2$ and $\omega_{s1} > \omega_{s2}$. During a short period of time – the lifetime of the geminate pair is 10^{-12} to 10^{-11} s – the phase angle between S_1 and S_2 changes because of the different Larmor frequencies ω_1 and ω_2 (Figure 15.9b).

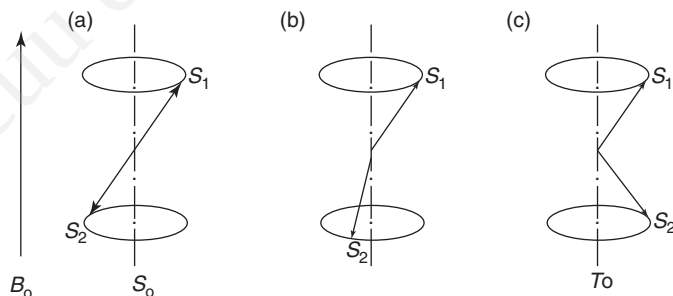


Figure 15.9 Spin states of a radical pair in the magnetic field B_0 : (a) singlet state S_0 with total spin 0; phase angle 180° ; (b) different precession frequencies of both electron spins lead to a change of the phase angle; (c) triplet state T_0 with total spin 1; the phase angle is now 0° .

Eventually, a situation is reached where both spins precess with the same phase (Figure 15.9c). This corresponds to the triplet state T_0 where the vector sum in the external field direction is zero and the addition of the x,y -components of S_1 and S_2 results in a total spin angular momentum of 1. The interaction of the electron spins with B_0 has thus induced a singlet–triplet transition, called *intersystem crossing*. The rate of intersystem crossing depends on Δg and, in turn, on $\Delta\omega_s$ and is faster the larger Δg is.

The situation is a little more complex if we consider scalar coupling between the electron spin and the protons with a coupling constant a . We assume coupling only for radical $R^{1\bullet}$. As a consequence and in analogy to scalar coupling between nuclear spins, the effective magnetic field at the electron of radical $R^{1\bullet}$ and therefore its Larmor frequency, changes. Since the protons can have two spin states, up or down, we anticipate the formation of two radical pairs $[R^{1\bullet}, \bullet R^2]$ with different Larmor frequencies ω_s for the electron at $R^{1\bullet}$. Induced by the different orientations of the nuclear spins and for positive a , in one pair B_0 is enhanced through the coupling (type I, $B_{\text{eff}} = B_0 + \frac{1}{2}a$, the nuclear spin is oriented in the field direction, ω_{s1} increases), and in the other pair B_0 is attenuated through the coupling (type II, $B_{\text{eff}} = B_0 - \frac{1}{2}a$, the nuclear spin is oriented against the field direction, ω_{s1} decreases). Because we assume the Larmor frequency of radical $\bullet R^2$ is constant (no coupling to nuclear spins), the result is $\Delta\omega_s(\text{I}) > \Delta\omega_s(\text{II})$ and radical pairs of type I reach the triplet state earlier than those of type II.

The life time of a radical pair is limited by diffusion and chemical reactions with the solvent and other compounds that are present. Furthermore, recombination is possible (Figure 15.10); however, only for the singlet state. Therefore, radicals $R^{1\bullet}$ of type II, which have a longer lifetime in the singlet state, will recombine more effectively than radicals $R^{1\bullet}$ of type I. The latter have a good chance to leave the radical pair by escape out of the solvent cage. Through diffusion processes these radicals come into contact with solvent molecules and the *escape* or *transfer* product is formed, for example, by hydrogen abstraction. The important point is that the protons of the former radical $R^{1\bullet}$ in the so-formed product have a non-equilibrium Boltzmann distribution because for radicals of type I the nuclear spin orientation was parallel to the external field B_0 . The nuclear spin system in the transfer product is thus polarized in such a way that the ground state has the higher population. Consequently,

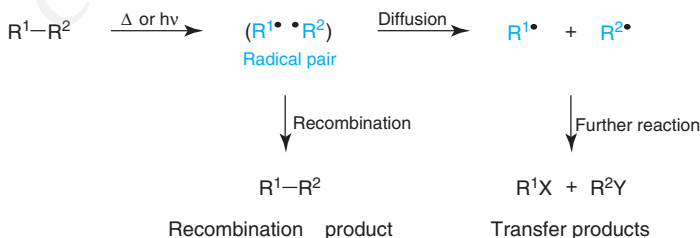


Figure 15.10 Possible reactions of a radical pair $[R^{1\bullet}, \bullet R^2]$ produced by thermolysis or photolysis of R^1-R^2 .

an NMR signal with enhanced absorption is observed at $\omega(^1\text{H})$. Later, this signal is transformed into the “normal” signal because of nuclear spin relaxation.

How does the result described so far compare with the experimental observation during the thermal decomposition of dibenzoyl peroxide where an emission signal for the transfer product benzene is observed? Above, we assumed $g_1 > g_2$, but for the benzoyloxy–phenyl radical pair $g_1 < g_2$ holds and Δg as well as $\Delta\omega$ [see Eq. (15.9)] is negative; g_1 is the Landé factor of the radical that yields the transfer product, in our case the phenyl radical. The proton–electron coupling a is again positive and for parallel proton spin orientation with respect to the external field B_0 as in radical pair type I, ω_{S1} increases but $\Delta\omega_S(\text{I})$ now decreases. For anti-parallel proton orientation, as in radical pair type II, the reverse changes occur: ω_{S1} decreases and $\Delta\omega(\text{II})$ increases. Thus $\Delta\omega_S(\text{I}) < \Delta\omega_S(\text{II})$ and radical pair I now has the longer singlet lifetime. The phenyl radicals of pair II with anti-parallel orientation of the proton spins yield the transfer product benzene. The protons in benzene are thus polarized such that the excited state is more populated and an emission signal, as shown in Figure 15.8, results.

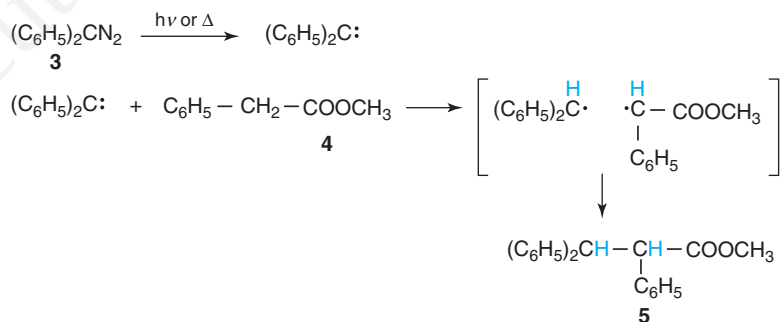
The surprising aspect of the CIDNP experiment, obviously, is the result that for the chemical reaction between phenyl radicals and cyclohexanone in the magnetic field B_0 a selection has taken place. Predominantly, phenyl radicals with a certain spin polarization have reacted. The benzoyloxy radical obviously disappeared by recombination or CO_2 loss, only a small signal indicated the presence of a transfer product in absorption ($g_1 > g_2$). This was later confirmed by the thermal decomposition of other peroxides.

15.3.2

Entropy Polarization (Multiplet Effect)

The effect described above is known as *energy polarization* or *net effect*. It is recognized by increased absorption or emission. In addition, a second phenomenon exists, which is known as *entropy polarization*.

During the thermal or photochemical decomposition of diphenyldiazomethane (3) in methyl phenylacetate (4) (Scheme 15.1) one observes, for example,



Scheme 15.1

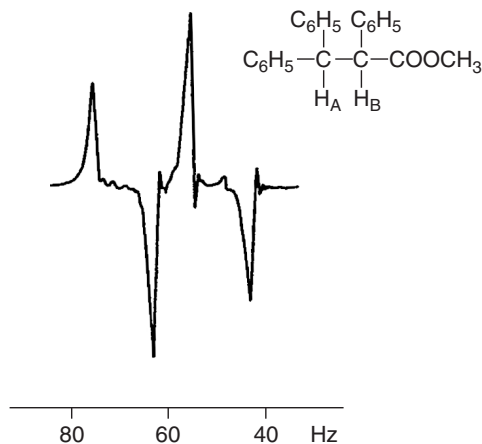


Figure 15.11 Spin-polarized AB-spectrum of the ethane protons H_A and H_B in methyl 2,3,3-triphenylpropionate after the thermal decomposition of diphenyldiazomethane in methyl phenylacetate at 140°C [13].

the lines of the AB-system of the tertiary protons in the product methyl 2,3,3-triphenylpropionate (**5**) simultaneously in absorption and emission (Figure 15.11).

This *multiplet effect* results apparently from a situation where the nuclear spin levels of the AB system with the total spin $m_T = 0$ are more strongly populated than those with total spin $m_T = +1$ or -1 . To understand this result we note that the Larmor frequencies of the electron spins of many organic radicals because of similar g -factors are practically identical. This is also true in the present case. Singlet–triplet interchange can then be achieved only if coupling between nuclear and electron spins induces a $\Delta\omega_s$ for the radicals in question.

As is known from the results of other investigations, diphenylcarbene formed by thermal decomposition of diphenyldiazomethane exists in the triplet state. The radical pair $[R^{\bullet 1}, \bullet R^2]$, formed by proton abstraction from **4**, therefore, also exists in the triplet state. For an AX nuclear spin system we consider the four eigenstates, $\alpha\alpha$, $\alpha\beta$, $\beta\alpha$, and $\beta\beta$. If the ESR hyperfine coupling constants $\mathbf{a}$ for both radicals are also identical, the effect of spin coupling between nuclei and electrons on the Larmor frequencies of the electrons in the radical pairs is eliminated for radical pairs with the proton states $\alpha\alpha$ and $\beta\beta$, respectively, since both radicals are affected in the same way. These radical pairs thus stay in the triplet state and have a good chance to yield after diffusion escape products.

For radical pairs with the nuclear spin combinations $\alpha\beta$ or $\beta\alpha$, on the other hand, a Larmor frequency difference $\Delta\omega_s$ is induced because for the state $\alpha\beta$ we have $\omega_1 = +\frac{1}{2}\mathbf{a}$ and $\omega_2 = -\frac{1}{2}\mathbf{a}$ while for the state $\beta\alpha$ the value $\frac{1}{2}\mathbf{a}$ is used with different sign. Thus, in both cases we have $\Delta\omega > 0$. Radicals of this pair can thus reach a singlet spin orientation and recombine after the triplet–singlet transition and cage recombination to **5** competes with diffusion. In the cage product the nuclear spins then populate the levels $\alpha\beta$ and $\beta\alpha$, respectively. The resulting spectrum,

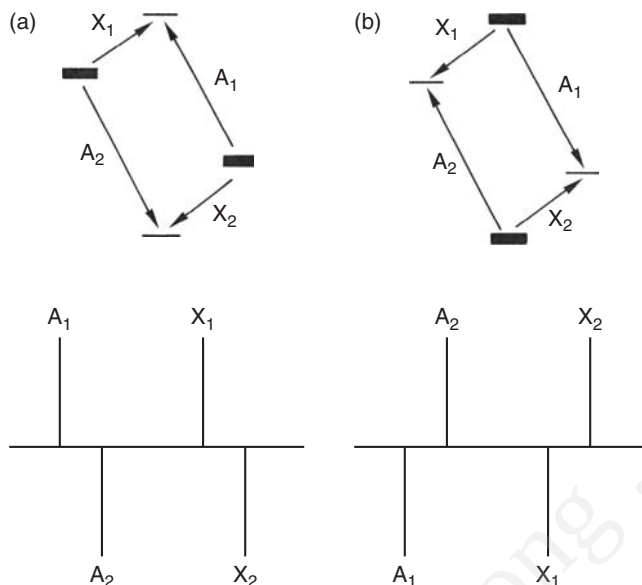


Figure 15.12 Entropy polarization in the AX system: result for (a) a triplet radical pair and (b) a singlet radical pair. The relative population of the nuclear spin levels is indicated by the light or heavy bar.

shown in Figure 15.11, is drawn again schematically in Figure 15.12a together with the corresponding Boltzmann distribution in the energy level system for the AX system.

Figure 15.12b shows, on the other hand, the result of an analogous reasoning for the case where a radical pair is formed in the singlet state. The reader may easily convince himself that in the recombination product the nuclear spin levels $\alpha\alpha$ and $\beta\beta$ with total spin $m_T = \pm 1$ should then be more strongly populated.

CIDNP spectroscopy is thus based on the finite lifetime of the radical pair during which spin–spin interactions between electrons and nuclei induce changes of the Larmor frequencies of the electrons. Since recombinations, which means bond formations, can arise only out of singlet states and since intersystem crossing rates can differ, there is a selection for the consecutive reactions that results in non-equilibrium Boltzmann distributions for the nuclear spins in the products.

Exercise 15.1

Label the electrons of the species shown in the center line of Scheme 15.1 and the electrons of the C–H bond of the radicals with their spin orientation [up ($\uparrow$) or down ($\downarrow$)] and convince yourself that the radical pair is in the triplet state.

15.3.3

The Kaptein Rules

From our discussion it has become clear that the CIDNP effect is an important tool for investigations of reaction mechanisms in radical and photochemistry. To interpret the experimental results correctly, a good knowledge of the theoretical background is necessary. Several important questions can, however, already be answered by a simple interpretation of the observed spectra on the basis of the Kaptein rules. According to these rules the sign of the expected polarization is calculated as a product of the signs of several factors that characterize the properties of the radicals and products. The effect of energy polarization (net effect, + for absorption, – for emission) is then described by the following equation:

$$\Gamma_N = \mu \times \varepsilon \times \Delta g \times a_i \quad (15.10)$$

and for entropy polarization (multiplet effect, + for the relation emission/absorption, – for absorption/emission) we have:

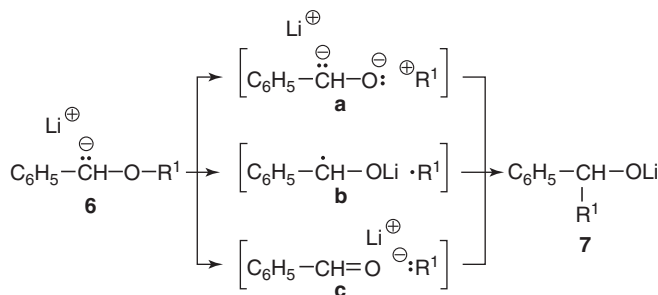
$$\Gamma_M = \mu \times \varepsilon \times a_i \times a_j \times J_{ij} \times \sigma_{ij} \quad (15.11)$$

The physical constants that appear in these equations, and which are only used with their sign, have the meaning given below.

μ	Characterizes the spin state of the correlated radical pair: + for a triplet precursor; – for a singlet precursor
ε	Characterizes the product: + for a recombination product; – for a transfer product
Δg	Stands for the sign of the difference $g_i - g_j$ of the Landé factors of the corresponding radicals where g_i belongs to the radical of the observed nucleus X_i
a_i	Sign of the ESR hyperfine coupling constant of radical fragment $R_i^\bullet$ that contains X_i
J_{ij}	Sign of the NMR coupling constant
σ_{ij}	Characterizes situations where the nuclei i and j are in the same or in different radicals: + if i and j are in the same radical; – if i and j are in different radicals
Γ_N	+ enhanced absorption (A); – emission (E)
Γ_M	+ high-frequency signal(s) of a multiplet show E, whereas the low-frequency signal(s) show A (E/A); –A/E

The signs of a and J_{ij} must be determined independently by ENDOR (electron–nuclear double resonance) and NMR investigations, which are not discussed here.

As can be easily understood, only one unknown factor can be determined through the application of Eqs (15.10) and (15.11). For example, if for a process where the multiplet effect is observed the signs of a , J_{ij} , and σ_{ij} are known, and the spin state of the correlated radical pair can be derived. Very often this is an important piece of information for chemistry. For the formation of **5** one obtains the following result. The ESR hyperfine coupling constants of the radicals involved as well as the vicinal ^1H , ^1H coupling constants of the product have positive signs, the nuclei i and j stem



Scheme 15.2

from different radical fragments ($\sigma_{ij} = -1$), and the experiment shows the relation A/E ($\Gamma_M = -1$). It then follows $(-) = (\mu)(+)(+)(+)(+)(-)$; μ is, therefore, positive, and the educt exists in the triplet state.

Application of the CIDNP effect is not restricted to photolysis or thermolysis reactions. CIDNP effects have also been observed during reactions of organolithium compounds and were used to study reaction mechanisms in organometallic chemistry. For example, the Wittig ether rearrangement, in which an α -methylated alkyl benzyl ether (6) is transformed into the corresponding alkyl phenyl carbinol (7), can be rationalized using either one of two ionic mechanisms (a, c) or a radical pair mechanism (b) (Scheme 15.2). While the path (a) could be excluded relatively easily on the basis of various experimental data, it was considerably more difficult to decide between the alternatives (b) and (c) using conventional methods. The observation that in the rearrangement of lithium *t*-butyl benzyl ether the signal of the tertiary proton in the corresponding lithium 1-phenyl-2,2-dimethylpropanolate appeared as an emission signal was a direct indication that the reaction can proceed via path (b). Whether alternative mechanisms, in our case (c), can be excluded completely needs quantitative evaluation of the experiment. The observation of a CIDNP effect alone is not a sufficient criterion for the intermediacy of radicals. Because signal enhancements by a factor of 10 – 10^3 are possible it may arise from a side-reaction.

15.4

Diffusion-Controlled Nuclear Magnetic Resonance Spectroscopy – DOSY

15.4.1

Measurement of Diffusion Coefficients

In Chapter 9 (p. 326) we introduced field gradients and the option of gradient pulses for the selection of coherence pathways. There it was assumed that the changes of the Larmor frequencies initiated by a gradient pulse $+\Delta G_z$ along the z -axis can be eliminated by application of a second pulse $-\Delta G_z$ of opposite polarity. This is, however, only true if the time interval Δt between the two gradient pulses is very

short, of the order of a few milliseconds or less. Diffusion processes could, therefore, be neglected and each spin then conserved its z -coordinate. If Δt increases, the translational motion of the molecules in the liquid, also called *self-diffusion*, can change the position of the spins on the z -axis and the consequence in an inhomogeneous field is that the change of the Larmor frequency caused by the first gradient pulse cannot be neutralized. Because the total external magnetic field at a position r is given by $B(r) = B_0 + \Delta G(r)$, where $\Delta G(r)$ is the gradient strength at position r , the first gradient produces along the z -axis a position-dependent phase angle:

$$\Phi(z) = \gamma B(z)\delta \quad (15.12)$$

where δ is the gradient pulse width that encodes the spins of the sample and $B(z)$ is the magnetic field at a certain z -coordinate. If after a short delay a second gradient pulse with a polarity opposite to that of the first pulse is applied, not all spins can be refocused because for those that changed their position on the z -axis through diffusion the phase angle and the pulse strength do not match. Consequently, the detected signal is attenuated (Figure 15.13).

This situation can be used to advantage for the measurement of diffusion coefficients. A slight modification of the spin echo sequence (cf. p. 248) leads to the PGSE (*pulsed gradient spin echo*) experiment (Figure 15.14) that was introduced in 1965 by E.O. Stejskal and J.E. Tanner. They showed that the addition of gradient pulses before and after the 180° pulse of the spin echo sequence allows us to measure diffusion coefficients of small molecules in solution.

After the first 90° pulse a gradient pulse, $\Delta G_z(1)$, applied along the z -direction, induces the position-dependent increase of the Larmor precession of the spins in the sample, for ^1H NMR this is the protons of an organic compound. This leads to a defocusing process for the transverse magnetization. During the diffusion time Δ ,

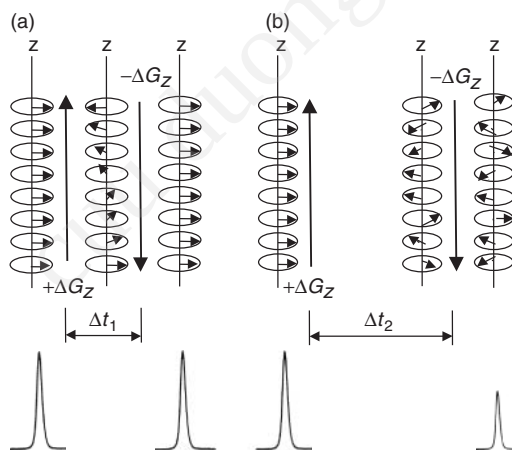


Figure 15.13 Effect of two field gradients of opposite polarity on an ensemble of spins: (a) without diffusion (small Δt_1); the spins are refocused and the signal is recovered; (b) with diffusion; $\Delta t_2 > \Delta t_1$ and refocusing of the spins is incomplete, the signal is attenuated or even completely destroyed.

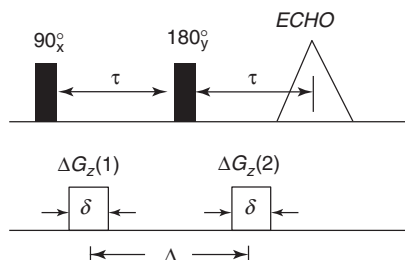


Figure 15.14 Pulse sequence of the pulsed gradient spin echo (PGSE) experiment [14].

which is of the order of 15–20 ms, a number of spins change their position on the z -axis. A 180°_y pulse refocuses T_2 effects and changes the coherence order so that the second gradient pulse, $\Delta G_z(2)$, starts to refocus the spins and leads finally to the spin echo of reduced intensity. In a series of experiments with increasing gradient strength ΔG or gradient length δ , the signal intensity, I_E , decreases exponentially according to:

$$I_E = I_0 \exp(-D\Delta t' \gamma^2 \delta^2 \Delta G^2) \quad (15.13)$$

or:

$$\ln(I_E/I_0) = -D\Delta t' \gamma^2 \delta^2 \Delta G^2 \quad (15.14)$$

where D ($\text{m}^2 \text{s}^{-1}$) is the diffusion coefficient, δ (ms) the pulse width, ΔG (T m^{-1}) the pulse amplitude, γ the gyromagnetic ratio, and $\Delta t' = \Delta t - \delta/3$ the delay where diffusion takes place with $\delta/3$ as correction for diffusion during the pulses. From the slope of a linear plot of $\ln(I_E/I_0)$ versus ΔG^2 , where γ and δ are constants, one obtains the diffusion coefficient D . An example of a measurement series with the PGSE sequence is shown in Figure 15.15.

With this widely used technique diffusion coefficients can be successfully measured for a large variety of molecules. Apart from protons, other nuclei like ^{31}P or ^{29}Si can be used to monitor self-diffusion. An often-utilized alternative is the PFGSTE (pulsed field gradient stimulated echo) sequence (Figure 15.16), which is based on the Hahn stimulated spin echo experiment that works with three 90° pulses. It is suitable for the measurement of very small diffusion coefficients and for diffusion of spin–spin coupled systems.

In this sequence, the second 90°_x pulse turns the y -components of the magnetization to the z -axis and the third pulse turns them back. The x -components are eliminated by the phase cycle or by spoil pulses. Notwithstanding that half of the magnetization is thereby lost the sequence has the advantage over the PGSE experiment that the magnetization is stored along the z -axis during the diffusion interval Δ and thus is only subject to T_1 relaxation. This is important for measurements with macromolecules where $T_1 : T_2 \approx 1 : 10$.

Many aspects of molecular structure like weight, size, or shape may be correlated with the diffusion coefficients, but aggregation and molecular interactions can also be studied. An example from supramolecular chemistry is shown in

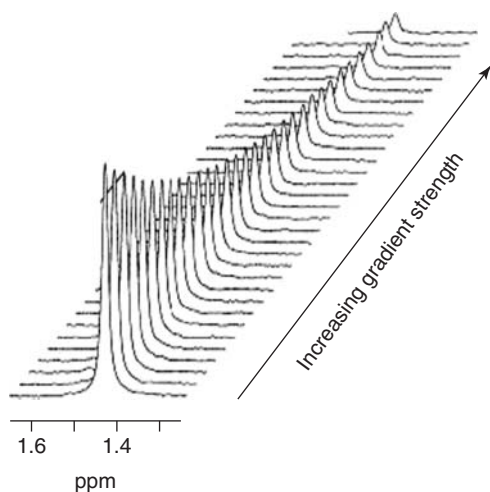


Figure 15.15 ^7Li NMR PGSE experiment for the tetrameric aggregate of *n*-butyllithium in tetrahydrofuran (Reimer, C. and Günther, H., unpublished) that yielded a diffusion coefficient D of $8.63 \pm 0.06 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}$ [15].

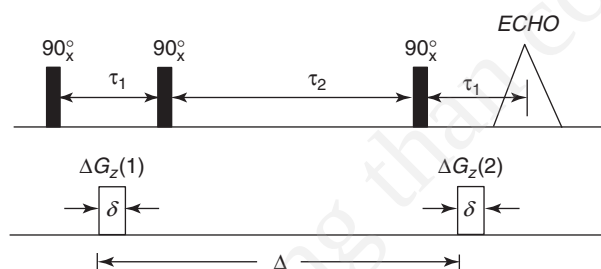


Figure 15.16 Pulse sequence for the PFGSTE experiment.

Figure 15.17 (p. 616). More sophisticated pulse sequences have been developed to remove artifacts and instrumental shortcomings like the so-called eddy currents.¹⁾

15.4.2

Mixture Analysis by Diffusion-Ordered Spectroscopy (DOSY)

An important aspect of diffusion-controlled NMR is the development of a pseudo-2D experiment called DOSY (*diffusion-ordered spectroscopy*). For a mixture of different compounds the data from a PGSE experiment can be used to construct a two-dimensional plot where the *x*-axis gives the chemical shifts (ppm) and the *y*-axis the diffusion coefficients D of each signal. Since diffusion of a certain component of the mixture affects all spins of this compound equally, their NMR signals are lined up at the same D value. Spectral assignments can then be made and the result

1) These are currents induced in conducting structures by magnetic field changes; they distort the gradient waveform shape and are especially disruptive in NMR imaging experiments.

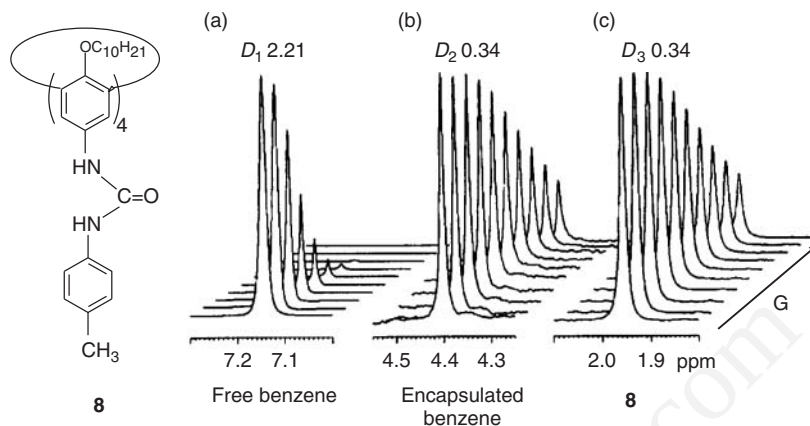


Figure 15.17 Detection of benzene encapsulated in the supramolecular dimer of the calix[2]arene **8**: (a) signal of “free” benzene; (b) signal of encapsulated benzene; (c) one signal of the dimer. The diffusion coefficients shown above the signals are those of free benzene, encapsulated benzene, and the dimer, respectively; the finding $D_1 > D_2 = D_3$ clearly demonstrates that benzene is encapsulated [16].

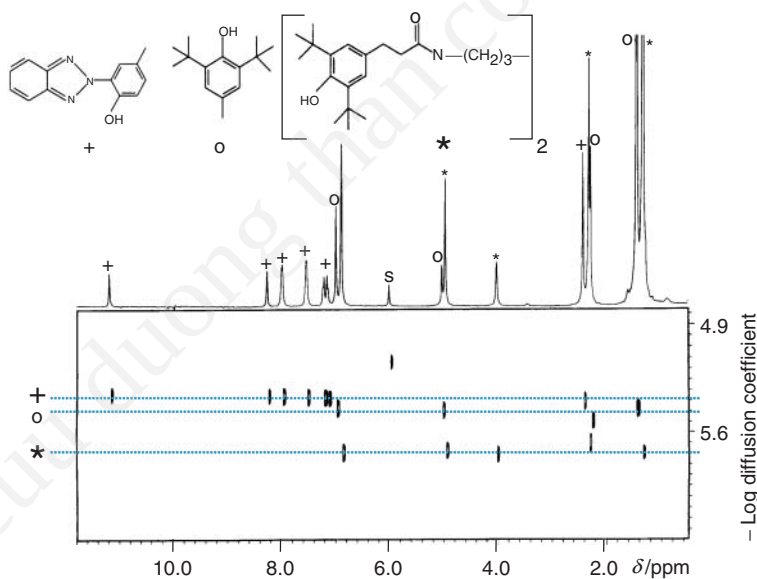


Figure 15.18 ^1H DOSY spectrum of a mixture of polymer additives; S = solvent [17].

is similar to the information one gets from HPLC-NMR²⁾ where the spectra of chromatography fractions are recorded separately. However, PGSE is much simpler because it does not require a physical separation of the mixture (Figure 15.18).

2) HPLC-NMR: combination of high-power liquid chromatography with NMR; one of the so-called “hyphenated” techniques.

15.5

Unconventional Methods for Sensitivity Enhancement – Hyperpolarization

In our introduction to NMR we have described several times the efforts made to increase NMR sensitivity. Important steps in this direction – that led to an improvement not imagined in the early days – were the introduction of high magnetic fields B_0 , spectral accumulation by Fourier transform NMR, and the applications of the nuclear Overhauser effect. Nevertheless, additional techniques have been developed in recent years that allow still higher sensitivity gains, even if the area of their application is more limited than that of the methods listed above. The following sections introduce the principles of some of these methods.

15.5.1

Hydrogenation Reactions and the Effect of *para*-Hydrogen

During the hydrogenation reaction of tricobalt-alkylidyne complexes performed in 1981 strange signals for the product molecules – anti-phase and intensity enhanced – were observed. This discovery was interpreted as resulting from a CIDNP effect and free radicals were assumed as intermediates. A few years later, however, it was recognized that these peculiar signals did not result from a CIDNP effect but originated from the action of *para*-hydrogen ($p\text{-H}_2$).

It is well known that the hydrogen molecule, H_2 , exists as an approximately 3:1 mixture of two nuclear spin isomers: *ortho*-hydrogen ($o\text{-H}_2$) with a total nuclear spin of 1 ($\uparrow\uparrow$) and *para*-hydrogen ($p\text{-H}_2$) with a total nuclear spin of zero ($\uparrow\downarrow$). With $I = 0$, $p\text{-H}_2$ shows no Zeeman interaction with B_0 and yields no NMR signal. The one observed for H_2 at about δ 4.5 in a ^1H spectrum results exclusively from $o\text{-H}_2$. The nuclear wavefunctions for the two species are thus a triplet with the symmetric functions $\alpha\alpha$, $1/\sqrt{2}(\alpha\beta + \beta\alpha)$, and $\beta\beta$ for $o\text{-H}_2$ and a singlet with the anti-symmetric function $1/\sqrt{2}(\alpha\beta - \beta\alpha)$ for $p\text{-H}_2$. These are the familiar functions that we introduced for the spin states of the A_2 system (p. 162 ff.).

If during a hydrogenation reaction performed inside the magnet in the field B_0 a $p\text{-H}_2$ molecule adds to a triple bond, say a substituted-acetylene of the general structure $\text{R}_1\text{--C}\equiv\text{C--R}_2$, the chemical shift of the added protons is different and they form an AX spin system. The energy level diagram of the AX system was shown on page 44 and is again reproduced in Figure 15.19a together with the nuclear spin functions. The spectrum observed results from the transitions 1, 2, 3, and 4 and the intensities of the signals are determined by the population differences between the spin states in thermal equilibrium. These depend on the B_0 field strength, but are in any case rather small (see p. 19). For the AX system that is formed by the addition of $p\text{-H}_2$ to the triple bond, however, a drastic increase in population results for states 2 and 3. Only these states become populated when the anti-symmetric wave function $1/\sqrt{2}(\alpha\beta - \beta\alpha)$ of

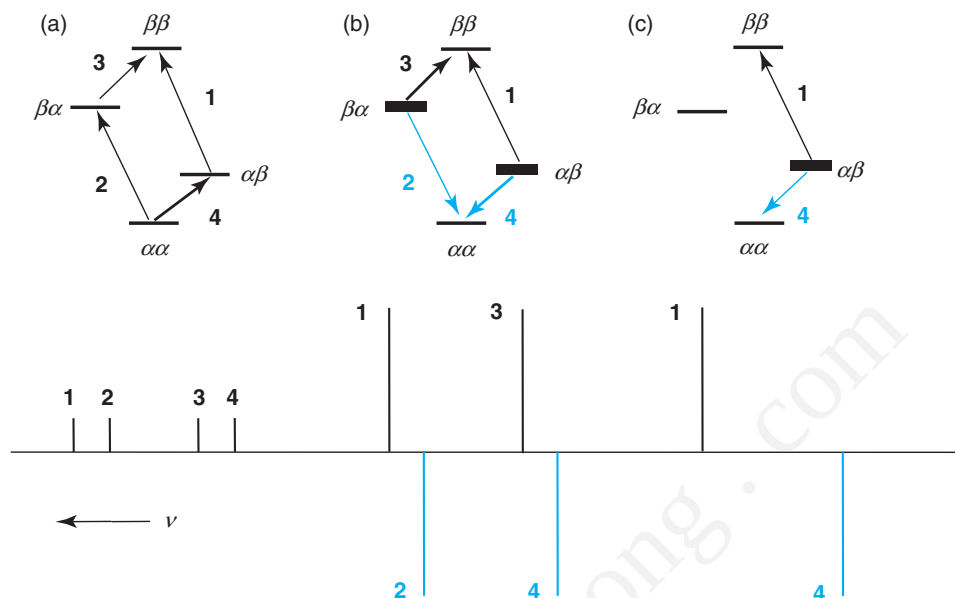


Figure 15.19 Energy level diagram with relative populations of an AX system with positive J_{AX} : (a) standard situation for thermal equilibrium; (b) PASADENA; (c) ALTADENA.

$p\text{-H}_2$ is transformed into $\alpha(1)\beta(2)$ and $\beta(1)\alpha(2)$ of the two individual hydrogen atoms 1 and 2 that are added to the triple bond. This leads in turn to enhanced absorption and emission (Figure 15.19b) and the intensity enhancement factor may exceed 10^3 . The acronym PASADENA (*para-hydrogen and synthesis allow dramatically enhanced nuclear alignment*) was coined for this experiment, but the more general acronym PHIP (*para-hydrogen induced polarization*) is used today. After a short period of time, about 10–20 s, the non-equilibrium magnetization disappears due to spin–lattice relaxation processes and the effect is lost.

A ^1H PHIP spectrum observed for the hydrogenation of phenylacetylene by $p\text{-H}_2$ is shown in Figure 15.20a, while Figure 15.20b shows a spectrum observed for hydrogen ligand exchange in the ruthenium complex **9**. This all-*cis* isomer fulfills the requirement of chemical non-equivalence of the two added hydrogens in the product that breaks the symmetry of the original A_2 spin system of $p\text{-H}_2$. Interestingly, a small 60-fold signal enhancement was also observed for the *trans-cis-cis* isomer **10** and was attributed to the presence of molecules with one ^{13}C O ligand in natural abundance. Full labeling proved this interpretation to be correct by making the species fully $p\text{-H}_2$ active due to the second-order spin system that was created. The symmetry breaking by the presence of carbon-13 has also been observed in more complicated cases.

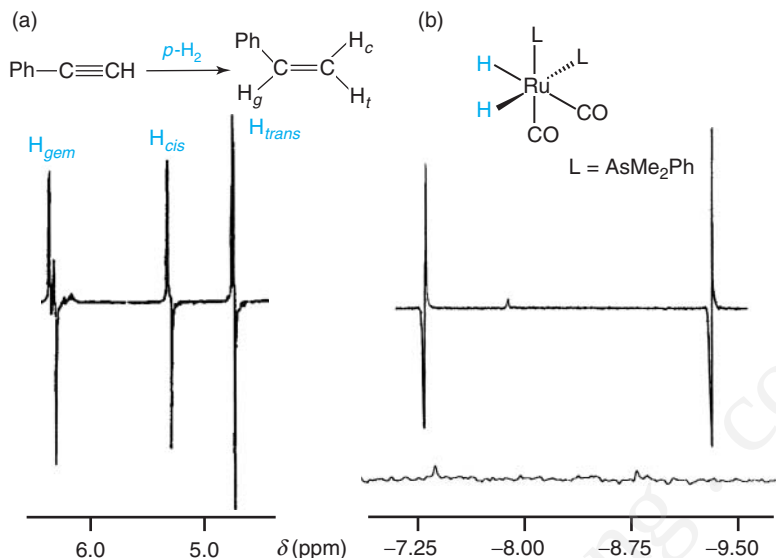
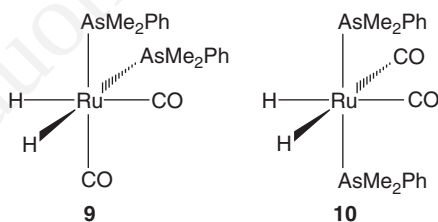


Figure 15.20 (a) Partial ^1H PHIP spectrum for the hydrogenation of phenylacetylene with $p\text{-H}_2$ catalyzed by $\text{Ru}(\text{BINAP})(\text{OAc})_2$ in CD_3OD at 53°C (Adapted with permission from Reference [18]. Copyright 1991 American Chemical Society); (b) 500 MHz ^1H PHIP spectrum for the hydrogen ligand exchange with free $p\text{-H}_2$ for the ruthenium complex $\text{ccc-RuH}_2(\text{CO})_2(\text{AsMe}_2\text{Ph})_2$ obtained at 323 K; top trace 1 scan employing a 45° pulse in the

presence of 3 atm $p\text{-H}_2$, the signals are 1035-fold enhanced; bottom trace, 34 scan spectrum with normal hydrogen (Reprinted from Reference [19]; Copyright 1999. With permission from Elsevier); please note the e/a ratio of the signals that results from the negative sign of the geminal $^1\text{H}, ^1\text{H}$ coupling constant, which leads to an exchange of lines 1 and 2 as well as 3 and 4 in the diagram of Figure 15.19b.



Another experiment with $p\text{-H}_2$ was also described: ALTADENA (*adiabatic longitudinal transport after dissociation engenders nuclear alignment*). If the hydrogenation is performed outside the magnet and the sample is then transferred adiabatically into the magnet, a completely different spectrum results. For each proton site only *one* signal is now observed. One proton shows enhanced absorption, the other one emission. Apparently, only one of the two spin states $\alpha(1)\beta(2)$ or $\beta(1)\alpha(2)$ is overpopulated, depending on the relative sign of the scalar coupling constant J and the chemical shift difference $\Delta\omega$ (Figure 15.19c). Since the new spin system of the product is formed at zero field, both protons have the same chemical shift and thus constitute an A_2 system. Using density matrix

theory, one can show that the singlet state of $p\text{-H}_2$ is correlated only with the $\alpha\beta$ or $\beta\alpha$ state of the weakly coupled AX system of the product.

From the two effects described above, the PHIP effect is of more general importance. It has been applied for the direct detection of reaction intermediates and their kinetic monitoring and for efficient spin state synthesis. The $o\text{-H}_2$: $p\text{-H}_2$ ratio of 3:1 can be changed in favor of $p\text{-H}_2$ to about 1:1 by lowering the temperature to 77 K and by using a catalyst like iron oxide or charcoal. Because the reverse reaction, $p\text{-H}_2 \rightarrow o\text{-H}_2$, is symmetry-forbidden, the lifetime of the $p\text{-H}_2$ excess approaches one year. For the PHIP experimental set-up, the sample can be prepared with the hydrogen saturated solution at low temperature (to avoid reaction) outside the magnet and frozen. After transfer into the magnet thawing starts the reaction and spectra are run continuously. Alternatively, hydrogen gas can be inserted into the NMR tube with the sample already within the magnet.

PHIP spectra are best recorded with 45° pulses, as can be rationalized with the help of the product operator approach. The initial magnetization of the new AX system is given by $2\hat{I}_z(A)\hat{I}_z(X)^3$ and develops after a 45° x-pulse according to Eq. (15.15):

$$2\hat{I}_z(A)\hat{I}_z(X) \xrightarrow{45^\circ} 2\hat{I}_z(A)\hat{I}_z(X)\cos^2\alpha + 2\hat{I}_y(A)\hat{I}_z(X)\sin\alpha\cos\alpha + 2\hat{I}_z(A)\hat{I}_y(X)\cos\alpha\sin\alpha + 2\hat{I}_y(A)\hat{I}_y(X)\sin^2\alpha \quad (15.15)$$

The first and the last term correspond to longitudinal scalar order and to double quantum magnetization, respectively; both are not observable. The remaining terms correspond to the observable anti-phase A- and X-magnetization that has its maximum for $\alpha = 45^\circ$. This differs from the situation for the conventional AX system that starts with $\hat{I}_z(A) + \hat{I}_z(X)$ and the maximum magnetization is observed with a 90°_x pulse:

$$\hat{I}_z(A) + \hat{I}_z(X) \xrightarrow{90^\circ} \hat{I}_x(A)\cos\alpha + \hat{I}_x(X)\cos\alpha + \hat{I}_y(A)\sin\alpha + \hat{I}_y(X)\sin\alpha \quad (15.16)$$

The special situation that exists for the starting magnetization of pulse experiments with $p\text{-H}_2$ has to be considered carefully, especially when multiple pulse sequences are used. Using field gradients, it was possible to construct a pulse sequence that shows only signals of $p\text{-H}_2$ enhanced nuclei, while those from spin states in thermal equilibrium are suppressed.

Finally, a limitation of the general utility of the PHIP experiment might be seen in its exclusive application to hydrogenation reactions. More recent experiments have shown, however, that the polarization can be transferred to a substrate via temporary association with a labile transition metal complex, formed by the reaction with $p\text{-H}_2$. Figure 15.21 shows the principle of this method. Not only the protons of various substrates showed enhanced signals but also the ^{13}C and ^{15}N nuclei present in natural abundance.

- 3) The product operator $2\hat{I}_z(A)\hat{I}_x(X)$ characterizes non-equilibrium population without observable magnetization and thus the anti-parallel orientation if the $p\text{-H}_2$ spins.

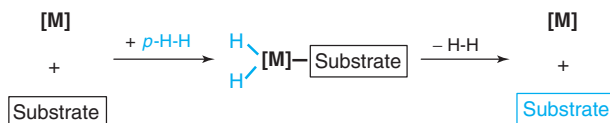


Figure 15.21 $p\text{-H}_2$ induced hyperpolarization of nuclei in a substrate using a transfer process from a transition metal complex [20].

15.5.2

Optical Pumping – Xenon-129 NMR

The French physicist Albert Kastler showed in 1948 that spin polarization of circularly polarized photons can be transferred to electron and nuclear spins of atoms. He called this phenomenon *optical pumping* and it was found that the effect can be observed especially for the atomic vapor of alkali metals. In particular, rubidium proved later to be a candidate of practical value. It is vaporized at modest temperatures where chemical reactions with the glass container are not a problem and several types of lasers can be used to provide the photons at the resonance line of 794.7 nm. A weak static magnetic field is applied to the sample cell to prevent spin depolarization by stray fields.

The usefulness of this effect for NMR was recognized when it was found that a considerable fraction of the electron spin angular momentum of polarized alkali atoms could be transferred to the nuclei of noble gases like helium, krypton, and xenon by exchange collisions. While Kastler in his original experiments could only use optical sources of a few hundred microwatts, today several watts of laser light are easily available for optical pumping experiments. Thus, for the resonance line of rubidium, one watt radiation yields 4×10^{18} photons per second that in turn yield the same number of polarized electron spins. If the rubidium vapor and the noble gas are in the same container, nearly 10% of the electron spin polarization can be transformed by spin exchange during collisions into nuclear spin polarization of the noble gas. The lifetime of this nuclear polarization depends on the spin–lattice relaxation time, T_1 , of the noble gas, which for spin $\frac{1}{2}$ nuclei like ^{129}Xe or ^3He can be hours or longer. As a result, of the order of 10^{21} polarized spins can be produced. Enhancement factors for the ^{129}Xe NMR signal as large as 2×10^4 have been observed.

Xenon-129, with $I = \frac{1}{2}$ and a natural abundance of 26.44%, has a large chemical shift range of about 7500 ppm, from xenon gas at low frequency to xenon hexa-oxide, XeO_6^{4-} (Figure 15.22). Xenon has an extremely polarizable electron cloud that makes it a valuable and sensitive probe for local atomic interactions. ^{129}Xe gas NMR shows a distinct pressure and temperature dependence and is used

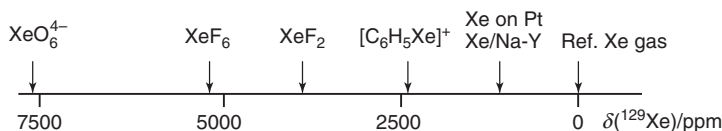


Figure 15.22 Chemical shift scale for xenon-129.

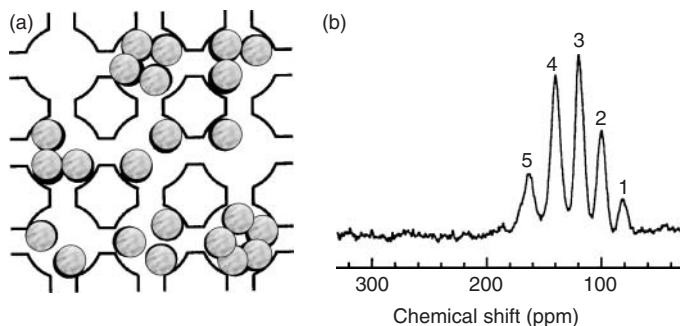


Figure 15.23 Schematic diagram of xenon atoms distributed within the cages of microporous Na-A zeolite (a) and room temperature ^{129}Xe NMR spectrum of the zeolite occluded with xenon at 523 K and 40 atm (b); the chemical shift of the signals is related to the number of xenon atoms in the cages and is at highest frequency for the highest occupation with five xenon atoms (Reprinted from Reference [21]; Copyright 1994; with kind permission of Springer Science+Business Media).

especially for studies of surfaces and microporous materials where small pores lead to high-frequency shifts, presumably as a consequence of steric crowding. For example, the xenon distribution in zeolites has been studied and different ^{129}Xe NMR signals were observed for micropores containing different numbers of xenon atoms (Figure 15.23). The exchange of xenon atoms between individual cages can be detected with ^{129}Xe 2D-EXSY spectroscopy; $\delta(^{129}\text{Xe})$ is also sensitive to the pore size of mesoporous silica (Figure 15.24a). The diffusion of xenon between the porous network and the intergranular space can again be documented by ^{129}Xe 2D-EXSY spectroscopy (Figure 15.24b). These shift changes are caused by the paramagnetic contribution to the shielding constant σ , which is strongly influenced by van der Waals interactions. All these NMR investigations profit from

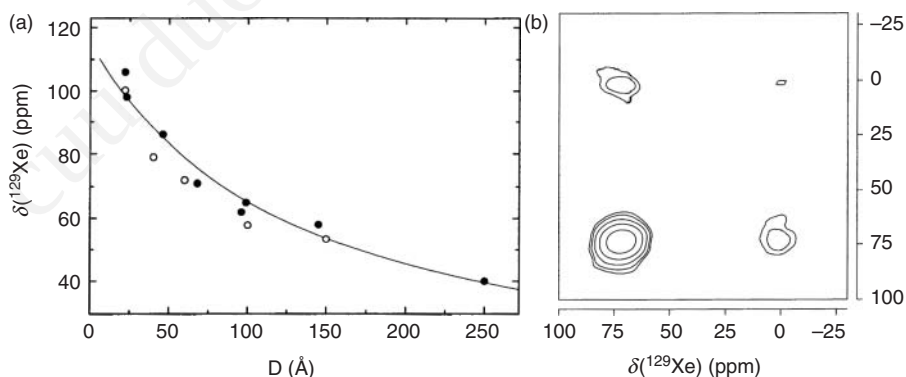


Figure 15.24 (a) Dependence of $\delta(^{129}\text{Xe})$ on the pore diameter D of mesoporous silica (● [22]; ○ [23]); (b) 110.68 MHz ^{129}Xe 2D-EXSY spectrum of xenon adsorbed at annealed (500°C) silica 60, mixing time 200 ms; the cross peaks indicate exchange of xenon between pores and inter-granular space [23].

the possibility of using polarized xenon gas, which is even applied in medicine for NMR imaging during lung examinations. Furthermore, a promising application is possible through cross-polarization experiments with other nuclei thereby enhancing, for example, carbon-13 signals.

15.5.3

Dynamic Nuclear Polarization

In Chapter 10 (p. 341) we introduced the *original Overhauser effect* where, by means of an electron-nuclear *double resonance* (ENDOR) experiment, spin polarization is transferred from unpaired electrons to nuclei. The nuclear Boltzmann distribution is then governed by the much larger energy difference that exists for the electrons between excited and ground state if compared to the nuclear spins. For technical reasons, however, this experiment had limited applications in chemistry and its primary importance was that it paved the way for the nuclear Overhauser effect, one of the major techniques in modern NMR.

More recently, however, the principle of the original Overhauser effect – generally known today as *dynamic nuclear polarization* (DNP), which may be seen as a combination of ESR and NMR – has received more attention and techniques for solid state and solution NMR are presently developed that make use of the polarization transfer from electron spins to nuclear spins governed by the ratio γ_e/γ_n with $\gamma_e > \gamma_n$. In liquids the effect is based on relaxation that follows the electron excitation, while in solids electron transitions are directly effected by microwave irradiation. In both cases, nuclear polarization starts with the nuclei that are in close proximity to an unpaired electron, provided, for example, by an organic radical. To observe the desired effect of signal enhancement for the complete sample, the polarization must be transported from the initial polarization zone to the other nuclei. The appropriate mechanism for this process in solids is spin diffusion and in the liquid it is translational diffusion.

Because of different experimental conditions and mechanistic variations DNP is not a simple technique for general applications. In solid state NMR experiments the so-called cross effect (CE) is used at low temperatures (typically 90 K) with high-power microwave irradiation of the electron resonance preceding magic-angle spinning (MAS) solid state NMR of the polarized sample (SS-DNP). Another method, carried out at even lower temperatures (<1.5 K) than those used for SS-DNP, is called dissolution dynamic nuclear polarization (D-DNP). The polarized NMR sample is thereby obtained by dissolving the material after irradiation in an appropriate liquid that is immediately transferred to the NMR spectrometer for measurement. Finally, the term Overhauser dynamic nuclear polarization (O-DNP) is used for experiments that are carried out entirely in the liquid phase.

For SS-DNP, mostly trityl radicals (Figure 15.25) that have a narrow ESR line are used as polarization source, and irradiation saturates the forbidden W_0 and W_2 transitions in the scheme given in Figure 10.1, p. 342. The resulting nuclear polarization is thus not caused by increased W_0 relaxation as in the liquid. More complicated situations (biradicals, electron–electron spin–spin coupling), which

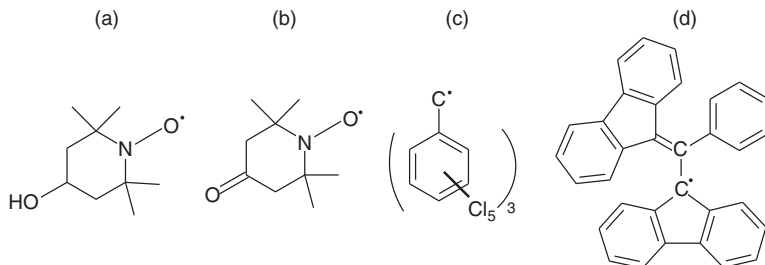


Figure 15.25 Some polarizing agents for DNP (nitroxide and trityl radicals):

(a) 4-hydroxytetramethylpiperidine oxide (TEMPOLE); (b) TEMPONE;
 (c) tri(perchlorophenyl)methyl; (d) difluorenyl(phenyl)methane.

we do not describe further, are known as thermal mixing (TM). Present-day work is tries to establish SS-DNP in combination with MAS as an advanced method for the study of polymers and biomolecules. Signal enhancements have been observed not only for protons but also for carbon-13, either directly or by cross polarization from protons. In addition, cross polarization from deuterons to ^{13}C was possible and very effective due to the large ratio $\gamma_{\text{e}}/\gamma_{\text{D}} = 4300$. High-field spectrometer combinations with 263 GHz for ESR and 400 MHz for NMR (^1H) have been used.

In D-DNP the extremely low temperature used for polarizing the sample has the additional advantage that the DNP effect is combined with a large Boltzmann effect [cf. Eq. (2.11), p. 19] and overall enhancements of the order of 10^4 have been observed. To prepare the liquid sample for transfer into the NMR spectrometer, a heated solvent or laser heating is employed and the time used for this procedure should not exceed 2–3 s.

DNP in the liquid phase is called *Overhauser dynamic nuclear polarization* (O-DNP) and has the advantage that the sample is not subjected to a freeze–thaw process. The necessary equipment is thus much simpler and the polarized sample can be used for NMR without further manipulations. The basic theory was outlined in Chapter 10 and the signal enhancement $\eta_{\text{O-DNP}}$ is described by Eq. (15.17):

$$\eta_{\text{O-DNP}} = \frac{\langle I_z \rangle}{I_0} = 1 - \rho \times f \times s \frac{|\gamma_{\text{S}}|}{\gamma_{\text{I}}} \quad (15.17)$$

The *coupling factor* ρ describes the relaxation situation and can assume values between 0.5 for cross relaxation of exclusively dipolar nature and -1 for cases with pure scalar relaxation. The *leakage factor* (f) describes the efficiency of relaxation by coupling to the electron ($f = 1$ for 100%, $f = 0$ for 0%). Finally, the *saturation factor* (s) gives the degree to which the electron transitions of all radicals in the sample have been saturated by the applied RF field. For complete saturation $s = 1$. All these factors can be determined experimentally. O-DNP experiments have been performed at very low B_0 fields (<0.1 T), where high-power ESR equipment is easily at hand and ν_{esr} is in the radiofrequency region, at moderate fields (~ 1 T), and at higher fields (>1 T). Difficulties in using high fields are due to the high electron Larmor frequency, which is then in the gigahertz region. However, if the

polarization step and NMR observation are separated, one can combine low-field ESR with high-field NMR by transporting the hyperpolarized sample between both fields with a flow or shuttle system. In conclusion, interesting possibilities for NMR sensitivity enhancement are provided by various DNP techniques and future developments in this area are promising.

15.6

Nuclear Magnetic Resonance in Biochemistry and Medicine

In the last quarter of the twentieth century the progress in NMR techniques that followed the introduction of FT NMR and the construction of high-field superconducting magnets allowed an expansion into other fields like biochemistry, biology, and medicine. Now, the study of large molecules with complicated structures, such as proteins and nucleic acids, came into reach and the invention of NMR imaging paved the way for applications in medicine. We conclude our introductory survey of NMR in chemistry in these last subsections that follow with a brief summary of selected areas that so far have not been covered in order to give the reader a feeling of what is going on.

15.6.1

Biomolecules

Molecules isolated from plants are generally known as *natural products*. A subgroup of these is marine natural products, which are isolated from living organisms in the sea. Many of these compounds play an important role in biology and medicine. Among them are, for example, alkaloids, terpenoids, antibiotics, and vitamins. Obviously, NMR occupies a major position in structural elucidations of these systems and the experiments we described in earlier chapters find broad applications. The recent book by Berger and Sicker gives an excellent introduction to this discipline (cf. Chapter 7, Ref. [3], p. 229) as well as a Special Journal Issue that contains applications from various areas of natural products (Reference [24] of the present Chapter, p. 647).

The term *biomolecules*, on the other hand, is used for compounds of polymeric structure (actually poly-condensates) that are constituents of living cells: peptides, proteins, nucleic acids, and polysaccharides. These molecules form the basis of *molecular biology* and they are of outstanding importance for biochemistry, a fact underlined by the Noble Prize awarded in 2002 to the Swiss chemist Kurt Wüthrich, who pioneered the structural NMR research in this field (cf. p. 233).

Biomolecules were already a target of NMR spectroscopic investigations in the early days of continuous wave (CW) NMR. The generally complex structure and the high molecular weight of most of these compounds, however, severely limited the success of such measurements at the low field strengths available because of low sensitivity and insufficient spectral dispersion. Detailed structural analyses of *biopolymers* like peptides, proteins, nucleic acids, and oligo- or polysaccharides

were beyond the borders of the experimental tools available at that time to NMR spectroscopists. The introduction of cryomagnets with high magnetic fields and the multidimensional measuring techniques of pulse FT spectroscopy have since changed this situation profoundly and NMR spectroscopy is today used with great success for structural investigation of complicated biological macromolecules. The progress that can be made by increasing the strength of B_0 even for a relatively small molecule is demonstrated in Figure 15.26 with the ^1H NMR spectrum of

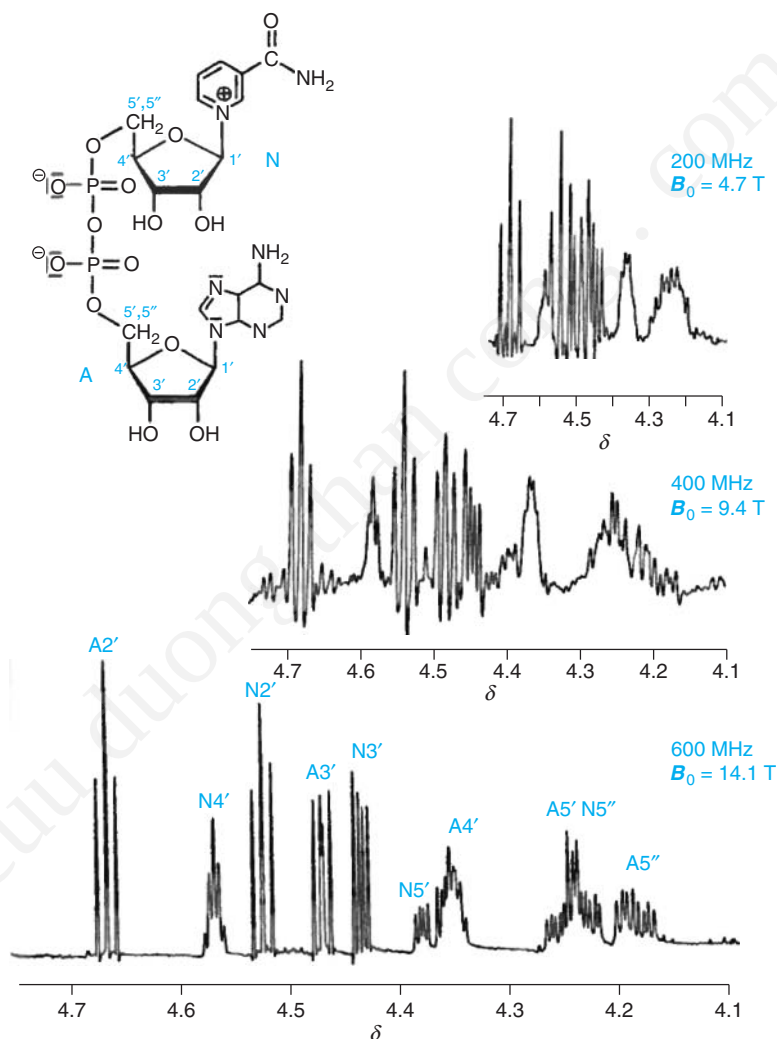


Figure 15.26 ^1H NMR spectrum of NAD^+ in the high field region of the ribose protons at three different field strengths and ^1H frequencies. Because of the more favorable Hz/ppm ratio, the resolution increases with increasing field strength and facilitates spectral analysis [25].

the coenzyme NAD^+ , a dinucleotide with two ribose units and two nucleobases, nicotinamide and adenine.

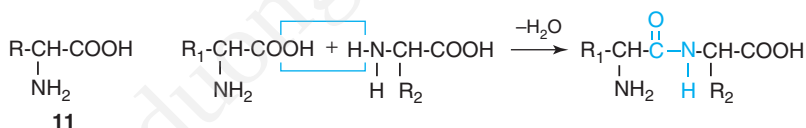
In contrast to other complex molecules such as found, for example, among natural products, the chemical structure of *biomolecules* is formed from a limited number of basic building blocks that are connected to large-chain molecules. In the case of peptides and proteins these building blocks are amino acids, while nucleic acids are built from nucleotides with only four different purine heterocycles. Biological active carbohydrates are usually oligomers of different hexoses, with seldom more than ten units. The nevertheless great structural variety of biomolecules is based on the different chain lengths and the large number of combinations that are possible for these building blocks. The inherent difficulty facing successful structure determinations by NMR was the structural similarity of the building blocks, which leads to strong signal overlap in certain regions of the spectra. This problem could only be overcome by high-field and multidimensional NMR spectroscopy.

Because all facets of biomolecular structure are treated in detail in appropriate biochemistry textbooks, we shall give in the following only a brief outline of some aspects that are important in connection with NMR structure determinations in this area.

15.6.2

Peptides and Proteins

α -Amino acids have the general structure 11 and the basic structural unit of *peptides* and *proteins* is the peptide bond formed by the condensation reaction between two amino acids; an acid chloride is usually employed as the carbonyl-providing unit:



The dipeptide allows further condensation reactions with the same or with other amino acids, leading to chain molecules, the peptides and proteins. About 20 essential amino acids provide the same number of different R groups and are the basis for the great structural diversity that ranges from oligopeptides with a few amino acids through to polypeptides and proteins with 50 and more amino acids to biological macromolecules with several hundred building blocks and a molecular weight of 100 000 Da and more.

The most important aspect of any peptide or protein structure is the *sequence* of amino acids. The classical method for sequence determination is chemical degradation, which leads, however, to sample loss. The non-destructive NMR method is based on the signal assignment in ^1H , ^{13}C , and ^{15}N NMR spectra and standard two-dimensional pulse sequences - introduced in Chapters 9, 10, and 11 - like COSY-DQF, TOCSY, HMQC and HSQC experiments as well as nuclear

Overhauser spectroscopy (NOESY). In addition, 3D and even 4D experiments and several other techniques tailored for special situations are available. Especially, correct interpretation of cross peaks in 2D COSY spectra often presents problems because of severe line overlap resulting from the large number of scalar coupling constants. One of the methods developed to facilitate 2D cross peak analysis and thus the determination of scalar coupling constants is the E.COSY (*exclusive correlation spectroscopy*) experiment that exploits the idea of subspectra we discussed in Chapter 6 (p. 184). Here one uses a *passive spin* to reduce or remove line overlap [26].

Consider a spin system of the ABX type with two protons and a heteronucleus like ^{13}C or ^{31}P as X-part. The COSY or COSY-DQF spectrum performed on a AB system yields cross peaks with four lines separated in both frequency dimensions by $J(\text{A,B})$ as shown in Figure 9.16 (p. 301). For a three-spin proton ABC system, the additional coupling constants $J(\text{A,C})$ and $J(\text{B,C})$ increase this number to 16. In the ABX case, on the other hand, the X-spin stays untouched, but modifies the cross peak multiplets through the coupling constants $J(\text{A,X})$ and $J(\text{B,X})$, giving rise to effective Larmor frequencies ν_a^* , ν_b^* and ν_a^{**} , ν_b^{**} , where $\nu_a^* = \nu_A + \frac{1}{2}J(\text{A,X})$, $\nu_a^{**} = \nu_A - \frac{1}{2}J(\text{A,X})$, $\nu_b^* = \nu_B + \frac{1}{2}J(\text{B,X})$, and $\nu_b^{**} = \nu_B - \frac{1}{2}J(\text{B,X})$ (Chapter 6, p. 186). $J(\text{A,X})$ and $J(\text{B,X})$ are called the *passive couplings*. The number of cross peak signals is reduced by 50%, from $4 \times 4 = 16$ in the general three-spin case to $2 \times 4 = 8$ (Figure 15.27). Small couplings $J(\text{B,X})$ can then be observed provided that $J(\text{A,X})$, called the *associated coupling*, is larger than the line width and the resolution in F_1 . Many long-range coupling constants of the $^{13}\text{C}, ^1\text{H}$ or $^{15}\text{N}, ^1\text{H}$ type are measured more easily in molecules isotopically enriched in ^{13}C and/or ^{15}N , where the large one-bond couplings $^1J(\text{X}, ^1\text{H})$ take the role of the associated coupling.

In a homonuclear three-spin system one of the spins must be weakly coupled in order to achieve an analogous result. Here, small flip angles for the pulses and a special phase cycle are required. Theory shows that coherence transfer is then restricted to transitions that have an energy level in common (*connected transitions*). Two pulse sequences are in use:

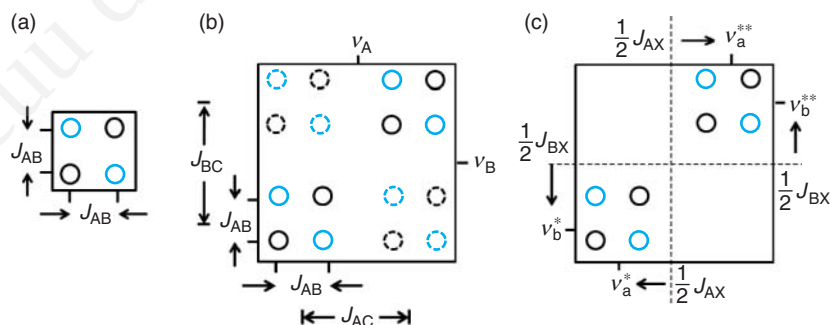


Figure 15.27 Schematic graph of the E.COSY principle: (a) cross peak of an AB system; (b) cross peak of a three-spin ABC system; (c) cross peak for an ABX spectrum: AB subspectra lead to different cross peaks.

- (1) $90_x^\circ \text{---} t_1 \text{---} \beta_y, \text{FID}(t_2)$ and
- (2) $90_\beta^\circ \text{---} t_1 \text{---} 90_\beta^\circ, 90_{-x}^\circ \text{FID}(t_2)$

The first employs a variable pulse angle β , while in the second β is a variable pulse phase. In addition, selective pulses have been used.

Another pulse sequence that is especially useful for measuring $X, ^1\text{H}$ coupling constants ($X = ^{13}\text{C}$ or ^{15}N) at very high field ($B_0 > 10$ T) is the TROSY (transverse relaxation optimized spectroscopy) experiment that has paved the way for structural investigations of proteins with masses in excess of 100 kDa. The problem with these large molecules is the reduced tumbling rate in solution, which leads to short transverse relaxation times T_2 (Chapter 8, p. 245) and broad lines of the order of 30–50 Hz. A severe overlap of cross peaks in 2D spectra results and hampers their interpretation. It can be shown – the details are beyond the level of this text – that in these cases, for example, in a ^{15}N – ^1H HSQC correlation experiment (p. 391 ff.), the individual multiplet components of the cross peaks have different relaxation properties. Relaxation contributions from dipolar interactions between bond vectors and from the chemical shift anisotropy of ^{15}N , which becomes important at high magnetic fields, are of different sign and one of the multiplet lines shows a small line width of less than 10 Hz. With a specially tailored pulse sequence this line can be selectively recorded to mark the particular ^{15}N – ^1H correlation. Furthermore, the smaller line width increases the peak intensity and an additional bonus of the experiment is an increase in sensitivity. Of course, one has to dispense with $^{15}\text{N}, ^1\text{H}$ decoupling in both frequency dimensions F_1 and F_2 (often used in HSQC correlation experiments) in order to exploit the TROSY effect. The drastic reduction

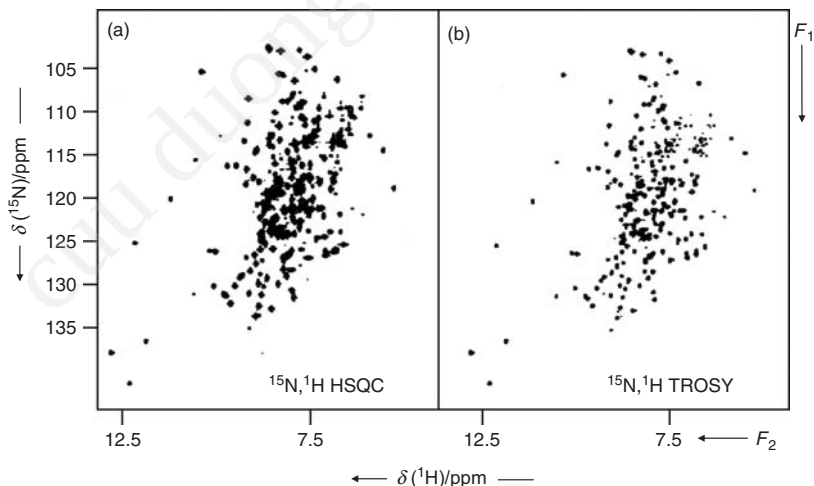


Figure 15.28 Comparison of a 2D HSQC (a) and a TROSY (b) $^{15}\text{N}, ^1\text{H}$ shift correlation spectrum of the enzyme diisopropyl-phosphatase. (Courtesy of Prof. H. Rüterjans, J. W. Goethe University, Frankfurt/M.)

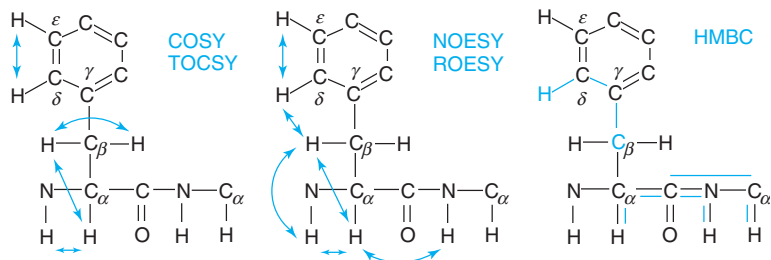


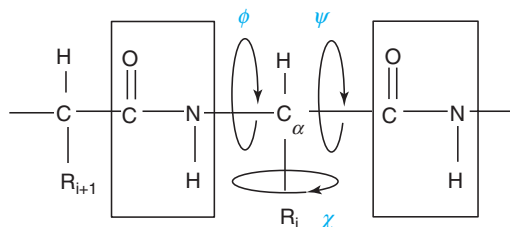
Figure 15.29 Correlations between atoms of a peptide partial structure (phenylalanine) obtained by different NMR experiments. After Reference [27].

in correlation peak overlap is convincingly demonstrated in Figure 15.28 with an example from the spectra for a 35-kDa enzyme.

Figure 15.29 shows the type of information available by various correlation experiments with the example of a phenylalanine partial structure in a peptide chain. Multidimensional experiments reduce the signal overlap and cross peaks in the NOESY or ROESY spectra establish the correlation of the NH proton with the C_α proton of the same amino acid and with the C_α proton of the preceding unit. This information is supplemented by results from long-range ^{13}C , ^1H coupling constants between the carbonyl carbon and the C_α - and C_β -protons of the same building block, measured by HMBC experiments. To avoid overlap in the small carbonyl carbon region, a special pulse sequence with selective ^{13}C excitation can be used.

Having established the amino acid sequence, evaluation of the *spatial structure* is the next step. Here, through-bond and through-space information, known as *constraints*, is necessary. The first comes from scalar coupling constants, the second from NOE results and the measurement of residual dipolar couplings.

The conformation of the backbone of peptides and polypeptides can be characterized by two dihedral angles, ϕ , and ψ , if the peptide groups OC-NH are assumed to be in the standard planar *trans* form due to the amide resonance that lends double bond character to the C-N bond. A third angle χ is used to describe the spatial arrangement of the amino acid side chain:



All three angles are connected by vicinal coupling constants and a whole family of empirical Karplus curves for homo- and heteronuclear ^3J values has been established to quantify this relationships. Various two-dimensional experiments that

Table 15.2 Parameters for Karplus-type curves ${}^3J = A \cos^2\theta + B \cos\theta + C$ of vicinal coupling constants in peptides and polypeptides^a.

Dihedral angle	Coupling constant	A	B	C
ϕ	${}^3J(\text{HN}, \text{H}_\alpha)$	9.4	−1.1	0.4
	${}^3J(\text{CO}, \text{NH})$	5.8	−2.7	0.1
	${}^3J(\text{C}_\beta, \text{NH})$	4.5	−1.5	−0.2
	${}^3J[\text{CO}-i, \text{H}_\alpha(i+1)]$	9.0	−4.4	−0.8
χ	${}^3J(\text{H}_\alpha, \text{H}_\beta)$	9.5	−1.6	1.9
	${}^3J(\text{CO}, \text{H}_\beta)$	6.1	−2.7	1.0

^aThe atoms or groups in parenthesis mark the endpoints of the vicinal coupling path over three bonds. Data from Reference [27].

we will not discuss in detail have been optimized for the successful measurement of these couplings. As shown in Table 15.2, four coupling constants can be used to characterize the angle ϕ , and two are available for χ , but the angle ψ is less well accessible. Two vicinal J values are sensitive to ψ , but both, the one to H_α , and the one to C_β , include the peptide nitrogen and can be measured only for ${}^{15}\text{N}$ -enriched samples. Furthermore, the range of the measured J values is rather small. In an alternative method for the determination of ψ , the sensitivity of the one-bond ${}^{13}\text{C}, {}^1\text{H}$ coupling constant, ${}^1J(\text{C}_\alpha \text{H}_\alpha)$, for both ϕ and ψ , which has been quantified, may be used.

Through-space distance information, now between different subunits of the molecular chain, comes again from nuclear Overhauser data, measured with NOESY or ROESY spectra – already described in detail in Chapter 10 – and from residual dipolar couplings (Chapter 14, p. 565 ff.) that yield in addition information about angles between bond vectors. As shown in Figure 10.5 (p. 350), the NOE may be positive or negative, depending on the product between the Larmor frequency and the correlation time of molecular motion, $\omega\tau_c$. Polypeptides and proteins with long τ_c values thus yield negative effects as large as −100% that show up in NOESY spectra as positive cross peaks. For smaller peptides, increasing mobility leads to a decrease of τ_c and NOE data become positive and yield negative cross peaks. If the product $\omega\tau_c$ is close to 1, cross peaks are weak and can be of either sign or disappear completely. Lowering the temperature slows down molecular motion and may then allow detection of the relevant information. Alternatively, ROESY spectra, which always yield positive Overhauser effects (Figure 10.21, p. 371), can be used.

From the NOE or ROE data proton–proton distances of up to 0.5–0.6 nm (5–6 Å) can be derived by measuring the initial build-up rates of cross peaks, provided short mixing times in the pulse sequence prevent spin diffusion. With a known reference distance, r_i , for example, 178 pm for the H–H distance of a geminal methylene group, the distance of interest, r_j , can be derived from the

proportionality of the cross peak intensities I :

$$I_r/I_i = r_r^{-6}/r_i^{-6} \quad (15.18)$$

Because residual dipolar couplings have a r^{-3} dependence instead of the r^{-6} dependence of the NOE, the upper limit of distance measurements using these parameters is raised to ~ 1 nm (10 Å). Finally, additional structural aspects have to be addressed such as the assignment of diastereotopic methylene protons – a consequence of the chiral center at C_α in the naturally occurring L-amino acids – or cis–trans isomerization at certain peptide bonds, often observed for proline or N-alkylated amino acids. From the information on distances and angles, used as constraints, a trial structure can then be calculated and optimized by molecular dynamics calculations in an iterative procedure that can also include the solvent cage.

For flexible molecules like small, linear peptides of less than ten amino acids a whole family of conformations exists and special provisions like low temperature or solvent effects have to be used to derive a solution. Less problematic in this respect are cyclic peptides and those linear peptides where intramolecular motions are reduced or blocked by the formation of hydrogen bonds. This feature leads for polypeptides and proteins of 100 and more amino acid residues to the formation of the β -sheet and to helix structures. In the β -sheet structure several linear peptide chains are connected via hydrogen bonds to form a pseudo-two-dimensional structure. For the helix, one peptide chain adopts a screw-like arrangement, similar to the helices known from nucleic acids like deoxyribonucleic acid (DNA). Many proteins contain both structural units that are coupled over single strands, so-called β -turns, where the direction of the polypeptide chain is reversed. This allows proteins to adopt a globular shape. An example is shown in Figure 15.30 with

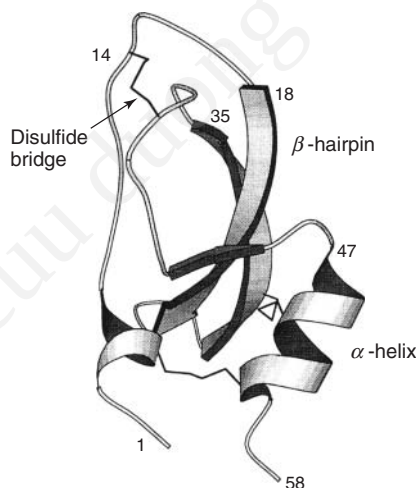


Figure 15.30 Schematic ribbon drawing of the three-dimensional NMR solution structure of the bovine pancreatic trypsin inhibitor BPTI; residues are numbered: 18–35 form a hairpin structure of two β -sheets, 47–56 an α -helix; three disulfide groups that link the side chains are marked with solid lines. After Reference [28].

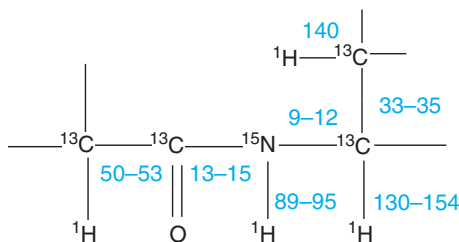


Figure 15.31 Polypeptide segment with scalar coupling constants $J(^{13}\text{C}, ^1\text{H})$, $J(^{15}\text{N}, ^1\text{H})$, $J(^{13}\text{C}, ^{13}\text{C})$, and $J(^{15}\text{N}, ^{13}\text{C})$ that provide the basis for sequential assignments in proteins; values are in hertz. After Reference [29].

the structure of bovine pancreatic trypsin inhibitor (BPTI) – a protein of 58 amino acids and a molecular weight of 6500 that was studied over many years and served as a playground for the development of NMR techniques for structural studies of proteins.

The NMR structure determination of large proteins follows the experimental recipe described above, but a further step to the successful investigations of protein structures, in particular of those with high molecular weight, was opened up by complete ^{13}C and/or ^{15}N labelling of biomolecules using techniques of biotechnology. This leads, as shown in Figure 15.31, to a wealth of additional homo- and heteronuclear J -couplings and allows – due to the improved sensitivity – the measurement of multidimensional NMR spectra, besides 2D there can also be 3D or even 4D experiments. Thus, protein structures with more than 200 amino acids could be solved.

For the unequivocal sequential backbone assignment of the uniformly with ^{13}C and ^{15}N labelled proteins a series of five three-dimensional spectra has been proposed and successfully tested [30]. They are known as *HNCO*, *HNCA*, *HCACO*, *HOHAHA-HMQC*, and *HCA(CO)N* experiment and are largely based on one-bond coupling constants. As the graphic in Figure 15.32 shows, *HNCO* correlates two connected amino acids via $^1\text{H} \rightarrow ^{15}\text{N} \rightarrow ^{13}\text{C}=\text{O}$; *HNCA* yields the internal correlation of the NH proton with the nitrogen and in turn with C_α of a particular amino acid (there are cases where additional cross peaks between C_α and ^{15}NH of the next amino acid via a geminal $^{13}\text{C}, ^{15}\text{N}$ coupling are observed); *HCACO* yields again an internal connectivity ($^1\text{H} \rightarrow \text{C}_\alpha \rightarrow ^{13}\text{C}=\text{O}$) as does *HOHAHA-HMQC* [$^1\text{H}(\text{C}_\alpha) \rightarrow ^1\text{H} \rightarrow ^{15}\text{N}$]. Finally, *HCA(CO)N* correlates H_α and C_α of one residue with the nitrogen of the next residue. The ultimate goal is automated n.m.r. sequence assignment for proteins and progress in this direction has been made.

Importantly, these NMR investigations make it possible to study biomolecular structures in solution and to investigate interactions of proteins with other molecules, for example, other peptides or drugs. Furthermore, and in contrast to X-ray studies, which only yield the structure in the solid (with, however, high precision), NMR is not limited to crystalline material.

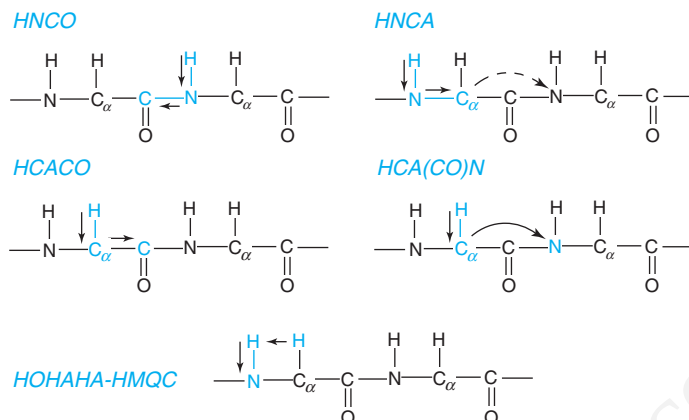


Figure 15.32 Standard 3D NMR experiments for the sequential backbone assignment of larger proteins [30].

15.6.3

Nucleic Acids

The whole arsenal of NMR methods applied to peptides and proteins as described in the last section is also available for structural research in the field of nucleic acids, another type of biological macromolecules. Their structural principles are already apparent from the formula of the dinucleotide NAD^+ shown in Figure 15.26: β -D-ribose or β -D-2'-deoxyribose units that bear at position 1' a nucleobase are connected by a phosphate (here a monophosphate) group. The large structural variety of nucleic acids results from the different sequence of nucleobases in the molecular chain. Two purine derivatives – adenine (A) and guanine (G) – and three derivatives of pyrimidine – cytosine (C), uracil (U), and thymine (T) – are the common bases that can occupy position 1' of the furanose ring via a glycosidic bond (Figure 15.33). The *nucleosides* (furanose and nucleobase) are then joined to macromolecules by phosphate groups that bridge position 5' of furanose (1) with position 3' (*not* 5' as in NAD^+) of furanose (2). Multiple units of nucleoside phosphate esters are the building blocks of DNA and RNA (ribonucleic acid). Phosphorus-31 is thus available as an additional nucleus for NMR studies.

As can be concluded from Figure 15.33, the number of torsional angles in a nucleoside backbone unit along the atomic chain $\text{-P(i)-O5'-C5'-C4'-C3'-O3'-P(i+1)-}$ exceeds with four by far the two angles characterizing torsion in peptides. A seventh angle describes rotation around the glycosidic bond to the base and additional variations are possible for the dihedral angles in the furanose rings because of pseudo-rotation. The universal secondary structure of nucleic acids is the famous double helix, stabilized by hydrogen bonds through the Watson–Crick pairs T–A and C–G.

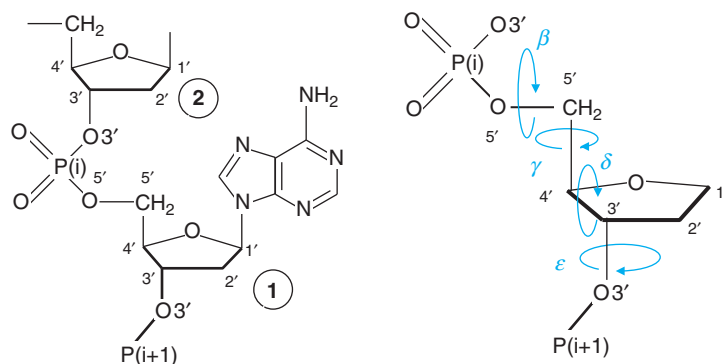


Figure 15.33 (a) Structural fragment of desoxyribonucleic acid (DNA) with adenine as nucleobase; ribonucleic acid (RNA) bears a hydroxyl group in position 2'. (b) Backbone torsional angles in DNA; in Table 15.3 $P(i) = P5$ and $P(i+1) = P3$.

Structural investigations start with short-range information from the mononucleotides and the secondary structural elements, the double helices. Again, NOE data between protons, J couplings, and residual dipolar couplings are available for distance and torsional angle measurements. A *NOE-based pathway* along the nucleotide chain is given by the interactions between the ring protons of the nucleobases and the H1' sugar protons. The J couplings, including the ^{31}P nuclei, are important for information about backbone torsions. Those that can be used for J analysis with various Karplus-type curves are collected in Table 15.3. They form a so-called *coherence pathway*.

Table 15.3 Scalar coupling constants that are important for backbone torsion in nucleic acids [31].

Torsion angle		Coupled nuclei			
β	C4', P5	H5', P5	H5'', P5	—	
γ	H4', H5'	H4', H5''	C3', H5'	C3', H5''	
δ	H3', H4'	C5', H3'	C5', C2'	—	
ϵ	H3', P3	C4', P3	C2', P3	—	

For the helix structure the distances between the ring protons of the nucleobase and the protons H1', H2', and (for DNA) H2'' at C1' and C2', respectively, of its own furanose and the same furanose protons of the next unit are important. Stereochemical assignments of the methylene protons at C2' and C5' of DNA and at C5' of RNA are also necessary. All these measurements are enormously facilitated by employing isotopic labeling for ^{13}C and/or ^{15}N .

For oligonucleotides, ^{31}P chemical shifts provide valuable information about the conformation of the phosphodiester backbone. Various multidimensional ^{31}P , ^1H NMR experiments, among them 2D J -resolved spectroscopy and shift

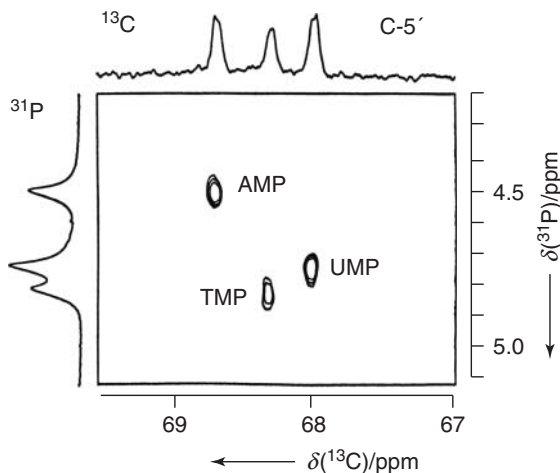
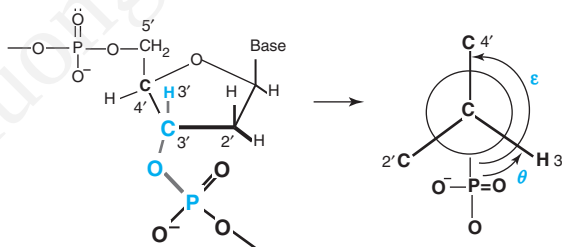


Figure 15.34 HMQC $^{13}\text{C},^{31}\text{P}$ shift correlation with ^{13}C detection via $^2J(^{13}\text{C},^{31}\text{P})$ for assignment of the ^{31}P resonances in a mixture of three mononucleotides: adenosine-5-phosphate (5'-AMP), thymidine-5-phosphate (5'-TMP), and uridine-5-phosphate (5'-UIMP) [32].

correlations via long-range couplings (COLOC, cf. p. 394 ff.), or those based on $^{31}\text{P},^{13}\text{C}$ couplings (Figure 15.34) have been used to assign ^{31}P resonances and to derive torsional angles. For example, observation of the vicinal $\text{H}3',\text{P}3$ coupling (Table 15.3), yields – on the basis of a Karplus-type relation for $^3J(^{31}\text{P},^1\text{H})$ – data for the torsional angle θ in the $\text{H}3'-\text{C}3'-\text{O}-\text{P}$ fragment, from which the $\text{C}4'-\text{C}3'-\text{O}-\text{P}$ torsional angle ε ($= -[\theta + 120^\circ]$) can be calculated:



15.6.4

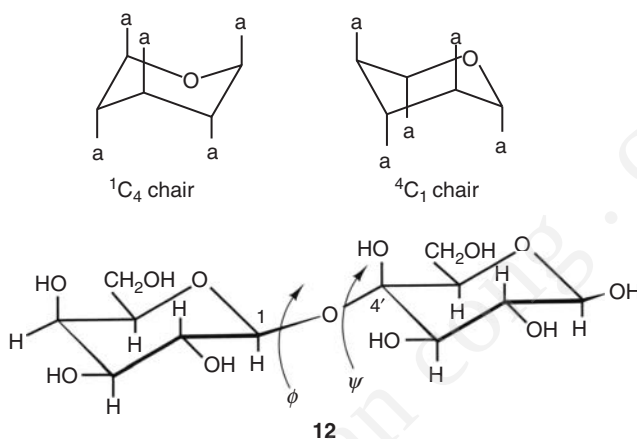
Oligo- and Polysaccharides

We conclude our excursion into the NMR of biomolecules with a section dealing with structure determinations of macromolecules formed from carbohydrates. These studies have to address the following points:

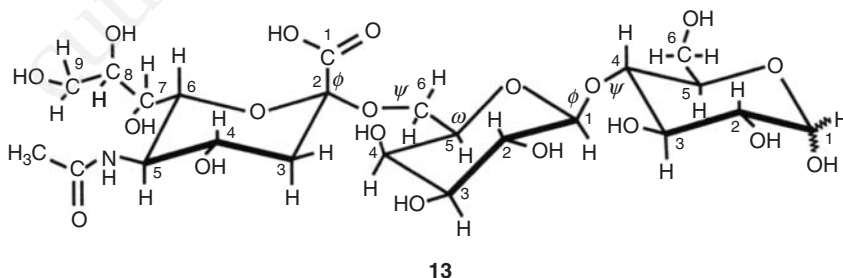
- 1) identification of the configuration of each residue (D or L , α or β),
- 2) determination of the conformation of each residue (chair or boat),

- 3) identification of the type of bond between neighboring residues,
- 4) determination of the conformation of linkages to various substituents or side chains.

Most of the pyranose rings exist in the well-known chair conformations ${}^1C_4$ and ${}^4C_1$ and the relation $\delta_{ax} < \delta_{eq}$ for the proton resonances is preserved. Boat conformations are found less frequently; nevertheless, the variety of building blocks in polysaccharides is larger than in nucleic acids and in proteins.



Structure 12 defines the torsion angles ϕ ($\angle 1\text{-H-C1-O-C4}'$) and ψ ($\angle \text{C1-O-C4}'\text{-H4}'$) used to describe the stereochemistry at a glycosidic linkage connecting two monomers where vicinal coupling constants ${}^3J(\text{H1}, \text{C4}')$ and ${}^3J(\text{C1-H4}')$ and NOE or ROE effects between H1 and H4' are used to characterize the conformation. Typical structural elements of a trisaccharide are found in the formula for sialyl- $\alpha(2\rightarrow6)$ lactose (13): a pyranose is substituted by side chains at positions 5 and 6 and a 2-acetyl group is connected by an α -linkage to C6 of a galactose residue that in turn has a β -linkage to C4 of the final glucose. These two carbohydrates form the partial lactose structure [33].



Structural analysis of oligo- and polysaccharides starts with the primary structure, which involves identification of the monomers. Over the years, numerous investigations have established several rules that make interpretation of the spectra

easier. Measurements in D₂O [reference compound [D₄]-2,2-dimethyl-2-silapentane-5-sulfonate (DSS), see p. 70] eliminate signals of OH protons. The signals from the remaining ring protons with the exception of the anomeric protons overlap closely between 3 and 4 ppm and are difficult to analyze. The doublets of the anomeric protons ¹H are well separated between δ 3.4 and 5.6 ppm. Equatorial protons for α -glycosidic linkages are found at $\sim$ 4.9–5.6 ppm, the axial ones for the β -forms at $\sim$ 4.3–4.7 ppm. These regions are at the near-left and near-right of the residual HDO signal at δ 4.8 ppm. From the coupling constants ³J(H1,H2) the orientation of H1 – axial or equatorial – can further be secured (cf. p. 129). The signals of non-anomeric protons attached to linkage sites, either from additional glycosyl residues or from non-carbohydrate side chains, are deshielded by $\sim$ 0.2–0.5 ppm from the 3–4 ppm region of the other ring protons ($3.9 < \delta < 4.4$).

Supplementary structural information comes from ¹³C NMR where signals of the ring C–H carbon are usually found between 65 and 110 ppm at higher frequency from DDS. Anomeric carbon resonances are found between 90 and 110 ppm and the one-bond coupling constant ¹J(¹³C1,H1) reflects the configuration at C1 with $\sim$ 170 Hz for the α -form and $\sim$ 160 Hz for the β -form. Glycosylation shifts are $\Delta\delta \sim$ 10 ppm for the substituted ¹³C and -1 to -2 ppm for its neighbors. Powerful databases for monosaccharides and simple oligosaccharides are available and assist computer analysis of the spectra.

Once the primary structure is known, extensive measurements of scalar coupling constants and information from NOESY and/or ROESY spectra allow to tackle the conformation of each residue and that of the glycosidic linkages as well as that of the side chains. Karplus-type curves are available for vicinal ¹H,¹H as well as for ¹³C,¹H coupling constants:

$$^3J(^1\text{H}, ^1\text{H}) = 13.22 \cos^2\phi - 0.99 \cos\phi + \Delta\chi_i[0.87 - 2.46(\xi_i, \phi)] \quad (15.19)$$

$$^3J(^{13}\text{C}, ^1\text{H}) = 5.7 \cos^2\phi - 0.6 \cos\phi + 0.5 \quad (15.20)$$

where ϕ is the H–C–C'–H' or H–C–O–C torsion angle, respectively, and $\Delta\chi_i$ in Eq. (15.19), the famous *Haasnoot–Altona equation*, are the Huggins electronegativities of the substituents relative to that of the proton. The factor ξ_i characterizes the orientation of a substituent with +1 or -1 . From the resonances of isolated protons, for example, H1, selective TOCSY experiments can be started to obtain ¹H spectra of individual residues, as shown for glucose in Chapter 10 (p. 370). The whole series of the known 1D and multidimensional homo- and heteronuclear pulse sequences is than available to address specific structural features. Finally, the topic of hydrogen bonding and of molecular dynamics can be tackled with relaxation time and temperature-dependent NMR measurements.

In concluding this section, we stress again the fact that the progress made in NMR of biomolecules is to a large extent a consequence of the construction of high-field magnets. Tribute has to be paid to the engineers who made this development possible that has by now reached the magic border of 1 GHz (= 1000 MHz) for the ¹H frequency. Figure 15.35 gives an impression of the advanced technology of these instruments and the requirements for their operation.



Figure 15.35 Laboratory with a superconducting magnet of 1 GHz ^1H NMR frequency. The superconducting coil is held at approximately 2 K by use of an additional Joule-Thompson valve (Courtesy: Bruker BioSpin, Karlsruhe, Germany).

15.6.5

Solvent Suppression

In NMR measurements quite often a solvent has to be used that also contains nuclei of the type to be observed. Large solvent signals may then cause problems by overlap with resonances of interest, by distortions of the baseline or just by saturation of the receiver and a loss of signals if the receiver gain is reduced. Small signals may then not be digitized by the analog–digital converter (ADC) of the particular spectrometer (cf. p. 254). In addition, the elimination of solvent signals in FT NMR is not possible by cutting out a certain frequency range from the sweep width used. To avoid these problems, a necessary requirement for routine NMR measurements and the use of an automatic sample changer, a large variety of deuterated solvents is thus available (cf. Table 4.1, p. 68 and Table A.5, page 659) for proton and carbon-13 NMR. In the latter case, measurements in chloroform depleted of ^{13}C can be used if necessary. However, in the field of biological NMR, during structure determinations of biomolecules, and for applications of NMR in medicine, obviously the solvent water cannot be simply replaced by deuterium oxide. Many efforts have thus been made to develop techniques that allow us to decrease or even to eliminate completely the water resonance. The principles of

some of these approaches, also applicable in other situations, will now be reviewed briefly.

A rather simple method is based on *presaturation* of the solvent signal by a selected soft pulse, for example, CW irradiation at the solvent frequency for period equal to solvent spin–lattice relaxation time T_1 before excitation of the signals of interest. This experiment may be combined with a short 1D NOESY sequence as the first increment of a 2D NOESY experiment that yields volume selection as an additional frequency filter. Solvent suppression by a factor of $\sim 10^3$ can be achieved by these methods. Another technique uses differences in the relaxation times T_1 and an *inversion-recovery experiment*. After rotating all magnetizations into the $-z$ -direction, the faster relaxing signals of the solute are excited when the solvent signal, for example, water, just reaches the zero-intensity passage ($\tau = \ln 2 \times T_1^{H_2O}$; cf. Figure 8.12, p. 247).

With the advent of linear field gradients new possibilities for solvent suppression arose. A widely used technique, called *WATERGATE*, is based on the PGSE diffusion sequence (cf. p. 614) modified by the use of a selective π -pulse that has zero intensity at the water resonance. Only the solute resonances are inverted and later refocused while the water resonance is destroyed by the gradients. To achieve selectivity, various techniques for the π -pulse that we cannot discuss in detail are used. For short echo times the water signal can be suppressed by a factor of at least 10^4 . Finally, a method that avoids solvent saturation is called *jump-and-return*. A hard 90_x° pulse at the solvent frequency, again that of water, turns all spins to the $+y$ direction of the rotating frame. In the following delay τ the solute spins rotate in the x,y plane with $\omega\tau$, where ω is the frequency offset from the water resonance. A second 90_{-x}° hard pulse of opposite phase to the first one brings all spins into the $z,-x$ plane, the water magnetization is directed along $+z$. Signals of the solute spins with positive and negative offset frequency have a phase difference of 180° and their amplitude varies with $\sin \omega\tau$. For those of interest τ is chosen such that $\omega\tau = \pi/2$.

In addition to pulse sequences of the type discussed, solvent suppression may also be achieved after processing the data of a certain FT experiment. There are methods applied to the time domain and others applied to the frequency domain of the signals but we shall not discuss these techniques further.

15.6.6

NMR of Body Fluids and *In-vivo* NMR Spectroscopy

Aside from investigations primarily directed to solve the structure of biomolecules, NMR is also a powerful technique to elucidate biochemical pathways where various nuclei (^{13}C , ^{15}N , ^{17}O , ^{31}P) can be used to follow a reaction of interest, for example, a biochemical transformation or a drug metabolism. The last aspect led to studies that use the analytical potential of high-field NMR for the investigation of body fluids. The wealth of information available from such spectra, where proton NMR is applied for sensitivity reasons, is demonstrated in Figure 15.36 with a spectrum of human blood plasma. Clinical studies showed that metabolic profiles obtained by NMR are valuable aids in diagnostic investigations of various diseases.

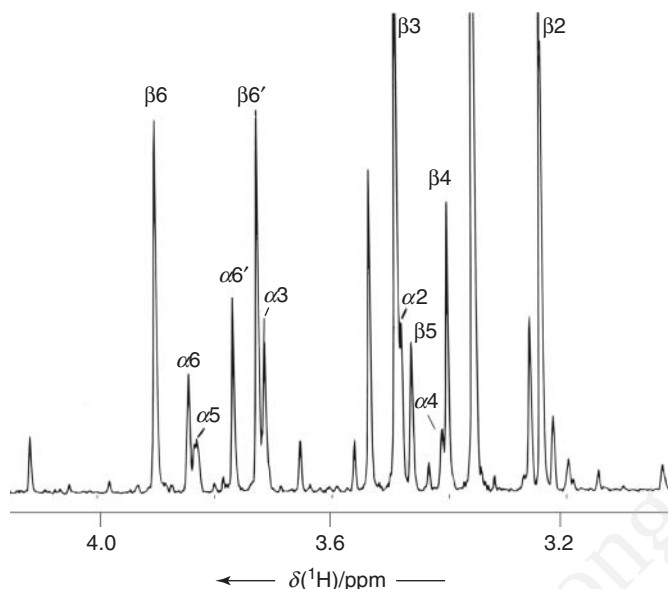


Figure 15.36 750 MHz ^1H NMR spectrum of human blood plasma with assignments of the signals for α - and β -glucose; other signals are due to various amino acids [34].

The experimental NMR techniques used for this purpose are, despite their sophistication, in many respects not very different from the techniques used in organic chemistry for the study of smaller molecules. A completely new field for NMR spectroscopy developed, however, with the design of experimental methods that allowed unconventional investigations in the life sciences and in medicine. We are now able to study biochemical processes *in vivo*, which is with the living object, for example, a cell culture or an intact organism. While cells can be studied as cell suspensions in the NMR sample tube, tissue investigations or the study of cell metabolism in perfused organs or living organisms require special transmitter and receiver coils that must be designed according to the needs of the experiment. In many cases, especially for larger objects, surface coils that can detect weak signals are used to allow the radiofrequency to penetrate into the object. These particular arrangements of RF coils that yield optimal signal excitation and detection are placed, together with the object under study, into the magnetic field of special wide-bore cryomagnets that have openings up to 50 cm in diameter. In this way NMR spectra of certain areas of interest of the object can be obtained at high B_0 fields. The objects studied extend from perfused organs (heart, liver) of animals to the extremities of human limbs (arm, leg).

From the nuclei that are available for such investigations as sensitive NMR probes, phosphorus ^{31}P is especially well suited because of its 100% natural abundance and high sensitivity [$\nu_0(^{31}\text{P})/\nu_0(^1\text{H}) \approx 1:2$] (see also Chapter 12). Protons, because of the abundance of water in living matter, are in general much too concentrated to yield simple spectra and carbon-13 is not sensitive enough.

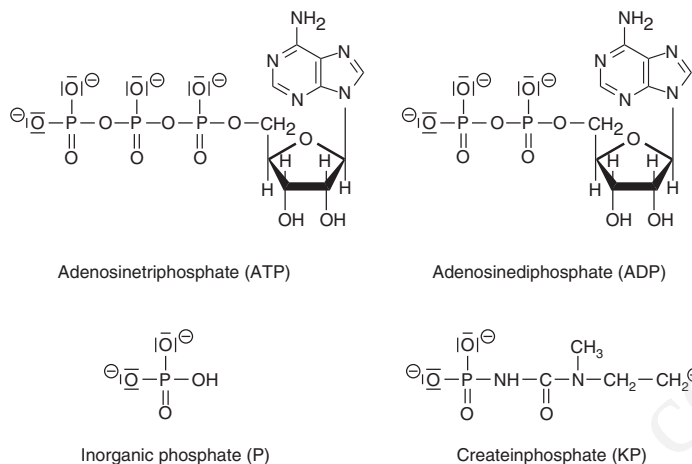


Figure 15.37 Molecules important for energy conversion in the cell: ATP (adenosine triphosphate, energy rich phosphate) is converted with energy production (-50 kJ mol^{-1}) by hydrolysis into ADP (adenosine diphosphate) and inorganic phosphate (P). Creatine phosphate

(CP) is a storage material in equilibrium with ATP: $\text{CP} + \text{ADP} \rightleftharpoons \text{ATP} + \text{creatine}$. It is used for ATP production if the ATP synthesis by respiration is blocked, for example, in the case of insufficient blood supply.

Phosphorus atoms are part of several important products of cell metabolism. For example, the molecules shown in Figure 15.37 are essential components in the reaction scheme that serves for energy production in the cell. Since these compounds contain only few chemically different phosphorus atoms, relatively simple high-resolution ^{31}P NMR spectra are obtained and the assignment of the observed ^{31}P resonances to adenosine triphosphate (ATP) and other key products, shown in Figure 15.38, is rather straightforward.

The excellent quality of the spectra that can be obtained allows us to detect metabolic changes by application of ^{31}P NMR spectroscopy. It has been shown, for example, that the position of the ^{31}P resonance of inorganic phosphate in the cell is a sensitive indicator for the intracellular pH value (Figure 15.38b). As shown in Figure 15.39 with the ^{31}P NMR spectrum from a human forearm, muscle contraction under ischemic conditions, that is, during insufficient blood supply, leads, aside from other characteristic changes, to a decrease in pH. After blood supply is stopped by blocking the arteries, the storage substance creatine phosphate is consumed. At the same time, lactate formation during glycolysis leads to a decrease in pH. After restoring the blood and thus the oxygen supply the normal state is slowly reached again.

15.6.7

NMR Imaging

Up to now we have dealt with NMR spectra that furnish information on individual molecules, either in the liquid or – as referred to in Chapter 14 – in the solid state.

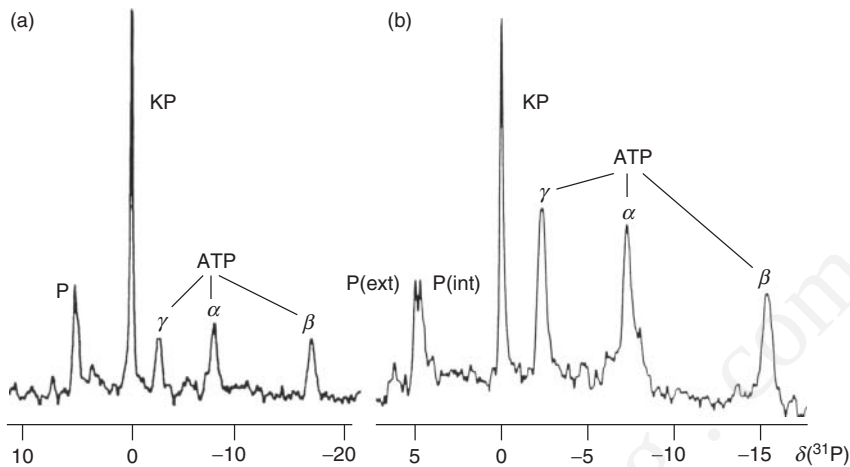


Figure 15.38 (a) ^{31}P NMR spectrum of a frog muscle (73.8 MHz); P: inorganic phosphate; KP: creatine phosphate; ATP: phosphorus resonances of adenosine triphosphate [35]; (b) ^{31}P NMR spectrum (73.8 MHz) of a perfused rat heart. Two signals are observed for inorganic

phosphate since the pH values in the cells and in the perfusion liquid are slightly different. The α - and γ -signals of ATP also contain contributions from the α - and β -phosphorus signals of ADP that in this experiment are not separated due to the low field strength [36, 37].

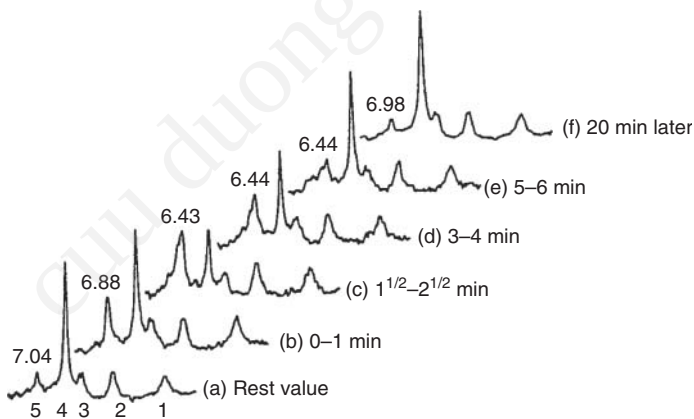


Figure 15.39 32.5 MHz ^{31}P NMR spectrum of a human forearm. The first spectrum (a) was recorded at rest, prior to exercise. Subsequent spectra (b) and (c) were recorded under ischemic conditions with exercise in the period 0–1.5 min. After 3 min arterial flow was restored and spectra (d)–(f) show the relaxation process to normal conditions [34, 36].

In this sense NMR spectra may be regarded as pictures or images of molecules since the spectroscopist performs an intellectual transformation of the recorded data (chemical shifts, spin–spin coupling constants, relaxation times, etc.) into an image of the molecule, mostly the structural formula.

A different kind of *NMR imaging* was developed in the 1970s, by which structures well above the molecular level are studied and a real two-dimensional representation of the object is derived from the spectral data. This field – also known as *MRI* (magnetic resonance imaging) or *spin mapping* – has found many applications in biology and even in medicine, where it is today a well established diagnostic tool (cf. Figure 15.40a). It seems appropriate to describe, even if in a rudimentary form, these developments in order to provide information about the underlying experimental principles.

In 1973 P.C. Lauterbur (cf. Figure 15.40b) first produced an NMR image by applying a linear field gradient ΔG at right angles to the $\mathbf{B}_0$ field axis as $\Delta G_{x,y}$ over the sample cell.⁴⁾ In such an experiment, nuclei in different regions of space will experience different external fields $\mathbf{B}_0 + \Delta \mathbf{B}_i$ and, correspondingly, their resonance frequencies will differ. In other words, the field gradient introduces a chemical shift between nuclei that would be isochronous in the conventional NMR experiment.

If the line width of the individual resonances is small compared to the field gradient, signals from different parts of the object – more precisely those from nuclei residing in various planes perpendicular to the gradient – can be discriminated. An intensity plot will then yield information about the spatial spin distribution.

One of the first NMR images produced by this technique was that of two capillaries of 1 mm diameter each filled with H_2O and fitted into a 5-mm sample tube containing $\text{D}_2\text{O}/\text{H}_2\text{O}$. The construction of a two-dimensional picture of this arrangement from the ^1H -NMR signals received is schematically illustrated in Figure 41a. The actual result obtained is shown in Figure 41b. Here the NMR data were processed by a computer using image reconstruction programs that allowed the printing of a spin density map for the protons in the sample. The two capillaries are clearly recognized.

Further refinements of the imaging technique have been achieved in the years that followed the original discovery, many of them in the laboratories of R.R. Ernst and P. Mansfield. Using alternating field gradients along orthogonal directions, an NMR-sensitive volume in space can be produced at the intersection of the three null planes of these gradients. The NMR signal from this selected region is then detected, while those from other parts of the sample are rejected. Scanning the object by this sensitive point yields the data necessary for image construction. Similarly, using only two time-dependent gradients a sensitive line is produced for the detection of NMR signals by FT-methods, thereby greatly reducing the time necessary for the experiment. The collected data are then subjected to computer image processing.

The progress made on the way to present-day instrumentation (see Figure 15.40a)—that found practical realization in several companies specialized

4) Please note the difference to the use of linear field gradients in high-resolution NMR, where ΔG is applied parallel to the $\mathbf{B}_0$ field axis (ΔG_z !).

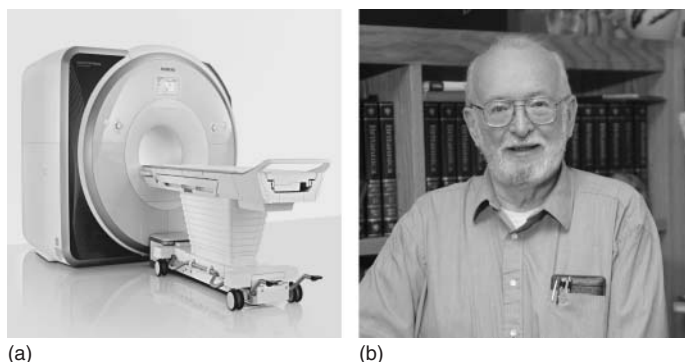


Figure 15.40 (a) Whole-body scanner (3 T NMR tomograph MAGNETOM Prisma) (Courtesy Siemens AG); (b) Professor Paul C. Lauterbur (1929 – 2007); Nobel Prize for Physiology and Medicine 2003. (Courtesy The University of Illinois at Urbana Champaign)

in the development and construction of medical instruments and medicine technology—was crowned in 2003 by the award of the Nobel prize for Physiology and Medicine to Paul C. Lauterbur and Sir Peter Mansfield “for their discoveries concerning magnetic resonance imaging”.

It is important to emphasize that the NMR images of the internal structure of these and other objects are obtained in a non-destructive manner. The technique is therefore comparable to röntgenography. Unlike X-rays, however, the magnetic and RF fields used are, to our present knowledge, without harm to living cells and this makes NMR imaging an important tool for biology and medicine. The construction of whole-body magnets with magnet bores of 50 cm and more have paved the way for investigations on human patients and NMR imaging today is an indispensable aid for medical diagnosis. The enormous improvement in image quality as well as a considerable shortening of the time necessary to produce these images has placed

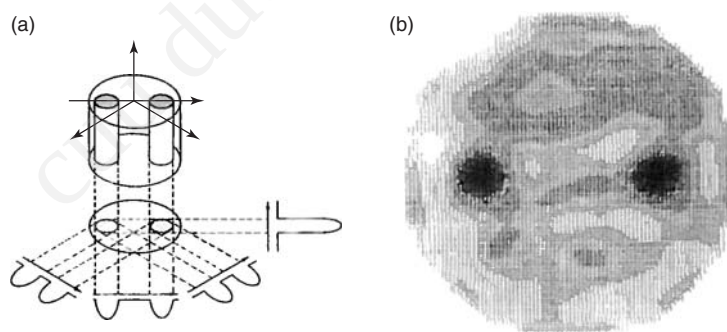


Figure 15.41 (a) NMR information obtained from two capillaries containing H_2O using four different experiments with field gradients in directions indicated by the arrows [38]; (b) NMR image produced from an arrangement shown

schematically in (a); two 1 mm capillaries filled with H_2O were fitted in a cylindrical sample tube of 4.2 mm inner diameter that contained a mixture of D_2O and H_2O [39].

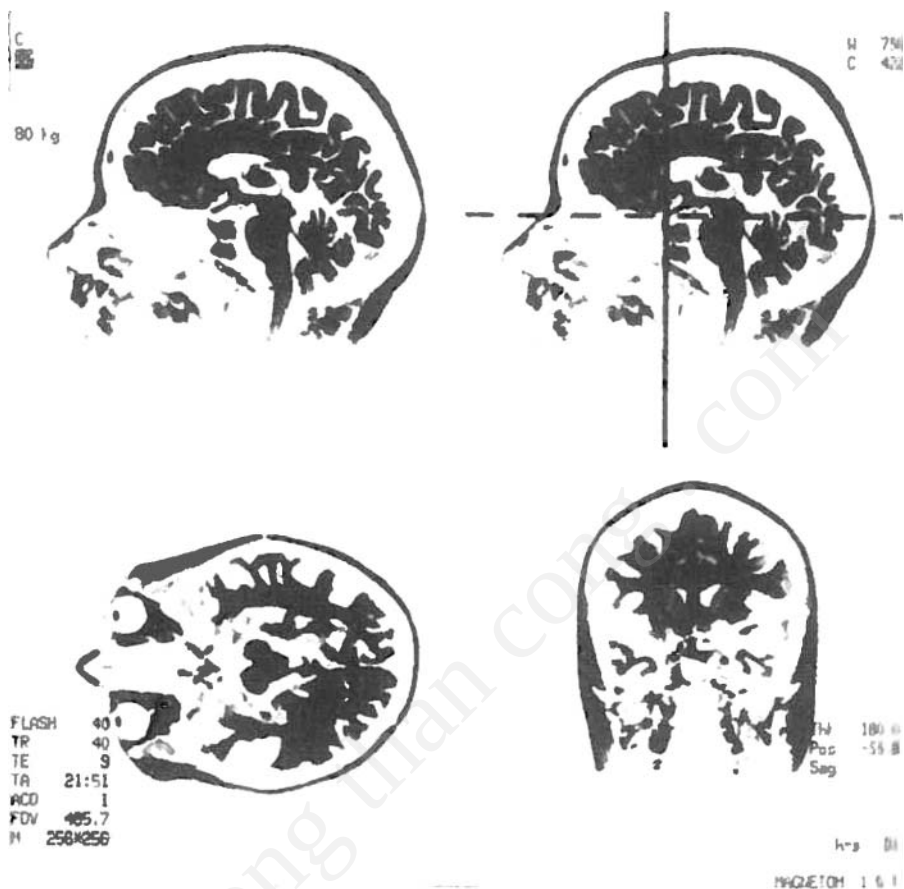


Figure 15.42 NMR images of the human skull at 1.5 T. (Courtesy of Siemens AG).

NMR imaging units today at the side of computer tomographs in the radiology departments of the big hospitals. In particular, brain investigations have been advanced by the new NMR technique that yield, as one can imagine from Figure 15.42, detailed information about brain structure and facilitates the localization of pathological regions such as tumors or damaged blood vessels. A noteworthy advantage of the NMR method over other techniques is the possibility to produce cross sections in every direction that is of interest. In addition, especially adapted surface coils allow more detailed investigations of certain regions of the human body. Furthermore, aside from the chemical shift, other parameters such as, for example, relaxation times can be used to produce an image and other sensitive nuclei like phosphorus-31 or sodium-23 can be employed. The large versatility of NMR in general classifies the NMR imaging method as one of the most important techniques in radiology.

References

- Aydin, R. and Günther, H. (1981) *J. Am. Chem. Soc.* **103**, 1301.
- Risley, J.M. and Van Etten, R.L. (1990) *NMR—Basic Principle*, Vol. 22, Springer-Verlag, Berlin, p. 81.
- Wesener, J.R., Moskau, D., and Günther, H. (1985) *J. Am. Chem. Soc.*, **107**, 7307.
- Ernst, L., Hopf, H., and Wullbrandt, D. (1983) *J. Am. Chem. Soc.*, **105**, 4469.
- Aydin, R., Frankmölle, W., Schmalz, D., and Günther, H. (1988) *Magn. Reson. Chem.*, **26**, 408.
- Everett, J.R. (1982) *Org. Magn. Reson.*, **19**, 86.
- Saunders, M., Jaffe, M.H., and Vogel, P. (1971) *J. Am. Chem. Soc.*, **93**, 2558.
- de Boer, E. and McLean, C. (1965) *Mol. Phys.*, **9**, 191.
- Wahl, G.H. and Peterson, Jr., M.R. Technical Bulletin (1970) Vol. 4, No. 4, Varian Associates, Palo Alto, CA, USA.
- Hofer, O. (1976) *Top. Stereochem.*, **9**, 111.
- Fischer, H. (1978) Diploma thesis. University of Cologne.
- Bargon, J., Fischer, H., and Johnson, U. (1967) *Z. Naturforsch. Teil A*, **22**, 1551.
- Closs, G.L. and Closs, L.E. (1969) *J. Am. Chem. Soc.*, **91**, 4549.
- Stejskal, E.O. and Tanner, J.E. (1965) *J. Chem. Phys.* **42**, 288.
- Keresztes, I. and Williard, P.G. (2000) *J. Am. Chem. Soc.*, **122**, 10228.
- Frish, L., Matthews, S.E., Böhmer, V., and Cohen, Y. (1999) *J. Chem. Soc., Perkin Trans. 2*, 669.
- Jayawickrama, D.A., Larive, C.K., McCord, E.F., and Roe, D.C. (1998) *Magn. Reson. Chem.*, **36**, 755.
- Eisenberg, R. (1991) *Acc. Chem. Res.*, **24**, 110.
- Duckett, S.B. and Sleight, C.J. (1999) Applications of the para-hydrogen phenomenon: a chemical perspective. *Prog. Nucl. Magn. Reson. Spectrosc.*, **34**, 71.
- Adams, R.W., Aguilar, J.A., Atkinson, K.D., Cowley, M.J., Elliott, P.I.P., Duckett, S.B., Green, G.G.R., Khazal, I.K., López-Serrano, J., and Willamson, D.C. (2009) *Science*, **323**, 1708.
- Raferty, D. and Chmelka, B.F. (1994) *NMR—Basic Principles*, Vol. 30, Springer-Verlag, Berlin, p. 111.
- Tersikh, V.V., Mudrskowski, I.L., and Mastikhin, V.M. (1993) *J. Chem. Soc., Faraday Trans.*, **89**, 4239.
- Oepen, S. (1995) PhD thesis, University of Siegen.
- Morris, G.A. (ed) (1992) *Special Issue: Structural Elucidation of Natural Products by NMR*, *Magn. Reson. Chem.* **30**, S1 – S142.
- Bast, P. (1995) PhD thesis, University of Siegen.
- Schwalbe, H., Schmidt, P., and Griesinger, C. (2010) in *Multidimensional NMR Methods for the Solution State*, (eds G.A. Morris and J.W. Emsley), John Wiley & Sons, Chichester, UK, p. 177.
- Kessler, H. and Schmitt, W. (1996) *Encyclopedia of Nuclear Magnetic Resonance* (editors in chief D.M. Grant and R.K. Harris), vol. 6, John Wiley & Sons, Ltd, Chichester, p. 3527.
- Wüthrich, K. (1996) *Encyclopedia of Nuclear Magnetic Resonance* (editors in chief D.M. Grant and R.K. Harris), vol. 5, John Wiley & Sons, Ltd, Chichester, p. 3449.
- Clare, G.M. and Gronenborn, A.M. (2010) in *Multidimensional NMR Methods for the Solution State* (eds G.A. Morris and J.W. Emsley), John Wiley & Sons, Inc., Hoboken, p. 351.
- a) Ikura, M., Kay, L.E., and Bax, A. (1990) *Biochemistry*, **29**, 4659; b) Marion, D., Driscoll, P.C., Kay, L.E., Wingfield, P.T., Bax, A., Gronenborn, A.M., and Clare, G.M. (1989) *Biochemistry*, **28**, 6150.
- Hilbers, C.W. and Wijmenga, S.S. (1996) *Encyclopedia of Nuclear Magnetic Resonance* (editors in chief D.M. Grant and R.K. Harris), vol. 5, John Wiley & Sons, Ltd, Chichester, p. 3346.
- Bast, P., Berger, S., and Günther, H. (1992) *Magn. Reson. Chem.*, **30**, 587.
- van Halbeck, H. (1996) *Encyclopedia of Nuclear Magnetic Resonance* (editors in chief D.M. Grant and R.K. Harris), vol. 2, John Wiley & Sons, Ltd, Chichester, p. 1107.

34. Bell, J.D. and Sadler, P.J. (1996) *Encyclopedia of Nuclear Magnetic Resonance* (editors in chief D.M. Grant and R.K. Harris), vol. 2, John Wiley & Sons, Ltd, Chichester, p. 989.
35. Gadian, D.G. (1982) *Nuclear Magnetic Resonance and Its Applications to Living Systems*, Clarendon Press, Oxford.
36. Grove, T.H., Ackermann, J.J.H., Radda, G.K., and Bore, P.J. (1980) *Proc. Natl. Acad. Sci. USA*, **77**, 299.
37. Ross, B.D., Radda, G.K., Gadian, D.G., Rocker, G., Esiri, M., and Falconer-Smith, J. (1981) *N. Engl. J. Med.*, **304**, 1338.
38. Lauterbur, P.C. (1973) *Nature*, **242**, 190.
39. Lauterbur, P.C. (1974) *Pure Appl. Chem.*, **40**, 149.
- Pelta, M.D., Bajart, H., Morris, G.A., Davis, A.L., and Hammond, S.J. (1998) Pulse sequences for high-resolution diffusion ordered spectroscopy (HR-DOSY), *Magn. Reson. Chem.* **36**, 706.
- Morris, G.A. (2010) Diffusion-Ordered Spectroscopy, in *Multidimensional NMR Methods for the Solution State*, (eds. Morris G.A., Emsley, J.W.), John Wiley & Sons, Chichester, UK, p. 515.
- Natterer, J. and Bargon, J. (1997) Parahydrogen Induced Polarization. *Prog. Nucl. Magn. Reson. Spectrosc.*, **31**, 293.
- Duckett, S.B. and Wood, N.J. (2008) Parahydrogen-based NMR methods as mechanistic probe in inorganic chemistry. *Coord. Chem. Rev.*, **252**, 2278.
- Romanenko, K.V. (2008) ^{129}X NMR studies of xenon adsorption. *Annu. Rep. NMR Spectrosc.*, **69**, 1.

Review Articles

Those cited in References [2, 19, 21, 26, 27, 28, 29, 31, 33, 34, 35] and in addition:

- Jameson, C.J. (1991) The dynamic and electronic factors in isotope effects on NMR parameters, in *Isotopes in the Physical and Biomedical Sciences* (eds E. Buncl and J.R. Jones), Elsevier, Amsterdam, p. 1.
- Berger, S. (1990) Chemical models for deuterium isotope effects in ^{13}C - and ^{19}F -NMR. *NMR–Basic Principles Prog.*, **22**, 1.
- Jankowski, S. (2007) Application of NMR spectroscopy in isotope effect studies. *Annu. Rep. NMR Spectrosc.*, **68**, 149.
- Martin, M.L. and Martin, G.J. (1991) Deuterium NMR in the study of site-specific natural isotope fractionation (SNIF-NMR). *NMR–Basic Principles and Progr.*, **23**, 1.
- Roth, H.D. (1996) Chemically induced dynamic nuclear polarization, in *Encyclopedia of Nuclear Magnetic Resonance* (editors in chief D.M. Grant and R.K. Harris), vol. 2, John Wiley & Sons, Ltd, Chichester, p. 1337.
- Goez, M. (2005) Photo-CIDNP spectroscopy. *Annu. Rep. NMR Spectrosc.*, **66**, 77.
- Cohen, Y., Avram, I., and Frish, L. (2005) Diffusion NMR Spectroscopy in Supramolecular and Combinatorial Chemistry; An Old Parameter – New Insights, *Angew. Chem.* **117**, 524; *Angew. Chem. Int. Ed. Engl.* **44**, 520.
- Günther, G.V. (2011) Dynamic nuclear hyperpolarization in liquids. *Top. Curr. Chem.*, **128**, 229.
- Lingwood, M.D. and Han, S. (2011) Solution state dynamic nuclear polarization. *Annu. Rep. NMR Spectrosc.*, **73**, 83.
- Jardetzky, O. (1996) Biological Macromolecules, in *Encyclopedia of Nuclear Magnetic Resonance* (editors in chief D.M. Grant and R.K. Harris), vol. 2, John Wiley & Sons, Ltd, Chichester, p. 901.
- Jardetzky, O. and Schmitt, T.H. (1996) Biological Macromolecules: NMR Parameters, in *Encyclopedia of Nuclear Magnetic Resonance* (editors in chief D.M. Grant and R.K. Harris), vol. 2, John Wiley & Sons, Ltd, Chichester, p. 921.
- Wüthrich, K. (1996) Biological Macromolecules: Structure Determination in Solution, in *Encyclopedia of Nuclear Magnetic Resonance* (editors in chief D.M. Grant and R.K. Harris), vol. 2, John Wiley & Sons, Ltd, Chichester, p. 932.
- Williamson, M.P. (2004) Applications of the NOE in molecular biology. *Annu. Rep. NMR Spectrosc.*, **65**, 77.
- Price, W.S. (1999) Water signal suppression in NMR spectroscopy. *Annu. Rep. NMR Spectrosc.*, **38**, 290.
- McKay, R.T. (2005) Recent advances in solvent suppression for solution NMR: a practical reference. *Annu. Rep. NMR Spectrosc.*, **66**, 33.

Appendix

1

The “Ring Current Effect” of the Benzene Nucleus

The effect of the magnetic anisotropy of the benzene nucleus on the resonance frequency of the neighboring protons is graphically represented in Figure A.1. Lines of equal shielding or deshielding are represented on a coordinate system, the origin of which lies at the center of the ring. The ordinate z (in units of the ring radius of 0.139 nm) runs along the sixfold rotational axis perpendicular to the plane of the ring and the abscissa ρ (also in units of the ring radius) runs from the center in the direction of a C–H bond. The contributions, $\Delta\sigma$ to the shielding constant σ are given in parts per million.

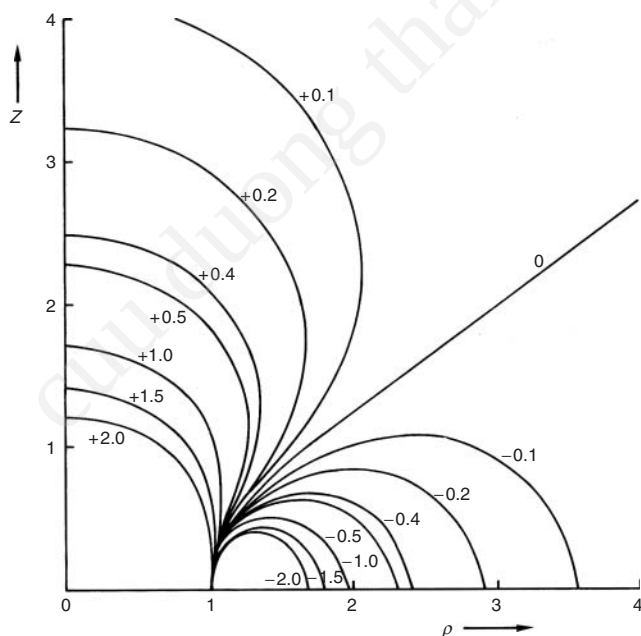


Figure A.1 Graphic representation of the influence of the diamagnetic anisotropy of the benzene ring on proton resonance frequencies. After Reference [1].

2

Tables of Proton Resonance Frequencies and Substituent Effects $S(\delta)$ Table A.1 Proton resonance frequencies (δ -scale, ppm) of selected organic compounds.

(a) Methyl and methylene protons

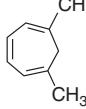
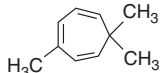
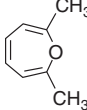
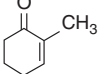
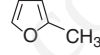
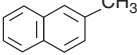
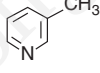
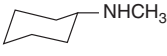
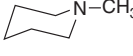
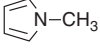
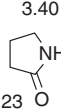
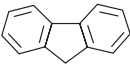
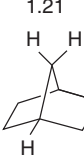
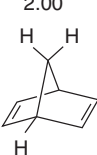
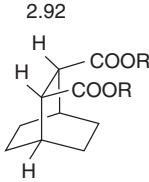
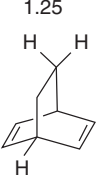
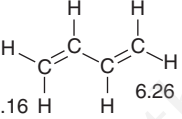
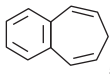
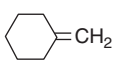
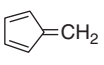
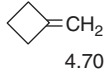
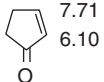
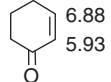
				
2.13	1.66	1.93	1.98	0.97
				
1.81	1.73	1.96	1.94	2.17
				
2.65	2.46	2.55	2.32	2.37
				
2.44	2.66	2.21	3.50	
				
0.22	0.86	1.51	1.54	2.04
				
1.27	0.93	2.57	2.60	2.20
				
1.96 3.03	2.22	2.23 3.40	3.75	1.51 3.52
				
3.81	3.92	2.01	1.84	

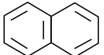
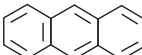
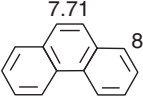
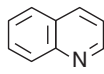
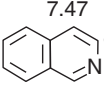
Table A.1 (Continued)

	5.90		2.87 3.67				
	1.21 1.49 1.18 2.20		2.00 3.53		2.92 2.02		1.25 3.59
(b) Aldehyde protons							
$\text{H}_3\text{C}-\text{CHO}$	9.72	$\text{H}_2\text{C}=\text{CH}-\text{CHO}$	9.53		10.0		
(c) Olefinic protons							
$\text{H}_2\text{C}=\text{CH}_2$	5.29		5.05 5.16 6.26		7.06		6.03
					5.60		
	5.59		5.70		6.43 6.28		5.79 5.68
					5.95		
	6.75		6.25		6.27		6.50 6.09
							5.27
	5.69		6.45 5.65		4.55		6.44 6.11 5.78
	4.70		7.71 6.10		6.88 5.93		4.82 6.22
							4.65 6.37

(continued overleaf)

Table A.1 (Continued)

(d) Aromatic protons

			
7.27	7.46 7.81	7.39 8.31 7.91	7.71 8.12 7.82 8.93 7.88
			
7.46 7.06 8.50	6.60 7.40	7.04 7.19	6.05 6.62 7.70 7.82 8.26 7.13 7.51 7.33
			
8.00 7.26 8.81	7.47 8.45 9.13	8.50	7.09 8.60 9.15

2.1

Substituent Effects $S(\delta)$ or SCS

The *Shoolery rule* provides information concerning the effect that the stepwise substitution of the hydrogen atoms in methane by other groups has on the proton resonance frequency. According to this rule, the δ value of a proton in the compound in question is given by Eq. (A.1), in which the $S(\delta)$ values given in Table A.2 are to be used:

$$\delta = 0.23 + \sum S(\delta) \quad (\text{A.1})$$

Table A.2 Substituent constants, $S(\delta)$, for proton resonances in substituted methanes.

Substituent	$S(\delta)$ (ppm)	Substituent	$S(\delta)$ (ppm)
Cl	2.53	$\text{C}\equiv\text{CH}$	1.44
Br	2.33	$\text{C}\equiv\text{N}$	1.70
I	1.82	CH_3	0.47
NRR'	1.57	Phenyl	1.85
OR	2.36	OH	2.56
SR	1.64	OCOR	3.13
CR-O	1.70	COOR	1.55
$\text{CR}=\text{CR}'\text{R}'$	1.32	CF_3	1.14

As an example, for the proton resonances in methyl chloride, methylene chloride, and chloroform, Eq. (A.1) yields values of δ 2.76, 5.29, and 7.82, respectively, which can be compared with the corresponding experimental data of δ 3.1, 5.3, and 7.27. Similarly, the resonance frequency of the tertiary proton in triphenylmethane is calculated as δ 4.22 and the experimental value is δ 4.70.

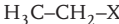
Table A.3 $S(\delta)$ values for substituted benzenes.

Substituent	$S(\delta)$ (ppm)		
	<i>ortho</i>	<i>meta</i>	<i>para</i>
NO ₂	0.95	0.17	0.33
CHO	0.58	0.21	0.27
COCl	0.83	0.16	0.3
COOH	0.8	0.14	0.2
COOCH ₃	0.74	0.07	0.20
COCH ₃	0.64	0.09	0.3
CN	0.27	0.11	0.3
C ₆ H ₅	0.18	—	0.08
CCl ₃	0.8	0.2	0.2
CHCl ₂	0.1	0.06	0.1
CH ₂ Cl	−0.0	0.01	0.0
CH ₃	−0.17	−0.09	−0.18
CH ₂ CH ₃	−0.15	−0.06	−0.18
CH(CH ₃) ₂	−0.14	−0.09	−0.18
C(CH ₃) ₃	0.01	−0.10	−0.24
CH ₂ OH	−0.1	−0.1	−0.1
CH ₂ NH ₂	−0.0	−0.0	−0.0
F	−0.30	−0.02	−0.22
Cl	0.02	−0.06	−0.04
Br	0.22	−0.13	−0.03
I	0.40	−0.26	−0.03
OCH ₃	−0.43	−0.09	−0.37
OCOCH ₃	−0.21	−0.02	—
OH	−0.50	−0.14	−0.4
<i>p</i> -CH ₃ C ₆ H ₄ SO ₃	−0.26	−0.05	—
NH ₂	−0.75	−0.24	−0.63
SCH ₃	−0.03	−0.0	—
N(CH ₃) ₂	−0.60	−0.10	−0.62
Ph ₃ C ⁺	+0.42	+0.57	+0.97
Ph ₃ C [−]	0.0	−0.73	−1.33

After Reference [2].

3 Tables of ^1H , ^1H Coupling Constants

Table A.4 ^1H , ^1H coupling constants (Hz) in selected organic molecules.

							
X	J_{cis}	J_{trans}	^2J	References	X	J	References
H	11.6	19.1	2.5	[3]	Li	8.90	[3]
Li	19.3	23.9	7.1	[3]	$\text{Si}(\text{C}_2\text{H}_5)_3$	8.0	[3]
COOH	10.2	17.2	1.7	[3]	H	7.5	[3]
CN	11.75	17.92	0.91	[3]	C_6H_5	7.62	[3]
C_6H_5	11.48	18.59	1.08	[3]	CN	7.60	[3]
CH_3	10.02	16.81	2.08	[3]	I	7.45	[3]
OCH_3	7.0	14.1	-2.0	[3]	Br	7.33	[3]
Cl	1.3	14.6	-1.4	[3]	CH_3	7.26	[3]
Br	7.1	15.2	-1.8	[3]	Cl	7.23	[3]
F	4.65	12.75	-3.2	[3]	$\text{N}(\text{C}_2\text{H}_5)_2$	7.13	[3]
					OC_2H_5	6.97	[3]
					$^+\text{O}(\text{C}_2\text{H}_5)_2$	4.7	[3]

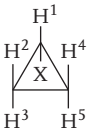
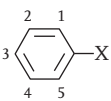
							
X	$J(1,2)$	$J(1,3)$	$J(2,4)$	$J(3,5)$	$J(2,5)$	$J(2,3)$	References
H	8.97	5.58	8.97	8.97	5.58	-4.34	[4]
Cl	7.01	3.58	10.26	10.58	7.14	-6.01	[5]
Br	7.13	3.80	10.16	10.45	7.01	-6.12	[5]
I	7.51	4.37	9.89	9.97	6.63	-5.94	[5]
NH_2	6.63	3.55	9.65	9.89	6.18	-4.29	[5]
CN	8.43	5.12	9.18	9.49	7.08	-4.72	[5]
COOH	8.04	4.57	9.26	9.66	7.14	-4.00	[5]
COCl	7.88	4.43	9.19	9.99	7.59	-4.46	[5]
COCH_3	7.96	4.55	8.76	9.60	6.94	-3.41	[5]

Table A.4 (Continued)



X	$J(1,2)$	$J(1,3)$	$J(1,4)$	$J(1,5)$	$J(2,3)$	$J(2,4)$	References
H	7.54	1.37	0.66	1.37	7.54	1.37	[6]
Li	6.73	1.54	0.77	0.74	1.42	1.29	^a
CH ₃	7.64	1.25	0.60	1.87	7.52	1.51 ^b	[7]
COOCH ₃	7.86	1.35	0.63	1.79	7.49	1.31	[8]
I	7.93	1.14	0.47	1.88	7.47	1.75	[8]
Br	8.05	1.12	0.46	2.1	7.44	1.78	[8]
Cl	8.05	1.13	0.48	2.27	7.51	1.72	[8]
NH ₂	8.02	1.11	0.47	2.53	7.39	1.60	[9]
N(CH ₃) ₂	8.40	1.01	0.43	2.76	7.29	1.76	[9]
N(CH ₃) ₃	8.55	0.92	0.48	3.05	7.46	1.69	[9]
NO ₂	8.36	1.18	0.55	2.40	7.47	1.48	[9]
OH	8.17	1.09	0.49	2.71	7.40	1.74	[9]
OCH ₃	8.30	1.03	0.44	2.94	7.36	1.76	[9]
F	8.36	1.07	0.43	2.74	7.47	1.82 ^c	[8]

^aS. Castellano (personal communication)^b $J(1, \text{CH}_3) -0.75$, $J(2, \text{CH}_3) 0.36$, and $J(3, \text{CH}_3) -0.62$.^c $J(1, \text{F}) 8.91$, $J(2, \text{F}) 5.69$, and $J(3, \text{F}) 0.22$.Substituent effects $S(j)$ for H,H coupling constants in mono-substituted benzenes [10].

J_{ij}	F	Cl	Br	I	NO ₂	OCH ₃
12	+0.81	+0.61	+0.53	+0.39	+0.77	+0.79
13	-0.34	-0.23	-0.27	-0.25	-0.20	-0.32
14	-0.24	-0.16	-0.20	-0.19	-0.16	-0.22
15	+1.21	+0.87	+0.71	+0.51	+1.02	+1.33
23	-0.04	+0.03	-0.05	-0.04	-0.07	-0.16
24	+0.39	+0.34	+0.36	+0.37	+0.08	+0.38

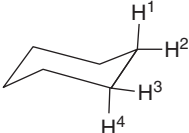
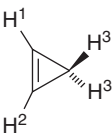
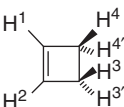
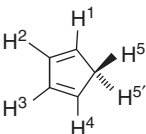
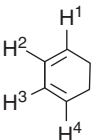
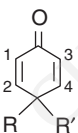
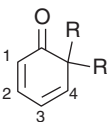
(continued overleaf)

Table A.4 (Continued)

$J(1,2)$	8.9	8.75	10.14	8.2	8.4
$J(1,3) + J(1,4)$	1.48	1.50	—	1.27	1.38
$J(1,5)$	—	—	-0.25	—	—
$J(1,6)$	—	—	0.22	—	—
$J(2,3)$	5.51	5.59	—	6.97	6.81
$J(2,4)$	0.72	0.54	—	0.73	0.77
$J(2,5)$	0.69	0.76	0.57	0.51	0.34
$J(3,4)$	11.17	10.96	—	8.45	8.43
$J(1,7)$	—	5.89	—	3.17	2.75
$J(1,7')$	6.7	—	6.47	8.90	8.70
$J(2,7)$	—	1.42	—	-1.07	-1.32
$J(2,7')$	0.4	—	-0.74	0.92	0.94
$J(3,7)$	—	0.32	—	—	—
$J(7,7')$	-13.0	—	—	-14.05	-14.14
References	[11]	[12]	[13]	[14]	[11]

Structure	Coupling constants			References
	$^3J_{\text{cis}}$ 4.45	$^3J_{\text{trans}}$ 3.1	^3J 5.5	[15]
	7.15	5.65	<0.4	[15]
	6.3	3.8	2.0	[15]

Table A.4 (Continued)

Structure	Coupling constants				References		
	$J(1,2)$	$J(1,3)$	$J(1,4)$	$J(2,3)$	[16]		
	-13.05	3.65	13.12	2.96			
	$J(1,2)$	$J(1,3)$			[17]		
	1.3	1.75					
	$J(1,2)$	$J(1,3)$	$J(1,4)$	$J(3,3')$	$J(3,4)$	$J(3,4')$	[18]
	2.85	-0.35	1.0	-12.00	4.65	1.75	
	$J(1,2)$	$J(1,3)$	$J(1,4)$	$J(2,3)$	$J(1,5)$	$J(2,5)$	[19]
	5.05	1.09	1.98	1.91	1.33	-1.51	
	$J(1,2)$	$J(1,3)$	$J(1,4)$	$J(2,3)$			[19]
	9.64	1.02	1.12	5.04			
	$J(1,2)$	$J(1,3)$	$J(1,4)$	$J(2,4)$			[20]
	10.2	1.9	0.1	3.0			
	$J(1,2)$	$J(1,3)$	$J(1,4)$	$J(2,3)$	$J(2,4)$	$J(3,4)$	[21]
	9.76	0.90	0.88	5.78	1.80	9.45	

(continued overleaf)

Table A.4 (Continued)

Structure	Coupling constants					References	
	$J(1,2)$	$J(1,3)$	$J(1,4)$	$J(1,5)$	$J(1,6)$	[22]	
	1.74	10.17	-0.86	0.60	1.30		
	$J(2,3)$	$J(2,4)$	$J(2,5)$	$J(3,4)$			
	17.05	-0.83	0.60	10.41			
	$J(1,2)$	$J(1,3)$	$J(1,4)$	$J(2,3)$	[6]		
	7.54	1.37	0.66	7.54			
	8.28	1.24	0.74	6.85	[23]		
	8.55	1.20	0.82	6.59	[23]		
	6.80	0.74	1.08	8.24	[24]		
	1.75	0.85	1.4	3.3	[25]		
	5.00	1.06	2.80	3.50	[26]		
	4.88	1.24	1.00	7.67	[27]		
	$J(1,5)$	$J(2,4)$					
	-0.13	1.97					
	X	$J(1,2)$	$J(1,3)$	$J(1,4)$	$J(2,3)$	[28]	
	CH ₂	8.97	-0.02	1.46	9.19		
	O	8.77	0.28	1.13	9.28		
	NH	8.82	0.06	1.50	9.31	[29]	

4

Chemical Shifts and Substituent Effects $S(\delta)$ of ^{13}C Resonances in Organic CompoundsTable A.5 ^{13}C resonances of common solvents.

Solvent	δ_{TMS} (ppm)	
	Hydrogen compound	Perdeuterated compound
Cyclohexane	27.51	26.06
Acetone	30.43	29.22
Dimethyl sulfoxide	40.48	39.56
Dichloromethane	54.02	53.61
Dioxane	67.40	—
Chloroform	77.17	76.91
Carbon tetrachloride	95.99	—
Benzene	128.53	127.96
Acetic acid (^aCO)	178.27	—
Carbon disulfide	192.8	—
Carbon disulfide ^a	193.7	—

After Reference [30].

^aRelative to external TMS at 0.0 ppm.Table A.6 δ (^{13}C) values (ppm) for selected compounds [31–37].

Alkanes				
Compound	C_1	C_2	C_3	C_4
Methane	−2.3	—	—	—
Ethane	5.7	—	—	—
Propane	15.4	15.9	—	—
Butane	3.0	24.8	—	—
Pentane	13.7	22.6	34.5	—
Hexane	13.9	22.9	32.0	—
Heptane	13.9	23.0	32.4	29.5

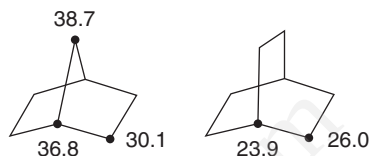
(continued overleaf)

Table A.6 (Continued)

Cycloalkanes

Ring size

3	-2.6		
4	23.3		
5	26.5		
6	27.8		
7	29.4		
8	27.8		
9	27.0		
10	26.2		



Alkenes

Compound	C ₁	C ₂
Ethylene	123.3	—
I-	85.3	130.4
Br-	115.5	122.0
Cl-	126.0	117.3
F-		
COOEt	129.7	130.4
OCH ₃	153.2	84.1
OCOCH ₃	141.6	96.3
CH ₂ =CH-	136.9	116.3

Cycloalkenes

Ring size

	—C=	α-CH ₂	β-CH ₂	γ-CH ₂
3	108.9	2.3	—	—
4	137.2	31.4	—	—
5	130.2	32.3	22.7	—
6	126.9	25.1	22.6	—
7	132.1	29.0	27.3	32.0

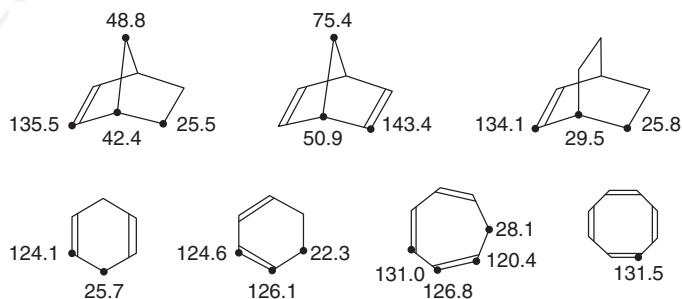
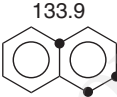
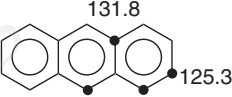
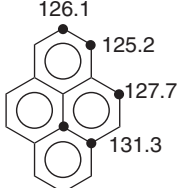
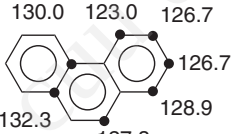
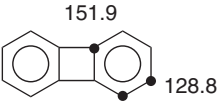
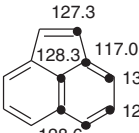
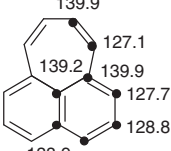
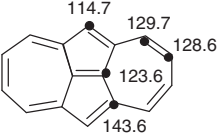
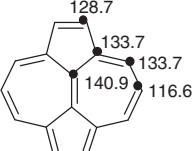


Table A.6 (Continued)

Benzocycloalkenes						
Ring size	C ₁	C ₂	C ₃	$\alpha\text{-CH}_2$	$\beta\text{-CH}_2$	$\gamma\text{-CH}_2$
3	125.4	114.7	128.8	18.4	—	—
4	145.2	122.1	126.5	29.5	—	—
5	143.3	124.0	125.8	32.7	25.2	—
6	136.4	128.8	125.2	29.3	23.3	—
7	142.7	128.7	125.7	36.6	28.2	32.6
8	140.6	128.7	126.0	32.1	25.8	32.1

Alkynes		
$\text{HC}^1\equiv\text{C}^2\text{-X}$	C ₁	C ₂
-H	71.9	71.9
-C ₄ H ₉	66.0	83.0
-C ₆ H ₅	77.7	83.3
-SCH ₂ CH ₃	81.4	72.6

Aromatic compounds		
		
128.5	128.3	128.1
		
124.9	132.3	137.4
		
129.7	128.8	128.6
		
128.7		

(continued overleaf)

Table A.6 (Continued)

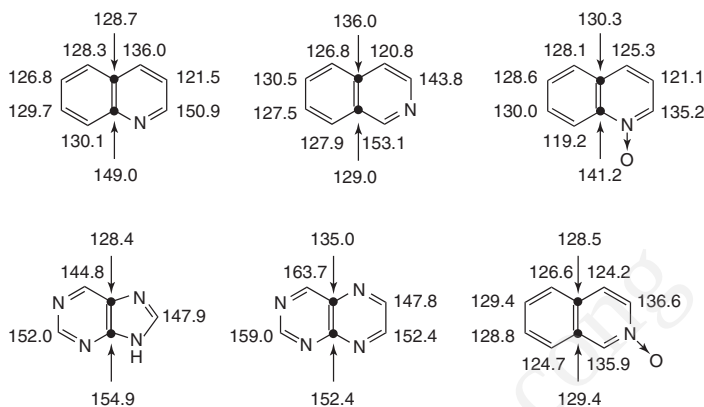
Substituted benzenes

$$\delta = 128.5 + S_i (\delta_j)$$

Substituent	$S_i (\delta_1)$	$S_i (\delta_\sigma)$	$S_i (\delta_m)$	$S_i (\delta_p)$
-H	0.0	0.0	0.0	0.0
-CH ₃	9.3	0.6	0.0	-3.1
-CH ₂ CH ₃	15.7	-0.6	-0.1	-2.8
-CH(CH ₃) ₂	20.1	-2.0	0.0	-2.5
-C(CH ₃) ₃	22.1	-3.4	-0.4	-3.1
-Cyclopropyl	15.1	-3.3	-0.6	-3.6
-CH ₂ Cl	9.1	0.0	0.2	-0.2
-CH ₂ Br	9.2	0.1	0.4	-0.3
-CF ₃	2.6	-2.2	0.3	3.2
-CH ₂ OH	13.0	-1.4	0.0	-1.2
-CH=CH ₂	7.6	-1.8	-1.8	-3.5
-C≡CH	-6.1	3.8	0.4	-0.2
-C ₆ H ₅	13.0	-1.1	0.5	-1.0
-F	35.1	-14.3	0.9	-4.4
-Cl	6.4	0.2	1.0	-2.0
-Br	-5.4	3.3	2.2	-1.0
-I	-32.3	9.9	2.6	-0.4
-OH	26.9	-12.7	1.4	-7.3
-OCH ₃	30.2	-14.7	0.9	-8.1
Substituent	$S_i (\delta_1)$	$S_i (\delta_\sigma)$	$S_i (\delta_m)$	$S_i (\delta_p)$
-NH ₂	19.2	-12.4	1.3	-9.5
-N(CH ₃) ₂	22.4	-15.7	0.8	-11.8
-N(C ₆ H ₅) ₂	19.3	-4.4	0.6	-5.9
-NO ₂	19.6	-5.3	0.8	6.0
-CN	-16.0	3.5	0.7	4.3
-NCO	5.7	-3.6	1.2	-2.8
-SC(CH ₃) ₃	4.5	9.0	-0.3	0.0
-COH	9.0	1.2	1.2	6.0
-COCH ₃	9.3	0.2	0.2	4.2
-COOH	2.4	1.6	-0.1	4.8
-COO ⁻	7.6	0.8	0.0	2.8
-COOCH ₃	2.1	1.2	0.0	4.4
-COCl	4.6	2.9	0.6	7.0

Table A.6 (Continued)

Heterocyclic compounds



Compound	C_α	C_β	C_γ
Oxirane	39.5	—	—
Oxetane	72.6	22.9	—
Tetrahydrofuran	68.4	26.5	—
Tetrahydropyran	69.8	27.0	24.2
Dioxane	67.4	—	—
Azirine, $N\text{-CH}_3$	28.5	—	—
Azetidine, $N\text{-CH}_3$	57.7	17.5	—
Tetrahydropyrrole	56.7	24.4	—
Piperidine	47.9	27.8	25.9
Thietane	18.7	—	—
Tetrahydrothiopyran	27.5	29.7	—
Furan	143.0	109.9	—
Pyrrole	118.7	107.7	—
Thiophene	124.9	126.4	—
Pyridine	149.9	123.8	136.0
Pyridinium ion	141.9	128.5	148.6
Pyridine N -oxide	139.1	126.4	126.4

5

The Hamiltonian Operator in Polar Coordinates

When polar coordinates are used instead of Cartesian coordinates, the following relations hold (Figure A.2):

$$x = r \sin \theta \cos \phi$$

$$y = r \sin \theta \sin \phi$$

$$z = r \cos \theta$$

With the substitution of these values, the Hamiltonian operator [Eq. (6.3)] becomes:

$$\mathcal{H} = \frac{-\hbar^2}{8\pi^2m} \left[\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial}{\partial r} \right) + \frac{1}{r^2 \sin \theta} \frac{\partial}{\partial \theta} \left(\sin \theta \frac{\partial}{\partial \theta} \right) + \frac{1}{r^2 \sin^2 \theta} \frac{\partial^2}{\partial \phi^2} \right] + V \quad (\text{A.2})$$

For the model of the electron on a circle, r is a constant and θ is 90° . Under these conditions the first and the second terms in the square brackets are zero and Eq. (A.2) simplifies to Eq. (6.4).

$$x = r \sin \theta \cos \phi \quad y = r \sin \theta \sin \phi$$

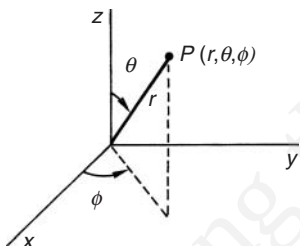


Figure A.2 Definition of polar coordinates.

6

Intensity Distribution in A-multiplets Caused by n Neighbouring X-Nuclei with Spin

$$I = 1 \text{ or } I = \frac{3}{2}$$

n	$I = 1$								$I = \frac{3}{2}$															
0	1								1															
1				1	1	1								1	1	1	1							
2				1	2	3	2	1				1	2	3	4	3	2	1						
3			1	3	6	7	6	3	1		1	3	6	10	12	12	10	6	3	1				
4		1	4	10	16	19	16	10	4	1	1	4	10	20	31	40	44	40	31	20	10	4	1	

Reference [38]

7

Commutable Operators

We consider two operators $\hat{Q}$ and $\hat{R}$. For $\hat{Q}$ the eigenvalue equation:

$$\hat{Q}\Psi_m = q_m\Psi_m \quad (\text{A.3})$$

with the eigenfunction Ψ_m and the eigenvalue q_m holds. A matrix element $\langle\Psi_n|\hat{R}\hat{Q}\Psi_m\rangle$ may then be rewritten as:

$$\langle\Psi_n|\hat{R}\hat{Q}\Psi_m\rangle = q_m\langle\Psi_n|\hat{R}\Psi_m\rangle \quad (\text{A.4})$$

Since $\hat{R}$ and $\hat{Q}$ commute it also holds that:

$$\langle\Psi_n|\hat{R}\hat{Q}\Psi_m\rangle = \langle\Psi_n|\hat{Q}\hat{R}\Psi_m\rangle \quad (\text{A.5})$$

and $\hat{Q}$ are Hermitian operators so it follows that:¹⁾

$$\langle\phi|\hat{R}|\lambda\rangle = \langle\hat{R}\phi|\lambda\rangle \text{ and } \langle\phi|\hat{Q}|\lambda\rangle = \langle\hat{Q}\phi|\lambda\rangle \quad (\text{A.6})$$

Then Eq. (A.5) yields:

$$\langle\Psi_n|\hat{Q}\hat{R}\Psi_m\rangle = \langle\hat{Q}\Psi_n|\hat{R}\Psi_m\rangle = q_n\langle\Psi_n|\hat{R}\Psi_m\rangle \quad (\text{A.7})$$

With Eqs (A.4) and (A.5) one obtains:

$$q_m\langle\Psi_n|\hat{R}\Psi_m\rangle = q_n\langle\Psi_n|\hat{R}\Psi_m\rangle$$

or :

$$(q_m - q_n)\langle\Psi_n|\hat{R}\Psi_m\rangle = 0 \quad (\text{A.8})$$

For $q_n \neq q_m$ this equation holds only if the expression $\langle\Psi_n|\hat{R}\Psi_m\rangle$ becomes zero. Thus we have proved the expression introduced on p. 163.

8

The F_z Operator

The magnetic quantum number of an individual nucleus, i , is $m_I(i)$. The product functions for a spin system with several nuclei are characterized by the total spin m_T , the sum of the magnetic quantum numbers of the individual nuclei:

$$m_T = \sum_i m_I(i) \quad (\text{A.9})$$

By analogy with this, $\hat{I}_z$ is defined as the nuclear spin operator for an individual nucleus and the operator $\hat{F}_z$ is defined as the sum of the nuclear spin operators of the nuclei of the spin system under consideration:

$$\hat{F}_z = \sum_i \hat{I}_z(i) \quad (\text{A.10})$$

1) All operators that are associated with real physical properties have this important property.

All product functions ϕ_k are eigenfunctions of $\hat{F}_z$ the eigenvalues of which are the m_T values. Since the $\hat{F}_z$ operator commutes with the Hamiltonian operator the Hamiltonian matrix factorizes into submatrices because matrix elements of the type $\langle \phi_k | H | \phi_1 \rangle$ vanish when ϕ_k and ϕ_1 are product functions with different total spin, that is, with different eigenvalues of the $\hat{F}_z$ operator.

9

Equations for the Direct Analysis of AA'BB' Spectra

The following equations, which we present without proof, are used for direct analysis of AA'BB' systems:

$$\nu_0 \delta = \sqrt{4ab} = \sqrt{2(ce - df)}$$

$$N = a - b$$

$$K = g + i + k - 2a - l$$

$$= 2b + k - h - j - l$$

$$= b + g + k - a - h - l$$

$$= b + i + k - a - j - l$$

$$M = (ce - df)/\nu_0 \delta$$

$$L = \sqrt{(c - e)^2 - M^2}$$

$$= \sqrt{(d - f)^2 - M^2}$$

The frequencies of the lines a , b , and so on are relative to the center of the spectrum at $(\nu_A + \nu_B)/2$.

In practice, the analysis begins with assignment of the experimental lines to the specific transitions of the energy level diagram (Figure 6.20, p. 196). For this purpose the following equations that relate certain line separations are helpful:

$$c - d = e - f$$

$$g - h = i - j$$

$$g - a = b - j$$

$$a - i = h - b$$

Difficulties may arise if too many transitions are degenerate. In several cases there is also an overlap of the AA' and BB' portion in the center of the spectrum. In general, however, enough experimental information can be gathered to derive at least an approximate parameter set that can be refined by iterative computer analysis [39–42].

10

Bloch Equations

According to classical theory, the behavior of a magnetic moment $\mathbf{M}$ in a magnetic field $\mathbf{B}$ is described by the equation of motion:

$$\frac{d\mathbf{M}}{dt} = \gamma[\mathbf{M} \times \mathbf{B}] \quad (\text{A.11})$$

In the NMR experiment the static magnetic field $\mathbf{B}_0$ and the rotating field $\mathbf{B}_1$ contribute to the field $\mathbf{B}$. $\mathbf{B}_0$ coincides with the z -axis in Cartesian coordinates while $\mathbf{B}_1$ rotates with a frequency ω clockwise in the x - y plane (cf. Figure 8.1, p. 235). Thus the components of $\mathbf{B}$ are:

$$\begin{aligned} B_x &= B_1 \cos \omega t \\ B_y &= -B_1 \sin \omega t \\ B_z &= B_0 \end{aligned}$$

and the vector product in Eq. (A.11) can be resolved as follows:

$$\frac{dM_x}{dt} = \gamma(M_y B_0 + M_z B_1 \sin \omega t) \quad (\text{A.12a})$$

$$\frac{dM_y}{dt} = \gamma(M_z B_1 \cos \omega t - M_x B_0) \quad (\text{A.12b})$$

$$\frac{dM_z}{dt} = \gamma(-M_x B_1 \sin \omega t - M_y B_1 \cos \omega t) \quad (\text{A.12c})$$

Here we made use of the general relation for the product of two vectors $\mathbf{A}$ and $\mathbf{B}$:

$$[\mathbf{A} \times \mathbf{B}] = (A_y B_z - A_z B_y)\mathbf{i} + (A_z B_x - A_x B_z)\mathbf{j} + (A_x B_y - A_y B_x)\mathbf{k}$$

where $\mathbf{i}$, $\mathbf{j}$, and $\mathbf{k}$ are the coordinate unit vectors.

For the time dependence of the magnetization we must, in addition, consider relaxation effects. These effects were included by Bloch phenomenologically in Eq. (A.3a–c). The relaxation time T_2 is characteristic for the transverse magnetization in the x - y plane while the variation of the longitudinal magnetization along the z -axis is a function of T_1 . The complete Bloch equations thus take the form:

$$\frac{dM_x}{dt} = \gamma(M_y B_0 + M_z B_1 \sin \omega t) - \frac{M_x}{T_2} \quad (\text{A.13a})$$

$$\frac{dM_y}{dt} = \gamma(M_z B_1 \cos \omega t - M_x B_0) - \frac{M_y}{T_2} \quad (\text{A.13b})$$

$$\frac{dM_z}{dt} = \gamma(-M_x B_1 \sin \omega t - M_y B_1 \cos \omega t) - \frac{M_z - M_0}{T_1} \quad (\text{A.13c})$$

One now introduces the rotating coordinate system C' in which B_1 is stationary, so that:

$$\begin{aligned} M_x &= M_{y'} \cos \omega t - M_{x'} \sin \omega t \\ M_y &= -M_{y'} \sin \omega t - M_{x'} \cos \omega t \end{aligned}$$

In the rotating frame, these equations simplify to:

$$\frac{dM_{x'}}{dt} = -(\omega_0 - \omega)M_{y'} - \frac{M_{x'}}{T_2} \quad (\text{A.14a})$$

$$\frac{dM_{y'}}{dt} = (\omega_0 - \omega)M_{x'} - \gamma B_1 M_z - \frac{M_{y'}}{T_2} \quad (\text{A.14b})$$

$$\frac{dM_z}{dt} = \gamma B_1 M_{y'} - \frac{M_z - M_0}{T_1} \quad (\text{A.14c})$$

Here M_0 is the equilibrium magnetization that is present in the magnetic field B_0 at the beginning of the experiment.

Under the conditions of slow adiabatic passage through the resonance – attained by variation of the frequency ω or the field strength B_0 , that is, the Larmor frequency ω_0 – the time dependence of the components M_z , $M_{x'}$, and $M_{y'}$ can be ignored. Equations (A.14) then have the following solutions:

$$M_{x'} = M_0 \frac{\gamma B_1 T_2^2 (\omega_0 - \omega)}{1 + T_2^2 (\omega_0 - \omega)^2 + \gamma^2 B_1^2 T_1 T_2} \quad (\text{A.15a})$$

$$M_{y'} = -M_0 \frac{\gamma B_1 T_2}{1 + T_2^2 (\omega_0 - \omega)^2 + \gamma^2 B_1^2 T_1 T_2} \quad (\text{A.15b})$$

$$M_z = M_0 \frac{1 + T_2^2 (\omega_0 - \omega)^2}{1 + T_2^2 (\omega_0 - \omega)^2 + \gamma^2 B_1^2 T_1 T_2} \quad (\text{A.15c})$$

From Equation (A.15b) the shape of the absorption signal can be derived. Back transformation into the fixed laboratory frame yields for M_x and M_y :

$$M_x = \frac{1}{2} M_0 \gamma T_2 \frac{T_2 (\omega_0 - \omega) 2B_1 \cos \omega t + 2B_1 \sin \omega t}{1 + T_2^2 (\omega_0 - \omega)^2 + \gamma^2 B_1^2 T_1 T_2} \quad (\text{A.16a})$$

$$M_y = \frac{1}{2} M_0 \gamma T_2 \frac{2B_1 \cos \omega t - T_2 (\omega_0 - \omega) 2B_1 \sin \omega t}{1 + T_2^2 (\omega_0 - \omega)^2 + \gamma^2 B_1^2 T_1 T_2} \quad (\text{A.16b})$$

Reference [43].

11

Bloch Equations Modified for Chemical Exchange

For the case in which two or more nuclei, as a result of a fast equilibrium, periodically exchange their chemical environment and thus their Larmor frequencies, the Bloch equations for NMR line shape calculations must be modified. This is

done most easily by combining Eqs (A.14a) and (A.14b) and defining a complex x - y magnetization, G :

$$G = M_{x'} + iM_{y'} \quad (\text{A.17})$$

If one assumes that $M_z \approx M_0$, as is reasonable for weak B_1 fields, it then follows that:

$$\frac{dG}{dt} = i(\omega_0 - \omega)G - i\gamma B_1 M_0 - \frac{1}{T_2} G \quad (\text{A.18a})$$

$$\frac{dM_z}{dt} = \gamma B_1 M_{y'} - \frac{M_z - M_0}{T_1} \quad (\text{A.18b})$$

In the absence of exchange for the positions A and B with the resonance frequencies ω_a and ω_b , it also holds that:

$$\frac{dG_A}{dt} + \alpha_A G_A = -i\gamma B_1 M_{0A} \quad (\text{A.19a})$$

and:

$$\frac{dG_B}{dt} + \alpha_B G_B = -i\gamma B_1 M_{0B} \quad (\text{A.19b})$$

with $\alpha_A = 1/T_{2A} - i(\omega_A - \omega)$ and $\alpha_B = 1/T_{2B} - i(\omega_B - \omega)$.

Through the equilibrium reaction x , y magnetization is transferred from A to B and back again. If one ignores the nuclear precession during the transitions from A and B and from B to A, Eq. (A.19) can be extended as follows:

$$\frac{dG_A}{dt} + \alpha_A G_A = -i\gamma B_1 M_{0A} + G_B/\tau_B - G_A/\tau_A \quad (\text{A.20a})$$

$$\frac{dG_B}{dt} + \alpha_B G_B = -i\gamma B_1 M_{0B} + G_A/\tau_A - G_B/\tau_B \quad (\text{A.20b})$$

where the quantities $1/\tau_A = k_A$ and $1/\tau_B = k_B$ denote the probability that a nucleus undergoes a transition from A to B or from B to A.

For adiabatic passage through resonance again a stationary state is assumed, that is, $dG_A/dt = dG_B/dt = 0$. With $M_{0A} = p_A M_0$ and $M_{0B} = p_B M_0$, where p_A and p_B are the corresponding molar fractions, one obtains:

$$G - G_A + G_B = -\gamma B_1 M_0 \frac{\tau_A + \tau_B + \tau_A \tau_B (\alpha_A p_B + \alpha_B p_A)}{(1 + \alpha_A p_A)(1 + \alpha_B p_B) - 1} \quad (\text{A.21})$$

This equation contains the real and the imaginary parts of the x , y magnetization. For the calculation of the absorption signal that, according to Eq. (A.21), corresponds to the imaginary part, the two must be separated. This can be done either by using a computer program or by solving Eq. (A.21) and separating the imaginary part. In the last case one obtains Eq. (A.22) shown below for the *line shape* $g(\nu)$, in which all quantities are expressed in hertz ($\omega = 2\pi\nu$) and the spectrum is related to $(\nu_A + \nu_B)/2$ as the reference point. In addition, for simplification it was assumed that $1/T_{2A} = 1/T_{2B}$:

$$g(\nu) = [(1 + \tau \pi \Delta_{1/2})P + QR]/(4\pi^2 P^2 + R^2) \quad (\text{A.22})$$

where:

P	$=$	$(0.25\Delta_{1/2}^2 - v^2 + 0.25\delta v^2)\tau + \Delta_{1/2}/4\pi$
Q	$=$	$[-v - 0.5(p_A - p_B)\delta v]\tau$
R	$=$	$0.5(p_A - p_B)\delta v - v(1 + 2\pi\tau\Delta_{1/2})$

The parameter τ represents $\tau_A\tau_B/(\tau_A + \tau_B)$ and the symbols above have the following meanings:

τ_A, τ_B	Average life-time times (s) of the nuclei in positions A and B, respectively
p_A, p_B	Molar fractions of components A and B, respectively
$\delta v = \nu_A - \nu_B$	Difference between the resonance frequencies of the nuclei in positions A and B (Hz)
$\Delta_{1/2}$	Width at half-height (Hz) of the signal in the absence of exchange ($\tau \rightarrow \infty$) in which case $\Delta_{1/2}(A)$ would be set equal to $\Delta_{1/2}(B)$ for simplicity
ν	Variable frequency (Hz).

Equation (A.22) was programmed and used to calculate the temperature-dependent spectra shown in Figure 13.4 (p. 508) [44, 45].

Finally, we shall show how the treatment of the Bloch equations set forth above may be extended to deal with exchange phenomena where more than two positions with different Larmor frequencies are involved. Assuming an exchange between three positions that have the Larmor frequencies ω_1 , ω_2 , and ω_3 , one obtains for adiabatic passage:

$$(\alpha_1 + k_{12} + k_{13})G_1 - k_{21}G_2 - k_{31}G_3 = -i\gamma B_1 p_1 M_0 \quad (\text{A.23a})$$

$$-k_{12}G_1 + (\alpha_2 + k_{21} + k_{23})G_2 - k_{32}G_3 = -i\gamma B_1 p_2 M_0 \quad (\text{A.23b})$$

$$-k_{13}G_1 - k_{23}G_2 + (\alpha_3 + k_{31} + k_{32})G_3 = -i\gamma B_1 p_3 M_0 \quad (\text{A.23c})$$

In matrix notation this can be written as:

$$\hat{\mathbf{A}}\hat{\mathbf{G}} = -iC\hat{\mathbf{P}} \quad (\text{A.24})$$

where $\hat{\mathbf{A}}$ is a quadratic matrix, C is a constant ($= \gamma B_1 M_0$), and $\hat{\mathbf{P}}$ and $\hat{\mathbf{G}}$ are column vectors. If one multiplies from the left by the inverse of $\hat{\mathbf{A}}$ one obtains:

$$\hat{\mathbf{G}} = -iC\hat{\mathbf{A}}^{-1}\hat{\mathbf{P}} \quad (\text{A.25})$$

For the summation over all G_i that must be carried out for the calculation of the total x, y magnetization, G_T , Eq. (A.25) is multiplied from the left by the row vector $\hat{\mathbf{1}}$:

$$G_T = \hat{\mathbf{1}}\hat{\mathbf{G}} = -iC\hat{\mathbf{1}}\hat{\mathbf{A}}^{-1}\hat{\mathbf{P}} \quad (\text{A.26})$$

The imaginary part of Eq. (A.26) gives the absorption signal, the calculation of which may be accomplished by using an appropriately programmed computer. For our example, Eq. (A.26) has the form:

$$G_T = -iC[1, 1, 1] \hat{A}^{-1} \begin{bmatrix} p_1 \\ p_2 \\ p_3 \end{bmatrix} \quad (\text{A.27})$$

According to above the matrix $\hat{A}$ is given by:

$$\hat{A} = 2\pi i(\hat{I}\nu - \hat{W}) + \pi\hat{\Delta} + \hat{X} \quad (\text{A.28})$$

where:

$\hat{I}$	=	The unit matrix
ν	=	The variable frequency (in hertz)
$\hat{W}$	=	The diagonal matrix of the Larmor frequencies ν_i in the individual positions (in hertz)
$\pi\hat{\Delta}$	=	The diagonal matrix of the natural line widths Δ (in hertz) in the individual positions.
$\hat{X}$	=	The matrix of the reaction rate constants k with the elements $x_{ii} = \sum_{j(j \neq i)} k_{ij}$ and $x_{ij} = -k_{ji}$

The same result is obtained on the basis of the theory of Anderson, Kubo, and Sack that was derived from quantum mechanical principles [44, 46].²⁾

Various software programs are available to deal with different mechanisms of chemical exchange in NMR spectra that affect chemical shifts or line splittings due to spin–spin coupling. The most advanced program is DNMR5 of G. Binsch and D.S. Stephenson [47]. To deal with two-site exchange the program MEXICO from the group of A. Bain [48] is a useful alternative.

12

Phase Behavior of Cross Peaks in 2D Nuclear Overhauser Spectroscopy (NOESY), Rotating-Frame Overhauser Spectroscopy (ROESY), Total Correlation Spectroscopy (TOCSY) and Chemical Exchange (EXSY) Experiments

Sign of the diagonal signal ^a	Origin of cross-peak	Sign of cross-peak
Positive	Positive NOE	Negative
	Negative NOE	Positive
	ROESY	Negative
	TOCSY	Positive
	EXSY	Positive

^aBy convention diagonal signals are phased to be positive.

- 2) One should note that the corresponding equations in the references cited are formally different because of a different choice of signs and the arrangement of certain quantities.

13

The International System (SI) of Units (MKSA System)

In the past, physical quantities in chemistry were expressed in general in units of the centimeter-gram-second (CGS) system. More recently, however, an international agreement to adopt the meter-kilogram-second-ampere (MKSA) or SI system was reached and the new convention began to be employed by chemists. Since 1973 the use of the SI system has been required by research journals in chemistry.

A comparison of the two systems can be made by a reference to Table A.7, where we have presented the units important to the subject of this text. Significantly, for nuclear magnetic resonance, in the SI system the units for magnetic field strength, H , and magnetic induction, B , differ by a factor of $4\pi \times 10^{-7}$ while in the CGS system the two quantities are measured in the same units ($\text{dyn}^{1/2} \text{cm}^{-1}$). Moreover, it has been customary to express field strength incorrectly in gauss rather than in the correct units of oersted. Since the observed physical properties are functions of B rather than H ($B = H$ only in vacuum), the use of B is correct in the SI system. The two systems also differ significantly in the units in which quantities of energy are expressed. Here the CGS unit of kcal mol^{-1} has been replaced by kJ mol^{-1} (conversion: $1 \text{ kcal} = 4.18 \text{ kJ}$).

Table A.7 Comparison of the SI and the CGS systems of units^a.

Quantity	Symbol	SI unit	Symbol of the unit	Equivalent SI unit	Equivalent unit in the CGS or other systems
Length	l, r	Meter	m	—	10^2 cm
Mass	m	Kilogram	kg	—	10^3 g
Time	t	Second	s	—	—
Force	F	Newton	N	kg m s^{-2}	10^7 dynes
Energy	U	Joule	J	$\text{kg m}^2 \text{s}^{-2}$	$10^7 \text{ erg; } 0.239 \text{ calories}$
Angle	θ	Radian	rad	$1/2\pi \text{ Hz}$	—
Frequency	ν	Hertz	Hz	—	—
Electric charge	q	Coulomb	C	A s	$2.9979 \times 10^9 \text{ e.m.u.}$ $4.803 \times 10^{-10} \text{ e.s.u.}$
Electric current	i	Ampere	A	—	10^{-1} e.m.u.
Magnetic induction field	B	Tesla	T	$\text{kg s}^{-2} \text{A}^{-1}$	10^4 gauss
Magnetic field intensity	H	Ampere meter ⁻¹	A m^{-1}	—	$4\pi \times 10^{-3} \text{ oersted}$
Magnetic dipole moment	μ	Ampere meter ²	A m^2	—	$10^3 \text{ e.m.u. s}^{-1}$
Magnetogyric ratio	γ	Radian tesla ⁻¹ second ⁻¹	$\text{rad T}^{-1} \text{s}^{-1}$	rad kg s A	$10^{-4} \text{ rad gauss}^{-1}$

^aAfter Reference [49].

References

- Haigh, C.W. and Mallion, R.B. (1972) *Org. Magn. Reson.*, **4**, 203.
- Jackman, L.M. and Sternhell, S. (1969) *Application of Nuclear Magnetic Resonance in Organic Chemistry*, Pergamon Press, Oxford.
- Bothner-By, A.A. (1965) *Adv. Magn. Reson.*, **1**, 195.
- Watts, V.S. and Goldstein, J.H. (1967) *J. Chem. Phys.*, **46**, 4165.
- Crecely, L.M., Watt, V.S., and Goldstein, J.J. (1969) *J. Mol. Spectrosc.*, **30**, 184.
- Read, J.M. Jr., Mayo, R.E., and Goldstein, J.H. (1967) *J. Mol. Spectrosc.*, **22**, 419.
- Williamson, M.P., Kostelnik, R., and Castellano, S. (1968) *J. Chem. Phys.*, **49**, 2218.
- Castellano, S., Kostelnik, R., and Sun, C. (1967) *Tetrahedron Lett.*, **8**, 4635.
- Castellano, S., Sun, C., and Kostelnik, R. (1967) *Tetrahedron Lett.*, **8**, 5207.
- Read, J.M. Jr., Crecely, R.W., Butler, R.S., Loemker, J.E., and Goldstein, J.H. (1968) *Tetrahedron Lett.*, **9**, 1215.
- Günther, H. and Wenzl, R. (1967) *Z. Naturforsch., Teil B*, **22**, 389.
- Günther, H., Görlitz, M., and Hinrichs, H.-H. (1968) *Tetrahedron*, **24**, 5665.
- Görlitz, M. (1969) PhD thesis, University of Cologne.
- Günther, H., Wenzl, R., and Grimme, W. (1969) *J. Am. Chem. Soc.*, **91**, 3808.
- Mortimer, F.S. (1962) *J. Mol. Spectrosc.*, **5**, 199.
- Garbisch, E.W. Jr., and Grith, M.G. (1968) *J. Am. Chem. Soc.*, **90**, 6543.
- Lambert, J.B., Jovanovich, A.P., and Oliver, W.L. Jr., (1970) *J. Phys. Chem.*, **74**, 2221.
- Hill, E.A. and Roberts, J.D. (1967) *J. Am. Chem. Soc.*, **89**, 2047.
- Cooper, M.A., Elleman, D.D., Pearce, C.D., and Manatt, S.L. (1970) *J. Chem. Phys.*, **53**, 2343.
- Regel, W. and von Philipsborn, W. (1969) *Helv. Chim. Acta*, **52**, 1354.
- Regel, W. and von Philipsborn, W. (1968) *Helv. Chim. Acta*, **51**, 867.
- Hobgood, R.T. Jr., and Goldstein, J.H. (1964) *J. Mol. Spectrosc.*, **12**, 76.
- Pawliczek, J.B. and Günther, H. (1970) *Tetrahedron*, **26**, 1755.
- Runsink, J. and Günther, H. (1980) *Org. Magn. Reson.*, **13**, 249.
- Read, J.M., Mathis, C.T., and Goldstein, J.H. (1965) *Spectrochim. Acta*, **21**, 85.
- Garbisch, E.W. Jr., (1968) *J. Chem. Educ.*, **45**, 492.
- Castellano, S., Sun, C., and Kostelnik, R. (1967) *J. Chem. Phys.*, **46**, 327.
- Günther, H. (1965) *Z. Naturforsch., Teil B*, **20**, 948.
- Günther, H. and Hinrichs, H.-H. (1968) *Tetrahedron*, **24**, 7033.
- Levy, G.C. and Cargioli, J.D. (1972) *J. Magn. Reson.*, **6**, 143.
- Levy, G.C. and Nelson, G.L. (1972) *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, Wiley-Interscience, New York.
- Stothers, J.B. (1972) *Carbon-13 NMR Spectroscopy*, Academic Press, New York.
- Clerc, J.T., Pretsch, E., and Sternhell, S. (1973) *¹³C-Kernresonanz-Spektroskopie*, Akademische Verlagsgesellschaft, Frankfurt.
- Kalinowski, H.-O. Berger, S., and Braun, S. (1984) *¹³C-NMR-Spektroskopie*, Georg Thieme Verlag, Stuttgart.
- Jones, A.J., Alger, T.D., Grant, D.M., and Litchman (1970) *J. Amer. Chem. Soc.* **92**, 2386.
- Wendisch, D., Hartmann, W., and Heine, H.-G. (1974) *Tetrahedron* **30**, 295.
- Günther, H. and Schmickler, H. (1975) *Pure Appl. Chem.* **44**, 807.
- Mason, J. (1987) *Multinuclear NMR*, Plenum Press, New York, p. 11.
- Dischler, B. and Maier, W. (1961) *Z. Naturforsch., Teil A*, **16**, 318.
- Dischler, B. and Englert, G. (1961) *Z. Naturforsch., Teil A*, **16**, 1180.
- Dischler, B. (1965) *Z. Naturforsch., Teil A*, **20**, 888.
- (a) Günther, H. (1972) *Angew. Chem.*, **84**, 907. (b) Günther, H. (1972) *Angew. Chem., Int. Ed. Engl.*, **1**, 861.
- Emsley, J.W., Feeney, J., and Sutcliffe, L.H. (1965) *High-Resolution Nuclear Magnetic Resonance Spectroscopy*, Pergamon Press, Oxford.

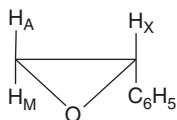
44. Binsch, G. (1968) *Topics in Stereochemistry*, vol. 3 (eds N.L. Allinger and E.L. Eliel), Interscience Publication, New York.
45. Gutowsky, H.S. and Holm, C.H. (1956) *J. Chem. Phys.* **25**, 1228.
46. (a) Anderson, P.W. (1954) *J. Phys. Soc. Jpn.*, **9**, 316. (b) Kubo, R. (1954) *J. Phys. Soc. Jpn.*, **9**, 935. (c) Sack, R.A. (1958) *Mol. Phys.*, **1**, 163.
47. Stephenson, D.S. and Binsch, G. (1980) *J. Magn. Reson.* **37**, 395 and 409.
48. Bain, A.D., Rex, D.M., and Smith, R.N. (2001) *Magn. Reson. Chem.*, **39**, 122.
49. Harris, R.K. (1986) *Nuclear Magnetic Resonance Spectroscopy*, Longman, Harlow.

Solutions for Exercises

- 3.1. The average area ratio for signals A and C is 28.8:64.4. Per proton this corresponds to 14.4:21.47 and a molar ratio of 1:1.491.
- 3.2. First, the correct assignments of the resonance signals must be made. According to Table 3.1 the signals at δ 7.27, δ 5.30, and δ 2.17 arise from chloroform, methylene chloride, and acetone, respectively. Considering the number of protons in each compound the integration indicates a molar ratio of 10:9:6 or 40, 36, and 24 mol.% in the above order.
- 3.3. Toluene : methylene chloride : benzene = 38.6 : 48.9 : 12.5.
- 3.4. The difference in chemical shifts of the signals is 4.78 ppm. This corresponds to 1290.6 Hz at 270 MHz. Reference to Table 3.1 and the molecular formula indicates that the substance is toluene.
- 3.5. (a) $\sim \delta$ 0.9, 3.5, 7.2 (9:2:5) and (a') $\sim \delta$ 1.2, 2.2, 3.5, 7.2 (6:3:3:4); (b) $\sim \delta$ 0.9, 2.0 (3:1) and (b') $\sim \delta$ 0.9, 2.7, 3.0 (9:1:2).
- 3.6. (a) 1,2-Dichloroethane; (b) 1,3,5-trimethylbenzene; (c) 1,2-dimethoxyethane; (d) 1,2,5,6-dibenzocycloheptadiene; (e) diphenylmethane; (f) 2,5-dimethylfuran; (g) chloroacetic acid methyl ester; (h) 1,2,4,5-tetramethylbenzene; (i) 9,10-dihydroanthracene; and (j) terephthaldehyde.
- 3.7. The X-transitions are $2 \rightarrow 1$ and $4 \rightarrow 3$; with coupling $2 \rightarrow 1$ increases by $2 \times \frac{1}{4} J_{AX}$ and $4 \rightarrow 3$ decreases by the same amount; the coupling is J_{AX} .
- 3.8.
- $$m_T = 2 \quad \alpha\alpha\alpha\alpha$$
- $$m_T = 1 \quad \alpha\alpha\alpha\beta \quad \alpha\alpha\beta\alpha \quad \alpha\beta\alpha\alpha \quad \beta\alpha\alpha\alpha$$
- $$m_T = 0 \quad \alpha\alpha\beta\beta \quad \alpha\beta\alpha\beta \quad \beta\alpha\alpha\beta \quad \beta\alpha\beta\alpha \quad \beta\beta\alpha\alpha$$
- $$m_T = -1 \quad \beta\beta\beta\alpha \quad \beta\beta\alpha\beta \quad \beta\alpha\beta\beta \quad \alpha\beta\beta\beta$$
- $$m_T = -2 \quad \beta\beta\beta\beta$$

For four neighbors Pascal's triangle yields for the intensity distribution 1:4:6:4:1.

- 3.9. 1. a, Doublet (1 : 1); b, quartet (1 : 3 : 3 : 1).
 2. a, Singlet; b, singlet for $J = 0$;
 a, triplet (1 : 2 : 1); b, ten-line multiplet (1 : 9 : 36 : 84 : 126 : 126 : 84 : 36 : 9 : 1)
 for $J > 0$.
 3. a, Doublet (1 : 1); b, quartet (1 : 3 : 3 : 1) of triplets (1 : 2 : 1); c, doublet
 (1 : 1); and d, singlet.
 4. a, Doublet (1 : 1) of doublets (1 : 1); b, doublet (1 : 1) of quartets (1 : 3 : 3 : 1)
 of quartets (1 : 3 : 3 : 1); c, as b; d, doublet (1 : 1) of doublets (1 : 1).
 5. a, Doublet (1 : 1); b, septet (1 : 6 : 15 : 20 : 15 : 6 : 1); c, quartet (1 : 3 : 3 : 1);
 d, triplet (1 : 2 : 1).
 6. a, Triplet (1 : 1 : 1); b, doublet (1 : 1).
- 3.10. (a) AMX ; $J_{AM} = 4$, $J_{AX} = 2$, and $J_{MX} = 0$ Hz; (b) AM_2X ; $J_{AM} = 1$, $J_{AX} = 5$, and
 $J_{MX} = 0$ Hz; (c) AM_2X ; $J_{AM} = 3$, $J_{AX} = 4$, and $J_{MX} = 1$ Hz; and (d) AMX_3 ;
 $J_{AM} = 5$, $J_{AX} = 2$, and $J_{MX} = 1$ Hz.
- 3.11. (a) $C_6H_5CHD_2 \sim 2.2$ Hz, respectively; (b) $^{15}NH_4^+$ 72 Hz; (c) $^{14}NH_4^+$ 51
 Hz; and (d) $Na[^{10}BH_4]$ and $Na[^{11}BH_4] \sim 25$ and ~ 8 Hz, respectively; cf.
 Table 2.1 (p. 26).
- 3.12. 1. (a) Isopropyl chloride; (b) $C_6H_5CH_2SH$; (c) diethyl phthalate; and (d)
 $CH_3CH(NO_2)-CO_2C_2H_5$.
 2. (e) In the δ -scale 1 mm ~ 4.2 Hz; thus in the expanded spectrum 1 mm
 ~ 2.1 Hz. Only resonances of the olefinic protons are shown, the group
 around δ 4.5 has double intensity (= 2 protons). The absorption at lowest
 field (δ 7.1) is split by 6.3 and 14.7 Hz, which must arise from cis and
 trans coupling across a double bond. This absorption is therefore due to
 the proton adjacent to the ester function. Splittings of 14.7 and 6.3 Hz
 are found at δ 4.7 and 4.4 so that these δ -values arise from the protons
 cis and trans, respectively, to the ester group. These protons are coupled
 to one another with a geminal coupling constant of about 1.5 Hz.
 3. (f) The spectrum shows two absorptions separated by about 50 Hz.
 The one at lower field can be recognized as two partially superimposed
 quartets, the separation and splitting of which leads to coupling constants
 of 15 and 6.6 Hz. At higher field four quartets are observed with coupling
 constants of 15, 7.8, and 1.5 Hz. Therefore, the proton adjacent to the
 methyl group absorbs at the higher frequency [$J(H,H)$, $J(CH_3,H)$] and
 the proton adjacent to the aldehyde group absorbs at the lower frequency
 $[J(H,H)$, $J(H,CHO)$, $J(CH_3,H)$].
- 3.13. $\delta(a)$ 7.36, $\delta(b)$ 8.77 ppm; $J(a,b)$ 5.0, $J(a,c)$ 1.5 Hz.
- 3.14. See Günther, H., Görlitz, M., and Meisenheimer, H. (1974) *Org. Magn.
 Reson.*, 6, 388.
- 3.15. Chemical shifts: 2.58 (H_A); 2.94 (H_M); and 3.66 (H_X) ppm. Coupling
 constants $J(A,X) \approx 2.5$, $J(M,X) \approx 4.1$, and $J(A,M) \approx 5.8$ Hz. Measuring
 frequency 60 MHz; assignment:

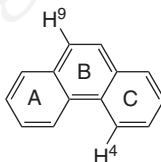


- 5.1. (a) δ_o 7.07; δ_m 7.27, δ_p 7.09; (b) δ_o 7.77, δ_m 7.87, δ_p 9.17; with the proportionality factor 12.7 one obtains δ_o 7.02, δ_m 7.27, δ_p 7.04. Compared with the empirical constants of Table A.3 of the Appendix (p. 653) the calculated $\Delta\delta$ values are too small.
- 5.2. The chemical shifts for compounds **b** and **e** relative to **a** and **d** show the charge polarization induced by the electron donor atom (S, O); for compounds **c** and **f** the electron-acceptor properties of the carbonyl group dominate.
- 5.3. From a scaled computer drawing with $R(\text{CC}) = 1.39 \text{ \AA}$ and $R(\text{CH}) = 1.10 \text{ \AA}$ we estimate the following distances:

$$\text{H}(4): R_A = 3.64 \text{ \AA}; R_B = 3.48 \text{ \AA};$$

$$\text{H}(4): R_A = 3.48 \text{ \AA}; R_C = 4.70 \text{ \AA};$$

This yields with Eq. (5.13b) $\Delta\sigma(4) = -1.22 \text{ ppm}$ and $\Delta\sigma(9) = -0.91 \text{ ppm}$. Relative to benzene ($\delta 7.27$) we find $\delta(4) 8.49$ and $\delta(9) 8.18$. The experimental values are 8.93 and 7.71 ppm, respectively. The deviations are, therefore, -0.44 ppm for H(4) and $+0.47 \text{ ppm}$ for H(9). The errors are $\sim 5\%$, but nevertheless indicate an extra deshielding for H(9) that can be assigned to the van-der-Waals effect (cf. p. 37), which has its origin in the steric interaction between H(4) and H(5).



Better results are obtained if we estimate the shielding effects from Figure A.1 in the Appendix (p. 649, please note that the abscissa ρ is given in ring radii) or calculate them with the McConnell Eq. (5.6) and a $\Delta\chi$ value of $-50 \times 10^{-36} \text{ m}^3 \text{ molecule}^{-1}$. In the first case we estimate $\Delta\sigma(\text{A}) \approx \Delta\sigma(\text{B}) \approx -0.4 \text{ ppm}$ and $\Delta\sigma(\text{C}) \approx -0.1 \text{ ppm}$ which yields (again relative to benzene with $\delta 7.27$) $\delta(4) 8.07$ and $\delta(9) 7.77$ with deviations of -0.86 and $+0.07 \text{ ppm}$. From Eq. (5.6) we derive $\delta(4) 8.02$ and $\delta(9) 7.78$ [note that here R has to be used in m ($1 \text{ \AA} = 0.1 \text{ nm} = 10^{-10} \text{ m}$)]. The deviations are -0.91 for H(4) and $+0.07 \text{ ppm}$ for H(9). The results for H(9) are now considerably improved with both approaches and the extra deshielding for H(4) is confirmed.

- 5.4. According to the π charge density, H(1) should resonate at higher field ($\delta 1.27$). The high-field shifts measured amount to $\Delta\delta\text{H}(1) = 6.54 \text{ ppm}$

and $\Delta\delta\text{H}(2) = 4.37$ ppm. The charge density contributions to these shifts, following Eq. (5.2), are 3.61 and 1.38 ppm, respectively. The paramagnetic ring current contribution for H(1) thus amounts to 2.93 ppm and for H(2) to 2.99 ppm [see Benken, R. and Günther, H. (1988) *Helv. Chim. Acta*, **71**, 694].

- 5.5. Comparison of the partial charges in pyridine and the pyridinium cation leads to the following $\Delta\rho_i$:

$$\begin{aligned}\Delta\rho_1 &= +0.413 \\ \Delta\rho_2 &= \Delta\rho_6 = -0.053 \\ \Delta\rho_3 &= \Delta\rho_5 = -0.077 \\ \Delta\rho_4 &= -0.152\end{aligned}$$

On the basis of trigonometric analysis (ring bonds 0.14 nm, C–H bond 0.11 nm, regular hexagon) it follows that for H_γ :

$$\begin{aligned}R_1 &= 0.390 \text{ nm}; \theta_1 = 0^\circ \\ R_2 = R_6 &= 0.341 \text{ nm}; \theta_2 = \theta_6 = 20^\circ 44' \\ R_3 = R_5 &= 0.217 \text{ nm}; \theta_3 = \theta_5 = 33^\circ 53' \\ R_4 &= 0.110 \text{ nm}; \theta_4 = 0^\circ\end{aligned}$$

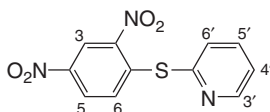
With these data we obtain from Eq. (5.17):

$$\begin{aligned}\Delta\sigma_\gamma &= 12.5 \left(\frac{0.413}{15.21} - 2 \frac{0.053}{11.62} 0.935 - 2 \frac{0.077}{4.71} 0.830 - \frac{0.152}{1.21} \right) \\ &\quad - 17.0 \left(\frac{0.413}{15.21} - 2 \frac{0.053}{11.62} - 2 \frac{0.077}{4.71} - \frac{0.152}{1.21} \right)^2 \\ \Delta\sigma_\gamma &= -1.68 - 0.33 = -2.01 \text{ ppm}.\end{aligned}$$

The experimental value is $\Delta\sigma_\gamma = -1.22$ ppm. The deviation that is found is rather typical for this type of approximate calculation. Certainly one can assume that in addition to the charge density effect still other factors are responsible for the variation of the resonance frequencies. Thus, the nitrogen in pyridine has a magnetic anisotropy ($\Delta\chi = -91 \times 10^{-36} \text{ m}^3$ per molecule perpendicular to the plane of the ring) that vanishes upon protonation. In addition, medium effects may not be neglected in this case. Nevertheless, it is often possible by consideration of all factors to obtain good results [compare, for example, Castellano, S., Günther, H., and Ebersole, S. (1965) *J. Phys. Chem.*, **69**, 4166; Günther, H. and Castellano, S. (1966) *Ber. Bunsenges. Phys. Chem.*, **70**, 913].

- 5.6. The negative allylic coupling shows that the π contribution dominates. Thus the more favorable conformation is **65b** in which the C–H⁷ bond is aligned nearly parallel to the $2p_z$ orbitals at C1 and C6. This is also the conformation that is necessary for the observation of a measurable homoallylic coupling.

- 5.7. A value of 13.1 Hz is typical for J_{aa} in cyclohexane. Therefore, **66** is the correct conformation.
- 5.8. Only in conformation **68** is a coplanar zigzag arrangement of σ -bonds, a prerequisite for the existence of a large ^4J coupling via the M mechanism, possible. The methyl protons couple with the axial hydrogens in the 2- and 6-positions.
- 5.9. The small value of the vicinal coupling is compatible only with structure **70** (cf. p. 133).
- 5.10. Bottino, F. and Pappalardo, S. (1981) *Org. Magn. Reson.*, **16**, 1.



- 5.11. The integration curve indicates that the resonance signals of the four olefinic protons begin with the signal 0 Hz. One finds 1 H (0, 11 Hz), 2 H (26–52 Hz), and 1 H (72–84 Hz). Taking only vicinal coupling constants into consideration it is advantageous to begin the analysis with the doublet at the highest frequency ($J = 11$ Hz), which must be assigned to H_a or H_d . There is a separation of 11 Hz between lines 35 and 46 and lines 41 and 52, so these signals probably arise from the neighboring proton. This conclusion is supported by the roof effect (35 and 41 are more intense than 46 and 52). In addition, this proton interacts, as indicated by the roof effect, with the proton at the lowest frequency with a coupling constant of 6 Hz. The latter proton is also coupled with a coupling constant of 6 Hz with the fourth proton, the resonance signals of which are found at 26 and 32 Hz. To make an assignment it must be decided whether $\delta(H_a) > \delta(H_d)$ or $\delta(H_a) < \delta(H_d)$. Both protons are deshielded: H_a by the effect of the benzene ring and H_d by the effect of the adjacent oxygen atom. It is difficult to predict which effect is more important. Thus, on the basis of chemical shifts alone the following assignments are possible:

$$\delta(H_a) > \delta(H_d) > \delta(H_b) > \delta(H_c) \text{ and } \delta(H_d) > \delta(H_a) > \delta(H_c) > \delta(H_b)$$

A decision between these possibilities can be made on the basis of the coupling constants: the electronegativity effect of the oxygen works to reduce J_{cd} so that J_{cd} must be smaller than J_{ab} . The first alternative is therefore correct and the coupling constants are:

$$J_{ab} = 11, J_{bc} = J_{cd} = 6 \text{ Hz}$$

Long-range coupling is observed in this system only if the spectrum is expanded or if it is recorded under conditions of higher resolution. The assignment problem could be solved much more easily with NOE experiments (cf. Chapter 10); H_a could be recognized by its proximity to one of the aromatic protons.

- 5.12. This is a mixture of the cis and trans isomers in the ratio 7 : 3. The coupling constants are: $^3J_{\text{trans}} = 19.6 \text{ Hz}$, $^3J_{\text{cis}} = 14.2 \text{ Hz}$, $^3J(\text{H}, \text{CH}_2)(\text{trans}) = 6.5 \text{ Hz}$, $^3J(\text{H}, \text{CH}_2)(\text{cis}) = 8.0 \text{ Hz}$, $|^4J(\text{H}, \text{CH}_2)(\text{trans})| = 1.4 \text{ Hz}$, and $|^4J(\text{H}, \text{CH}_2)(\text{cis})| = 1.2 \text{ Hz}$. The difference in couplings between the olefinic protons and the methylene protons in the two isomers are functions of conformation. In the cis isomer the conformation with the methylene chain *gauche* is more stable than that conformation in the trans isomer because of the large silyl group (cf. 54, p. 140). The vicinal coupling $^3J(\text{H}, \text{CH}_2)$ therefore has a larger “trans-component,” that is, its magnitude increases according to the Karplus curve. Simultaneously, the π contribution to the allylic coupling $^4J(\text{H}, \text{CH}_2)$ decreases and the magnitude of this coupling becomes smaller.

- 6.1. (a) $\text{AA}'\text{BB}'$ (e) A_6X (i) A_3B_2 (m) A_3KMX
 (b) $\text{AA}'\text{BB}'\text{C}$ (f) $\text{AA}'\text{MM}'\text{XY}$ (j) A_2X_6
 (c) ABC (g) $\text{AA}'\text{BB}'$ (k) ABCD
 (d) A_3B (h) $\text{AA}'\text{BB}'$ (l) ABC_2

- 6.2. With Eq. (6.2) we have

$$-\frac{h^2}{8\pi^2m} \frac{\partial^2}{\partial x^2} N \sin ax = EN \sin ax$$

$$\frac{h^2}{8\pi^2m} a^2 N \sin ax = EN \sin ax$$

From this it follows that $E = a^2(h^2/8\pi^2m)$.

Now we have to determine whether all values of a in our trial function are allowed. If the electron is moving in a one-dimensional box of length L this is not the case. Under these conditions $\Psi(0)$ and $\Psi(L)$ must equal zero, that is, the wave function must vanish at $x=0$ and $x=L$. Thus:

$$\Psi(0) = N \sin a0 = 0 \quad \Psi(L) = N \sin aL = 0$$

The second condition is met only if $aL = q$, where q is an integer. It follows that $a = q\pi/L$ and one obtains the eigenvalues:

$$E_q = \frac{h^2}{8mL^2} q^2 \text{ with } q = 1, 2, 3, \dots, n$$

The eigenfunctions are then:

$$\Psi_q = N \sin q\pi x/L$$

with $N = \sqrt{2/L}$.

- 6.3. The basis functions are given on page 172. The Hamiltonian operator is $\mathcal{H}^{(0)} = \hat{I}_z(\text{A}) + \hat{I}_z(\text{B}) + \hat{I}_z(\text{C})$. From this one obtains:

$$\begin{aligned}
E_1 &= \frac{1}{2}(v_A + v_B + v_C) & E_5 &= \frac{1}{2}(v_A - v_B - v_C) \\
E_2 &= \frac{1}{2}(v_A + v_B - v_C) & E_6 &= \frac{1}{2}(-v_A + v_B - v_C) \\
E_3 &= \frac{1}{2}(v_A - v_B + v_C) & E_7 &= \frac{1}{2}(-v_A - v_B + v_C) \\
E_4 &= \frac{1}{2}(-v_A + v_B + v_C) & E_8 &= \frac{1}{2}(-v_A - v_B - v_C)
\end{aligned}$$

$$\begin{aligned}
6.4. \quad I(f_1) : \langle \beta\alpha \mid \hat{I}_x(A) + \hat{I}_x(B) \mid \alpha\alpha \rangle^2 &= [\langle \beta\alpha \mid \hat{I}_x(A) \mid \alpha\alpha \rangle + \langle \beta\alpha \mid \hat{I}_x(B) \mid \alpha\alpha \rangle]^2 \\
&= [\langle \beta\alpha \mid \tfrac{1}{2}\beta\alpha \rangle + \langle \beta\alpha \mid \tfrac{1}{2}\alpha\beta \rangle]^2 \\
&= \frac{1}{4}
\end{aligned}$$

$$\begin{aligned}
I(f_2) : \langle \beta\beta \mid \hat{I}_x(A) + \hat{I}_x(B) \mid \alpha\beta \rangle^2 &= [\langle \beta\beta \mid \hat{I}_x(A) \mid \alpha\beta \rangle + \langle \beta\beta \mid \hat{I}_x(B) \mid \alpha\beta \rangle]^2 \\
&= [\langle \beta\beta \mid \tfrac{1}{2}\beta\beta \rangle + \langle \beta\beta \mid \tfrac{1}{2}\alpha\alpha \rangle]^2 \\
&= \frac{1}{4}
\end{aligned}$$

One obtains $I(f_3)$ and $I(f_4)$ analogously.

$$6.6. \quad C = \frac{1}{2}\sqrt{v_0\delta^2 + J^2} = \frac{1}{2}\sqrt{400 + 225} = 12.5;$$

$$\sin 2\theta = J/2C = 15/25 = 0.6;$$

$$f_1 = 7.5 + 12.5 = 20.0; I_1 = 0.4$$

$$f_2 = -7.5 + 12.5 = 5.0; I_2 = 1.6$$

$$f_3 = 7.5 - 12.5 = -5.0; I_3 = 1.6$$

$$f_4 = -7.5 - 12.5 = -20.0; I_4 = 1.4$$

$$6.7. \quad \begin{vmatrix} H_{22} - E & H_{23} & H_{24} \\ H_{32} & H_{33} - E & H_{34} \\ H_{42} & H_{43} & H_{44} - E \end{vmatrix}$$

$$H_{22} = \frac{1}{2}(v_A + v_B - v_C) + \frac{1}{4}(J_{AB} - J_{AC} - J_{BC})$$

$$H_{33} = \frac{1}{2}(v_A - v_B + v_C) + \frac{1}{4}(-J_{AB} + J_{AC} - J_{BC})$$

$$H_{44} = \frac{1}{2}(-v_A + v_B + v_C) + \frac{1}{4}(-J_{AB} - J_{AC} + J_{BC})$$

$$H_{23} = H_{32} = \frac{1}{2}J_{BC}$$

$$H_{24} = H_{42} = \frac{1}{2}J_{AC}$$

$$H_{34} = H_{43} = \frac{1}{2}J_{AB}$$

- 6.8. (a) $1/\sqrt{3}$; (b) 1 : 3 : 3 : 1; (c) variation of the spectrometer frequency or solvent effects can influence $v_0\Delta$ in an AB system and, as a result, the separation $f_2 - f_3$ and the intensity ratio are variable.

$$6.9. \quad v_A = 31.55 \text{ Hz}, v_B = 16.95 \text{ Hz}; J = 10.5 \text{ Hz}; I_1 = I_4 = 0.42, I_2 = I_3 = 1.58.$$

$$6.10. \quad v_A = 95.00 \text{ Hz}, v_B = 105.00 \text{ Hz}, J_{AB} = 6.00 \text{ Hz}.$$

$$6.11. \quad \text{Solution 1, } I_{11} = 0.993; \text{ solution 2, } I_{11} = 0.595.$$

- 6.12. Analyses of the ab subspectra (1) 43.29, 45.78, 47.75, 50.29 Hz and (2) 45.21, 47.75, 54.03, 56.52 Hz give an average value of 2.52 Hz for $|J_{AB}|$. We also find that:

Solution 1:

$$\nu_A = 45.76 \text{ Hz}; J_{AX} = 1.67 \text{ Hz};$$

$$\nu_B = 51.86 \text{ Hz}; J_{BX} = 6.47 \text{ Hz}$$

Solution 2:

$$\nu_A = 50.00 \text{ Hz}; J_{AX} = 10.17 \text{ Hz};$$

$$\nu_B = 47.61 \text{ Hz}; J_{BX} = -2.03 \text{ Hz}$$

Here X is the fluorine nucleus. To determine which solution is correct the ^{19}F spectrum of the compound must be measured. When this is carried out one finds the following resonance frequencies (in hertz relative to ν_X) for the lines f_9 , f_{10} , and f_{11} , respectively, where the intensities are indicated in parentheses: 6.66 (0.822), 4.08 (1.000), and 2.15 (0.178). It follows then from Eq. (6.25) that solution 2 is correct. That is, *ortho* and *para* H,F couplings have opposite signs (the combination -10.17 and 2.03 is also possible). J_{AB} , as the *meta* H,H coupling, is assumed to be positive. For the experimental spectrum see the textbook by Corio cited in the References p. 210.

- 6.13. Since the inner lines of one of the ab subspectra are not resolved and the positions of the four signals must be estimated, only an approximate analysis is possible. The relative chemical shifts in this subspectrum can be calculated only if the separation $f_2 - f_3$ can be evaluated from the line width. In this case a value of 0.25 Hz seems reasonable. One then obtains:

ab subspectrum 1:	0.0	9.78	10.02	(19.8) Hz
ab subspectrum 2:	6.2	16.2	20.4	30.8 Hz

From subspectrum 2 an average value for $|J_{AB}|$ of 10.2 Hz can be determined. In addition the analysis yields:

Solution 1:

$$\nu_A = 10.55 \text{ Hz}; J_{AX} = 3.5 \text{ Hz}; I_{11} = 0.92;$$

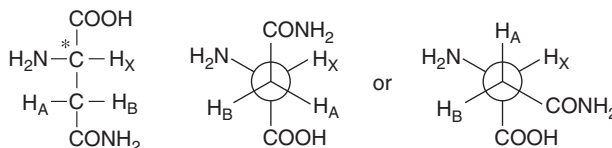
$$\nu_B = 16.75 \text{ Hz}; J_{BX} = 11.5 \text{ Hz}$$

Solution 2:

$$\nu_A = 15.7 \text{ Hz}; J_{AX} = 13.7 \text{ Hz}; I_{11} = 0.78;$$

$$\nu_B = 11.7 \text{ Hz}; J_{BX} = 1.3 \text{ Hz}$$

The experimental X portion indicates that solution 1 is the correct one. For the assignment of these parameters to the protons of L-asparagine it can be assumed that the AB portion is formed from the methylene protons. J_{AB} , as a geminal coupling constant, would then be negative (cf. p. 123). The X proton shows a large trans coupling with H_B and a small *gauche* coupling with H_A so that the following conformation for the compound can be assumed



- 6.15. After determining that $N = 9.0$ Hz, analysis of the ab subspectrum gives $L = 7.0$, $K = 11.0$ (7.0), and $M = 7.0$ (11.0) Hz. One then derives the following coupling constants: $J = 8.0$, $J' = 1.0$, $J_A = 9.0$ (2.0), and $J_X = 2.0$ (9.0) Hz. We find that $N = 9.67$ Hz and that the ab subspectra consist of the lines:

- (1) 0.0 7.7 10.6 18.7 Hz;
 (2) 1.7 7.4 11.4 16.9 Hz

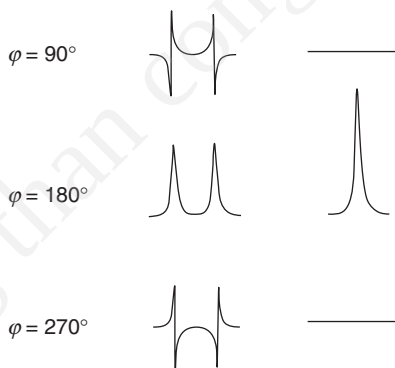
Thus $L = 7.4$ or 7.8 Hz or an average of 7.6 Hz, $K = 7.9$, and $M = 5.6$ Hz. Another assignment of the lines to the ab subspectra leads to very different values of L and thus can be eliminated from consideration. The coupling constants are $J = 8.6$, $J' = 1.1$, $J_A = 6.8$, and $J_X = 1.1$ Hz. On the basis of the structure J_A must be J_{23} . The results of an AA'BB' analysis are, in the same order, 8.65, 1.04, 6.79, and 1.03 Hz, so the X approximation can be tolerated here.

- 7.1. (a) ABX_2 (c) A_4 (e) $AA'BB'$
 (b) $AA'XX'$ (d) ABCD
- 7.2. 2-Acetylpyridine is an example of an ABCD system that produces a multitude of lines (Kowalewski, V.J. and de Kowalewski, D.G. (1962) *J. Chem. Phys.*, **37**, 2603). The 3-isomer yields a spectrum of nearly first-order simplicity (Kowalewski, V.J. and de Kowalewski, D.G. (1962) *J. Chem. Phys.*, **36**, 266), while the 4-isomer can be recognized by the characteristically symmetric appearance of the $AA'XX'$ or $AA'BB'$ system.
- 7.3. Only (b) possesses the molecular symmetry required for only one $AA'BB'$ system.
- 7.4. Spectrum 1: **e** (plane of symmetry); spectrum 2: **d** (two-fold symmetry axis).
- 7.5. Four products: RR, RS, SR, SS (see organic chemistry textbooks for the R,S nomenclature).
 If we neglect any long range effect on the chemical shifts through the COO linkage the two endgroups yield identical spectra in all four products because

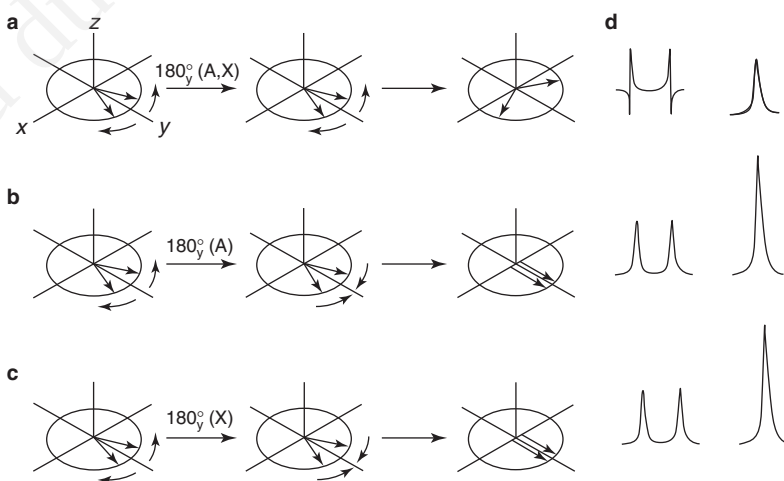
the R and S form give the same spectrum. In case of a chemical shift effect through the COO linkage, two different spectra are expected because RS and SR as well as RR and SS configurations are mirror images. Use sawhorse drawings to derive these conclusions.

- 7.6. Enantiotopic = **e**; diastereotopic = **d**.
 (a) **d**; (b) **e**; (c) **e**; (d) **d**; (e) **e**; (f) **e**; (g) **d**; (h) **e**; (i) **e**; (j) **d**.
- 7.7. ^1H n.m.r.: methylene groups **a** two singlets; **b** one AA'/BB' system. ^{13}C n.m.r.: **a** six sp^2 signals; **b** also six sp^2 signals and in each case two $^{13}\text{CH}_2$ signals; ^1H n.m.r. is the right choice.
- 7.8. (a) AX; (b) AX; (c) AX_2 ; (d) AA'XX'; (e) AX_2Y ; (f) A_2X_6 .
- 8.1. From Figure 8.2 we have $B_1^2 + (B_0^2 + \frac{\omega}{\gamma})^2 = B_{\text{eff}}^2$ or, with Eq. (8.3), $B_1^2 + B_0^2 (1 - \frac{\omega}{\omega_0})^2 = B_{\text{eff}}^2$. From the squared expressions several can be neglected if the conditions $B_1 \ll B_0$ and $\omega \ll \omega_0$ hold; this yields $B_{\text{eff}} \approx B_0$. On the other hand for $\omega \approx \omega_0$ we obtain $B_{\text{eff}} \approx B_1$.

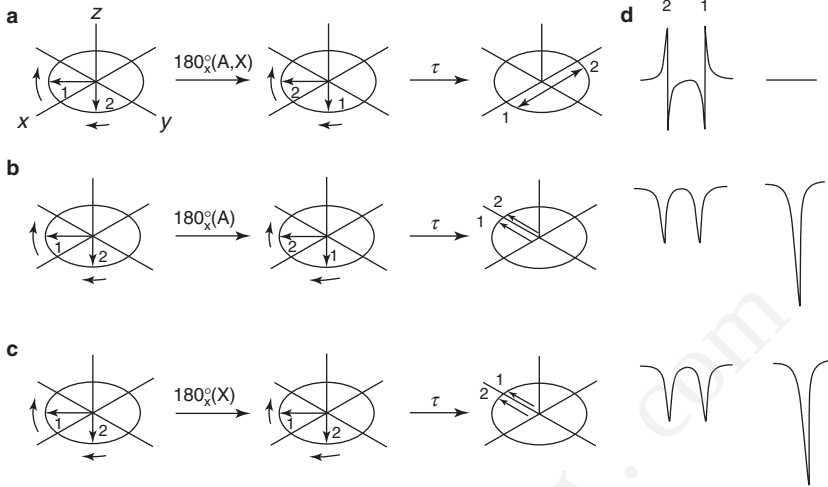
9.1.



9.2.

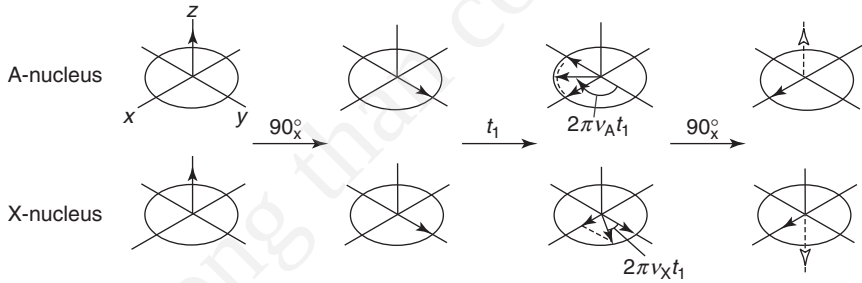


9.3.

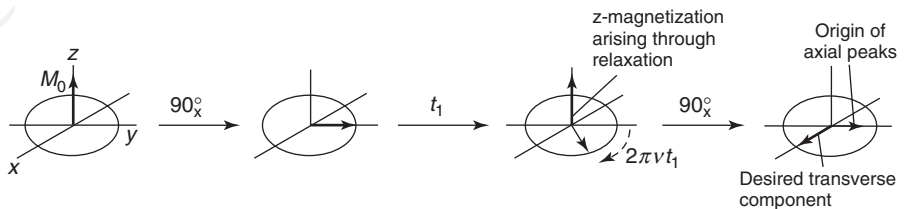


If compared with Figure 9.7, p. 288, the result shows that the effect of different Larmor frequencies is eliminated by the spin echo experiment.

9.4.

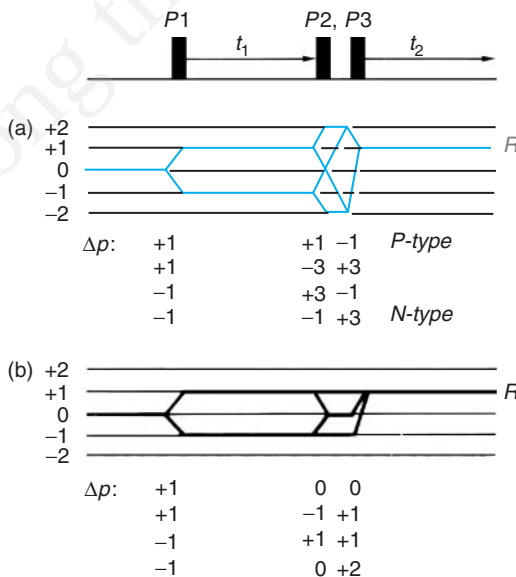


At the end of the evolution time t_1 the vectors have progressed differently because of their different Larmor frequency. The second 90°_x pulse leads to a situation where only the x -component is retained as transverse magnetization and finally as t_2 signal. Its amplitude depends on t_1 and ν_A and ν_X , respectively.

9.5. During the evolution time t_1 , z -magnetization is formed by relaxation which

yields, after the second 90°_x pulse, the unwanted transverse component. This signal increases with increasing t_1 . It is, however, not amplitude-modulated and has a constant F_1 value.

- 9.6. The t_1 increment corresponds to the dwell time in the F_1 dimension. A prolongation would reduce the spectral window (see Chapter 8). For the COSY experiment, however, the condition $F_1 = F_2$ must be met.
- 9.7. $H_a, H_b = 1, 2; H_c = 5; H_d = 6; H_e = 4; H_f = 3$.
- 9.8. $\hat{I}_x \xrightarrow{90^\circ[\hat{I}_y]} \hat{I}_z; \hat{I}_y \xrightarrow{90^\circ[\hat{I}_x]} \hat{I}_x; \hat{I}_x \xrightarrow{90^\circ[-\hat{I}_y]} -\hat{I}_z; \hat{I}_y \xrightarrow{90^\circ[-\hat{I}_x]} \hat{I}_y$
- 9.9. $2\hat{I}_z(X)\hat{I}_y(A)\sin X1 \sin J1 \rightarrow \text{Larmor precession} \rightarrow \text{spin spin coupling}$
 $2\hat{I}_z(X)\hat{I}_y(A)\sin X1 \sin J1 \cos A2 \cos J2 + \hat{I}_x(A)\sin X1 \sin J1 \cos A2 \sin J2$
 $+ 2\hat{I}_z(X)\hat{I}_x(A)\sin X1 \sin J1 \sin X2 \cos J2 - \hat{I}_y(A)\sin X1 \sin J1 \sin X2 \sin J2$
- 9.10. For the diagonal signals the expressions 3, 4, 5, 6, 9, 10 and 12 are responsible. The cross peaks result from 13 and 14. For $\beta = 0^\circ$, all expressions which contain $\sin\beta$ are eliminated and only diagonal peaks are detected. For $\beta = 90^\circ$, all expressions which contain $\cos\beta$ are eliminated and the diagonal peaks arise from 3 and 4, the cross peaks from 13 and 14. For $\beta = 45^\circ$, $\sin\beta = 0.85$ and $\cos\beta = 0.53$. The diagonal peaks are thus more strongly reduced than the cross peaks.
- 9.11. Coherence A is cancelled, B is detected. For P1 we have $\Delta\theta = 0$ and thus $\Delta\phi(A) = \Delta\phi(B) = 0$. For P2, $\Delta p(A) = 0$ and thus again $\Delta\phi(A) = 0$. For coherence B $\Delta p = +2$; this yields $\Delta\phi(B) = 2 \times \Delta\theta$ and signal phases of 0246 = 0202 (see Figure 9.26c), whereas for coherence A 0000 results. For detection of A or B the receiver phase has to be adjusted accordingly.
- 9.12.



(a) double quantum coherence

(b) zero- and one-quantum coherence

Starting on level 0, the following coherence level pathways exist:

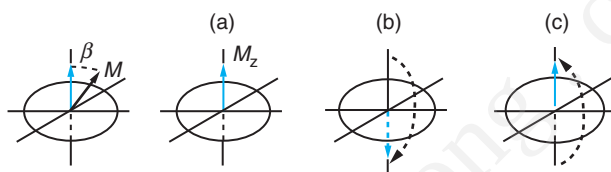
P-type $(-1) \rightarrow (-2) \rightarrow (+1)$ and $(-1) \rightarrow (+2) \rightarrow (+1)$: cancelation in both cases;

zero- and one-quantum coherences: $(+1) \rightarrow (+1) \rightarrow (+1)$; $(+1) \rightarrow (0) \rightarrow (+1)$; $(-1) \rightarrow (0) \rightarrow (+1)$; $(-1) \rightarrow (-1) \rightarrow (+1)$; cancelation in all cases.

- 9.13. If we use $1/2J_{AX}$ for the t_1 delay, we obtain for $\cos(\pi J_{AX}t_1)$ the expression $\cos(\pi/2)$ and for $\sin(\pi J_{AX}t_1)$ the expression $\sin(\pi/2)$. Consequently, $\hat{I}_y(A)$ yields $2\hat{I}_x(A)\hat{I}_z(X)$ and $\hat{I}_y(X)$ correspondingly $2\hat{I}_x(X)\hat{I}_z(A)$ [$= 2\hat{I}_z(A)\hat{I}_x(X)$], respectively.

- 10.1. See Figure 10.11, p. 358; $X1 = +10$; $X2 = -3$; [Figure 10.12 (c), p. 359]

- 11.1.



For an excitation pulse with the angle $\beta < 90^\circ$, part of the *z*-magnetization is retained (a). This is transformed into negative *z*-magnetization by the first 180° pulse (b), which would be transformed into transverse magnetization by the excitation pulse of the next FT experiment. The 180° pulse of the additional spin echo sequence directs this magnetization again along the positive *z*-axis (c) and for the following experiment complete *z*-magnetization is available.

- 11.2. Three negative signals can be assigned to the methyl groups 18 and 19 and to C8-H according to their chemical shifts.
- 11.3. The important aspect of this pulse sequences is the magnetization transfer from the sensitive A-nucleus (^1H) to the insensitive X-nucleus (^{13}C). To simplify our treatment, we neglect the evolution of the Larmor frequencies in the t_1 period.

Sequence (a): After the excitation pulse, transverse A-magnetization $\hat{I}_y(A)$ is obtained. The components of the chemically different nuclei A_i are labeled during the evolution time with their Larmor frequencies $\omega_{A_i}^i$. The $180^\circ(X)$ pulse leads to A,X decoupling. During the delay Δ_1 , antiphase A-magnetization, $2\hat{I}_x(A)\hat{I}_z(X)$, develops under the action of the propagator $\pi J\Delta_1 2\hat{I}_z(A)\hat{I}_z(X)$, which, because $\Delta_1 = 1/2J_{AX}$ [Eqs (9.23a) and (9.23b)], p. 315), has the simple form $(\pi/2)2\hat{I}_z(A)\hat{I}_z(X)$. Polarization transfer is then introduced by the 90° pulse pair at the A and X channel:

$$2\hat{I}_x(A)\hat{I}_z(X) \xrightarrow{90^\circ \hat{I}_y(A)} 2\hat{I}_z(A)\hat{I}_z(X) \xrightarrow{90^\circ \hat{I}_x(X)} 2\hat{I}_z(A)\hat{I}_y(X)$$

Antiphase A-magnetization is, therefore, transformed into antiphase X-magnetization, which is now modulated during t_2 with ω_X^i . This yields, after double Fourier transformation, cross peaks at ω_A^i, ω_X^i . A refocusing delay before detection with $\Delta_2 = 1/2J_{AX}$ leads for an AX system (CH group) to in-phase X-magnetization $\hat{I}_x(X)$. In this case A-decoupling can be applied.

Sequence (b): The experiment starts after the excitation pulse with a delay $\Delta_1 = 1/2J_{AX}$, at the end of which antiphase A-magnetization is formed. The 90° pulse transforms this into double and zero quantum magnetization:

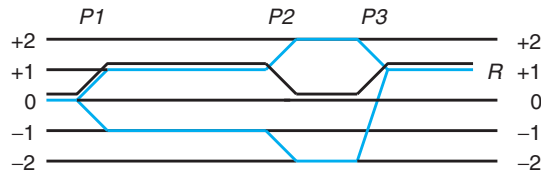
$$2\hat{I}_x(A)\hat{I}_z(X) \xrightarrow{90^\circ \hat{I}_x(X)} 2\hat{I}_x(A)\hat{I}_y(X)$$

These develop during the following evolution time t_1 with the sum and the difference of the Larmor frequencies ω_A and ω_X , respectively. Again a 180° pulse is used for A,X decoupling. The second $90^\circ(X)$ pulse, which is phase cycled in order to select double-quantum magnetization, yields antiphase A-magnetization that is now modulated in t_2 with ω_A leading to cross peaks:

$$2\hat{I}_x(A)\hat{I}_y(X) \xrightarrow{90^\circ \hat{I}_x(X)} -2\hat{I}_x(A)\hat{I}_z(X)$$

Sequence (c): The sequence starts with an INEPT transfer from A to X that yields single quantum coherence $2I_z(A)I_y(X)$. X chemical shift develops during t_1 , and the $180^\circ(A)$ pulse decouples A from X. This yields $2I_z(A)I_y(X)\cos\omega_X t_1 + 2I_z(A)I_x(X)\sin\omega_X t_1$. The last pulse pair $90_y^\circ(A)/90_x^\circ(X)$ (a reverse INEPT sequence) transforms the cosine term into antiphase A magnetization modulated by $\cos\omega_X [2I_x(A)I_z(X)\cos\omega_X t_1]$ and yields the A,X cross peaks.

- 11.4. Main signal magnetization S_0 (black), satellite magnetization $s_{\pm 1}$ (red), the 180° pulse is neglected:

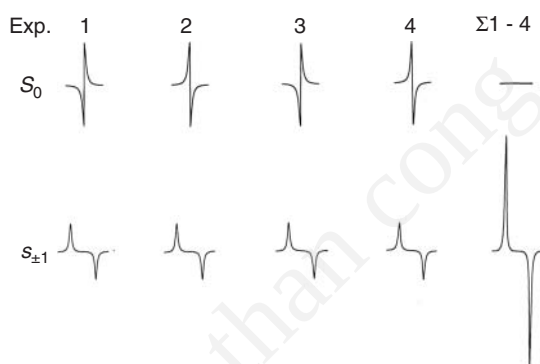


Starting with situation (e) in Figure 11.18 (p. 400), the selection of $s_{\pm 1}$ is possible on the basis of the phase rule $\Delta\phi = \Delta p \times \Delta\theta$ [Eq. (9.39), p. 322] with a phase cycle for the last 90° pulse P3. From the phase diagram we have for $s_{\pm 1}$ $\Delta p = -1$ and $+3$, while the z-magnetization S_0 follows the classical Bloch vector rules with $\Delta p = +1$.

This yields:

Experiment	$\theta(P3)$	S_0	s_{+1}	s_{-1}	Detector phase
1	$+x$	$-\gamma$	$+x$	$-x$	$+x$
2	$+\gamma$	$+x$	$-\gamma$	$+\gamma$	$-\gamma$
3	$-x$	$+\gamma$	$-x$	$+x$	$-x$
4	$-\gamma$	$-x$	$+\gamma$	$-\gamma$	$+\gamma$

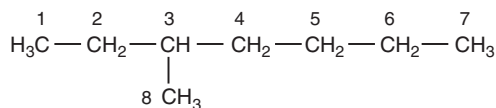
The detector phase follows the phase of the satellite magnetization. One detects the following signals and addition leads to elimination of S_0 while the satellite magnetization $s_{\pm 1}$ is retained:



According to the coherence level diagram shown above, a first gradient pulse ΔG_z after the pulse $P2$ and a second one with amplitude $-2\Delta G_z$ after pulse $P3$ refocuses selectively the satellite magnetization [see Willker, W. and Leibfritz, D. (1994) *Magn. Reson. Chem.*, 32, 665].

11.5. See Figure 9.7a, p. 288.

11.6.



	1	2	3	4	5	6	7	8
δ_{exp}	11.3	22.7	34.7	36.5	29.7	23.3	14.1	19.3
δ_{calc}	11.4	29.9	33.9	36.3	29.7	23.3	14.1	19.7

For C(2) as example: $\delta_{\text{calc}} = -2.6 + 2 \times 9.1 - 2.5 + 0.3 + 0.2 - 2.5 = 29.9$.

- 11.7. We start at $=C(3)H_2$ and use Eq. (11.16). This yields $s(i) = 32.2\%$ and for the CH-bonds $sp^{2.11}$ -hybrids. For the C(3)-C(2) bond 35.6% s -character remains, which leads to an $sp^{1.81}$ -hybrid. Equation (11.14) then yields $95.2 = 550 \times 0.356 \times x$ and $x = 0.486$. The C(2)-C(3)-hybrid, therefore, has 48.6% s -character and is a $sp^{1.06}$ -hybrid. The residual s -character at C(2) is distributed between the two bonds in the three-membered ring, with each bond receiving 25.7%. Within the framework of the Walsh model a $sp^{0.95}$ -hybrid is directed towards the ring. Equation (11.14) yields $23.2 = 550 \times 0.257 \times x$ and $x = 0.164$. C(l) has, therefore, 16.4% s -character for the C(l)-C(2) bond. If one assumes the same s -character for the C(l)-C(l') bond, 67.2% remain for the CH bonds a C(l), that is 33.6% for each bond. These are then formed by $sp^{1.98}$ -hybrids. The $^{13}C, ^1H$ coupling at the three-membered ring should then amount to 168.0 Hz. The difference found in relation to the experimental result has its origin in the unknown coupling C(l)-C(l') and in an accumulation of the errors in the last equation.
- 12.1. At 3.523 T the ^1H frequency of TMS is 150 MHz (rounded); for ^{19}F we derive from the data of Table 12.2 (94.094 011 MHz at 2.3548 T) 141.5 MHz. This yields after step 3 above for the zero-point relative to TMS 141.141 016 5 MHz. The position of the measured ^{19}F signal is thus 306.5 Hz to higher frequency, which yields $\delta_{TMS} = 2.17$ ppm.

- 12.2. The different acquisition periods yield the following development of the ^{17}O magnetization into the final orientation in italics:

$$\begin{aligned} (1) \hat{I}_z &\xrightarrow{90^\circ[\hat{I}_x]} \hat{I}_y; (2) \hat{I}_z \xrightarrow{90^\circ[-\hat{I}_x]} -\hat{I}_y; \\ (3) \hat{I}_z &\xrightarrow{180^\circ[\hat{I}_x], 90^\circ[-\hat{I}_x]} -\hat{I}_z, \hat{I}_y; (4) \hat{I}_z \xrightarrow{180^\circ[\hat{I}_x], 90^\circ[\hat{I}_x]} -\hat{I}_z, -\hat{I}_y \end{aligned}$$

The receiver follows $\hat{I}_y$ and the signal from acoustic ringing, which is always positive, is eliminated.

- 12.3. The ratio of the natural abundances is $^{13}C : ^{29}Si \approx 1:4$, however in the $(CH_3)_3Si$ -group we have three carbons and only one silicon atom.
- 12.4. The sequence follows the HMQC sequence shown in Figure 11.11b (p. 391) and described for Exercise 11.3, but the evolution time t_1 is eliminated. The magnetization of interest is that of the ^{13}C satellites that develops anti-phase Li magnetization until the 180° pulse. The $90^\circ(X)$ pulse produces double-quantum coherence $2\hat{I}_x(A)\hat{I}_y(X)$ that is transformed into anti-phase Li magnetization $2\hat{I}_x(A)\hat{I}_z(X)$ by the second $90^\circ(X)$ pulse for detection. The main ^6Li signal not coupled to ^{13}C follows the pathway $\hat{I}_y, -\hat{I}_y$ and is eliminated by the phase cycle.
- 15.1. For the carbene we have $\uparrow\uparrow$, for the CH bond of **4** (Scheme 15.1) $\uparrow\downarrow$; the new CH bond of $(C_6H_5)_2C-H$ uses $\uparrow\downarrow$, this leaves $\uparrow\uparrow$ for the radical pair.

Glossary

ACAC	acetylacetone
ADC	analog-to-digital converter
ADP	adenosine diphosphate
ALTADENA	adiabatic longitudinal transport after dissociation engenders nuclear alignment
APT	attached proton test
ATP	adenosine triphosphate
BB	broadband decoupling
BIRD	bilinear rotation decoupling
CE	cross effect
CGS	centimeter-gram-second system
CIDNP	chemically induced dynamic nuclear polarization
CIP	contact ion pair
C.N.	coordination number
CNDO	complete neglect of differential overlap
COLOC	correlation via long-range couplings
COSY	correlation spectroscopy
COSY-45	COSY with a 45° pulse
COSY-90	COSY with a 90° pulse
COSY-DQF	COSY with double-quantum filter
CP	cross polarization
cp*	pentamethyl cyclopentadienyl
CPD	composite pulse decoupling
CPMAS	cross polarization magic angle spinning
CPMG	Carr-Purcell-Meiboom-Gill pulse train
Cr(acac) ₃	chromium(III)acetylacetonate
CRAMPS	combined rotation and multiple pulse spectroscopy
CSA	chemical shift anisotropy
CW	continuous wave
CYCLOPS	cyclically ordered phase cycle
DAC	digital-analog-converter
DANTE	delays alternating with nutation for tailored excitation
D-DNP	dissolution dynamic nuclear polarization

DEPT	distortionless enhancement by polarization transfer
DFHD	decafluoroheptanedione
DFT	density functional theory
DMF	N,N-dimethylformamide
DMSO	dimethylsulphoxide
DNA	deoxyribonucleic acid
DNMR	dynamic NMR
DNP	dynamic nuclear polarization
DOR	double rotation
DPM	dipivaloylmethane
DQ	double quantum coherence
DSS	[D ₄]-2,2-dimethyl-2-silapentane-5-sulfonate
e.m.u.	electromagnetic units
E.COSY	exclusive correlation spectroscopy
ENDOR	electron nuclear double resonance
EPR	electron paramagnetic resonance
ESR	electron spin resonance
e.s.u	electrostatic units
EXORCYCLE	phase cycle to suppress phantom and ghost signals
EXSY	exchange spectroscopy
FACAM	trifluoroacetyl-D-campher
FID	free induction decay
FOD	dimethylheptafluoro-octane dione
FT	Fourier transform
GARP	globally optimized alternating-phase rectangular pulses
GAUSSIAN	program package for theoretical calculations of molecular structures and properties
HMBC	heteronuclear multiple bond correlation
HMO	Hückel molecular orbital method
HMQC	heteronuclear multiple quantum coherence
HEHAHA	heteronuclear Hartmann Hahn experiment
HOESY	heteronuclear Overhauser effect spectroscopy
HOHAHA	homonuclear Hartmann-Hahn experiment
HOMO	highest occupied molecular orbital
HSQC	heteronuclear single quantum coherence
IGLO	individual gauge for localized orbitals
INADEQUATE	incredible natural abundance double quantum transfer experiment
INDO	intermediate neglect of differential overlap
INDOR	internuclear double resonance
INEPT	insensitive nuclei enhanced by polarization transfer
LCAO	linear combination of atomic orbitals
LEFE	linear electric field effect

LIS	lanthanide-induced shift
LUMO	lowest unoccupied molecular orbital
MAS	magic angle spinning
MLEV	composite pulse decoupling
MO	molecular orbital
MRI	magnetic resonance imaging
MQ	multiple quantum
MQMAS	multiple quantum magic angle spinning
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	NOE spectroscopy
NQR	nuclear quadrupole resonance
QD	quadrature detection
O-DNP	Overhauser dynamic nuclear polarization
OR	off-resonance
PASADENA	para-hydrogen and synthesis allow dramatically enhanced nuclear alignment
PBLG	poly- γ -benzyl L-glutamate
PFGSTE	pulsed field gradient stimulated echo
PGSE	pulsed gradient spin echo
PHIP	para-hydrogen induced polarization
ppb	parts per billion
ppm	parts per million
REDOR	rotational echo double resonance
RF	radio frequency
RIDE	ring down elimination
RMS	root-mean-square
RNA	ribonucleic acid
ROESY	rotation frame NOESY
SEPT	spin echo polarization transfer
SI	système internationale
S/N	signal-to-noise ratio
SPI	selective population inversion
SPT	selective population transfer
SQ	single quantum coherence
SSB	spinning side band
SS-DNP	solid state dynamic nuclear polarization
SSIP	solvent-separated ion pair
TEMPOLE	4-hydroxytetramethylpiperidine oxide
TEMPONE	4-oxotetramethylpiperidine oxide
TM	thermal mixing
TMEDA	tetramethylethylenediamine

TMS	tetramethylsilane
TOCSY	total correlation spectroscopy
TPPI	time-proportional phase incrementation
VASS	variable angle sample spinning
WAHUHA	Waugh-Huber-Haeberlen pulse sequence
WALTZ	broadband decoupling method
WATERGATE	water suppression by gradient-tailored excitation

Index

a

- A₂ system 158 ff.
 - eigenfunctions 168
 - eigenvalues 168
 - energy level diagram 161
 - oriented 560
 - relative intensities 162
 - secular determinant 160
 - transition energies 168
 - transition probabilities 168
 - variational method 160
- AA'BB' spectrum 205
 - direct analysis 666
- A₂X₂ system 55, 194, 203
- AA'XX' system 193 ff.
 - 4-bromoanisole 201
 - deceptively simple 203
 - direct analysis 198
 - eigenvalues 183
 - energy level diagram 196
 - furan 204
 - half spectrum 197
 - Hamilton matrix 195
 - 2-methylbenzotriazole 200
 - morpholine 203
 - subspectra 195, 197
 - symmetry functions 195
 - transition energies 199
- A₂B system 177, *see also* AB₂ system
- absolute value representation 285
- AB system 164
 - chemical exchange 522
 - CIDNP effect 609
 - deceptively simple 170
 - direct analysis 175
 - eigenfunctions 168
 - eigenvalues 168
 - energy level diagram 157
 - geometric solution 176
 - ratio $J/\nu_0\delta$ 176
 - spectrum 166
 - spin-polarized 609
 - transition energies 168
 - transition probabilities 168
- AB₂ system 177
 - basis functions 179, 182
 - direct analysis 180
 - eigenfunctions 179, 182
 - energy level diagram 180
 - Hamilton matrix 183
 - irreducible representation 182
 - particle spin 181
 - spectrum 178
 - subspectra 182
- AB_n system 182
- ABC system 191, 628
 - COSY cross peaks 628
- ABX system 628
 - AB part 190
 - deceptively simple 189
 - dependence on $\nu_A - \nu_B$ 192
 - E.COSY 628
 - effective Larmor frequencies 186, 628
 - passive spin 183, 628d
 - product functions 184
 - relative sign of coupling constants 190
 - solutions 187
 - subspectra 184
 - virtual coupling 190
 - X-approximation 183
 - X-part 188
- ABX₂ system 185
- ABX₃ system 185
- accumulation, of spectra 79
- acetylacetone 550
- acidic protons 37

- acquisition time 257
 - acoustic ringing 446
 - acrylnitrile, spectrum 57
 - acyloxonium salt 547
 - 2-adamantanol, spectrum in the presence of Eu(DPM)_3 602
 - ADC, analog-digital-converter 254
 - adenosine diphosphate (ADP) 642
 - adenosine triphosphate (ATP) 642, 643
 - adsorbed hydrocarbons, MAS 587
 - alanine, spectral change with pH 93
 - aldehyde proton deshielding 99
 - aldehydes, unsaturated 99, 100
 - alignment 565
 - degree of 566
 - in electric field 565
 - in phospholipids 565
 - in poly- γ -benzyl L-glutamate (PBLG) 567
 - tensor 566
 - and variable angle sample spinning 567
 - allenes, long-range ^1H , ^1H coupling 142
 - allylic ^1H , ^1H coupling 141
 - allyl magnesium bromide 542
 - alpha-helix 632
 - ALTADENA 621
 - AX system 618
 - aluminum-27, *see also heteronuclei* 468 ff.
 - ammonium ion, ^{14}N NMR 51
 - amine protons 37
 - ammonia 525
 - amplitude modulation 282
 - AMXsystem 226
 - analog–digital converter (ADC) 254
 - analysis of spin systems, *see spectral analysis* 149 ff.
 - Anderson–Kubo–Sack theory 536, 671
 - angular momentum 13, 16
 - angular velocity 16
 - anisotropy, chemical shift 30, 433, 571
 - diamagnetic, *see diamagnetic anisotropy*
 - [18]annulene, ^1H NMR 104, 533
 - annulenes 104 ff.
 - ring inversion, *see dynamic NMR*
 - anthracene, ring current 103
 - anti-aromatic molecules 106, 541
 - anti-echo signal 325
 - antimony(V) fluoride 67
 - anti-phase magnetization 316
 - antisymmetric wave functions 164
 - aromatic compounds, ^1H data 652, 655
 - ^{13}C data 661
 - aromatic ions 89, 411
 - aromatic solvent induced shifts (ASIS) 121
 - Arrhenius activation energy, E_a 507
 - artifacts in COSY spectra 302
 - ASIS (aromatic solvent induced shifts) 73
 - assignment techniques, in ^{13}C NMR 381 ff.
 - associated coupling 630
 - association effects 72
 - asymmetric carbon 219
 - asymmetry parameter 586, 587
 - atropic molecules 106
 - aufbau principle 105
 - axial shielding 96
 - AX system 61, 169 ff.
 - CIDNP effect 612
 - COSY spectrum 61
 - double quantum selection 331
 - double resonance 59
 - energy level diagram 44, 168 ff.
 - eigenfunctions 168
 - eigenvalues 168
 - eigenstates 45
 - entropy polarization 612
 - first order approximation 167
 - operator basis 311
 - partially aligned 566
 - transition energies 168
 - transition probabilities 168
 - SPI experiment 358
 - SPI experiment, CHCl_3 359
 - spin echo experiment 288
- b**
- B_0 fields 33
 - backbone angles, in peptides 630
 - backbone assignment, sequential 633, 634
 - basis functions 170
 - benzene, chloroform complex 118
 - 1,2-dichloro- 76
 - ethyl, sensitivity test 78
 - disubstituted 212, 334
 - heptamethyl 546
 - hexamethyl 545
 - monsubstituted 91
 - oxide, valence tautomerism 538
 - *ortho*-disubstituted 334
 - *para*-disubstituted 334
 - partially oriented 562
 - ring current 69, 101
 - spectrum of partially oriented 562
 - spin-lattice relaxation 242
 - spin-spin coupling, ^1H , ^1H 658
 - – ^{13}C , ^1H 424, 426
 - 1,2,3-trichloro- 178
 - 1,2,4-trichloro- 183
 - benzenium ion, heptamethyl- 546
 - hexamethyl- 545

- benzoxepine, ^1H spectrum 146
 - benzyl acetate 33, 41
 - benzyl alcohol 72
 - biochemistry, NMR in 625 ff.
 - biomolecules 625 ff.
 - bio NMR, nucleic acids 634 ff.
 - backbone torsion, scalar coupling 635
 - coherence pathway 635
 - COLOC experiment 636
 - ^{13}C , ^{31}P HMQC shift correlation 636
 - DNA structure 635
 - Haasnoot-Altona equation 638
 - helix structure 635
 - Karplus curves 635
 - mononucleotides 636
 - NOE-based pathway 635
 - phosphorus-31 NMR 635
 - torsional angles 634, 635
 - bio NMR, oligo- and polysaccharides 636 ff.
 - anomeric protons 638
 - chair $^1\text{C}_4$ 637
 - chair $^4\text{C}_1$ 637
 - galactose 637
 - glycoside linkage 637
 - Karplus curves 638
 - pyranose rings, chair conformation 637
 - sialyl- $\alpha(2\rightarrow6)$ lactose 637
 - stereochemistry 637
 - torsional angles 637
 - trisaccharide 637
 - bio NMR, peptides and proteins 627 ff.
 - α -helix 632
 - backbone angles, in peptides 630
 - backbone assignment, sequential 633, 634
 - HCA(CO)N experiment 633
 - HCACO experiment 633
 - HNCA experiment 633
 - HNCO experiment 633
 - HOHAHA-HMQC experiment 633
 - β -sheet 632
 - β -turn 632
 - bovine pancreatic trypsin inhibitor (BPTI), 3D structure 632
 - BPTI, 3D structure 632
 - constraints 630
 - E.COSY (exclusive correlation spectroscopy) 628
 - ABC system 628
 - ABX system 628
 - effective Larmor frequencies 628
 - passive coupling 628
 - pulse sequence 629
 - three spin system, homonuclear 628
 - hairpin 632
 - Karplus curve, in peptides 631
 - peptide partial structure, NMR experiments 630
 - polypeptides, ^{13}C , ^{15}N enriched, scalar coupling 633
 - shift correlation ^{15}N , ^1H 629
 - spatial structure 630
 - transverse relaxation optimized spectroscopy, *see* TROSY
 - TROSY 629
 - enzyme spectrum 629
 - biphenylene 112, 585
 - 2-methyl- 400
 - BIRD pulses 329
 - bis*(trimethylsilyl)mercury 49
 - bis*-methano[14]annulene, 1,6;8,13-*anti*- 109
 - bis*-methano[14]annulene, 1,6;8,13-*syn*- 109
 - bit, binary digit 255
 - Bloch equations 667
 - for chemical exchange 668
 - Bloch vector model 289, 297, 309
 - Bloch-Siegert shift 272
 - boat form 526, 637
 - blood plasma 640
 - body fluids, NMR of 640
 - Boltzmann relation 19
 - bond length 130, 132, 426
 - bond order 130, 132, 426
 - bond shifts, *see also* dynamic NMR 538 ff.
 - boron-11, *see also* heteronuclei 435 ff.
 - bovine pancreatic trypsin inhibitor (BPTI), 3D structure 632
 - BPTI, 3D structure 632
 - broadband decoupling 275 ff.
 - by CW modulation 275
 - by pulse methods 275
 - composite pulse sequences 278
 - MLEV 277
 - building blocks for pulse sequences 329
 - bullvalene, *see also* dynamic NMR 535, 537
 - butadiene-1.3 658
 - n*-butyllithium, PGSE experiment 615
 - t*-butylgroup, hindered rotation 522
- c**
- cadmium-113, *see also* heteronuclei 488
 - carbanions 92
 - carbenium ions 67
 - carbocations, *see also* dynamic NMR 545
 - carbohydrates 636 ff.
 - carbon chemical shifts, *see also* carbon-13 NMR 659 ff.
 - alkenes 659
 - alkynes 661

- carbon chemical shifts, *see also carbon-13 NMR*
(*contd.*)
- aromatic compounds 661
 - benzenes, substituted 662
 - benzocycloalkanes 661
 - cycloalkanes 660
 - cycloalkenes 660
 - heterocycles 663
 - hydrocarbons 659
 - solvents 659
- carbon-13 NMR**
- APT, attached proton test 383
 - – delays for CH, CH₂, CH₃ group detection 384
 - assignment techniques 383 ff.
 - attached proton test (APT) 383
 - 4-*t*-butylcyclohexanone, spectrum 386
 - C60 416
 - C70 416
 - chemical shift 407, 408, 659 ff.
 - – α -effect 419
 - – aromatic ions 411 ff.
 - – β -effect 419
 - – carbocations 415
 - – charge density effect, aromatic systems 411 ff.
 - – dicyclopentaheptalene 414
 - – fullerenes 416
 - – γ -effect 419 ff.
 - – heavy atom effect 409
 - – Lamb formula 409
 - – NICS values 416
 - – non-alternant hydrocarbons 414
 - – paramagnetic term 410
 - – pH dependence in pyridine 414
 - – π electron density 411
 - – protonation 413
 - – pyrene 414
 - – Ramsay equation 410
 - – theoretical models 409 ff.
 - constant time experiment 394
 - correlation via long-range couplings (COLOC) 394
 - CW spectrum 378
 - DEPT sequence 388
 - – product operator formalism 388
 - – spectrum of longifolene 390
 - – subspectra 389
 - dicycloheptapentalene 414
 - diphenyl acetylene 407
 - empirical correlations 418
 - experimental aspects 381 ff.
 - first-order splitting 405
 - fullerene anions 417
 - fullerene, encapsulated ³He 417
 - gated decoupling 382
 - HETCOR 389
 - – pulse sequence 391
 - – spectrum of a paracyclophane 399
 - – – of 2,7-dilithionaphthalene 393
 - – – of angelica acid 398
 - – – of bis-dehydrobenzo[20]annulene 399
 - – – of tiglic acid 398
 - HETCOR COLOC 394
 - heavy atom effect 409
 - historical development 378
 - HMBC
 - – gradient enhanced 397
 - – spectrum of 3-fluorophenanthrene 397
 - HMQC 389, 394
 - – ¹³C, ²H shift correlation with BIRD pulse 396
 - – pulse sequence 391
 - – spectrum of
 - benzo[c]1,7-methano[12]annulene 393
 - – with single quantum A elimination by BIRD 394
 - pulse sequence 391
 - HSQC 391
 - INADEQUATE experiment, 1D ¹³C, ¹³C 398 ff.
 - – spectrum of 2-methylbiphenylene 400
 - pulse sequence and vector diagrams 400
 - INADEQUATE experiment, 2D ¹³C, ¹³C, nicotine amide adenine dinucleotide (NAD⁺) 402
 - INEPT, refocused 387
 - inversion recovery experiment 381
 - isotope effects, deuterium induced, 1,6-indane oxide 406
 - *J*, δ spectrum, heteronuclear 401
 - – of norbornane 403
 - *J*-resolved spectrum, heteronuclear 401
 - longitudinal relaxation, measurement 381
 - magnetization modulated by CH coupling 387
 - multiplicity selection 383 ff.
 - polarization transfer experiments 387 ff.
 - – DEPT 388
 - – refocused INEPT 387
 - pyridine spectrum 378
 - receptivity 377
 - refocused INEPT 387
 - SEFT, spin echo Fourier transform 383
 - – delays for CH, CH₂, CH₃ group detection 384
 - – magnetization vector orientation 385
 - selective excitation 403 ff.

- selective INEPT, phenylacetylene 404
- shift increments 419
- signal selection 384 ff.
- spherical aromaticity 416
- spin echo experiment 383
- spin flip method 402
- spin-lattice relaxation rates,
 - diphenylacetylene 407
- spin-lattice relaxation 428
 - rotational barriers 429
 - segmental motion 429
- spin-spin coupling constants 420 ff.
 - and chemical structure 422 ff.
 - ^{13}C , ^{13}C coupling, ^1J 422 ff.
 - bond length dependence 422
 - cyclopropane 423
 - Fermi contact term 422
 - s-character 422
 - silacycloheptene 423
 - table 424
 - ^{13}C , ^{13}C coupling, ^3J , 423 ff.
 - π bond contribution 423
 - dihedral angle dependence 423
 - Karplus curve 423
 - ^{13}C , ^1H coupling, ^1J 424 ff.
 - benzocyclopropane 425
 - s-character dependence 424
 - correlation with bond length 426
 - correlation with HMO π -bond order 426
 - Karplus curve 427
 - ^{13}C , X coupling 427
 - testosterone spectrum 380
 - T_1 measurement 381
 - two-dimensional chemical shift correlation 389 ff.
 - vitamin B₁₂ spectrum 379
 - *m*-xylene, T_1 measurement 381
- cell metabolism 641
- charge density effects, for ^1H NMR 89, 91
- chemical equivalence 52
 - shift, *see also* heteronuclei
 - aluminum-27 470
 - boron-11 435
 - ^{13}C , *see also* carbon-13 NMR 407 ff., 659 ff.
 - difference, notation of 45
 - fluorine-19 450 ff.
 - ^1H , *see also* proton chemical shift 16, 29 ff.
 - lithium-6, 7 464
 - measurement 32 ff.
 - nitrogen-15 439
 - origin of 30
 - oxygen-17 446
 - phosphorus-31 459 ff.
 - silicon-29 455 ff.
 - tin-119 472 ff.
 - transition metals, *see also* heteronuclei 474 ff.
 - xenon-129 621
- chemical exchange, *see* dynamic NMR
- chemically induced nuclear polarization (CIDNP), *see also* CIDNP 604 ff.
- chiral, liquid crystals 568
 - enantiomeric excess 568, 569
- shift reagents 219
- chirality 211 ff.
 - and ^{13}C 224
 - influence on spectrum 216
- 2-chloroacrylic acid, 2D INADEQUATE 333
- COSY-DQF 308
- chloroform 76
 - ^{13}C ^1H coupling 76
- chloroform-benzene complex 118
- chromium acetylacetonate 243
- CIDNP (chemically induced nuclear polarization) 604 ff.
 - AB system, spin polarized 609
 - dibenzoyl peroxide, thermal decomposition 605
 - energy polarization 605
 - entropy polarization 608
 - Kaptein rules 611
 - multiplet effect 608
 - Net effect 605
 - radical pair mechanism 606 ff.
 - radical pair, spin state 606
 - recombination product 607
 - transfer product 607
 - AX system 610
 - spin polarized AB system 609
 - Wittig ether rearrangement 612
- classical model, for NMR 16
- clinical studies 640
- CNDO method 85
- coalescence point, *see also* dynamic NMR 505
- coaxial tube 69
- cobalt-59, *see also* heteronuclei 482 ff.
- coherence 309
 - diagram 323
 - COSY-90 324
- double quantum 313, 326
- level 322
- order 328
- transfer echo 325
- COLOC 394
- commutable operators 665

- complex spin systems 170
 - composite pulses 264
 - Computer, acquisition time 257
 - ADC, analog-digital-converter 254
 - bit, binary digit 255
 - digital analog converter (DAC) 256, 257
 - dwell time 257
 - dynamic range 256
 - memory locations 254
 - Nyquist theorem 257
 - resolution, of ADC 256
 - sampling rate 256
 - storage 254
 - word length 254
 - concentration dependence, of spectrum 72
 - constant time experiment 329
 - constraints 630
 - contact ion pairs (CIP) 586
 - contact shifts 597
 - continuous wave method (CW) 20 ff.
 - contour plot 284
 - copper-63, *see also* heteronuclei 484
 - coupling constants $^1\text{H}, ^1\text{H}$ 654 ff.
 - cyclopropanes 654
 - olefins 654
 - substituted benzenes 655
 - correlation time 240
 - COSY-90 experiment 296 ff.
 - AX system 61
 - experimental aspects 300 ff.
 - gradient enhanced 327
 - pulse sequence 61
 - COSY, *see* COSY-90
 - COSY-45 experiment 304
 - 2,3-bromopropionic acid 305
 - relative sign of coupling constants 305
 - COSY-DQF experiment 307
 - gradient enhanced 307
 - product operator treatment 320
 - COSY-LR (COSY long range) 305
 - coupling constant 43
 - reduced 43
 - sign 43
 - coupling mechanism 42
 - coupling, dipolar 22
 - $\text{Cr}(\text{acac})_3$ 243
 - CRAMPS (combined rotation and multi-pulse NMR spectroscopy) 576
 - cross coils 19
 - cross peaks 296
 - cross polarization 365, 571
 - cryomagnet 24, 79, 638
 - cryoprobe 81, 82
 - ^{13}C satellites 76
 - CW method, *see* continuous wave method
 - cyclobutanes, substituted 213
 - cyclo-octatetraene dimer 225
 - cyclopropane, diamagnetic anisotropy 113
 - ring current 113
 - substituted 213
 - CYCLOPS phase cycle 266
 - cyclosilane $[\text{D}_{18}]$ 83
- d**
- DANTE sequence 263
 - data flow 283
 - data improvement 269 ff.
 - decoupled COSY, ω_1 - 329
 - decoupling, broadband 275
 - GARP 277
 - gated- 382
 - heteronuclear 59, 273
 - homonuclear 58
 - in FT NMR 273
 - MLEV 277
 - noise- 275
 - off-resonance- 277
 - pulse methods 277
 - spin-spin 58
 - WALTZ-16 277
 - degeneracy 14
 - degenerate spin systems 226
 - bis-dehydrobenzo[18]annulene, 2D NMR 298
 - delay time 259
 - delta scale 33 ff.
 - of carbon-13 407, 408
 - of heteronuclei 437
 - of protons in organic compounds 37
 - delta sigma ($\Delta\sigma$) 34
 - density matrix theory 309
 - deshielding 32
 - detection time t_2 61, 281
 - detector 19
 - phase-sensitive 259
 - deuterated solvents 68
 - deuterium-induced isotope shifts 593 ff.
 - deuterium quadrupole splitting 568
 - deuteriochloroform 67
 - diagonal peak 7, 60, 296
 - diamagnetic anisotropy 95
 - benzene 103
 - carbonyl group 98
 - cyclohexane 72
 - cyclopropane 113
 - nitro group 98
 - single bond 96
 - triple bond 97
 - diamagnetic effect 31

- shift 32
- susceptibility 94
- – exaltation of 110
- diastereomers 217, 294
- diastereomeric complexes 217
- diastereotopic molecules 220
- diatropic 104
- diatropicity, measurement 110
- dibromo-1,6-methano[10]annulene, 2,7- 222
- dichloroethene, *trans*-1,2- 226, 228
- diclorobenzene, 1,2- 76
- diffusion and field gradients 613
- coefficient, measurement 612
- diffusion-controlled NMR 612 ff.
- diffusion-ordered spectroscopy (DOSY) 615
- difluoroethylene, spectrum 55
- difluoromethane, spectrum 55
- dihydroheptalene 225
- dimethyl-2-silapentane-5-sulfonate, [D₄]2,2- 70
- dinitrophenol, 2,4- 47
- dipolar coupling 22, 143, 241, 561
- residual 565
- – for AX system 566
- – measurement by HMQC, HSQC 566
- – ¹³C NMR spectrum of strychnine 567
- dipolar relaxation 241
- dipole-dipole relaxation 241
- disila[6]radialene 215
- distance ratio 355
- di-*t*-butylmercury, ¹⁹⁹Hg NMR 51
- 2D-NMR, *see two-dimensional NMR*
- 3D NMR 371ff.
- DNMR, *see dynamic NMR*
- DNP, *see dynamic nuclear polarization*
- DOSY (diffusion-ordered spectroscopy) 656
- spectrum 616
- double bond shift, *n*-butyl-cyclo-octatetraene 540
- double quantum coherence (DQ) 307, 310, 313, 326
- phenomena 307
- selection, AX system 331
- double resonance, *see also decoupling* 58, 272 ff.
- Bloch-Siegert shift 272
- Hamilton operator 272
- heteronuclear 59, 273
- homonuclear 58, 272
- downfield 32
- DQ, *see double quantum coherence*
- DSS reference compound 70
- dwelt time 257
- dynamic NMR (DNMR):**
 - AB system, chemical exchange 519, 520
 - acetylacetone 549, 550
 - activation enthalpy 507
 - activation entropy 507
 - allylmagnesium bromide 542
 - [18]annulene 514, 531
 - annulenes, ring inversion 531 ff
 - – bond shift 531 ff.
 - approximate solution of DNMR analysis 509
 - – sources of error 509
 - Arrhenius activation energy 507
 - Arrhenius equation 507
 - Arrhenius plot 507
 - A-value 528
 - average life-times 505
 - averaging of parameters 505
 - benzene oxide, valence tautomerism 537
 - Bloch equations 505, 668
 - bond shifts 538 ff.
 - broadening due to inhomogeneity 509
 - bromocyclohexane, ring inversion 528
 - bullvalene, valence tautomerism 535
 - carbocations 545
 - carbon-13 and DNMR 512
 - chlorocyclohexane, ring inversion 528
 - coalescence point 505
 - complex exchange phenomena 512
 - COPE rearrangement 536
 - correlation times 504
 - cycloalkanes, ring inversion 522, 529
 - cyclohepta-1.3.5-triene, ring inversion 529
 - cyclohexane, ring inversion 526
 - cyclohexene, ring inversion 529
 - cyclo-octatetraene, double bond shift 538
 - – ring inversion 540
 - dicarbomethoxycycloheptatriene, valence tautomerism 537
 - dimethylcadmium 551
 - dimethylformamide *N,N*- 4, 501, 511
 - double bond shift 532
 - energy barrier 501, 506
 - enthalpy of reaction 508
 - entropy of reaction 508
 - equilibrium constant *K* 508
 - exchange broadening 509
 - exchange, of Larmor frequencies 501
 - – of AB ⇌ A₂ 519, 520
 - – approximate solution at coalescence 520
 - – complex phenomena 512

dynamic NMR (DNMR): (*contd.*)

- – intermolecular 549
 - EXSY spectroscopy 515
 - – spectrum of
 - 2,3-dimethylanthraquinone-9-cyanimine 512, 516 ff.
 - – ^{11}B , ^{11}B EXSY spectrum of halogen
 - exchange in boron halides 516, 519
 - – carbon-13 EXSY spectra 516
 - – phase of diagonal and cross peaks 515, 671
 - – pulse sequence 516
 - – rate constants, first order 505
 - – – by integration 516
 - – – pseudo first-order 552
 - Eyring equation 508
 - fast exchange 505, 509
 - fast relaxing nuclei, line broadening by 554
 - fluxional molecules 533
 - field strength influence 510
 - first order rate constants by integration 516, 520
 - first-order reactions 506
 - free energy of activation 508
 - frequency factor 507
 - hexamethylbenzene 545
 - hindrance to internal rotation 518
 - – activation energies 519
 - 3,4-homotropilidene, valence tautomerism 533
 - intermolecular exchange 549
 - internal dynamics of organic molecules 517 ff.
 - internal rotation 501, 518 ff.
 - inversion of configuration 523 ff.
 - – ammonia 523
 - – diazines 524
 - – diaziridine 524
 - – trialkyloxonium salt 526
 - inversion recovery experiment 513
 - isomers of different energy 502
 - life-time τ 503
 - line broadening by fast relaxing
 - neighboring nuclei 554
 - line shape, two-sites exchange 506
 - – calculation 505
 - – essential parameters 505
 - – sources of error 509
 - metal carbonyl complexes 543
 - methanol 503
 - 2-methyloxepine 502
 - natural line width 509
 - norbornyl cation 546
 - organometallic compounds 542 ff.
 - oxepine, valence tautomerism 537
 - [6]paracyclophane, ring inversion 529
 - π -bond shift 538
 - population 505
 - pseudo rotation 526
 - rate constants, magnitude of 506
 - reaction enthalpy 508
 - reaction entropy 508
 - reaction kinetics 505
 - reaction order 506
 - ring inversion 526 ff.
 - – annulenes 531
 - – bromocyclohexane 528
 - – chlorocyclohexane 528
 - – cycloalkanes 522, 529
 - – cyclohepta-1.3.5-triene 529
 - – cyclohexane 526
 - – cyclhexene 529
 - – cyclo-octatetraene 538 ff.
 - – [6]paracyclophane 529
 - – slow exchange 505, 509
 - spin echo experiment 508
 - spin-spin splitting, loss of 503
 - substituted ethanes 521
 - temperature dependence of parameters 511
 - theoretical line shape 506
 - thiopene dioxide, influence of B_0 510
 - transition state theory 507
 - transmission coefficient 507
 - trimethylaluminium 550
 - two-dimensional exchange spectroscopy, *see* EXSY
 - valence tautomerism 532 ff.
 - – benzene oxide 537
 - – bullvalene 535
 - – cyclo-octatetraene 538 ff.
 - – dicarbomethoxycycloheptatriene, 537
 - – 3,4-homotropilidene 533
 - – oxepine 537
 - – van't Hoff equation 508
- dynamic processes, in the solid 588 ff.
- dynamic nuclear polarization (DNP) 623 ff.
- – cross effect (CE) 623
 - – dissolution DNP (D-DNP) 623
 - – Overhauser DNP (O-DNP) 623
 - – – in liquids 624
 - – polarizing agents 624
- solid state DNP (SS-DNP) 623
- dynamic range 256, 269

e

echo-planar imaging (EPI) 337
 echo signal 249
 E.COSY (exclusive correlation spectroscopy) 628
 eddy currents 615
 editing 383
 effective Larmor frequencies 226, 628
 eigenfunction 14, 152
 eigenstate 14, 151
 eigenvalue problem 173
 eigenvectors 171
 electric field effect 114
 – in nitrobenzene 115
 – in pyridine 115
 – linear 115
 – quadratic 116
 electromagnetic spectrum 23
 electron density, on neighboring carbon 87
 electronegativity 87, 451
 electron on a circle 105, 152
 electron paramagnetic resonance (EPR) 623
 – spin resonance (ESR) 623
 electron-nuclear double resonance (ENDOR) 623
 empirical substituent constants, for protons 121, 652 ff.
 – for carbon-13 418 ff., 662
 enantiomeric excess 568, 569
 enantiomers 217
 enantiotopic molecules 220
 ENDOR (electron-nuclear double resonance) 623
 energy difference 15, 19
 energy, of spin states 14
 – level diagram 44
 – – A_2 system 161
 – – $AA'XX'$ system 196
 – – AB system, $J = 0$ 157
 – – AB_2 system 180
 – – ABX system 184
 – – AX system 44
 – separation 15
 enhancement factor, NOE 344
 enhancement factors, table of 361
 enzyme spectrum 629
 EPR (electron paramagnetic resonance) 623
 Ernst angle 258
 ESR (electron spin resonance) 623
 estrone, spectrum 80
 ethylbenzene 78, 255
 ethyl formate 35, 41
 ethynylphenanthrene, proton deshielding 97
 europium, shift reagents 603 ff.

Eu(FOD)₃-induced contact shifts 604
 evolution time t_1 61, 281
 exaltation, of diamagnetic susceptibility 110
 exchange, *see also dynamic NMR* 501
 – broadening, *see also dynamic NMR* 509
 excitation 21
 – selective 260 ff.
 exponential multiplication 269 ff.
 external standard 70
 – correction for 71
 extreme narrowing limit 241
 EXSY spectroscopy 514 ff.
 Eyring equation 508
 E,Z-isomers 294

f

Fermi contact mechanism 42
 FID, *see free induction decay*
 field effect, *see electric field effect*
 field gradients 75, 326, 612, 644
 – homogeneity 75
 – strength 79
 field sweep 21
 field/frequency ratio 33, 75
 filter functions 285
 first order approximation 167, 181
 first-order rules 45, 46
 – spectra 45
 flemingin B 215
 flip angle 239
 flip-flop mechanism 244
 – heteronuclear 366
 – homonuclear in solids 365
 fluorenyllithium, TMEDA complex, solid state NMR 588
 fluorine-19 447 ff.
 fluorine shielding 32, 450
 fluoropyridine, 2-, J-resolved spectrum 295
 fluxional molecules 533
 folding 264, 267
 formaldoxim 72
Fourier transform spectroscopy 13, 21, 233 ff.
 – acquisition time 257
 – complications 267 ff.
 – composite pulses 264
 – computer, *see above*
 – data collection 257, 273
 – data improvement 269 ff.
 – decoupling 273
 – delay time 259
 – digitizer 256
 – dwell time 257
 – double resonance 273

Fourier transform spectroscopy (contd.)

- dynamic range 269
- filter functions 272
- frequency folding 264, 267
- intensity measurements 269
- presaturation 269
- parameters 257
- phase cycles 266
- phase error 259 ff.
- presaturation 269
- pulse calibration 263, *see also* pulse and pulses
- quad-images 265
- quadrature detection 265
- repetition time 250, 262
- sampling rate 256
- single detection 264
- spectral width 257, 267
- time domain 253
- time sequence 259
- weighting functions 272
- window functions 272
- word length 254
- zero-filling 272
- Fourier transformation 283
- free induction decay (FID) 21, 22, 61, 76, 238, 253
 - measurement 79
- frequency-dependend phase error 259
- frequency, domain 252
 - filter 264, 268
 - folding 264, 267
 - sweep 21
 - precision 77
- frog muscle 643
- FT NMR, *see* Fourier transform spectroscopy
- FT NMR spectrometer 254 ff.
 - diagram 256
- fullerenes 416
- furan, ^1H spectrum 55
- F_z operator 665

g

- γ -effect 419
- GARP 277
- gated decoupling 382
- GAUSS pulse, excitation profile 262
- GAUSSIAN method 85
- geminal, ^1H , ^1H coupling 123
 - and hybridization 123
 - effect of substituents 124 ff.
 - MO model 126
 - neighboring π -bonds 124
 - ^{13}C , ^1H coupling 425

- geminate pair 608
- g-factor 608
- glucose α -D- and β -D-, 1D TOCSY spectrum 370
- glycolysis 642
- gradient enhanced NMR 326 ff.
- gyroscope 234

h

- Haasnoot-Altona equation 638
- hairpin 632
- half-width, of signal 247
- Hamilton matrix 173
- Hamilton operator 151, 153, 314
 - for isotropic mixing 367
 - for partially oriented systems 560
 - for solid state NMR 570
 - for spin-decoupling 272
 - in polar coordinates 664
- hard pulses 260
- Hartmann-Hahn experiment, *see also* HOHAHA, HEHAHA 364 ff.
 - in liquids 366 ff.
 - in solids, pulse sequence 367
- H,D coupling 229
 - substitution 228
- HEHAHA (heteronuclear Hartmann-Hahn) experiment 366
- Henderson-Hasselbalch equation 94
- Herzfeld-Berger method 573
- heteronuclear two-dimensional shift correlations** 389 ff.
 - HETCOR experiment 389
 - pulse sequence 391
 - spectrum of a paracyclophane 399
 - of 2,7-dilithionaphthalene 393
 - of angelica acid 398
 - of *bis*-dehydrobenzo[20]annulene 399
 - of tiglic acid 398
 - HETCOR COLOC 394
 - HMBC experiment 394
 - gradient enhanced 397
 - spectrum of 3-fluorophenanthrene 397
 - HMQC experiment 391
 - ^{13}C , ^2H shift correlation with BIRD pulse 396
 - pulse sequence 391
 - spectrum of benzo[c]1,7-methano[12]annulene 393
 - with single quantum A elimination by BIRD 394
 - HSQC experiment 391
 - pulse sequence 391
- heteronuclei** 431 ff.

- **aluminum-27** 468 ff.
 - chemical shifts 469, 470
 - multiple quantum MAS (MQMAS) 469
 - referencing 469
 - spin-spin coupling 471
 - asymmetry parameter 433, 587
- **boron-11** 435 ff.
 - chemical shifts 438
 - COSY spectrum 440
 - polyhedral boranes 438
 - referencing 437
 - selected compounds 439
 - spin-spin coupling 438
 - chemical shift anisotropy 434
 - chemical shifts 433, 437
 - classification 432
- **cadmium-113** 488 ff.
 - chemical shifts 488
 - referencing 488
 - spin-spin coupling 489
- **cobalt-59** 482 ff.
 - chemical shift 483, 484
 - referencing 483
 - spin-spin coupling 483
- **copper-63** 484
 - chemical shifts 484
 - CSA mechanism, for relaxation 434
- **fluorine-19** 447 ff.
 - chemical shifts 448 ff.
 - of methylhalides 448 ff.
 - of selected fluorides 448 ff.
 - of selected organic fluorine compounds 451
 - referencing 448
 - spectra 450
 - spin-spin coupling 452
 - in organic fluorine compounds 453
 - through-space coupling 454
 - INADEQUATE, 1D ^6Li , ^6Li 468
 - intensity enhancements 485
- **iron-57** 489 ff.
 - chemical shifts 491
- **lithium-6,7** 462 ff.
 - 1D ^6Li , ^6Li INADEQUATE 468
 - 1D HMQC 466
 - 2D HMQC 466
 - aggregates 465
 - chemical shifts 463, 464
 - ring current effect 464
 - referencing 463
 - solid state NMR 467, 586
 - spin-spin coupling 464 ff.
 - multiplets 464 ff.
- magnetic strength, of hetero nuclei 432
 - main group metals 462 ff.
- **manganese-55** 491 ff.
 - chemical shifts 491
 - spin-spin coupling 492
- **mercury-199** 494 ff.
 - chemical shifts 495
 - referencing 495
 - relaxation 494
 - satellite spectra 494
 - spin-spin coupling 495
- **molybdenum-95** 492
 - natural abundance 432
- **nitrogen-15** 439 ff.
 - adenosine, interaction with metal salts 444
 - chemical shifts 442
 - metal salt interaction 444
 - INEPT 440
 - spectrum of pteridine 441
 - inverse detection 440
 - NOE 440
 - protonation shifts 443
 - 7-methylpurine, spectrum 444
 - referencing 443
 - spin-spin-coupling 445
 - nuclear properties 436, 437, 475, 478
- **osmium-187** 496
- **oxygen-17** 445 ff.
 - acoustic ringing 446
 - chemical shifts 446
 - measurement 445
 - referencing 446
 - RIDE sequence 446
 - spin-spin-coupling 447
- **phosphorus-31** 458 ff.
 - chemical shifts 459
 - coordination number 458, 459, 461
 - dependence on P-P-P bond angle 462
 - effect of charge 460
 - of phosphines important for homogeneous catalysis 460
 - ranges for different bonding situations 460
 - diphosphanes, conformation 460
 - referencing 458
 - spin-spin coupling 461
- **platinum-195** 480 ff.
 - chemical shifts 480
 - relaxation 480
 - spin-spin coupling 481, 482
 - quadrupolar nuclei 432
 - coupling constant 433
 - electric field gradient 433
 - line width 433

heteronuclei (*contd.*)

- relaxation times 433
 - quadrupole moment 433
 - reference compounds 434
 - reference, universal 434
 - **rhodium-103** 485 ff.
 - chemical shifts 486
 - spin-spin coupling 487
 - Tolman angle 487
 - RIDE (ring down elimination) sequence 446
 - RIDE spectrum 447
 - sagging behavior 454, 458
 - semimetals 435 ff.
 - **silicon-29** 454 ff.
 - chemical shifts 454 ff.
 - methylsilanes 455
 - sagging behavior 454, 458
 - NOE 454
 - referencing 454
 - satellites, ^{29}Si , ^{13}C , in ^{29}Si spectrum 457
 - spin-spin coupling 457
 - ranges of Si, X coupling 458
 - satellite lines 457
 - **tin-119** 471 ff.
 - chemical shifts 472, 473
 - inverse detection 471
 - magnetically active isotopes 471
 - referencing 472
 - satellites in ^1H spectra 471
 - spin-spin coupling 473
 - transition metals 474 ff.
 - nuclear properties 475
 - referencing 478 ff.
 - chemical shift ranges 478 ff.
 - $\mathcal{E}$ -values 478 ff.
 - Tolman angle 487
 - **tungsten-183** 492 ff.
 - chemical shift 493
 - COSY spectrum, ^{183}W , ^{183}W 493
 - spin-spin coupling 493
 - universal reference $\mathcal{E}$ 434
 - **vanadium-51** 476 ff.
 - chemical shifts 477, 480
 - spin-spin coupling 480
 - **xenon-129** 621 ff.
- heterolock 75
- heterotactic 223
- high resolution NMR 153
- higher order spectra 56
- high-field magnet 24, 79, 638
- high-resolution solid state NMR** 568 ff.
- assignment methods 576
 - NQS (non quaternary carbon suppression) 576
 - J -resolved spectroscopy 577
 - spectrum of camphor 577
 - side band suppression by TOSS 573
 - by SELTICS 573, 575
 - alkalide 584, 585
 - anisotropy of chemical shift 571
 - adsorbed molecules 583
 - applications, spin $\frac{1}{2}$ nuclei 580 ff.
 - ^{13}C CP/MAS spectra of aromatics adsorbed on Al_2O_3 585
 - ^{13}C CP/MAS NMR spectrum of 2-methylal zinc chloride 581
 - ^{13}C CP/MAS spectra of aromatics adsorbed on Al_2O_3 585
 - ^{29}Si CP/MAS NMR spectrum silca-60 582
 - ^{29}Si , ^{29}Si 2D INADEQUATE spectrum of the zeolite ZMS-12 584
 - ^{29}Si MAS NMR spectrum of aluminosilicate analcite
 - silicates, chemical shift range 583
 - ^{119}Sn CP/MAS NMR spectrum tetramethylactelyd tin 581
 - asymmetry parameter 586, 587
 - caesium NMR
 - caesium-133 spectrum 586
 - chemical shift tensor 571
 - anisotropy, angular term 572
 - contact ion pairs (CIP) 586
 - cross polarization (CP) 571
 - dipolar coupling, intermolecular 569
 - double rotation (DOR) 579
 - dynamic processes, in the solid 588 ff.
 - ^{13}C MAS spectrum of fluorenyllithium(TMEDA) 588
 - EXSY spectroscopy 589
 - $T_{1\rho}$ measurements 589
 - electride 585
 - experimental techniques 570
 - Hamilton operator 570
 - Hartmann-Hahn experiment 571
 - high power ^1H decoupling 569
 - high-resolution CP/MAS spectrum 573
 - line narrowing 569, 570 ff.
 - for adsorbed molecules, ^{13}C , ^1H NMR 585
 - lithium NMR 584 ff.
 - lithium-7 585
 - magic angle spinning (MAS) 567, 569
 - magic angle 572
 - multiple quantum MAS 579

- powder spectra, molecules with axial symmetry 572
- – molecules without axial symmetry 572
- quadrupolar nuclei 572, 577 ff.
- energy level diagrams for $I = 1$ and $I = 3/2$ 578
- quadrupole coupling constant 578, 585 ff.
- rotational side bands 574
- rotor 572
- sample rotation 573, 574
- side band suppression by TOSS 573
- – by SELTICS 573
- – – pulse sequence 575
- – – spectrum of tyrosine hydrochloride 575
- solvent-separated ion pairs (SSIP) 586
- spectrum of solid triphenylmethyl lithium quinuclidine 587
- spin-flip narrowing 574
- spinning rate 572
- – effect for ^{31}P NMR of triphenylphosphine 574
- static ^2H solid state NMR spectra 579
- WAHUA-sequence 575, 576
- zeolite 584
- hindered rotation 518 ff.
- HOESY (heteronuclear NOE) 355
- pulse sequence 355
- spectrum 356
- HOHAHA (homonuclear Hartmann-Hahn) experiment 366
- homoallyl ^1H , ^1H coupling 141
- 3,4-homotropilidene, valence tautomerism 533 ff.
- EXSY spectrum 534
- Hückel MO calculation 107
- Hückel rule 104
- Huggins electronegativity 638
- human skull 646
- hump test 77
- hydrogen bonding 117
- fluoride 42
- hyerpolarization 617 ff.
- i*
- IGLO method 85
- imaging, by NMR 642
- impurities, paramagnetic 73
- INADEQUATE experiment, 1D, ^{13}C , ^{13}C 400
- INADEQUATE experiment 2D, ^1H , ^1H 331
- o-disubstituted benzenes 334
- p-disubstituted benzenes 334
- adenosine 336
- product operator formalism 332
- INADEQUATE experiment, 2D ^{13}C , ^{13}C 402
- indirect or scalar coupling, *see also* spin-spin coupling 43
- INDO method 85
- INEPT, pulse sequence 360 ff.
- enhancement factor 360
- indirect 363
- inverse 363
- multiplicities 361
- of NH group 362
- product operator formalism 363
- refocused 361
- reverse 363
- signal-to-noise ratio 364
- INEPT⁺ 361
- inorganic phosphate 642
- integration 35 ff., 77
- intensity distribution, for AX_n systems with $I(X) = 1, 3/2$ 664
- intensity, relative 47
- interferogram 253
- intermolecular exchange, *see also* dynamic NMR 549
- internal rotation, *see also* dynamic NMR 518 ff.
- internal standard 70
- intersystem crossing 607
- intramolecular NOE 348
- intrinsic isotope effect 592
- inverse probe head 81
- inverse INEPT 363
- signal-to-noise ratio 364
- inversion of configuration, *see also* dynamic NMR 523 ff.
- inversion recovery experiment 247, 248, 640
- for ^{13}C , *m*-xylene 381
- for rate constant determination 513
- in-vivo* NMR 640
- irreducible representation 181
- isochronous nuclei 52
- isodynamic 533
- isomerism 211 ff.
- isotactic polymers 223
- isotope effects, in NMR 591
- $\Delta^{13}\text{C}(^{2/1}\text{H})$, cyclohexane 593
- $\Delta^{15}\text{N}(^{18/16}\text{O})$, sodium nitrate 593
- empirical correlation 592, 594
- intrinsic isotope effect 592
- isotopic perturbation of equilibrium 597 ff.
- ^{18}O isotope shifts for carbonyl groups 595
- potential curve for vibrational states 593
- primary isotope effect 591
- secondary isotope effect 591

isotope effects, in NMR (*contd.*)
 – SNIF (site specific natural isotope fractionation) 595
 isotopic perturbation of equilibrium 595
 isotropic coupling 367
 isotropic mixing 366
 iterative analysis 206 ff.

j

Jeener experiment 296
 – modification of 304
 J coupling, *see* spin-spin coupling
 J, δ spectra, *see* J -resolved spectra
 Joule-Thomson effect 81
 J -resolved spectra 289 ff.
 – applications 291
 – *n*-butylbromide 293
 – data treatment 293
 – EXCORCYCLE 295
 – fluoropyridine 295
 – ghost signals 295
 – heteronuclear 373
 – – pulse sequence 373
 – homonuclear 291
 – measuring time 295
 – of mixture 293
 – phantom signals 295
 – practical aspects 294 ff.
 jump-and-return 640

k

Kaptein rules 611
 Karplus curve, $^3J(^1\text{H}, ^1\text{H})$ 129, 631, 638
 – $^{13}\text{C}, ^{13}\text{C}$ 423
 – $^{13}\text{C}, ^1\text{H}$ 427
 – Haasnoot-Altona 638
 – in peptides 631
 – in oligo- and polysaccharides 638
 – $^{31}\text{P}, ^1\text{H}$ 636
 keto-enol equilibrium 549
 ketones, protonated 67
 – unsaturated 99

l

laboratory frame 234
 lactate formation 642
 Lamb formula 31, 409
 Landé- or g -factor 606
 lanthanide complex 601 ff.
 – induced shift (LIS) 601 ff.
 Laplace operator 152
 LAOCOON program 207
 Larmor frequency 16, 21
 Larmor precession 234

LCAO (linear combination of atomic orbitals) 481

leakage factor 624
 LEFE (linear electric field effect) 115
 life sciences 641
 life-time 503
 line broadening 22, 73, 494
 – by fast relaxing neighboring nuclei 554
 – narrowing 570
 – shape 246, 285
 – splitting 43
 – width 76, 246
 linear combination 160
 linear electric field effect 115
 linearly polarized field 237
 liquid crystals 82
 – NMR in 558
 liquids, NMR in 22
 LIS (lanthanide induced shift) values 601
 lithium-6, 7, *see also* heteronuclei 462 ff.
 living objects 641
 local diamagnetic contribution to the shielding constant 86
 local field 30
 lock level 76
 – signal 75
 long-range correlation, 2D, $^{13}\text{C}, ^1\text{H}$ 394
 – $^1\text{H}, ^1\text{H}$ (COSY-LR) 305 ff.
 long-range coupling, $^1\text{H}, ^1\text{H}$ 137 ff.
 – M (W) mechanism 138
 – saturated systems 138
 – unsaturated systems 139
 longitudinal or spin-lattice relaxation 237
 – relaxation time 237, 239
 Lorentz curve 253
 Lorentz-Gauss transformation 270
 Lorentzian line shape 246
 lowering operator 154, 312
 low-pass filter 330
 L-valin 219

m

macroscopic sample, pulse excitation 236 ff.
 magic angle 23
 – spinning 433, 569, 625
 magnet, superconducting, *see also* cryomagnet 24, 79, 638
 magnetic anisotropy, *see* diamagnetic anisotropy
 magnetic dipole 14
 – equivalence 52 ff.
 – field, local 16
 – – increase of field strength 79
 – moment 13, 14, 16
 – non-equivalence 220

- properties of nuclei 25, 432, 436, 475
- quantum number 14
- resonance imaging (MRI) 642 ff.
- magnetization 70
- macroscopic 21
- magnetogyric ratio 13
- magnitude or absolute value representation 285
- main group metals 464
- manganese-55, *see also* heteronuclei 492
- McConnell equation 95
- medicine, NMR in 626 ff.
- mercury-199 495
- memory locations 254
- metabolic changes 642
- metal carbonyl π -complexes, $\delta(^1\text{H})$ 120
- metal hydrides, proton resonances in 120
- 1,6-methano[10]annulene, spectrum 107, 109
- 1,6-methano[10]annulene, dianion, $\delta(^1\text{H})$ 107
- 1,7-methano[12]annulene, spectrum 109
- methoxygalactose 96
- microcell 676
- mixing operator 366
- time 366
- mixture of *n*-butyl halides 299
- MLEV pulse method 277
- molecular, biology 625 ff.
- motion 241
- symmetry 211 ff.
- MO model for $^2J(^1\text{H}, ^1\text{H})$ 126
- molybdenum-95, *see also* heteronuclei 494
- MRI (magnetic resonance imaging) 642 ff.
- multidimensional experiments 80, 371, 373
- 3D NMR principle 373
- NOESY-TOCSY sequence 375
- multiple quantum, coherence 312
- MAS solid state experiment 469, 579
- multinuclear probe head 81
- multiplicity, of NMR signals 41, 46, 201
- selection by SEFT, APT 383
- by DEPT (distortionless by polarization transfer) 387
- n**
- NAD^+ , ^1H nmr spectra at different B_0 fields 626
- 2D ^{13}C , ^{13}C INADEQUATE experiment 402
- naphthalene, ring current 103
- naphthobiphenylene, COSY-LR 307
- natural abundance 26, 50
- natural products 625
- neighboring group 32
- π -bonds 124
- nematic phases, *see also* liquid crystals 558
- nicotinamide adeninedinucleotide (NAD^+) 402, 626
- NICS values (nucleus independent chemical shift) 111, 416
- ortho*-nitroanilin, COSY spectrum 297
- COSY-LR 306
- nitrobenzene, electric field effect in 115
- nitrogen-15, *see also* heteronuclei 441 ff.
- nitropropane, ^1H NMR spectrum of 89
- NMR, frequency increase for ^1H 79
- other nuclei, tables 26, 436, 475
- signal 20
- spectrometer, *see below*
- thermometer for measurements at variable temperature 82
- NOE difference spectroscopy 346 ff.
- assignment of ^1H configuration 347
- NOE (nuclear Overhauser effect) 343 ff.
- NOESY, Bloch vector diagram 351
- spectrum, of [6]paracyclophane-8,9-dimethylbicarboxylate 354
- of benzo[*b*]biphenyldication, 352
- distance ratio 355
- product operator formalism 353
- pulse sequence 351
- NOESY-TOCSY, 3D pulse sequence 375
- noise decoupling 275
- non-alternating hydrocarbons 104
- nonbonding electron pairs 124
- nonplanar annulene 109
- normalized function 155
- NQR (nuclear quadrupole resonance) 26
- N-type signal 325
- nuclear Overhauser effect 80, 341 ff.
- $^{13}\text{C}\{^1\text{H}\}$ 345
- complications 348
- dependence on $\omega_0\tau_c$ 350
- distance measurements 345
- enhancement factors 81, 344, 361, 485
- table 361, 485
- heteronuclear 345
- heteronuclear, 2D (HOESY) 355 ff.
- homonuclear, 1D 345
- homonuclear 2D (NOESY) 350 ff.
- Bloch vector diagram and pulse sequence 351 ff.
- signal enhancement 344
- spin diffusion 349
- nuclear properties, tables 26, 436, 475

- nuclear quadrupole moment 25
 - quadrupole resonance (NQR) 26
 - spin operators 154
 - spin vector 42
 - Zeeman splitting 15
- nuclei, even-even 25
 - even-odd 25
 - odd-odd 25
- nucleic acids, *see also* bio-NMR, nucleic acids 634 ff.
- Nyquist theorem 257
- o**
 - off-diagonal matrix elements 171
 - off-resonance decoupling 277
 - oligosaccharides, *see also* bio-NMR, oligo- and polysaccharides 636 ff.
 - one-dimensional homonuclear NOE 345 ff.
 - intramolecular 348
 - NOE difference spectroscopy 346
 - one-dimensional INADEQUATE sequence 398 ff.
 - one-dimensional selective TOCSY 368
 - operators, evolution of 313 ff.
 - optical isomers 217
 - pumping 621 ff.
 - purity, by NMR 217
 - optically active center, intramolecular 219
 - order matrix or order tensor 565
 - order parameter 561
 - organic molecules, proton resonances in 122 ff.
 - organic molecules, spin–spin coupling constants in 144
 - organometallic compounds, $\delta(^1\text{H})$ 119
 - dynamic processes 542
 - orthogonal function 155
 - ortho-hydrogen 617
 - ortho-coupling 201
 - osmium-187, *see also* heteronuclei 498
 - O-DNP (Overhauser dynamic nuclear polarization) 623, 624
 - Overhauser enhancement 81, 344
 - Overhauser effect, original 341
 - oxygen, line broadening effect 73
 - oxygen -17, *see also* heteronuclei 447
- p**
 - [6]paracyclophane-8,9-dimethylbicarboxylate, NOESY spectrum 354
 - para-hydrogen induced polarization (PHIP) 618
 - para-hydrogen 617 ff.
 - paramagnetic, shift 32
 - materials 597 ff.
 - – contact shifts 597
 - – pseudo-contact shifts 599
 - – shift reagents 599
 - moment 31
 - ring current effect 105
 - paratropic molecules 106
 - partial orientation 558
 - partially oriented molecules, *see also* alignment 557 ff.
 - in chiral liquid crystals 568
 - in nematic phases of liquid crystals 558 ff.
 - – benzene, spectrum of partially oriented 562
 - – dipolar coupling 561
 - – order parameter 561
 - – oriented A_2 system 560
 - – Saupe matrix 563
 - – spectral analysis 563
 - – spectrum of partially oriented methylene chloride 559
 - – structural data for cyclopropane 564
 - – structure determination 563
 - – – for cyclobutane 564
 - – – for ethylene 564
 - residual dipolar couplings, *see also* individual entry 565
 - particle spin 181
 - PASADENA, AX system 618
 - Pascal's triangle 172
 - passive, coupling 628
 - spin 43, 183
 - PBLG (poly- γ -benzyl-glutamate) 567
 - pentachloropropane, 1,1,2,3,3-, spectrum 57
 - peptide partial structure, NMR experiments 630
 - peptides, *see also* bio-NMR, peptides and proteins 627 ff.
 - perfused organs 641, 643
 - perturbation of equilibrium 595
 - PFGSTE (pulsed field gradient stimulated echo experiment) 614, 615
 - PFT NMR, *see* Fourier transform spectroscopy
 - PGSE (pulsed field gradient spin echo) 613, 614
 - pH, and proton chemical shift 93
 - in the cell 642, 643
 - phase, behavior in 2D NMR 671
 - correction 261
 - – by spin echo experiment 287
 - cycles 266, 322 ff.
 - error 259, 260
 - modulation 282
 - shift 301

- phasesensitive 2D spectra 266
- phenylacetylene hydrogenation, PHIP spectrum 619
- PHIP (*para*-hydrogeninduced polarization) 618
- measurements 620
- polarization transfer 620, 621
- product operator formalism 620
- spectra 619
- phosphorus-31 NMR, *see also* heteronuclei 641 ff.
- π -complexes, $\delta(^1\text{H})$ 120
- π -electron density, ^1H NMR 89
- ^{13}C NMR 410 ff.
- pK_a determination 93
- platinum-195, *see also* heteronuclei 482 ff.
- polarization transfer 357 ff.
- polyacetylenes, long-range ^1H , ^1H coupling 142
- polyhedral boranes 440
- polypeptides, ^{13}C , ^{15}N enriched, scalar coupling 633
- polymer spectroscopy 223
- poly- γ -benzyl-glutamate (PBLG) 567
- polysaccharides, *see also* bio-NMR, oligo- and polysaccharides 636 ff.
- preparation time 281
- presaturation 269, 640
- primary isotope effect 591
- probability, of transition 19
- probe 25
- probe head 25, 77
- cryo 81
- inverse 81
- multinuclear 81
- product operator formalism 309 ff.
- coherence 309
- COSY experiment within 317
- double quantum coherence 313
- multiple-quantum coherences 312
- observables 316
- operator basis for AX system 311
- operators, evolution of 313
- single quantum coherence (SQ) 307, 310
- zero-quantum coherences 310
- propionamide, ^1H spectrum 39
- propylnaphthalene, hyperfine coupling 599, 600
- proteins, *see also* bio-NMR, peptides and proteins 627 ff.
- proton chemical shift** 650 ff.
- aldehydes 99, 651
- and electronegativity 87
- and structure 85
- annulenes 104 ff.
- anthracene 103
- aromatic ions 89, 90
- aromatic protons 651
- carbanions 92
- carbocations 92
- charge density at carbon 89
- charge density effects 91
- diamagnetic anisotropy 87, 95
- diamagnetic susceptibility 94
- dimethyl-15,16-dihydropyrene, *trans*-15,16-dianion, $\delta(^1\text{H})$ 107
- electric field effect 114
- electron density 87
- ethyl halides 87
- for selected organic compounds 38
- hydrogen bonding 117
- induced magnetic moments 94
- inductive effect 89
- McConnell equation 95
- methano[10]annulene 1,6-, dianion, $\delta(^1\text{H})$ 107
- methano[10]annulene, 1,6- 104
- methano[12]annulene, 1,7- 108
- methyl derivatives 88
- methyl protons 650
- methylene protons 650
- naphthalene 103
- neighboring atoms, influence of 86
- NICS values 111
- olefinic protons 651
- origin of 86 ff.
- π -electron density 89
- pH dependence 93
- ring current 101 ff.
- – [18]annulene 104
- – annulenes 104 ff.
- – cyclopropane 113
- – dimethyl-15,16-dihydropyrene, *trans*-15,16-dianion $\delta(^1\text{H})$ 107
- – intensity 108
- – methano[10]annulene 1,6-, dianion, $\delta(^1\text{H})$ 107
- – methano[10]annulene, 1,6- 104, 107
- – methano[12]annulene, 1,7- 108
- – non-alternating hydrocarbons 104
- – paramagnetic 106
- – *trans*-15,16-dimethyl-15,16-dihydropyrene 104
- – tricycloazines 109
- Shoolery rule 652
- solvent effects 120 ff.
- substituent constants 121
- substituent effect 652

proton chemical shift (*contd.*)

- for methanes 652
- for substituted benzenes 653
- van-der-Waals effect 86, 114, 116
- proton coupling constants and chemical structure, *see also spin-spin coupling* 122 ff.
- dipolar coupling 143
- geminal coupling 122, 123 ff.
- long-range coupling 122, 137 ff.
- through-space coupling 143
- vicinal coupling 122, 128 ff.
- proton screening 86
- shielding 32
- pseudo contact shifts 599
- P-type signal 325
- pulse angle 77, 239
- calibration 263
- excitation 234
- frequency 33
- length 22
- r.f. 21
- sequence 296
- width t_p 250, 258
- pulsed field gradient, spin echo (PGSE) 613
- stimulated echo (PFGSTE) 614, 614
- pulses, selective 261
- soft 261
- BIRD 329
- GAUSS 262
- composite 263
- hard 260
- pyramidal atomic inversion 525
- pyridine, electric field effect 115
- pyrogallol (1,2,3-trihydroxybenzol) 178
- Pythagoras 176, 236

q

- quad-images 265
- quadratic field effect 116
- quadrature detection 265
- quadrupolar nuclei 568, 577, 584
- relaxation 243, 433
- coupling 433, 568, 586
- moment 25
- splitting for nuclei with $I = 1$, angular dependence 568
- for deuterium 568
- quadrupole relaxation 243, 433
- quantization 14
- quantum condition 13, 105, 153
- mechanical formalism 151
- number 14
- theory 13

quantum mechanical model for isolated

- proton 13
- angular momentum 13
- eigenfunctions 14
- magnetic dipole 14
- magnetic quantum number 13
- magnetogyric ratio 13
- nuclear Zeeman splitting 15
- quantized magnetic moment 13
- quantum condition 13
- spin quantum number 14
- wave functions 14

r

- Rabi experiment 18
- racemate 217
- radiation, electromagnetic 16
- radiofrequency (r.f.) 19
- radicals 601
- radiofrequency impulses 237
- radiation 19
- radiology 646
- raising operator 154
- rare nuclei 49
- rate constants, determination of 515
- ratio $J(\text{H,H})/J(\text{H,D})$ 229
- $J/\nu_0\delta$, significance of 56
- receiver 21
- coil 16
- gain 77
- signal 252 ff.
- receptivity 26
- rectangular pulse, excitation profile 262
- REDOR (rotational echo double resonance) 580
- reduced coupling constant 43
- reference compound 33, 67, 70, 434, 439
- aluminum-27 471
- fluorine-19 450
- lithium-6,7, 465
- nitrogen-15 443
- oxygen-17 448
- phosphorus-31 460
- proton
- silicon-29 456
- tin-119 474
- transition metals 478 ff.
- relative intensity 47
- relaxation 21, 23, 239 ff., 243
- by chemical exchange 246
- by chemical shift anisotropy 43
- by paramagnetic species 242
- by scalar coupling 243
- in the rotating frame ($T_{1\rho}$) 247, 580, 587

- quadrupole - 243, 433
- rate constant R_1 240
- reagent $[\text{Cr}(\text{acac})_3]$ 243
- spin rotation 243, 482
- spin-lattice or longitudinal - 239
- spin-spin or transverse - 23, 234, 243
- time measurements 247 ff
- – longitudinal (T_1) 237, 239
- – – inversion recovery experiment 247
- – transverse (T_2)
- – – spin echo experiment 248 ff.
- relayed spectra 367
- repetition time t_r 250
- residual dipolar couplings, *see also* dipolar coupling 565 ff.
- resolution 76
- of ADC 256
- resonance condition 16
- equation 17
- frequency 16, 26, 436, 475
- reverse INEPT 363
- signal-to-noise ratio 364
- RF (r.f.) pulse 21, 237
- RF source 19, 258
- rhodium-103 487, *see also* heteronuclei, 485 ff.
- ring current 101 ff.
- [18]annulene 104
- annulenes 104 ff.
- cyclopropane 113
- dimethyl-15,16-dihydropyrene, *trans*-15,16-dianion $\delta(^1\text{H})$ 107
- intensity 108
- methano[10]annulene 1,6-, dianion, $\delta(^1\text{H})$ 107
- methano[10]annulene, 1,6- 104, 107
- methano[12]annulene, 1,7 108
- non-alternating hydrocarbons 104
- paramagnetic 106
- *trans*-15,16-dimethyl-15,16-dihydropyrene 104
- tricycloazines 109
- ring inversion, *see also* dynamic NMR 526 ff.
- ROESY effect, dependence on $\omega_0\tau_c$ 371
- experiment 369
- spectrum, trisaccharide 372
- roof effect 56
- rotating field vector 235
- frame 235
- – experiments 364 ff.
- – – HEHAHA 366
- – – HOHAHA 366
- – – ROESY 369
- – – TOCSY 366, 368
- rotor 23
- ruthenium complex, PHIP spectrum 619
- s**
- sagging behavior 456, 474
- sample cell 69
- concentration 80
- preparation 67
- spinning 74
- tube 19, 69
- – coaxial 69
- sampling rate 256
- satellite lines 49
- satellites, ^{13}C 226 ff.
- saturation 23
- factor 624
- Saupe matrix 565, 568
- scalar coupling, *see spin-spin coupling* 43
- scalar product, of nuclear magnetic moments 42
- scanner, whole body 645
- Schrödinger equation 14, 151
- screening constant 30
- secondary isotope effect 591
- secular determinant 160
- equations 161
- selection rules 156
- selective, inversion recovery 269
- population inversion (SPI) 357
- – transfer (SPT) 358
- pulses 261
- semimetals 437 ff.
- self-diffusion 613
- sensitive line 644
- point 644
- sensitivity 19, 26, 76, 78 ff., 364, 599
- enhancement 617 ff.
- test, with ethylbenzene 78
- SELTICS (side band suppression) 573
- pulse sequence 575
- spectrum of tyrosin hydrochloride 575
- shielding constant 30
- shift correlation $^{15}\text{N}, ^1\text{H}$ 629
- shifted sine bell 285
- shift reagents, chiral 219
- table 603
- Shigemi tube 67
- shim coils 75
- shimming 75
- SHR (States-Haberland-Ruben) 301
- SI sytem (système international) 672
- side bands 74
- sigma, shielding or screening constant 30
- value, calculation 31

- signal enhancement 344
 - height 36, 245
 - phase 75, 259 ff., 671
 - shape 75
 - superposition 72
 - width, *see line width*
- signal-to-noise ratio 78, 364
 - table 364
- silanes 455
- silica spectra, solid state NMR 582
- sine bell window function 285
- single coil spectrometer 19
 - quantum coherence (SQ) 307, 310
 - scan NMR 337
- silicon-29, *see also heteronuclei* 456 ff.
- soft pulses 261
- solid state NMR, *see also high-resolution solid state NMR* 22, 568 ff.
- Solomon diagram for **IS** 342
 - for **II** 343
- solvent effects 120 ff.
 - and proton exchange 73
 - aromatic 73
 - for chemical shifts 72
 - for coupling constants 72
- solvent, suppression 74, 639 ff
 - WATERGATE
 - optically active 217
 - for variable temperature measurements 82
 - highly purified 80
 - table 68, 659
 - solvent-separated ion pairs (SSIP) 586
- spatial structure 630
- spectra, high field effect 57, 510, 626
- spectral accumulation 79
 - density function 240
 - types 211, 150
- spectral analysis** 149 ff.
 - combination line 171
 - computer analysis 206
 - complex spin systems 170
 - degenerate 189, 195
 - eigenfunction 152
 - eigenstate 151
 - eigenvalue 151, 209
 - eigenvector 171, 209
 - electron on a circle 152
 - first order approximation 167
 - forbidden transition 180
 - Hamilton operator 151, 153
 - Hamilton matrix 173
 - high resolution NMR 153
 - iterative analysis 208
 - Laplace operator 152
 - LAOCOON program 207
 - lowering operator 154
 - normalized function 155
 - notion for spin systems 150
 - nuclear spin operators 154
 - orthogonal function 155
 - particle spin 181
 - product functions 156
 - quantum condition 153
 - quantum mechanical formalism 151 ff.
 - raising operator 154
 - relative intensities 151, 162
 - Schrödinger equation 151
 - secular determinant 160
 - selection rules 156
 - spin system, *see also individual entries* 42, 149
 - – A_2 158
 - – $AA'BB'$ 205, 666
 - – $AA'XX'$ 192 ff.
 - – AB 164 ff.
 - – – with $J = 0$ 157
 - – AB_2 (A_2B) 177 ff.
 - – ABX 182 ff.
 - – AX 167 ff.
 - – – calculation 155 ff.
 - – – degenerate 226
 - – general rules for 170
 - – notation for 150
 - stationary state 151, 156
 - subspectral analysis 182
 - subspectrum 182
 - transition moment 162
 - unitary transformation 174
 - variational method 158
 - virtual coupling 190
 - wave function 151, 154
 - – antisymmetric 163
 - – symmetric 163
 - X-approximation 183
- spectral density function 240
- spectrometer 16
 - schematic diagram 20, 256
 - tuning 74 ff
- spherical aromaticity 416
- SPI (selective population inversion)
 - experiment 357 ff.
 - AX system 358
 - chloroform 359
 - multiplicity and intensity of A_nX groups 360
- spin chromatography 335
- spin decoupling, *see spin-spin decoupling*
- spin diffusion 349

- spin echo experiment 248 ff., 285 ff.
 - for ^{13}C assignment (SEFT) 383 ff.
 - for coupled spin systems 286 ff.
 - PFGSTE 614, 615
 - PGSE 613
 - pulse sequence 249
 - with AX system 288
 - with pulsed gradients 613
- spin echo spectroscopy, two-dimensional, *see*
also J-resolved spectra
- spin-flip method 402
- spin functions 43
 - lock 364 ff.
 - quantum number 14
 - states 14, 43
 - of A_2X_3 system 46
- spin-lattice relaxation 239 ff.
 - benzene 242, 248
 - in ^{13}C NMR 428
 - mechanism 240
- spinlock 364
 - experiments in solution 366 ff.
- spin mapping 644
- spinning side bands 74
- spin quantum number 14
 - rotation relaxation 243, 480
 - spin temperature 19
 - orientation in B_0 15
- spin-spin coupling** 41 ff
 - $^{13}\text{C}, ^{13}\text{C}$ 422
 - – Karplus curve 423
 - $^{13}\text{C}, ^1\text{H}$ 424
 - – Karplus curve 427
 - carbon-13 420 ff.
 - chemical exchange, influence of 503
 - energy of 42
 - $^1\text{H}, ^1\text{H}$ 122 ff.
 - – allenes 142
 - – allylic 141
 - $^1\text{H}, ^2\text{H}$ (H,D) 229
 - – benzene 658
 - – benzenes, monosubstituted 655
 - – bond length dependence 130
 - – 1,3-butadiene 658
 - – cumulenes 142
 - – dihedral angle dependence (Karplus curve) 129
 - – dipolar 143
 - – direct 143
 - – electronegativity 124, 133
 - – geminal 123
 - – HCC valence angles 132
 - – homoallylic 142
 - – hybridization 123
 - – Karplus curve 229
 - – long-range 137 ff.
 - – M (W) mechanism 138
 - – magnitude 47
 - – MO model 126
 - – naphthalene 658
 - – neighboring π -bonds 124
 - – olefins 654
 - – π -mechanism 137 ff.
 - – polyacetylenes 142
 - – propenes 140
 - – saturated systems 138
 - – solvent effects 72
 - – tables 654 ff.
 - – through space 143
 - – transition metal complexes 136
 - – W (M) mechanism 138
 - – unsaturated systems 122, 133, 139
 - – vicinal 128 ff.
 - – with other nuclei 49 ff.
 - $J/\delta\nu$ ratio 56
 - magnitude 47
 - nuclei with $I = \frac{1}{2}$ 49
 - with $I > \frac{1}{2}$ 51, 664
 - of heteronuclei, *see heteronuclei*
 - of transition metals, *see heteronuclei*
 - rare nuclei 49
 - strong coupling 56
 - structural dependence 62
 - through-space 143, 454
 - virtual 190
 - weak coupling 56
- spin-spin decoupling 58 ff., 272
 - broadband 59
 - – by CW modulation 275
 - – by pulse methods 275
 - – GARB 277
 - – MLEV 277
 - – WALTZ-16 277
 - – noise 275
 - – table 278
 - off-resonance 278
- spin, spin relaxation, *see also* relaxation 43
- splitting, first order 49
 - simple rules for 52
- SPT (selective population transfer) 349, 358
- SQ *see single quantum coherence*
- stacked plot 284
- standard, *see also reference, referencing* 33, 69
 - external 70
 - internal 70
- static aggregates of organolithium compounds 465
- stationary state 14, 151, 156

- stereochemistry, ^{13}C chemical shifts and 419
 - ^1H , ^1H coupling and 128
- Stern-Gerlach experiment 17
- steroid chemistry 72
- strong coupling 56
- structural dependence, of proton chemical shift 37, 85 ff.
- styrene oxide 66
- subspectral analysis 182
- subspectrum 182
- substituent constants 121, 652, 653, 662
- sulfur dioxide 67
- superconducting magnet, *see cryomagnet*
- supramolecular chemistry 616
- surface coils 641
- suszeptibility, diamagnetic 71, 94
 - correction 71
 - exaltation 110
 - volume 70 ff.
- sweep direction 75
- sweep 21
- symmetrization 301
- syndiotactic polymers 223

- t**
- T_1 measurement 247
- t_1 noise 302
- temperature measurement 81 ff.
 - with liquid crystals 82
- tensor, chemical shift 14, 571
- testosterone, ^{13}C spectrum 380
- tetramethylsilane 33, 67
- thermal mixing (TM) 626
- thermotropic compounds 558
- three-dimensional experiment 372
- through space coupling 143, 454
- time, domain 252
 - increment 61
 - scales 281
 - sharing 259
 - signal 21
- tin-119, *see also heteronuclei* 473 ff.
- tissue investigation 641
- titration curve 93
- TOCSY spectroscopy 366
 - spectrum 2D, β -D-glucose 368
 - – 1D, β -D-glucose + α -D-glucose 370
 - one dimensional 368
 - pulse sequence, 2D 367
- Tolman angle 487
- total spin 45
- total correlation spectroscopy, *see TOCSY* 366 ff.
- TOSS (total suppression of side bands) 573
- TPPI (time proportional phase increment) 301
- trans*-ethyl crotonate, spectrum 58
- transition 16
 - probability 19
 - metal complexes, ^1H , ^1H coupling 136
 - metals, *see also heteronuclei* 476 ff.
- transmission coefficient 507
- transmitter 259 ff.
 - coil 16
- transition state, transoid 533
- transverse magnetization 238
 - effect of spin-spin coupling 287
 - time-dependence 285
 - by chemical exchange 246
 - in solids 569
 - optimized spectroscopy, *see TROSY*
 - mechanism 244
- triads, in polymers 223
 - heterotactic 223
 - isotactic 223
 - syndiotactic 223
- “trial and error” method 207
- trialkylxonium salt 526
- trimethylaluminium 550
- triphenylphosphine 574
- 1,2,3- trichlorobenzene, spectrum 57
- trifluoroacetic acid 67
- [D₄]3-trimethylsilyl)propionic acid 70
- triplet state 166
- tris(dipivaloylmethanato)-Eu(III) 601
- tropylium ion 89
- TROSY (transverse magnetization optimized spectroscopy) 629
- tungsten-183, *see also heteronuclei* 494 ff.
- tuning, of spectrometer 74 ff.
- two spin system 43
- two-dimensional NMR** 60, 281 ff.
 - absolute value representation 285
 - amplitude modulation 282
 - anti-echo signal 325
 - axial peaks 302
 - BIRD pulse 330
 - chemical shift correlation:
 - heteronuclear, *see also individual entries*
 - – HEHAHA 366
 - – HETCOR 389
 - – HMBC 395, 397
 - – HMQC 389, 474, 566
 - – HSQC 391, 566
 - homonuclear, *see also individual entries*
 - – COLOC experiment 394

- COSY-90 experiment 296 ff., 317
 - COSY-45 304
 - COSY-DQF 307, 320, 327
 - COSY-LR 305
 - E.COSY 630
 - coherence transfer echo 325
 - constant time experiment 395
 - contour diagram, plot 7, 284
 - cross peak 7, 60, 301
 - data improvement 269
 - detection time t_2 282
 - diagonal peak 7, 60, 301
 - echo signal 288, 325
 - evolution of operators 313
 - evolution time t_1 61, 281
 - exchange spectroscopy (EXSY) 516
 - ω_1 -decoupled COSY 329
 - filter functions 285
 - gradient enhanced spectroscopy 303, 326
 - graphical presentation 284
 - HOESY experiment 355
 - INADEQUATE experiment 331
 - Jeener experiment 296
 - J -resolved NMR, heteronuclear 372, 403
 - homonuclear 289 ff.
 - in solid state MAS 577
 - long-range correlation, heteronuclear 395
 - homonuclear 305
 - low-pass filter 330
 - magnitude representation 285
 - mixing time 281
 - multiple quantum coherences 312
 - multiple quantum magic angle spinning (MQMAS) 469
 - NOESY experiment 350 ff.
 - N-type signal 325
 - P-type signal 325
 - phase 259
 - correction 286
 - cycles 266
 - error, frequency-dependent 259
 - modulation 282
 - rule 322
 - phase-sensitive detection 300
 - preparation period 317
 - time 381
 - principles of 2D NMR 281 ff.
 - product operator formalism 309
 - propagator 314
 - quad-images 265
 - quadrature detection 264
 - ROESY experiment 369
 - signal phase, *see phase*
 - single quantum coherences 307
 - stacked plot 284
 - t_1 noise 302
 - TOCSY experiment, 2D 366
 - 1D 368
 - TPPI method 301, 325
 - window or weighting functions 272
 - z-filter 331
 - zero-quantum coherences 310
- u**
- unitary transformation 174
 - upfield 32
- v**
- valence tautomerism, *see also dynamic NMR* 532 ff.
 - L-valin 219
 - van-der-Waals effect 86, 114
 - variable angle sample spinning (VASS) 567
 - variable temperature 81 ff.
 - variational method 158
 - vicinal ^1H , ^1H coupling 128 ff.
 - and bond length 130
 - and bond order 132
 - and dihedral angle 129
 - and HCC valence angles 132
 - substituent effects 133
 - transition metal complexes 136
 - vinylcyclopropane 113
 - virtual coupling 190
 - volume susceptibility 70
 - measurement of 71
- w**
- Wagner–Meerwein rearrangements 548
 - WAHUHA sequence 573
 - W(M)-arrangement 138
 - WALTZ-16 277
 - WATERGATE 640
 - wave function 14, 154
 - antisymmetric 163
 - symmetric 163
 - weak coupling 56
 - weighting functions 272
 - whole-body scanner 645
 - wide-bore cryomagnets 641
 - Wiedemann's law 71
 - wiggles 75
 - window or weighting functions 272
 - word length 254

x

- X-approximation 183
- Xenon-129 NMR 621 ff.
 - chemical shift scale 621
 - in zeolite 622
 - on mesoporous silica 622
 - – EXSY spectrum 622
- m*-xylene, ^{13}C T_1 measurement 381

z

- Zeeman effect 15
- Zeeman splitting 15
- zeolite 584, 622
- zero filling 270
- zero quantum coherence 312
- z-filter 329
- zig-zag-arrangement 138