

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*

Contents

- 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

Contents

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

Contents

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