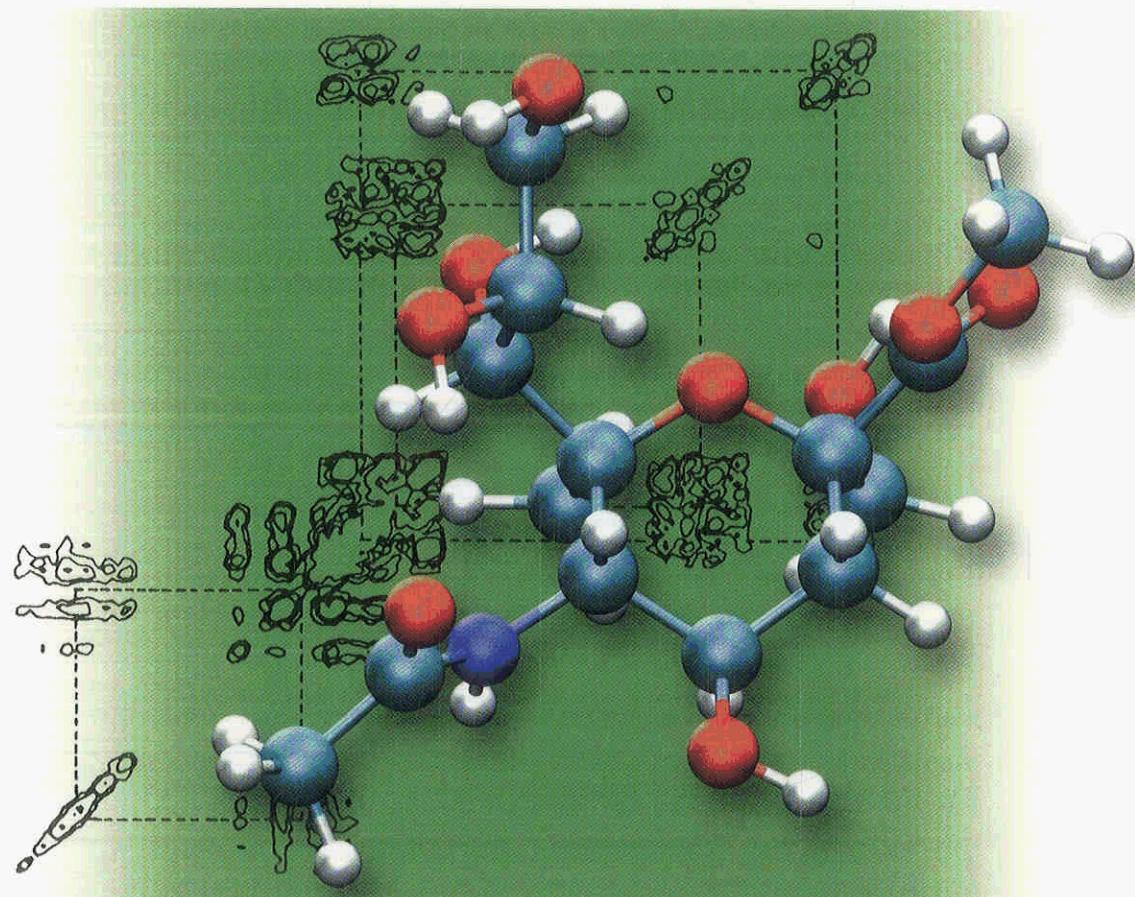


Horst Friebolin

WILEY-VCH

# Basic One- and Two-Dimensional NMR Spectroscopy

Fifth, Completely Revised and Updated Edition



# Contents

<b>1</b>	<b>The Physical Basis of NMR Spectroscopy</b>	1
<b>1.1</b>	<b>Introduction</b>	1
<b>1.2</b>	<b>Nuclear Angular Momentum and Magnetic Moment</b>	2
<b>1.3</b>	<b>Nuclei in a Static Magnetic Field</b>	4
1.3.1	Directional Quantization	4
1.3.2	Energy of the Nuclei in the Magnetic Field	4
1.3.3	Populations of the Energy Levels	6
1.3.4	Macroscopic Magnetization	6
<b>1.4</b>	<b>Basic Principles of the NMR Experiment</b>	7
1.4.1	The Resonance Condition	7
1.4.2	Basic Principle of the NMR Measurement	8
<b>1.5</b>	<b>The Pulsed NMR Method</b>	9
1.5.1	The Pulse	9
1.5.2	The Pulse Angle	10
1.5.3	Relaxation	13
1.5.4	The Time and Frequency Domains; the Fourier Transformation	14
1.5.5	Spectrum Accumulation	16
1.5.6	The Pulsed NMR Spectrometer	18
<b>1.6</b>	<b>Spectral Parameters: a Brief Survey</b>	22
1.6.1	The Chemical Shift	22
1.6.1.1	Nuclear Shielding	22
1.6.1.2	Reference Compounds and the $\delta$ -Scale	24
1.6.2	Spin-Spin Coupling	26
1.6.2.1	The Indirect Spin-Spin Coupling	26
1.6.2.2	Coupling to One Neighboring Nucleus (AX Spin System)	27
1.6.2.3	Coupling to Two Equivalent Neighboring Nuclei (AX <sub>2</sub> Spin System)	29
1.6.2.4	Coupling to Three or More Equivalent Neighboring Nuclei (AX <sub>n</sub> Spin System)	30
1.6.2.5	Multiplicity Rules	30
1.6.2.6	Couplings between Three Non-equivalent Nuclei (AMX Spin System)	31
1.6.2.7	Couplings between Equivalent Nuclei (A <sub>n</sub> Spin Systems)	32
1.6.2.8	The Order of a Spectrum	33

1.6.2.9	Couplings between Protons and other Nuclei; <sup>13</sup> C Satellite Spectra . . . . .	33
1.6.3	The Intensities of the Resonance Signals. . . . .	34
1.6.3.1	<sup>1</sup> H Signal Intensities . . . . .	34
1.6.3.2	<sup>13</sup> C Signal Intensities . . . . .	35
1.6.4	Summary . . . . .	37
<b>1.7</b>	<b>“Other” Nuclides</b> . . . . .	38
1.7.1	Nuclides with Spin $I = 1/2$ . . . . .	39
1.7.2	Nuclides with Spin $I > 1/2$ . . . . .	40
	Exercises . . . . .	41
<b>1.8</b>	<b>Bibliography for Chapter 1</b> . . . . .	41
<b>2</b>	<b>The Chemical Shift</b> . . . . .	43
<b>2.1</b>	<b>Introduction</b> . . . . .	43
2.1.1	Influence of the Charge Density on the Shielding	44
2.1.2	Effects of Neighboring Groups . . . . .	47
2.1.2.1	Magnetic Anisotropy of Neighboring Groups . .	47
2.1.2.2	Ring Current Effects . . . . .	49
2.1.2.3	Electric Field Effects . . . . .	51
2.1.2.4	Intermolecular Interactions – Hydrogen Bonding and Solvent Effects . . . . .	51
2.1.2.5	Isotope Effects . . . . .	51
2.1.3	Summary . . . . .	52
<b>2.2</b>	<b><sup>1</sup>H Chemical Shifts of Organic Compounds</b> . .	53
2.2.1	Alkanes and Cycloalkanes . . . . .	54
2.2.2	Alkenes . . . . .	56
2.2.3	Arenes . . . . .	56
2.2.4	Alkynes . . . . .	57
2.2.5	Aldehydes . . . . .	58
2.2.6	OH, SH, NH . . . . .	59
<b>2.3</b>	<b><sup>13</sup>C Chemical Shifts of Organic Compounds</b> . .	60
2.3.1	Alkanes and Cycloalkanes . . . . .	61
2.3.2	Alkenes . . . . .	63
2.3.3	Arenes . . . . .	64
2.3.4	Alkynes . . . . .	66
2.3.5	Allenes . . . . .	66
2.3.6	Carbonyl and Carboxy Compounds . . . . .	66
2.3.6.1	Aldehydes and Ketones . . . . .	67
2.3.6.2	Carboxylic Acids and Derivatives . . . . .	68
<b>2.4</b>	<b>Relationships between the Spectrum and the Molecular Structure</b> . . . . .	70
2.4.1	Equivalence, Symmetry and Chirality . . . . .	70
2.4.2	Homotopic, Enantiotopic and Diastereotopic Groups . . . . .	74
2.4.3	Summary . . . . .	77
<b>2.5</b>	<b>Chemical Shifts of “Other” Nuclides</b> . . . . .	78
	Exercises . . . . .	83
<b>2.6</b>	<b>Bibliography for Chapter 2</b> . . . . .	83

<b>3</b>	<b>Indirect Spin-Spin Coupling . . . . .</b>	85
3.1	<b>Introduction . . . . .</b>	85
3.2	<b>H,H Coupling Constants and Chemical Structure . . . . .</b>	87
3.2.1	Geminal Couplings $^2J(\text{H},\text{H})$ . . . . .	87
3.2.1.1	Dependence on Bond Angle . . . . .	87
3.2.1.2	Substituent Effects . . . . .	88
3.2.1.3	Effects of Neighboring $\pi$ -Electrons . . . . .	88
3.2.2	Vicinal Couplings $^3J(\text{H},\text{H})$ . . . . .	89
3.2.2.1	Dependence on the Dihedral Angle . . . . .	90
3.2.2.2	Substituent Effects . . . . .	94
3.2.3	H,H Couplings in Aromatic Compounds . . . . .	95
3.2.4	Long-range Couplings . . . . .	96
3.3	<b>C,H Coupling Constants and Chemical Structure . . . . .</b>	97
3.3.1	C,H Couplings through One Bond $^1J(\text{C},\text{H})$ . . . . .	97
3.3.1.1	Dependence on the s-Fraction . . . . .	97
3.3.1.2	Substituent Effects . . . . .	98
3.3.2	C,H Couplings through Two or More Bonds . . . . .	99
3.3.2.1	Geminal Couplings (i. e. $^2J(\text{C},\text{H})$ in $\text{H}-\text{C}-^{13}\text{C}$ ) . . . . .	99
3.3.2.2	Vicinal Couplings (i. e. $^3J(\text{C},\text{H})$ in $\text{H}-\text{C}-\text{C}-^{13}\text{C}$ ) . . . . .	99
3.3.2.3	Long-range Couplings $^{3+n}J(\text{C},\text{H})$ . . . . .	100
3.3.3	C,H Couplings in Benzene Derivatives . . . . .	100
3.4	<b>C,C Coupling Constants and Chemical Structure . . . . .</b>	101
3.5	<b>Correlations between C,H and H,H Coupling Constants . . . . .</b>	101
3.6	<b>Coupling Mechanisms . . . . .</b>	103
3.6.1	The Electron-Nuclear Interaction . . . . .	103
3.6.2	H,D Couplings . . . . .	105
3.6.3	Relationship between the Coupling and the Lifetime of a Spin State . . . . .	106
3.6.4	Couplings through Space . . . . .	106
3.7	<b>Couplings of “Other” Nuclides (Heteronuclear Couplings) . . . . .</b>	107
	Exercises . . . . .	109
3.8	<b>Bibliography for Chapter 3 . . . . .</b>	109
<b>4</b>	<b>Spectrum Analysis and Calculations . . . . .</b>	111
4.1	<b>Introduction . . . . .</b>	111
4.2	<b>Nomenclature . . . . .</b>	113
4.2.1	Systematic Notation for Spin Systems . . . . .	113
4.2.2	Chemical and Magnetic Equivalence . . . . .	114
4.3	<b>Two-Spin Systems . . . . .</b>	116
4.3.1	The AX Spin System . . . . .	116
4.3.2	The AB Spin System . . . . .	118

<b>4.4</b>	<b>Three-Spin Systems</b>	120
4.4.1	The AX <sub>2</sub> , AK <sub>2</sub> , AB <sub>2</sub> and A <sub>3</sub> Spin Systems	120
4.4.2	The AMX and ABX Spin Systems	121
<b>4.5</b>	<b>Four-Spin Systems</b>	123
4.5.1	A <sub>2</sub> X <sub>2</sub> and A <sub>2</sub> B <sub>2</sub> Spin Systems	123
4.5.2	The AA'XX' and AA'BB' Spin Systems	124
<b>4.6</b>	<b>Spectrum Simulation and Iteration</b>	125
<b>4.7</b>	<b>Analysis of <sup>13</sup>C NMR Spectra</b>	126
	Exercises	127
<b>4.8</b>	<b>Bibliography for Chapter 4</b>	127
<b>5</b>	<b>Double Resonance Experiments</b>	129
<b>5.1</b>	<b>Introduction</b>	129
<b>5.2</b>	<b>Spin Decoupling in <sup>1</sup>H NMR Spectroscopy</b>	130
5.2.1	Simplification of Spectra by Selective Spin Decoupling	130
5.2.2	Suppression of a Solvent Signal	132
<b>5.3</b>	<b>Spin Decoupling in <sup>13</sup>C NMR Spectroscopy</b>	133
5.3.1	<sup>1</sup> H Broad-band Decoupling	133
5.3.2	The Gated Decoupling Experiment	135
5.3.3	<sup>1</sup> H Off-Resonance Decoupling	136
5.3.4	Selective Decoupling in <sup>13</sup> C NMR Spectroscopy	137
	Exercises	138
<b>5.4</b>	<b>Bibliography for Chapter 5</b>	138
<b>6</b>	<b>Assignment of <sup>1</sup>H and <sup>13</sup>C Signals</b>	139
<b>6.1</b>	<b>Introduction</b>	139
<b>6.2</b>	<b><sup>1</sup>H NMR Spectroscopy</b>	140
6.2.1	Defining the Problem	140
6.2.2	Empirical Correlations for Predicting Chemical Shifts	141
6.2.2.1	Alkanes (Shoolery's Rule)	141
6.2.2.2	Alkenes	142
6.2.2.3	Benzene Derivatives	143
6.2.3	Decoupling Experiments	145
6.2.4	Altering the Chemical Structure of the Sample	145
6.2.5	Effects of Solvent and Temperature	146
<b>6.2.6</b>	<b>Shift Reagents</b>	147
6.2.6.1	Lanthanide Shift Reagents (LSRs)	147
6.2.6.2	Chiral Lanthanide Shift Reagents	150
<b>6.3</b>	<b><sup>13</sup>C NMR Spectroscopy</b>	152
6.3.1	Defining the Problem	152
6.3.2	Empirical Correlations for Predicting Approximate Chemical Shifts	154
6.3.2.1	Alkanes	154
6.3.2.2	Alkenes	157
6.3.2.3	Benzene Derivatives	158
6.3.3	Decoupling Experiments	159

6.3.4	<b><i>T<sub>1</sub></i> Measurements . . . . .</b>	160
6.3.5	<b>Chemical Changes to the Sample . . . . .</b>	160
6.3.6	<b>Solvent and Temperature Effects and Shift Reagents . . . . .</b>	161
<b>6.4</b>	<b>Computer-aided Assignment of <sup>13</sup>C NMR Spectra . . . . .</b>	161
6.4.1	<b>Searching for Identical or Related Compounds . . . . .</b>	161
6.4.2	<b>Spectrum Prediction . . . . .</b>	162
	<b>Exercises . . . . .</b>	164
<b>6.5</b>	<b>Bibliography for Chapter 6 . . . . .</b>	165
<b>7</b>	<b>Relaxation . . . . .</b>	167
<b>7.1</b>	<b>Introduction . . . . .</b>	167
<b>7.2</b>	<b>Spin-Lattice Relaxation of <sup>13</sup>C Nuclei (<i>T<sub>1</sub></i>) . . . . .</b>	168
7.2.1	<b>Relaxation Mechanisms . . . . .</b>	168
7.2.2	<b>Experimental Determination of <i>T<sub>1</sub></i>; the Inversion Recovery Experiment . . . . .</b>	170
7.2.3	<b>Relationships between <i>T<sub>1</sub></i> and Chemical Structure . . . . .</b>	174
7.2.3.1	<b>Influence of Protons in CH, CH<sub>2</sub> and CH<sub>3</sub> Groups . . . . .</b>	174
7.2.3.2	<b>Influence of Molecular Size . . . . .</b>	175
7.2.3.3	<b>Segmental Mobilities . . . . .</b>	176
7.2.3.4	<b>Anisotropy of the Molecular Mobility . . . . .</b>	176
7.2.4	<b>Suppression of the Water Signal . . . . .</b>	177
<b>7.3</b>	<b>Spin-Spin Relaxation (<i>T<sub>2</sub></i>) . . . . .</b>	177
7.3.1	<b>Relaxation Mechanisms . . . . .</b>	177
7.3.2	<b>Experimental Determination of <i>T<sub>2</sub></i>; the Spin-Echo Experiment . . . . .</b>	179
7.3.3	<b>Line-widths of NMR Signals . . . . .</b>	183
	<b>Exercises . . . . .</b>	185
<b>7.4</b>	<b>Bibliography for Chapter 7 . . . . .</b>	185
<b>8</b>	<b>One-Dimensional NMR Experiments using Complex Pulse Sequences . . . . .</b>	187
<b>8.1</b>	<b>Introduction . . . . .</b>	187
<b>8.2</b>	<b>Basic Techniques Using Pulse Sequences and Pulsed Field Gradients . . . . .</b>	188
8.2.1	<b>The Effect of the Pulse on the Longitudinal Magnetization (<i>M<sub>z</sub></i>) . . . . .</b>	189
8.2.2	<b>The Effect of the Pulse on the Transverse Magnetization Components (<i>M<sub>x</sub></i>, <i>M<sub>y</sub></i>) . . . . .</b>	190
8.2.3	<b>Spin-Locking . . . . .</b>	193
8.2.4	<b>The Effect of Pulsed Field Gradients on the Transverse Magnetization . . . . .</b>	195
<b>8.3</b>	<b>The <i>J</i>-Modulated Spin-Echo Experiment . . . . .</b>	199
<b>8.4</b>	<b>The Pulsed Gradient Spin-Echo Experiment . . . . .</b>	208
<b>8.5</b>	<b>Signal Enhancement by Polarization Transfer . . . . .</b>	210

8.5.1	The SPI Experiment . . . . .	210
8.5.2	The INEPT Experiment . . . . .	213
8.5.3	The Reverse INEPT Experiment with Proton Detection . . . . .	221
8.6	<b>The DEPT Experiment . . . . .</b>	226
8.7	<b>The Selective TOCSY Experiment . . . . .</b>	230
8.8	<b>The One-Dimensional INADEQUATE Experiment . . . . .</b>	233
	Exercises . . . . .	237
8.9	<b>Bibliography for Chapter 8 . . . . .</b>	237
<b>9</b>	<b>Two-Dimensional NMR Spectroscopy . . . . .</b>	239
9.1	<b>Introduction . . . . .</b>	239
9.2	<b>The Two-Dimensional NMR Experiment . . . . .</b>	240
9.2.1	Preparation, Evolution and Mixing, Data Acquisition . . . . .	240
9.2.2	Graphical Representation . . . . .	244
9.3	<b>Two-Dimensional J-Resolved NMR Spectroscopy . . . . .</b>	245
9.3.1	Heteronuclear Two-Dimensional <i>J</i> -Resolved NMR Spectroscopy . . . . .	245
9.3.2	Homonuclear Two-Dimensional <i>J</i> -Resolved NMR Spectroscopy . . . . .	249
9.4	<b>Two-Dimensional Correlated NMR Spectroscopy . . . . .</b>	254
9.4.1	Two-Dimensional Heteronuclear (C,H)-Correlated NMR Spectroscopy (HETCOR or C,H-COSY) . . . . .	255
9.4.2	Two-Dimensional Homonuclear (H,H)-Correlated NMR Spectroscopy (H,H-COSY; Long-Range COSY) . . . . .	263
9.4.3	Reverse Two-Dimensional Heteronuclear (H,C)-Correlated NMR Spectroscopy (HSQC; HMQC) . . . . .	271
9.4.4	The Gradient-Selected (gs-)HMBC Experiment . . . . .	276
9.4.5	The TOCSY Experiment . . . . .	281
9.4.6	Two-Dimensional Exchange NMR Spectroscopy: The Experiments NOESY ROESY and EXSY . . . . .	284
9.5	<b>The Two-Dimensional INADEQUATE Experiment . . . . .</b>	289
9.6	<b>Summary of Chapters 8 and 9 . . . . .</b>	294
	Exercises . . . . .	295
9.7	<b>Bibliography for Chapter 9 . . . . .</b>	295
<b>10</b>	<b>The Nuclear Overhauser Effect . . . . .</b>	297
10.1	<b>Introduction . . . . .</b>	297
10.2	<b>Theoretical Background . . . . .</b>	298

<b>10.2.1</b>	The Two-Spin System . . . . .	298
<b>10.2.2</b>	Enhancement Factors . . . . .	301
<b>10.2.3</b>	Multi-Spin Systems . . . . .	302
<b>10.2.4</b>	From the One-Dimensional to the Two-Dimensional Experiments, NOESY and ROESY . . . . .	303
<b>10.3</b>	<b>Experimental Aspects</b> . . . . .	305
<b>10.4</b>	<b>Applications</b> . . . . .	306
	Exercises . . . . .	311
<b>10.5</b>	<b>Bibliography for Chapter 10</b> . . . . .	311
<b>11</b>	<b>Dynamic NMR Spectroscopy (DNMR)</b> . . . . .	313
<b>11.1</b>	<b>Introduction</b> . . . . .	313
<b>11.2</b>	<b>Quantitative Calculations</b> . . . . .	317
<b>11.2.1</b>	Complete Line-shape Analysis . . . . .	317
<b>11.2.2</b>	The Coalescence Temperature $T_C$ and the Corresponding Rate Constant $k_C$ . . . . .	319
<b>11.2.3</b>	Activation Parameters . . . . .	320
<b>11.2.3.1</b>	The Arrhenius Activation Energy $E_A$ . . . . .	320
<b>11.2.3.2</b>	The Free Enthalpy of Activation $\Delta G$ . . . . .	321
<b>11.2.3.3</b>	Estimating the Limits of Error . . . . .	322
<b>11.2.4</b>	Rate Constants in Reactions with Intermediate Stages . . . . .	323
<b>11.2.5</b>	Intermolecular Exchange Processes . . . . .	324
<b>11.3</b>	<b>Applications</b> . . . . .	325
<b>11.3.1</b>	Rotation about CC Single Bonds . . . . .	325
<b>11.3.1.1</b>	$C(sp^3)-C(sp^3)$ Bonds . . . . .	326
<b>11.3.1.2</b>	$C(sp^2)-C(sp^3)$ Bonds . . . . .	326
<b>11.3.1.3</b>	$C(sp^2)-C(sp^2)$ Bonds . . . . .	327
<b>11.3.2</b>	Rotation about a Partial Double Bond . . . . .	327
<b>11.3.3</b>	Inversion at Nitrogen and Phosphorus Atoms . .	329
<b>11.3.4</b>	Ring Inversion . . . . .	330
<b>11.3.5</b>	Valence Tautomerism . . . . .	333
<b>11.3.6</b>	Keto-Enol Tautomerism . . . . .	334
<b>11.3.7</b>	Intermolecular Proton Exchange . . . . .	335
<b>11.3.8</b>	Reactions and Equilibration Processes . . . . .	337
	Exercises . . . . .	340
<b>11.4</b>	<b>Bibliography for Chapter 11</b> . . . . .	340
<b>12</b>	<b>Synthetic Polymers</b> . . . . .	343
<b>12.1</b>	<b>Introduction</b> . . . . .	343
<b>12.2</b>	<b>The Tacticity of Polymers</b> . . . . .	343
<b>12.3</b>	Polymerization of Dienes . . . . .	347
<b>12.4</b>	Copolymers . . . . .	348
<b>12.5</b>	Solid-State NMR Spectroscopy of Polymers . . .	349
	Exercises . . . . .	352
<b>12.6</b>	<b>Bibliography for Chapter 12</b> . . . . .	352

<b>13</b>	<b>NMR Spectroscopy in Biochemistry and Medicine</b> .....	355
<b>13.1</b>	<b>Introduction</b> .....	355
<b>13.2</b>	<b>Elucidating Reaction Pathways in Biochemistry</b> 355	
13.2.1	Syntheses using Singly $^{13}\text{C}$ -Labeled Precursors .....	356
13.2.1.1	Low Levels of $^{13}\text{C}$ Enrichment .....	356
13.2.1.2	High Levels of $^{13}\text{C}$ Enrichment .....	357
13.2.2	Syntheses using Doubly $^{13}\text{C}$ -Labeled Precursors .....	358
<b>13.3</b>	<b>Biopolymers</b> .....	360
13.3.1	Peptides and Proteins .....	361
13.3.1.1	Sequence Analysis .....	362
13.3.1.2	The Three-Dimensional Structure of Proteins ..	363
13.3.2	Polynucleotides .....	365
13.3.3	Oligosaccharides and Polysaccharides .....	367
<b>13.4</b>	<b>Saturation Transfer Difference NMR Spectroscopy (STD)</b> .....	371
	Exercises .....	372
<b>13.5</b>	<b>Bibliography for Chapter 13</b> .....	372
<b>14</b>	<b>In vivo NMR Spectroscopy in Biochemistry and Medicine</b> .....	375
<b>14.1</b>	<b>Introduction</b> .....	375
<b>14.2</b>	<b>High-Resolution <i>in vivo</i> NMR Spectroscopy</b> ..	376
14.2.1	The Problem and its Solution .....	376
14.2.2	$^{31}\text{P}$ NMR Experiments .....	377
14.2.3	$^1\text{H}$ and $^{13}\text{C}$ NMR Experiments .....	380
<b>14.3</b>	<b>Magnetic Resonance Tomography</b> .....	381
14.3.1	Basic Principles and Experimental Considerations .....	381
14.3.2	Applications .....	387
<b>14.4</b>	<b>Magnetic Resonance Spectroscopy, <math>^1\text{H}</math> MRS</b> ..	391
	Exercises .....	393
<b>14.5</b>	<b>Bibliography for Chapter 14</b> .....	393
	<b>Solutions</b> .....	395
	<b>Subject Index</b> .....	407
	<b>Index of Compounds</b> .....	411