

Contents

1	The Physical Basis of NMR Spectroscopy	1
1.1	Introduction	1
1.2	Nuclear Angular Momentum and Magnetic Moment	2
1.3	Nuclei in a Static Magnetic Field	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
1.4	Basic Principles of the NMR Experiment	7
1.4.1	The Resonance Condition	7
1.4.2	Basic Principle of the NMR Measurement	8
1.5	The Pulsed NMR Method	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
1.6	Spectral Parameters: a Brief Survey	22
1.6.1	The Chemical Shift	22
1.6.1.1	Nuclear Shielding	22
1.6.1.2	Reference Compounds and the δ -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 ₂ Spin System)	29
1.6.2.4	Coupling to Three or More Equivalent Neighboring Nuclei (AX _n 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 _n Spin Systems)	32
1.6.2.8	The Order of a Spectrum	33

1.6.2.9	Couplings between Protons and other Nuclei; ¹³ C Satellite Spectra	33
1.6.3	The Intensities of the Resonance Signals.	34
1.6.3.1	¹ H Signal Intensities	34
1.6.3.2	¹³ C Signal Intensities	35
1.6.4	Summary	37
1.7	“Other” Nuclides	38
1.7.1	Nuclides with Spin $I = 1/2$	39
1.7.2	Nuclides with Spin $I > 1/2$	40
	Exercises	41
1.8	Bibliography for Chapter 1	41
2	The Chemical Shift	43
2.1	Introduction	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
2.2	¹H Chemical Shifts of Organic Compounds . . .	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
2.3	¹³C Chemical Shifts of Organic Compounds . . .	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
2.4	Relationships between the Spectrum and the Molecular Structure	70
2.4.1	Equivalence, Symmetry and Chirality	70
2.4.2	Homotopic, Enantiotopic and Diastereotopic Groups	74
2.4.3	Summary	77
2.5	Chemical Shifts of “Other” Nuclides	78
	Exercises	83
2.6	Bibliography for Chapter 2	83

3	Indirect Spin-Spin Coupling	85
3.1	Introduction	85
3.2	H,H Coupling Constants and Chemical Structure	87
3.2.1	Geminal Couplings ${}^2J(\text{H,H})$	87
3.2.1.1	Dependence on Bond Angle	87
3.2.1.2	Substituent Effects	88
3.2.1.3	Effects of Neighboring π -Electrons	88
3.2.2	Vicinal Couplings ${}^3J(\text{H,H})$	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	C,H Coupling Constants and Chemical Structure	97
3.3.1	C,H Couplings through One Bond ${}^1J(\text{C,H})$	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. ${}^2J(\text{C,H})$ in $\text{H}-\text{C}-{}^{13}\text{C}$)	99
3.3.2.2	Vicinal Couplings (i. e. ${}^3J(\text{C,H})$ in $\text{H}-\text{C}-\text{C}-{}^{13}\text{C}$)	99
3.3.2.3	Long-range Couplings ${}^{3+n}J(\text{C,H})$	100
3.3.3	C,H Couplings in Benzene Derivatives	100
3.4	C,C Coupling Constants and Chemical Structure	101
3.5	Correlations between C,H and H,H Coupling Constants	101
3.6	Coupling Mechanisms	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	Couplings of "Other" Nuclides (Heteronuclear Couplings)	107
	Exercises	109
3.8	Bibliography for Chapter 3	109
4	Spectrum Analysis and Calculations	111
4.1	Introduction	111
4.2	Nomenclature	113
4.2.1	Systematic Notation for Spin Systems	113
4.2.2	Chemical and Magnetic Equivalence	114
4.3	Two-Spin Systems	116
4.3.1	The AX Spin System	116
4.3.2	The AB Spin System	118

4.4	Three-Spin Systems	120
4.4.1	The AX ₂ , AK ₂ , AB ₂ and A ₃ Spin Systems	120
4.4.2	The AMX and ABX Spin Systems	121
4.5	Four-Spin Systems	123
4.5.1	A ₂ X ₂ and A ₂ B ₂ Spin Systems	123
4.5.2	The AA'XX' and AA'BB' Spin Systems	124
4.6	Spectrum Simulation and Iteration	125
4.7	Analysis of ¹³C NMR Spectra	126
	Exercises	127
4.8	Bibliography for Chapter 4	127
5	Double Resonance Experiments	129
5.1	Introduction	129
5.2	Spin Decoupling in ¹H NMR Spectroscopy	130
5.2.1	Simplification of Spectra by Selective Spin Decoupling	130
5.2.2	Suppression of a Solvent Signal	132
5.3	Spin Decoupling in ¹³C NMR Spectroscopy	133
5.3.1	¹ H Broad-band Decoupling	133
5.3.2	The Gated Decoupling Experiment	135
5.3.3	¹ H Off-Resonance Decoupling	136
5.3.4	Selective Decoupling in ¹³ C NMR Spectroscopy	137
	Exercises	138
5.4	Bibliography for Chapter 5	138
6	Assignment of ¹H and ¹³C Signals	139
6.1	Introduction	139
6.2	¹H NMR Spectroscopy	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
6.2.6	Shift Reagents	147
6.2.6.1	Lanthanide Shift Reagents (LSRs)	147
6.2.6.2	Chiral Lanthanide Shift Reagents	150
6.3	¹³C NMR Spectroscopy	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	T_1 Measurements	160
6.3.5	Chemical Changes to the Sample	160
6.3.6	Solvent and Temperature Effects and Shift Reagents	161
6.4	Computer-aided Assignment of ^{13}C NMR Spectra	161
6.4.1	Searching for Identical or Related Compounds	161
6.4.2	Spectrum Prediction	162
	Exercises	164
6.5	Bibliography for Chapter 6	165
7	Relaxation	167
7.1	Introduction	167
7.2	Spin-Lattice Relaxation of ^{13}C Nuclei (T_1)	168
7.2.1	Relaxation Mechanisms	168
7.2.2	Experimental Determination of T_1 ; the Inversion Recovery Experiment	170
7.2.3	Relationships between T_1 and Chemical Structure	174
7.2.3.1	Influence of Protons in CH, CH ₂ and CH ₃ Groups	174
7.2.3.2	Influence of Molecular Size	175
7.2.3.3	Segmental Mobilities	176
7.2.3.4	Anisotropy of the Molecular Mobility	176
7.2.4	Suppression of the Water Signal	177
7.3	Spin-Spin Relaxation (T_2)	177
7.3.1	Relaxation Mechanisms	177
7.3.2	Experimental Determination of T_2 ; the Spin-Echo Experiment	179
7.3.3	Line-widths of NMR Signals	183
	Exercises	185
7.4	Bibliography for Chapter 7	185
8	One-Dimensional NMR Experiments using Complex Pulse Sequences	187
8.1	Introduction	187
8.2	Basic Techniques Using Pulse Sequences and Pulsed Field Gradients	188
8.2.1	The Effect of the Pulse on the Longitudinal Magnetization (M_z)	189
8.2.2	The Effect of the Pulse on the Transverse Magnetization Components (M_x , M_y)	190
8.2.3	Spin-Locking	193
8.2.4	The Effect of Pulsed Field Gradients on the Transverse Magnetization	195
8.3	The J-Modulated Spin-Echo Experiment	199
8.4	The Pulsed Gradient Spin-Echo Experiment	208
8.5	Signal Enhancement by Polarization Transfer	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	The DEPT Experiment	226
8.7	The Selective TOCSY Experiment	230
8.8	The One-Dimensional INADEQUATE Experiment	233
	Exercises	237
8.9	Bibliography for Chapter 8	237
9	Two-Dimensional NMR Spectroscopy . . .	239
9.1	Introduction	239
9.2	The Two-Dimensional NMR Experiment	240
9.2.1	Preparation, Evolution and Mixing, Data Acquisition	240
9.2.2	Graphical Representation	244
9.3	Two-Dimensional <i>J</i>-Resolved NMR Spectroscopy	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	Two-Dimensional Correlated NMR Spectroscopy	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	The Two-Dimensional INADEQUATE Experiment	289
9.6	Summary of Chapters 8 and 9	294
	Exercises	295
9.7	Bibliography for Chapter 9	295
10	The Nuclear Overhauser Effect	297
10.1	Introduction	297
10.2	Theoretical Background	298

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

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