

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
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
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	93
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	97
3.3.2	C,H Couplings through Two or More Bonds	98
3.3.2.1	Geminal Couplings (i. e. $^2J(\text{C,H})$ in $\text{H}-\text{C}-^{13}\text{C}$)	98
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 $^{3+n}J(\text{C,H})$	99
3.3.3	C,H Couplings in Benzene Derivatives	99
3.4	C,C Coupling Constants and Chemical Structure	100
3.5	Correlations between C,H and H,H Coupling Constants	101
3.6	Coupling Mechanisms	102
3.6.1	The Electron-Nuclear Interaction	102
3.6.2	H,D Couplings	104
3.6.3	Relationship between the Coupling and the Lifetime of a Spin State	105
3.6.4	Couplings through Space	106
3.7	Couplings of "Other" Nuclides (Heteronuclear Couplings)	106
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
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
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	Effects of Solvent and Temperature	145
6.2.5	Altering the Chemical Structure of the Sample	146
6.3	¹³C NMR Spectroscopy	147
6.3.1	Defining the Problem	147
6.3.2	Empirical Correlations for Predicting Approximate Chemical Shifts	148
6.3.2.1	Alkanes	148
6.3.2.2	Alkenes	151
6.3.2.3	Benzene Derivatives	153
6.3.3	Decoupling Experiments	154
6.3.4	T ₁ Measurements	154
6.3.5	Solvent and Temperature Effects and Shift Reagents	154
6.3.6	Chemical Changes to the Sample	154

6.4	Computer-aided Assignment of ^{13}C NMR Spectra	156
6.4.1	Searching for Identical or Related Compounds	156
6.4.2	Spectrum Prediction	157
6.5	Bibliography for Chapter 6	159
7	Relaxation	161
7.1	Introduction	161
7.2	Spin-Lattice Relaxation of ^{13}C Nuclei (T_1)	162
7.2.1	Relaxation Mechanisms	162
7.2.2	Experimental Determination of T_1 ; the Inversion Recovery Experiment	164
7.2.3	Relationships between T_1 and Chemical Structure	168
7.2.3.1	Influence of Protons in CH , CH_2 and CH_3 Groups	168
7.2.3.2	Influence of Molecular Size	169
7.2.3.3	Segmental Mobilities	170
7.2.3.4	Anisotropy of the Molecular Mobility	170
7.2.4	Suppression of the Water Signal	171
7.3	Spin-Spin Relaxation (T_2)	171
7.3.1	Relaxation Mechanisms	171
7.3.2	Experimental Determination of T_2 ; the Spin-Echo Experiment	173
7.3.3	Line-widths of NMR Signals	177
7.4	Bibliography for Chapter 7	178
8	One-Dimensional NMR Experiments using Complex Pulse Sequences	181
8.1	Introduction	181
8.2	Basic Techniques Using Pulse Sequences and Pulsed Field Gradients	182
8.2.1	The Effect of the Pulse on the Longitudinal Magnetization (M_z)	183
8.2.2	The Effect of the Pulse on the Transverse Magnetization Components (M_x , M_y)	184
8.2.3	The Effect of Pulsed Field Gradients on the Transverse Magnetization	187
8.3	The J-Modulated Spin-Echo Experiment	192
8.4	The Pulsed Gradient Spin-Echo Experiment	200
8.5	Signal Enhancement by Polarization Transfer	202
8.5.1	The SPI Experiment	202
8.5.2	The INEPT Experiment	205
8.5.3	The Reverse INEPT Experiment with Proton Detection	213

8.6	The DEPT Experiment	218
8.7	The Selective TOCSY Experiment	223
8.8	The One-Dimensional INADEQUATE Experiment	225
8.9	Bibliography for Chapter 8.	229
9	Two-Dimensional NMR Spectroscopy	231
9.1	Introduction	231
9.2	The Two-Dimensional NMR Experiment	232
9.2.1	Preparation, Evolution and Mixing, Data Acquisition	232
9.2.2	Graphical Representation.	236
9.3	Two-Dimensional <i>J</i>-Resolved NMR Spectroscopy	237
9.3.1	Heteronuclear Two-Dimensional <i>J</i> -Resolved NMR Spectroscopy	237
9.3.2	Homonuclear Two-Dimensional <i>J</i> -Resolved NMR Spectroscopy	241
9.4	Two-Dimensional Correlated NMR Spectroscopy	246
9.4.1	Two-Dimensional Heteronuclear (C,H)-Correlated NMR Spectroscopy (HETCOR or C,H-COSY)	247
9.4.2	Two-Dimensional Homonuclear (H,H)-Correlated NMR Spectroscopy (H,H-COSY; Long-Range COSY)	255
9.4.3	Reverse Two-Dimensional Heteronuclear (H,C)-Correlated NMR Spectroscopy (HSQC; HMQC)	263
9.4.4	The Gradient-Selected (gs-)HMBC Experiment	268
9.4.5	The TOCSY Experiment	273
9.4.6	Two-Dimensional Exchange NMR Spectroscopy: The Experiments NOESY ROESY and EXSY	276
9.5	The Two-Dimensional INADEQUATE Experiment	281
9.6	Summary of Chapters 8 and 9.	286
9.7	Bibliography for Chapter 9.	287
10	The Nuclear Overhauser Effect	289
10.1	Introduction	289
10.2	Theoretical Background	290
10.2.1	The Two-Spin System.	290
10.2.2	Enhancement Factors.	293
10.2.3	Multi-Spin Systems.	294
10.2.4	From the One-Dimensional to the Two-Dimensional Experiments, NOESY and ROESY	295

10.3	Experimental Aspects	296
10.4	Applications	298
10.5	Bibliography for Chapter 10	303
11	Dynamic NMR Spectroscopy (DNMR) . .	305
11.1	Introduction	305
11.2	Quantitative Calculations	309
11.2.1	Complete Line-shape Analysis	309
11.2.2	The Coalescence Temperature T_C and the Corresponding Rate Constant k_C	311
11.2.3	Activation Parameters	312
11.2.3.1	The Arrhenius Activation Energy E_A	312
11.2.3.2	The Free Enthalpy of Activation ΔG	313
11.2.3.3	Estimating the Limits of Error	314
11.2.4	Rate Constants in Reactions with Intermediate Stages	315
11.2.5	Intermolecular Exchange Processes	316
11.3	Applications	317
11.3.1	Rotation about CC Single Bonds	317
11.3.1.1	C(sp ³)–C(sp ³) Bonds	318
11.3.1.2	C(sp ²)–C(sp ³) Bonds	318
11.3.1.3	C(sp ²)–C(sp ²) Bonds	319
11.3.2	Rotation about a Partial Double Bond	319
11.3.3	Inversion at Nitrogen and Phosphorus Atoms . .	321
11.3.4	Ring Inversion	322
11.3.5	Valence Tautomerism	325
11.3.6	Keto-Enol Tautomerism	326
11.3.7	Intermolecular Proton Exchange	327
11.3.8	Reactions and Equilibration Processes	329
11.4	Bibliography for Chapter 11	332
12	Shift Reagents	335
12.1	Lanthanide Shift Reagents (LSRs)	335
12.1.1	Fundamentals	335
12.1.2	Applications and Quantitative Interpretation . .	337
12.2	Chiral Lanthanide Shift Reagents	340
12.3	Chiral Solvents	342
12.4	Bibliography for Chapter 12	345
13	Macromolecules	347
13.1	Introduction	347
13.2	Synthetic Polymers	348
13.2.1	The Tacticity of Polymers	348
13.2.2	Polymerization of Dienes	351
13.2.3	Copolymers	352
13.2.4	Solid-State NMR Spectroscopy of Polymers . . .	353

13.3	Biopolymers	355
13.3.1	Peptides and Proteins	356
13.3.1.1	Sequence Analysis	357
13.3.1.2	The Three-Dimensional Structure of Proteins . .	358
13.3.2	Polynucleotides	360
13.3.3	Oligosaccharides and Polysaccharides	362
13.4	Bibliography for Chapter 13	366
14	NMR Spectroscopy in Biochemistry and Medicine	369
14.1	Introduction	369
14.2	Elucidating Reaction Pathways in Biochemistry	370
14.2.1	Syntheses using Singly ¹³ C-Labeled Precursors	370
14.2.1.1	Low Levels of ¹³ C Enrichment	370
14.2.1.2	High Levels of ¹³ C Enrichment	372
14.2.2	Syntheses using Doubly ¹³ C-Labeled Precursors	373
14.3	High-Resolution <i>in vivo</i> NMR Spectroscopy . .	375
14.3.1	The Problem and its Solution	375
14.3.2	³¹ P NMR Experiments	376
14.3.3	¹ H and ¹³ C NMR Experiments	379
14.4	Magnetic Resonance Tomography	380
14.4.1	Basic Principles and Experimental Considerations	380
14.4.2	Applications	386
14.4.2.1	Magnetic Resonance Tomography	386
14.4.2.2	Magnetic Resonance Spectroscopy, ¹ H MRS . .	390
14.5	Bibliography for Chapter 14	392
	Subject Index	395
	Index of Compounds	403

