

SECOND EDITION

Nuclear Magnetic Resonance Spectroscopy

An Introduction to Principles, Applications, and Experimental Methods

Joseph B. Lambert • Eugene P. Mazzola • Clark D. Ridge



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An Introduction to Principles,
Applications, and Experimental
Methods

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Contents

Preface to First Edition	<i>xiii</i>
Acknowledgments	<i>xiv</i>
Preface to Second Edition	<i>xv</i>
Acknowledgments	<i>xvi</i>
Solutions	<i>xvii</i>
Symbols	<i>xix</i>
Abbreviations	<i>xxi</i>

1	Introduction	1
1.1	Magnetic Properties of Nuclei	1
1.2	The Chemical Shift	6
1.3	Excitation and Relaxation	10
1.4	Pulsed Experiments	13
1.5	The Coupling Constant	16
1.6	Quantitation and Complex Splitting	23
1.7	Commonly Studied Nuclides	25
1.8	Dynamic Effects	28
1.9	Spectra of Solids	30
	Problems	33
	Tips on Solving NMR Problems	36
	References	37
	Further Reading	38
2	Introductory Experimental Methods	39
2.1	The Spectrometer	39
2.2	Sample Preparation	41
2.3	Optimizing the Signal	42
	2.3.1 Sample Tube Placement	42
	2.3.2 Probe Tuning	43
	2.3.3 Field/Frequency Locking	43
	2.3.4 Spectrometer Shimming	44
2.4	Determination of NMR Spectral-Acquisition Parameters	48
	2.4.1 Number of Data Points	50
	2.4.2 Spectral Width	50

	2.4.3	Filter Bandwidth	52
	2.4.4	Acquisition Time	52
	2.4.5	Transmitter Offset	52
	2.4.6	Flip Angle	52
	2.4.7	Receiver Gain	54
	2.4.8	Number of Scans	55
	2.4.9	Steady-State Scans	55
	2.4.10	Oversampling and Digital Filtration	56
	2.4.11	Decoupling for X Nuclei	56
	2.4.12	Typical NMR Experiments	57
2.5		Determination of NMR Spectral-Processing Parameters	58
	2.5.1	Exponential Weighting	59
	2.5.2	Zero Filling	59
	2.5.3	FID Truncation and Spectral Artifacts	60
	2.5.4	Resolution	62
2.6		Determination of NMR Spectra: Spectral Presentation	63
	2.6.1	Signal Phasing and Baseline Correction	63
	2.6.2	Zero Referencing	66
	2.6.3	Determination of Certain NMR Parameters	66
		2.6.3.1 Chemical Shifts and Coupling Constants	66
		2.6.3.2 ¹ H Integration	68
2.7		Calibrations	70
	2.7.1	Pulse Width (Flip Angle)	70
	2.7.2	Decoupler Field Strength	72
		Problems	73
		References	74
		Further Reading	74

3 The Chemical Shift 75

3.1		Factors That Influence Proton Shifts	75
	3.1.1	Local Fields	75
	3.1.2	Nonlocal Fields	77
3.2		Proton Chemical Shifts and Structure	85
	3.2.1	Saturated Aliphatics	85
		3.2.1.1 Alkanes	85
		3.2.1.2 Functionalized Alkanes	86
	3.2.2	Unsaturated Aliphatics	87
		3.2.2.1 Alkynes	87
		3.2.2.2 Alkenes	88
		3.2.2.3 Aldehydes	89
	3.2.3	Aromatics	89
	3.2.4	Protons on Oxygen and Nitrogen	90
	3.2.5	Programs for Empirical Calculations	91
3.3		Medium and Isotope Effects	92
	3.3.1	Medium Effects	92
	3.3.2	Isotope Effects	95
3.4		Factors That Influence Carbon Shifts	96

3.5	Carbon Chemical Shifts and Structure	98
3.5.1	Saturated Aliphatics	98
3.5.1.1	Acyclic Alkanes	98
3.5.1.2	Cyclic Alkanes	101
3.5.1.3	Functionalized Alkanes	101
3.5.2	Unsaturated Compounds	103
3.5.2.1	Alkenes	103
3.5.2.2	Alkynes and Nitriles	104
3.5.2.3	Aromatics	104
3.5.3	Carbonyl Groups	105
3.5.4	Programs for Empirical Calculations	105
3.6	Tables of Chemical Shifts	106
	Problems	110
	Further Tips on Solving NMR Problems	119
	References	122
	Further Reading	122
4	The Coupling Constant	125
4.1	First- and Second-order Spectra	125
4.2	Chemical and Magnetic Equivalence	126
4.3	Signs and Mechanisms of Coupling	132
4.4	Couplings over One Bond	134
4.5	Geminal Couplings	136
4.6	Vicinal Couplings	139
4.7	Long-range Couplings	143
4.7.1	σ - π Overlap	143
4.7.2	Zigzag Pathways	144
4.7.3	Through-Space Coupling	145
4.8	Spectral Analysis	146
4.9	Second-order Spectra	147
4.9.1	Deceptive Simplicity	147
4.9.2	Virtual Coupling	149
4.9.3	Shift Reagents	150
4.9.4	Isotope Satellites	150
4.10	Tables of Coupling Constants	151
	Problems	157
	References	169
	Further Reading	170
5	Further Topics in One-Dimensional NMR Spectroscopy	173
5.1	Spin-Lattice and Spin-Spin Relaxation	173
5.1.1	Causes of Relaxation	173
5.1.2	Measurement of Relaxation Time	175
5.1.3	Transverse Relaxation	176
5.1.4	Structural Ramifications	177
5.1.5	Anisotropic Motion	177
5.1.6	Segmental Motion	178
5.1.7	Partially Relaxed Spectra	178
5.1.8	Quadrupolar Relaxation	178

- 5.2 Reactions on the NMR Time Scale 180
 - 5.2.1 Hindered Rotation 181
 - 5.2.2 Ring Reversal 183
 - 5.2.3 Atomic Inversion 183
 - 5.2.4 Valence Tautomerizations and Bond Shifts 185
 - 5.2.5 Quantification 187
 - 5.2.6 Magnetization Transfer and Spin Locking 187
- 5.3 Multiple Resonance 188
 - 5.3.1 Spin Decoupling 188
 - 5.3.2 Difference Decoupling 190
 - 5.3.3 Classes of Multiple Resonance Experiments 190
 - 5.3.4 Off-resonance Decoupling 191
- 5.4 The Nuclear Overhauser Effect 194
 - 5.4.1 Origin 194
 - 5.4.2 Observation 195
 - 5.4.3 Difference NOE 198
 - 5.4.4 Applications 199
 - 5.4.5 Limitations 200
- 5.5 Spectral Editing 200
 - 5.5.1 The Spin–Echo Experiment 201
 - 5.5.2 The Attached Proton Test 201
 - 5.5.3 The DEPT Sequence 204
- 5.6 Sensitivity Enhancement 205
 - 5.6.1 The INEPT sequence 206
 - 5.6.2 Refocused INEPT 208
 - 5.6.3 Spectral Editing with Refocused INEPT 208
 - 5.6.4 DEPT Revisited 210
- 5.7 Carbon Connectivity 212
- 5.8 Phase Cycling, Composite Pulses, and Shaped Pulses 213
 - 5.8.1 Phase Cycling 213
 - 5.8.2 Composite Pulses 215
 - 5.8.3 Shaped Pulses 215
 - Problems 217
 - References 231
 - Further Reading 231
- 6 Two-Dimensional NMR Spectroscopy 237**
- 6.1 Proton–Proton Correlation Through *J* Coupling 237
 - 6.1.1 COSY45 247
 - 6.1.2 Long-Range COSY (LRCOSY or Delayed COSY) 248
 - 6.1.3 Phase-Sensitive COSY (ϕ -COSY) 249
 - 6.1.4 Multiple Quantum Filtration 250
 - 6.1.5 Total Correlation Spectroscopy (TOCSY) 252
 - 6.1.6 Relayed COSY 252
 - 6.1.7 *J*-Resolved Spectroscopy 252
 - 6.1.8 COSY for Other Nuclides 254

6.2	Proton–Heteronucleus Correlation	254
6.2.1	HETCOR	255
6.2.2	HMQC	257
6.2.3	BIRD-HMQC	257
6.2.4	HSQC	260
6.2.5	COLOC	260
6.2.6	HMBC	260
6.2.7	Heteronuclear Relay Coherence Transfer	263
6.3	Proton–Proton Correlation Through Space or Chemical Exchange	264
6.4	Carbon–Carbon Correlation	268
6.5	Higher Dimensions	270
6.6	Pulsed Field Gradients	273
6.7	Diffusion-Ordered Spectroscopy	277
6.8	Summary of 2D Methods	279
	Problems	280
	References	305
	Further Reading	306
7	Advanced Experimental Methods	309
7.1	Part A: One-Dimensional Techniques	309
7.1.1	T_1 Measurements	309
7.1.2	^{13}C Spectral Editing Experiments	311
7.1.2.1	The APT Experiment	311
7.1.2.2	The DEPT Experiment	312
7.1.3	NOE Experiments	313
7.1.3.1	The NOE Difference Experiment	314
7.1.3.2	The Double-Pulse, Field-Gradient, Spin-Echo NOE Experiment	315
7.2	Part B: Two-Dimensional Techniques	316
7.2.1	Two-Dimensional NMR Data-Acquisition Parameters	316
7.2.1.1	Number of Data Points	316
7.2.1.2	Number of Time Increments	317
7.2.1.3	Spectral Widths	317
7.2.1.4	Acquisition Time	317
7.2.1.5	Transmitter Offset	318
7.2.1.6	Flip Angle	318
7.2.1.7	Relaxation Delay	318
7.2.1.8	Receiver Gain	318
7.2.1.9	Number of Scans per Time Increment	319
7.2.1.10	Steady-State Scans	319
7.2.2	Two-Dimensional NMR Data-Processing Parameters	319
7.2.2.1	Weighting Functions	319
7.2.2.2	Zero Filling	321
7.2.2.3	Digital Resolution	321
7.2.2.4	Linear Prediction	322
7.2.3	Two-Dimensional NMR Data Display	324
7.2.3.1	Phasing and Zero Referencing	324

	7.2.3.2	Symmetrization	325
	7.2.3.3	Use of Cross Sections in Analysis	325
7.3		Part C: Two-Dimensional Techniques: The Experiments	325
	7.3.1	Homonuclear Chemical-Shift Correlation Experiments via Scalar Coupling	326
	7.3.1.1	The COSY Family: COSY-90°, COSY-45°, Long-Range COSY, and DQF-COSY	326
	7.3.1.2	The TOCSY Experiment	330
	7.3.2	Direct Heteronuclear Chemical-Shift Correlation via Scalar Coupling	331
	7.3.2.1	The HMQC Experiment	331
	7.3.2.2	The HSQC Experiment	332
	7.3.2.3	The HETCOR Experiment	334
	7.3.3	Indirect Heteronuclear Chemical-Shift Correlation via Scalar Coupling	335
	7.3.3.1	The HMBC Experiment	336
	7.3.3.2	The FLOCK Experiment	338
	7.3.3.3	The HSQC–TOCSY Experiment	340
	7.3.4	Homonuclear Chemical-Shift Correlation via Dipolar Coupling	342
	7.3.4.1	The NOESY Experiment	342
	7.3.4.2	The ROESY Experiment	343
	7.3.5	1D and Advanced 2D Experiments	345
	7.3.5.1	The 1D TOCSY Experiment	345
	7.3.5.2	The 1D NOESY and ROESY Experiments	347
	7.3.5.3	The Multiplicity-Edited HSQC Experiment	347
	7.3.5.4	The H2BC Experiment	348
	7.3.5.5	Nonuniform Sampling	352
	7.3.5.6	Pure Shift NMR	355
	7.3.5.7	Covariance NMR	358
	7.3.6	Pure Shift-Covariance NMR	362
		References	362
8		Structural Elucidation: Two Methods	365
8.1		Part A: Spectral Analysis	365
	8.1.1	¹ H NMR Data	365
	8.1.2	¹³ C NMR Data	366
	8.1.3	The DEPT Experiment	369
	8.1.4	The HSQC Experiment	370
	8.1.5	The COSY Experiment	370
	8.1.6	The HMBC Experiment	372
	8.1.7	General Molecular Assembly Strategy	372
	8.1.8	A Specific Molecular Assembly Procedure	374
	8.1.9	The NOESY Experiment	379
8.2		Part B: Computer-Assisted Structure Elucidation	382
	8.2.1	CASE Procedures	383
	8.2.2	T-2 Toxin	384

Appendix A	Derivation of the NMR Equation	389
Appendix B	The Bloch Equations	391
Reference		395
Appendix C	Quantum Mechanical Treatment of the Two-Spin System	397
Appendix D	Analysis of Second-Order, Three- and Four-Spin Systems by Inspection	409
Appendix E	Relaxation	415
Appendix F	Product-Operator Formalism and Coherence-Level Diagrams	421
Reference		433
Appendix G	Stereochemical Considerations	435
G.1	Homotopic Groups	436
G.2	Enantiotopic Groups	438
G.3	Diastereotopic Groups	440
References		441
Index		443

Preface to First Edition

Nuclear magnetic resonance (NMR) has become the chemist's most general structural tool. It is one of the few techniques that may be applied to all three states of matter. Some spectra may be obtained from less than a microgram of material. In the early 1960s, spectra were taken crudely on strip-chart recorders. The field has since seen one major advance after another, culminating in the Nobel prizes awarded to Richard R. Ernst in 1991 and to Kurt Wüthrich in 2002. The very richness of the field, however, has made it intimidating to many users. How can they take full advantage of the power of the method when so much of the methodology seems to be highly technical, beyond the grasp of the casual user? This text was written to answer this question. The chapters provide an essentially nonmathematical introduction to the entire field, with emphasis on structural analysis.

The early chapters introduce classical NMR spectroscopy. A thorough understanding of proton and carbon chemical shifts (Chapter 3) is required in order to initiate any analysis of spectra. The role of other nuclei is key to the examination of molecules containing various heteroatoms. An analysis of coupling constants (Chapter 4) provides information about stereochemistry and connectivity relationships between nuclei. The older concepts of chemical shifts and coupling constants are emphasized, because they provide the basis for the application of modern pulse sequences.

Chapters 5 and 6 describe the basics of modern NMR spectroscopy. The phenomena of relaxation, of chemical dynamics, and of multiple resonance are considered thoroughly. One-dimensional multipulse sequences are explored to determine the number of protons attached to carbon atoms, to enhance spectral sensitivity, and to determine connectivities among carbon atoms. Concepts that have been considered advanced, but are now moving towards the routine, are examined, including phase cycling, composite pulses, pulsed field gradients, and shaped pulses. Two-dimensional methods represent the current apex of the field. We discuss a large number of these experiments. It is our intention to describe not only what the pulse sequences do, but also how they work, so that the user has a better grasp of the techniques.

Two chapters are dedicated to experimental methodologies. Although many people are provided with spectra by expert technicians, increasing numbers of chemists must record spectra themselves. They must consider and optimize numerous experimental variables. These chapters address not only the basic parameters, such as spectral width and acquisition time, but also the parameters of more advanced techniques, such as spectral editing and two-dimensional spectra.

To summarize modern NMR spectroscopy, Chapter 8 carries out the total structural proof of a single complex natural product. This chapter illustrates the tactics and strategies of structure elucidation, from one-dimensional assignments to two-dimensional spectral correlations, culminating in stereochemical analysis based on Overhauser effects.

The theory behind NMR not only is beautiful in itself, but also offers considerable insight into the methodology. Consequently, a series of appendices presents a full treatment of this theoretical underpinning, necessary to the physical or analytical chemist, but possibly still edifying to the synthetic organic or inorganic chemist.

This text thus offers

- classical analysis of chemical shifts and coupling constants for both protons and other nuclei,
- modern multipulse and multidimensional methods, both explained and illustrated,
- experimental procedures and practical advice relative to the execution of NMR experiments,
- a chapter-long worked-out problem that illustrates the application of nearly all current methods to determine the structure and stereochemistry of a complex natural product,
- appendices containing the theoretical basis of NMR, including the most modern approach that uses product operators and coherence-level diagrams, and
- extensive problems throughout the book.

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Preface to Second Edition

During the 15 years since the first edition of this book was published, experimental techniques have gained prominence and are changing the way that NMR is, and will continue to be, practiced. In this second edition, we introduce and explain several new techniques in a manner that should be comprehensible to advanced undergraduate and junior graduate students in chemistry.

The first new procedure is “nonuniform sampling,” which is a data-processing method to enhance indirect-dimension NMR data. It has the capability of enabling either (i) NMR spectra of equal resolution in the nondetected, f_1 dimension to be acquired in less time than in the past or (ii) spectra of greater f_1 resolution to be acquired in the same time as standard two-dimensional NMR spectra.

The second new technique is “pure shift NMR,” which involves both NMR data accumulation and processing. This method permits the acquisition of both one- and two-dimensional proton-decoupled, NMR spectra to be acquired. The procedure is extremely useful when heavily overlapping proton NMR spectra are encountered, an increasingly prevalent situation.

The third procedure, “covariance NMR,” is also a data-processing technique, which comes in two forms: homonuclear “direct” and heteronuclear “general indirect” covariance. Direct covariance is applied to symmetrical, homonuclear 2D data, such as COSY and NOESY, to produce two-dimensional data in which the resolution is identical in both the f_1 and the f_2 domains. General indirect covariance is employed with heteronuclear data so that two, relatively short, NMR experiments, such as HSQC and TOCSY, can be combined to yield the HSQC + TOCSY spectrum in far less time than it would take to acquire the HSQC-TOCSY spectrum directly.

We consider this book to be introductory, and these topics at present are covered in no other introductory book. In addition to adding these topics, we have revised the entire book, made minor corrections throughout, and added many new problems, to bring the material up to a standard for the 2020s.

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Solutions

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Symbols

B_0	main magnetic field
B_1	magnetic field due to transmitter
B_2	magnetic field in double-resonance experiments
Hz	hertz (a unit of frequency)
I	dimensionless spin
I_z	spin quantum number in the z direction
J	indirect spin–spin coupling constant
M	magnetization
p	coherence order
T	tesla (unit of magnetic flux density, commonly, the magnetic-field strength)
T_1	spin–lattice (longitudinal) relaxation time
$T_{1\rho}$	spin–lattice relaxation time (spin locked) in the rotating frame
T_2	spin–spin (transverse) relaxation time
T_2^*	effective spin–spin relaxation time (includes magnetic-field inhomogeneity effects on xy magnetization)
T_c	coalescence temperature
t_a	acquisition time
t_p	transmitter pulse duration or pulse width (in μs)
t_1	two-dimensional (2D) incremented time
t_2	two-dimensional (2D) acquisition time
W	designation for relaxation pathways, with units of rate constants
α	flip angle
α^0	optimum (Ernst) flip angle
γ	gyromagnetic or magnetogyric ratio
γB_0	resonance or Larmor frequency (ω_0)
γB_2	decoupler field strength (ω_2)
δ	chemical shift
η	nuclear Overhauser enhancement
μ	magnetic moment
ν	linear frequency
σ	magnetic shielding
τ	time delay or lifetime
τ_c	effective correlation time
τ_m	mixing time
ω	angular frequency

Abbreviations

APT	attached proton test
ASIS	aromatic solvent-induced shift
BIRD	bilinear rotation decoupling
COLOC	correlation spectroscopy via long-range coupling
COSY	correlation spectroscopy
CP	cross polarization
CW	continuous wave
CYCLOPS	cyclically ordered phase sequence
DANTE	delays alternating with nutation for tailored excitation
DEPT	distortionless enhancement by polarization transfer
DPFGSE	double pulsed field gradient spin echo
DQF	double quantum filtered
DR	digital resolution
DT	relaxation delay time
EXSY	exchange spectroscopy
FID	free-induction decay
F_n	Fourier number
FT	Fourier transform or transformation
H2BC	heteronuclear two-bond correlation
HETCOR	heteronuclear chemical-shift correlation
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum correlation
HOD	monodeuterated water
HSQC	heteronuclear single quantum correlation
INADEQUATE	incredible natural abundance double-quantum transfer experiment
INEPT	insensitive nuclei enhanced by polarization transfer
LP	linear prediction
MAS	magic angle spinning
MQC	multiple quantum coherence
MRI	magnetic resonance imaging
n_i	number of time increments
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect or enhancement
NOESY	NOE spectroscopy
np	number of data points

ns	number of scans
ns/i	number of scans per time increment
NUS	nonuniform sampling
PFG	pulsed field gradient
ppm	parts per million
PSYCHE	pure shift yielded by chirp excitation
RF	radio frequency
ROESY	rotating frame nuclear Overhauser effect spectroscopy
RT	repetition time ($DT + t_a$)
S/N	signal-to-noise ratio
SR	spectral resolution
sw	spectral width
TMS	tetramethylsilane
TOCSY	total correlation spectroscopy
WALTZ	wideband, alternating-phase, low-power technique for zero residual splitting
WATERGATE	water suppression by gradient tailored excitation

1

Introduction

Structure determination of almost any organic or biological molecule, as well as that of many inorganic molecules, begins with nuclear magnetic resonance (NMR) spectroscopy. During its existence of more than half a century, NMR spectroscopy has undergone several internal revolutions, repeatedly redefining itself as an increasingly complex and effective structural tool. Aside from X-ray crystallography, which can uncover the complete molecular structure of some pure crystalline materials, NMR spectroscopy is the chemist's most direct and general tool for identifying the structure of both pure compounds and mixtures, as either solids or liquids. The process often involves performing several NMR experiments to deduce the molecular structure from the magnetic properties of the atomic nuclei and the surrounding electrons.

1.1 Magnetic Properties of Nuclei

The simplest atom, hydrogen, is found in almost all organic compounds and is composed of a single proton and a single electron. The hydrogen atom is denoted as ^1H , in which the superscript signifies the sum of the atom's protons and neutrons, that is, the atomic mass of the element. For the purpose of NMR, the key aspect of the hydrogen nucleus is its angular momentum properties, which resemble those of a classical spinning particle. Because the spinning hydrogen nucleus is positively charged, it generates a magnetic field and possesses a *magnetic moment* $\boldsymbol{\mu}$, just as a charge moving in a circle creates a magnetic field (Figure 1.1). The magnetic moment $\boldsymbol{\mu}$ is a vector, because it has both magnitude and direction, as defined by its axis of spin in the figure. In this context, *boldface* symbols connote a vectorial parameter; when only the magnitude is under consideration, the symbol is depicted without boldface, as μ . The NMR experiment exploits the magnetic properties of nuclei to provide information on the molecular structure.

The spin properties of protons and neutrons in the nuclei of heavier elements combine to define the overall spin of the nucleus. When both the atomic number (the number of protons) and the atomic mass (the sum of the protons and neutrons) are even, the nucleus has no magnetic properties, as signified by a zero value of its *spin quantum number*, I (Figure 1.2). Such nuclei are considered not to be spinning. Common non-magnetic (nonspinning) nuclei are carbon (^{12}C) and oxygen (^{16}O), which therefore are invisible to the NMR experiment. When either the atomic number or the atomic mass is odd, or when both are odd, the nucleus has magnetic properties that correspond to spin.

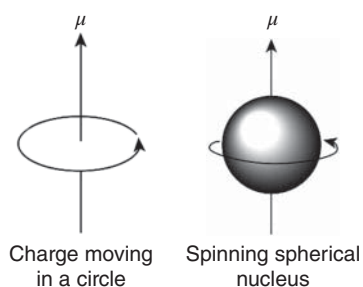


Figure 1.1 Analogy between a charge moving in a circle and a spinning nucleus.

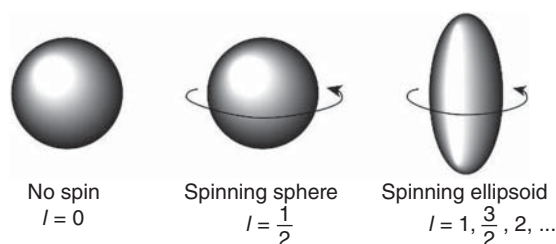


Figure 1.2 Three classes of nuclei.

For spinning nuclei, the spin quantum number can take on only certain values, which is to say that it is quantized. Those nuclei with a spherical shape have a spin I of $\frac{1}{2}$, and those with a nonspherical, or quadrupolar, shape have a spin of 1 or more (in increments of $\frac{1}{2}$).

Common nuclei with a spin of $\frac{1}{2}$ include ^1H , ^{13}C , ^{15}N , ^{19}F , ^{29}Si , and ^{31}P . Thus, many of the most common elements found in organic molecules (H, C, N, P) have at least one isotope with $I = \frac{1}{2}$ (although oxygen does not). The class of nuclei with $I = \frac{1}{2}$ is the most easily examined by the NMR experiment. *Quadrupolar nuclei* ($I > \frac{1}{2}$) include ^2H , ^{11}B , ^{14}N , ^{17}O , ^{33}S , and ^{35}Cl .

The magnitude of the magnetic moment produced by a spinning nucleus varies from atom to atom in accordance with the equation $\mu = \gamma\hbar I$ (see Appendix A for a derivation of this equation). The quantity \hbar is Planck's constant h divided by 2π , and γ is a characteristic of the nucleus called the *gyromagnetic* or the *magnetogyric ratio*. The larger the gyromagnetic ratio, the larger is the magnetic moment of the nucleus. Nuclei that have the same number of protons, but different numbers of neutrons, are called *isotopes* ($^1\text{H}/^2\text{H}$, $^{14}\text{N}/^{15}\text{N}$). The term *nuclide* generally is applied to any atomic nucleus.

To study nuclear magnetic properties, the experimentalist subjects nuclei to a strong laboratory magnetic field B_0 with units of tesla, or T ($1\text{ T} = 10^4$ Gauss, or G). In the absence of the laboratory field, nuclear magnets of the same isotope have the same energy. When the B_0 field is turned on along a direction designated as the z -axis, the energies of the nuclei in a sample are affected. There is a slight tendency for magnetic moments to move along the general direction of B_0 ($+z$) rather than the opposite direction ($-z$). (This motion will be more fully described presently.) Nuclei with a spin of $\frac{1}{2}$ assume only these two modes of motion. The splitting of spins into specific groups has been called the *Zeeman effect*.

The interaction is illustrated in Figure 1.3. At the left is a magnetic moment with a $+z$ component, and at the right is one with a $-z$ component. The nuclear magnets are

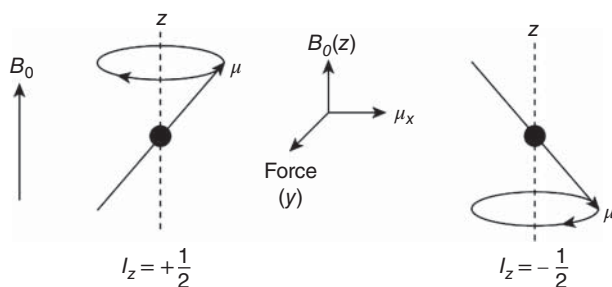


Figure 1.3 Interaction between a spinning nucleus and an external magnetic field B_0 .

not actually lined up parallel to the $+z$ or $-z$ direction. Rather, the force of B_0 causes the magnetic moment to move in a circular fashion about the $+z$ direction in the first case and about the $-z$ direction in the second. In terms of vector analysis, the B_0 field in the z -direction operates on the x component of μ to create a force in the y -direction (Figure 1.3, inset in the middle). The force F is the cross, or vector, product between the magnetic moment μ and the magnetic field B (a vector with magnitude only in the z -direction at this stage with value B_0), that is, $F = \mu \times B$. The nuclear moment then begins to move toward the y -direction. Because the force of B_0 on μ , is always perpendicular to both B_0 and μ (according to the definition of a cross product), the motion of μ describes a circular orbit around the $+z$ or the $-z$ -direction, in complete analogy to the forces present in a spinning top or gyroscope. This motion is termed *precession*.

As the process of quantization allows only two directions of precession for a spin- $1/2$ nucleus (Figure 1.3), two assemblages or *spin states* are created, designated as $I_z = +1/2$ for those precessing with the field ($+z$) and $I_z = -1/2$ for those precessing against the field ($-z$) (some texts refer to the quantum number I_z as m_I). The assignment of signs (+ or -) is entirely arbitrary. The designation $I_z = +1/2$ is given to the slightly lower energy. In the absence of B_0 , the precessional motions are absent, and all nuclei have the same energy.

The relative proportions of nuclei with $+z$ and $-z$ precession in the presence of B_0 is defined by Boltzmann's law (Eq. (1.1)),

$$\frac{n\left(+\frac{1}{2}\right)}{n\left(-\frac{1}{2}\right)} = \exp\left(\frac{\Delta E}{kT}\right) \quad (1.1)$$

in which n is the population of a spin state, k is Boltzmann's constant, T is the absolute temperature in kelvin (K), and ΔE is the energy difference between the spin states. Figure 1.4a depicts the energies of the two states and the difference ΔE between them.

The precessional motion of the magnetic moment around B_0 occurs with angular frequency ω_0 , called the *Larmor frequency*, whose units are radians per second (rad s^{-1}). As B_0 increases, so does the angular frequency, that is, $\omega_0 \propto B_0$, as is demonstrated in Appendix A. The constant of proportionality between ω_0 and B_0 is the gyromagnetic ratio γ , so that $\omega_0 = \gamma B_0$. The natural precession frequency can be expressed as linear frequency in Planck's relationship $\Delta E = h\nu_0$, or as angular frequency $\Delta E = \hbar\omega_0$

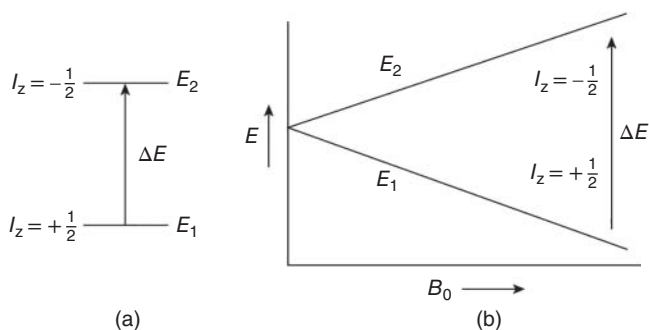


Figure 1.4 (a) The energy difference between spin states. (b) The energy difference as a function of the external field B_0 .

($\omega_0 = 2\pi\nu_0$). In this way, the energy difference between the spin states is related to the Larmor frequency by the formula of Eq. (1.2).

$$\Delta E = \hbar\omega_0 = h\nu_0 = \gamma\hbar B_0 \quad (1.2)$$

Thus, as the B_0 field increases, the difference in energy between the two spin states increases, as illustrated in Figure 1.4b. Appendix A provides a complete derivation of these relationships.

The foregoing equations indicate that the natural precession frequency of a spinning nucleus ($\omega_0 = \gamma B_0$) depends only on the nuclear properties contained in the gyromagnetic ratio γ and on the laboratory-determined value of the magnetic field B_0 . For a proton in a magnetic field B_0 of 7.05 T, the frequency of precession is 300 MHz, and the difference in energy between the spin states is only $0.0286 \text{ cal mol}^{-1}$ (0.120 J mol^{-1}). This value is extremely small in comparison with the energy differences between vibrational or electronic states. At a higher field, such as 14.1 T, the frequency increases proportionately to 600 MHz in this case.

In the NMR experiment, the two states illustrated in Figure 1.4 are made to interconvert by applying a second magnetic field B_1 at radio frequency (RF) range. When the frequency of the B_1 field is the same as the Larmor frequency of the nucleus, energy can flow by absorption and emission between this newly applied field and the nuclei. Absorption of energy occurs as $+\frac{1}{2}$ nuclei become $-\frac{1}{2}$ nuclei, and emission occurs as $-\frac{1}{2}$ nuclei become $+\frac{1}{2}$ nuclei. Since there is an excess of $+\frac{1}{2}$ nuclei at the beginning of the experiment, there is a net absorption of energy. The process is called *resonance*, and the absorption may be detected electronically and displayed as a plot of frequency vs amount of energy absorbed. Because the resonance frequency ν_0 is highly dependent on the structural environment of the nucleus, NMR spectroscopy has become the structural tool of choice for chemists. Figure 1.5 illustrates the NMR spectrum for the protons in benzene. Absorption is represented by a peak directed upward from the baseline.

Because gyromagnetic ratios vary among elements and even among isotopes of a single element, resonance frequencies also vary ($\omega_0 = \gamma B_0$). There is essentially no overlap in the resonance frequencies of different nuclides, including isotopes. At the field strength at which protons resonate at 300 MHz (7.05 T), ^{13}C nuclei resonate at 75.45 MHz, ^{15}N nuclei at 30.42 MHz, and so on. At 14.1 T, the frequencies would be doubled, respectively, 600, 150.9, and 60.84 MHz.

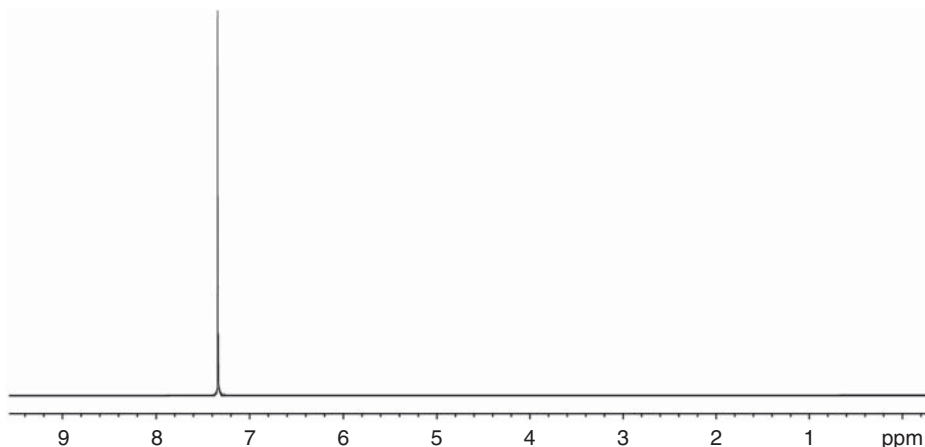


Figure 1.5 The 300 MHz ^1H spectrum of benzene.

The magnitude of the gyromagnetic ratio γ also has an important influence on the intensity of the resonance. The difference in energy, $\Delta E = \gamma\hbar B_0$ (Eq. (1.2)), between the two spin states is directly proportional not only to B_0 , as illustrated in Figure 1.4b, but also to γ . From Boltzmann's law (Eq. (1.1)), when ΔE is larger, there is a greater population difference between the two states. A greater excess of $I_z = +1/2$ spins (designated the E_1 state) means that more nuclei are available to flip to the E_2 state with $I_z = -1/2$, so the resonance intensity is larger. The proton has one of the largest gyromagnetic ratios, so its spin states are relatively far apart, and the value of ΔE is especially large. The proton signal, consequently, is very strong. Many other important nuclei, such as ^{13}C and ^{15}N , have much smaller gyromagnetic ratios and hence have smaller differences between the energies of the two spin states (Figure 1.6). Thus, their signals are much less intense.

When spins have values greater than $1/2$, more than two spin states are allowed. For $I = 1$ nuclei, such as ^2H and ^{14}N , the magnetic moments may precess about three directions relative to B_0 : parallel ($I_z = +1$), perpendicular (0), and opposite (-1). In general, there are $(2I + 1)$ spin states—for example, six for $I = 5/2$ (^{17}O has this spin). The values

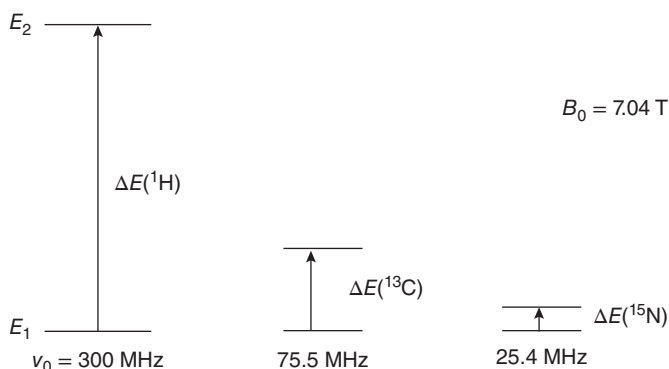


Figure 1.6 The energy difference between spin states for three nuclides with various relative magnitudes of the gyromagnetic ratio ($|\gamma|$): 26.75 for ^1H , 6.73 for ^{13}C , and 2.71 for ^{15}N .

of I_z extend from $+I$ to $-I$ in increments of 1 ($+I, (+I-1), (+I-2), \dots, -I$). For example, $I_z = +1, 0,$ and -1 for $I = 1$, and $+3/2, +1/2, -1/2,$ and $-3/2$ for $I = 3/2$. Hence, the energy state picture is more complex for quadrupolar than for spherical nuclei.

In summary, the NMR experiment consists of immersing magnetic nuclei in a strong field B_0 to distinguish them according to their values of I_z ($+1/2$ and $-1/2$ for spin- $1/2$ nuclei), followed by the application of a B_1 field whose frequency corresponds to the Larmor frequency of the nuclei under examination ($\omega_0 = \gamma B_0$). This application of energy results in a net absorption, as the excess $+1/2$ nuclei are converted to $-1/2$ nuclei. The resonance frequency varies from nuclide to nuclide according to the value of the gyromagnetic ratio γ . The energy difference between the I_z spin states, $\Delta E = h\nu$, which determines the intensity of the absorption, depends on the value of B_0 (Figure 1.4) and on the gyromagnetic ratio of the nucleus ($\Delta E = \gamma \hbar B_0$) (Figure 1.6).

1.2 The Chemical Shift

The remaining sections in this chapter discuss the various factors that determine the content of NMR spectra. Uppermost is the location of the resonance in the spectrum, the so-called resonance frequency ν_0 (or ω_0 as angular frequency), which depends on the molecular environment as well as on γ and B_0 ($\nu_0 = \gamma B_0 / 2\pi$ or $\omega_0 = \gamma B_0$). This dependence of the resonance frequency on structure is the ultimate reason for the importance of NMR spectroscopy in chemistry.

The electron cloud that surrounds the nucleus also has charge, motion, and, hence, a magnetic moment. The magnetic field generated by the electrons alters the B_0 field in the microenvironment around the nucleus. The actual field present at a given nucleus thus depends on the nature of the surrounding electrons. This electronic modulation of the B_0 field is termed *shielding* and is represented quantitatively by the Greek letter sigma (σ). The actual field at the nucleus becomes B_{local} and may be expressed as $B_{\text{local}} = B_0(1 - \sigma)$, in which the electronic shielding σ is positive for protons. The variation of the resonance frequency with shielding has been termed the *chemical shift*.

By substituting B_{local} for B_0 in Eq. (1.2), the expression for the resonance frequency in terms of shielding becomes Eq. (1.3).

$$\nu_0 = \frac{\gamma B_0(1 - \sigma)}{2\pi} \quad (1.3)$$

Decreased shielding thus results in a higher resonance frequency ν_0 at constant B_0 , since σ enters the equation after a negative sign. For example, the presence of an electron-withdrawing group in a molecule reduces the electron density around a proton so that there is less shielding and, consequently, a higher resonance frequency than in the case of a molecule that lacks the electron-withdrawing group. Hence, protons in fluoromethane (CH_3F) resonate at a higher frequency than those in methane (CH_4), because the fluorine atom withdraws electrons from around the hydrogen nuclei.

Figure 1.7 separately shows the NMR spectra of the protons and the carbons of methyl acetate ($\text{CH}_3\text{CO}_2\text{CH}_3$). Although 98.9% of naturally occurring carbon is the nonmagnetic ^{12}C , the carbon NMR experiment is carried out on the 1.1% of ^{13}C , which has an I of $1/2$. Because of differential electronic shielding, the ^1H spectrum contains separate resonances for the two types of protons ($\text{O}-\text{CH}_3$ and $\text{C}-\text{CH}_3$), and the ^{13}C spectrum