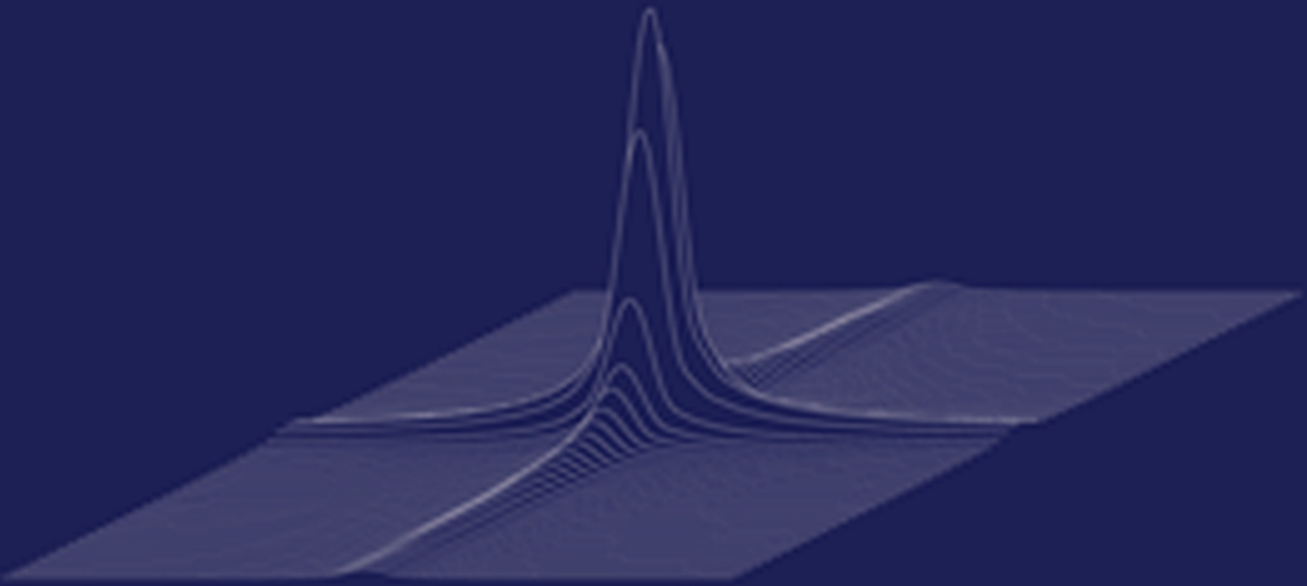
Organic Structures from 2D NMR Spectra



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PREFACE

Obtaining structural information from spectroscopic data is an integral part of organic chemistry courses at all universities. At this time, NMR spectroscopy is arguably the most powerful of the spectroscopic techniques for elucidating the structure of unknown organic compounds, and the method continues to evolve over time.

This text *Organic Structures from 2D NMR Spectra* builds on the popular series *Organic Structures from Spectra*, which is now in its fifth edition. The aim of *Organic Structures from Spectra* is to teach students to solve simple structural problems efficiently by using combinations of the major spectroscopic and analytical techniques (UV, IR, NMR and mass spectroscopy). Probably the most significant advances in recent years have been in the routine availability of quite advanced 2D NMR techniques. This text deals specifically with the use of more advanced 2D NMR techniques, which have now become routine and almost automatic in almost all NMR laboratories.

In this book, we continue the basic philosophy that learning how to identify organic structures from spectroscopic data is best done by working through examples. Solving real problems as puzzles is also addictive – there is a real sense of achievement, understanding and satisfaction. About 70% of the book is dedicated to a series of more than 60 graded examples ranging from very elementary problems (designed to demonstrate useful problem-solving techniques) through to very challenging problems at the end of the collection.

The underlying theory has been kept to a minimum, and the theory contained in this book is only sufficient to gain a basic understanding of the techniques actually used in solving the problems. We refer readers to other sources for a more detailed description of both the theory of NMR spectroscopy and the principles underpinning the NMR experiments now in common use.

The following books are useful sources for additional detail on the theory and practice of NMR spectroscopy:

(i) T. D. W. Claridge, *High-Resolution NMR Techniques in Organic Chemistry*, 2nd edition, Elsevier, Amsterdam, 2009. ISBN 978-0-08-054628-5.

(ii) J. Keeler, *Understanding NMR Spectroscopy*, 2nd edition, John Wiley & Sons, UK, 2010. ISBN 978-0-470-74609-7.

(iii) H. Friebolin, *Basic One- and Two-Dimensional NMR Spectroscopy*, 5th edition, Wiley-VCH, Weinheim, 2011. ISBN 978-3-527-32782-9.

(iv) H. Günther, *NMR Spectroscopy: Basic Principles, Concepts and Applications in Chemistry*, 3rd edition, Wiley-VCH, Weinheim, 2013. ISBN 978-3-527-33000-3.

In this book, the need to learn data has been kept to a minimum. It is more important to become conversant with the important spectroscopic techniques and the general characteristics of different types of organic compounds than to have an encyclopaedic knowledge of more extensive sets of data. The text does contain sufficient data to solve the problems, and again there are other excellent sources of data for NMR spectroscopy.

The following collections are useful sources of spectroscopic data on organic compounds:

(i) http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/cre_index.cgi?lang=eng, maintained by the National Institute of Advanced Industrial Science and Technology, Tsukuba, Ibaraki, Japan.

(ii) http://webbook.nist.gov/chemistry/, which is the NIST Chemistry WebBook, NIST Standard Reference Database Number 69, June 2005, Eds. P. J. Linstrom and W. G. Mallard.

(iii) E. Pretch, P. Bühlmann and M. Badertscher, *Structure Determination of Organic Compounds, Tables of Spectral Data*, Springer-Verlag, Berlin/Heidelberg, 2009. ISBN 978-3-540-93810-1.

ASSUMED KNOWLEDGE

The book assumes that students have completed an elementary organic chemistry course, so there is a basic understanding of structural organic chemistry, functional groups, aromatic and non-aromatic compounds, stereochemistry, etc. It is also assumed that students already have a working knowledge of how various spectroscopic techniques (UV, IR, NMR and mass spectroscopy) are used to elucidate the structures of organic compounds.

The following books are useful texts dealing with the elucidation of the structures of organic compounds by spectroscopy:

(i) L. D. Field, S. Sternhell and J. R. Kalman, *Organic Structures from Spectra*, 5th edition, John Wiley & Sons, UK, 2013. ISBN 978-1-118-32545-2.

(ii) R. M. Silverstein, F. X. Webster, D. J. Kiemle and D. L. Bryce, *Spectrometric Identification of Organic Compounds*, 8th edition, John Wiley & Sons, USA, 2014. ISBN 978-0-470-61637-6.

STRUCTURE OF THE BOOK

- *Chapter 1* deals with the basic physics of the NMR experiment and the hardware required to acquire NMR spectra.
- *Chapter 2* deals with the general characteristics of NMR spectroscopy for commonly observed nuclei. While most NMR deals with ^{1}H or ^{13}C NMR spectroscopy, this chapter also provides an introduction to ^{19}F, ^{31}P and ^{15}N NMR.
- *Chapter 3* deals with 2D NMR spectroscopy. First the principles, and then a basic description of the commonly used 2D NMR experiments – COSY, NOESY, TOCSY, INADEQUATE, HSQC/HMQC and HMBC.
- *Chapter 4* covers a group of special topics which are important in interpreting NMR spectra. Topics include (i) the common solvents used for NMR; (ii) the standard reference materials used for the observation of the spectra of different nuclei; (iii) the effects of molecular exchange and molecular motion on NMR spectra; and (iv) the effect of chirality on NMR spectra.
- *Chapter 5* contains two worked solutions as an illustration of a logical approach to solving problems. However, with the exception that we insist that students should perform all routine measurements first, we do not recommend a mechanical attitude to problem solving – intuition has an important place in solving structures from spectra.

INSTRUMENTATION

The NMR spectra presented in the problems contained in this book were obtained under conditions stated on the individual problem sheets. Spectra were obtained on the following instruments:

(i) 300 MHz ^{1}H NMR spectra, 75 MHz ^{13}C NMR spectra and 283 MHz ^{19}F spectra on a Bruker DPX-300 spectrometer;

(ii) 400 MHz ^{1}H NMR spectra, 100 MHz ^{13}C NMR spectra and 376 MHz ^{19}F spectra on Bruker Avance III 400 spectrometers;

(iii) 500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR spectra on a Bruker Avance III 500 spectrometer;

(iv) 600 MHz ^{1}H NMR and 150 MHz ^{13}C NMR spectra were obtained on Avance III 600 or Avance III HD 600 Cryoprobe spectrometers.

There is a companion Instructor's Guide which provides a comprehensive step-by-step solution to every problem in the book.

Bona fide instructors may obtain a list of solutions (at no charge) by emailing the authors at L.Field@unsw.edu.au or fax (+61 2 9385 8008).

We wish to thank Dr Donald Thomas and Dr James Hook at the Mark Wainwright Analytical Centre at the University of New South Wales, and Dr Joanna Cosgriff and Dr Roger Mulder at CSIRO Materials Science and Engineering who helped to assemble the additional samples and spectra used in this book. Thanks are also due to Dr Samantha Furfari and Dr Manohari Abeysinghe who helped with the synthesis of several of the compounds used in the problems.

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January 2015

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1 NMR Spectroscopy Basics

1.1 THE PHYSICS OF NUCLEAR SPINS

Any nucleus that has an odd number of protons and/or neutrons has a property called "nuclear spin". Such nuclei are termed "NMR-active nuclei" and, in principle, these nuclei can be observed by Nuclear Magnetic Resonance (NMR) spectroscopy.

Any nucleus that has an even number of protons *and* an even number of neutrons has no nuclear spin and cannot be observed by NMR. Nuclei with no nuclear spin are "NMR-silent nuclei". Common nuclei that fall into the NMR-silent category include carbon-12 and oxygen-16. Fortunately, with a few exceptions, most elements do have at least one isotope that has a nuclear spin, and so while ^{12}C and ^{16}O are NMR-silent, we can observe NMR spectra for the less abundant isotopes of carbon and oxygen, ^{13}C and ^{17}O. So even the elements where the most abundant isotope is NMR-silent can usually be observed via one or more of the less abundant isotopes.

Each nucleus has a unique nuclear spin, which is described by the spin quantum number, I. Nuclear spin is quantised, and I has values of 0, ½, 1, $^3\!/_2$ *etc*. NMR-silent nuclei have $I = 0$. Each nuclear spin also has a magnetic moment, μ. The nuclear spin and the magnetic moment are related by Equation 1-1:

$$\mu = \gamma I \tag{1-1}$$

The constant of proportionality, γ, is known as the *magnetogyric ratio*, and γ is unique for each NMR-active isotope. Table 1-1 provides a summary of the nuclear spins of some of the common NMR-active nuclei.

The combination of spin and charge means that NMR-active nuclei behave like small magnets and when a nucleus with a nuclear spin I is placed in an external magnetic field, that nucleus may assume one of $2I + 1$ orientations relative to the direction of the applied field.

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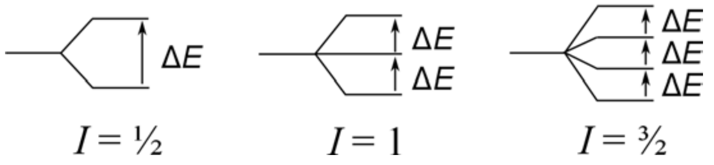
Table 1-1 Nuclear spins and magnetogyric ratios for some common NMR-active nuclei.

Nucleus	Spin *I*	Natural Abundance (%)	Magnetogyric Ratio ($\gamma \times 10^7$ rad/T/s)
^{1}H	$^{1}/_{2}$	99.98	26.75
^{2}H	1	0.015	4.11
^{10}B	3	19.58	2.87
^{11}B	$^{3}/_{2}$	80.42	8.58
^{13}C	$^{1}/_{2}$	1.108	6.73
^{14}N	1	99.63	1.93
^{15}N	$^{1}/_{2}$	0.37	−2.71
^{17}O	$^{5}/_{2}$	0.037	−3.63
^{19}F	$^{1}/_{2}$	100.0	25.17
^{29}Si	$^{1}/_{2}$	4.7	−5.31
^{31}P	$^{1}/_{2}$	100.0	10.83

So, for a nucleus with $I = ½$ like ^{1}H or ^{13}C, there are two possible orientations, which can be pictured as having the nuclear magnet aligned either parallel or antiparallel to the applied field. For nuclei with $I = 1$ there are three possible orientations; for nuclei with $I = {}^{3}/_{2}$ there are four possible orientations and so on.



The various orientations of a nuclear magnet in a magnetic field are of unequal energy, and the energy gap (Δ*E*) is proportional to the strength of the applied magnetic field ($\boldsymbol{B}_0$) according to Equation (1-2:

$$\Delta E = \frac{h\gamma \boldsymbol{B}_0}{2\pi} \qquad \text{(1-2)}$$

where *h* is the Planck constant.

Nuclei in a lower energy orientation can be excited to the higher energy orientation by a radiofrequency (Rf) pulse of the correct frequency (ν) according to Equation (1-3:

$$\nu = \frac{\Delta E}{h} \tag{1-3}$$

It follows from Equations (1-2 and (1-3 that the fundamental equation that relates frequency (ν) to magnetic field strength ($\boldsymbol{B}_0$) is Equation (**1-4** which is known as **the Larmor Equation**:

$$\nu = \frac{\gamma \boldsymbol{B}_0}{2\pi} \tag{1-4}$$

The Larmor equation specifies that the frequency required to excite an NMR-active nucleus is proportional to the strength of the magnetic field and to the magnetogyric ratio of the nucleus being observed. For magnetic fields that are currently accessible routinely for NMR spectroscopy (up to about 21 T), the frequencies required to observe most common NMR-active nuclei fall in the Rf range of the electromagnetic spectrum (up to about 900 MHz).

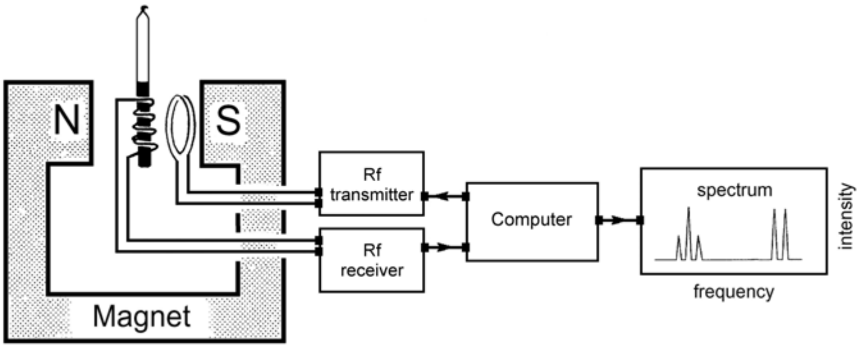
Table 1-2 summarises the NMR frequencies of common NMR-active nuclei.

Table 1-2 Resonance frequencies for some common NMR-active nuclei in different magnetic fields.

Nucleus	NMR Frequency (MHz) at 4.698 T	NMR Frequency (MHz) at 9.395 T	NMR Frequency (MHz) at 18.79 T
^{1}H	200.0	400.0	800.0
^{2}H	30.7	61.4	122.8
^{10}B	21.5	43.0	86.0
^{11}B	64.2	128.3	256.6
^{13}C	50.3	100.6	201.1
^{14}N	14.4	28.9	57.8
^{15}N	20.3	40.5	81.0
^{17}O	27.1	54.2	108.5
^{19}F	188.2	376.3	752.6
^{29}Si	39.7	79.4	158.9
^{31}P	81.0	161.9	323.8

1.2 BASIC NMR INSTRUMENTATION AND THE NMR EXPERIMENT

Samples for NMR spectroscopy are typically liquids (solutions) or solids. In order to observe Nuclear Magnetic Resonance, the sample must be placed in a strong magnetic field.



Magnets for NMR spectroscopy may be either permanent magnets or electromagnets. Most modern magnets are electromagnets based on superconducting solenoids, cooled to liquid helium temperature.

NMR spectrometers require an Rf transmitter which can be tuned to the appropriate frequency for the nucleus one wishes to detect (Equation (**1**-**4**) and an Rf detector or receiver to observe the Rf radiation absorbed and emitted by the sample. In most modern instruments, the Rf transmitter and the Rf receiver are controlled by a computer and the detected signal is captured in a computer which then allows processing and presentation of the data for analysis.

2 One-Dimensional Pulsed Fourier Transform NMR Spectroscopy

A short pulse of radiofrequency radiation will simultaneously excite all of the nuclei whose resonance frequencies are close to the frequency of the pulse. If a sample placed in a magnetic field of 9.395 T contains ^{31}P nuclei, then a pulse whose frequency is close to 161.9 MHz will excite all of the ^{31}P nuclei in the sample. Typically, the excitation pulse is very short in duration (microseconds). Once the pulse is switched off, the magnetisation which builds up in the sample begins to decay exponentially with time. A pulsed NMR spectrometer measures the decrease in sample magnetisation as a function of time, and records the ***free-induction decay*** (FID) (Figure 2-1).

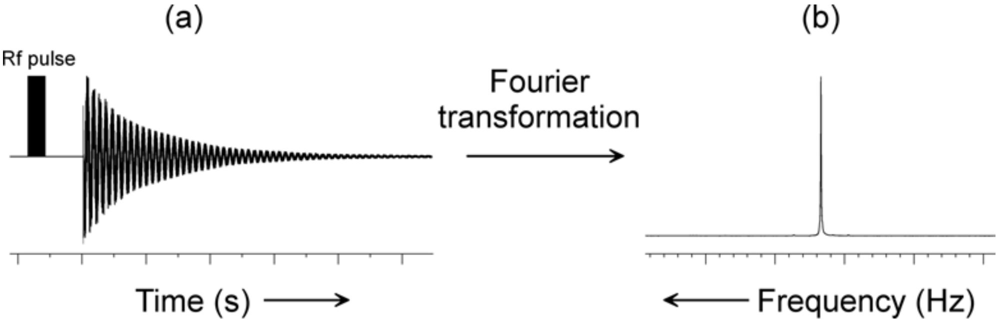


Figure 2-1 ^{1}H NMR spectra: *(a)* time domain spectrum (FID); *(b)* frequency domain spectrum obtained after Fourier transformation of *(a).*

The FID is a time domain signal (*i.e.* a signal whose amplitude is a function of time), and contains information for each resonance in the sample, superimposed on the information for all the other resonances. The FID signal may be transformed into the more easily interpreted frequency domain spectrum (*i.e.* a signal whose amplitude is a function of frequency), by a mathematical procedure known as ***Fourier transformation*** (FT). The frequency domain spectrum is the typical NMR spectrum that is used to provide information about chemical compounds. An NMR spectrum which contains intensity information as a function of one frequency domain is termed a *one-dimensional (1D) NMR spectrum*.

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There are typically multiple signals in any sample and the FID is then a complex superposition of all signals from the sample. The FT then provides a frequency domain spectrum with multiple resonances. The magnetisation in the sample decays back to equilibrium, typically over a period of seconds, by processes generally known as **relaxation**. The NMR experiment only works because there are mechanisms that restore the system back to equilibrium once it has been excited by absorption of Rf energy.

After a suitable delay to let the sample relax, the excitation pulse is repeated and another FID recorded. The FIDs collected can be added together to improve the intensity of the signal in the final spectrum.

For organic liquids and samples in solution, it may take several seconds for the system to relax. In the presence of paramagnetic impurities or in very viscous solvents, relaxation can be very efficient and, as a consequence, NMR spectra obtained become broadened.

If relaxation is too efficient (*i.e.* it takes a very short time for the nuclear spins to relax after being excited in an NMR experiment), the lines observed in the NMR spectrum are very broad. If relaxation is too slow (*i.e.* it takes a long time for the nuclear spins to relax after being excited in an NMR experiment), the resonances are sharp but then there must be a longer delay between pulses.

Not all NMR-active nuclei are easily observed using NMR spectroscopy:

i. Some nuclei suffer from a very low natural abundance, which simply means the concentration of NMR-active nuclei in a sample is low and the signal is weak.

ii. Nuclei with $I > ½$ have an electric quadrupole which broadens NMR signals and makes spectra more difficult to observe. In contrast, those nuclei with $I = ½$ typically give rise to signals which are sharp and easily observed. ^{1}H, ^{13}C, ^{19}F and ^{31}P all have $I = ½$ and are the most commonly observed nuclei by NMR spectroscopy.

iii. Equation (1-2 indicates that ΔE is proportional to the strength of both the magnetic field and the magnetogyric ratio of the nucleus being observed. The intensity of the NMR signal depends on the population difference between the states – larger ΔE means a larger population difference and a stronger observed NMR signal. Nuclei with a low magnetogyric ratio give rise to only a small ΔE, which results in poor sensitivity.

iv. Nuclei which are associated with a paramagnetic atom, *i.e.* where there are unpaired electrons, relax very efficiently and give rise to NMR signals which are broadened and more difficult to observe.

2.1 THE CHEMICAL SHIFT

While the Larmor equation and the information in Table 1-2 provide the broad distinction between the isotopes of different elements, the chemical significance of NMR spectroscopy relies on the subtle differences between nuclei of the same isotope which are in chemically different environments.

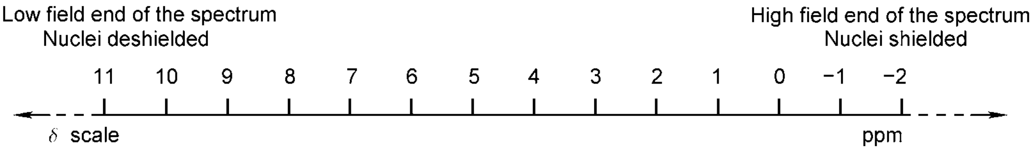
All ^{1}H nuclei in a sample are not necessarily equivalent, and the chemical environment that each ^{1}H finds itself in within the structure of the molecule determines its exact resonance frequency. Each nucleus is screened or shielded from the applied magnetic field by the electrons that surround it. Unless two ^{1}H environments are precisely identical (by symmetry) *their resonance frequencies must be slightly different*. Nuclei that are close to strongly electronegative functional groups have the local electronic environment distorted and may have less electron density to screen or shield them from the magnetic field and the nuclei are said to be **deshielded**. Nuclei that are in electron-rich sections of a molecule have more electron density to screen or shield them from the magnetic field and the nuclei are said to be **shielded**.

A typical NMR spectrum is a graph of resonance frequency against intensity. The frequency axis is calibrated in dimensionless units called “parts per million” (abbreviated to ppm). The chemical shift scale in ppm, termed the δ scale, is usually calibrated relative to the signal of a reference compound whose frequency is set at 0 ppm. For ^{1}H NMR spectroscopy, the reference is the proton resonance of tetramethylsilane ($Si(CH_3)_4$, TMS) and for ^{13}C NMR spectroscopy the reference is the carbon resonance of TMS. The frequency difference between the resonance of a nucleus and the resonance of the reference compound is termed the **chemical shift** (Equation 2-1).

$$\text{Chemical shift } (\delta) \text{ in ppm} = \frac{\text{Frequency difference from TMS in Hz}}{\text{Spectrometer frequency in MHz}} \qquad (2\text{-}1)$$

Note that for a spectrometer operating at 500 MHz, 1 ppm corresponds to 500 Hz, *i.e.* for a spectrometer operating at x MHz, 1 ppm always corresponds to exactly x Hz.

For the majority of organic compounds, the chemical shift range for ^{1}H covers approximately 0–10 ppm (from TMS) and the chemical shift range for ^{13}C covers approximately 0–220 ppm (from TMS). By convention, the δ scale runs (with increasing values) from right to left with the signals of the most shielded nuclei at the right hand end of the spectrum and the least shielded nuclei to the left.

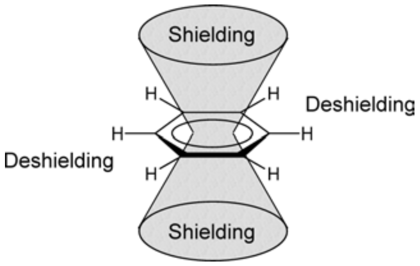


Any effect which alters the density or spatial distribution of electrons around a ^{1}H nucleus will alter the degree of shielding and hence its chemical shift. ^{1}H chemical shifts are sensitive to both the hybridisation of the atom to which the ^{1}H nucleus is attached (sp^2, sp^3, *etc.*) and to electronic effects (the presence of neighbouring electronegative/electropositive groups).

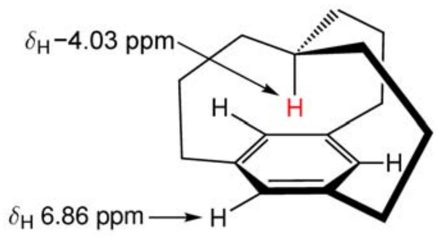
The chemical shift of a nucleus reflects its local environment in a molecular structure and this makes NMR spectroscopy a powerful tool for obtaining structural information.

π-Electrons in organic structures generate a local magnetic field which can shield or deshield nearby NMR-active nuclei. Functional groups such as double and triple bonds, aromatic rings and carbonyl, nitro and nitrile groups distort the local magnetic field and these types of functional groups are termed *magnetically anisotropic* groups.

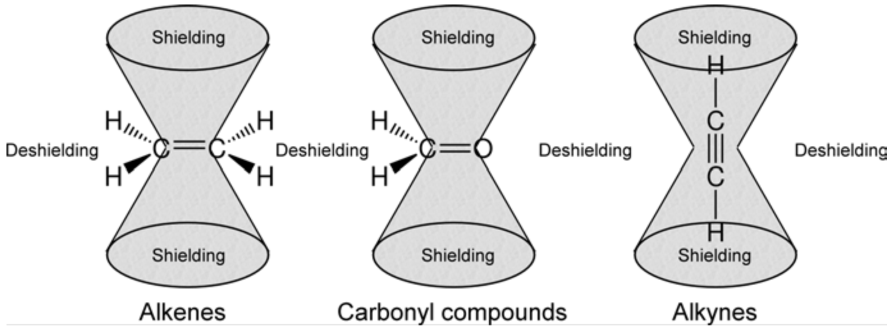
In aromatic rings, for example, the circulation of the π-electrons induces a small, localised magnetic field which deshields any nuclei which are in the plane of the aromatic ring and shields nuclei which are in the zone above or below the plane of the aromatic ring.



Shielding and deshielding by an aromatic ring is clearly illustrated by the compound on the right, in which the aromatic protons are deshielded, and resonate at 6.86 ppm, while the central bridge-head proton experiences significant shielding and resonates at −4.03 ppm, well upfield of most other proton signals.*



Alkenes and carbonyl compounds also display deshielding effects for protons directly bound to the functional group, while the terminal protons of alkynes fall in the shielding zone of the triple bond.



2.2 ^{1}H NMR SPECTROSCOPY

Proton NMR is the most commonly acquired type of NMR spectrum. Almost all organic compounds contain hydrogen; ^{1}H is the overwhelmingly most abundant isotope of hydrogen and ^{1}H is amongst the most sensitive nuclei to observe by NMR spectroscopy.

2.2.1 Chemical Shifts in ^{1}H NMR Spectroscopy

The chemical shifts for protons in organic compounds are summarised in Figure 2-2. A significant amount of information about the functional groups contained in a molecule can be deduced simply from the chemical shift ranges of the protons it contains.

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* Pascal, R. A., Jr.; Winans, C. G.; Van Engen, D. Small, strained cyclophanes with methine hydrogens projected toward the centers of aromatic ring. *J. Am. Chem. Soc.*, **1989**, *111*, 3007–3010.

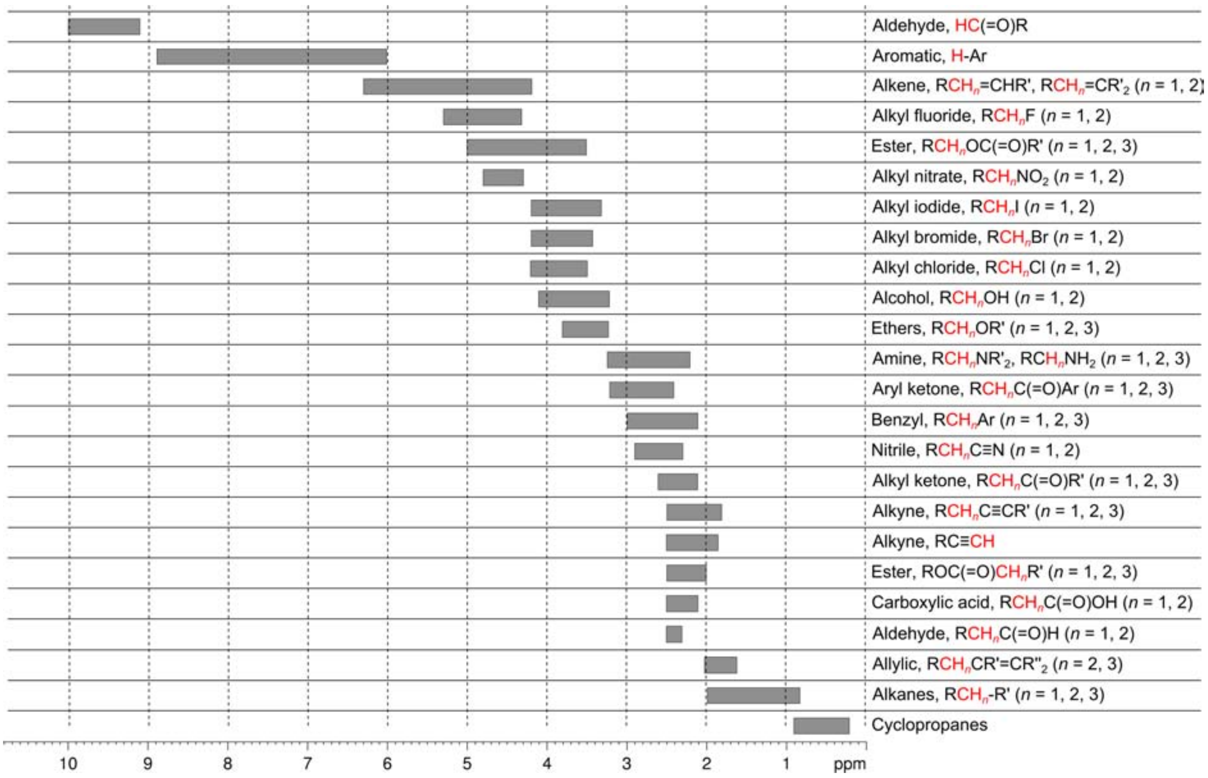

Figure 2-2 Approximate ^{1}H chemical shift ranges for protons in organic compounds.

2.2.2 Spin–Spin Coupling in ^{1}H NMR Spectroscopy

Most organic molecules contain more than one magnetic nucleus (*e.g.* more than one ^{1}H). When one NMR-active nucleus can sense the presence of other NMR-active nuclei ***through the bonds of the molecule*** the signals will exhibit fine structure (*splitting or multiplicity*).

Signal multiplicity arises because the energy of a nucleus, which can sense the presence of other magnetic nuclei, is perturbed slightly by the spin states of those nuclei.

The presence (or absence) of splitting due to spin–spin coupling provides valuable structural information when correctly interpreted. **Spin–spin coupling** is transmitted through the bonds of a molecule and so it is not observed between nuclei in different molecules. The effect of coupling falls off quite rapidly as the number of bonds between the coupled nuclei increases.

Signal multiplicity – the n+1 rule. Spin–spin coupling gives rise to multiplet splittings in ^{1}H NMR spectra. The NMR signal of a nucleus coupled to ***n*** equivalent hydrogens will be split into a multiplet with (***n***+1) lines (Figure 2-3). The CH_2 signal of bromoethane (H_1) is split into a multiplet with four lines by coupling with the three protons on the adjacent carbon (n+1 = 4). The CH_3 signal (H_2) is split into a multiplet with three lines by coupling with the two protons on the adjacent carbon (n+1 = 3).

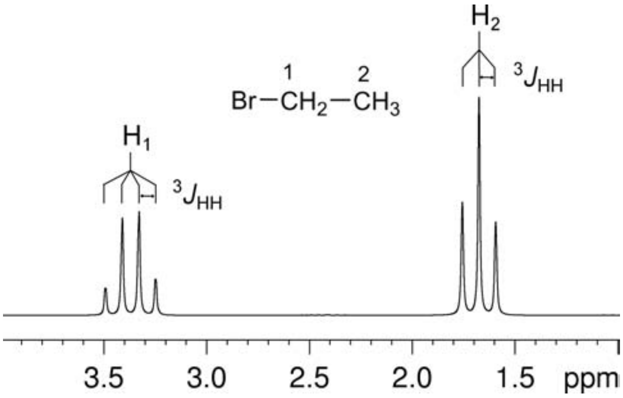

Figure 2-3 ^{1}H NMR spectrum of bromoethane (simulated at 90 MHz, $CDCl_3$) showing the multiplicity of the two ^{1}H signals.

Nuclei which are chemically equivalent (*i.e.* have exactly the same chemical environment) do not show coupling to each other.

A signal with no splitting is commonly termed a singlet; a multiplet with two lines is termed a doublet; a multiplet with three lines is a triplet and a multiplet with four lines a quartet. For simple multiplets, the spacing between the lines (in Hz) is the coupling constant which is given the symbol "J". $^3J_{XY}$ indicates a coupling between nuclei X and Y through three intervening bonds.

The NMR signal of a nucleus coupled to more than one group of hydrogen atoms will be split into a multiplet-of-multiplets. In the ^{1}H NMR spectrum of 1,2,4-trichlorobenzene (Figure 2-4), the H_3 signal is split into a doublet by coupling to the *meta* proton (H_5). Similarly, the H_6 signal is split into a doublet by coupling to the *ortho* proton (H_5). The H_5 signal is split into a doublet-of-doublets by coupling to both the *ortho* and *meta* protons (H_6 and H_3, respectively).

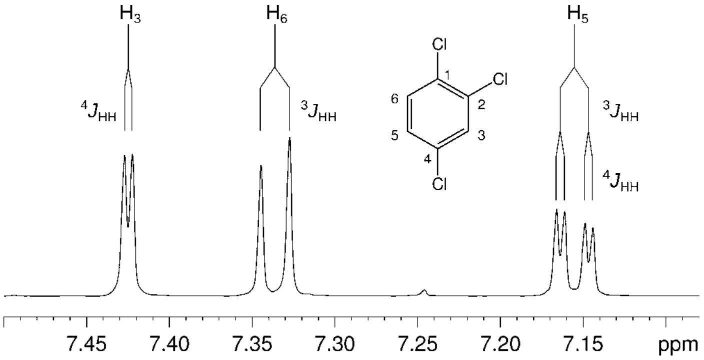

Figure 2-4 ^{1}H NMR spectrum of 1,2,4-trichlorobenzene (500 MHz, $CDCl_3$) showing the multiplicity of the three ^{1}H signals.

In saturated aliphatic systems, the two-bond coupling ($^2J_{HH}$) between two protons attached to the same tetrahedral carbon atom (*geminal* protons) typically falls in the range 10–16 Hz.

The coupling between protons attached to adjacent saturated carbons in an alkyl chain (*vicinal* protons) is typically near 7 Hz but vicinal coupling constants (H–C–C–H) in rigid saturated systems depend strongly on the dihedral angle (φ) between the two protons. $^3J_{HH}$ coupling constants in saturated systems are large for dihedral angles which approach 0° or 180°, and small for dihedral angles which are close to 90°. This relationship is known as **the Karplus relationship** (Figure 2-5). While the shape of the Karplus curve remains essentially unchanged for different molecules, the values of the constants *A*, *B* and *C* vary depending on the type of system being studied.

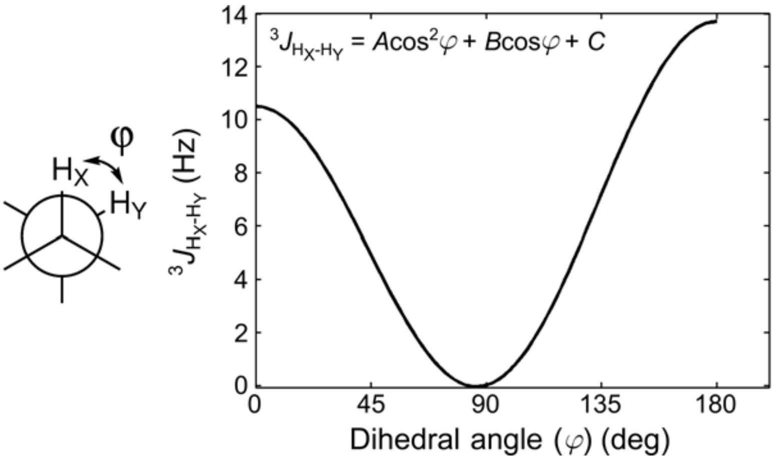

Figure 2-5 The dependence of vicinal coupling constants ($^3J_{HH}$, Hz) on dihedral angle (φ) (Karplus relationship).