Atta-ur-Rahman

Nuclear Magnetic Resonance

Basic Principles

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With 290 Illustrations

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Preface

Nuclear magnetic resonance spectroscopy is presently going through an explosive phase of development. This has been brought about largely on account of the advent of Fourier transform NMR spectrometers linked to powerful microcomputers which have opened up a whole new world for structural chemists and biochemists. This is exemplified by a host of publications, especially on new pulse sequences, which continue to provide new exciting modifications for recording two-dimensional NMR. Moreover, NMR is no longer confined to structural chemists but has moved firmly into the area of medicine as a powerful nondestructive body scanning technique.

With this background, I felt that there was need for a text which would provide a fairly comprehensive account of the important features of ^{1}H- and ^{13}C-NMR spectroscopy in one book, as well as make available an up-to-date account of recent developments of new pulse sequences, with particular reference to 2D-NMR spectroscopy. Since this book is written for students of chemistry and biochemistry as well as for biology students who have chemistry as a subsidiary, it was decided to avoid a complex mathematical treatment and to present, as far as possible without oversimplification, a qualitative account of ^{1}H- and ^{13}C-NMR spectroscopy as it is today. I hope that the book satisfactorily meets these objectives.

I would like to thank a number of students of my research groups for their help in the drawing of diagrams. They are Mr. Mohammad Iqbal Choudhary, Miss Kishwar Jahan, Mr. Sohail Malik, Miss Anjum Muzaffar, and Miss Khurshid Zaman. I am particularly grateful to Mr. Siraj-ud-din Nizami, Lecturer, Department of Chemistry, for his help in the drawing of figures. I wish to thank my wife, Nargis, for her assistance in the preparation of figures and her enduring patience over the innumerable evenings which went to the writing of this book. Finally I wish to record my indebtedness to the numerous research papers, reviews, books, and monographs which I consulted, all of

which are acknowledged as references or as recommended reading at the end of various chapters.

I dedicate this book to my parents, Jamil-ur-Rahman and Amtul Subhan Begum, who lit a candle in me many many years ago.

Karachi, Pakistan   Prof. Atta-ur-Rahman

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Chapter 1

Chemical Shift in ¹H-NMR Spectroscopy

1.1 INTRODUCTION

The phenomenon of nuclear magnetic resonance is based on the fact that
nuclei of certain elements possess a spin angular momentum and an associated
magnetic moment. When such nuclei are placed in a magnetic field, they can
adopt one of a number of quantized orientations, each orientation corre-
sponding to a particular energy level. The orientation with the lowest energy is
the one in which the nuclear magnetic moment is most closely aligned with the
external magnetic field while the orientation with the highest energy is the one
in which the nuclear magnetic moment is least closely aligned with the
magnetic field. Nuclear magnetic resonance involves transitions between these
energy levels (or changes in the orientation of the nuclei) with respect to the
external magnetic field. These transitions may be induced by the absorption of
radio frequency radiation of the correct frequency, which is measurable on a
recorder in the form of an NMR signal of the nucleus. Pauli first postulated
such magnetic properties of nuclei in 1924[*] but it was not until 1946 that the
first NMR experiments were independently carried out by two groups, Bloch[†]
at Stanford University and Purcell[‡] at Harvard University. These experiments
have ushered in a new era in which nuclear magnetic resonance spectroscopy
has become well established as a powerful tool for structure elucidation, and
more recently has also been increasingly employed to obtain sectional pictures
of human organs.

It is a fundamental fact of physics that a spinning charged body produces a
magnetic moment. Since a nucleus is positively charged, if it then has a spin
angular momentum, P, its spinning will result in the rotation of the positive
charge which may be compared to a current flowing in a circle. This would
produce a magnetic field parallel to the spin axis, and the nucleus would have a

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[*] W. Pauli, *Naturwissenschaften* 12, 741 (1924).

[†] F. Bloch, W.W. Hansen, and M.E. Packard, *Phys. Rev.* 69, 127 (1946).

[‡] E.M. Purcell, H.C. Torrey, and R.V. Pound, *Phys. Rev.* 69, 37 (1946).

magnetic moment, μ. In quantum mechanics, the angular momentum P is given by the relationship

$$P = I\frac{h}{2\pi} \tag{1.1}$$

where I is the spin quantum number and h is Planck's constant. The spin quantum number is quantized and in different nuclei it may have values of 0, $\frac{1}{2}$, 1, $\frac{3}{2}$, etc. Thus if I is zero, the nucleus will not have any angular momentum. Examples of such nuclei are ^{12}C and ^{16}O. This results in a great simplification of the proton nuclear magnetic resonance spectra of organic molecules as no interaction is observed between the protons and ^{12}C or ^{16}O nuclei to which the protons may be attached. The spin quantum number I is related to the atomic number and mass number as follows:

Atomic number	Mass number	Spin quantum number
Even or odd	Odd	$\frac{1}{2}$, $\frac{3}{2}$, $\frac{5}{2}$, etc.
Even	Even	0
Even	Odd	1, 2, 3, etc.

The above relationships emerge from the fact that the protons and neutrons in the nucleus possess spins. Protons will thus form pairs with other protons in the nucleus with opposite spins. Similarly, neutrons will "pair" with other neutrons in the same nucleus but with opposite spins. In nuclei which have even numbers of protons and neutrons, all the spins will be paired and the spin number I will be zero. However if there is an odd number of either protons or neutrons, the spin quantum number I will have a quantized value of $\frac{1}{2}$, 1, $\frac{3}{2}$, etc. If the sum of protons and neutrons is even, I will be zero or a multiple of 1. If the sum is odd, I will be an integral multiple of $\frac{1}{2}$. The nuclei with which the organic chemist is most frequently concerned are ^{1}H and ^{13}C, both of which have a spin quantum number of $\frac{1}{2}$. Other elements which may be of interest are ^{19}F and ^{31}P which also have $I = \frac{1}{2}$ while deuterium, ^{2}H, and ^{14}N have a spin quantum number of 1.

When placed in a uniform magnetic field, the angular momentum of a nucleus is quantized and it will adopt one of $(2I + 1)$ orientations with respect to the external magnetic field. In nuclei such as ^{1}H or ^{13}C where $I = \frac{1}{2}$, there will be $(2 \times \frac{1}{2}) + 1$ orientations, i.e., two orientations. In the lower-energy orientation, the nucleus will have its magnetic moment μ aligned with the magnetic field while in the higher-energy orientation it will be aligned against the magnetic field. In each orientation the nucleus will have a particular potential energy equal to $\mu B_0 \cos\theta$ where B_0 is the strength of the external field while θ is the angle between the nuclear spin axis and the direction of the external field. Nuclei with $I = \frac{1}{2}$ have a symmetrical distribution of charge around the nucleus.

In nuclei such as ^{2}H or ^{14}N which have $I = 1$, there will be $(2 \times 1) + 1$ orientations, i.e., three different orientations, each having its characteristic
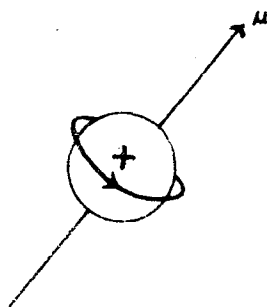
Figure 1.1. The spinning positively charged nucleus produces a magnetic moment μ.

potential energy. Nuclei with $I > \frac{1}{2}$ have unsymmetrical distributions of charge, which result in an electric quadrupole moment, Q.

As mentioned earlier, electromagnetic radiation of the correct frequency can cause transitions between adjacent energy levels. The relationship between the electromagnetic frequency v and the magnetic field strength B_0 is governed by the Larmor equation

$$v = \frac{\gamma B_0}{2\pi} \tag{1.2}$$

where γ is the gyromagnetic ratio, and is a characteristic constant for a particular nucleus (Figure 1.1). This is the basic mathematical equation for NMR.*

Now let us consider a nucleus such as a proton (^{1}H) with a spin number of $\frac{1}{2}$. When placed in a magnetic field, it behaves like a tiny magnet, with the difference that while a magnet can adopt any number of orientations with respect to the external field, the tiny spinning "proton magnet" is allowed only two orientations, the lower-energy orientation being the one in which its north pole is aligned with the south pole of the external field. The energy difference ΔE between the two energy levels is proportional to the external magnetic field. Since the nucleus is spinning on its axis, the external magnetic field causes it to "precess", i.e., instead of the spinning axis remaining stationary, it undergoes a circular motion such as that exhibited by a spinning gyroscopic top before it is about to topple, i.e., the two ends of the spinning axis trace two opposite but circular paths (Figure 1.2). Nuclear magnetic resonance experiments are concerned with the measurement of this precessional motion (Figure 1.3).

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* The equation can be simply derived, and its derivation is reported in numerous standard texts of NMR (see list of recommended books at end of chapter).
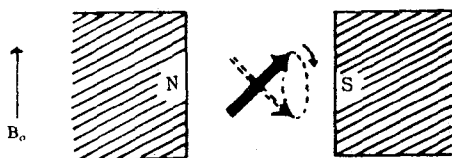
Figure 1.2. Precessional motion of the magnetic dipole when placed between the poles of a magnet.
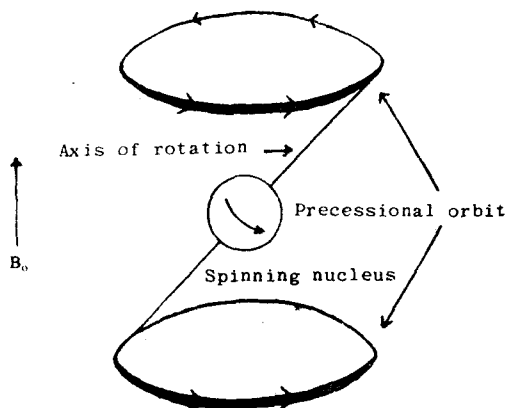
Figure 1.3. Precessional motion of a nucleus in a magnetic field.

In order to cause transitions between the two spin states, a second radio frequency field is applied perpendicular to the original field. When the value of this electromagnetic radiation reaches the precessional frequency of the nucleus, absorption of energy will occur. It is important to note that the frequency of the electromagnetic radiation required to induce transitions from one nuclear spin state to the other is *exactly* equal to the precessional frequency ω_0 of the nucleus. The precessional frequency ω_0 is directly proportional to the applied magnetic field B_0 and also to the gyromagnetic ratio

$$\omega_0 = \gamma B_0 \qquad\qquad (1.3)$$

Thus with increasing values of the applied magnetic field, B_0, there will be increasing differences in energy (ΔE) between the two spin states (Figure 1.4), and since the precessional frequency of the nucleus is proportional to B_0, the nucleus will precess at increasing frequency values. In order to bring it into "resonance," correspondingly higher frequencies of the applied electromagnetic radiation will therefore be necessary. The advantage of observing resonances at higher frequency values of the electromagnetic radiation (which
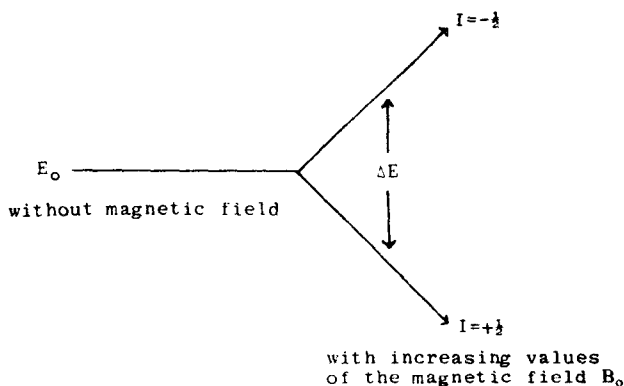
Figure 1.4. Increasing difference in energy levels of the two magnetic states with increasing value of magnetic field B_0.

is generated from a suitable oscillator) is that it results in increased dispersion of signals and a greater sensitivity. One can therefore induce resonances in different protons by keeping a constant value of the applied magnetic field and gradually increasing the oscillator frequency. As the precessional frequencies of the different nuclei are reached, resonance will occur and NMR signals will be observed. Alternatively, and this is more convenient in practice, one can keep the oscillator frequency constant at, say, 60 MHz or 100 MHz, and vary the magnetic field. With increasing values of the magnetic field, the nucleus will precess at correspondingly higher frequencies and when the frequency of precession reaches the value of the oscillator frequency, resonance will occur, i.e., energy will be absorbed by the nucleus at its "chemical shift" and it will be tilted away from the direction of the applied magnetic field, causing a change in the impedance of the oscillator coils which can be measured on a recorder.

As mentioned above, for a nucleus with spin quantum number $I = \frac{1}{2}$, only two energy levels are possible. When I is 1, there will be three energy levels, but only transitions between adjacent energy levels are allowed, i.e., from $m = +1$ to $m = 0$, or from $m = 0$ to $m = -1$; transitions from $m = +1$ to $m = -1$ are not allowed (Figure 1.5).
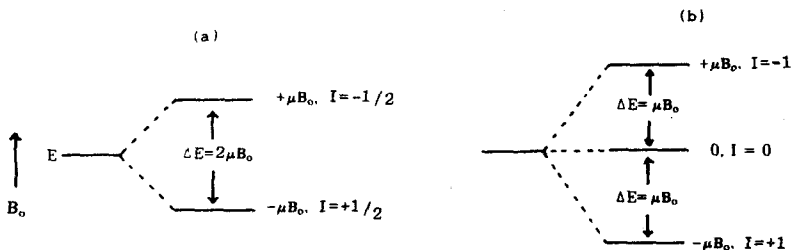
Figure 1.5. Magnetic energy levels for nuclei (a) with spin $\frac{1}{2}$ and (b) with spin 1.

1.2   RELAXATION PROCESSES

The theory of electromagnetic radiation tells us that by absorption of energy, transitions of the nuclei will occur to a higher-energy state while by emission of energy, resulting in downward transitions, the nuclei will relax to the lower-energy state. If the two spin states of a set of protons, for instance, were equally populated, then the total number of protons undergoing transitions from the lower spin state to the upper spin state would be exactly equal to the total number of protons undergoing transitions in the opposite direction, and no absorption or emission of energy would be observed and there would be no NMR signal. Fortunately, the population of the upper- and lower-energy spin states is not the same, there being a Boltzmann distribution of the nuclei with a slight excess in the lower state. In practice what this means for a 100-MHz instrument is that if we have one million nuclei in the lower-energy state, there will be 999,987 nuclei in the upper-energy state, leaving a population excess of 13 nuclei in the lower state. In order to detect this slight excess of nuclei, one has to have a very sensitive detection system. Thus, when a solution of an organic compound is placed between the poles of a magnet and irradiated with a suitable radio frequency, the nuclei simultaneously undergo transitions in two opposing directions. Absorption of radio frequency results in transitions to the higher-energy state while relaxation processes cause transitions from the upper to the lower spin state. Since the probability of upward transitions is slightly higher than that of downward transitions due to the greater population of the ground state, a *net* absorption of energy will occur. With this absorption of energy, the population of nuclei in the ground state will decrease while the population in the higher-energy state will increase till there is no further excess in the population of the ground state, resulting in the weakening of the intensity of the NMR signal, and finally in its disappearance. A "saturation" state is then said to have been reached. In order to reestablish the Boltzmann excess of the ground state, there are a number of mechanisms involving radiationless transitions by which the nuclei in the upper energy state can relax back to the lower spin state. The result is that while the Boltzmann excess of nuclei is somewhat diminished, it is not totally eliminated and an equilibrium state is established at an intermediate value, so that an NMR signal can continue to be obtained.

There are two main types of relaxation processes by which nuclei in upper energy states can relax to lower energy states. These are *spin–lattice relaxation* (or longitudinal relaxation), T_1, and *spin–spin relaxation* (or transverse relaxation), T_2.

1.2.1   Spin–Lattice Relaxation (T_1)

The assembly of molecules constituting gases, liquids, or solids under study are together referred to as the lattice. In gases or liquids, the molecules are undergoing rapid rotational and translational motions, and in those molecules which have magnetic nuclei, these motions will result in corre-

sponding magnetic fields of varying magnitudes which may be considered to be built up of a number of oscillating components. A magnetic nucleus precessing under the influence of an external magnetic field will also be subjected to the fluctuating fields generated by the lattice, and whenever the oscillating component of the lattice field becomes correctly oriented and its frequency becomes exactly equal to the precessional frequency of the magnetic nucleus, exchange of energy from the nucleus in the higher-energy state to the lattice can occur. This energy is transferred to the lattice in the form of translational or rotational energy. The energy of the magnetic nucleus is thus converted to the thermal energy of the molecular system comprising the lattice. Spin–lattice relaxation, T_1, is therefore directly responsible for maintaining the Boltzmann excess of nuclei in the lower-energy state. The more efficient the relaxation process, the smaller will be the value of the relaxation time T_1. Spin-lattice relaxation is dependent not only on the type and rapidity of the molecular motions of the molecule in the lattice but also on the gyromagnetic ratio of the magnetic nucleus. In solids in which the molecular motions are very restricted, T_1 values are very large on account of the inefficiency of the spin–lattice relaxation process. T_1 relaxation times may be used with great advantage in structure elucidation of organic compounds as T_1 values can vary in different compounds, providing a valuable insight into the chemical environment of the nuclei being observed.

1.2.2 Spin–Spin Relaxation (T_2)

The field generated by a precessing nucleus will contain a static component, which will be aligned in the direction of the applied field, and a rotating component, which will be moving at the precessional frequency in a plane perpendicular to the applied field (Figure 1.6).

static component

rotating component

B_o
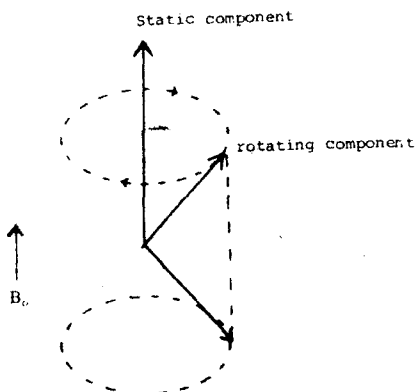
Figure 1.6. Static and rotating components of the field generated by a precessing nucleus. The static component is aligned with the applied field while the rotating component rotates at the precessional frequency in a plane perpendicular to the applied field.

If another nucleus is located near the first nucleus, it will experience the effect of the static component as a variation in the main field. A "spread" in the value of the main field will, therefore, be caused since the total field experienced by a neighboring nucleus will be the sum of the main field and the static components generated by the local field. This will result in a broadening of the resonance signals.

The rotating component of the magnetic vector, which is in a plane at right angles to the external field, is correctly set up to induce a transition in a neighboring nucleus provided that the neighboring nucleus is precessing at the same frequency. This would result in a mutual exchange of spin energies between the two nuclei and it would also cause a broadening of the resonance signals.

1.3 CHEMICAL SHIFT

The frequency at which a given nucleus comes to resonance is dependent not just on the magnitude of the applied field and the gyromagnetic ratio of the nucleus, but also on a third factor—the molecular environment of the nucleus. Thus for a given nucleus, say protons, it is observed that the atoms in different chemical environments give NMR signals at different characteristic values of the applied field. This means that when the NMR spectrum of, for example, ethyl alcohol is recorded, the signals for CH_3, CH_2, and OH protons will not appear together as one signal but as three distinctly different groups of peaks. One important reason for this is the electronic clouds circulating around the nucleus which "shield" or protect the nucleus, to an extent, from the influence of the applied magnetic field. The circulation of these electrons results in the generation of a small but finite induced magnetic field which is oriented so as to oppose the external field (Figure 1.7). Thus the nucleus experiences a magnetic field which is slightly less than the applied field. Equation (1.2) can therefore be modified as

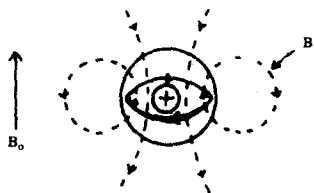$$v = \frac{\gamma B_0 (1 - \sigma)}{2\pi} \tag{1.4}$$

Figure 1.7. The electron circulation around the nucleus produces a resulting magnetic field B'.

where σ is a field-independent shielding factor. If an electron-attracting group is attached to a proton, it will tend to pull electrons away from it and decrease the shielding effect of the electronic clouds around it, thus allowing the proton to come to resonance at a lower value of the applied magnetic field. It therefore follows that the greater the electronegativity of the attached atom the greater will be its "pull" and resonance will occur at a correspondingly lower value of the applied magnetic field. Thus the shielding of methyl group protons decreases in the order: $SiCH_3$, CCH_3, NCH_3, OCH_3. As a result of oxygen being the most electronegative atom in the group, the $—OCH_3$ protons give a signal at a lower value of the applied field than, say, $—CCH_3$ protons; on the other hand, silicon is the least electronegative of the group and the signal of the methyl group attached to it therefore appears at the highest value of the applied magnetic field. Tetramethylsilane [TMS, $(CH_3)_4Si$] affords a sharp signal for the methyl protons at a high value of the magnetic field and is, therefore, conveniently used as an internal standard when recording NMR spectra, and the "chemical shifts" or resonance positions of various protons in a molecule are reported in the literature as distances from the TMS signal. The NMR spectrum is normally calibrated in cycles per second (cps or Hz, frequency units). However, it follows from Equation (1.4) that the frequency at which a resonance signal is observed for a particular proton is dependent on the applied magnetic field, B_0. Thus if the resonance of the methyl protons of an acetyl group appears at 120 Hz on a 60-MHz NMR spectrometer, it would appear at 200 Hz on a 100-MHz NMR spectrometer. Since there are several types of NMR spectrometers with different magnetic field strengths, it is necessary that the position of a resonance signal be given in units which are independent of the field of the magnet. A parameter δ is used for this purpose which is defined as

$$\delta = \frac{v_s - v_{TMS}}{Z} \tag{1.5}$$

where v_s is the resonance frequency, in Hz, of the protons, v_{TMS} is the resonance frequency, in cycles per second, of TMS, and Z is the operating frequency of the instrument in megacycles per second or 10^6 cycles per second. As the numerator in the above equation is in cycles per second while the denominator is in megacycles per second, the units of δ are *parts per million* or ppm. An alternative parameter which was formerly employed is τ (tau], which is equal to $10 - \delta$. Thus, on a 200-MHz instrument the chemical shift will be expressed as

$$\delta = \frac{\text{Distance (in cycles per second) from TMS}}{200} \text{ ppm} \tag{1.6}$$

Protons attached to differently hybridized carbon atoms or elements of different electronegativity, or having different environments exhibit different