NMR in Chemistry

A Multinuclear Introduction

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To Louie, Again

Preface

In the last few years the horizons of nuclear magnetic resonance spectroscopy have all but been pushed out of sight as new and ever more sophisticated instruments are built and reports of new applications flood the literature.

For chemists who are active developers of the science, in whatever aspect, it is difficult merely to read all of the new publications. For chemists who use the method, among other methods, to solve their chemical problems it is well-nigh impossible to keep up to date.

This book is an attempt to introduce NMR to a wide audience of users, in such a cohesive way that all of its potential can be tapped and exploited: it is not a book about the physics and mathematics of NMR, but concerns the interpretation of NMR spectra by those who do not consider themselves particularly mathematical by inclination: the minimum prerequisites are some knowledge of general spectroscopic principles and a familiarity with the chemical properties of common functional classes.

Clear non-mathematical pictures of magnetic resonance must inevitably be distortions of more fundamental laws, but a worthwhile sacrifice is made in forming a bridge between physics and chemical application. The book is obviously not monographic in style or depth, but it will serve its intent if, having read it, the reader is thereby equipped and encouraged to tackle the necessarily more rigorous specialist works.

The emphasis is multinuclear, with a deliberate attempt being made to demystify the NMR studies of the less common NMR elements. Likewise, Fourier transforms and superconducting magnets are introduced very early, and are not given any special status as 'recent developments': continuous wave spectrometers are not referred to as 'conventional', and the use of the terms upfield and downfield is minimised for the same pedagogic reasons (being replaced by lower frequency and higher frequency respectively).

The problem of order of presentation, of finding a beginning, a middle and an end, is not unique to the study of NMR: the chapter sequence adopted should not therefore be taken as a recommended learning programme, but merely as an approximate indicator of the way in which most teachers introduce the subject, building upon the familiar to construct a framework of advanced understanding.

Chapter 1 is set at the most elementary conceptual level, and is an obligatory launching point for the multinuclear approach.

Chapter 4 (on proton NMR) and chapter 5 (on carbon-13 NMR) form the mainstay of the subject; some teachers begin with proton while others begin with carbon-13. Surprisingly little theory is needed to interpret such spectra: for this reason, while chapter 2 is fairly full in explanation, most students will tend to attack this chapter in several short sorties, as the need to know becomes more expansive. The same is true of the instrument details given in chapter 3 which, while fairly detailed and self-contained, can profitably be absorbed in separate parts at different times.

The set of chapters 2, 3, 4 and 5 completes a study of NMR to intermediate level.

Chapters 6 and 7 interrelate with each other at the next most advanced conceptual level: here are introduced the theories and practice made accessible only by microprocessor controlled instrumentation. An argument can be made for introducing some of the chapter 6 theory at an earlier stage, and of course this is not precluded: but there is a strong case to be adduced for consolidating the basic applications in the early chapters before tackling the three-dimensional complexities of the rotating frames of reference, with all the perceptual traps involved.

The study of dynamic molecular processes by NMR is treated separately in chapter 8. Some of the simpler ideas of dynamic NMR are, however, interspersed in the earlier chapters, since to gather them all in a late chapter would be artificial and distorting.

Chapters 9-13 are all self-sufficient to a degree, and are the barest indications, by example, of the kind of information contained in the NMR spectra of a selection of other nuclei. Given the multinuclear treatment of the earlier chapters, there is no need here for extensive detail.

Chapter 14 very much embodies two personal views.

Many details of physics are easily forgotten (or may not have been learnt) and having them gathered together serves as a useful aide-memoire for non-physicists. We also often learn nothing about the people who helped to assemble the enormous construct of science, and the sparse biographical notes given here on a few of the famous names in NMR may whet an appetite or two.

Although informative data are supplied as necessary throughout the book, chapter 15 contains a large amount of reference data, which can be accessed for systematic or detailed needs. Extensive tables of chemical shifts, coupling constants and relaxation times are gathered here, with details of common NMR solvents.

There are many problem examples throughout the book. It has been established that one major reason for lack of success in problem solving is an inability to collect and identify only that information which is necessary for solution. In an endeavour to side-step this difficulty, most of the problem examples are preceded by worked examples, so that confidence will rise through knowing which method to apply. Most problems are also seen within the context of the learning objectives under discussion (although other problem examples test more comprehensive understanding).

While it is demonstrably possible to interpret many NMR spectra without intimate study of theory or of spectrometer operation, hopefully the presentation of the subject matter in this book will stimulate an intellectual curiosity, such that a spectrum can be interpreted in the morning, and explained in the afternoon. If the book fulfils its purpose, the user will go back the following morning for more. There is always another experiment to be done.

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The photograph of Felix Bloch shown in the Frontispiece was kindly supplied by Stanford University, California: that of E. M. Purcell was furnished by E. M. Purcell himself.

Bruker Spectrospin published the material in figures 5.3, 5.13, 5.14, 6.12, 7.4, 7.14, 7.16 and 13.2.

Japan Electronic Optical Laboratories, JEOL, supplied the photographs of the spectrometers shown at the head of chapter 3, and the spectra in figures 1.13, 5.1(b), 5.2 (lower), 5.4, 6.14, head of chapter 7 (also used on the book cover) and 11.1.

Oxford Instruments supplied the photograph of the superconducting magnet core and are copyright holders of the diagram showing the cryostat system in figure 3.1.

Oxford Research Systems supplied the photographs of the brain images in figure 7.21 and of the whole-body NMR magnet shown at the head of chapter 10.

Perkin-Elmer published the spectra used in figures 4.18, 4.24, 8.2, 9.2 and at the head of chapter 6.

The figures at the head of chapters 8 and 12 were used with the permission, respectively, of the Royal Society of Chemistry and the American Chemical Society.

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CONTENTS

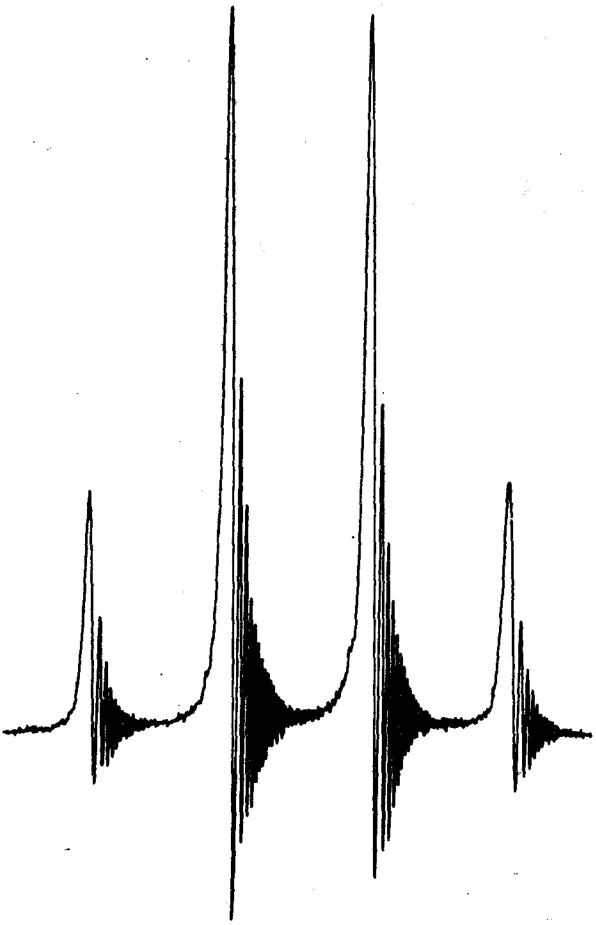
Proton Data

Carbon-13 Data

Other Data

1

Introduction to Nuclear Magnetic Resonance — NMR



NMR signal from the aldehyde proton in acetaldehyde (CH_3CHO)

This chapter presents an overview of the NMR experiment and the chemical information which it can provide; it will not be essential reading for those who have previously met the basics of the technique, but for others it will supply a perspective which would be lacking if the beginnings were treated too rigorously.

1.1 THE PRINCIPLES OF NMR SPECTROSCOPY

The atomic nuclei of many elements are magnetic because they are charged and because they behave as if they were spinning. We can investigate this magnetic property by studying the way in which these nuclei interact with an externally applied magnetic field, $\mathbf{B}_0$. Typical magnetic nuclei are those of hydrogen (^{1}H), carbon (the ^{13}C isotope only), nitrogen (^{14}N and ^{15}N), oxygen (^{17}O only), fluorine (^{19}F), and phosphorus (^{31}P).

The simplest case is exemplified by the nucleus of hydrogen (the proton) and also by the nucleus of carbon-13 (^{13}C). These nuclei behave like bar magnets in an applied field, and in the manner of compass needles tend to align themselves along the same direction as the field. Unlike bar magnets and compass needles however, which always come to rest *aligned with* the field, magnetic nuclei such as ^{1}H and ^{13}C have quantum restrictions which result in two different orientations being allowed – either *aligned with* the field or *opposed to* the field. These two orientations clearly have different energies, the aligned position being of lower energy than the opposed.

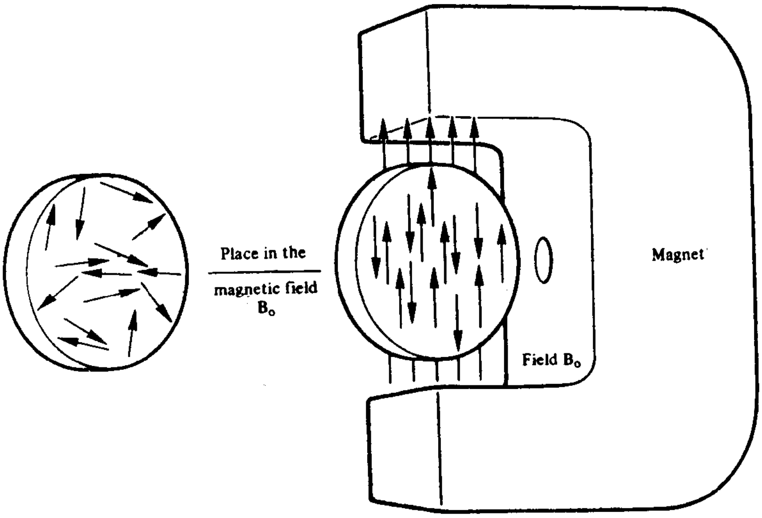


Figure 1.1 In the absence of the field $\mathbf{B}_0$, the magnetic nuclei in the sample are oriented randomly. In the magnetic field, they must adopt either the aligned orientation (of lower energy) or the opposed orientation (of higher energy)

> Whenever an external magnetic field is present, some of the nuclei in the sample become aligned (adopt the lower energy configuration) while others become opposed (adopt the higher energy configuration).

The situation is summarised in figure 1.1.

The energy difference (ΔE) between the two nuclear configurations corresponds to a particular, precise electromagnetic frequency since, by the Bohr relationship, $\Delta E = h\nu$. These energy relationships are illustrated in figure 1.2. To take a specific example, if the external magnetic field strength is 2.35 tesla (T), then the energy gap (ΔE) for the hydrogen nucleus is approximately 6.6×10^{-26} J, and the corresponding frequency (ν) is 100 MHz (lying in the radiofrequency (RF) band of the electromagnetic spectrum). For ^{13}C nuclei in the same magnetic field, the energy gap (ΔE) is 1.7×10^{-26} J, and the frequency $\nu = 25$ MHz.

If a sample containing ^{1}H nuclei is placed in such a magnetic field, and the sample then irradiated with the

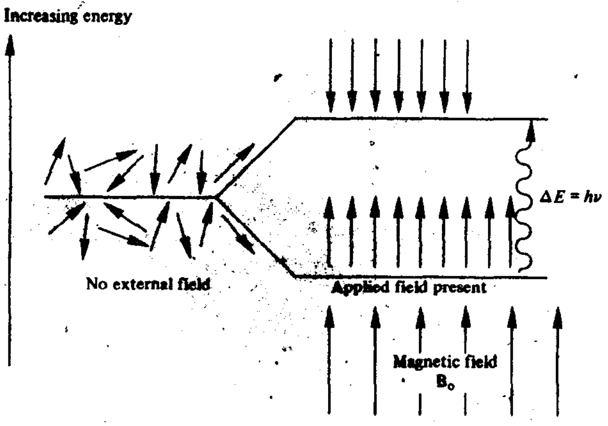


Figure 1.2 In the absence of B_0 the magnetic nuclei all have the same energy. When B_0 is applied, the aligned and opposed orientations correspond to different energies, the energy difference, ΔE, having the dimension $h\nu$

correct radiofrequency, we find that the nuclei interact with the radiofrequency.

Some of the lower-energy nuclei *absorb* radiation and move up to the higher-energy state: that is, they undergo a transition from being aligned with the field to become opposed to the field. At the same time, some of the higher-energy nuclei are stimulated to *emit* energy, and they therefore change their opposed orientation and become aligned with the field.

These transitions will only arise when the magnetic energy gap between the nuclear energy levels is matched exactly with the incoming radiofrequency, that is, when they are 'in resonance', and $\Delta E = h\nu$. The process can be pictured as in figure 1.3.

In Table 1.1 are listed a few important nuclei, with the corresponding RF energy necessary to bring about the nuclear magnetic resonance condition and to stimulate transitions among the available magnetic energy levels. (For more comprehensive details see the Appendix at the back of the book.)

The study of nuclear magnetic resonance (NMR) is concerned with these energy levels, and with the frequency of radiation absorbed during resonance.

1.2 THE NMR SPECTROMETER

A primitive lay-out for an NMR instrument is shown in figure 1.4, with a magnetic field strength of 2.35 T. Assuming that the sample contains carbon and hydrogen, then the ^{13}C nuclei will be partitioned between their two allowed energy levels (1.7×10^{-26} J apart); likewise the protons will be partitioned between their two allowed energy levels (6.6×10^{-26} J apart).

With the RF transmitter/receiver tuned to 25 MHz, the ^{13}C nuclei will undergo upward and downward transitions between the levels and this resonance condition will be detected by observing the absorption of radiofrequency power.

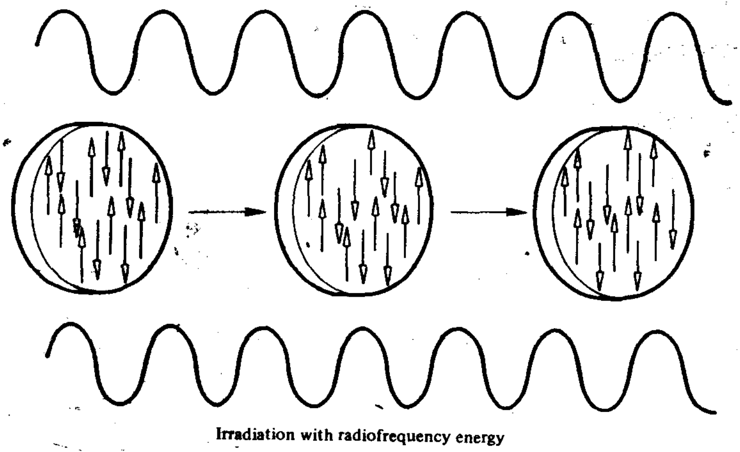


Figure 1.3 When the nuclei (in the magnetic field) are irradiated with radiofrequency energy of the appropriate frequency, some of them undergo transitions from the aligned to the opposed orientations and vice versa

Table 1.1 Common magnetic nuclei. The values shown for ΔE (in joules) and for ν (in MHz, 10^6 s^{-1}) are for nuclei in a magnetic field of 2.35 T

Nucleus	Natural abundance (%)	For B_0 = 2.35 T	
		ΔE/J	ν/MHz
^1H	99.98	6.6×10^{-26}	100
^{13}C	1.1	1.7×10^{-26}	25
^{19}F	100	6.2×10^{-26}	94
^{31}P	100	2.7×10^{-26}	40.5
^{14}N	99.63	0.5×10^{-26}	7
^{15}N	0.37	0.6×10^{-26}	10
^{17}O	0.037	0.9×10^{-26}	13.5

Tuned to 100 MHz, the instrument will again record the absorption of RF power, this time because the protons are in resonance and undergoing transitions. The spectrometer will detect ^{19}F at 94 MHz and ^{31}P at 40.5 MHz, and so on.

By convention, the static magnetic field of the instrument is labelled $\mathbf{B}_0$, and the RF electromagnetic field is labelled $\mathbf{B}_1$.

1.3 CHEMICAL SHIFTS

Not all protons resonate at exactly 100 MHz in this instrument. Protons attached to carbon atoms for example are surrounded by different electron densities compared with those attached to oxygen or nitrogen atoms; this affects their magnetic susceptibilities.

Depending on their chemical environment the precise resonance frequency will be shifted from 100 MHz by a few parts per million; we name this phenomenon *chemical shift*, and it is the most important reason for the development of NMR as a routine and powerful analytical technique in chemistry.

For a simple organic molecule like *tert*-butyl alcohol (see figure 1.5) there are protons in two different chemical environments – nine of them are in methyl groups and one is attached to oxygen. The nine methyl protons come to resonance about 130 Hz higher in frequency than 100 MHz (that is, about 1.3 parts per million to higher frequency) and the OH proton absorbs at about 400 Hz (about 4 ppm) higher frequency than 100 MHz.

Figure 1.5 is the proton magnetic resonance spectrum (^{1}H NMR spectrum) for *tert*-butyl alcohol; it is essentially a plot of RF absorption against frequency.

Note that the integrated area of the larger peak (for the methyl protons) is nine times that of the smaller (OH) signal; in other words

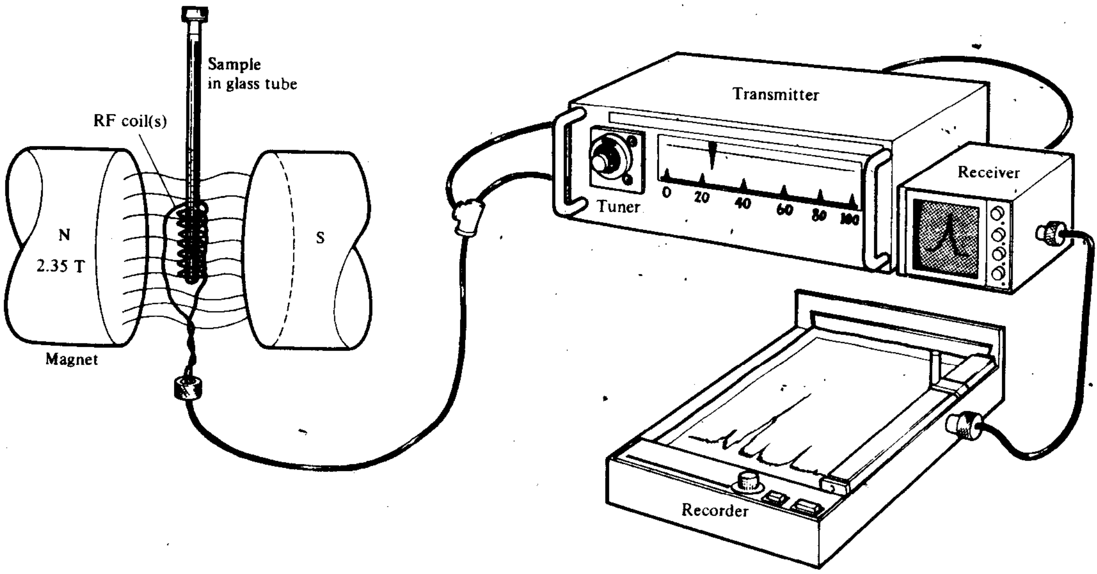


Figure 1.4 Nuclear magnetic resonance spectrometer. The sample is placed in the magnetic field; when the radiofrequency transmitter is tuned to the resonance frequency, a signal arises in the receiver

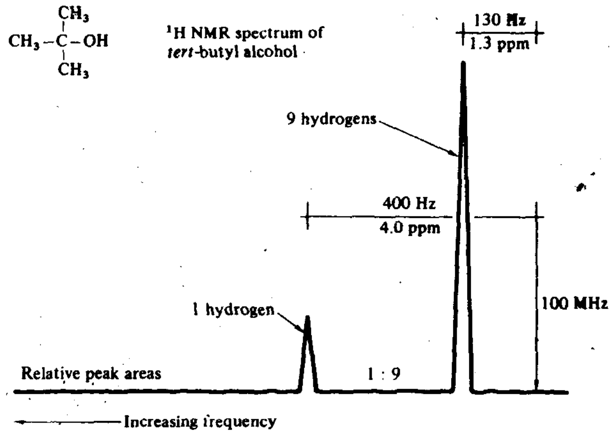


Figure 1.5 Chemical shift. In the proton magnetic resonance spectrum (^1H NMR spectrum) of *tert*-butyl alcohol, the nine methyl protons give a signal 1.3 ppm higher in frequency than 100 MHz. The hydroxyl proton signal is about 4.0 ppm higher than 100 MHz. The field strength for this 100 MHz proton NMR spectrum is 2.35 T

Signal intensity is proportional to the number of protons present in each of the chemical environments within the molecule.

Figure 1.6 is the carbon-13 NMR spectrum for *tert*-butyl alcohol. Again, since there are only two different kinds of carbon atom in the molecule (the three CH_3 carbons and the C–OH carbon) each comes to resonance, not at 25 MHz, but chemically shifted so that the CH_3 carbons give a signal about 750 Hz higher in frequency, and the C–OH carbon signal appears around 1750 Hz higher in frequency. Note again that the signals are of different intensity; for reasons that we shall meet later, it is not as easy in ^{13}C NMR to treat these intensities quantitatively.

The carbon-12 isotopes in the sample of *tert*-butyl alcohol make no contribution to this spectrum since they are non-magnetic; the fact that only 1.1 per cent of the carbon atoms are ^{13}C (see table 1.1) makes the carbon-13 NMR spectrum more difficult to record than the proton spectrum. A glance at table 1.1 shows that

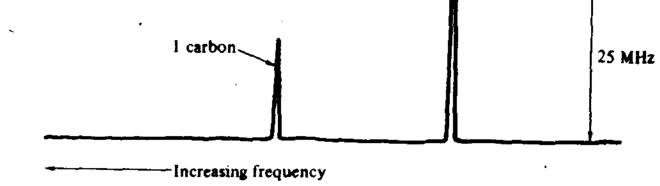


Figure 1.6 Chemical shift. In the routine carbon-13 NMR spectrum of *tert*-butyl alcohol, the three methyl carbons give a signal 30 ppm higher in frequency than 25 MHz. The C–O signal is 70 ppm higher than 25 MHz. The field strength for this 25 MHz ^{13}C NMR spectrum is 2.35 T

^{15}N spectra are even more difficult to obtain, with a natural abundance of only 0.37 per cent, and that ^{17}O is exceedingly rare; ^{19}F and ^{31}P NMR spectra in contrast are relatively easily recorded.

Worked Example 1.1

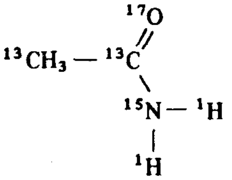
For the molecule of methyl acetate (methyl ethanoate) CH_3COOCH_3, (a) state how many different chemical shift environments exist for the hydrogen, carbon and oxygen nuclei, (b) note from table 1.1 the natural abundance of each principal magnetic isotope and (c) state the frequency at which each NMR spectrum would be recorded in a spectrometer with a 2.35 T magnet.

Answer 1.1

There are two chemically distinctive hydrogen environments: the natural abundance of the most important hydrogen isotope (^{1}H) is 99.98 per cent, and the spectrum would be recorded at 100 MHz and 2.35 T. There are three carbon environments: carbon-13 abundance is only 1.1 per cent, and the required frequency (for 2.35 T) is 25 MHz. (Carbon-12 is non-magnetic and does not exhibit NMR.) There are also two oxygen environments; oxygen-17 NMR at natural abundance is handicapped by the very low natural abundance (0.037 per cent) but oxygen-17 NMR spectra are acquired at 13.5 MHz in a 2.35 T instrument. (Oxygen-16 is non-magnetic and does not exhibit NMR.)

Problem Example 1.1

Formula 1.1 is an imaginary 'isotope isomer' or *isotopomer* of acetamide. In a 2.35 T magnet, state the frequencies at which the NMR spectrum of each element would be recorded. For each spectrum, state how many signals (that is, chemical shift positions) would be seen. (Detail: because of restricted rotation around the C–N bond, consider the protons on nitrogen to be in different environments, one being nearer to oxygen than the other.)



(1.1)

1.4 FIELD STRENGTH AND FREQUENCY

Figure 1.2 and table 1.1 show that magnetic nuclei can occupy various magnetic sublevels, and that the frequency necessary to cause nuclear transitions is different for each element or isotope. This resonance frequency is found to vary in direct proportion to the applied field (for *all* magnetic nuclei); thus the larger the magnetic field the higher the frequency necessary to achieve resonance. That is

$$\nu \propto \mathbf{B}_0$$

For the proton we can represent this fact as in figure 1.7.

Although the arithmetic of these field-frequency relationships is simple, a few examples will help to emphasise their crucial importance.

Worked Example 1.2

What is the frequency needed to induce transitions between the ^{13}C nuclear energy levels, when the field strength is (a) 4.7 T and (b) 1.88 T?

Answer 1.2

Since from table 1.1 the ^{13}C NMR frequency is 25 MHz at 2.35 T, then by simple proportion it is 50 MHz at 4.7 T and 20 MHz at 1.88 T.

Problem Example 1.2

What field strength is necessary in an instrument designed for studying proton NMR at (a) 60 MHz, (b) 200 MHz, (c) 600 MHz?

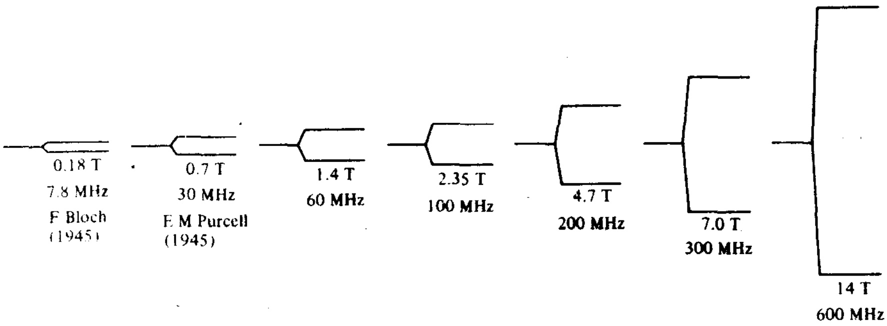


Figure 1.7 Field-field relationship. The energy gaps ($\Delta E = h\nu$) are shown for protons in different field strengths. For other elements the same simple proportion holds; table 1.1 lists frequencies for a field strength of 2.35 T