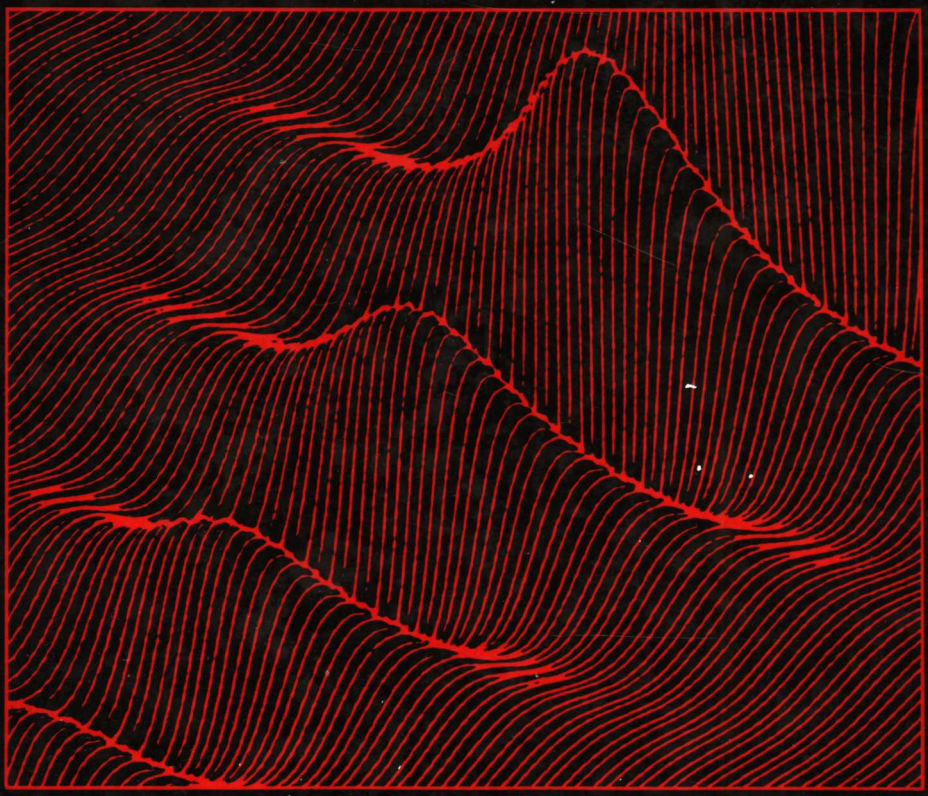
A HANDBOOK OF

NUCLEAR MAGNETIC RESONANCE



RAY FREEMAN

A Handbook of

NUCLEAR MAGNETIC RESONANCE

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Preface

Those of us who practise the art of high resolution NMR spectroscopy usually have a background in chemistry or biochemistry, yet the technique itself has a strong physical bias and its description is steeped in the vocabulary of quantum mechanics. Characteristically, the chemist's reaction has been to use NMR in a largely empirical fashion, interpreting the spectra according to familiar chemical principles, and avoiding too close a brush with the heavy physics. This approach has been remarkably successful and nowadays no self-respecting chemistry department can operate without an NMR spectrometer. However, in recent years a bewildering array of specialized NMR techniques has been introduced, each presenting an interesting problem in spin physics, and each requiring its own theoretical treatment. This leaves the hard-working spectroscopist struggling a little to keep pace with new ideas like multiple-quantum coherence and two-dimensional spectroscopy. Worse still, the new experiments come with their own protective armour of specialist terminology, discouraging to the beginner.

This book starts from the premise that it is possible to explain some of these new concepts (and some older ones) in a pictorial and largely non-mathematical manner, in the belief that this is the approach favoured by most practitioners of NMR. (After all, they have chemistry, biochemistry or even medicine as their prime concern, not the spin Hamiltonian.) It is not a treatise for the complete novice in the field – there are no entries under chemical shift or spin–spin coupling – but it is written for those who already have a grounding in practical NMR spectroscopy and who would like to understand it better. In order to focus on the difficult bits instead of embedding them in a bland matrix like a plum pudding, I have adopted an unusual format. There are about sixty separate entries arranged alphabetically, rather like a very specialized encyclopaedia. These sections are self-contained, but they are cross-referenced to related sections (indicated by an asterisk (*)) and there is also an index to help the reader to find topics that are nested within one of the main entries. This

form owes a considerable debt to Peter Atkins' book *Quanta* (1) which I have always admired. It has the advantage that the busy spectroscopist can go directly to the subject in question without having to search through a lot of extraneous material. Indeed, the handbook will have achieved its aim if it sits on the spectrometer console next to the coffee, rather than on the library shelf. There are even a few cartoons to help while away the time during long signal accumulations.

The late Andy Warhol has taught us that in the future everyone will be famous for 15 minutes. Failing that, everyone can aspire to inventing a pulse sequence and bestowing on it a suitably outrageous acronym. My attempts to compile a catalogue of pulse sequences and their mnemonics proved to be a disaster and had to be abandoned. The entries were too numerous and perhaps too ephemeral. In the final version of the book, the use of acronyms has been kept to an absolute minimum; they are employed where a full description of the experiment would be cumbersome and repetitive.

In a certain sense, this is a specialist glossary or lexicon, one definition of which is a 'vocabulary characteristic of a particular group of people'. NMR spectroscopists certainly constitute such a group, constantly coining new terminology (not to say jargon) and protecting the exclusiveness of their club. Without wishing to perpetuate any of this, I have nevertheless tried to retain the most commonly used form of words, for example *solvent suppression* and *saturation transfer*, although these are really just codes for more complex ideas. The real danger with jargon lies in its very *familiarity*; this can lull us into a false sense of security about our understanding of the terms.

The scope of this book had to be restricted, and I have excluded solid-state NMR, nuclear quadrupole resonance, magnetic resonance imaging and most of the experiments performed by physicists – they have their own club anyway. If this leaves an incongruous collection of topics, this may well be unavoidable in anything remotely resembling a dictionary. This is a book for dipping into when there is nothing more exciting to do on the spectrometer. The desire to keep each entry reasonably self-contained has led to repetition of certain ideas; the alternative was a rather tedious cross-referencing scheme that made the sections hard to read. Controversy has been positively encouraged, hence the space devoted to subjects like *maximum entropy* and *zero filling* which are guaranteed to arouse the passions of most NMR spectroscopists with their hint of witchcraft and something-for-nothing.

For a work largely concerned with *explanations* of NMR phenomena, it seemed reasonable to adopt the viewpoint taken in Professor Abragam's excellent book (2) and refrain from quoting the literature simply to give credit for a particular piece of work. The references are intended more as a guide to further reading; many are to general articles and reviews. An exception had to be made when it came to acknowledging the source of spectra used as examples. Unfortunately, since I took the path of least resistance and used the spectra closest to hand, there is a discernible narcissistic tendency in these references. For both these reasons it seemed wiser not to compile a name index.

Where does the reader start in a book of this kind? Probably not with the index, nor with the list of contents, but more likely with one of the 'cartoons'. Actually, these are not mere cartoons; they are intended to highlight some of the anecdotes used in the text to illustrate NMR concepts. The drawings

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themselves are the work of a young Italian art student, Valeria Petrone, who is also a close family friend. They have given me a lot of pleasure, and I am most grateful to Valeria for her excellent work. Some connoisseurs may well want the book for the illustrations rather than the undoubtedly limited appeal of the magnetic resonance ideas.

In the early years of this battle with words and word processors I was greatly helped by the drive and enthusiasm of my co-author, Gareth Morris, but he was unfortunately forced to withdraw through ill-health. Several colleagues were kind enough to read the final manuscript and made many valuable comments – Geoffrey Bodenhausen, James Keeler, Peter Bloch, Simon Davies, Jan Friedrich, Sally Davenport and Patrick Cook – they have saved me much embarrassment and I am greatly in their debt. Many of the spectra have been taken from the work of these and other Oxford students and I am grateful for their permission to use this material. My colleague Peter Hore was kind enough to perform several computer simulations specifically for illustrations in this book. Finally, I would also like to thank Bernhard Blümich, Andrew Derome and Tom Frenkiel for providing original spectra.

Magdalen College, Oxford. September 1986

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Contents

Adiabatic Fast Passage

In most cases of interest to the NMR spectroscopist the interaction of nuclear magnetization with a radiofrequency field can be described in terms of the steady-state solutions of the Bloch equations for continuous-wave spectrometers or of the transient impulse response for Fourier transform machines. There is, however, another mode of excitation known as *adiabatic fast passage*. In this mode, the radiofrequency is applied continuously and its intensity is increased well above the normal level for continuous-wave NMR and it is swept through resonance rapidly compared with the slow-passage condition. Two inequalities must be satisfied.

$$\gamma B_1 \gg \frac{1}{B_1}\frac{dB_0}{dt} \gg T_1^{-1}, T_2^{-1} \qquad [1]$$

We shall see below that the linewidth of the NMR response is of the order of B_1, so the expression in the centre is the inverse of the time taken to sweep through the NMR response. Consequently the left-hand inequality requires that the sweep rate be slow with respect to γB_1; this is called the *adiabatic condition*. The right-hand inequality requires the sweep rate to be fast in comparison with the rates of relaxation T_1^{-1} and T_2^{-1}, so that the nuclear magnetization does not decay during passage through resonance.

Consider the motion of the nuclear magnetization vector M in a reference frame rotating about the Z axis in synchronism with the radiofrequency field, such that B_1 is a static field along the X axis, and the spins experience an effective field B_{eff} given by

$$\begin{aligned} B_{eff}^2 &= B_1^2 + \Delta B^2 \\ \tan\theta &= \Delta B/B_1, \end{aligned} \qquad [2]$$

where θ is the inclination of B_{eff} with respect to the X axis in the X–Z plane. During an adiabatic fast passage, the magnetization vector M follows the

effective field B_{eff} exactly. It starts aligned along the +Z axis (Fig. 1) and follows a semicircular path in the X–Z plane, ending up aligned along the −Z axis. The maximum induced signal is proportional to M_0 and occurs at the exact resonance condition, but the vector is aligned along the X axis rather than along the Y axis, so the receiver must be adjusted as if it were to detect the dispersion-mode component. Nevertheless, the general form of the signal resembles the well-known absorption-mode lineshape, passing through a maximum at resonance and falling asymptotically to zero far from resonance. The linewidth is, however, very much greater than that in normal high-resolution work; the signal reaches half its maximum height at $\Delta B = \pm 3^{1/2} B_1$, where $\theta = \pm 60°$. Since B_1 must be quite strong in order to satisfy the adiabatic condition, the technique is not suitable for high-resolution work.

There is a second unusual property of the adiabatic fast passage signal. Provided that the inequalities [1] are satisfied, the signal does not exhibit saturation effects as B_1 is increased, it remains always proportional to M_0. For the early field-sweep spectrometers this was a very important asset, making it possible to search for an unknown resonance that might have a very long spin–lattice relaxation* time, for example silicon-29.

Failure to sweep sufficiently fast in comparison with the relaxation rates causes some loss of magnetization due to spin–spin and spin–lattice relaxation. Infringement of the adiabatic condition allows the vector M to lag behind the effective field B_{eff} and to begin a forced precession around B_{eff}, which leads to

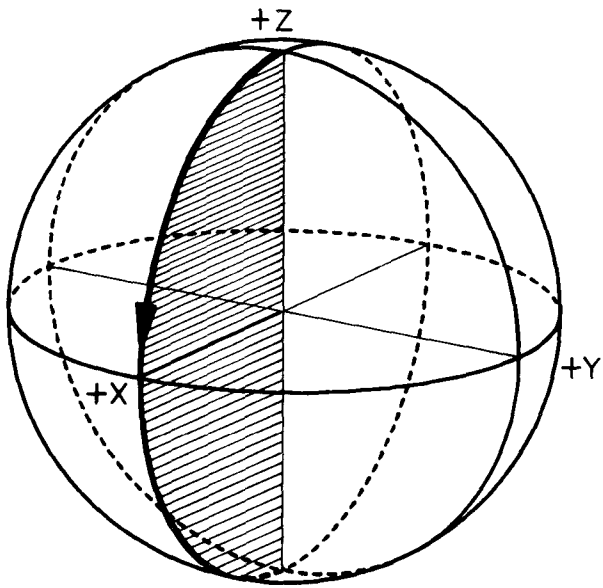

Fig. 1. Trajectory followed by the effective field B_{eff} during an adiabatic fast passage through resonance. Far below resonance B_{eff} is aligned along the +Z axis and it moves in the (shaded) Z–X plane, passing through the +X axis at exact resonance, reaching the −Z axis far above resonance. The magnetization vector remains always parallel to B_{eff} if the adiabatic condition is satisfied.

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'wiggles' on the trailing edge of the observed response. This approaches the regime used in a technique (1) known as *rapid-scan correlation spectroscopy* (not to be confused with chemical shift correlation*). This is an alternative to pulse-excited Fourier transform spectroscopy, where the high-resolution spectrum is scanned rapidly with a sawtooth sweep. The transient 'wiggles' on the trailing edge of the resonances interfere with each other and produce complicated beat frequencies, and the linewidths are much broader than in slow-passage spectra. However, the broadening and beat patterns can be removed by cross-correlation with the lineshape and wiggle pattern from an isolated single line. After this data processing stage, the original high-resolution spectrum can be recovered. Two practical advantages are claimed for rapid-scan correlation spectroscopy. First, it achieves a uniform excitation of the nuclear spins over a wide spectral width with a relatively low-intensity B_1 field. (This is a more efficient use of radiofrequency power than in a Fourier transform spectrometer.) Second, it circumvents the problem of very intense solvent peaks, since it can be set up so that the sweep ramp does not pass through the solvent resonance. (*See* Solvent suppression*.) The sensitivity of correlation spectroscopy is considerably higher than that of continuous-wave slow passage methods and approaches that of Fourier transform spectroscopy. However, time must be allowed between consecutive sweeps for transverse magnetization to decay essentially completely, otherwise complicated steady-state effects* would ensue.

Adiabatic passage through resonance produces a population inversion (M aligned along the $-Z$ axis). If a return sweep is undertaken before any appreciable relaxation has occurred, the process is reversed and a normal Boltzmann population is restored. Alternatively, some delay may be introduced to allow spin–lattice relaxation and this can be made the basis for a method for measuring the relaxation time (2) by varying the time for which the spin populations are inverted between two consecutive adiabatic fast passages.

An adiabatic fast passage which is interrupted at exact resonance provides a simple method for aligning M along the radiofrequency field direction (X axis); this is the first step in a spin-locking* experiment, thus avoiding the necessity for a 90° radiofrequency phase shift. Recently, there have been some new techniques for wideband spin inversion related to adiabatic fast passage (3). Another innovation has been to perform adiabatic fast passage with a nonlinear frequency sweep (4).

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Cross-references

Continuous-wave spectroscopy
Fourier transformation
Rotating frame
Shift correlation
Solvent suppression
Spin–lattice relaxation
Spin-locking
Steady-state effects
Vector model

Alignment of Molecules

High resolution NMR spectra are normally obtained from mobile liquids in which molecules tumble rapidly and isotropically: molecular motion is sufficiently fast and random that the observed resonant frequencies of individual nuclei represent an average over all possible orientations. For example, the chemical shift is known to be a function of the orientation of the molecule with respect to the applied magnetic field direction, but in a liquid we observe an average value: the 'isotropic' chemical shift. The field B_{DD} due to a dipole of strength μ at a distance r, subtending an angle θ with respect to the applied magnetic field direction, is given by the formula

$$B_{DD} = \pm(\mu_0/4\pi)\mu(3\cos^2\theta - 1)/r^3 \qquad [1]$$

Here, the term $(\mu_0/4\pi)$ is the conversion factor for SI units. In an isotropic liquid the mean value of $(3\cos^2\theta - 1)$ vanishes and no dipole–dipole splittings are observed. Similarly, nuclear quadrupole splittings do not appear in conventional high-resolution spectra of liquids. In complete contrast, solid-state NMR spectra exhibit very broad lines since dipolar couplings, chemical shift anisotropy and quadrupolar coupling exert their full effect.

It can, however, be useful to restrict molecular motion so that the dipolar coupling is only partly averaged. Although this can be achieved for polar molecules by applying a very large electric field gradient, the principal method used is to dissolve small molecules in a nematic liquid crystal. This is an intermediate state of matter which behaves like a liquid except that the rod-shaped molecules exert anisotropic forces on one another, inducing a degree of alignment of their long axes. This is shown schematically in Fig. 1. These local domains of one-dimensional order would normally be oriented at random, but in the intense magnetic field of a high-resolution spectrometer they all acquire the same preferred direction. Usually, the liquid crystal molecules are not themselves observed, but a small solute molecule is added in low concentration. Although the small solute molecule still tumbles rapidly, it

acquires a slight net orientation through its interactions with the neighbouring liquid crystal molecules. The degree of ordering is measured by an *order parameter* S, which is normally very much less than unity. As a result, dipole–dipole splittings appear in the high-resolution spectrum, but they are scaled down considerably by the factor S.

The great advantage of this controlled reintroduction of dipolar couplings is that, unlike the solid case, only intramolecular couplings are seen. Thus, for solute molecules with comparatively few magnetic nuclei, it is usually possible to resolve all the solute lines just as in an isotropic spectrum, although the very large number of lines that can result often makes analysis difficult. (The signals from the liquid crystal itself are usually broad and unresolved, since such systems tend to be tumbling rather slowly and they contain large numbers of protons.) Iterative computer analysis may be employed to extract accurate dipolar coupling constants from experimental spectra. From the known orientational dependence of the dipolar coupling it is then possible to derive very accurate information on molecular geometry. In general, the order parameter S is not known; however it is possible to take one internuclear distance as the standard for measuring all the others, thus bypassing the need to know S. In this manner the *relative* internuclear distances can be determined with high accuracy provided that the molecule is rigid.

The alignment methods described above rely on a cooperative effect between molecules with large anisotropies in their bulk magnetic susceptibilities. In the very intense magnetic fields now being introduced for high-resolution spectrometers (protons at 600 MHz) some *simple* molecules begin to show a small alignment, sometimes aided by dimerization. It is reported, for example, that many deuterated aromatic compounds (1) and monodeuterobenzene (2) at high field (14.1 tesla) show splittings attributable to the interaction of the deuteron nuclear quadrupole with the electric field gradient of the molecule. This interaction would average to zero in a strictly isotropic liquid. This raises important questions about the suitability of some deuterated reference materials (e.g. chloroform-d) for field/frequency regulation*.

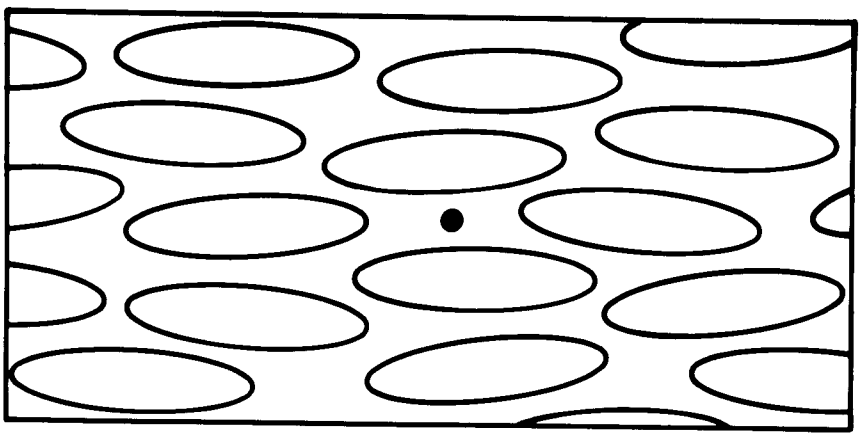

Fig. 1. Schematic representation of a solute molecule (black circle) dissolved in a nematic liquid crystal matrix where the long axes of the molecules are aligned.

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Cross-reference

Field/frequency regulation

Apodization

Apodization is a term borrowed from infra-red Fourier transform spectroscopy, with the literal meaning 'removing the feet'. The feet in question are the set of small sidelobes which appear on each side of the resonances in the frequency domain; they are derived from the sinc function character imposed on the lineshape by truncation of the time-domain signal before it has completely decayed.

Although an ideal free induction signal* in Fourier transform NMR would decay smoothly to zero, in practice the process of acquisition is usually terminated before the decay is complete, introducing a step function at the end. Often the data table is then completed by zero-filling*. The signal fed into the Fourier transformation* program may thus be regarded as the 'ideal' free induction decay multiplied by a step function. The convolution* theorem tells us that this corresponds to the convolution of the ideal frequency-domain lineshape with a sinc function; the more severe the discontinuity in the time-domain signal, the more marked are the sinc function 'wiggles'.

The effect may be removed by the application of a suitably chosen sensitivity enhancement* weighting function to the free induction signal, but this sacrifices resolution. Apodization is used to describe attempts to remove the sinc function 'wiggles' without significantly altering the resolution or signal-to-noise ratio. The idea is to apply a particular type of weighting function to the last 20–30% of the time-domain signal in order to bring it smoothly to zero at the end of the acquisition period. A widely used apodization function is made up from a half cycle of a cosine wave, $\frac{1}{2}(1 + \cos x)$. In fact, this only alleviates the problem and does not eliminate the wiggles (Fig. 1). Only a weighting function which operates on the entire time-domain signal can eradicate the sinc function artifacts entirely.

The frequency-domain spectrum obtained by digital Fourier transformation is of course discrete. It turns out that a step function at the very end of the free induction decay (with no zero filling) leads to a spectrum where the data points

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