

# **Modern NMR Techniques for Chemistry Research**

ANDREW E. DEROME



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# Foreword

The development of commercially available high resolution NMR spectrometers in the 1950's provided the chemist with a new tool of enormous power. The direct relationship between spectral symmetry and the molecular symmetry of the sample enabled the routine solution of structural problems which previously required a level of intellectual power and chemical insight given to few. All this was achieved in the 100 milligram range, with instruments based on powerful electro- or permanent magnets.

A second revolution has now occurred in the NMR field. This has come about through the development of reliable superconducting magnets coupled to the application of the pulse technique and its associated Fourier transform. Now dispersion and sensitivity have increased in leaps and bounds, so that sample size can be in the microgram range. Perhaps more important have been developments consequent on the pulse technique which permit enormously greater control and manipulation of the sample's magnetisation. As a result, the structural information now available to the chemist, through pulse NMR, is probably greater and more readily obtained than by any other single technique.

In this book Andrew Derome takes the practising chemist through the practical aspects of this new method. Through this work a chemist, not trained as a physical NMR spectroscopist, can understand and use the enormously powerful tools for structural investigation available through this new generation of superconducting FT machines. It is strongly recommended to chemists and biologists both in academe and industry, who wish to realise the full possibilities of the new wave NMR.

Jack E. Baldwin, FRS

The Dyson Perrins Laboratory  
Oxford University

# Preface

If you have just picked up this book with the thought of buying it, you may be asking yourself 'why go to all this trouble'. Here is a text which, although set in a qualitative framework, does spend a good deal of time discussing the physical principles behind NMR experiments; if you are a chemist or biologist you may shy away from such material. There is also a lot of experimental detail, which may seem superfluous if you are used to placing your spectroscopic problems in the hands of specialists. Presumably you are curious about the new developments in NMR, but maybe you would feel more comfortable with a survey which concentrated on spectral interpretation, leaving the technical details for somebody else. I believe there are several reasons why the application of NMR to chemical and biological problems cannot be made properly using such a 'black box' approach, and I hope the following paragraphs will convince you of this. You can find a detailed description of what this book contains in the first chapter.

Why is NMR such a useful technique? There are many reasons, but a central theme is that it can identify *connections* between entities. The gross features of chemical shift and signal intensity have, essentially, the same character as other spectroscopic methods such as infra-red absorption, and if that was all there was to NMR it would not outpace other methods to such a degree. But there is more: the fine structure in spectra, which arises from the coupling between nuclei, and various other interactions such as the nuclear Overhauser effect, depend on the relationships *between* nuclei; this is what gives NMR its special usefulness. Whether the aim is to probe the structure of an isolated, pure compound, or to measure proton-proton distances in a protein, or to extract the signal of a labelled metabolite from some biological soup, it is to those properties relating one nucleus with another that we turn.

Over the last ten years or so the peculiar advantages of pulse NMR have come to be fully appreciated, leading to the development of many ingenious new ways to exploit these connections. Simply glancing at a list of experiments can be daunting; there are so many that it seems impossible to even begin to understand them. However, *it is not so difficult*. A few basic principles have been applied in various permutations; once these principles have been grasped any new experiment can be fitted easily into the overall picture. This is an important reason for making the effort to understand what is happening during pulse experiments; you will be better able to judge whether some new method is applicable to your particular problem. A nice feature of pulse NMR is that it is, on the whole, easier to understand than continuous wave NMR, even though the latter may be more familiar. In a pulse experiment the system spends most of its time evolving independently of outside stimuli, so there are less things to think of at once.

Modern pulse NMR is performed exclusively in the Fourier transform mode. The reasons for this are set out in detail later in the text, but the use of the FT method is another important motivation for thinking about the mechanics of NMR experiments. Of course, it is useful to appreciate the advantages of the transform, and particularly the spectacular results which can be achieved by applying it in more than one dimension, but it is also essential to understand the limitations imposed by digital signal analysis. The sampling of signals, and their manipulation by computer, often limit the accuracy of various measurements of frequency and amplitude, and may even prevent the detection of signals altogether in certain cases. These are not difficult matters to understand, but they often seem rather abstract to newcomers to FT NMR. Even if you do not intend to operate a spectrometer, it is irresponsible not to acquire some familiarity with the interaction between parameters such as acquisition time and resolution, or repetition

rate, relaxation times and signal intensity. Many errors in the use of modern NMR arise because of a lack of understanding of its limitations.

Another reason for studying NMR, and especially its practical side, is that it is *fun*. Many chemical and, nowadays, biological projects culminate in an NMR experiment. After a year-long slog to synthesise some labelled substrate, it may only take a few days to perform the *real* experiment by NMR, whether it be following the mechanism of an organic reaction or watching a metabolic pathway inside whole cells. It is not fair that the excitement associated with such experiments should be reserved for specialist NMR operators: *learn to do it yourself*. The investment is the initial effort required to become familiar with a spectrometer (which may require a few late nights, unless you are very lucky), and the struggle to understand the experiments. The return is a broad understanding of the most important spectroscopic technique, and a refreshing and stimulating change from everyday lab. routine.

Many people have helped during the preparation of this book, and I will now try to thank them; to anyone who has been inadvertently omitted I extend my apologies. First, I am indebted to Jane MacIntyre, for originally persuading me that the project was possible. Several of my colleagues in the Dyson Perrins and Inorganic Chemistry Laboratories have read the text, from the diverse perspectives of graduate student, NMR operator, electronics engineer, university lecturer and postdoctoral researcher, and provided many helpful suggestions. My sincere thanks to: Barbara Domayne-Hayman, Elizabeth McGuinness, Dermot O'Hare, Mike Robertson, Mike Robinson, Chris Schofield and Nick Turner. I also especially have to thank Elizabeth McGuinness and Tina Jackson for bearing the brunt of the NMR requirements of hundreds of research workers in the Oxford chemistry departments, thus leaving me sufficiently undisturbed to work on the text. Mike Robertson carried out extensive modifications to a commercial instrument to permit some of the more unusual experiments to be performed, while Tina Jackson provided technical assistance.

A number of people have been kind enough to contribute figures, or to permit me to perform devilish experiments on their compounds. I thank, from the Dyson Perrins Laboratory, Oxford: John Brown (for Figures 9.6, 9.7), George Fleet (for compound 1, Chapters 8-10), Nick Turner (for compound 6, Chapter 5) and Rob Young (for compound 6, Chapter 8); from the Inorganic Chemistry Laboratory, Oxford: Dermot O'Hare (for Figures 8.45, 9.10, 10.11); from the Physical Chemistry Laboratory, Oxford: Chris Bauer (for Figure 7.19), Ray Freeman (for Figure 8.21) and Peter Hore (for Figure 2.23); from the Biochemistry Department, Oxford: Jonathan Boyd (for Figure 8.36); from the University Chemical Laboratory, Cambridge: James Keeler (for Figures 8.24, 10.13); from the Ruđer Bošković Institute, Zagreb: Dina Keglević (for compound 2, Chapter 8). Oxford Instruments Ltd. and Bruker Spectrospin also provided a number of figures, which are acknowledged in the relevant captions. Figure 5.10 was reproduced with permission from: J. H. Noggle and R. E. Schirmer, *The Nuclear Overhauser Effect - Chemical Applications*, Academic Press, 1972.

In common with the other books in the Organic Chemistry series, this text was reproduced photographically from camera-ready copy. However, in order to achieve an acceptable appearance, I typeset the material myself on a Monotype Lasercomp phototypesetter at Oxford University Computing Service. I thank the Computing Service for access to this device, and Catherine Griffin for advice on its use. Christine Palmer, of the Inorganic Chemistry Laboratory, Oxford, miraculously produced the line drawings from my semi-legible sketches, often at high speed; I thank her for this vital contribution. Final paste-up of the text was performed at Pergamon, under the expert supervision of Colin Drayton, who also managed to avoid making me feel bad even when the whole project was months behind schedule.

Andrew Derome

# Introduction

Nuclear resonances are affected by a variety of weak interactions between the nuclei and the electrons of molecules, between nuclei within the molecules and between nuclei in neighbouring molecules. If these interactions can be disentangled and interpreted, they are found to contain an extraordinarily rich mine of information about the structures and conformations of the molecules of the sample, about interactions between molecules and about molecular motion.

All this is made possible by the very long relaxation times that characterise NMR spectra of spin  $\frac{1}{2}$  nuclei in mobile liquids; line widths of 0.1 Hz or less at 500 MHz are by no means uncommon. This means that even resonances which lie very close together can be resolved.

High resolution spectra, even of molecules of modest molecular weight, are therefore often quite complicated, but because the interactions are weak, cross terms are not very important if the measurements are made in strong magnetic fields, and the spectra are relatively easy to interpret. It is not surprising, therefore, that high resolution NMR has become such an indispensable tool for the organic chemist.

As the size of the sample molecules becomes greater, the complexity of the NMR spectra increases rapidly, lines overlap, and their interpretation becomes more difficult. At this stage much more sophisticated sequences of experiments must be made, the analysis of which can be technically demanding. Here the organic chemist is faced with a dilemma. How much effort should he or she invest in grappling with the not inconsiderable technicalities of the very powerful NMR techniques now available? It is certain that without some understanding of these methods he may not even realise how NMR can help him solve his particular problems, and even if he thinks help is available, he must beware of using NMR as an imperfectly understood black box.

Most organic chemists to-day need to understand what NMR can do for them, and in this book Dr Derome sets out the principles and provides a practical guide to the use of NMR spectroscopy in terms accessible to organic chemists; it is a long journey but one which will be well worth while. The reader who perseveres with the book will be considerably enlightened. I hope the reader will also be sufficiently fired by the enthusiasm running through the text to read at some later stage the further references provided and achieve still greater depths of understanding of these elegant experiments.

Sir Rex Richards, FRS  
University of Oxford

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# 1

## What This Book Is About

### 1.1 INTRODUCTION

Figure 1.1 is a proton NMR spectrum of cholesteryl acetate, run at 60 MHz on a continuous wave spectrometer. During the sixties and early seventies, a period when much research into compounds of this type was carried out, such a spectrometer would have been regarded as a top rank research instrument. It is a remarkable reflection on the power of NMR to illuminate chemical problems (and on the prowess of those who pioneered its use) that the availability of spectra even as crude as this revolutionised organic chemistry.

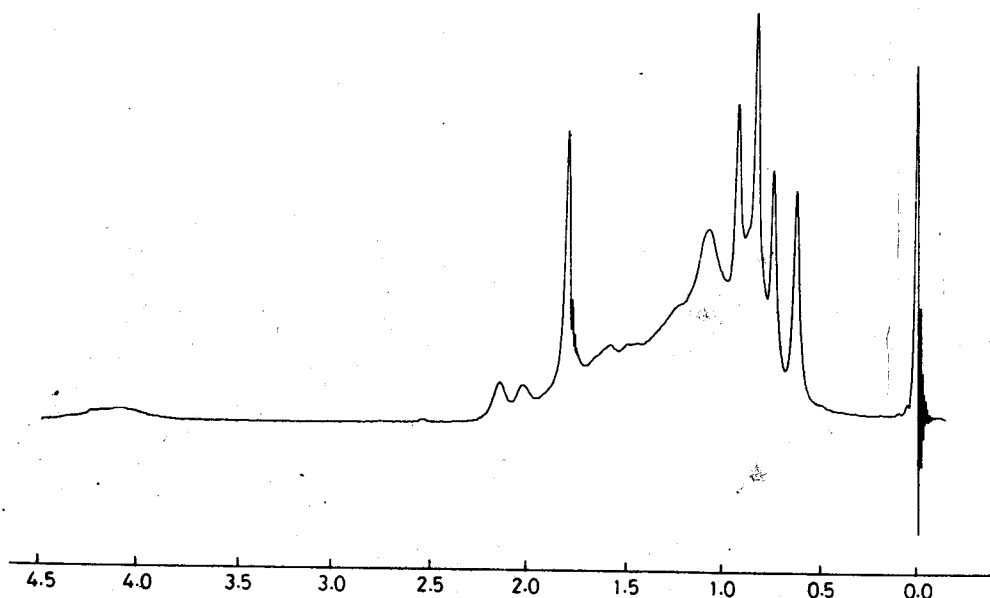
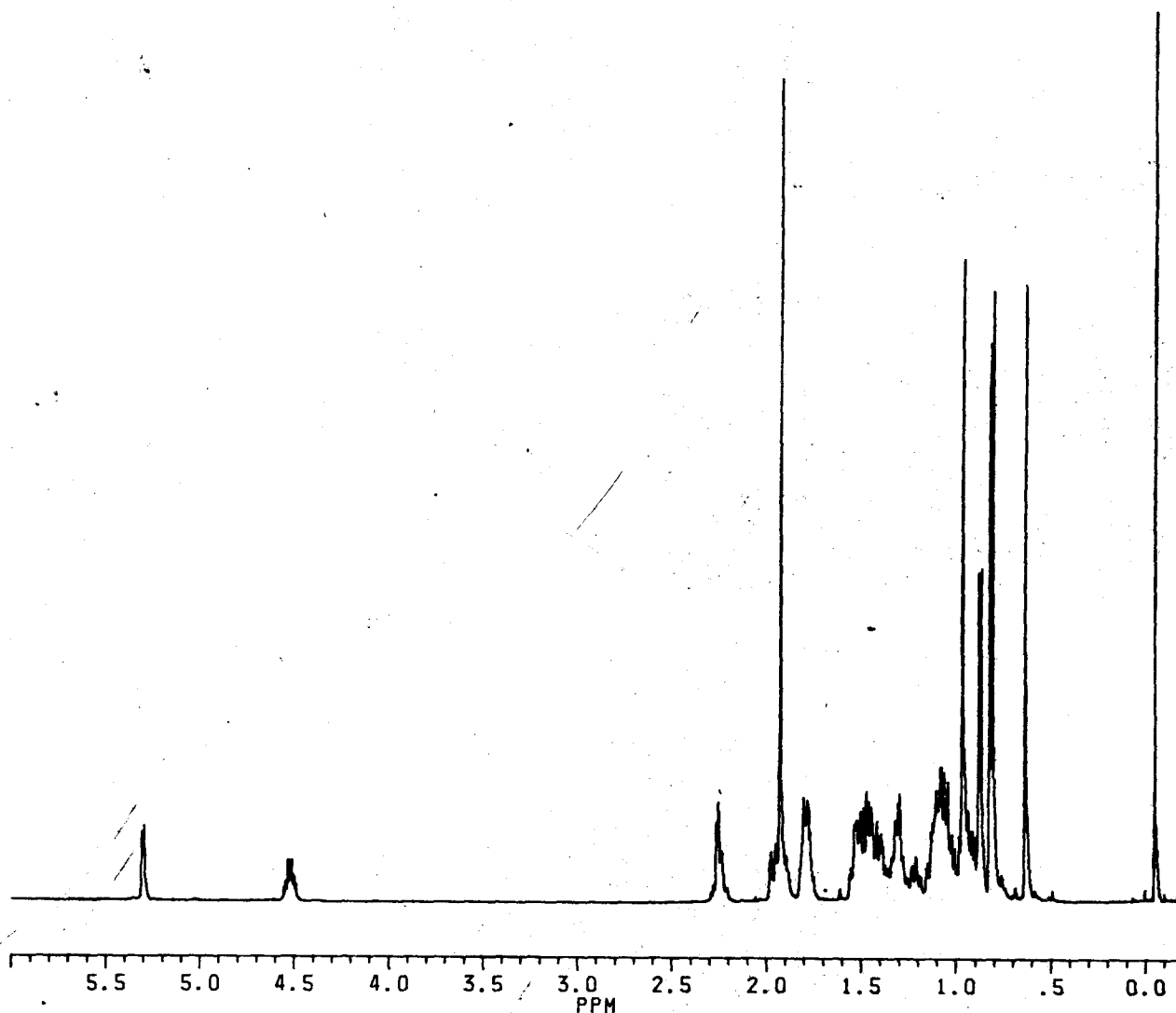


Figure 1.1 A low-field, continuous wave NMR spectrum.

Nowadays we can expect much more from our spectrometers (Figure 1.2), with instruments operating at almost ten times the frequency (and costing at least thirty times as much). The improvements in this spectrum are obvious, but the point I wish to make by showing it to you is perhaps less so. *It is not good enough.* The intrinsic limitations of NMR are such that, however strenuous our efforts to improve spectrometer technology, we will not be able to interpret the proton spectra of relatively simple compounds at sight. This will remain so into the foreseeable future, barring some entirely unexpected development in magnet construction. It is worth bearing in mind that, while the switch from electromagnets to superconducting magnets allowed an immediate jump in field strength of a factor of 3-4, further efforts in superconducting magnet design over almost twenty years have resulted in only another doubling of routinely available field.



**Figure 1.2** The same sample as for Figure 1.1, but run at 500 MHz in Fourier transform mode.

We cannot rely on progress in instrument design to solve our spectroscopic problems for us, but fortunately we do not need to do so. In parallel with technological development of NMR spectrometers, there has been an astonishing growth in our understanding of the properties of nuclear spin systems. Since about 1980, this has reached some kind of critical point, with the sudden development of a wide range of new experimental techniques. Everyone involved in chemistry research will certainly be aware by now that something unusual is happening to NMR, but still the impact of these developments has been fairly restricted. The technical nature of most NMR papers, and their spread through an unusual range of chemical, physical and biological journals, means that the non-specialist has little hope of keeping abreast of developments. In the teaching of NMR to students of chemistry, it sometimes seems that pulsed FT NMR has yet to supplant CW NMR in many courses pitched at organic chemists; modern NMR methods are almost never treated. This cannot remain so for much longer, because understanding how to use NMR to solve problems is fundamental to success in chemical research.

In this book I hope to provide an introduction to modern NMR accessible to the non-specialist. It is intended to be self-contained, aside from some basic background knowledge requirements described in the next section. The reader I have in mind is the advanced student or beginning research worker, or those with more experience who wish to learn about



new techniques. The bare skeleton of the material (without experimental details or such a wide range of methods) derives from a short course for graduate students at Oxford, but despite this I think that much of the contents should be accessible to undergraduates. The application of modern NMR methods is rarely taught at undergraduate level at present, but this reflects the speed with which we have been overtaken by events, rather than any extreme conceptual difficulties in the subject.

## 1.2 WHAT YOU NEED TO KNOW

I take it you have already encountered 'traditional' NMR. Thus, I assume a good deal of familiarity with the use of proton NMR for structure elucidation. You will find no discussion of the variation of chemical shifts or coupling constants with structure here. This is partly because the information is readily available elsewhere, but more importantly because modern NMR experiments can reduce our reliance on such empirical correlations. We can move away from 'the spectrum is consistent with structure *X*' and much closer to 'the proof of structure *X* follows from ...'. The only proton NMR 'method' I expect you to have met is homonuclear decoupling, which is mentioned several times but not explained in detail. You might also have come across the nuclear Overhauser effect, but if not never mind, as it merits a whole chapter of its own.

As to other nuclei, you should be aware of the possibility of observing  $^{13}\text{C}$ , and of the consequences of its low natural abundance. If you have used carbon spectra, then you must have seen the 'off-resonance' decoupling experiment, which helps to determine the number of protons borne by each carbon. If you are an inorganic chemist, or a biologist, you might make more use of  $^{31}\text{P}$  NMR. It is not really important, though, as the treatment is entirely multi-nuclear. While examples will often be drawn from proton and carbon spectroscopy, as a natural reflection of the fact that I work in an Organic Chemistry department, the only real distinction is between nuclei with spin  $\frac{1}{2}$  and those with greater spin (quadrupolar nuclei). Most of the discussions in this book centre on spin- $\frac{1}{2}$  nuclei, with extensions to quadrupolar nuclei mentioned when appropriate.

Some rudimentary mathematics crops up from time to time, but fear not, because it is never essential to understanding the material. This is not a book for physical chemists, and there are no derivations or detailed mathematical analyses, but the occasional formula does help sometimes. All you need to understand the physical model introduced in Chapter 4 is a knowledge of basic trigonometry and Cartesian coordinates. Some first-order rate equations also occur in a few places, but not calculus more difficult than that (apart from a small burst of vector calculus in Chapter 4, which can safely be ignored). In one or two places I assume slight familiarity with computer terms such as 'memory' or 'byte'.

## 1.3 WHAT IS IN THE BOOK

This book is *not* a comprehensive review of recent NMR methods. Any attempt to include a review of this kind in a reasonably short text would leave little room for explanation or examples. Instead, I have chosen to survey several broad classes of experiment, to try to demonstrate the principles involved in - and the practical aspects of - modern NMR. In discussing new experiments, I have tried very hard to convey the physical essence of how they work, taking the explanations as far as I could subject to the restriction of no mathematics. Naturally, the point at which such an approach should be abandoned as vague and unenlightening is a matter of personal taste, and if I sometimes seem to oversimplify, or to push physical analogy too far, I hope you will bear with me.