Modern NMR Spectroscopy

A Guide for Chemists

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Preface

Many chemists have access to NMR spectrometers that are capable of far more than is ever demanded of them. The modern NMR spectrometer can solve chemical problems in ways that could barely be imagined ten years ago, but these new methods are, as yet, effectively exploited by very few. We believe that a major reason for this gap between potential and actual performance is a lack of communication between the chemist and spectroscopist. The chemist formulates structural or mechanistic problems in chemical terms, while the spectroscopist uses pulse sequences that are rooted in physics and expressed in mathematical language. This book is an attempt to bridge that gap. Our only credentials are that we are accused by chemists of being mere spectroscopists; spectroscopists, of course, realize that we are mere chemists.

We could not have produced this text without help from the following:

Michael Springett devoted much care and time to planning and drawing the line diagrams and structures. Eric Smith, Neil Cray, and Julie Hulyer produced, as always, superb photography.

James Keeler and David Neuhaus gave us many patient and lucid explanations of what NMR is really about, and helpful criticism of some draft chapters. Laurie Colebrook read most of the text and suggested many improvements in presentation.

John Anderson, Mike Baird, Laurie Colebrook, Jimmy Cowan, Heinz Egge, Jason Elliott, G. Englert, John Evans, Russell Grimes, Bill Hull, Brian Johnson, Greg Johnstone, James Keeler, Katalin Kover, John Markley, Ralph Mason, Ray Matthews, Andre Merbach, John Mersh, David Neuhaus, Albert Norris, Steven Patt, Clive Pearce, Dallas Rabenstein, Jacques Reuben, Peter Sadler, Francisco Sanchez-Ferrando, Dudley Williams, and Michael Williamson provided details of their work before publication, or copies of spectra.

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Where no reference or acknowledgement is given, the spectrum is previously unpublished. Most of the unpublished spectra were run by us specifically for this book; Brian Crysell, Philip Leighton, Ralph Mason, and Steve Wilkinson also ran some spectra for us. Other spectra were generously provided by the friends and colleagues whose names appear above.

Louise Sanders gave us expert help with English and other editorial

matters. The staff of Oxford University Press gave us much encouragement and advice throughout the project.

Seven computers, using four incompatible disk formats, in three cities, on two continents, acted as patient hosts during the gestation of this one text, and also produced all the simulations.

Our families and research groups put up with much less attention than they deserved, for much longer than they, or we, expected.

The origins of this book can be traced to Professor Laurie Hall's laboratory at the University of British Columbia, where we first met in 1979. Somehow, the friendship arising from that chance meeting has survived the writing of this book.

To all of those mentioned above, we are deeply indebted, and we express our grateful thanks.

Cambridge and J.K.M.S.
Kingston B.K.H.
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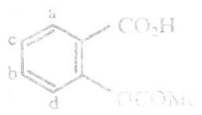
Introduction

This book is for the chemist who has interesting molecules and access to an NMR spectrometer. We feel that it is necessary because NMR (nuclear magnetic resonance) spectroscopy has recently experienced a revolution that leaves even the professional spectroscopist bewildered. High-field magnets have dramatically improved the sensitivity and chemical shift separations that are available; improved electronics and design make the observation of formerly 'exotic' nuclei such as deuterium, tin, or silicon routine; and advances in computers and spin physics have led to formidable arrays of new techniques, and their associated acronyms.

How then can chemists decide which approach will solve their particular structural or mechanistic problems? They need to know what is possible and what is sensible, when to invest a large amount of spectrometer time on a two-dimensional experiment, and when a simple decoupling will do. This book attempts to answer these questions from the point of view of the chemist rather than the spectroscopist. One of our aims has been to show how the spectrometer can provide the maximum amount of useful information in the minimum amount of time. Our approach is pictorial, descriptive and non-mathematical, and our examples are drawn from organic, inorganic and biological chemistry. Much of the thrust for the development of new techniques comes from the application of NMR to biological problems. This is partly a result of the drive to study ever larger molecules, and partly due to the wish to observe the molecule of choice in the complex mixture which constitutes a living cell. As a result, many of the literature examples we quote are biological, but the techniques they exemplify are equally applicable to many types of chemical problem. To date, the new techniques have been applied mainly to ^{1}H and ^{13}C NMR of organic compounds, and this is reflected in our examples, but inorganic applications will surely follow.

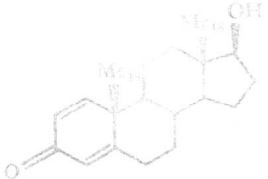
We restrict our discussions to pulsed Fourier transform (FT) experiments because continuous wave (CW) techniques are no longer used except in low-field routine proton spectrometers and for some solid-state studies. The NMR experiment is intrinsically insensitive when compared to other forms of spectroscopy, and was for many years restricted to a few nuclei with high natural abundance and high magnetic moment such as ^{1}H, ^{19}F, and ^{31}P. It is possible to improve the signal-to-noise ratio in spectra by signal averaging but, since individual CW spectra may take several minutes to collect, the averaging process tends to be prohibitively time consuming. With pulsed spectrometers, individual spectra can be collected more rapidly so signal averaging becomes more efficient. Previously slow experiments on less-receptive nuclei such as ^{13}C or ^{29}Si become routine even on low-field spectrometers. It has become common among chemists to describe spectrometers by the proton frequency rather than by the magnetic field strength. In accordance with this convention,



0.1

we may refer to a 200 MHz spectrometer rather than a 4.7 tesla (or 47 000 gauss) spectrometer.

The increased convenience of signal averaging led to what could be considered the first revolution in NMR spectroscopy. The high fields available from superconducting magnets have further improved the sensitivity of the NMR experiment, and the increased chemical shift dispersion has made it possible to study more complicated chemical systems. However, the major breakthroughs in recent years have come from improvement in our ability to use pulses to manipulate the nuclear spins to generate information.



0.2

Why are these new techniques of NMR necessary? If classical NMR spectroscopy operating at 60–100 MHz was so valuable, surely it is even more so at 200–500 MHz? This is undoubtedly true, if only because coupling constants have units of hertz, and chemical shifts have units of parts per million (ppm). If the shift difference between two coupled protons is Δ ppm, then at higher field Δ/J is larger, and the spectrum is more nearly first order and readily analysable. Figure 0.1 illustrates this point with 80 and 250 MHz ^{1}H spectra of aspirin, **0.1**. The 80 MHz spectrum is analysable by classical mathematical methods such as spin simulation,[1] but the final result, with its second-order transitions and barely separated multiplets, lacks immediacy. The 250 MHz spectrum is analysable by inspection and virtually 'tells' us the structure.

High fields, however, also present problems which are quite new. Consider, for example, the ^{1}H spectra of Δ_1-dehydrotestosterone, **0.2**, at 80 and 400 MHz (Fig. 0.2). The 80 MHz spectrum usefully displays only the olefinic signals (which are not shown), the hydroxyl resonance, and two methyl singlets. This information has for many years been an invaluable tool for structure determination and spectrum assignment,[2]

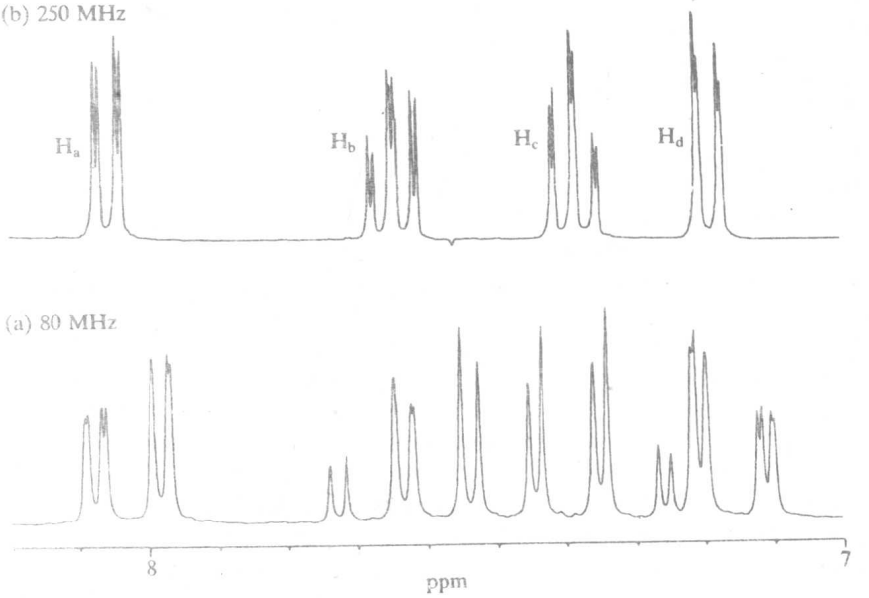


Fig. 0.1. 80 and 250 MHz ^{1}H spectra of aspirin in acetone-d_6 solution.

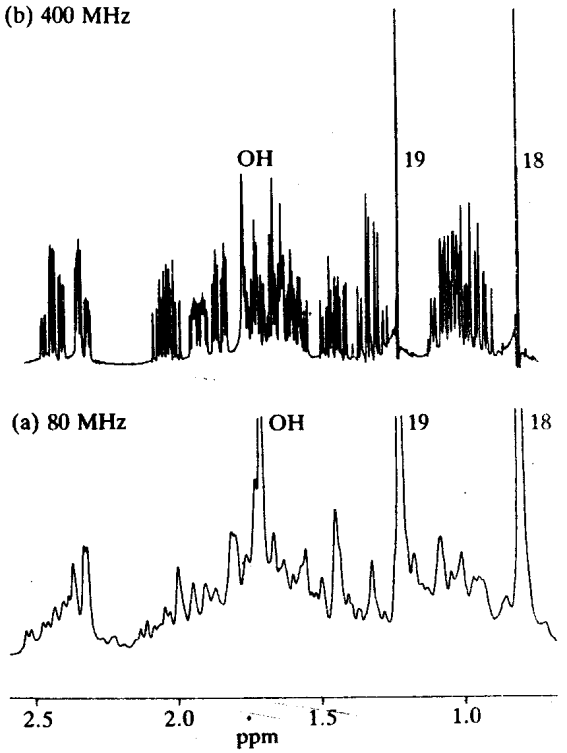


Fig. 0.2. 80 and 400 MHz ^1H spectra of Δ_1-dehydrotestosterone in $CDCl_3$ solution. The same sample was used for both spectra; the shift of the hydroxyl resonance between the spectra reflects the different temperatures at which they were acquired.

but it is very limited. Most of the proton spectrum consists of a broad and uninterpretable 'methylene envelope'. By contrast, the corresponding high-field spectrum of the same sample is extremely rich in information. The smooth methylene envelope has been transformed into a forest of sharp resonances.

The high-field spectrum presents us with the problem that it is now too rich in signals. These signals contain all the information we need for a complete determination of structure and conformation, but how do we extract that information? There are so many overlapping multiplets that we cannot easily disentangle them, and even if we can, which is which? Chemical shift correlation tables will be very little help with so many similar signals in such a narrow region.

The spectrum clearly needs to be dissected in some way so as to relieve the crowding. This can be done either by spreading into an extra dimension or by editing out many of the peaks. The first process is nicely illustrated by an analogy which is summarized in Fig. 0.3.[3] Consider a line of people, standing facing you, in order of increasing age. You are told that they belong to three families A, B, and C. How do you know who belongs to which family? By inspection, you can only see their ages. If, however, you ask Family A to step forward two paces and Family B to step forward one pace, then the problem is solved. You now have an array of people, sorted by family in one dimension and by age in another. Two-dimensional NMR tries to achieve a similar result with complex

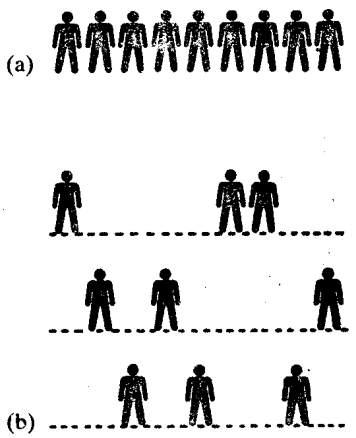


Fig. 0.3. (a) a single row of people; (b) the same set of people, sorted according to family.

spectra, giving some kind of useful separation or correlation in a second dimension together with the classical chemical shift in the other dimension. An illuminating account of the principles and early history of two-dimensional NMR, i.e. the period 1971–8, has been given by Freeman and Morris.[4]

There are many other ways of sorting the single row of people. They may be sorted by mobility—who runs fastest?—or by their reaction to particular types of excitation, or by many other criteria. The important point is to identify the type of sorting required, and then to apply a suitable test. Modern NMR spectroscopy is precisely the same. We can sort carbons by the number of attached protons, or by their mobility, or by the chemical shift of the spins to which they are *J*-coupled. We can manipulate the spectrum to tell us what we need to know to solve our particular problem. Even if the sample in the spectrometer is a complex living cell culture, it is often possible, by careful experimental design, to observe essentially only the molecules of interest for a particular study.

NMR is not a linear subject which can be taught in just one correct way. The richness and diversity which make it so powerful and interesting also make it difficult to choose a satisfactory order of presentation. Inevitably, some deserving aspects are postponed until too late, and some concepts have to be used before they are properly explained. We hope that the reader will bear with us, and with our order of priorities. Most of the theoretical ideas which are necessary for understanding and manipulating both one- and two-dimensional Fourier transform NMR spectra are introduced in the first four chapters. We have tried to remove the 'magic' from two-dimensional NMR, showing that (with hindsight!) it is merely an obvious extension of classical NMR, and that all two-dimensional experiments have one-dimensional counterparts. Indeed, we have tried to abolish the difference between 'routine' spectroscopy and 'special pulse sequences' which is beginning to appear in some treatments. The intimidating array of new techniques and acronyms is actually put together from a very small number of basic building blocks. Each building block consists of one or more pulses which have a predictable effect on the spins in the sample. More complex sequences merely contain more than one block, combined in a variety of ways to give the desired final spectroscopic effect and chemical information.

Chemists will find that the chapters with a substantial physics content contain concepts and information which they generally prefer to ignore. While it is tempting to treat the NMR spectrometer as a 'black box', it is difficult to exploit effectively its capabilities without a rudimentary knowledge of how it works. If chemists are to exploit the ideas of modern NMR spectroscopy then they will have to come to terms at least with the vocabulary of these concepts. To make this process as easy as possible, theoretical treatments are followed by relatively non-technical sections which summarize the chemical consequences of the theory. The reader can consult the chemical consequences section for an encapsulated account of the theory which precedes it, and for an indication of the kinds of practical applications which are possible.