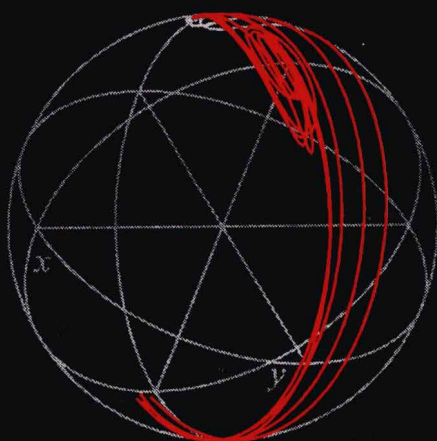
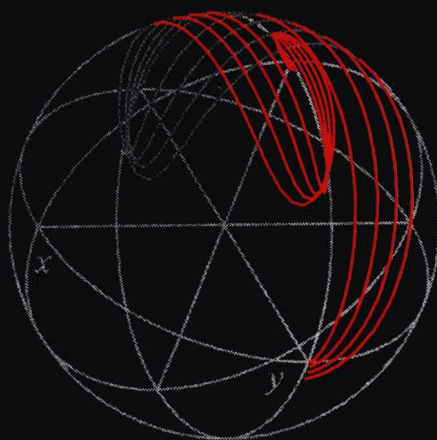


Tetrahedron Organic Chemistry Series Volume 19

High-Resolution NMR Techniques in Organic Chemistry

TIMOTHY D.W. CLARIDGE



PERGAMON

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Foreword

It is now more than ten years since the late Andy Derome's book "*Modern NMR Techniques for Chemistry Research*" was published. This book had a tremendous impact on organic chemists' use of the developing field of pulsed NMR spectroscopy, bringing to the chemist the power of these methods in a practical form for the elucidation of molecular structure. It is probably true that NMR spectroscopy has had the greatest impact on chemical research since the development of the accurate balance. Interestingly both of these techniques, i.e. weighing and NMR, are based on nuclear properties.

In this new book, Tim Claridge carries on from Andy Derome and brings together the more recent methods in a practical context. This book will be essential for those in academe or industry who have a direct intent in applying NMR to chemical problems.

J.E. Baldwin
Dyson Perrins Laboratory
Oxford 1999

Preface

From the initial observation of proton magnetic resonance in water and in paraffin, the discipline of nuclear magnetic resonance (NMR) has seen unparalleled growth as an analytical method and now, in numerous different guises, finds application in chemistry, biology, medicine, materials science and geology. Despite its inception in the laboratories of physicists, it is in the chemical laboratory that NMR spectroscopy has found greatest use and, it may be argued, has provided the foundations on which modern organic chemistry has developed. Modern NMR is now a highly developed, yet still evolving, subject that all organic chemists need to understand, and appreciate the potential of, if they are to be effective in and able to progress their current research. An ability to keep abreast of developments in NMR techniques is, however, a daunting task, made difficult not only by the sheer number of available techniques but also by the way in which these new methods first appear. These are spread across the chemical literature in both specialised magnetic resonance journals or those dedicated to specific areas of chemistry, as well as the more general entities. They are often referred to through esoteric acronyms and described in a seemingly complex mathematical language that does little to endear them to the research chemist. The myriad of sequences can be wholly bewildering for the uninitiated and can leave one wondering where to start and which technique to select for the problem at hand. In this book I have attempted to gather together the most valuable techniques for the research chemist and to describe the operation of these using pictorial models. Even this level of understanding is perhaps more than some chemists may consider necessary, but only from this can one fully appreciate the capabilities and (of equal if not greater importance) the limitations of these techniques. Throughout, the emphasis is on the more recently developed methods that have, or undoubtedly will, establish themselves as the principle techniques for the elucidation and investigation of chemical structures in solution.

NMR spectroscopy is, above all, a practical subject that is most rewarding when one has an interesting sample to investigate, a spectrometer at one's disposal and the knowledge to make the most of this (sometimes alarmingly!) expensive instrumentation. As such, this book contains a considerable amount of information and guidance on how one implements and executes the techniques that are described and thus should be equally at home in the NMR laboratory or on the chemist's or spectroscopist's desk.

This book is written from the perspective of an NMR facility manager in an academic research laboratory and as such the topics included are naturally influenced by the areas of chemistry I encounter. The methods are chosen, however, for their wide applicability and robustness, and because, in many cases, they have already become established techniques in NMR laboratories in both academic and industrial establishments. This is not intended as a review of all recent developments in NMR techniques. Not only would this be too immense to fit within a single volume, but the majority of the methods would

have little significance for most research chemists. Instead, this is a distillation of the very many methods developed over the years, with only the most appropriate fractions retained. It should find use in academic and industrial research laboratories alike, and could provide the foundation for graduate level courses on NMR techniques in chemical research.

Acknowledgements

The preparation of this book has benefited from the co-operation, assistance, patience, understanding and knowledge of many people, for which I am deeply grateful. I must thank my colleagues, both past and present, in the NMR group of the Dyson Perrins Laboratory, in particular Elizabeth McGuinness and Tina Jackson for their first-class support and assistance, and Norman Gregory and Dr. Guo-Liang Ping for the various repairs, modifications and improvements they have made to the instruments used to prepare many of the figures in this book. Most of these figures have been recorded specifically for the book and have been made possible by the generosity of various research groups and individuals through making their data and samples available to me. For this, I would like to express my gratitude to Dr. Harry Anderson, Prof. Jack Baldwin, Dr. Paul Burn, Dr. John Brown, Dr. Duncan Carmichael, Dr. Antony Fairbanks, Prof. George Fleet, Dr. David Hodgson, Dr. Mark Moloney, Dr. Jo Peach and Prof. Chris Schofield, and to the members of their groups, too numerous to mention, who kindly prepared the samples; they will know who they are and I am indebted to each of them. I am similarly grateful to Prof. Jack Baldwin for allowing me to use the department's instrumentation for the collection of these illustrative spectra.

I would like to thank Drs. Carolyn Carr and Nick Rees for their assistance in proof-reading the manuscript and for being able to spot those annoying little mistakes that I read past time and time again but still did not register. Naturally I accept responsibility for those that remain and would be grateful to hear of these, whether factual or typographical. I also thank Eileen Morrell and Sharon Ward of Elsevier Science for their patience in waiting for this project to be completed and for their relaxed attitude as various deadlines failed to be met.

I imagine everyone entering into a career in science has at some time been influenced or even inspired by one or a few individual(s) who may have acted as teacher, mentor or perhaps role-model. Personally, I am indebted to Dr. Jeremy Everett and to John Tyler, both formally of (what was then) Beecham Pharmaceuticals, for accepting into their NMR laboratory for a year a 'sandwich' student who was initially supposed to gain industrial experience elsewhere as a chromatographer analysing horse urine! My fortuitous escape from this and subsequent time at Beechams proved to be a seminal year for me and I thank Jeremy and John for their early encouragement that ignited my interest in NMR. My understanding of what this could really do came from graduate studies with the late Andy Derome, and I, like many others, remain eternally grateful for the insight and inspiration he provided.

Finally, I thank my wife Rachael for her undying patience, understanding and support throughout this long and sometimes tortuous project, one that I'm sure she thought, on occasions, she would never see the end of. I can only apologise for the neglect she has endured but not deserved.

Tim Claridge
Oxford, May 1999

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Chapter 1

Introduction

From the initial observation of proton magnetic resonance in water [1] and in paraffin [2], the discipline of nuclear magnetic resonance (NMR) has seen unparalleled growth as an analytical method and now, in numerous different guises, finds application in chemistry, biology, medicine, materials science and geology. Despite its inception in the laboratories of physicists, it is in the chemical laboratory that NMR spectroscopy has found greatest use. To put into context the range of techniques now available in the modern organic laboratory, including those described in this book, we begin with a short overview of the evolution of high-resolution (solution-state) NMR spectroscopy and some of the landmark developments that have shaped the subject.

1.1. THE DEVELOPMENT OF HIGH-RESOLUTION NMR

It is now a little over fifty years since the first observations of nuclear magnetic resonance were made in both solid and liquid samples, from which the subject has evolved to become the principal structural technique of the research chemist. During this time, there have been a number of key advances in high-resolution NMR that have guided the development of the subject [3,4] (Table 1.1) and consequently the work of organic chemists and their approaches to structure elucidation. The seminal step occurred during the early 1950s when it was realised that the resonant frequency of a nucleus is influenced by its chemical environment, and that one nucleus could further influence the resonance of another through intervening chemical bonds. Although these observations were seen as unwelcome chemical complications by the investigating physicists, a few pioneering chemists immediately realised the significance of these chemical shifts and spin–spin couplings within the context of structural chemistry. The first high-resolution proton NMR spectrum (Fig. 1.1) clearly

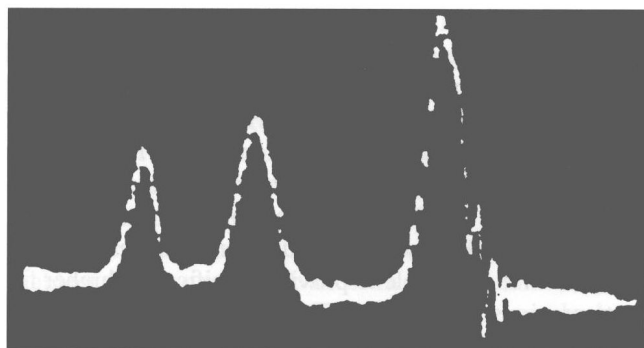


Figure 1.1. The first published 'high-resolution' proton NMR spectrum, recorded at 30 MHz, displaying the proton chemical shifts in ethanol (reproduced with permission from reference [5]).

Table 1.1. A summary of some key developments that have had a major influence on the practice and application of high-resolution NMR spectroscopy in chemical research

Decade	Notable advances
1940s	First observation of nuclear magnetic resonance in solids and liquids (1945)
1950s	Development of chemical shifts and spin–spin coupling constants as structural tools
1960s	Use of signal averaging for improving sensitivity Application of the pulse-Fourier transform (FT) approach The nuclear Overhauser effect employed in structural investigations
1970s	Use of superconducting magnets and their combination with the FT approach Computer controlled instrumentation
1980s	Development of multipulse and two-dimensional NMR techniques Automated spectroscopy
1990s	Routine application of pulsed field gradients for signal selection Development of coupled analytical methods e.g. LC–NMR
2000+	Use of high-sensitivity superconducting probes? Use of flow-injection NMR ('tubeless' NMR) in routine structural characterisation? ... ?

demonstrated how the features of an NMR spectrum, in this case chemical shifts, could be directly related to chemical structure and it is from this that NMR has evolved to attain the significance it holds today.

The 1950s also saw a variety of instrumental developments that were to provide the chemist with even greater chemical insight. These included the use of sample spinning for averaging to zero field inhomogeneities which provided a substantial increase in resolution, so revealing fine splittings from spin–spin coupling. Later, spin-decoupling was able to provide more specific information by helping the chemists understand these interactions. With these improvements, sophisticated relationships could be developed between chemical structure and measurable parameters, leading to such realisations as the dependence of vicinal coupling constants on dihedral angles (the now well-known Karplus relationship). The application of computers during the 1960s was also to play a major role in enhancing the influence of NMR on the chemical community. The practice of collecting the same continuous-wave spectrum repeatedly and combining them with a CAT (computer of average transients) led to significant gains in sensitivity and made the observation of smaller sample quantities a practical realisation. When the idea of stimulating all spins simultaneously with a single pulse of radio frequency energy, collecting the time-domain response and converting this to the required frequency-domain spectrum by a process known as Fourier transformation (FT) was introduced, more rapid signal averaging became possible. This approach provided an enormous increase in signal-to-noise ratio, and was to change completely the development of NMR spectroscopy. The mid 1960s also saw the application of the nuclear Overhauser effect to conformational studies. Although described during the 1950s as a means of enhancing the sensitivity of nuclei through the simultaneous irradiation of electrons, the Overhauser effect has since found widest application in sensitivity enhancement between nuclei, or in the study of the spatial proximity of nuclei, and remains one of the most important tools of modern NMR. By the end of the 1960s, the first commercial FT spectrometer was available, operating at 90 MHz for protons. The next great advance in field strengths was provided by the introduction of superconducting magnets during the 1970s, which were able to provide significantly higher fields than the electromagnets previously employed. These, combined with the FT approach, made the observation of carbon-13 routine and provided the organic chemist

with another probe of molecular structure. This also paved the way for the routine observation of a whole variety of previously inaccessible nuclei of low natural abundance and low magnetic moment. It was also in the early 1970s that the concept of spreading the information contained within the NMR spectrum into two separate frequency dimensions was presented in a lecture. However, because of instrumental limitations, the quality of the first two-dimensional spectra were considered too poor to be published, and not until the mid 1970s, when instrument stability had improved and developments in computers made the necessary complex calculations feasible, did the development of 2D methods begin in earnest. These methods, together with the various multipulse one-dimensional methods that also became possible with the FT approach, were not to have significant impact on the wider chemical community until the 1980s, from which point their development was nothing less than explosive. This period saw an enormous number of new pulse techniques presented which were capable of performing a variety of 'spin gymnastics' and so providing the chemist with ever more structural data, on smaller sample quantities and in less time. No longer was it necessary to rely on empirical correlations of chemical shifts and coupling constants with structural features, but instead a collection of spin interactions (through-bond, through-space, chemical exchange) could be mapped and used to determine structures more reliably and more rapidly. The evolution of new pulse methods has continued throughout the 1990s, alongside which has emerged a fundamentally different way of extracting the desired information from molecular systems. Pulsed field gradient selected experiments have now become routine structural tools, providing better quality spectra, often in shorter times, than was previously possible. These have come into widespread use not so much from a recent theoretical breakthrough (their use for signal selection was first demonstrated in 1980) but again as a result of progressive technological developments defeating practical difficulties. Similarly, the recent emergence of coupled analytical methods, such as liquid chromatography and NMR (LC-NMR), has come about after the experimental complexities of interfacing these very different techniques have been overcome, and these methods are proving particularly popular in the pharmaceutical industry, for example.

As the new century begins, it remains to be seen what new developments emerge and the impact these have on structural organic chemistry and the operation of the research laboratory. Already new breeds of 'shielded' superconducting magnets are available which have significantly smaller 'stray fields' and therefore demand less laboratory space. Advances in high-temperature superconducting materials may lead to still smaller and more economical liquid-nitrogen cooled magnets and possibly to yet higher field strengths. Could these advances, together with the ongoing miniaturisation of all electronic equipment, mean bench-top high-resolution, high-field instruments become standard in the future? The use of superconducting materials in probe detection coils is already providing significant improvements instrument sensitivity, and although such probes are now becoming commercially available, it remains to be seen whether they become an integral part of routine spectrometers. The advent of 'tubeless' NMR in high-throughput applications is also an emerging method utilising flow-injection technology, and may in due course force the demise of the NMR tube in routine structural characterisations after nearly half a century of service. Undoubtedly, all developments will be paralleled by advances in computational power and the added flexibility and opportunities for data handling this provides.

Modern NMR spectroscopy is now a highly developed and technologically advanced subject. With so many advances in NMR methodology in recent years it is understandably an overwhelming task for the research chemist, and even the dedicated spectroscopist, to appreciate what modern NMR has to offer.

This text aims to assist in this task by presenting the principal modern NMR techniques to the wider audience.

1.2. MODERN HIGH-RESOLUTION NMR AND THIS BOOK

There can be little doubt that NMR spectroscopy now represents the most versatile and informative spectroscopic technique employed in the modern chemical research laboratory, and that an NMR spectrometer represents one of the largest single investments in analytical instrumentation the laboratory is likely to make. For both these reasons it is important that the research chemist is able to make the best use of the available spectrometer(s) and to harness modern developments in NMR spectroscopy in order to promote their chemical or biochemical investigations. Even the most basic modern spectrometer is equipped to perform a myriad of pulse techniques capable of providing the chemist with a variety of data on molecular structure and dynamics. Not always do these methods find their way into the hands of the practising chemist, remaining instead in the realms of the specialist, obscured behind esoteric acronyms or otherwise unfamiliar NMR jargon. Clearly this should not be so and the aim of this book is to gather up the most useful of these modern NMR methods and present them to the wider audience who should, after all, find greatest benefit from their application.

The approach taken throughout is non-mathematical and is based firmly on using pictorial descriptions of NMR phenomena and methods wherever possible. In preparing this work, I have attempted to keep in mind what I perceive to be the requirements of three major classes of potential readers:

- those who use solution-state NMR as tool in their own research, but have little or no direct interaction with the spectrometer,
- those who have undertaken training in directly using a spectrometer to acquire their own data, but otherwise have little to do with the upkeep and maintenance of the instrument, and
- those who make use spectrometers and are nominally responsible for the day-to-day upkeep of the instrument (although they may not consider themselves dedicated NMR spectroscopists).

The first of these could well be research chemists and students in an academic or industrial environment who need to know what modern techniques are available to assist them in their efforts, but otherwise feel they have little concern for the operation of a spectrometer. Their data is likely to be collected under fully-automated conditions, or provided by a central analytical facility. The second may be a chemist in an academic environment who has hands-on access to a spectrometer and has his or her own samples which demand specific studies that are perhaps not available from fully automated instrumentation. The third class of reader may work in a small chemical company or academic chemistry department which has invested in NMR instrumentation but does not employ a dedicated NMR spectroscopist for its upkeep, depending instead on, say, an analytical or synthetic chemist for this. This, it appears (in the UK at least), is often the case for new start-up chemical companies. With these in mind, the book contains a fair amount of practical guidance on both the execution of NMR experiments and the operation and upkeep of a modern spectrometer. Even if you see yourself the first of the above categories, some rudimentary understanding of how a spectrometer collects the data of interest and how a sequence produces, say, the 2D correlation spectrum awaiting analysis on your desk, can be enormously helpful in correctly extracting the information it contains or in identifying and eliminating artefacts that may arise from instrumental imperfections or the use of less than optimal conditions for

your sample. Although not specifically aimed at dedicated spectroscopists, the book may still contain new information or may serve as a reminder of what was once understood but has somehow faded away. The text should be suitable for (UK) graduate level courses on NMR spectroscopy, and sections of the book may also be appropriate for use in advanced undergraduate courses. The book does not, however, contain descriptions of the basic NMR phenomena such as chemical shifts and coupling constants, and neither does it contain extensive discussions on how these may be correlated with chemical structures. These topics are already well documented in various introductory texts [6–9] and it is assumed that the reader is already familiar with such matters.

The emphasis is on techniques in solution-state (high-resolution) spectroscopy, principally those used throughout organic chemistry as appropriate for this series, although extensions of the discussions to inorganic systems should be straightforward, relying on the same principles and similar logic. Likewise, greater emphasis is placed on small to mid-sized molecules (with masses up to a few thousand say) since it is on such systems that the majority of organic chemistry research is performed. That is not to say that the methods described are not applicable to macromolecular systems, and appropriate considerations are given when these deserve special comment. Biological macromolecules are not covered however, but are addressed in a number of specialised texts [10–12].

1.2.1. What this book contains

The aim of this text is to present the most important NMR methods used for organic structure elucidation, to explain the information they provide, how they operate and to provide some guidance on their practical implementation. The choice of experiments is naturally a subjective one, partially based on personal experience, but also taking into account those methods most commonly encountered in the chemical literature and those recognised within the NMR community as being most informative and of widest applicability. The operation of many of these is described using pictorial models (equations appear infrequently, and are only included when they serve a specific purpose) so that the chemist can gain some understanding of the methods they are using without recourse to uninviting mathematical descriptions. The sheer number of available NMR methods may make this seem an overwhelming task, but in reality most experiments are composed of a smaller number of comprehensible building blocks pieced together, and once these have been mastered an appreciation of more complex sequences becomes a far less daunting task. For those readers wishing to pursue a particular topic in greater detail, the original references are given but otherwise all descriptions are self-contained.

Following this introductory section, Chapter 2 introduces the basic model used throughout the book for the description of NMR methods and describes how this provides a simple picture of the behaviour of chemical shifts and spin-spin couplings during pulse experiments. Following this, the model is used to visualise nuclear spin relaxation, a factor of central importance for the optimum execution of all NMR experiments (indeed, it seems early attempts to observe NMR failed most probably because of a lack of understanding at the time of the relaxation behaviour of the chosen samples!). Methods for measuring relaxation rates also provide a simple introduction to multipulse NMR sequences. Chapter 3 describes the practical aspects of performing NMR spectroscopy. This is a chapter to dip into as and when necessary and is essentially broken down into self-contained sections relating to the operating principles of the spectrometer and the handling of NMR data, how to correctly prepare the sample and the spectrometer before attempting experiments, how to calibrate the instrument and how to monitor and measure its performance,