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HIGH RESOLUTION NMR
Theory and Chemical Applications

SECOND EDITION

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Second Edition

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Preface to Second Edition

During the eleven years since publication of the first edition of this book, applications of NMR in chemistry and biochemistry have mushroomed. With the discovery of new NMR phenomena and the spectacular development of NMR instrumentation, the types of problems amenable to solution by NMR are steadily increasing. For example, two major areas that had only limited NMR study eleven years ago—solid state phenomena and biochemical processes—are now among the most exciting and rapidly growing fields of NMR research. The advent of routine carbon-13 NMR spectrometers has had a major impact on the use of NMR in organic structure elucidation, and the now routine high field multinuclear spectrometers promise to be of great value in inorganic and metallo-organic chemistry.

In revising this book, I have tried to retain the basic organization and presentation that proved successful in the first edition. Large sections on basic principles, chemical shifts, coupling constants, and analysis of complex spectra have been changed only slightly. On the other hand, many parts have been expanded substantially—for example, carbon-13, nuclear Overhauser effect, relaxation mechanisms, and use of superconducting magnets, each of which was treated only briefly in the first edition. Fourier transform methods, which were covered in one paragraph in the first edition, now take up an entire chapter. As in the first edition, problems are given at the ends of most chapters, with answers to selected problems provided in Appendix D. The original collection of proton spectra of "unknowns" (Appendix C) has been augmented with a number of carbon-13 spectra.

Preface to First Edition

Few techniques involving sophisticated instrumentation have made so rapid an impact on chemistry as has nuclear magnetic resonance. Within five years after the discovery that NMR frequencies depended upon the chemical environments of nuclei, commercial instruments capable of resolving resonance lines separated by less than 0.1 part per million (ppm) were available. Chemists immediately found NMR to be a valuable tool in structure elucidation, in investigations of kinetic phenomena, and in studies of chemical equilibria. Rapid developments in our understanding of NMR phenomena and their relation to properties of chemical interest continue today unabated, and dramatic instrumental developments have improved resolution and sensitivity by factors of ~50 from the first commercial instruments. Today more than 1500 NMR spectrometers are in use, and the scientific literature abounds in reference to NMR data.

In the course of teaching the background and applications of NMR both to graduate students and to established chemists who wanted to learn more of this technique, I have felt the need for a textbook at an ''intermediate'' level of complexity—one which would provide a systematic treatment of those portions of NMR theory most needed for the intelligent and efficient utilization of the technique in various branches of chemistry and yet one which would avoid the mathematical detail presented in the several excellent treatises on the subject.

In this book I have attempted to present an explanation of NMR theory and to provide sufficient practical examples of the use of NMR to permit the reader to develop a clear idea of the many uses—and the limitations—of this technique. Many practical points of experimental methods are discussed, and pitfalls pointed out. A large collection of problems and spectra of ''unknown'' compounds of graded difficulty permits the student to test his knowledge of NMR principles. Answers to selected problems are given. I have not attempted to include large compendia of data,

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but ample literature references and lists of data tabulations and reviews should permit the reader to locate the specialized data needed for specific applications. Many of the literature references are to recent reviews or to other books, rather than to original articles, since the references are intended to provide guides to further reading, not to give credit for original contributions. Under these circumstances an author index would be pointless and has not been included.

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Chapter 1

Introduction

1.1 Historical

Many atomic nuclei behave as though they are spinning, and as a result of this spin they possess angular momentum and magnetic moments. These two nuclear properties were first observed indirectly in the very small splittings of certain atomic spectral lines (hyperfine structure). In 1924 Pauli[1] suggested that this hyperfine structure resulted from the interaction of magnetic moments of nuclei with the already recognized magnetic moments of electrons in the atoms. Analysis of the hyperfine structure permitted the determination of the angular momentum and magnetic moments of many nuclei.

The concept of nuclear spin was strengthened by the discovery (through heat capacity measurements) of *ortho* and *para* hydrogen[2]— molecules that differ only in having the two constituent nuclei spinning in the same or opposite directions, respectively.

In the early 1920s Stern and Gerlach[3] had shown that a beam of atoms sent through an inhomogeneous magnetic field is deflected according to the orientation of the electron magnetic moments relative to the magnetic field. During the 1930s refinements of the Stern–Gerlach technique permitted the measurement of the much smaller values of *nuclear* magnetic moments.[4] A major improvement in this type of experiment was made by Rabi and his co-workers[5] in 1939. They sent a beam of hydrogen molecules through first an inhomogeneous magnetic field and then a homogeneous field, and they applied radio-frequency (rf) electromagnetic energy to the molecules in the homogeneous field. At a sharply defined frequency, energy was absorbed by the molecular beam and caused a small but measurable deflection of the beam. This actually was the first observation of nuclear magnetic resonance, but such studies were

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performed only in molecular beams under very high vacuum. It was not until 1946 that nuclear magnetic resonance was found in bulk materials (solids or liquids). In that year Purcell and his co-workers at Harvard reported nuclear resonance absorption in paraffin wax,[6] while Bloch and his colleagues at Stanford found nuclear resonance in liquid water.[7] (They received the 1952 Nobel Prize for their discovery.) When we speak of nuclear magnetic resonance, we are really thinking of the kind of NMR discovered by Bloch and Purcell; that is, nuclear magnetic resonance in bulk materials.

The early work in NMR was concentrated on the elucidation of the basic phenomena and on the accurate determination of nuclear magnetic moments. NMR attracted little attention from chemists until, in 1949 and 1950, it was discovered that the precise resonance frequency of a nucleus depends on the state of its chemical environment.[8] In 1951 separate resonance lines were found for chemically different protons in the same molecule.[9] The discovery of this so-called *chemical shift* set the stage for the use of NMR as a probe into the structure of molecules; this is the aspect of NMR that we shall explore in this book.

1.2 High Resolution NMR

It is found that chemical shifts are very small, and in order to observe such shifts one must study the material in the right state of aggregation. In solids, where intermolecular motion is highly restricted, internuclear interactions cause such a great broadening of resonance lines that chemical shift differences are masked. In solution, on the other hand, the rapid molecular tumbling causes these interactions to average to zero, and sharp lines are observed. Thus there is a distinction between *broad line NMR* and *high resolution,* or narrow line, NMR. We shall deal almost exclusively with the latter. (With sophisticated methods that we shall mention later, it is possible in some cases to mask the effects of internuclear interactions in solids and thus obtain relatively narrow lines.)

An NMR spectrum is obtained by placing a sample in a homogeneous magnetic field and applying electromagnetic energy at suitable frequencies. In Chapter 2 we shall examine in detail just how NMR spectra arise, and in Chapter 3 we shall delve into the procedures by which NMR is studied. Before we do so, however, it may be helpful to see by a few examples the type of information that can be obtained from an NMR spectrum.

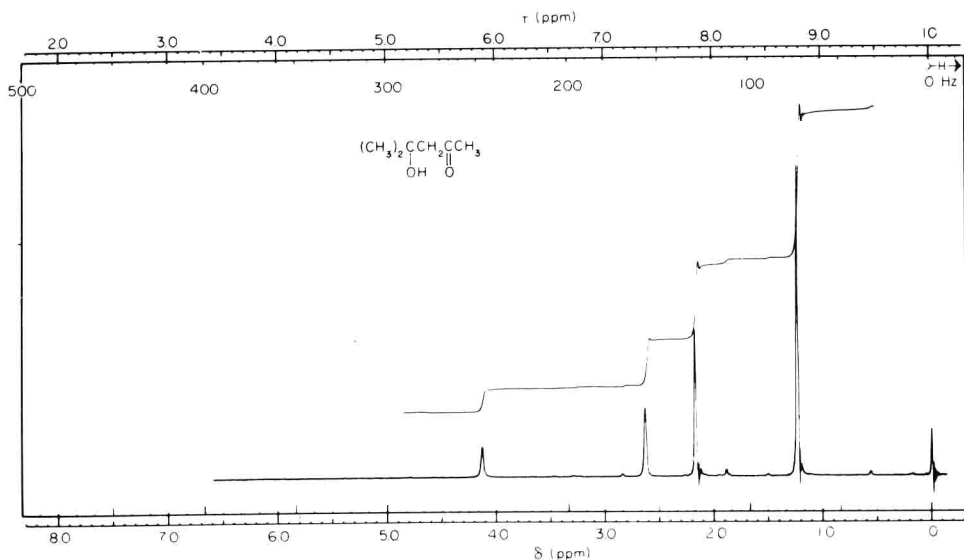Basically there are three quantities that can be measured in a high res-

Fig. 1.1 Proton magnetic resonance spectrum of 4-hydroxy-4-methyl-2-pentanone (diacetone alcohol). Assignments of lines to functional groups as follows: $\delta = 1.23$, $(CH_3)_2$; 2.16, $CH_3C{=}O$; 2.62, CH_2; 4.12, OH. (For definition of δ scale, see Chapter 4.)

olution NMR spectrum: (1) frequencies, (2) areas, and (3) widths or shapes of the resonance lines. Figure 1.1 shows the spectrum of a simple compound, diacetone alcohol. This spectrum, as well as the others shown in this chapter, arises only from the resonance of the hydrogen nuclei in the molecule. (We shall see in Chapter 2 that we normally obtain a spectrum from only one kind of nucleus and discriminate against the others.) The line at zero on the scale below the spectrum is a reference line (see Chapters 3 and 4). Each of the other lines can be assigned to one of the functional groups in the sample, as indicated in the figure. The step function shown along with the spectrum is an integral, with the height of each step proportional to the area under the corresponding spectral line. There are several important features illustrated in this spectrum: First, the chemical shift is clearly demonstrated, for the resonance frequencies depend on the chemical environment, as we shall study in detail in Chapter 4. Second, the areas under the lines are different and, as we shall see when we examine the theory in Chapter 2, the area of each line is proportional to the number of nuclei contributing to it. Third, the widths of the lines are different; in particular, the line due to the OH is considerably broader than the others. We shall examine the reasons for different line widths in Chapters 2, 8, and 11.
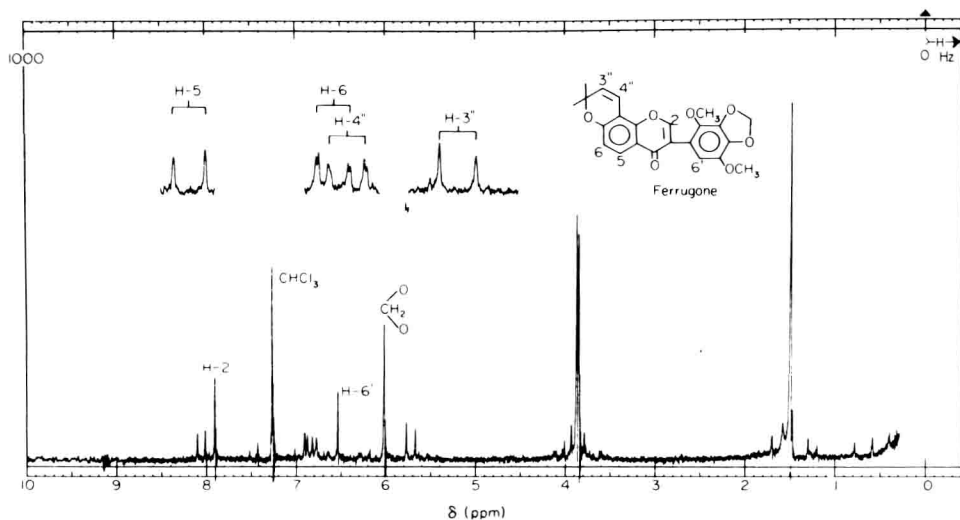
Fig. 1.2 Proton magnetic resonance spectrum of ferrugone in $CDCl_3$, showing multiplets due to spin–spin coupling between protons 5 and 6 and between protons 3″ and 4″. Assignments to functional groups: $\delta = 1.5$, CH_3; ~ 3.85, OCH_3; ~ 5.7, $H_{3''}$; 6.0, OCH_2O; 6.55, $H_{6'}$; 6.8, H_6; 6.9, $H_{4''}$; 7.27, $CHCl_3$; 7.9, H_2; ~ 8.1 H_6 (Highet[10]).
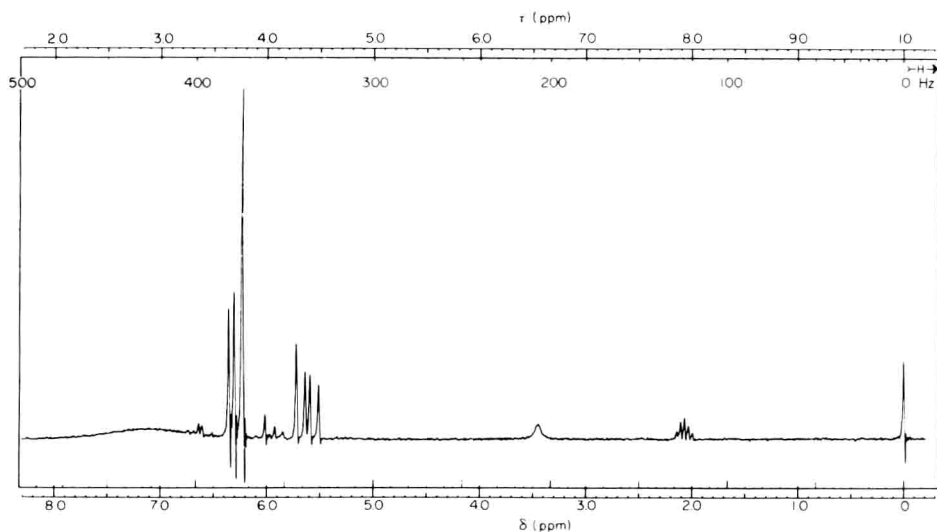
Fig. 1.3 Proton magnetic resonance spectrum of $CH_2{=}CH{-}C(O){-}NH_2$ (acrylamide) in acetone-d_6. Assignments: $\delta = 5.5$–6.7, $CH_2{=}CH$; 7.1 (very broad), NH_2; acetone-d_5, 2.07; impurities, 3.45, 6.0.

The spectrum in Fig. 1.1 is particularly simple. A more typical spectrum—that of a natural product, ferrugone—is given in Fig. 1.2. This spectrum consists of single lines well separated from each other, as were the lines in Fig. 1.1, and of simple multiplets. (The inset shows the multiplets on an expanded abscissa scale.) The splitting of single lines into multiplets arises from interactions between the nuclei called *spin–spin coupling*. This is an important type of information obtainable from an NMR spectrum. In Chapter 5 we shall inquire into the origin of spin coupling and what information of chemical value we can get from it.

Figure 1.3 shows the spectrum of a simple molecule, acrylamide. The three vinyl protons give rise to the 12-line spectrum at $\delta = 5.5$–6.7, which shows little regularity in spacing or intensity distribution. A spectrum of this sort must be analyzed by procedures that we shall discuss in detail in Chapter 7. However, the appearance of such complex spectra can be altered substantially by examining the sample at a different magnetic field
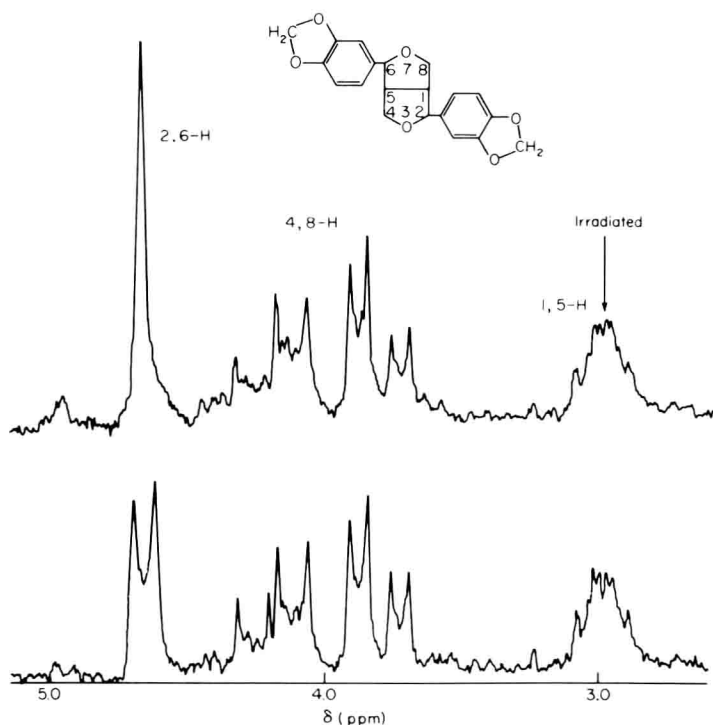

Fig. 1.4 Part of the proton NMR spectrum of sesamin. Bottom, ordinary spectrum; top, with additional radio-frequency irradiation in the vicinity of the complex multiplet at the right of the spectrum.
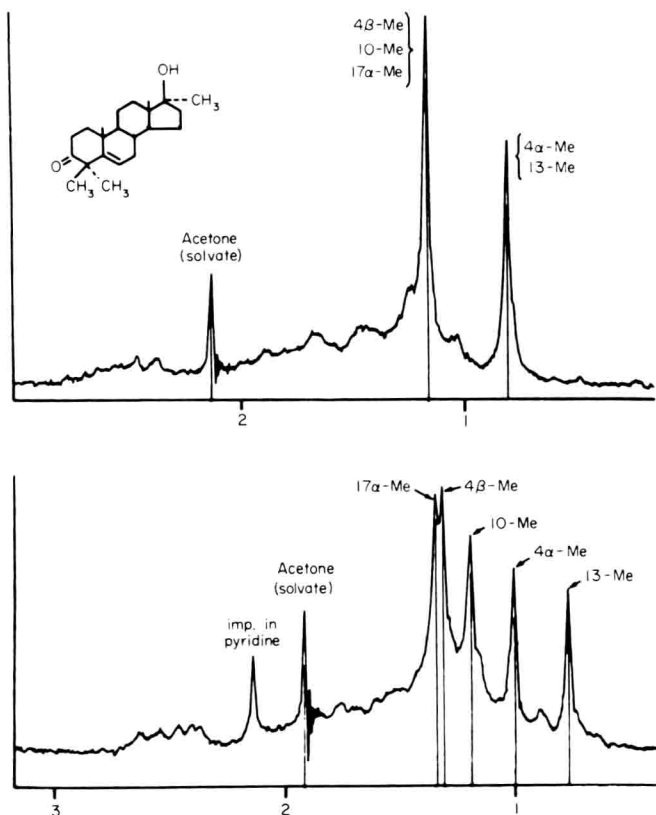
Fig. 1.5 Portions of the proton NMR spectra of 4,4,17α-trimethyl-17β-hydroxy-5-androsten-3-one in CDCl₃ (upper) and in pyridine (lower). Reprinted with permission from G. Slomp and F. MacKellar, *J. Am. Chem. Soc.* **82**, 999 (1960). Copyright by the American Chemical Society.

strength. Often by increasing the field (and the corresponding observation frequency) by a sufficient amount the apparently irregular spacings of lines give way to more readily discerned simple multiplets. In Chapters 4 and 5 we shall see why NMR spectra are dependent on magnetic field strength, while in Chapter 3 we shall look into many aspects of NMR instrumentation.

A powerful method for unraveling complex spectra is *double resonance,* in which two radio frequencies are applied to the sample simultaneously. Figure 1.4 shows the results of one type of double resonance experiment. Application of an intense rf field at the frequency of the complex multiplet near the right of the spectrum causes the doublet near the left end of the spectrum to collapse to a single line, while the remainder of