1
Introduction

Of the important spectroscopic aids that are at the disposal of the chemist for use in structure elucidation, nuclear magnetic resonance (NMR) spectroscopy is one of the major tools. When, in December 1945 and in January 1946, two groups of physicists in the United States working independently – Edward M. Purcell, Howard C. Torrey, and Richard V. Pound at Harvard University on the US east coast and Felix Bloch, William W. Hansen, and Martin Packard at Stanford University in California – first succeeded in observing the phenomenon of NMR in solids and liquids they set the starting point for the unforeseen development of a new branch of science. The impact of their discovery was soon recognized and Bloch and Purcell received the Nobel Prize in Physics in 1952 (Figures 1.1 and 1.2).

At the beginning of the 1950s, the phenomenon was called upon for the first time in the solution of a chemical problem. Since then its importance has steadily increased – a situation highlighted by three additional Nobel Prizes: in 1991 to Richard R. Ernst from the Eidgenössische Technische Hochschule (ETH) Zürich, Switzerland, for his outstanding contributions to the development of experimental NMR techniques, in 2002 to Kurt Wüthrich from the same institution for his

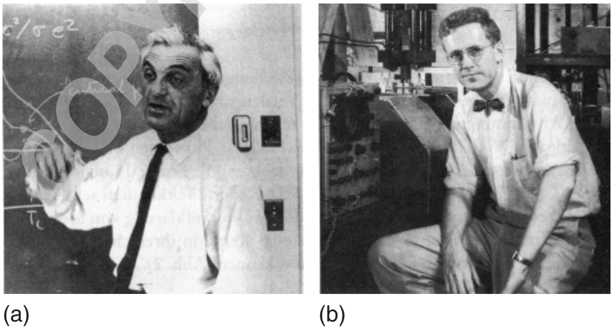

(a) (b)

Figure 1.1 The founding fathers of nuclear magnetic resonance: Felix Bloch (1905–1983) (a) (Reprinted with permission from Reference [1]. Copyright 1985 International Society of Magnetic Resonance.) and Edward M. Purcell (1912–1997) (b). Courtesy of Physics Department, Harvard University.

NMR Spectroscopy: Basic Principles, Concepts, and Applications in Chemistry, Third Edition. Harald Günther.

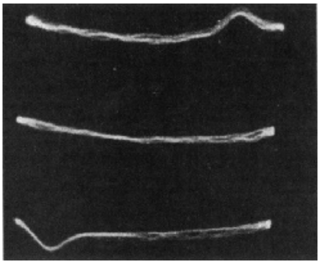


Figure 1.2 The first proton NMR signal from a water sample as seen on the screen of an oscilloscope by Bloch, Hansen, and Packard at Stanford University, California, USA, in January 1946 (Reprinted with permission from [2]. Copyright 1946 by the American Physical Society).

contributions to structural biology, and in 2003 to Paul C. Lauterbur from the University of Illinois at Urbana-Champaign, and Sir Peter Mansfield, University of Nottingham, UK, for the invention of NMR imaging, known today as magnetic resonance imaging (MRI).

The physical foundation of NMR spectroscopy lies in the magnetic properties of atomic nuclei. The interaction of the nuclear magnetic moment with an external magnetic field, $\boldsymbol{B}_0$, leads, according to the rules of quantum mechanics, to a nuclear energy level diagram, because the magnetic energy of the nucleus is restricted to certain discrete values E_i, the so-called *eigenvalues*. Associated with the eigenvalues are the *eigenstates*, which are the only states in which an elementary particle can exist. They are also called *stationary states*. Through a radiofrequency (RF) transmitter, transitions between these states can be stimulated. The absorption of energy is then detected in an RF receiver and recorded as a spectral line, the so-called *resonance signal* (Figure 1.3).

In this way a *spectrum* can be generated for a molecule containing atoms whose nuclei have non-zero magnetic moments. Among these nuclei are the proton, ^{1}H,

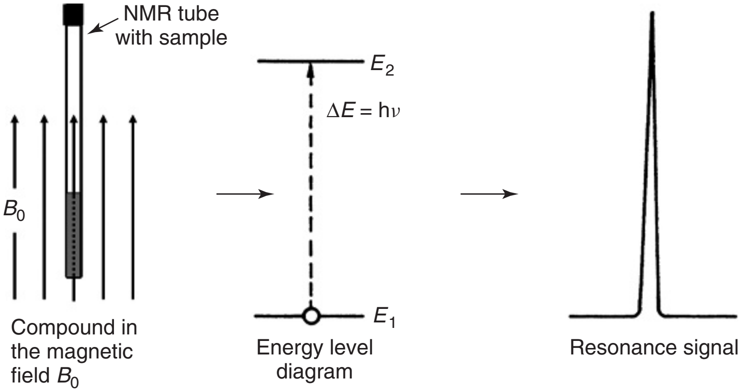


Figure 1.3 Formation of an NMR signal.

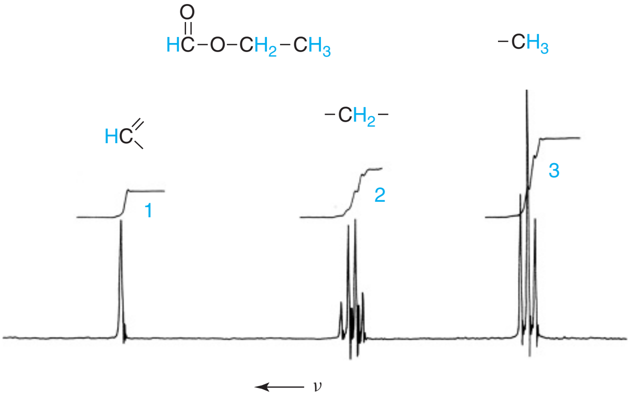


Figure 1.4 ^1H NMR spectrum of ethyl formate.

the fluorine nucleus, ^{19}F, the nitrogen isotopes, ^{14}N and ^{15}N, and many others of chemical interest. However, the carbon nucleus, ^{12}C, that is so important in organic chemistry has, like all other nuclei with even mass and even atomic number, no magnetic moment. Therefore, NMR studies with carbon are limited to the stable isotope ^{13}C, which has a natural abundance of only 1.1%.

To illustrate a NMR spectrum and its essential characteristics, the proton NMR spectrum of ethyl formate is reproduced in Figure 1.4. The spectrum was measured in a magnetic field of 1.4 T with a frequency ν of 60 MHz. In addition to the resonance signals observed at different frequencies, it shows a step curve produced by an electronic *integrator*. The heights of the steps are proportional to the areas under the corresponding spectral lines.

The following points should be noted:

1) Different resonance signals or groups of resonance signals are found for the protons. These arise because the protons reside in different chemical environments. The resonance signals are separated by a so-called *chemical shift*.
2) The area under a resonance signals is proportional to the number of protons that give rise to the signals. It can be measured by integration.
3) Not all proton resonances are simple (i.e., singlets). For some, characteristic splitting patterns are followed, forming triplets or quartets. This splitting is the result of *spin–spin coupling* – a magnetic interaction between different nuclei.

Empirically determined correlations between the spectral parameters, chemical shift and spin–spin coupling, on the one hand, and the structure of chemical compounds on the other hand form the basis for the application of proton and, in general, NMR to the *structure determinations* of unknown samples. In this respect the nuclear magnetic moment has proved itself to be a very sensitive probe with which one can gather extensive information. Thus, the chemical shift characterizes the chemical environment of the nucleus that is responsible for a signal. Integration of the spectrum allows one to draw conclusions concerning the relative numbers of nuclei present. Spin–spin coupling makes it possible

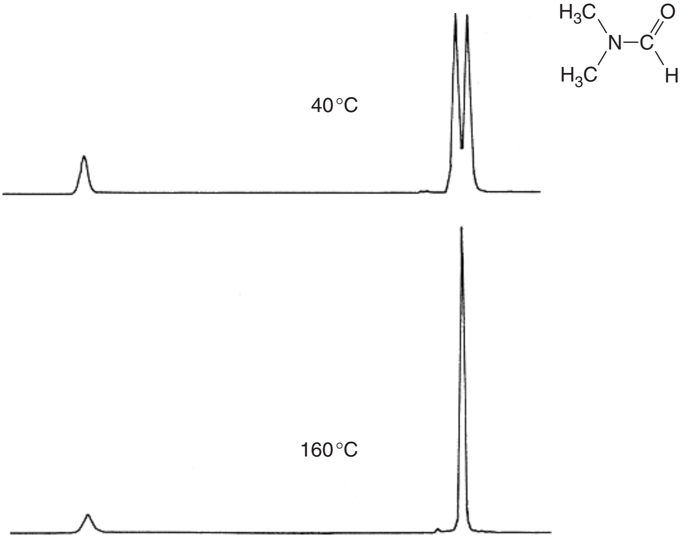
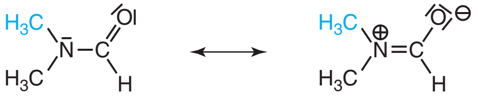


Figure 1.5 Temperature dependence of the ^{1}H NMR spectrum of *N,N*-dimethylformamide.

to define the positional relationship between the nuclei since the magnitude of this interaction – the coupling constant *J* – depends upon the number and type of bonds separating them. The multiplicity of the resonance signals and the intensity distribution within the multiplet are, moreover, in simple cases, as illustrated by the ethyl group of ethyl formate, clearly dependent upon the number of nuclei on the neighboring group.

Numerous additional applications of NMR have been developed. One of general importance is based on the observation that the NMR spectra of many compounds are temperature dependent and apparently sensitive to *dynamic processes*. Such a case is found with dimethylformamide, the spectrum of which shows a doublet for the resonance of the methyl protons at 40°C while at 160°C a singlet is observed (Figure 1.5).

The cause of this different behavior at the two temperatures is the high barrier to rotation about the carbonyl carbon–nitrogen bond (88 kJ mol^{-1}), which possesses partial double bond character as illustrated by the resonance form (a). The two methyl groups therefore have a relatively long life-time in different chemical environments, cis or trans to the carbonyl oxygen, and this leads to separate resonances. At higher temperatures the rate of internal rotation is increased and frequent interconversion of methyl groups between chemically different positions results, so that we are obviously no longer able to distinguish between them.



a

It follows that, for several molecules, the line shape of NMR signals is dependent upon dynamic processes and the *rates* of such processes can be studied with the aid of NMR spectroscopy. What is even more significant is that one can study fast reversible reactions that cannot be followed by means of classical kinetic methods. Thus, the progress achieved in the fields of fluxional molecules, like bullvalene, and in other areas, such as conformational analysis, would have been unimaginable without NMR spectroscopy.

NMR spectroscopy is also used successfully to study *reaction mechanisms* in all branches of chemistry. In these experiments, magnetic isotopes of hydrogen, carbon, or nitrogen (^{2}H, ^{13}C, ^{15}N) and many others can be used in labeling experiments that are devised to follow the fate of a particular atom during the reaction of interest. Labeling with radioactive carbon, ^{14}C, can be replaced today in many cases by labeling experiments with the stable but NMR active carbon isotope ^{13}C. Only where the highest sensitivity is indispensable does the use of the radiocarbon method still prevail.

The various aspects of the application of NMR to problems of inorganic, organic, and physical chemistry are supplemented by a remarkable variety of experimental techniques that lend a special position to NMR spectroscopy in comparison with other spectroscopic methods. In addition to the versatile physics of the NMR experiment, the large number of magnetic nuclei that are of significance to chemistry also contributes to this situation.

In the fields of organic chemistry and biochemistry, ^{13}C NMR plays a major role, but NMR investigations of ^{19}F, ^{15}N, and ^{31}P nuclei also yield valuable information. As is demonstrated in Figure 1.6 with the ^{13}C and ^{15}N NMR spectra of purine anion, the chemical shifts of these nuclei are sensitive to the chemical structure. With additional information from proton NMR, each position in the molecule is labeled with a reporter that provides data about bonding, structure, and reactivity.

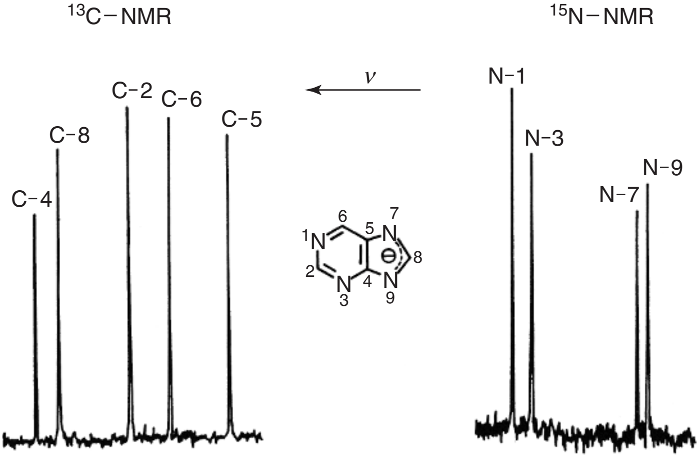


Figure 1.6 Carbon-13 (^{13}C) and nitrogen-15 (^{15}N) NMR spectra of the purine anion.

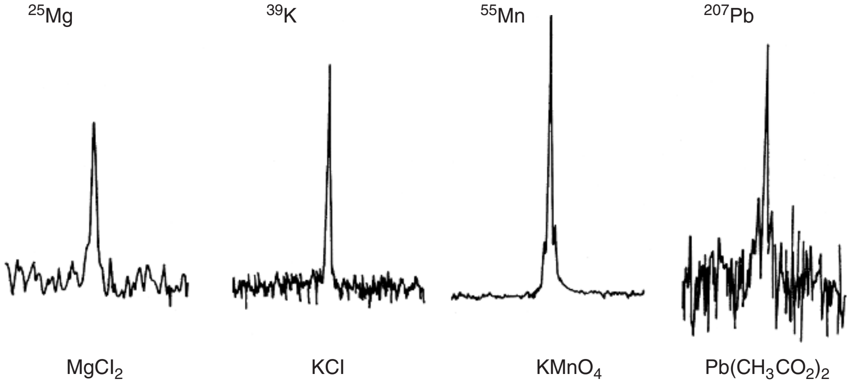


Figure 1.7 Nuclear magnetic resonance signals of metal nuclei.

For inorganic chemistry numerous metal nuclei are of interest and have become available for NMR experiments due to the rapid development of experimental techniques (Figure 1.7). Since nearly all elements of the Periodic Table contain a stable isotope with a magnetic moment, a large area is accessible for NMR investigations, even if the natural abundance of many of these isotopes is rather small.

Another innovation of general importance is *high-resolution NMR spectroscopy of solids*, which opened up new areas of structural research in inorganic and organic chemistry. Fast sample rotation and magnetization transfer from sensitive to insensitive nuclei – methods known as magic-angle spinning (MAS) and cross polarization (CP) – provide the basis for the measurement of chemical shifts and the study of dynamic processes even in solids.

All these topics have been accompanied by an improvement of existing, and the invention of completely new, measuring techniques. Three major events characterize this development:

1) Introduction of *cryomagnets* with high magnetic fields, $\boldsymbol{B}_0$, that are provided by a superconducting coil;
2) replacement of the continuous wave (CW) method by the pulse Fourier transform (PFT) method;
3) introduction of the concept of two-dimensional (2D) NMR.

These achievements have revolutionized practically all branches of NMR spectroscopy, for liquids as well as for solids:

- because the energy difference, ΔE, between the ground and excited state of NMR spectroscopy as well as the chemical shift are field dependent, the increase in $\boldsymbol{B}_0$ has strongly improved *sensitivity* and *spectral dispersion;*
- while the older CW method used monochromatic signal excitation and the time needed to record a spectrum signal by signal was 250 or 500 s, the PFT method provides polychromatic signal excitation and the whole spectrum is measured in 1 s. The receiver signal is then analyzed mathematically by a Fourier transformation;

- *two-* and later *multidimensional NMR* became possible because special techniques of impulse spectroscopy allow the recording of NMR spectra with two or more independent frequency dimensions.

A 2D spectrum, for example, is characterized by two frequency axes, F_1 and F_2, and the signals appear as frequency pairs (f_1, f_2). In some experiments, the frequency axis F_2 only contains chemical shifts, while F_1 only contains spin–spin coupling constants. Both parameters are, therefore, separated by the 2D NMR experiment. For practical purposes spectra with chemical shift data on both frequency axes are the most important because they allow a so-called *shift correlation* between resonance frequencies of different nuclei and in this way a spectral assignment. One distinguishes homo- and heteronuclear shift correlations because F_1 and F_2 can contain frequencies of the same nuclides, for example, of protons, or of different nuclides, for example, of protons in F_1 and of carbon-13 in F_2.

A homonuclear two-dimensional shift correlation, a so-called COSY spectrum (*co*rrelated *s*pectroscop*y*), is shown in Figure 1.8 for the protons of ethyl formate. The new and important aspect is the observation of *cross peaks* that appear in addition to the normal spectrum recorded on the diagonal. Cross peaks have coordinates $F_1 \neq F_2$ and indicate spin–spin coupling between the respective nuclei, here those of the CH_2 and CH_3 group. Diagonal signals have the coordinates $F_1 = F_2$ and reproduce the 1D spectrum. The so-called *contour diagram* shown in Figure 1.8b gives a particularly clear demonstration of the characteristic cross peak positions.

COSY spectroscopy is important for the analysis of complex spectra with intensive signal overlap, where coupled nuclei can no longer be recognized on the basis of simple multiplet structures. Other 2D NMR spectra show cross peaks resulting from non-scalar interactions between nuclei that are close in space or that participate in a chemical exchange process. In this way information about atomic distances

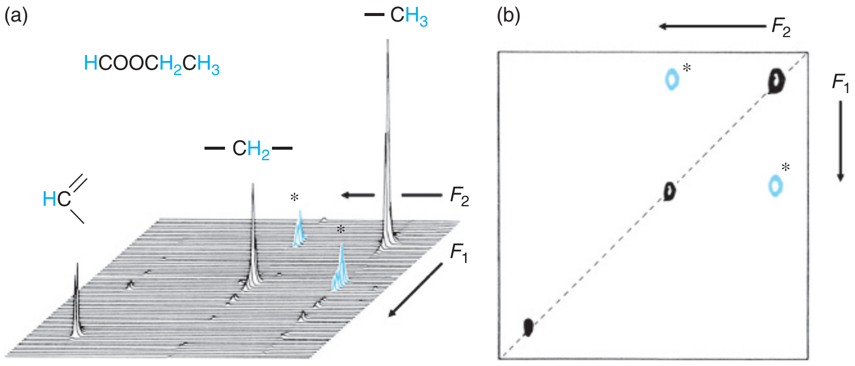


Figure 1.8 Two-dimensional $^1H,^1H$ COSY spectrum of ethyl formate with the axes F_1 and F_2 with diagonal and cross peaks (the latter are marked with an asterisk, *); (a) stacked plot and (b) contour plot. The splitting due to spin-spin coupling is hidden in the line width.

or the mechanism of intramolecular dynamic processes becomes available. Two-dimensional NMR thus paved the way to successful investigation of the structures of complex molecules like natural products and biopolymers such as proteins or nucleic acids. In many cases even the complete three-dimensional structure could be derived solely on the basis of NMR data.

In summary, this short overview may convince the reader that NMR spectroscopy is an indispensable tool for all branches of chemistry. In addition, the method has its place in other sciences such as physics, biology, and even medicine, where in addition to the NMR imaging techniques the measurement of NMR spectra *in vivo* yields new information about body fluids or chemical processes in living tissue.

1.1
Literature

Numerous textbooks and monographs deal with NMR, ranging from physics to chemistry and biology to medicine. A complete biography is, therefore, beyond the limits of our introduction.

For the present textbook, we have adopted the following procedure: after each chapter we provide first a list with the original citations for material used in the text. Then, where required, selected textbooks or monographs are recommended for further reading, followed by a list of review articles on topics treated in the particular chapter. The following review series are frequently cited throughout the book:

Webb, G.A. (ed) *Annual Reports on NMR Spectroscopy*, Elsevier, Amsterdam.
Harris, R.K. and Grant, D.M. (eds) (1996) *Encyclopedia of Nuclear Magnetic Resonance*, John Wiley & Sons, Ltd, Chichester.
Diehl, P., Fluck, E., Kosfeld, R., Günther, H., and Seelig, J. (eds) *NMR - Basic Principles and Progress*, Springer-Verlag, Berlin.
Bodenhausen, G., Gadian, D.G., Meier, B.H., and Morris, G.A. (eds) *Progress in Nuclear Magnetic Resonance Spectroscopy*, Pergamon Press, Oxford.

To conclude this section, three classic books should also be listed:

1) Abragam, A. (1961) *The Principles of Nuclear Magnetism*, Clarendon Press, Oxford, 599 pp.
2) Ernst, R.R, Bodenhausen, G., and Wokaun, A. (1987) *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*, Clarendon Press, Oxford, 610 pp.
3) Pople, J.A., Schneider, W.G., and Bernstein, H.J. (1959) *High-Resolution Nuclear Magnetic Resonance*, McGraw-Hill Book Co., Inc., New York, 501 pp.

The first two books are physics-oriented and the last one was the first monograph with the emphasis on chemistry.

1.2
Units and Constants

The Système International (SI), based on the meter, kilogram, second, and ampere, is now accepted for all units of physicochemical quantities. Accordingly, SI units have generally been used in the present text. In chemistry, however, the old centimeter, gram, second (CGS) system is still in use and, of course, older textbooks and research papers employed this system. It seems, therefore, necessary to point out some of the main changes that occur when SI units are used:

1) For the magnetic field we use the symbol $\boldsymbol{B}$, the magnetic induction field or magnetic flux density, a vector with magnitude B. The former use of $\boldsymbol{H}$ is incorrect, since this symbolizes the magnetic field intensity. The SI unit for the magnetic induction field is the tesla ($\mathrm{T} = \mathrm{kg\ s^{-2}\ A^{-1}}$), which is 10^4 times the electromagnetic unit, the gauss (G). Nevertheless, the simple expressions ''magnetic field'' or ''field strength'' are still in use when $\boldsymbol{B}$ is discussed.
2) The SI unit for energy is the joule ($\mathrm{J} = \mathrm{kg\ m^2\ s^{-2}}$), and this replaces the calorie. Accordingly, activation energies are now given in $\mathrm{kJ\ mol^{-1}}$, entropies in $\mathrm{J\ K^{-1}\ mol^{-1}}$ (4.184 times the numerical values in $\mathrm{kcal\ mol^{-1}}$ or $\mathrm{cal\ K^{-1}\ mol^{-1}}$, respectively).
3) The SI system uses rationalized equations. In these, the factors 2π or 4π appear where expected on geometrical grounds, that is, if the equation refers to situations where circular or spherical symmetry is involved.
4) The permeability of free space, μ_0, often appears explicitly in SI equations.

Table 1.1 lists the constants that may be used for the physical relations given in the different chapters. In relevant situations we shall indicate which system is used.

Table 1.1 Constants for use in this book[a,b].

Symbol	Name	Magnitude	Unit
h	Planck's constant	6.625×10^{-34}	J s
e	Elementary charge	1.602×10^{-19}	C
m_e	Electron mass	0.9108×10^{-30}	kg
k or k_B	Boltzmann's constant	1.380×10^{-23}	$\mathrm{J\ K^{-1}}$
n_L	Loschmidt's number	6.0252×10^{23}	molecules $\mathrm{mol^{-1}}$
n_A	Avogadro's number	2.6870×10^{25}	gas molecules $\mathrm{m^{-3}}$
μ_0	permeability of free space	$4\pi \times 10^{-7}$	$\mathrm{kg\ m\ s^{-2}\ A^{-2}}$

[a] More information on units is given in Table A.7 (p. 672) in the Appendix.
[b] Taken from reference [3]; please note that in the anglosaxon literature Loschmidt's number is called Avogadro's number.

References

1. Andrew, E.R. (1985) *Bull. Magn. Reson.*, **7**, 81.
2. Bloch, F., Hansen, W.W., and Packard, M. (1946) *Phys. Rev.*, **70**, 474.
3. Gerthsen, C., and Kneser, H.O. (1971) *Physik*, 11th ed., Springer, Berlin, p. 545.