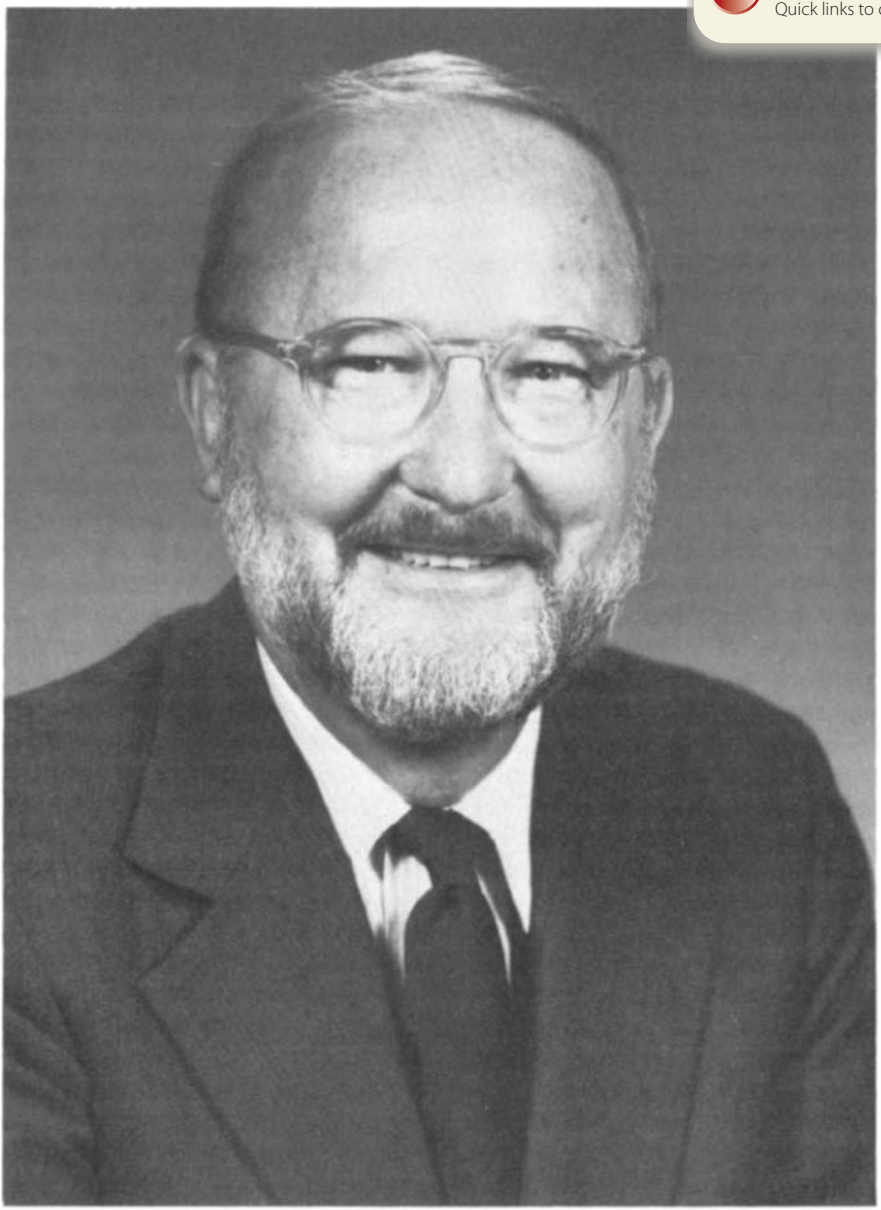

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NMR IN CHEMISTRY— AN EVERGREEN

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INTRODUCTION

Within three decades, nuclear magnetic resonance spectroscopy has developed into the most important spectroscopic technique in chemistry, such that today most chemical laboratories use NMR as a routine tool. Nonetheless, even though NMR is a highly diversified and mature field, new developments and applications continue to appear at a rate that shows no signs of slowing down. Perhaps the best characterization of it was coined by a participant during the 1979 Gordon Research Conference on Magnetic Resonance: "NMR is a true evergreen."

By necessity, our description of this evergreen must be brief, but we hope to give a realistic picture of its development as a powerful technique in chemistry. After a few comments on the unique character of NMR spectroscopy, we describe some of the major breakthroughs in its early years, then document the very rapid growth of NMR in chemistry and give our ideas about the reasons for this phenomenal expansion. Both the original rapid acceptance of NMR as a major spectroscopic tool and its continued success are closely coupled to instrumental capabilities, so we summarize the major advances and trends in NMR instrumentation. Finally, we not only dwell on the history of the development of NMR in chemistry but also point out and discuss some of the present activities in this remarkably broad field. Again, we have to be brief and, therefore, we mention only a few of the areas of current interest.

The question of a bibliography troubled us. Comprehensive coverage, giving credit where credit is due, is well beyond our scope. So we have limited our references to those general articles, reviews, and books that serve to illustrate the major points in our narrative. We apologize ahead of time to those of our NMR friends whose excellent work has not been mentioned.

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UNIQUE FEATURES OF NMR

NMR was so rapidly accepted in chemistry and applied in so many different directions because of its inherent, unique features. In contrast to other spectroscopic techniques, NMR experiments are performed at frequencies in the MHz radio frequency region. Because of this, the radiation used in an NMR experiment is monochromatic to begin with so that one is not burdened by the sometimes complicated task of rendering broad-band radiation as monochromatic as possible. Moreover, the transitions between nuclear spin energy levels involve very small energy changes. Thus, the NMR experiment causes only a slight perturbation of the system in contrast to optical spectroscopy experiments. In fact, the typical NMR "photon" at 60 MHz has only approximately 10^{-6} of the energy of a typical infrared photon and only 10^{-7} to 10^{-8} of a UV photon.

An important aspect of NMR is the fact that the transition probabilities are dependent upon nuclear properties that are not affected by differences in chemical environment, except for relaxation phenomena. Therefore, if one has a complex spectrum for a given nuclear species in a sample, there is a large amount of information in the line intensities that can usually be extracted quite readily. A related point in the NMR experiment is that the spacing of the nuclear spin energy levels, and the transition probabilities, increase with the applied external magnetic field, H_0. Also, the Boltzmann factor is larger at higher fields, adding to the increase in sensitivity.

Progress in magnet technology has led to higher and higher magnetic fields and to continued improvements in the sensitivity of NMR experiments. However, increased sensitivity is not the only important motivation for doing NMR experiments at higher magnetic fields. One of the parameters determining the high resolution spectrum is the chemical shift, $\delta\nu$, which increases with the magnetic field, whereas the other parameter, the spin-spin coupling J, is field independent. The relative values of the chemical shift and the spin-spin coupling constants determine the complexity of the observed NMR spectrum, and a higher applied magnetic field H_0 means much simpler spectra. Unlike other forms of spectroscopy, in which the detailed analysis of a spectrum is feasible only for the simplest molecules, the interpretation of NMR spectra in terms of fundamental parameters is relatively straightforward. The various NMR parameters obtained during the NMR experiment give detailed information about the chemical structure and geometry of the chemical system studied. In addition to the static structural information, one can also learn much about dynamic processes, many of which affect the appearance of an NMR spectrum.

Compared with other spectroscopic techniques, the perturbations affecting the results of an NMR experiment are relatively weak and the corresponding time scale is relatively long. Nonetheless, a wide variety of relaxation and rate processes govern the NMR line shape in several distinguishable and measurable ways. As a consequence, NMR measurements provide unique information about dynamic processes with rates in the range from roughly 10^{-2} to 10^{10} sec^{-1}.

The large majority of NMR applications in chemistry deal with liquids in which the NMR lines are narrowed by motional averaging to a natural line width of the order of 0.1 to 1 Hz. High resolution NMR spectra of complex molecules in the liquid phase usually exhibit a great deal of structure and yield a wealth of information about the molecule. If the proton resonance frequency is, for example, 360 MHz, then the resolution is truly amazing—nearly one part in 10^{10}. This not only indicates the success of current instrumentation, but also points out the demanding requirements for an NMR spectrometer. In contrast, the NMR lines are broad in solids, but thanks to new developments one can now obtain high resolution spectra of solids with valuable information about various anisotropic interactions. In liquids only isotropic interactions can be observed because of the motional averaging.

Finally, an important advantage of NMR is the fact that nuclear properties differ so much that one is always sure of the identity of the species being observed. Furthermore, many nuclei possess magnetic moments and, with the availability of more sensitive spectrometers,

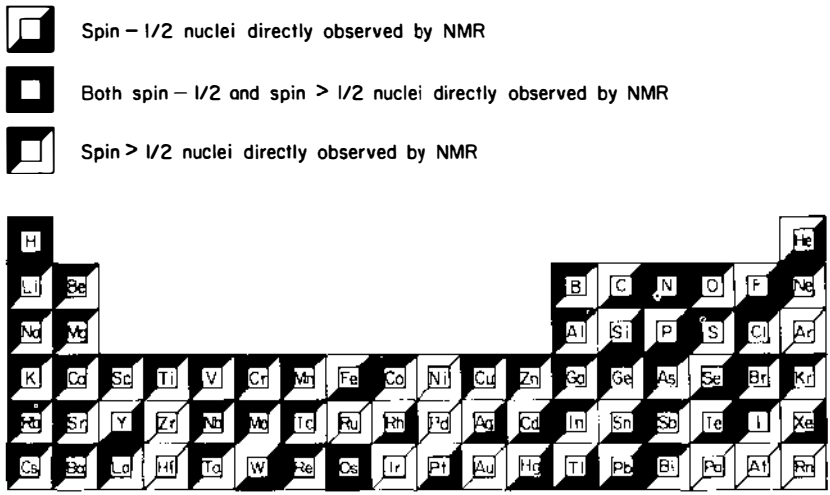

Figure 1 The periodic table of elements up to radon (excluding the lanthanides) with indications of those which can be studied by NMR. [Reproduced from Reference (1)].

chemists are beginning to take greater advantage of the species available. In addition to the favorite NMR nuclei such as ^{1}H, ^{2}H, ^{13}C, ^{14}N, ^{15}N, ^{19}F, and ^{31}P, NMR experiments on many additional nuclei are now beginning to be carried out. For illustration, we include Figure 1, which gives the periodic table up to radon (excluding the lanthanides), indicating which elements have nuclei more or less suitable for use in NMR measurements (1).

THE FIRST DECADE OF NMR: 1946—1956

The first ten years following the discovery of NMR in 1946 were not only a period of exciting new developments in the technique but also a period that firmly established NMR spectroscopy as a major tool in chemistry. It is remarkable that chemists realized so early in the game that NMR would have a major impact in solving a wide range of chemical problems. The reviews of NMR published in the *Annual Review of Physical Chemistry* are a convenient source of information on this early work. The first full-length review (2) on NMR was written by Gutowsky in 1954. It stated that about 400 articles had been published on NMR in the eight years since its discovery in 1946 and that more than half of these were related to problems in the structure of matter.

In the four subsequent years, reviews were written by Shoolery & Weaver (3), by Hutchinson (4), and by McConnell (5). It is of interest to follow the increasing number of chemical applications of NMR, and with the help of hindsight to trace the beginning of various subfields and directions that emerged subsequently. The earliest trends visible are, of course, the development of the more chemical applications and the increased emphasis on NMR studies of liquids in contrast to the period prior to, say 1952, when studies of solids dominated the NMR field.

We present in Figure 2 a survey of the major discoveries in these beginning years, which largely governed the development of NMR in its first decade. In our opinion, these were the discoveries that led to the initial enthusiastic acceptance of NMR by chemists and to the later phenomonal growth of NMR. It is not possible to discuss in detail all of these topics; instead we choose to follow a more subjective, personal approach. In particular, one of us was involved in the early development of NMR in chemistry, and we shall focus on his work on the chemical shift and the discovery of multiplet structure in liquids due to spin-spin coupling. This work helped lay the foundation for the high resolution NMR field, a field of immense importance to chemistry. The following section is an excerpt from an address (6) given by Gutowsky

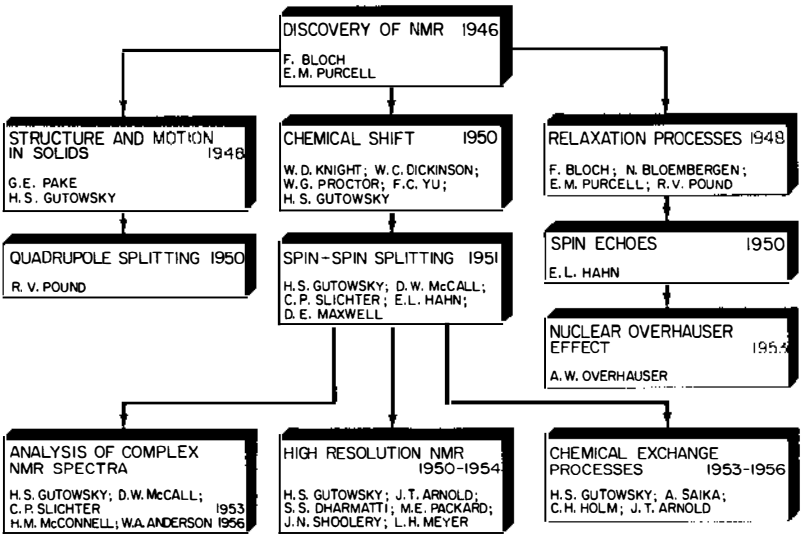

Figure 2 Survey of early developments in NMR in the period 1946–1956.

after the presentation in Bombay of the 1974 award of the International Society of Magnetic Resonance:

The magnet was delivered in early October 1949, and on October 20 we saw our first proton resonance in a water sample. However, my original plans to continue studying the motional narrowing of the broad resonances in solids ran into two snags. Our electronics, especially the lock-in amplifier and the preamplifier just after the RF bridge we were using, did not have the sensitivity needed. Moreover, my initial efforts at designing and building an all-metal cryostat were not very successful, in spite of having a 2 in. gap in which to place it. Fortunately, Knight's report of the resonance shifts in metals appeared at that time, and it included the observation of ^{31}P shifts in several compounds. Also, in early 1950 Proctor and Yu reported chemical shifts between the ^{14}N resonances in the NH_4^+, CN^- and NO_3^- ions, and Dickinson found shifts for fluorine in several compounds. So we turned our interest to chemical shifts in liquids, which we could readily observe for ^{19}F.

At first we looked at whatever compounds we could lay our hands on. Then we began to see if we could resolve the fluorine resonances from structurally nonequivalent nuclei in the same molecule and on April 26, 1950 we looked at the fluorine resonance in a benzene derivative with a CF_3 group and three fluorines on the ring and were able to resolve them. This encouraged us greatly and led me to think about how the shifts might be related to molecular structure. Chemists learn very early to look for periodicities in the chemical and physical properties of compounds, or they don't stay in chemistry very long. We deal with such a large number and wide variety of systems that we have to oversimplify their diversity to be able to remember them. Moreover, in my senior year at Indiana University I was exposed to Linus Pauling's book, "The Nature of the Chemical Bond," which is a masterpiece of such oversimplifications. In any case, it seemed to me that the chemical shift, as an electronic phenomenon, should be related in some way to the nature of the

chemical bonds. This in turn depends upon the nature of the atoms bonded together, so I chose to study the simple binary fluorides, which was a very happy choice.

I was encouraged in this approach because at about that time, I acquired my first graduate student, Charles Hoffman, who had a strong interest in inorganic chemistry. He undertook to synthesize the fluorides needed for the study, many of which were difficult, and he measured their fluorine shifts. At this juncture, in May of 1950, good fortune favored me again. I found exceptionally able help with our electronics problems from R. E. McClure, a senior in Electrical Engineering, who worked part-time with my group while he finished his bachelor's and master's degrees.

Bob was an immediate help, not only in maintaining, designing and constructing our apparatus, but in running many of the early experiments. With his able help, we set out to see if we could find shifts in proton resonances. We convinced ourselves of them on June 30, 1950, when Bob found small but reproducible shifts, several times larger than experimental error, between the protons in benzene, mineral oil, and aqueous solutions of strong acids. At this stage, we started a major effort on improving the homogeneity of the magnetic field by plotting it and hand polishing the pole tips in those areas where the field was high. And later, we broadened the shift study to include the simple hydrides. The shifts for the fluorides showed a strong correlation with the electronegativity of the atom bonded to the fluorine, which subsequently led Apollo Saika and Charlie Slichter to their elegant paper attributing it to the second-order paramagnetic term of Ramsey's theory and its dependence upon the p-electron bonding orbital of the fluorine.

The discovery and characterization of the multiplets, or the indirect, scalar internuclear coupling as the phenomenon is often called, is a very interesting and often exciting story. In my lab, the first observation of the effect was by Charlie Hoffman on September 8, 1950. He observed a double line in the fluorine resonance of the small sample of PF_3 which he had synthesized as part of his fluorine shift study. However, in making the sample he fluorinated PCl_3 so we interpreted the double line as due to $PClF_2$ and/or PCl_2F impurities in his sample. It's an excellent example of something new not being recognized as real and different, but being attributed to a conventional, more or less plausible cause.

Nonetheless, Hoffman repurified the sample, and the second line wouldn't go away. Another sample of PF_3 was synthesized by a different route, and the same double resonance obtained. PF_5 was sythesized and the fluorine resonance in it was found to be a double line, this time attributed to a chemical shift between the three equatorial and two apex fluorines in the trigonal pyramid structure. It was not until March of 1951 that it became completely clear we were really seeing something entirely new. At that time, I encouraged a beginning graduate student, Dave McCall, to look at some phosphorus shifts in several fluoro-chloro phosphorus compounds of known purity. When the ^{31}P resonance in the $POCl_2F$ compound exhibited a 1–1 doublet structure, it finally dawned on me that we had been observing a new type of internuclear interaction related to the spin states of the two nuclei. It was a great thrill to Dave and me when shortly thereafter, we first saw a ^{31}P resonance such as that for CH_3OPF_2, a 1–2–1 triplet as I had predicted.

In our subsequent characterization during 1951 of this scalar or indirect coupling of nuclear spins, we were able to show that the "slow beats" observed by Erwin Hahn in proton spin echoes originated from the multiplets we had found in steady-state fluorine spectra. Furthermore, we turned up some anomalies which clued us in on the importance of chemical exchange in determining the observability

of such splittings. The best case was that of aqueous HBF_4, in which the proton and fluorine resonances were instrumentally determined, at about 0.01 gauss, while that of ^{11}B may have been somewhat larger. ^{11}B has a large g-value, so we expected to resolve a splitting of the fluorine resonance as we found in aqueous HPF_6. After a great deal of debate, we attributed the absence to chemical exchange of fluorines among the BF_4^- ions, which led C. P. Slichter to develop a mathematical treatment of the effect based upon the Bloch equations.

Following this personal view of two of the important developments, we now add a few more general comments about this exciting period. In Figure 2, we have associated the individual discoveries with several major future directions in the development of NMR. For example, the classic work by Bloembergen, Purcell & Pound (1948) on relaxation processes can be regarded as the beginning of the investigation of the dynamic structure of liquids by NMR. The subsequent discovery of spin echoes by Hahn laid the foundation of pulsed NMR spectroscopy, which has been so useful in measuring relaxation times and which fully blossomed later when the Fourier transform techniques were introduced in NMR. Similarly, the nuclear Overhauser effect, discovered in 1953, is a basic relaxation phenomenon, although its applications to chemical problems had to wait for some time.

A second line of discovery starts with the chemical shift and spin-spin splitting. In the course of studying the latter, it was found that the NMR spectrum is modified if the nuclei are taking part in various types of chemical exchange. This discovery provided chemists with an important new tool to measure chemical exchange rates and to determine the nature of the exchange processes. Even in the early years, we see examples of studies of proton exchange, electron exchange, ligand exchange, internal rotation, and various types of conformational change in a wide variety of chemical systems. However, the "main-line product" from the discovery of chemical shifts and spin-spin splitting is high resolution NMR spectroscopy, which rapidly developed into an indispensable tool in the chemical laboratory for establishing molecular structure.

In discussing the growth in chemical applications of NMR, one has to recognize the important role of commercial NMR spectrometers. It is remarkable that by 1953–1955, Varian Associates (Palo Alto, California) had delivered their first three high resolution NMR spectrometers to the Humble Oil Company in Texas, to the DuPont Experimental Station in Delaware, and to the Shell Development Company in California. M. E. Packard, J. N. Shoolery, and H. E. Weaver were NMR researchers who played a leading role at Varian Associates. In contrast to the time gap between the discovery of infrared spectroscopy (1900) and the introduction of the first commercial infrared spectrometer

(1946), the rapidity of development of commercial NMR spectrometers is really amazing. One reason for this rapidity is that the technological base as well as the climate for innovation were excellent in the postwar years; another is the strong interaction between a local, aggressive, electronics-based industry (Varian) and Bloch's NMR group at Stanford.

There are two possible interpretations of the fact that all of the first three spectrometers were delivered to industry: Either it shows that industry was quick to learn of and realize the potential of NMR for solving chemical problems or it merely reflects the inadequate funding of academic research. Most likely, both explanations have some merit. For example, at this early stage of development, a considerable proportion of the publications dealt with applied problems, including NMR studies about polymers, coal, and the determination of water content in various hydroscopic and agricultural materials.

In addition to the names given in Figure 2, it is appropriate to briefly mention at least some of the researchers associated with the pioneering effort of using NMR to solve chemical problems. In the US the list includes (in alphabetical order), W. A. Anderson, A. A. Bothner-By, B. P. Dailey, P. C. Lauterbur, H. M. McConnell, W. D. Phillips, C. A. Reilly, J. D. Roberts, R. G. Shulman, and J. E. Wertz. In Europe, E. R. Andrew, J. G. Powles, and R. E. Richards carried out NMR research in the United Kingdom; names such as G. Béné, R. Gabillard, and M. Soutif are associated with NMR work in continental Europe. In Japan, I. Itoh, A. Saika, and S. Fujiwara are those who come to mind in connection with early NMR work. We at Illinois are pleased that since the early years both the Departments of Chemistry and Physics have had a strong tradition in NMR research. In addition to the work of Gutowsky and C. P. Slichter, it should be noted that two graduate students in physics made major NMR advances while at Illinois: Erwin Hahn discovered spin-echoes in 1950 and A. Overhauser discovered the nuclear Overhauser effect in 1953.

To summarize the activities in the first decade of NMR, we can clearly see the beginning of a widely accepted spectroscopic field that had already demonstrated a unique potential for solving chemical problems. It is also evident that some of the major directions of NMR research were already established but that the major expansion of its uses was still to come. We finish this section on a lighter note by quoting from a lecture (7) of M. E. Packard: "Chemists got the point very quickly, thanked the physicists, and took over." In essence, this statement is an apt characterization of the first decade of NMR.

NMR—A RAPIDLY EXPANDING FIELD

As discussed in the preceding section, NMR gained early and wide acceptance as a physical technique in all fields of chemistry and showed great potential for further growth and expansion. The subsequent expansion of NMR and the appearance of new subfields and novel applications were truly phenomenal. In this section we spend some time documenting the actual growth and reflecting upon the reasons for its remarkable scope.

The Annual Review of Physical Chemistry bears strong testimony of the growth and amazing diversification of the NMR field. In early years, the reviews (8–12) usually covered both NMR and ESR, then concentrated only on NMR (13–18), and later began to discuss specialized topics in NMR. For example, as early as 1965, Bothner-By & Pople (19) reviewed the effects of diamagnetic anisotropy upon chemical shifts; recent examples include NMR at high pressures by Jonas (20) in 1975 and NMR relaxation in thermotropic liquid crystals by Wade (21) in 1977. In the last several years, specialized reviews of several different topics have become not only the standard but the only way to cover the broad diversity and widespread research in NMR. The best evidence is found in Volume 29 of this series. In this single volume (1978), reviews appeared on the following four topics: "NMR Relaxation Studies of Solute-Solvent Interactions" by Bryant (22); "NMR Studies of Membrane Structure and Dynamics" by Bocian & Chan (23); "High Resolution NMR Studies of the Structure and Dynamics of tRNA in Solution" by Patel (24); and "High Resolution Solid State NMR" by Vaughan (25).

Another indication that NMR has become a mature field is the appearance of review series devoted to NMR. In 1965, Waugh (26) started the successful series, *Advances in Magnetic Resonance*, which was followed in 1966 by the series, *Progress in Nuclear Magnetic Resonance Spectroscopy* (27), edited by Emsley, Feeney & Sutcliffe. These were followed in 1968 and 1969 by *Annual Reports on NMR Spectroscopy* (28), edited by Mooney, and the extensive series, *NMR: Basic Principles and Progress* (29), edited by Diehl, Fluck & Kosfeld. In addition, there are series published by the Chemical Society: *NMR Specialist Periodical Reports* (30) and *Topics in Carbon-13 NMR Spectroscopy* (31), edited by Levy. Two journals devoted to NMR started publication in 1969: the highly successful *Journal of Magnetic Resonance* edited by Brey and *Organic Magnetic Resonance* edited by Manatt. In addition, the *Magnetic Resonance Review*, edited by Poole, began publication in 1972 and

the *Bulletin of Magnetic Resonance*, published by the International Society of Magnetic Resonance, just appeared in 1979.

Among the many excellent monographs on NMR, we mention only two classic works essential to any physical chemist who wants to learn about NMR. One of them is *The Principles of Nuclear Magnetism* by Abragam (32); the other is *Principles of Magnetic Resonance* by Slichter (33). Two early monographs (1959) on high resolution NMR, one by Pople, Schneider & Bernstein (34) and the other by Roberts (35), have helped many chemists to become acquainted with NMR.

The large numbers of reviews, journals, and monographs reflect the magnitude of the research being accomplished with NMR methods. A more direct measure is found in the research articles themselves. In his 1954 review, Gutowsky (2) stated that about 400 articles had been published between 1946 and December 1953, an average of 50 per year. But as early as 1962, Meiboom (13) indicated that the number of compounds whose NMR spectra had been reported was so large that even a simple enumeration was beyond the scope of his review. In 1964, Grant (14) specifically pointed out that well over 1000 manuscripts dealing with high resolution NMR had appeared in 1963. In 1967, Jonas & Gutowsky (16) estimated that NMR publications were appearing at a rate of perhaps 550 per month, including all publications that contained any NMR information such as organic studies in which NMR was only used as a routine tool.

For this article, we were able to obtain information on publication rates from the Chemical Abstracts System files for the period 1967 to 1978. Figure 3 gives the number of articles for each year in which NMR key words were listed by the author or appeared in the title or the index terms. The number of such applications was already high in 1967 (about 2700 per year); it grew rapidly to about 4500 in 1971 and since then has

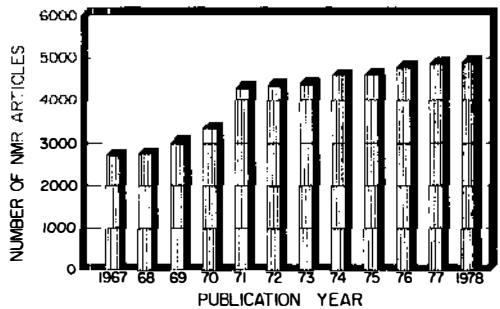

Figure 3 NMR articles contained in Chemical Abstracts System (CAS) files in the period 1967–1978.

crept up to 5000 per year. There are two reasons for presenting Figure 3. First, we thought it might help the non-NMR specialist to realize the scope and extent of the NMR field. Second, we want to show that at the present stage of development of NMR, it is an impossible task for anyone to present an overview, including ourselves.

Another interesting statistic is the number of faculty members in the American PhD-granting departments who are engaged in NMR research, which we have estimated from the *American Chemical Society Directory of Graduate Research* for 1957, 1967, and 1977. From approximately 50 researchers in 1957 who listed some aspect of NMR as an area of their research interests, the number grew to 290 in 1967 and to 370 in 1977. About half of this increase is attributable to an expansion of the departments from a faculty of 2000 in 1957 to 4000 in 1967, which then leveled off at about 4350 in 1977; the other half is a result of the doubling over the two decades of the fraction of faculty members engaged in NMR research. These statistics show that the major expansion of NMR between 1957 and 1967 coincides with a major expansion in research and development, and that one of the factors contributing to rapid growth of NMR in that period was increased research activity in all areas of chemistry. These statistics also show that the days of expansion of chemistry departments are over; however, the actual number of chemists active in NMR research is still increasing.

An important factor in the rapid development of NMR in chemistry is the progress in NMR instrumentation. This effort led, on the one hand, to the development of easy-to-use NMR spectrometers which became routine tools in the chemical laboratory, and on the other hand, it has produced sophisticated research instruments whose capabilities and performance features have improved each year. We quote from the 1963 review by Meiboom (13): "The appearance in 1961 of the Varian Associates A-60 NMR spectrometer has greatly contributed to putting routine NMR spectroscopy within the reach of average chemical laboratories." Varian Associates, a pioneer in the development of commercial NMR spectrometers, has been joined in its efforts by a number of manufacturers both in the US and abroad. Presently, these manufacturers are producing a wide variety of NMR spectrometers. In view of the importance that NMR instrumentation has had in the development of NMR, we shall discuss this topic in more detail in the next section.

Some of the major discoveries that led to new applications and played dominant roles in the further expansion of NMR are listed in Table 1. As we have already mentioned, it is fascinating to trace the new discoveries in NMR and their impact on various fields of chemistry.

Table 1 Chronological list of important developments in NMR since 1956

Year	Development	Initial work
1957	^{13}C spectroscopy	P. C. Lauterbur D. M. Grant J. D. Roberts A. Allerhand
1959	Dependence of spin-spin coupling constants on bond angles	M. Karplus H. S. Gutowsky D. M. Grant
1959	High resolution NMR spectra in solids: magic angle spinning	E. R. Andrew I. J. Lowe
1961	Spin-rotation interaction relaxation mechanism	H. S. Gutowsky
1961	Proton-relaxation enhancement technique	R. G. Shulman
1961	Double resonance techniques	F. Bloch (1958) R. Freeman J. D. Baldeschwieler
1962	Cross-polarization experiments	S. R. Hartman E. L. Hahn A. Pines (1972) M. G. Gibby J. S. Waugh
1963	Partially oriented molecules in nematic solvents	A. Saupe
1964	Rotating frame experiments	C. P. Slichter D. Ailion
1965	Dynamic nuclear polarization	R. E. Richards W. Muller-Warmuth
1965	Contact shifts	W. D. Phillips
1965	Chemical applications of nuclear Overhauser effect	F. A. L. Anet
1967	Chemically induced dynamic nuclear polarization	H. Fischer R. G. Lawler G. L. Closs
1968	High resolution NMR spectra in solids: multiple pulse experiments	J. S. Waugh
1969	Lanthanide shift reagents	C. C. Hindley
1976	Two-dimensional Fourier transform NMR spectroscopy	R. R. Ernst

The continued success of NMR is due to the steady stream of innovations that have occurred. For example, in the last ten years, in addition to various sophisticated high resolution NMR techniques used to solve structural problems, much new work has been done in the field of high resolution spectroscopy of solids, pioneered by J. S. Waugh, and in expanding the already diverse biological applications.

To illustrate the applied aspects of NMR, we mention a favorite example of midwesterners—the nondestructive analysis of the oil content in living seeds. In the case of corn, the oil content of individual kernels can be determined rapidly by looking at the motionally narrowed proton resonance of the oil molecules. The kernels with high oil content are planted and, as a result, within a few generations of such highly selective breeding, new commercial corn hybrids have been developed with significantly higher oil contents (36). Nor is this an isolated case. NMR has become a technique with a remarkable scope of applications ranging from the estimation of potential oil yields from oil shales to medical applications involving whole body NMR and ^{31}P spectra of functioning hearts from animals.

In summary, the main factors responsible for the rapid incorporation of NMR into all fields of chemistry are (*a*) the inherent, unique features of NMR as a physical phenomenon, (*b*) the new discoveries that have given continued vitality to the field, and (*c*) the remarkable progress in instrumentation.

PROGRESS IN NMR INSTRUMENTATION

Continued improvement in NMR instrumentation was the key to new discoveries in NMR and to new applications in various areas of chemistry. Therefore, a discussion of the major developments in NMR instrumentation is clearly necessary. In this section we consider the main trends in instrumentation and, particularly, in the high resolution NMR of liquids. A time scale is given in Table 2 for most of the important developments. The recent techniques for the NMR of solids are treated in the following section.

The NMR experiment is concerned with resonance phenomena of magnetic moments precessing in a strong static magnetic field. During the experiment, one places the sample in the static field (H_0), irradiates it with RF energy in order to produce coherent excitation of the magnetic moments, and then detects the absorption or emission of the RF energy. One of the major shortcomings of NMR is its limited sensitivity. Very early it was realized that it would be extremely useful if

Table 2 Survey of progress in high resolution NMR instrumentation

Year	Instrumentation	Early work
1946	CW single coil; cross-coil techniques	F. Bloch W. W. Hansen M. E. Packard E. M. Purcell H. C. Torrey R. V. Pound
1950	Pulse techniques	E. L. Hahn
1952	High resolution magnet systems	W. A. Anderson J. T. Arnold H. S. Gutowsky
1954	Rotating sample	F. Bloch W. A. Anderson J. T. Arnold
1954	Phase-sensitive detection	E. B. Baker
1957	Magnetic field stabilization	H. Primas H. H. Gunthard
1957	Field-frequency stabilization technique	E. B. Baker L. W. Burd
1958	Magnetic field control	M. J. E. Golay
1958	Side-band modulation system	H. Primas
1961	Double resonance techniques Homonuclear decoupling Heteronuclear decoupling	F. Bloch (1958) R. Freeman J. D. Baldschweiler
1964	High-field NMR: superconducting solenoids	F. A. Nelson H. E. Weaver
1966	Computer averaging	R. R. Ernst W. A. Anderson
1966	Fourier transform techniques	I. J. Lowe (1957) R. E. Norberg (1957) R. R. Ernst W. A. Anderson
1966	Broad band decoupling	R. R. Ernst

NMR could be applied to nuclei such as ^{13}C or ^{15}N at natural abundance in order to study important problems in biochemistry and biology. Therefore, continued efforts to improve sensitivity have been a major trend in NMR instrumentation. However, only in recent years has it become routine to observe ^{13}C at natural abundance.

The sensitivity problem with ^{13}C spectroscopy may be seen from the fact that signal-to-noise (S/N) in an NMR experiment is proportional to $Ng^{5/2}I(I+1)\ H_0^{3/2}$, where N is the number of nuclei in the sample, g is the nuclear magnetogyric ratio, and I is the nuclear spin. For ^{13}C, the g is relatively small, about 1/4 that of the proton, and its natural

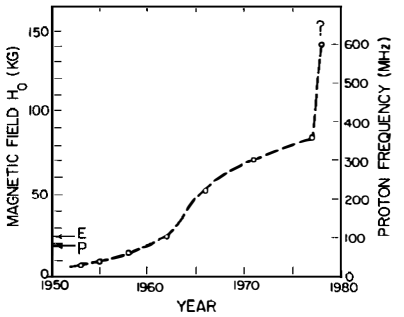

Figure 4 The increase with time of the maximum magnetic field strength (H_0) used in NMR spectrometers and of the corresponding proton frequency. The letters P and E indicate the maximum fields with permanent and electromagnets. The maximum fields since 1960 are with supercon systems.

abundance is only 1.1%. So the inherent sensitivity for ^{13}C at natural abundance is down by a factor of 4×10^{-4} from that of protons. In achieving increased sensitivity, two major developments played an important role: (*a*) technological progress in building magnets, particularly superconducting solenoids, with higher static magnetic fields and with larger volumes of high homogeneity in H_0 so that larger samples could be used and (*b*) the introduction of the Fourier transform method (37).

High fields are desirable not only for improving sensitivity but also for spreading out closely shifted lines that overlap at low fields and for simplifying the interpretation of complex spectra in which spin-spin coupling constants (J) are comparable with the chemical shifts ($\delta\nu$) at low fields. We show in Figure 4 how the magnetic field strength used in NMR spectrometers has increased through the years. Permanent magnets are convenient for field strengths of about 14 kG (60 MHz frequency protons) and up to 21 kG in narrow gaps. The upper limit for electromagnets is about 25 kG. Developments in the technology of building superconducting magnets has enabled the maximum H_0 to be increased considerably since 1965. A major problem with superconducting magnets, obtaining the field homogeneity necessary for a high resolution NMR experiment, has been attacked by using both superconducting and room temperature shim coils. It is an interesting game to follow the current trend to larger H_0 and speculate on its upper limit. At present, the NMR spectrometer built by J. Dadok and A. A. Bothner-By (1978) employs the highest magnetic field strength of 140 kG, which gives a proton resonance frequency of 600 MHz.

Until recently most NMR spectrometers were based on the continuous wave technique, in which the spectrum is slowly plotted out by sweeping either the radio frequency applied to a sample at fixed H_0, or the H_0 at fixed radio frequency, usually the latter. The pulse techniques

introduced by E. L. Hahn in 1950 were used mainly for specialized experiments in chemical physics on both solids and liquids but were rarely, if ever, employed by chemists who used NMR as a routine tool. In 1957 I. J. Lowe and R. E. Norberg pointed out that the time dependence of the free induction decay of the signal after an RF pulse forms a Fourier transform pair with the spectrum. It wasn't until 1966 that R. R. Ernst and W. A. Anderson tried the FT NMR approach and demonstrated that if one accumulates the signals from a number of induction decays by computer averaging and then Fourier transforms, one achieves a major improvement in sensitivity.

Widespread utilization of this approach was retarded by technical difficulties in digitizing the induction decay and interfacing with a computer for accumulation, averaging, calculating the Fourier transform, and displaying the final spectrum. However, the rapid advances in solid state electronics and the extraordinary evolution of powerful, low-cost microcomputers soon made it feasible to build FT capabilities into NMR spectrometers for routine as well as for more sophisticated research applications. At present, most of the high quality commercial NMR spectrometers are pulsed FT systems.

The FT NMR approach is more sensitive than the CW for two reasons. In the CW method one observes only a narrow segment of the spectrum at a given time, whereas the whole spectrum contributes to the induction decay used for the FT. Also, a considerably smaller fraction of the equilibrium nuclear magnetization contributes to the CW absorption than to the pulsed induction decay. As a consequence, the overall observation time required to achieve a given S/N is of the order of 10 to 100-fold less for FT operation than for CW, all other factors being equal.

Other important aspects of NMR include the requirements for homogeneity in H_0 and for instrumental stability. In contrast to solids, the natural widths of NMR lines in liquids are often in the range of 0.1 to 1 Hz. If one is to resolve a line of 0.1 Hz at a frequency of the order of hundreds of MHz, the homogeneity of the static magnetic field should be one part in 10^8 or 10^9 over the sample volume, and the spectrometer should be stable to this degree for the time required (often hours) to obtain a spectrum. Thus, the introduction of sample spinning and the use of field homogeneity correction techniques had a major effect on the development of high resolution NMR spectroscopy, and the great success of the A-60 spectrometer designed for routine use was made possible by the use of field-frequency locking techniques to improve stability.

Additional efforts in NMR instrumentation were focused on the development of various double resonance techniques (38) including

homonuclear, heteronuclear, and broad-band decoupling (39). These irradiation techniques resulted in simplification of complex spectra, helped in their analysis, and in some cases also improved sensitivity. For example, broad-band decoupling of protons (39) was essential for the development of ^{13}C spectroscopy. Otherwise all of the resonances from carbon atoms with protons attached would be split into at least 2 to 4 lines with a corresponding loss in peak intensity, making interpretation much more difficult.

NMR RESEARCH AREAS OF HIGH CURRENT INTEREST

High Resolution NMR in Solids

It is well known that conventional NMR spectra of liquids and solids differ in a major way. The NMR lines in liquids are typically of the order of 0.1 Hz to 1 Hz wide, whereas those of solids are broad and usually featureless, with a width of up to about 40 kHz. The major source of the line broadening in solids is the dipole-dipole interaction of neighboring nuclei. Additional sources of broadening include anistropic interactions such as the chemical shift anistropy, and quadrupolar interactions for nuclei with a spin greater than 1/2.

Until about ten years ago, NMR studies of solids dealt with line shape analysis, second moments, relaxation times, and angular dependence studies of single crystals. A large number of investigations were made of the dynamic structure of solids because various motions in crystals, such as molecular reorientation and diffusion, produce partial averaging of dipole-dipole interactions and result in the narrowing of the resonance. The interpretation of line shapes, sometimes quite difficult, yields information about crystal structure and the nature of the molecular motions, whereas the spin-lattice relaxation time is a good indicator of the rates of the motions.

In liquids, the resonance lines become narrow enough to permit the resolution of chemical shifts and the determination of spin-spin coupling constants as small as a few parts per 10^9 and 0.2 Hz, respectively. All chemists know that this narrowing is due to motional averaging of the dipolar and other anistropic interactions of the spins by the rapid, random, reorientational, and translational motions of molecules in the liquid. However, only the isotropic parts of the interactions remain to be seen in the high resolution spectrum of a liquid whereas in a solid, the isotropic as well as the anistropic contributions to the line shape are obscured by the usually much larger dipolar broadening. Fortunately, during the past decade these limitations have been circumvented to a

significant degree by the development of a new field of NMR—the high resolution NMR spectroscopy of solids (25, 40–44). These developments have already changed the character of NMR studies of solids and polymers, and there is a steady stream of new applications.

The first attempts to overcome the dipolar broadening (40–44) were made independently by E. R. Andrew and I. J. Lowe (1959) using rapid sample rotation with the rotation axis tilted at the "magic angle" of 54° 44′ to the external magnetic field, H_0. The dipole-dipole interaction between any two nuclei is proportional to $(3\cos^2\theta - 1)$, where θ is the angle between H_0 and the internuclear vector. In turn, if the sample rotates about an axis at an angle γ with respect to H_0, all of the dipole-dipole interactions acquire a multiplicative term $(3\cos^2\gamma - 1)$, which becomes zero at the "magic angle." However, for the averaging by sample rotation at this angle to be effective, the rotation frequency must exceed the dipolar interaction, i.e. be $\gtrsim 10$ kHz, which is a major technical challenge. Also, magic-angle sample spinning removes the chemical shift anistropy so that only the isotropic shift is retained.

The more recent development of multiple pulse techniques (40, 41) for suppression of homonuclear dipolar broadening actually started true high resolution NMR spectroscopy of solids. The basic idea underlying these multiple pulse techniques can be called motional averaging in nuclear spin space, because it is analogous to motional averaging in spatial coordinate space. These techniques may also be characterized more generally as manipulations in spin space.

The 4-pulse cycle of Waugh, Huber & Haeberlen (40, 41) (1968) is the first successful multiple pulse sequence applied to improve resolution in solids. Figure 5 shows the high resolution ^{19}F spectrum obtained in C_6F_{12} with the 4-pulse sequence; also included is the ordinary NMR spectrum of the solid at 200 K (41). No chemical shift anistropy was observed at this temperature because isotropic motions in the solid average out the anistropic shielding, leaving only the scalar interactions between the two nonequivalent fluorines in the CF_2 groups and giving a typical high resolution spectrum for a coupled AB system. At lower temperatures, the effects of anisotropic interactions would be observed. This and other multiple pulse sequences have been developed for and applied to the measurement of chemical shift tensors of abundant spins in a variety of solids. The research groups led by Waugh in the US and by Mansfield (45) in the United Kingdom have been particularly active in this specific area of NMR.

A different approach has received considerable attention in obtaining high resolution NMR spectra of less abundant species such as ^{13}C at natural abundance in various solids. In this and similar cases, the

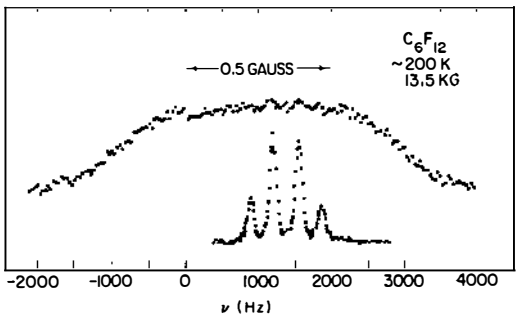

Figure 5 Application of the multiple pulse method to ^{19}F in polycrystalline C_6F_{12} at 200 K by Ellett, Haeberlen & Waugh (1970). Upper spectrum: Normal NMR spectrum governed by dipolar coupling among the ^{19}F nuclei. Lower spectrum: AB type spectrum ($J = 310$ Hz, $\delta = 17.5$ ppm) after removal of the dipolar interactions by applying a multiple pulse sequence introduced by Waugh, Huber & Haeberlen (1968). Chemical shift anisotropy is removed by isotropic molecular motion in the solid, but it is observed at lower temperatures. [Reproduced from Reference (41)].

dipolar broadening of one type of spin (^{13}C) is primarily heteronuclear, rather than homonuclear as for the ^{19}F resonance of C_6F_{12} in Figure 5. The broad structureless resonance observed for ^{13}C at natural abundance in most organic compounds is really an envelope of a very large number of lines caused almost entirely by dipolar interactions with neighboring protons. Therefore, the dipolar broadening of the ^{13}C resonance can be averaged out by decoupling the protons in a double resonance experiment. The sample is irradiated with a strong RF field at the Larmor frequency of protons, which causes rapid transitions of the proton spins. If the RF field is strong enough it will cause the proton spin states to change fast enough ($\sim$10 kHz) to average out the dipolar field at the carbons. A schematic example (43) of this nature is given in Figure 6.

The spectrum at the top of Figure 6 is a single resonance ^{13}C line shape broadened by dipolar interactions with protons in a amorphous solid; the effect of decoupling the protons is shown in the upper-middle spectrum. Even though the protons have been decoupled and the spectrum is several-fold narrower, the ^{13}C line shape is still broadened by overlapping chemical shift anisotropies. For a single crystal one would observe a sharp line for each chemically shifted type of ^{13}C, with positions depending upon the orientation of the crystal with respect to H_0. Therefore, in the amorphous solid or crystal powder each orientation contributes to the spectrum according to the anisotropy for each type of chemical shift. This produces several asymmetric envelopes of lines, which add up to give the still broad, overall lineshape, as indicated

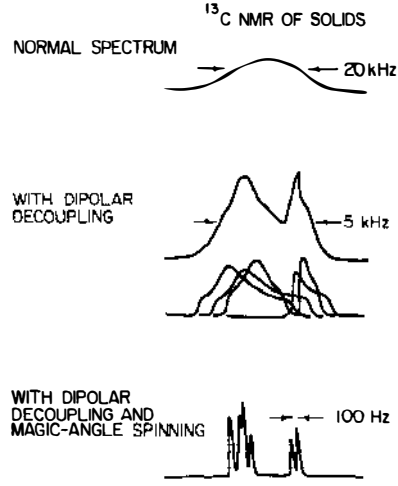

Figure 6 Schematic representation of ^{13}C spectrum of an amorphous solid. Top spectrum is a single-resonance ^{13}C lineshape broadened by dipolar interactions with protons in an amorphous solid. The middle spectrum is a double-resonance ^{13}C lineshape broadened by overlapping chemical shift anisotropies. The bottom spectrum is a double resonance ^{13}C lineshape under high-speed, magic-angle spinning. [Adapted from figures in Reference (43)].

in the lower-middle spectrum. However, magic-angle sample spinning can now be readily used to average out the chemical shift anistropy because, with the large dipolar broadening removed by decoupling, only a modest rotation rate ($\sim$1 kHz) is required. The dramatic effect is shown at the bottom of Figure 6, which is a true high resolution spectrum.

There is an important limitation on the use of this technique. In order to obtain ^{13}C spectra at natural abundance one needs the higher sensitivity of the Fourier transform method with computer averaging. However, the spin-lattice relaxation time, T_1, of ^{13}C in solids is usually quite long and a delay of several T_1s is necessary for the ^{13}C nuclei to regain thermal equilibrium after each RF pulse. This can extend unduly the data acquisition time necessary to obtain an adequate S/N. Fortunately, the problem can be alleviated with an ingenious scheme of cross polarization introduced by Hartmann & Hahn in 1962 and first applied to ^{13}C nuclei by Pines, Gibby & Waugh (40, 44) in 1973. Cross-polarization is based on the idea that an abundant spin system with a short T_1 can provide polarization for (i.e. help relax) a rare spin system with a long T_1.

Ordinarily, the transfer of polarization from protons to carbons is slow because of the mismatch between the Zeeman splittings of the two nuclear species. Their mutual spin-flips are not energy conserving, and the energy difference must be provided by lattice phonons in a rather inefficient relaxation process. Hartmann & Hahn proposed that by doing the cross-polarization in a double rotating-frame, spin-locking experiment, the energies could be matched. The RF rotating field

amplitudes for protons H_H and for carbon H_C are independently adjusted so that $\gamma_H H_H$ is equal to $\gamma_C H_C$, the so-called Hartmann-Hahn condition. This condition provides energy matching for the mutual spin flips between carbons and protons. The resulting cross relaxation is a T_2 process in solids, usually having a 10 to 100 μsec time scale, much shorter than the T_1 of protons or carbon. It enables the ^{13}C nuclei to relax with the shorter T_1 of the protons and reduces substantially the data acquisition time for good ^{13}C spectra.

There are two different ways of accomplishing the cross polarization —spin locking and adiabatic demagnetization in the rotating frame (40, 44). In addition, Pines and co-workers (25, 41) introduced in 1976 double quantum schemes for eliminating first-order quadrupolar interactions and suppressing heteronuclear dipolar interactions. For lack of space, we omit any discussion of these and other ingenious multiple pulse experiments (25) recently proposed; however, these experiments are helping high resolution NMR spectroscopy in solids to rapidly become an important tool in obtaining information about various anisotropic interactions. Such experiments have already yielded voluminous information (40) on shielding tensors of nuclei such as ^{1}H, ^{19}F, ^{13}C, ^{15}N, ^{29}Si, ^{31}P, ^{77}Se, and ^{125}Te in a variety of chemical compounds.

Many new applications of these techniques are just appearing, including studies of molecules adsorbed on metal catalysts, analysis of coal (46), studies of solid biopolymers, and applications in polymer chemistry (43, 44, 47). Their success is attributable in large measure to the rapid progress in solid state digital and RF components that has made feasible the high power RF pulse sequences, better recovery and sensitivity of the receiver detection system, and the use of Fourier transform methods.

Biological Applications

The potential of NMR in the study of biological systems was recognized early, but progress in this area of NMR was delayed by inadequate sensitivity. Nonetheless, as early as 1960 to 1961, some NMR experiments (11, 12) were performed on molecules of biological interest. For example, M. Cohn (1960) studied the structure and conformation of a new nucleoside isomeric with uridine that was found in RNA and C. D. Jardetzky (1961) investigated the conformation of deoxyribose in DNA nucleotides. Also, in connection with the current extensive use of ^{31}P in biological NMR studies, it is noteworthy that as early as 1960 Cohn (11) showed that the ^{31}P resonances of the phosphates of adenosine are sensitive to pH and other experimental variables.

The introduction of the proton relaxation enhancement (PRE) technique (48) by R. G. Shulman in 1961 opened a fruitful area of biochemical research. In this method, one measures the proton relaxation time of the water solvent and the effect upon it of adding a small amount of a paramagnetic ion in the presence of a biological macromolecule. After adding the macromolecule, the proton relaxation rate is enhanced because the paramagnetic ion binds to the macromolecule so that the rotational correlation time is greatly increased. This technique was used to investigate the number of binding sites in various proteins and to determine their binding constants (15–17, 48). In their pioneering work, Shulman and co-workers (1961) studied the binding of paramagnetic ions to DNA. The first study of a protein using this technique was carried out by Cohn (1962), who investigated the binding of Mn(II) to creatine kinase and enolase; all through the 1960s most of the studies using the PRE technique originated in her laboratory.

An interesting variation on the PRE theme was proposed by Stengle & Baldeschwieler (1966) who used halide ions to study various aspects of protein structure and interactions (15). For example, broadening of the ^{35}Cl resonance has been used to study antibody-hapten interactions, sulfhydryl groups of hemoglobin, and the helix-coil transition in synthetic poly-L-glutamate (Bryant, 1967).

In our NMR review covering the period up to 1967 [Jonas & Gutowsky (16)], we commented on the rapid increase in NMR studies of biological systems due to the improvement in instrumentation. Earlier, such studies were hampered by inadequate sensitivity and overlap of the many resonances belonging to various nonequivalent but similar protons. In this connection, the introduction of high frequency, high resolution proton spectrometers using superconducting magnets was a major advance, as discussed by Ferguson & Phillips in their 1967 review (49). Moreover, Phillips and co-workers demonstrated that high field, high resolution NMR is ideally suited to investigate the structure and interaction of nucleic acids and proteins in solution and predicted that it would contribute greatly in the future to a better understanding of the highly specific biological functions of these complex molecules.

The rapid expansion of NMR biological applications is readily apparent in the 1970 NMR review by Allerhand & Trull (17), who gave a thorough analysis of the field. The review includes so many studies of natural abundance ^{13}C NMR that it clearly provides a firm foundation for future applications of this approach to biological systems. In particular, the research groups of D. M. Grant and of J. D. Roberts did much to establish the feasibility of ^{13}C high resolution NMR at natural abundance in liquids.

Several years later, Allerhand and co-workers (1973) used natural abundance ^{13}C NMR spectra to investigate proteins (50). These studies were made possible by several advances in instrumentation, such as the FT techniques, large (20 mm diameter) samples, and proton decoupling. Wide-band proton decoupling not only reduced the spectrum complexity but increased the signal-to-noise ratio by the narrowing and coalescing of multiplet lines and also via the nuclear Overhauser effect. Such developments have caused the major expansion of NMR during the past ten years or so into an important tool for the study of biological systems (51–53). We cannot discuss in detail the numerous applications, but we try to point out the main directions of the work and its scope. Presently, the NMR applications range from structural determination of simple, biologically important molecules to studies of cell membranes and of whole organs and organisms.

A major area of NMR biological applications is the study of biological macromolecules. X-ray crystallography is the technique of choice for determining the structure of proteins and nucleic acids in their crystalline state. However, the properties of biological macromolecules in solution are important; therefore, high resolution NMR has emerged as a vital tool for their study. NMR is presently used not only to study the structure of proteins, including the chain dynamics in the native or folded state and in the process of unfolding or denaturation, but also to study the binding of substrates, inhibitors, and cofactors. In transfer RNA studies (24) high resolution NMR experiments monitor and map out the sites at which purified t-RNA interacts with antibiotics, carcinogens, enzymes, and with other classes of ribonucleic acids. These NMR studies are beginning to provide information about changes in secondary and tertiary structure caused by the interactions of t-RNA and its complexes with other macromolecules during protein synthesis.

One of the prime areas in which NMR is proving invaluable is in the study of the structure and dynamics of phospholipid bilayer membranes (23, 54). Until NMR was used, the electron spin resonance experiments on spin-labeled lipids incorporated in the bilayer provided the main source of information about the motional state of the bilayer. From the early NMR studies of motions of phospholipid phases by Chapman and co-workers (1966), this field has expanded rapidly, incorporating the use of ^{2}H, ^{13}C, and ^{31}P resonance in addition to proton spectroscopy; a great deal of new insight is being obtained thereby about the effects of protein-lipid and other interactions upon the dynamic structure of artificial and natural membranes (54).

Another area of interest is the study of some enzymatic reactions (55) by using ^{31}P NMR. These experiments provide extensive information on

the environment at the active site, chemical identification of products, dissociation constants, and exchange rates in phosphorylation reactions.

The sensitivity of NMR is now sufficient for the study of the simplest functioning biological system, the cell, and even for some organs and organisms under limited circumstances. Shulman and co-workers (56) have used the ^{31}P resonance to investigate intracellular pH and the concentration of phosphorylated metabolites such as adenosine triphosphate, adenosine diphosphate, and inorganic phosphate. ^{13}C NMR experiments on *Escherichia coli* and liver cells show how ^{13}C enriched substrates are metabolized by the cells, providing information on the various metabolic pathways. ^{31}P NMR has found extensive use in studies of intact tissues (57).

The simplest experiment is the observation of an isolated tissue to determine the chemical changes when it is deprived of nutrients or blood supply. Another type of NMR experiment involves suprafusion in which an oxygenated nutrient is passed through a thin piece of sample. The effects of oxygen removal and stoppage of the flow can readily be followed by ^{31}P NMR. More sophisticated experiments deal with the perfused whole organ (58) approximating the in vivo state. This approach has been used in studies of the heart and kidneys of the rat. For example, NMR ^{31}P experiments on intact, perfused, beating hearts are shedding light on the biochemical changes, e.g. in pH, that are associated with the mechanical performance of the heart.

In addition to the role of NMR in studying biochemical and biophysical processes, the recent development of NMR zeugmatographic imaging (59) offers promise as a noninvasive, noninterfering technique for medical diagnosis. This new technique spatially resolves the NMR signal in order to distinguish various processes in different regions of an organism. The spatial information is obtained from the NMR signals by the use of nonuniform magnetic fields (either H_0 or RF). This approach differs from optical imaging in which resolution is limited by the wavelength of the radiation used.

In zeugmatographic imaging, the resolution is determined by the field gradient, the concentration of the nuclear species observed (e.g. aqueous protons), and the ability of the spectrometer to detect NMR signals from a small volume element. At the present time, due to sensitivity problems, the best resolution is in the 5-10 μm range. The goal of this effort is to permit the examination of organs, entire animals, or even whole human beings. Although clearly there is still much development to be done, the prospects are promising for whole body NMR imaging systems that may compete with or significantly complement X-ray computer-assisted tomography.

OTHER RESEARCH DIRECTIONS AND FUTURE TRENDS

Our selection of current research areas in NMR represents a much larger and diverse amount of interesting work that is going on in this broad field. We have, of necessity, omitted discussion of many sophisticated techniques (60) that have become routine in structural investigations by high resolution NMR. It seems worthwhile, however, to at least mention several of the other main directions. For example, the long tradition of using NMR to study polymers (61–63) is being expanded these days by taking advantage of the new discoveries and progress in high resolution NMR spectroscopy of solids (43, 44, 47). The same techniques are being applied to the important field of surfaces and catalysts (64). The various relaxation time measurements, including rotating coordinate frame experiments and the spin-echo techniques, have become indispensable in studying the dynamic structure of liquids (65); they have already helped to improve our understanding of the structure of liquids and electrolytic solutions (66). Other areas of continued high interest are chemically induced dynamic nuclear polarization (67) and chemical exchange processes (68).

To conclude, we offer some views about the future trends of NMR spectroscopy. In the most important area—high resolution NMR—the increased sophistication both in instrumentation and in spectral techniques will increase the information content of even the routine spectra obtained during everyday use in chemical laboratories. From current activity, it appears that ^{15}N spectroscopy at natural abundance (69) will join that of ^{13}C as a routine tool. Major expansion will also occur in the use of nontraditional, less sensitive nuclei, extending even more the scope of chemical problems investigated by NMR. Also, it seems safe to expect major new applications of the high resolution solid state NMR techniques, in particular with catalytic and polymer systems. Undoubtedly, NMR methods will become even more important in the study of biological systems, and we also may see the day when NMR zeugmatographic imaging techniques are a routine diagnostic tool in medicine.

Finally, we are optimistic enough to think that NMR will be an evergreen for at least a few more years, that in the future it will continue to surprise the chemical community with new fundamental developments, new instrumentation, and new applications. We expect from the past and current trends in this remarkable field that it will continue to help solve an ever growing number of increasingly diverse chemical problems.

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