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Nuclear Magnetic Resonance

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I. Introduction

In thinking of what I might say at this Conference on Modern Developments in Analytical Chemistry, it struck me that the question could be approached from two different points of view. In the one, I could review the very wide range of analytical applications of magnetic resonance which have been developed in recent years and which are now in general use, or soon will be. In many ways this is the simplest approach; at least it is the most direct and, being factual, it is the least controversial.

On the other hand, I could interpret the phrase, "Modern Developments," in a more general sense and consider the question of how analytical chemistry has changed and may continue to change in the future, using my acquaintance with magnetic resonance research and applications as a basis for my interpretations and crystal ball gazing. This approach is more difficult and certainly not without danger, as it requires some value judgments, some philosophizing about the nature of science, and some extrapolations. Actually, in the earlier discussions at this Conference, both approaches have been used to some extent, and considerable interest has been shown in the role of analytical chemistry in chemistry today.

In any case, I believe that the evolution of magnetic resonance research illustrates so well some of the major factors which determine the present and future nature of analytical chemistry that I should emphasize these aspects rather than attempt a detailed review of the many analytical applications of magnetic resonance. Therefore, I will start out with a general summary of these factors, all of which have been alluded to earlier to some extent, and then I will present in some detail a particular application which is still evolving, namely the use of nuclear magnetic resonance methods for the study of fast reactions and the possibilities of radiofrequency pulse methods in such experiments. And finally, with this application as an example, I will conclude with some comments on the future of analytical chemistry.

II. Factors Governing Developments in Analytical Chemistry

There are, I believe, three major factors which have led to the modern developments in analytical chemistry. These are: (1) The growth of industrial capacity for making reliable scientific instruments and also the existence of a market for them. The instruments are relatively easy to operate and maintain, yet they have great sensitivity for measuring various physical properties. Moreover, there are funds available, federal or otherwise, for the purchase of the instruments. (2) The invention of new instruments which can measure quantitatively an increasingly-complex and wide range of physical properties. (3) The increasing sophistication of the "analytical questions" which are being asked. These three factors are, of course, not independent, but I believe them to be recognizable components in the major evolution which analytical chemistry has undergone during the past twenty years.

The importance today of the instrument manufacture is suggested by comparison of the very different histories for the use of infra red spectroscopy and of magnetic resonance in chemical analysis. In the case of infra red radiation, as referred to on Monday by Dave Stevenson, observations were made as early as about 1900 of the fact that different molecules absorb radiation at different frequencies characteristic of the molecular structure. However, commercial IR spectrometers were not sold until about fifty years later; I believe the first ones were sold in 1946.

Also in 1946, Felix Bloch[1] and Ed Purcell[2] were developing independently their methods for observing the absorption of radio frequency energy by magnetic nuclei in a bulk sample of matter. However, in the case of NMR, it took only a little over five years for a commercial spectrometer to be delivered. It was in 1953, I believe, that the first Varian high resolution spectrometer was delivered to the Humble Oil laboratory, here in Houston. And today most chemical laboratories in this country have at least one magnetic resonance spectrometer, usually a high resolution instrument, for chemical analysis.

The other two general factors are tied rather closely together. These are the importance of new instruments to measure physical properties and the increasing sophistication of the analytical questions being asked. Both of these factors are apparent in the early history of NMR. This is a well-known story to many of you, but I think it bears repetition.

III. Analytical Applications of NMR and Their Development

At first, the basic phenomena of nuclear magnetism were of interest only to the physicist. The physicist found that in addition to the more familiar properties of mass and electric charge, many nuclei have about them a weak magnetic field which can be described in terms of a magnetic dipole moment, which we call $\underset{\sim}{\mu}$. The origin of the nuclear magnetic field lies in the more or less complex circulation of the electric charges in the nucleus. This charge circulation is the electric current which generates the magnetic field.

Also, the nucleus has an angular momentum, $\underset{\sim}{p}$, or spin, which results from the circulation of the mass associated with each element of electric charge. Moreover, because of this association of mass and charge, there is a direct proportionality between the magnetic moment $\underset{\sim}{\mu}$ and the angular momentum $\underset{\sim}{p}$. And there is a proportionality factor, the nuclear g value, which depends upon the details of the nuclear structure, as does the nuclear angular momentum or spin, I.

Therefore, in the 1930's and '40's, the measurement of nuclear g values and spins was of great interest in connection with our then rapidly evolving understanding and manipulation of nuclei. However, the first methods available for such measurements were limited. The atomic beam method was relatively clumsy and even today it still requires exceptional experimental skill and a lot of hardware. The use of atomic spectra was also limited. A better method, a simpler method for observing and measuring nuclear magnetism was desirable. It was, as you know, supplied in 1946 by Bloch and Purcell.[1,2]

The theoretical basis of their method can be described in the following manner. When a magnetic field generated by a magnet in the laboratory is applied to a magnetic nucleus, there is an interaction which tends to orient the nuclear magnetic moment $\underset{\sim}{\mu}$ parallel to $\underset{\sim}{H}_o$. The interaction energy is given by $-\mu_H H_o$, where μ_H is the component of the nuclear magnetic moment along H_o. However, quantum mechanical laws permit only certain orientations of μ with respect to H_o. As I am fond of saying at Illinois, the nuclei are smarter than many graduate students, they understand quantum mechanics.

In particular, p_H, the component of the nuclear angular momentum along H_o, is restricted to discreet values of m, where m = I, I-1, ..., - I, in units of $h/2\pi$, h is Planck's constant, I is the nuclear spin, and m is the nuclear magnetic quantum number. It has been found that I may be integral or half integral for a nucleus, depending upon its structure, and values as large as 9/2 are not uncommon.

The quantization of p_H leads to a corresponding quantization of μ_H and to the formation of a discreet set of nuclear magnetic energy levels,

$$E_m = -\mu_H H_o = -mg\beta H_o \ . \qquad (1)$$

In Eq. (1), β is the nuclear magneton, a combination of fundamental constants. Thus, the spacing of the levels is determined by the nuclear g value, and by H_0, the value of the external magnetic field at the nucleus. Transitions can be induced among these energy levels subject to the selection rule, $\Delta m = \pm 1$, which limits transitions to adjacent levels. The electromagnetic radiation which produces these transitions must meet the Bohr frequency condition, $\Delta E = h\nu_0$, which when combined with Eq. (1) gives the Larmor equation,

$$\nu_0 = \Delta E/h = g\beta H_0/h \ . \qquad (2)$$

Also, the radiation must be circularly polarized in the plane containing H_0.

What Bloch and Purcell did was to invent spectrometers which would detect the absorption of such radiation by nuclei in ordinary bulk samples, solids, liquids or gases with a mass of the order of a gram. The Larmor equation shows that if the frequency of the absorbed radiation is measured and also the magnetic field, both of which can be done with considerable accuracy in independent experiments, then you can obtain from these numbers the nuclear g value. Also, with a bit more work, you can obtain in similar experiments the nuclear spin and the sign of the nuclear magnetic moment, that is, the orientation of the magnetic moment with respect to the angular momentum vector.

The basic experiment is spectroscopic in its general nature.[1-3] It consists of a source of radiation, a cell containing the sample, a detector to measure how much radiation is absorbed by the sample or transmitted through it, and some device for plotting the energy absorbed by the sample as a function of frequency. There are a couple of ways in which an NMR spectrometer differs from optical instruments. The nuclear magnetic energy levels are closely spaced so that radio frequency energy is required to induce transition; therefore, the source of radiation is monochromatic and you don't need to worry about prisms or gratings. Another point is that the spacing of the energy levels is determined by the external applied magnetic field, so the spectrum can be scanned by sweeping the magnetic field while keeping the frequency of the radiation constant, as well as by the reverse procedure as in more conventional spectroscopy.

In any event, the physicists turned with enthusiasm to the NMR methods of measuring nuclear spins and g values. In a very few years, measurements were obtained for virtually all stable nuclei and extensive tabulations of such results are now available.[3] It has been found that at applied magnetic fields of convenient laboratory magnitude, say 10,000 gauss, the Larmor frequency for different nuclear species covers a range from 1 Mc/sec or less to about 50 Mc/sec. Moreover, the frequencies for different nuclear species seldom overlap. The importance of the methods was soon recognized by the award of the Nobel Prize to Bloch and Purcell. Also, as a footnote, I think it is of interest that this year's Nobel Prize in physics included Maria Goeppert Mayer and J. Hans D. Jensen for their work on the nuclear shell theory, which work was based, in part, on the NMR results for nuclear spins and nuclear g values.

But to return to my main theme, even before the first successful NMR experiment was performed, it was appreciated by the physicists that the detailed characteristics of the NMR absorption could be very sensitive to the chemical matrix in which the nuclei reside. And once the experimental breakthrough occurred, the physicists, chemical physicists, and physical chemists began to study the various ways in which interactions between a nucleus and its surroundings could modify various details of the NMR absorption. The appreciation that such interactions could serve as the basis for chemical analysis was not long in coming, but I believe that it is significant that Bloch's patent on nuclear induction[4] refers only to classical analytical chemistry, namely elemental or isotopic analysis, which has turned out to be one of the least important analytical applications of NMR. The reason for this is suggested by Table I, in which I have listed the types of NMR instrumentation and

Table I. Analytical Applications of Nuclear Magnetic Resonance

I. High Resolution NMR (liquids and gases)

Chemical Shifts and Spin-Spin Coupling

- A. Determination of structural formulae
- B. Theory of electronic structure of molecules
- C. Investigate intermolecular and interionic forces
- D. Dynamic processes
- E. Quantitative analysis

II. Broad Line NMR (solids)

Dipole-Dipole Interactions

- A. Internuclear distances and crystal structure
- B. Dynamic structure - molecular rotation, diffusion rates
- C. Crystal imperfections, polymer crystallinity, shift anisotropy

III. Radiofrequency Pulse Experiments (s, l, and g)

Nuclear Relaxation Times, T_1 and T_2

- A. Rates and nature of molecular motions, e.g. rotation
- B. Paramagnetic species - solvent interactions
- C. Rates of exchange type kinetic processes

phenomena somewhat arbitrarily in three classes, and indicated typical problems which can be studied by observing each group of phenomenon with each type of instrumentation.

Most of you probably have been exposed to high resolution NMR. It involves the first group of phenomena, the chemical shifts and the electron coupling of the nuclear magnetic moments. High resolution NMR is the most widely applied type of NMR.[3,5] Certainly it's the most dramatic. The high resolution NMR spectrum of a liquid or gas is very sensitive to the molecular structure and many subtle structural problems are being solved by this technique. Often these problems could be solved by other methods, but with much greater difficulty. In some cases, no other method would serve. Perhaps in the discussion Dr. Shoolery can present some current examples.

The second group of applications depends upon the interactions among the nuclear dipoles themselves. Most of these applications, or at least many of them, are probably closer to physical than to analytical chemistry. However, one such application, the determination of the relative percentages of crystalline and amorphous regions in a polymer such as polyethylene, is certainly a good analytical application. And I might add again as a footnote that when George Pake and I set out to investigate the effect of molecular mobility upon the dipolar broadening of NMR lines in solids,[6] we weren't concerned about polymer crystallinity.

The last group of phenomena, the relaxation times, are relatively unpromising as far as routine analytical applications are concerned. I am afraid that most chemists will continue to think of the nuclear relaxation times only when their values are unfavorable for high resolution NMR; and then, of course, they are a nuisance.

The main point I wish to draw from Table I is the wide range of physical properties which can be measured in NMR experiments and the correspondingly wide range and the sophisticated nature of the analytical problems which can be solved. A subsidiary point is that most of these phenomena and their analytical applications were not predicted. In other words, if you are an analytical chemist and you want to discover a new phenomenon to perform a new type of analysis, the odds are overwhelmingly against success.

IV. Study of Fast Reactions by NMR

This brings me to the second main part of my talk. It is concerned with a particular NMR application, namely the study of fast chemical exchange processes. One of the main reasons I have selected this problem is that it is of current interest to us at Illinois, at least Dr. Adam Allerhand should be back there now hard at work on it while I am here enjoying the hospitality of Texas. Another reason to discuss this problem is that the methods are still evolving and they will illustrate further why most basically new analytical concepts and methods originate with the phenomenon- or problem-oriented scientist rather than being produced by analytical chemists of a more traditional variety.

A. General Considerations

NMR studies of chemical exchange processes can be based on either the chemical shift or on the splittings of high resolution spectra produced by electron coupling of the nuclear spins. The exchange process of concern to us in the application I will describe involves the chemical shift. The nature of the chemical shift may be illustrated by considering the fluorine spectrum for 1,3,5-trifluoro-benzotrifluoride. There are four main groups of lines, three of essentially equal intensity and the fourth about three times the integrated intensity of the other three. A major advantage of NMR is that the transition probabilities which determine the intensity of the absorption lines depend very largely upon nuclear properties. Thus, except for usually minor environmental effects, one proton will absorb as strongly as another, and one fluorine atom as strongly as another. In consequence, there is a simple direct relationship between the intensities of the NMR lines and the relative concentrations of the nuclei contributing to the lines.

Therefore, in the case of 1,3,5-trifluoro-benzotrifluoride, we can assign without any difficulty the most intense line to the three fluorines in the CF_3 group and the other three lines to various of the fluorine nuclei attached to the ring. Also, if you want to go through a more detailed analysis of simpler substituted fluorobenzenes, you can determine which of the other three lines corresponds to which fluorine on the ring.[3]

The chemical shift arises because H_o, the magnitude of the field at the nucleus, differs from H_a, that applied to the sample. There is a magnetic shielding of the nucleus by a fractional amount σ which depends upon the electronic structure of the molecule or other chemical species containing the nucleus. Thus, one can write

$$H_o = H_a(1-\sigma) \ . \qquad (2)$$

As to the nature of the interaction producing σ, it should be remembered that electrons have magnetic properties so it is reasonable to have them interacting with a magnetic field.

In any case, physicists discovered the phenomenon of the chemical shift. They considered it, at least initially, as a nuisance which leaves one with uncertainties in the nuclear g value. That is, if you don't know the extent to which the nucleus is shielded by these interactions between the electrons and the external magnetic field, you don't know whether you have a smaller g value or a higher shielding constant. The chemical shifts result, of course, from the fact that there are different shielding parameters for different nuclei in different chemical environments.

The chemical exchange process in question is suggested by the structural formulae given below for the N,N-dimethyl amides.

(3)

When R is H or CH_3, these are the two main resonance structures for dimethylformamide and dimethylacetamide, respectively. Pauling, a number of years ago, predicted that because the N-C bond has double-bond character, the backbone of the molecule would have a planar configuration.[7] This is a very important point in biology because the α-helix structure proposed by Pauling for proteins was based upon the assumption that the amide group, the heavy atom skeleton in this type of compound, is planar. The properties of proteins depend upon how stiff this planar structure is so the question arises as to how the stiffness of the amide group can be measured.

This is really, then, a problem of determining the ease of rotating the molecule about the nitrogen carbon bond, or of determining the rate of exchange of the N-CH_3 groups between the sites <u>cis</u> and <u>trans</u> to the oxygen. If we measure the reorientation rate as a function of temperature and plot the log of the rate constant versus 1/T, the slope of the resulting curve would be the energy barrier to reorientation, which would be a quantitative measure of the stiffness of the group.

How can the reorientation rate be measured in such compounds? This is a classical sort of analytical problem. In principle, it could be solved by labelling the CH_3 group <u>cis</u> to the oxygen atom, say by putting a deuterium on it, and then observing the rate at which the labeled groups appear in the position trans the oxygen. It is a matter of measuring the relative concentration of two species of molecules as a function of time at different temperatures. In favorable circumstances, some such more or less classical analytical techniques could be applied successfully to this problem. However, the average time required for these molecules to undergo internal rotation is about 0.1 sec at room temperature, and in these days of increasingly slow moving graduate students, chemical separation is not the answer to the problem even if one could synthesize the proper isotopically-labelled compound.

B. Steady State NMR Studies of Amides

There is, however, a more subtle label attached to two N-methyl groups in amides. If there weren't, I wouldn't be discussing the amides. The room temperature proton magnetic resonance spectrum of dimethylformamide (DMF) consists of three lines, two closely spaced and of equal intensity and the other only about 1/3 this intensity.[8] It is clear that the two equal, stronger lines come from the two structurally non-equivalent methyl groups in the dimethylformamide. The weak line is assigned to the CH group. The proton spectrum of dimethylacetamide (DMA) has three lines of equal intensity, two of which are close together at positions similar to those of the close pair from DMF. There are three CH_3 groups in DMA and by reference to the spectrum of DMF we assign the close pair of lines to the two $N-CH_3$ groups and the other to the $C-CH_3$ group.[8]

What can be said, then, is that the two different $N-CH_3$ groups in either DMF or DMA are labelled by their different chemical shifts. Furthermore, the room temperature exchange rate is too slow to affect this magnetic label. But if the exchange rate is increased by raising the temperature of the sample, the chemical shift is averaged out in a manner which can be related to the exchange rate.

This is illustrated in Fig. 1, which is a composite of the N-methyl group doublet in N,N-dimethyltrichloroacetamide ($R = CCl_3$ in formula 3) at successively increasing temperatures. At low temperatures the two lines are sharp and clearly resolved. As the temperature is raised, the two components broaden and then eventually coalesce at the center of the original doublet. At still higher temperatures, the single broad line begins to narrow and soon becomes as narrow as one of the two lines in the low temperature spectrum.

There are several ways to describe the origin of this effect. Mathematically the problem is relatively easy. In fact, it is easier to go through the detailed mathematics than to construct a simple physical model or picture to explain why it happens. The results of such a mathematical analysis are given graphically in Fig. 2. Here we consider a two site case, which is the analogue of the amides, and assume that each of these two sites have equal populations of nuclei. The average time between exchanges of a nucleus between the sites is defined as 2τ, and the exchange process is assumed to be that which occurs in the N,N-dimethylamides, namely nuclei are interchanged between the two sites.

For our purposes, the line shapes can be calculated most simply by starting with the Bloch equations[9] which describe the nuclear magnetization for a single set of nuclei, with the static magnetic field H_o in the z-direction.

$$
\begin{aligned}
du/dt + (\omega_o - \omega)v &= -u/T_2 \\
dv/dt - (\omega_o - \omega)u &= -(v/T_2) - \omega_1 M_z \qquad (4) \\
dM_z/dt - \omega_1 v &= (M_z - M_o)/T_1
\end{aligned}
$$

The quantities u, v, and M_z are the three components of nuclear magnetization along a set of axes rotating with the angular frequency ω of the applied rf field. Also, ω_o is the Larmor frequency γH_o, where $\gamma = 2\pi g\beta/h$, and M_o is the value of M_z when the nuclear spin system is in thermal equilibrium

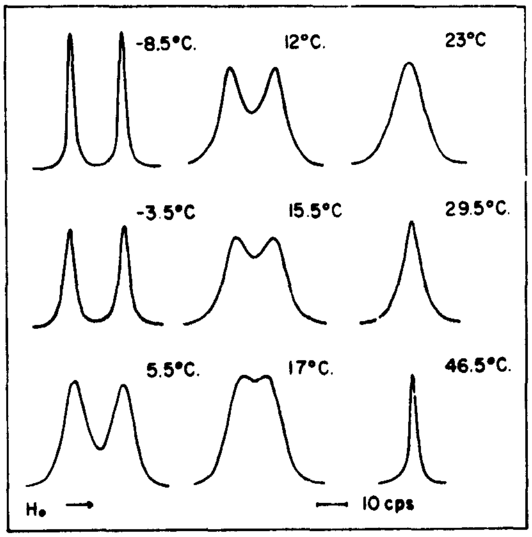


Fig. 1. The proton magnetic resonance spectrum of N,N-dimethyltrichloroacetamide (DMTCA) as a function of temperature, at 60 Mc/sec. The frequency scale, but not the intensity scale, is the same for all temperatures.

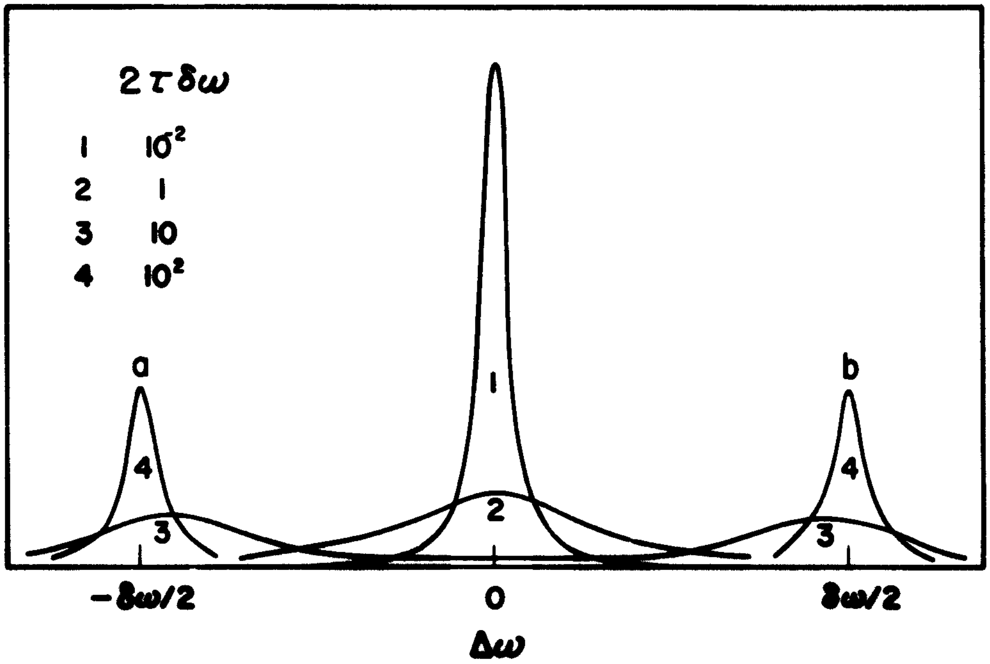


Fig. 2. The averaging by chemical exchange of a chemical shift in a high resolution NMR spectrum. It is assumed that mutual exchange occurs between two sites (a and b) which are equally populated ($P_a = P_b$) and which have resonance frequencies separated by $\delta\omega$ radians/sec in the absence of the exchange; 2τ is the average time that a nucleus stays at one site.

with its surroundings. In Eq. (4), $\omega_1 = \gamma H_1$ and H_1 is the strength of the applied rf magnetic field rotating at the angular frequency ω. H_1 is taken as parallel to u. T_1 is the spin-lattice relaxation time and T_2 is the inverse line-width, often called the transverse relaxation time.

If the rf field H_1 is small, and T_1 is relatively short, both reasonable approximations, saturation effects are negligible and $M_z \cong M_o$. In this case, the NMR absorption line shape is given by the imaginary part of the nuclear magnetization in the x-y plane, $G = u + iv$, where G must satisfy the following simplified version of Eq. (4).

$$dG/dt + [(1/T_2) - i(\omega_o - \omega)]G = -i\omega_1 M_o \tag{5}$$

Equation (5) leads to a single resonance line, of Lorentzian shape, centered at ω_o and with a full width at half-maximum intensity of $(2/T_2)$ sec^{-1}. Thus, our two site situation with no exchange can be represented by two such equations, in G_a and G_b with ω_o replaced by $\omega_o - (\delta\omega/2)$ and $\omega_o + (\delta\omega/2)$, respectively.[10,11] The spectrum labelled 4 in Fig. 2 was calculated in this manner, for $G = G_a + G_b$ with $T_{2a} = T_{2b}$, and it agrees well with the observed low temperature spectrum for DMTCA given in Fig. 1.

The chemical exchange of a nucleus between sites a and b transfers its nuclear magnetization between G_a and G_b or, in the more general case, between Eq. (4) for a and b. In the original treatment of such effects,[8,10,11] the "life-history" of the magnetization was calculated for a single nucleus and then the appropriate averages were taken over the ensemble of nuclei involved in the exchange process. Since then an equivalent procedure has evolved[12,13] which has advantages in treating more complex systems. The effects of exchange can be incorporated directly in Eq. (4); as an example, the result for u_a is

$$du_a/dt + (\omega_a - \omega)v_a = -(u_a/T_{2a}) - C_a u_a + C_b u_b \qquad (6)$$

where C_a and C_b are the rates at which nuclei leave sites a and b, respectively. The equations for v_a, v_b, M_{za}, and M_{zb} are obtained in the same fashion, and solution of the set of six gives the line shape as a function of exchange rate.

Whether the approach be <u>via</u> Eq. (5) or Eq. (6), the result for our equally populated two-site case is

$$G = \frac{-i\omega_1 M_0 \tau[2 + \tau(\alpha_a + \alpha_b)]}{(1+\alpha_a\tau_a)(1+\alpha_b\tau_b) - 1} \qquad (7)$$

where $\alpha_j = (1/T_{2j}) - i(\omega_j - \omega)$, and $\tau_a = \tau_b = 2\tau$ is the mean lifetime of a nucleus in each of the two sites. Equation (6) was used to calculate the line shapes in Fig. 2 for different exchange rates $1/2\tau$. These are universal curves in the sense that their shape depends upon the ratio $\delta\omega/(1/2\tau)$, or the product $2\tau\delta\omega$, and not upon 2τ and $\delta\omega$ independently. It is seen that these theoretical curves are identical in nature to the experimental ones in Fig. 1.

Thus, the theory appears to be valid and the calculated curves enable us to take the observed coalescence of the lines and obtain from it the exchange rate. Three main approaches have been used for this purpose. The one which Chuck Holm and I first tried[8] was the dependence of the apparent separation between the two components of the doublet as a function of the exchange rate, i.e. of the temperature. In this case the sample is cooled to get the maximum separation between the lines, which is assumed to be that characteristic of no exchange, namely $|\omega_a - \omega_b| = \delta\omega$. By using this value for $\delta\omega$, one can calculate 2τ, the mean lifetime for exchange, from each of the smaller splittings observed at higher temperatures.

Another aspect of the line shape which is affected by the exchange rate is the peak intensity of the two components in comparison to the central intensity. In the absence of exchange, if you have completely resolved lines, there would be zero intensity at the center of the doublet. However, it can be seen in both Figs. 1 and 2 that as the exchange rate increases there is a decrease in the intensity of the two peaks and a building up of intensities in the center. The ratio of the peak to the central intensity can be related to τ by means of Eq. (7) and such measurements have been used in rate studies.[14]

Another possibility is that if the two lines have coalesced into one line but the exchange rate is still "slow" that line is still broader than it would be if the exchange were "fast." In such cases this extra broadening can be measured as a function of exchange rate, or temperature, until the line becomes completely exchange narrowed. Similar considerations apply to the initial broadening of the separate components in the very slow exchange limit. Line broadening of both varieties[15] has been applied to rate studies. In some more complicated systems, rate studies have been made by calculating the entire line shape as a function of exchange rate and comparing the theoretical curves with the observed line shapes.

Returning to the amides, in our early work[8] we used the coalescence of the N-methyl doublet to determine the exchange rate, $1/2\tau$, as a function of temperature for DMF and DMA. Arrhenius type plots of log $(1/2\tau)$ versus $1/T$ are straight lines. The slopes correspond to activation energies E_a of about 10 kcal/mole for the internal rotation of both amides. Recently, a much more extensive study[16] of a variety of substituted N,N-dimethylamides, using the intensity ratio method, has yielded E_a's ranging from 7.3 ± 0.5 kcal/mole for the carbamyl chloride derivative to 18.3 ± 0.7 for DMF. These are generally somewhat smaller than, but still in reasonable agreement with, Pauling's estimate of 20 kcal resonance stabilization of the planar amide group by the double bond contribution.[7] For one would expect the double bond energy to be approximately the barrier. To reorient one end of the molecule with respect to the other, you would, in effect, have to break the double bond and convert it to a single bond.

One aspect of our early results[8] which troubled us at the time is that the Arrhenius frequency factor is only about 10^7 to 10^8. This is low compared with the 10^{12} to 10^{14} which one would predict for a pseudo first-order rate process proceeding via bimolecular collisions.

C. Rate Studies by NMR Spin Echoes

The NMR steady-state methods outlined above have been applied very widely to the study of fast, exchange-type rate processes. One limitation of the method, however, is that it is sensitive only to rate processes for which the exchange rate, $(1/2\tau)$ sec^{-1}, is comparable with the chemical shift in cps, or other splittings being averaged out. Once the exchange narrowed limit of a single narrow line has been approached, further increases in rate do not affect the usual high resolution spectrum appreciably. In part this is because inhomogeneities and/or instabilities in the applied magnetic field then govern the line widths and resolution, and in part because the fractional line narrowing with increased exchange rate becomes smaller at the higher rates. This limits, often rather severely, the cases which can be studied.

Nonetheless, the information as to the dynamic processes going on within the sample is contained in the sample, and we would like to get it out. And, in fact, this can be done by another magnetic resonance technique. Recent work of Don Woessner[13] at the Socony Mobile labs at Dallas and of Saul Meiboom[17] at the Bell Telephone labs has suggested that exchange rates too fast for accurate measurement by the high resolution steady state NMR method just described can be determined by radio frequency pulse methods.

The pulse methods differ from the steady state slow passage experiment in that you in effect control the length of time you look at the nuclear magnetization and, of more importance, you can adjust the length of time between looks. Thus, there is the possibility of decreasing the time between looks so that it is comparable with the exchange lifetime. Thereby, you can hope to observe effects of the exchange upon the nuclear magnetization even though such effects are averaged out during the longer time scale of the steady state experiment.

The theory of the rf pulse experiments can be developed[13,17] from the Bloch equations including exchange, Eq. (6), with the result that when the time between looks is approximately the exchange lifetime, observable effects are predicted from which can be obtained not only the exchange lifetime but also the frequency difference of the sites involved in the exchange. And this is true even though the exchange narrowing of the steady state spectrum is virtually complete.

During the past several months we have been assessing, mathematically and experimentally, the utility of rf pulse methods, in particular, the spin-echo technique[18,19] for studying fast chemical exchange. The apparatus used in our experiments is quite standard.[20] It includes a stable cw rf oscillator, a frequency doubler and a powerful rf amplifier. There is a set of pulse generators which drives gating circuits on the frequency doubler and rf amplifier. In this manner, the rf pulses are formed with adjustable width, separation and intensity, and in various sequences. These pulses are applied to a tuned circuit which contains the sample in the field of the magnet. The output of the sample circuit goes to a broad band rf receiver, and from there to an oscilloscope display.

The nuclear spin echo, which is the quantity observed in our experiments, is illustrated by the oscilloscope photograph in Fig. 3, where the abscissa is a time axis going from left to right. In this case the sample was glycerine at room temperature, and the proton resonance was observed at a fixed magnetic field corresponding to the resonance frequency of 26.9 Mc/sec. At the far left of Fig. 3 is the first rf pulse. It's a so-called 90° pulse; its intensity H_1 and width t_w are adjusted so that it turns the nuclear magnetization (initially M_o) from the z-direction (H_o) into the x-y plane, i.e. $\gamma H_1 t_w = \pi/2$. As M_o precesses in the x-y plane, it induces an rf signal in the sample coil at the resonance frequency γH_o. However, the individual nuclei whose moments combine to give M_o, precess about H_o at slightly different frequencies, centered at γH_o, because of the inhomogeneities in H_o and also because of the intrinsic width $2/T_2$ of the resonance line. Therefore, the nuclear moments get out of phase, their net magnetic moment decreases, and the signal they induce after the 90° pulse falls off to give what is called the Bloch induction decay.

Near the center of Fig. 3 is a little spike corresponding to a second rf pulse which is of the same intensity as the first pulse but which lasts twice as long. Therefore, it's a 180° pulse. The pulse itself isn't visible because its voltage is much greater than that of the nuclear induction signals. So the pulse is off scale; also, the writing speed of the oscilloscope trace is too fast for the rise and descent of the pulses to register. The 180° pulse reverses the orientation of the individual nuclear magnetic moments, and thereby it changes the sign of the dephasing which each nucleus has experienced. This dephasing depends upon the magnetic fields experienced by each nucleus during the time t_p between the first and second rf pulses. If the magnetic fields did not change with time, then after the second pulse, the individual nuclei would continue to precess at the same

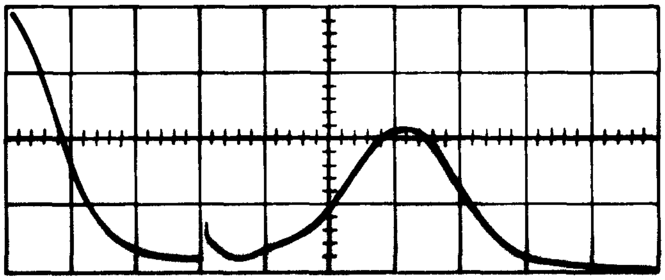


Fig. 3. An oscilloscope tracing of the proton spin echo from glycerine at room temperature with a resonance frequency of 26.9 Mc/sec. The total sweep is 40 msec. The 90° pulse is at $t = 0$; the Bloch induction decay is over at $t_p = 13$ msec at which time the 180° pulse is applied. The echo is the signal peaked at 26 msec.

different rates as before and would thereby cancel the (now reversed) dephasing which occurred between the first and second pulses. Thus, at the time t after the second pulse, the nuclei would be rephased and would induce a nuclear signal, the spin echo which is at the right of Fig. 3.

Actually, some of the dephasing is irreversible so the peak amplitude of the echo is less than the initial amplitude of the induction signal after the first pulse. This irreversible dephasing results here from the random interactions which determine the intrinsic line width $2/T_2$. The major contribution to T_2 in liquids usually is the spin-lattice relaxation which in the present case returns nuclear magnetization from the x-y plane to M_z. Inspection of Eq. (4) shows that, at least in the simpler situations covered by this single set of Bloch equations, the time dependence of the irreversible dephasing is of the form $M_o(1-e^{-t/T_2})$. From this and Fig. 3, it is apparent that one way to determine T_2 is to measure the echo amplitude as a function of the pulse separation t_p in the 90°, 180° two-pulse sequence. Another way, which has several advantages, is to obtain a Carr-Purcell train of echoes[19] by extending the pulse sequence in Fig. 3 with additional 180° pulses, spaced at intervals of $2t_p = t_{cp}$ after the first 180° pulse. Such trains of echoes are reproduced in Figs. 4 and 5. It may be seen, particularly in Fig. 5, that there is an exponential decay in the peak amplitudes A of the echoes, or in the echo envelope as it is called. A plot of log $[(A-A_o)/A_o]$ <u>versus</u> t yields a straight line of slope $1/T_2$.

If there are no chemical exchange effects, then T_2 is independent of the pulse separation. But if there are exchange effects, then the T_2 observed does depend upon the pulse separation. This occurs because the chemical exchange produces a random, irreversible dephasing of the nuclear moments. If a nucleus jumps from one site to another, say a to b, the base precessional frequency changes from ω_a to ω_b, and the dephasing rate changes correspondingly

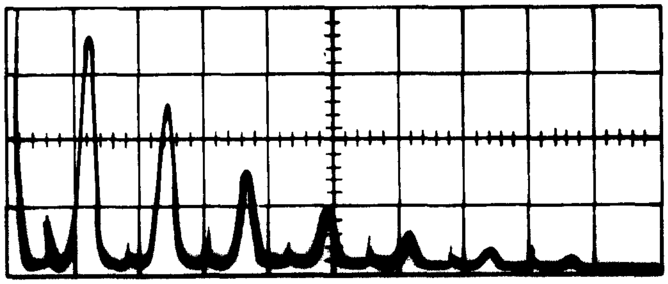


Fig. 4. An oscilloscope tracing of a Carr-Purcell train of proton spin echoes from glycerine. Conditions were as in Fig. 3 except that the total sweep is 200 msec and additional 180° pulses follow the first 180° pulse at intervals of $t_{cp} = 13$ msec.

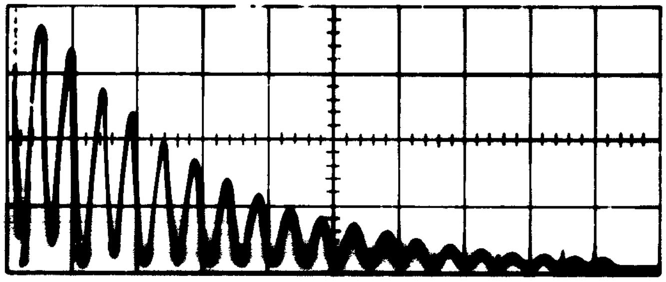


Fig. 5. An oscilloscope tracing of a Carr-Purcell train of spin echoes from glycerine under conditions the same as in Fig. 4 except for a smaller pulse separation, t_{cp} = 5 msec.

for that nucleus. But if the Carr-Purcell pulse separation t_{cp} is small enough, compared with the characteristic time τ for the exchange, the irreversible dephasing resulting from the exchange is negligible and the observed T_2 is T_2^o, the value for the system without exchange. On the other hand, if t_{cp} is large compared with τ, all of the nuclei will have exchanged many times between two pulses, thereby undergoing the maximum additional irreversible dephasing so that the total, observed T_2 is a lower limit, T_2^{∞}, where $T_2^{\infty} < T_2^o$.

These qualitative considerations are borne out by calculations of the apparent T_2 for the equally populated two-site case, as a function of the pulse separation t_{cp} for different exchange rates, $1/2\tau$. The calculations were made numerically with an IBM 7094 computer. The first step was to obtain the echo envelope for a particular set of parameters by stepwise integration, for the periods between rf pulses, of Eq. (6) in the appropriate form[13] for pulse experiments. The decay constant T_2 was then obtained from the echo envelope. Such calculations were made for a wide range of parameters and a typical set of results is summarized in Fig. (6).[21] It may be seen that T_2^o/T_2 approaches unity, for all exchange rates, as t_{cp} becomes very small. Also, T_2^o/T_2 approaches a value several-fold larger than unity as t_{cp} becomes large. Moreover, T_2^o/T_2^{∞} is larger for faster exchange rates. Also, it is noteworthy that the change in T_2^o between its limiting values is centered about $t_{cp} \cong 2\tau$.

Experiments corresponding to these theoretical curves were performed on the proton resonance of N,N-dimethyltrichloroacetamide (DMTCA), at a resonance frequency of 26.9 Mc/sec. The apparent T_2 was measured by the Carr-Purcell echo-envelope method, as a function of pulse separation for a number of different temperatures from 4° to 60°C. Typical results obtained are given in Figs. 7-9 as log-log plots of T_2^o/T_2 versus T_2^o/t_{cp}, for six different temperatures. The points for each temperature define curves which agree in general

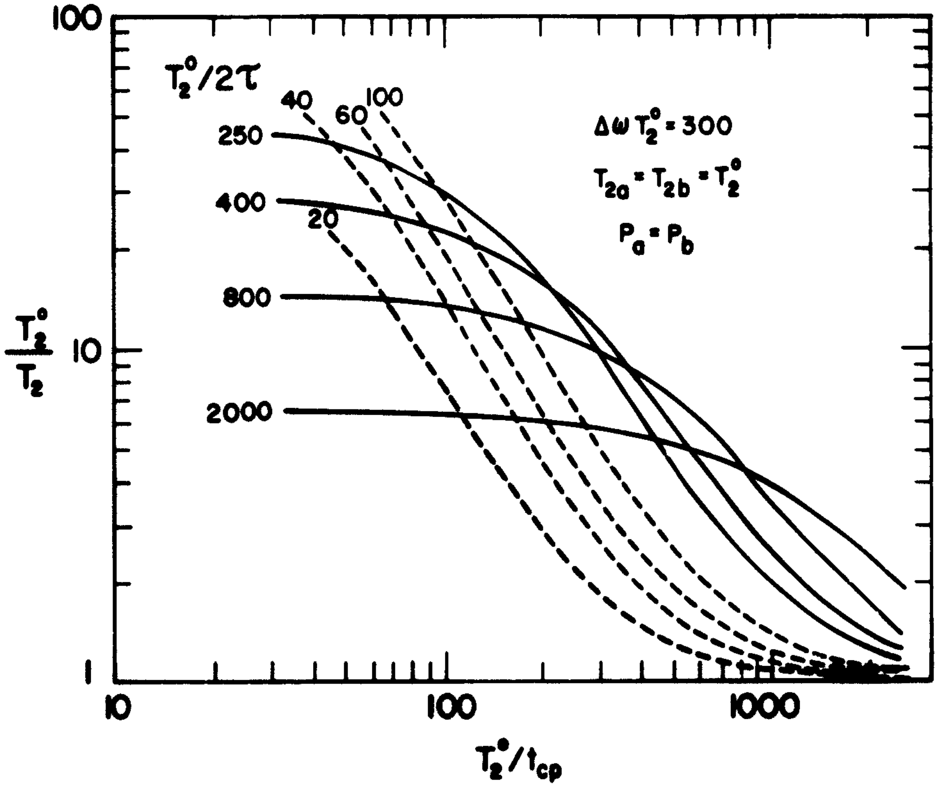


Fig. 6. Theoretical results for the dependence of the apparent T_2 upon the Carr-Purcell pulse separation t_{cp} at different nuclear exchange rates $1/2\tau$, for the equally populated two-site case with a chemical shift of $\Delta\omega$.

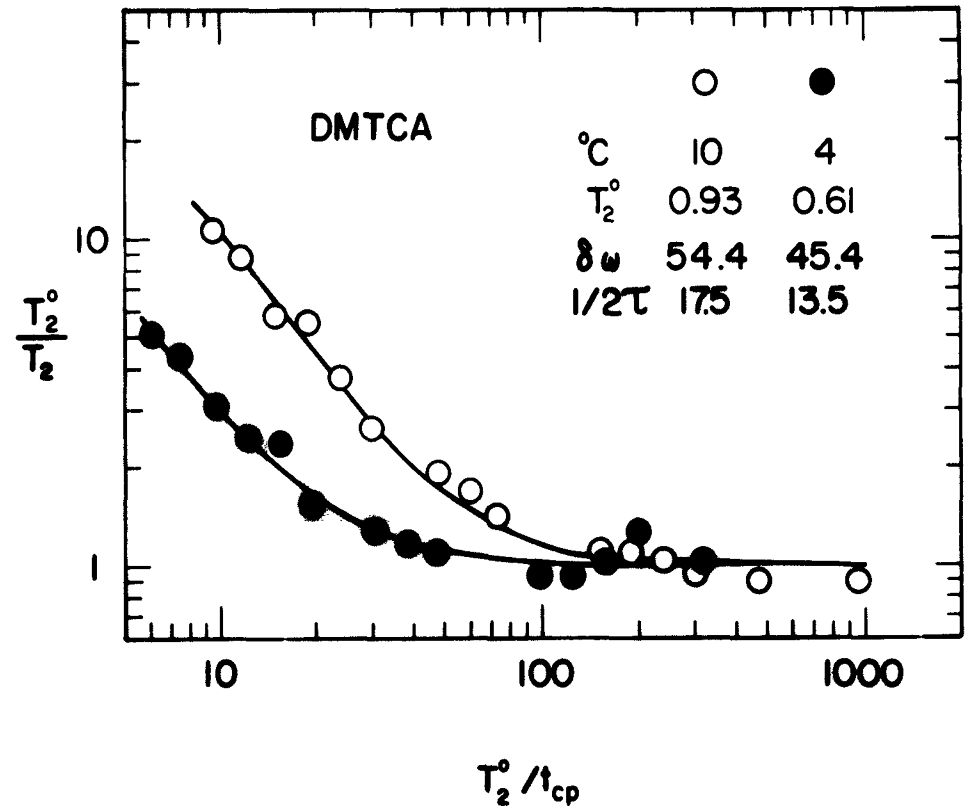


Fig. 7. The proton apparent T_2 observed at 26.9 Mc/sec as a function of pulse separation t_{cp} in Carr-Purcell echo envelopes for DMTCA at 4° and 10°C. The lines are best-fit theoretical curves corresponding to the parameters in the figure.

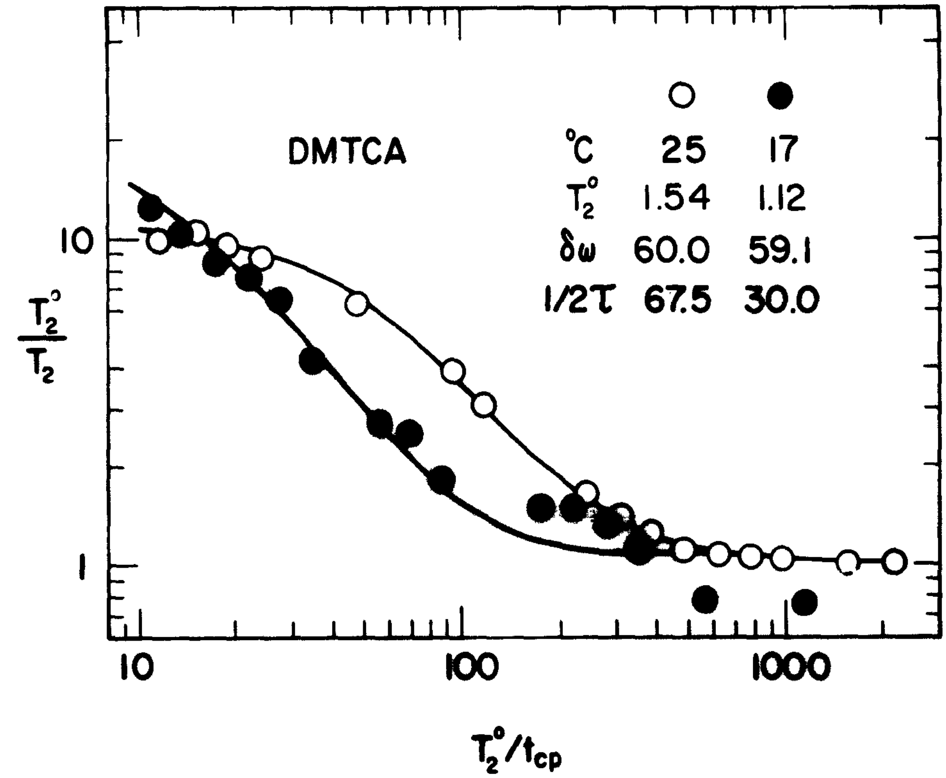


Fig. 8. The proton apparent T_2 observed at 26.9 Mc/sec as a function of pulse separation t_{cp} in Carr-Purcell echo envelopes for DMTCA at 17° and 25°C. The lines are best fit theoretical curves corresponding to the parameters in the figure.

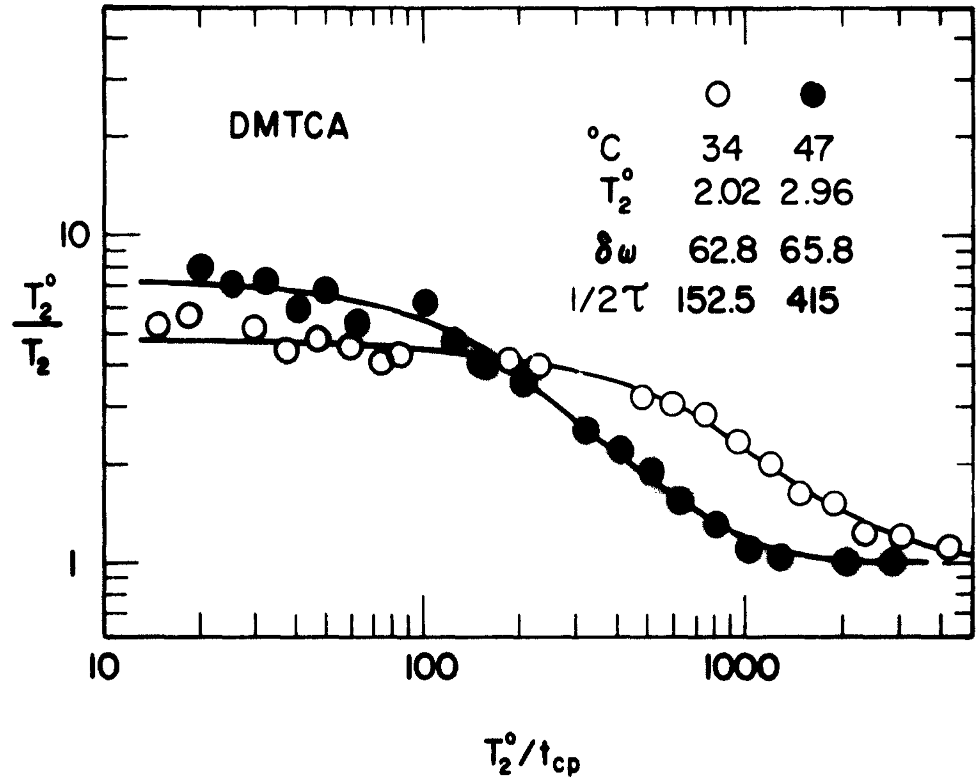


Fig. 9. The proton apparent T_2 observed at 26.9 Mc/sec as a function of pulse separation t_{cp} in Carr-Purcell echo envelopes for DMTCA at 34° and 47°C. The lines are best fit theoretical curves corresponding to the parameters in the figure.

shape with portions of the theoretical curves in Fig. 6. In fact, the solid line through each set of data is the Meiboom theoretical curve[17,21] fitted to the data by an iterative computer program and then checked with our exact, stepwise integration program. The theoretical curve has three adjustable parameters, T_2^o, $\delta\omega$, and $1/2\tau$. Initial values were obtained as follows: $T_2^o \cong T_2$ for small t_{cp}; $\delta\omega$ is approximately the chemical shift between components of the low temperature, high resolution doublet; and $1/2\tau$ is approximately the $1/t_{cp}$ at which T_2 changes most rapidly with t_{cp}. A major advantage of this approach is that the iterative program obtains best-fit values for each of the three parameters from the data for a given temperature. These values are given in Table II.

The internal rotation of DMTCA has been studied previously[16] by means of the steady state high resolution spectra at 60 Mc/sec, using the peak to center intensity procedure mentioned in Section IV.B. In such studies, one has to assume that the chemical shift is temperature independent, and that the low temperature value of the chemical shift is the best approximation to that shift. However, our results for DMTCA indicate that the shift actually has an appreciable temperature dependence. That is, the true chemical shift between the two sites is, itself, temperature dependent because of expansion of the liquid and changes in molecular association with temperature. The experiments were done on the pure liquid and the amides are quite highly associated, so a considerable temperature dependence of the "internal shift" is not too surprising once you have seen it.

Another interesting feature of the results in Table II is the temperature dependence of T_2^o, which increases from 0.61 sec at 4°C to 3.91 sec at 60°C. This decrease is predicted by nuclear relaxation theory for liquids,[3,5] and it has probably at most a secondary effect on the accuracy of the high resolution methods. This is because the apparent inverse line width T_2^* is used in the

Table II. **Parameters Describing the Internal Exchange Averaging of the Proton Magnetization in N,N-dimethyltrichloroacetamide as Obtained from Spin-echo Experiments at 26.9 Mc/sec.**

Temp. °C	T_2^0 sec	$\delta\omega$ rad/sec	$1/2\tau$ sec^{-1}	$\delta\nu$[a] cps
4	0.61	45.4	13.5	16.1
10	0.93	54.4	17.5	19.3
17	1.12	59.1	30.0	21.0
25	1.54	60.0	67.5	21.3
34	2.02	62.8	152.5	22.3
41	2.31	63.9	235.	22.7
47	2.96	65.8	415.	23.3
60	3.91	60.0	760.	21.3

[a] These values were calculated from $\delta\omega$ at 26.9 Mc/sec for comparison with the value reported in ref. 16, of 17.6 cps at 60 Mc/sec for -28.6°C.

latter, and T_2^* is governed usually by the inhomogeneities in H_o. This use of T_2^* is in itself an approximation. Moreover, the value of T_2^* must be obtained at each temperature by observing the line width of a non-exchanging reference sample, and if $T_2^* \cong T_2^0$, the temperature dependence of T_2^0 could lead to appreciable inaccuracies in the analysis.

Arrhenius plots are given in Fig. 10 of the exchange rates $1/2\tau$ versus $1/T$ for our spin echo results on DMTCA and also for the results of the steady state intensity ratio experiments.[16] The comparison has several noteworthy features. First, the shortness of the temperature range in the steady state, high resolution experiments is seen to be a real limitation. Or if you wish to phrase it another way, the rf pulse method measures exchange rates at least tenfold faster than the steady state method. Moreover, the rf pulse method can be extended to even faster rates by using shorter, more intense rf pulses, and receivers with faster recovery and response times. There does not seem to be any reason in principle why the range of the pulse methods can not be extended to 100-fold faster rates, or perhaps even more.

Here a word of caution is in order. The rf pulse method does suffer from a lack of "resolution." Unless the chemical shifts are very large, all of a given nuclear species will contribute to the spin echo for this species. And if all of these nuclei do not participate in the chemical exchange, the analysis of the echo envelope to give an accurate T_2 for only those nuclei exchanging is difficult, if not impossible.

Another point is that the activation energy from the pulse data differs significantly from that found in the high resolution work.[16] The slope of the line through our data corresponds to an activation energy of 14.1 kcal/mole, while the value obtained from the high resolution work is 9.9 kcal/mole, which is a significant difference. Also, and this pleases me a good bit, the frequency factor obtained from our data is about 5×10^{12}, which is a good deal more reasonable than the values of about 10^9 from the high resolution studies.

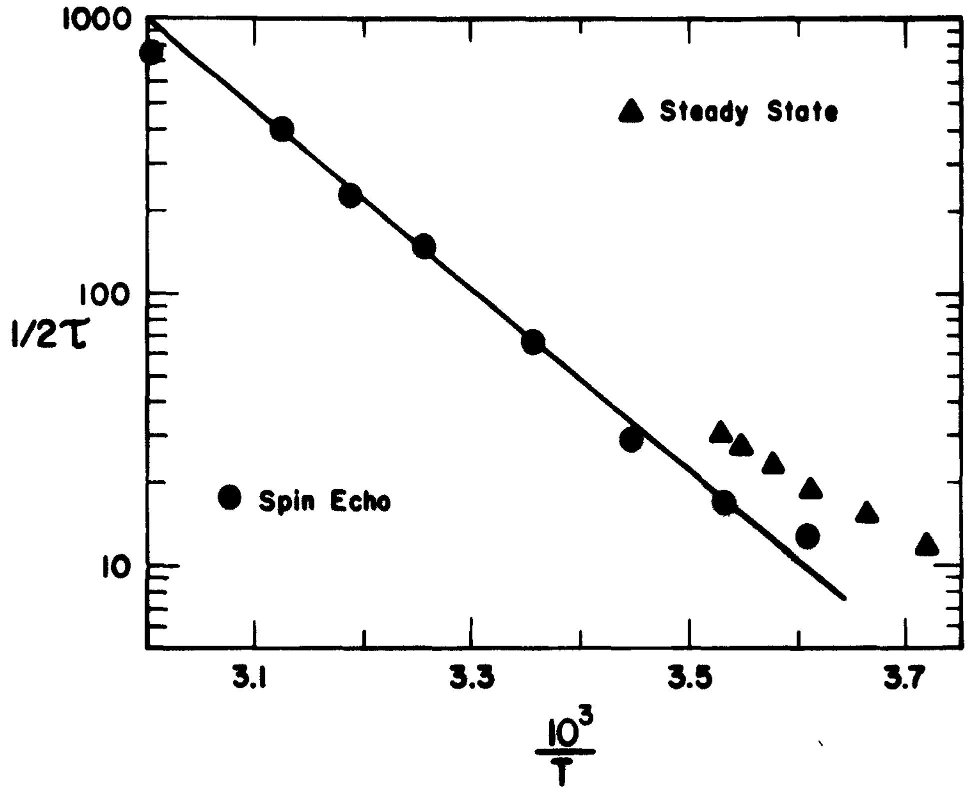


Fig. 10. Arrhenius plots of log (1/2τ) versus 1/T for the internal reorientation of N,N-dimethyltrichloacetamide. The circles are the results from our Carr-Purcell spin echo experiments; the triangles are data, from ref. 16, obtained by the high resolution, steady state, peak to center intensity ratio method.

If there are no systematic errors hidden in the rf pulse results and analysis, the discrepancies between them and the high resolution work are attributable to the temperature dependence of the chemical shift $\delta\omega$, which is assumed constant in the high resolution analysis.

In summary, it seems fair to say that the rf pulse methods do have promising features compared with the steady state NMR methods for measuring the concentrations of rapidly exchanging chemical species.

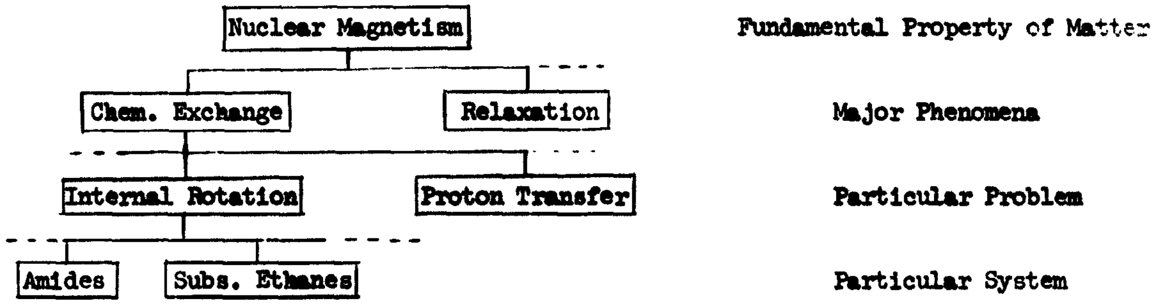
IV. The Modern Role of the Analytical Chemist

At the beginning of my talk I was brash enough to say that at the end I would use this case of NMR rate studies as a basis for commenting on the current state and future of analytical chemistry. For this purpose, consider Table III, which is a synopsis of the main steps by which this particular analytical method has evolved, and which applies to science more or less in general.

We start with nuclear magnetism, which is a fundamental property of matter. Then you go on to a set of major phenomena, which depend upon the existence of this property. The one with which we were concerned is chemical exchange. There are several others which can be put here, such as nuclear relaxation, chemical shifts, dipolar interactions, and so on. This might be called the particular phenomenon level in the structure of science. Like most classification schemes, it is somewhat arbitrary because phenomena may "overlap," as do for example chemical exchange and nuclear relaxation.

The next level involves particular types of problem. And here I classify our particular problem as one of internal rotation. We were using the phenomena associated with chemical exchange effects upon the nuclear magnetism to investigate the internal rotation of molecules. There are many other particular types of chemical exchange which can be investigated, such as proton

Table III. The Steps in the Evolution and Use of NMR Methods for Rate Studies



transfer, hydration of ions and hydrogen bonding. These are labelled as the particular problem level. At the last stage in the diagram is the particular system. In our case we were concerned with amides. Similar NMR studies might be made of substituted ethanes, substituted silanes, propylenes, and others.

In terms of this diagram in Table III and similar ones which can be drawn for other relevant scientific disciplines, the role of analytical chemistry should be describable by the area of the diagram within which analytical chemists operate. Three facts must be recognized, however. The lower you get in this diagram, the larger is the number of experiments and the more routine are the measurements and observations. You end up at the bottom with operations which can be performed by technicians. Very often such technicians are very skillful and essential, but generally they will not need either the aptitude or the background for truly independent work.

The higher you get on the diagram the fewer are the experiments, the harder they are to conceive, and the more facility you need in mathematics, physics and in chemical principles in order to be able to do the experiments. As to the province of analytical chemistry, I believe it lies more or less in the bottom one-half of the diagram. But the most important point, it seems to me, is that if there is such a person as an analytical chemist, he is not a specialist in NMR or in mass spectrometry. He is not concerned primarily with electrode processes or with the relations between biological specificity and molecular structure, or with organic reaction mechanisms. The analytical chemist should be a specialist in chemical analysis and separation, <u>in general</u>. He should know the advantages and limitations of, say, activation analysis compared with polarography. He should know when to use NMR rather than IR or mass spectrometry. He should also be familiar with how to make separations and now to do microanalyses.

The main current problem in analytical chemistry, I believe, is that the physicist and non-analytical chemists have been developing new analytical tools faster than they can be assimilated by analytical chemists and certainly much faster than college curricula change. Accordingly, if analytical chemistry is to survive as a label for an identifiable scientific discipline, graduate instruction for it will have to be at a much more fundamental level. It will have to provide the background in mathematics, physics and physical chemistry for an adequate understanding of the tremendous range of phenomena and of instrumentation now available for chemical analysis. The analytical chemist will have to supply an understanding and command of analytical methods, *in general*, which is superior to that of the scientist in some other specialty who needs those talents. In conclusion, I think it is possible for such people to be trained. I think it won't be easy.

Acknowledgments

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[22] A. Allerhand and H. S. Gutowsky, to be published.

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