

Rate Processes and Nuclear Magnetic Resonance Spectra. II. Hindered Internal Rotation of Amides*

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(Received January 30, 1956)

Mathematical methods are presented for calculating rate constants of processes which narrow nuclear magnetic resonance absorption lines having discrete components. High resolution proton spectra show that the $R_1CO-NR_2R_3$ skeletons of *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA) are planar and suggest that *N*-methylformamide, *N*-methylacetamide, *N*-methylformanilide and *N*-methylacetanilide exist predominantly in one configuration. The presence of a significant amount of double bond character in the C—N amide bond is proved by the temperature dependent coalescence observed for the chemically shifted proton doublet of the $N(CH_3)_2$ groups in DMF and DMA, which gives values of about 22 and 19 kcal respectively for the free energy of activation required for reorientations about the bond.

I. INTRODUCTION

MOST characteristics of nuclear magnetic resonance spectra¹ are influenced to some extent by the various motions of the molecules, ions or atoms containing, or in the vicinity of, the nuclei observed. These effects provide several methods of studying a wide range of kinetic phenomena. Bloembergen, Purcell, and Pound² (BPP) made the first extensive theoretical and experimental analysis demonstrating the importance of "lattice motions" as a mechanism for spin-lattice relaxation and for narrowing the absorption lines. This article is concerned with a line narrowing phenomenon differing superficially from that described by BPP² but identical in principle; both belong to a general class containing a number of such effects.

In the case investigated by BPP the widths and structure of the absorption line were determined directly by the local magnetic dipole fields of the magnetic nuclei. The dipole fields depend upon the direction and distance of the observed nuclei from the neighboring dipoles; and it is this dependence which leads to the motional effects, as may be seen from the following qualitative argument. Suppose two nuclei have Larmor precessional and resonance frequencies differing by $\Delta\nu$ because of differences in the local dipole fields. If the nuclei are precessing in phase at a given instant they will be 180° out of phase ($\frac{1}{2}\Delta\nu$) sec later. However, if the local fields change during this time, then the rate of getting out of phase changes and the difference in precessional and resonance frequency is modified. The spectrum of the dipole fields is symmetric, with negative as well as positive values, so the lattice motions will reduce the effective dipolar splitting or broadening, providing the frequency of the motions is comparable to the frequency equivalent of the perturbation to be reduced. The detailed analysis of

this motional narrowing² is complicated by the continuous character of the local field spectrum.

Similar arguments apply to other perturbations which are time dependent. A motional model was proposed to account for the absence in certain liquids of the multiple NMR spectra produced by the local magnetic fields from electrons polarized by magnetic nuclei.³ In this case, the resonance absorption of one group of nuclei is split into discrete components depending on the spin coordinates of a second group of nuclei in the same molecule. Fluctuations in the spin coordinates of one group, if fast enough, will average out the splitting and narrow the resonance of the second group to a single line. Ogg has reported^{4,5} several instances in which such a transition from a multiple to a single resonance can be effected by adjusting the chemical exchange rate of one of the interacting groups. Estimates of specific rate constants for the exchange were made⁵ by applying the qualitative criterion outlined above to the conditions under which the transitions occurred. In a related experiment, an rf field at the resonance frequency can be used to change "artificially" the spin coordinates of one group of nuclei at a known and adjustable rate while observing the multiplet resonance of the other group. Multiplet resonances have been observed to coalesce in a predictable manner in such experiments,⁶ which differ from the "naturally occurring" processes such as chemical exchange in that the latter produce random rather than coherent fluctuations in the spin coordinates.

In this paper we are concerned primarily with differences in the local magnetic fields and resonance positions produced by chemical differences in the magnetic shielding of nuclei in different electronic environments, which also can be averaged by the proper rate processes.⁷ This case is equivalent to that of the multiplets. In the first paper of this series,⁷ the

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¹ E. R. Andrew, *Nuclear Magnetic Resonance* (Cambridge University Press, Cambridge, 1955), gives a general introduction to the field.

² Bloembergen, Purcell, and Pound, *Phys. Rev.* **73**, 679 (1948).

³ Gutowsky, McCall, and Slichter, *J. Chem. Phys.* **21**, 279 (1953).

⁴ R. A. Ogg, Jr., *J. Chem. Phys.* **22**, 560 (1954).

⁵ R. A. Ogg, Jr., *Discussions Faraday Soc.* **17**, 215 (1954).

⁶ A. L. Bloom and J. N. Shoolery, *Phys. Rev.* **97**, 1261 (1955).

⁷ H. S. Gutowsky and A. Saika, *J. Chem. Phys.* **21**, 1688 (1953).

theory developed for the multiplets was used to interpret the single proton resonance lines with concentration dependent positions resulting from proton exchange among the various chemical species in aqueous solutions of HNO_3 , H_2SO_4 and others. Line shapes were computed for several exchange rates in the transition region and it was pointed out that rate constants could be calculated directly from observations of such line shapes. Details of these calculations are given here, and the methods are used to analyze the proton spectra observed for several amides, yielding numerical values for the rate at which internal molecular reorientations take place about the C-N bond in N,N-dimethylformamide and N,N-dimethylacetamide.

II. MATHEMATICAL METHODS

Our starting point is very nearly the model used previously.⁷ More general theories of motional effects have since been developed.^{8,9} However, the analysis³ based on the Bloch equations¹⁰ is much simpler yet entirely adequate for handling most cases of immediate chemical interest. We consider a liquid in which there is negligible dipolar broadening of a proton (or other) resonance because of motional narrowing, but in which there are sites with different local fields giving a resonance with two components *A* and *B* shifted by $+\delta\omega/2$ and $-\delta\omega/2$ from their average angular frequency. The relative intensities of these components are directly proportional to the proton fractions p_A and p_B contributing to each component.

The process in question interchanges protons between sites *A* and *B*, so if the protons N_A and N_B at each site are labeled N_A^* and N_B^* at some instant

$$dN_A^*/dt = -k_A N_A^* \quad \text{and} \quad dN_B^*/dt = -k_B N_B^*, \quad (1)$$

where $k_A p_A = k_B p_B$. The average lifetime of protons at each site is therefore

$$\tau_A = 1/k_A = \tau/p_B \quad \text{and} \quad \tau_B = 1/k_B = \tau/p_A, \quad (2)$$

where $\tau = \tau_A \tau_B / (\tau_A + \tau_B)$. The proton absorption line shape is described by the imaginary part of the total rf nuclear magnetization of the two states. When averaged over the proton interchange, the total magnetization *M* is that given by Eq. (18) of reference 7,

$$M = \frac{i\omega_1 M_0 [(\tau_A + \tau_B) + \tau_A \tau_B (\alpha_A p_B + \alpha_B p_A)]}{(1 + \alpha_A \tau_A)(1 + \alpha_B \tau_B) - 1}, \quad (3)$$

where ω_1 describes the applied rf field, M_0 is the static nuclear magnetization at thermal equilibrium, while $\alpha_A = (1/T_2) - i(\Delta\omega + \delta\omega/2)$ and $\alpha_B = (1/T_2) - i(\Delta\omega - \delta\omega/2)$. This assumes the resonance absorption is plotted at a constant static magnetic field as a

function of the different $\Delta\omega$ between the applied radiofrequency and the frequency at the center of the two resonance components. T_2 is related to the line width. In the absence of exchange effects or overlap of the components $\Delta\omega$, the width of each component at half-maximum is $2/T_2$; this includes all contributions to the line width such as field inhomogeneities and implies a Lorentzian line shape. $\delta\omega$ is the separation of the components assuming no exchange and no overlap of the components.

Expanding Eq. (3) and retaining only the imaginary part *v*, we find

$$v = \frac{\omega_1 M_0 [(1 + \tau/T_2)P + QR]}{P^2 + R^2} \quad (4)$$

where

$$P = \tau [(1/T_2^2) - (\Delta\omega)^2 + (\delta\omega/2)^2] + 1/T_2$$

$$Q = \tau [\Delta\omega - (\delta\omega/2)(p_A - p_B)]$$

$$R = \Delta\omega [1 + (2\tau/T_2)] + (\delta\omega/2)(p_A - p_B).$$

Experimentally, the separation of the two components is measured and from such values we wish to find τ . The positions of the two components and their dependence on τ are given by the maxima of Eq. (4), which can be located by solving the fifth order equation obtained upon differentiating *v* with respect to $\Delta\omega$. For the case of immediate interest, $p_A = p_B$, $\tau_A = \tau_B = 2\tau$, and the result is

$$\begin{aligned} & \frac{\tau^4}{T_2} (\Delta\omega)^5 + 2\tau^2 S \left(1 + \frac{\tau}{T_2}\right) (\Delta\omega)^3 \\ & + \left[\left(1 + \frac{\tau}{T_2}\right) \left(1 + \frac{2\tau}{T_2}\right)^2 - \tau S \left(2 + \frac{3\tau}{T_2}\right) \right] S (\Delta\omega) = 0 \end{aligned} \quad (5)$$

where

$$S = \left[\frac{1}{T_2} + \frac{\tau}{T_2^2} + \tau \left(\frac{\delta\omega}{2}\right)^2 \right].$$

One solution of Eq. (5) is always at $\Delta\omega = 0$, which corresponds to either a minimum or a maximum depending on whether τ is long or short.

If the line widths ($\sim 1/T_2$) are small compared to the separation $\delta\omega$ (i.e., if $T_2 \delta\omega$ is large), the terms in T_2 in Eq. (5) can be neglected; the observed separation is not influenced by overlap of the components and depends only on τ . This gives the particularly simple result that $\delta\omega_e$, the experimentally observed separation, is

$$\delta\omega_e \equiv 2\Delta\omega = (1 - 2/\tau^2 \delta\omega^2)^{1/2} \delta\omega \quad \text{if} \quad \tau \delta\omega > \sqrt{2},$$

and

$$\delta\omega_e = 0 \quad \text{if} \quad \tau \delta\omega \leq \sqrt{2}. \quad (6)$$

This simple result for the limiting case is the same as Eq. (60) of reference 8. The general nonzero solution

⁸ P. W. Anderson, J. Phys. Soc. Japan 9, 316 (1954).

⁹ R. Kubo, J. Phys. Soc. Japan 9, 935 (1954).

¹⁰ F. Bloch, Phys. Rev. 70, 460 (1946).

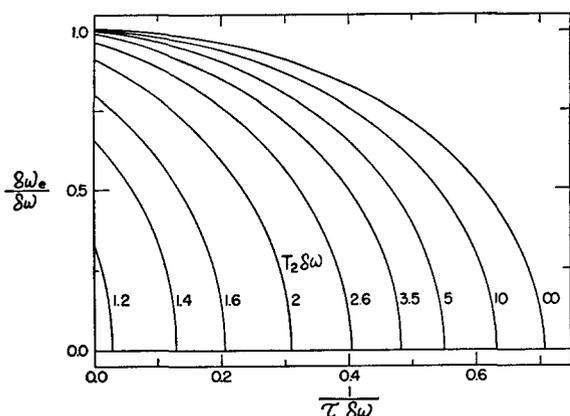


FIG. 1. The separation, $\delta\omega_e$, of two equally intense resonance components, relative to $\delta\omega$, as a function of exchange rate, $1/\tau\delta\omega$, for several values of $T_2\delta\omega$. The separation between the components in the absence of exchange, with no overlap of the components, is $\sqrt{2}\delta\omega$.

of Eq. (5), which includes the effects of overlap is

$$\Delta\omega = \pm \left\{ -S \left(\frac{1}{\tau} + \frac{T_2}{\tau^2} \right) \pm S^{\frac{1}{2}} \left(\frac{\delta\omega}{2} \right) \left(\frac{T_2^2}{\tau^3} + \frac{4T_2}{\tau^2} + \frac{4}{\tau} \right)^{\frac{1}{2}} \right\}^{\frac{1}{2}} \quad (7)$$

The dependence of $\delta\omega_e$ on τ and T_2 has been computed using Eqs. (6) and (7); the results are shown in Fig. 1 which gives plots of the positions of the components, relative to $\delta\omega$, as a function of $1/\tau\delta\omega$ for several values of $1/T_2\delta\omega$. The curves in this figure show the coalescence of the two components as the exchange time decreases.

The curves in Fig. 1 also show that if $1/T_2\delta\omega$ is greater than about $\frac{1}{3}$, overlap of the components reduces their apparent separations by an appreciable amount. This means that the limiting value of $\delta\omega_e$, when the exchange is slow, does not equal $\delta\omega$. This overlap effect was important in the study of the amides. If we let $\delta\omega_\infty$ be the observed separation of the components as $\tau \rightarrow \infty$, we find from Eq. (7) that the true limiting separation, $\delta\omega$, is given by

$$\delta\omega = \frac{\delta\omega_\infty}{\sqrt{3}} \left[2 \left(\frac{1}{T_2^4(\Delta\omega_\infty)^4} + \frac{1}{T_2^2(\Delta\omega_\infty)^2} + 1 \right)^{\frac{1}{2}} + \left(1 - \frac{1}{T_2^2(\Delta\omega_\infty)^2} \right) \right]^{\frac{1}{2}} \quad (8)$$

where $\delta\omega_\infty \equiv 2\Delta\omega_\infty$. In practice T_2 was found by measuring the line width under conditions such that the resonance components had coalesced to a single line ($\tau \rightarrow 0$), while $\delta\omega_\infty$ was the limiting separation observed for long exchange lifetimes ($\tau \rightarrow \infty$). $\delta\omega$ can be calculated with Eq. (8) from the experimental $\delta\omega_\infty$ and T_2 values, or obtained from the graph of $\delta\omega/\delta\omega_\infty$ as a function of $2/T_2\delta\omega_\infty$ in Fig. 2. For all practical cases $2/T_2\delta\omega_\infty$ will

not exceed the value one. The experimental values of the separation of the components, $\delta\omega_e$, in the transition region can be applied to Fig. 1 and the values of $1/\tau\delta\omega$ read off from the curve for the proper $1/T_2\delta\omega$ value. Figure 1 gives a good representation of the actual coalescence of the resonance components, but it is not very satisfactory for interpolating for different values of $1/T_2\delta\omega$. Figure 3 gives plots of $1/T_2\delta\omega$ versus $1/\tau\delta\omega$ for various values of $\delta\omega_e/\delta\omega$; and $1/\tau\delta\omega$ is more readily obtained from this figure. Equation (8) is a general form and can be applied to any pair of equally intense spectral lines with Lorentzian shapes to correct for overlap, provided of course the T_2 is known or can be estimated for the components.

The above analysis assumes that the exchange rate does not influence T_2 . This may or may not be true depending on the system and experimental conditions. For the results reported in this work the exchange rate was varied by changing the temperature and strictly speaking the temperature dependence¹¹ of T_2 should be included. However, the line widths in the absence of exchange effects were most likely due mainly to inhomogeneities in the magnetic field so any temperature dependence of the effective T_2 was slight.

III. RESULTS AND DISCUSSION

Experimental Procedure

The high resolution NMR spectrometer and experimental techniques used in these experiments have been described previously,¹² except for certain modifications. A new field sweep system incorporates a well regulated saw tooth generator (non-linearity $<1\%$), with an adjustable period from 0.1 to 100 sec, which is connected to two 1000 turn coils mounted about the pole caps and produces sweep fields from 2 to 1500 milligauss. Spectra can be recorded automatically by means of a dc amplifier driving a Sanborn Model 127 Oscillograph. A thermally insulated box has been placed about the permanent magnet and the temperature of the in-

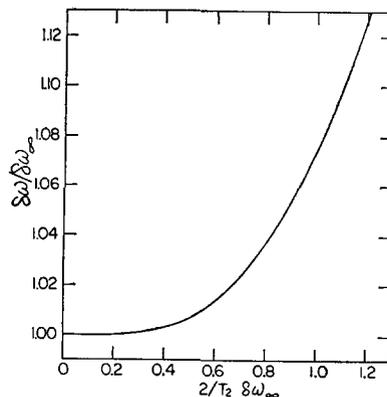


FIG. 2. The effect of overlap of two equally intense resonance components on their apparent separation, as a function of line width $2/T_2$. The observed separation is $\delta\omega_\infty$ while the separation corrected for overlap is $\delta\omega$.

¹¹ R. Kubo and K. Tomita, J. Phys. Soc. Japan 9, 888 (1954).

¹² Gutowsky, Meyer, and McClure, Rev. Sci. Instr. 24, 644 (1953).

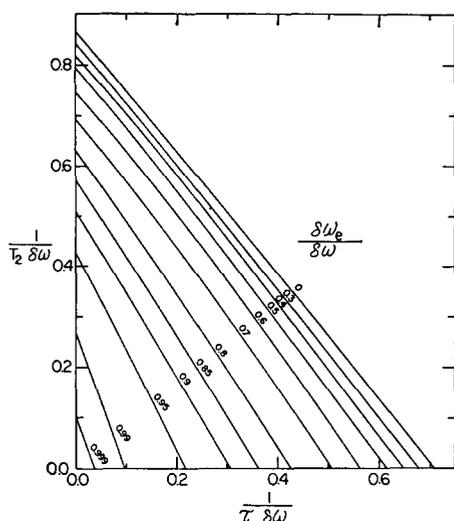


FIG. 3. A plot of Eq. (7), in a form different from Fig. 1, to permit easier interpolation in determining values of $1/\tau\delta\omega$ from experimental observations of $\delta\omega_e/\delta\omega$.

closure regulated in order to minimize drifts in the magnetic field with changes in room temperature.

The samples used in the studies of temperature effects were contained in melting point tubes (1.5 mm ID and 2 mm OD) and the sample volume in the rf coil was about 0.01 cm³. Larger samples, ~ 0.03 cm³, were used in obtaining the room temperature spectra. The samples themselves were Eastman Kodak Co. white label grade chemicals, except for the N-methylformamide ($n_D^{20}=1.4300$) which was very kindly synthesized and provided for us by Mr. R. A. Vierling and Dr. C. S. Marvel. A simple air driven device was used to spin the samples as a means of averaging out inhomogeneities in the applied field and improving resolution.¹³

The temperature of the sample was controlled by putting the entire rf probe into a Dewar vessel in the magnet gap, with a Styrafoam plug as insulation at the top of the Dewar. The outer part of the probe is a copper box into the bottom of which a copper rod is screwed; a heating coil of Teflon coated copper wire is wound non-inductively about the rod. The copper box serves both as an rf shield and also as a means of maintaining a uniform temperature throughout the probe. The temperature of the probe was measured with a copper-constantan thermocouple; this gave the temperature of the sample to within $\pm 1^\circ$, sufficient for the present purpose. Temperatures below that of the room were obtained by placing dry ice or liquid nitrogen in the bottom of the Dewar.

¹³ Bloch, Anderson, and Arnold, *Phys. Rev.* **94**, 496 (1954). An earlier experiment using spinning sample techniques has been described by H. Y. Carr, Ph.D. Thesis, Free Precession Techniques in Nuclear Magnetic Resonance (Harvard University, 1952).

N,N-Methylformamide and N,N-Methylacetamide

The proton magnetic resonance spectra of several substituted amides at room temperature are given in Fig. 4. The structural formula that has usually been used for these compounds is (I),



but it was postulated by Pauling¹⁴ that form (II), with a nitrogen-carbon double bond rather than a single bond makes a significant contribution to the actual electronic structure of the compounds. The various components in the observed spectra are readily assigned to the particular substituents on the basis of relative intensities and the known chemical shift values characteristic of the substituents.¹⁵ In N,N-dimethylformamide (DMF) the weak single component at a δ of +0.29 is assigned to the proton (R_1) in the HCO— group while the much stronger absorption at -0.22 corresponds in position to N—CH₃ groups in other compounds. The main point of interest is the doublet structure in this region which must be due to a non-equivalence of the two CH₃ groups (R_2 and R_3). This doublet was apparently first observed by Meyer

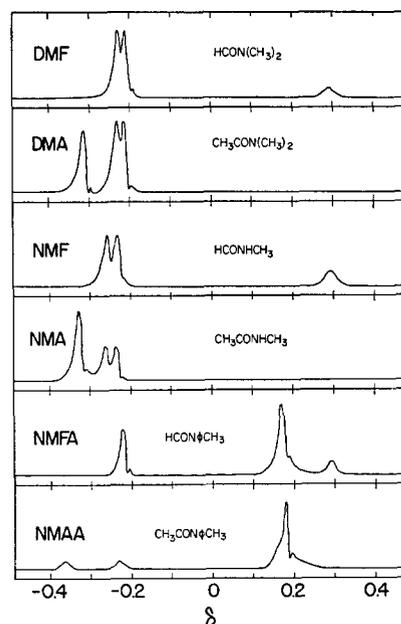


FIG. 4. Proton magnetic resonance spectra recorded at 29°C, as a function of applied magnetic field, at a fixed frequency of 17.735 Mc. δ is defined as $10^6(H_r - H_c)/H_r$ with H₂O the reference compound. The total sweep is 40.7 milligauss; the sweep period, 21 sec. The N-methylacetanilide (NMAA) was a saturated solution in benzene; all other samples were the pure liquids.

¹⁴ L. Pauling, *The Nature of the Chemical Bond* (Cornell University Press, Ithaca, New York, 1948), 2nd Edition, p. 207.

¹⁵ Meyer, Saika, and Gutowsky, *J. Am. Chem. Soc.* **75**, 4567 (1953).

TABLE I. Temperature dependence of $1/\tau\delta\omega$.

N,N-dimethylformamide			N,N-dimethylacetamide		
T°K	$\delta\omega_e$ radian sec ⁻¹	$1/\tau\delta\omega$ radian ⁻¹	T°K	$\delta\omega_e$ radian sec ⁻¹	$1/\tau\delta\omega$ radian ⁻¹
236	20.1±0.3 ^a	0.00±0.03 ^b	249	24.4±0.9 ^a	0.00±0.1 ^b
322.5	19.2±0.9	0.08±0.04	293	23.7±0.7	0.08±0.07
325	18.5±1.2	0.11±0.04	303	22.8±0.9	0.14±0.07
344	17.3±0.6	0.17±0.03	307	21.9±1.1	0.19±0.07
347	16.6±1.2	0.20±0.03	310.5	21.7±0.9	0.20±0.06
354.5	15.4±0.6	0.24±0.02	313	20.4±0.9	0.25±0.04
359	13.8±0.6	0.29±0.01	316.5	17.5±0.7	0.34±0.03
360.5	15.4±0.6	0.24±0.02	319.7	15.4±0.9	0.39±0.03
362.5	13.2±0.3	0.30±0.01	321.2	13.4±1.3	0.43±0.03
367	12.6±0.6	0.32±0.01	322.5	9.8±0.7	0.48±0.01
369	11.9±0.6	0.33±0.01			

^a The error given is the standard deviation from the average of about ten measurements.

^b The error in $1/\tau\delta\omega$ is obtained from Fig. 3 using the error given for $\delta\omega_e$.

although it was not explicitly reported in the summary of his results.¹⁵

If the doublet were a result of electronic coupling of the CH₃ group protons with the HCO-proton, the resonance of the latter would be a multiplet, which is not the case. Moreover, N,N-dimethylacetamide (DMA) in which R₁ is itself a CH₃ group has a similar doublet, as shown in Fig. 4, while a quartet would be predicted for the electronic coupling mechanism. So we assign the doublets in both DMF and DMA to a chemical shift in the resonance positions of protons in the two methyl groups. This assignment was confirmed by measuring the separation of the doublet at 6300 gauss as well as at 4165 gauss; the separation in milligauss was proportional to the field, whereas a multiplet splitting would have been field independent.³ The chemical shifts originate in differences in electronic environment of the nuclei, and in DMF and DMA such differences will occur if the double bonded form (II) makes a significant contribution to the structure of the amides. In this event the skeleton of the molecule is coplanar, one of the CH₃ groups (R₂) is *trans* and the other (R₃) is *cis* to the oxygen atom. The double bond character provides a potential barrier to reorientations about the C—N bond, and as reported qualitatively by Phillips¹⁶ the hindrance to such internal rotation must be "high" in order that the reorientation rate be too slow at room temperature to average out the small resonance shift between the two methyl groups.¹⁷

At higher temperatures the rate of reorientation increases and, as shown in Fig. 5 for DMA, the doublet coalesces to give a single line. Table I summarizes the experimentally observed doublet separations $\delta\omega_e$ as a function of temperature for DMF and DMA and also gives the values of $1/\tau\delta\omega$ calculated from these observations using the methods of Sec. II. The experimental values of T_2 and $\delta\omega_\infty$ applying to these calculations are

¹⁶ W. D. Phillips, J. Chem. Phys. 23, 1363 (1955).

¹⁷ A preliminary estimate, based on our work, of 15 kcal for the barrier was reported at the April, 1955, Discussion of the Faraday Society [19, 247 (1955)], assuming a normal frequency factor for the rate process.

in Table II along with the value for $\delta\omega$ calculated from $\delta\omega_\infty$, and also the temperature T_c at which the components were observed to coalesce. In practice the measurements at various temperatures for a given sample were made by holding constant the field sweep amplitude, sweep rate, recorder speed and position of the sample in the magnetic field, throughout a run. All parameters in the calculation of $1/\tau\delta\omega$ are dimensionless, so the line widths (T_2) and separations were measured in units of centimeters on the recorder paper. A calibration was made for each run, relating chart distance to field sweep, in order to obtain $\delta\omega$ in radian sec⁻¹ and calculate τ in sec.

If the reorientations can be treated as a typical rate process, their temperature dependence should be of the form

$$k = \nu_0 \exp(-E_a/RT), \quad (9)$$

where k is the reorientation rate constant; ν_0 is a frequency factor; and the activation energy E_a is the potential barrier hindering the internal rotation. Equation (2) gives $k = 1/2\tau$, so Eq. (9) can be rewritten as

$$\log_{10}(1/\tau\delta\omega) = \log_{10}(2\nu_0/\delta\omega) - E_a/2.3RT. \quad (10)$$

The data of Table I are plotted in Fig. 6 as $\log_{10}(1/\tau\delta\omega)$ versus $1/T$, giving points which are fitted reasonably well by Eq. (10). The values of E_a and ν_0 which fit the data best are listed in Table II. The activation energies are 7 ± 3 and 12 ± 2 kcal mole⁻¹ for DMF and DMA respectively.

The errors were estimated by trial calculations with idealized data. For example, a 10% error in the value of T_2 , when carried through the calculations for a $\delta\omega$ of about 20, introduces an error of approximately 1 kcal in E_a ; whereas the same percentage error in $\delta\omega_\infty$ gives a non-linear plot for Eq. (10) and the best straight line fit has an E_a about 5 kcal in error. So special care should be taken in measuring $\delta\omega_\infty$. It should be noted that while the errors in measuring $\delta\omega_e$ are the order of 0.15 cps throughout, the resulting percentage error in determining $1/\tau\delta\omega$ becomes very large when $\delta\omega_e$ approaches the limiting value $\delta\omega_\infty$. In general, the errors in the final results of these experiments are quite large. One of the main reasons for this is the small value of $\delta\omega$. At higher magnetic fields $\delta\omega$ would be proportionately larger, and more accurate results could be obtained providing the other experimental parameters were no worse.

TABLE II. Summary of results for N,N-dimethylformamide and N,N-dimethylacetamide.

	T_2 sec radian ⁻¹	$\delta\omega_\infty$ radian sec ⁻¹	$\delta\omega$ radian sec ⁻¹	T_c °K	E_a kcal	ν_0 sec ⁻¹
DMF	0.14±0.03	20.1±0.3	20.4±0.3	372 ^a	7±3	10 ⁸ to 10 ⁷
DMA	0.18±0.04	24.4±0.9	24.6±1.1	325	12±2	10 ⁷ to 10 ⁶

^a This is the temperature at which the doublet coalesces to a single line.

N-Methylformamide and N-Methylacetamide

Superficially, the spectra of these compounds, NMF and NMA in Fig. 4, are very similar to the spectra of DMF and DMA. The resonances of the N-methyl groups are split into doublets; however, the splitting was checked at 6300 gauss as well as at 4165 gauss and was found not to be proportional to the applied field. So the splitting is not a simple chemical shift but is caused by the indirect coupling³ of the N-H proton with the protons in the CH₃ group. No resonance attributable to the N-H proton was found. In the parent compound formamide,¹⁵ HCONH₂, the NH₂ and HCO- proton resonances at δ 's of 0.29 and 0.37 are weak and broad at room temperature, about 3 to 4 milligauss, perhaps because of molecular association and hydrogen bonding or due to unresolved chemical shifts and splittings. In the N-methyl derivatives the N-H resonance would be split into a quartet by coupling with the CH₃ group protons with further splitting by the nitrogen nucleus possible, and this in addition to broadening by molecular association is a plausible explanation for not detecting the resonance.

Phillips¹⁶ mentions observing single methyl proton resonances in the two N-methyl amides and concludes that only one of the two possible rotational isomers is present. In the sense that the doublets we find are not caused by a chemical shift, this conclusion is a reasonable one. Mizushima¹⁸ has reported a detailed study of the infrared and Raman spectra of N-methylacetamide,

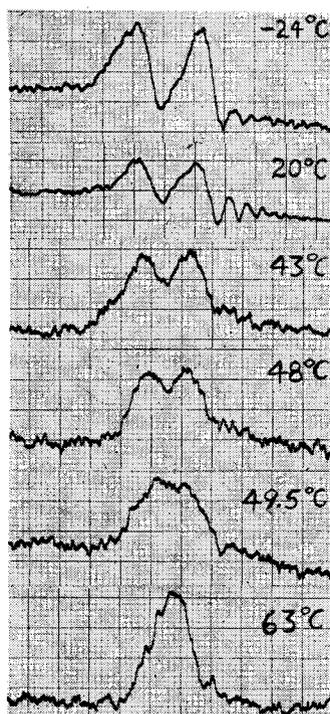


FIG. 5. The proton magnetic resonance spectrum of N-methyl groups in N,N-dimethylacetamide at several temperatures. The spectra were recorded at a fixed frequency of 17.735 Mc; the magnetic field sweep amplitude corresponds to 19.5 cps.

¹⁸ S. Mizushima, *Structure of Molecules and Internal Rotation* (Academic Press, Inc., New York, 1954), pp. 117-152.

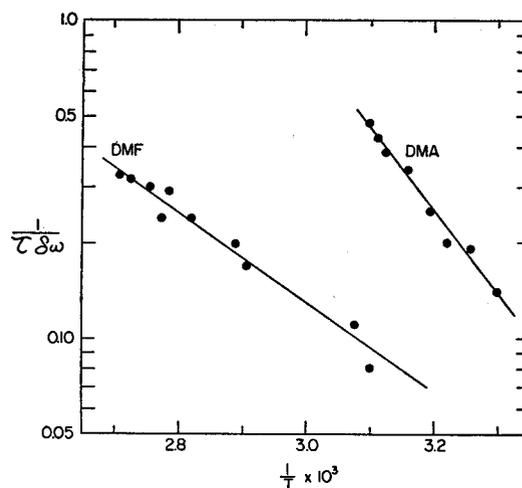


FIG. 6. Temperature dependence of the reorientation rate constant ($1/2\tau$) for N,N-dimethylformamide (DMF) and N,N-dimethylacetamide (DMA). The energy barriers to reorientation obtained from these plots are 7 ± 3 and 12 ± 2 kcal mole⁻¹ for DMF and DMA respectively.

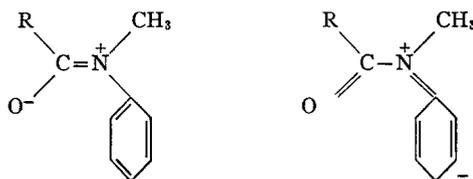
from which it was concluded that almost all of the molecules are in the configuration with the N-H bond *trans* to the C-O. Arguments based on the proton spectra as to which is the stabler form appear to be rather indirect. However, it is clear that the form of the N-methylformamide is the same as that of the N-methylacetamide.

This is seen by comparing the spectra of the N-methyl amides with the N,N-dimethyl amides. For the latter, Fig. 4 shows that replacement of the HCO- group with CH₃CO- produces no discernible shift in the N(CH₃)₂ group. Therefore, the chemical shift observed between the two CH₃ groups on the nitrogen is due to a *cis-trans* difference in their interaction with the oxygen. On going from the N,N-dimethyl amides to the N-methyl amides there is a chemical shift of the N-CH₃ group resonance because the other CH₃ group on the nitrogen is replaced with a hydrogen. However, the N-CH₃ resonance positions are the same in both N-methyl amides, so the configuration of the N-CH₃ group with respect to the oxygen must be the same in the two compounds. If the N-methylacetamide has a stable *trans* configuration, then so does the N-methylformamide.

Another interpretation of the present NMR data may be made. If the *cis* and *trans* forms were of about the same energy, and the barrier to reorientation were low enough, the internal reorientations could average out the chemical shift leaving the observed indirect spin-spin coupling. In this regard, it is of interest that preliminary experiments by A. Saika in this laboratory show that the doublet in our sample of N-methylacetamide coalesces at about 160°C; this seems to be a result of chemical exchange because the doublet is also reduced to a single line at 29°C by the addition of HCl, but the details remain to be established.

N-Methylformanilide and N-Methylacetanilide

The situation with this pair of compounds is identical with that of N-methylformamide and N-methylacetamide except that there are no multiplets. However, whereas there is independent evidence supporting the existence of only one stable configuration for NMA, there appears to be none for either NMFA or NMAA. In addition, the phenyl group on the nitrogen in the latter compounds could compete with the oxygen for the unshared pair of electrons on the nitrogen, which would tend to decrease the double bond character of the C—N bond and promote more rapid reorientations.



If it is assumed that the interpretations based on the existence of only one configuration are correct, a lower limit can be set on the free energy difference between the *cis* and *trans* forms of NMF, NMA and NMFA. As a conservative estimate, 10% of a second form would have been detectable, giving

$$K_{eq} \geq 10 \quad \text{and} \quad |\Delta F^\circ| \geq 1.4 \text{ kcal.}$$

General Comments

The planar configurations found in this research for the $R_1CONR_2R_3$ skeletons of DMF and DMA are consistent with the microwave results on formamide¹⁹ and with the broad line proton magnetic resonance studies of solid urea,²⁰ which have shown both molecules to be planar. It is clear that the oxygen of the amide group contributes a significant amount of double bond character to the C—N amide bond. The added stability afforded in this way should be closely related to the internal barrier to reorientation, because the transition state most likely involves the structure with a single C—N bond. Pauling estimated¹⁴ the resonance energy

¹⁹ R. J. Kurland, J. Chem. Phys. **23**, 2202 (1955).

²⁰ E. R. Andrew and D. Hyndman, Discussions Faraday Soc. **19**, 195 (1955).

associated with the C—N double bond in amides to be about 21 kcal. This value compares favorably with the values of 22 and 19 kcal we find for the free energy of activation, ΔF^\ddagger , associated with the molecular reorientations in DMF and DMA.

The activation energies and frequency factors differ markedly for DMF and DMA. DMF has a low activation energy and a low frequency factor while DMA has a higher activation energy and a much higher frequency factor. This is consistent with the elementary theory of absolute reaction rates, but the effect observed is off by a few orders of magnitude. Equation (9) for the reorientation rate may be written as

$$k \cong \nu_t \exp(-E_a/RT) \quad (11)$$

where the frequency factor is the internal torsional frequency ν_t . ν_t will be larger for a greater E_a , but for DMA it would be only about twice as great as for DMF, while the observed ratio is the order of 10^4 . The uncertainty in the experimental values is large enough that further discussion of the matter seems unwarranted except to note that similar effects have been found and treated in detail for *cis-trans* isomerization reactions²¹ which require reorientations about double bonds.

Because of the importance of amides in biological systems and the general lack of quantitative data on the rigidity of the amide group, we are continuing these studies with the hope that better values can be obtained for DMF and DMA and that the effects of other substituents can be determined.

IV. ACKNOWLEDGMENT

Several people contributed to the development of the apparatus. J. C. Buchta was responsible for the electronics; J. P. Heeschen, the thermoregulation of the permanent magnet; and R. L. Rutledge, the construction of the saw tooth field sweep generator. A. Saika assisted in the experiments on NMF, NMA, NMFA and NMAA. We are grateful to the E. I. duPont de Nemours and Company for a grant-in-aid supporting the research.

²¹ Douglas, Rabinovitch, and Looney, J. Chem. Phys. **23**, 315 (1955).