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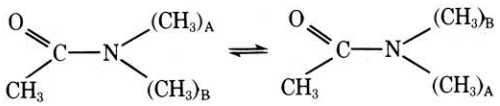
# NMR Determination of the Rotational Barrier in N,N-dimethylacetamide

## *A physical chemistry experiment*

Nuclear magnetic resonance spectroscopy has long been taught at the undergraduate level as an effective tool for structural studies. Although it has been almost 20 years since the first studies of rate processes by nmr spectroscopy were reported (*1*) little about this technique has filtered down to the undergraduate level. Consider, for example, the lack of dynamic nmr experiments in the current physical chemistry laboratory manuals (*2*). In this experiment the barrier to rotation in N,N-dimethylacetamide is determined by measuring changes in nmr line shapes as a function of temperature. This study is an example of dynamic nuclear magnetic resonance spectroscopy.

The beauty of this method is twofold. First, dynamic aspects of systems which are at chemical equilibrium can be studied. For example, rate information can be obtained for virtual reactions, such as the cis-trans isomerization of N,N-dimethylacetamide in which reactants and products are chemically identical




Second, due to the characteristic period of the nmr measurement, a range of reaction rates usually encountered in the laboratory is easily accessible ($10^{-1}$–$10^{-5}$ $s^{-1}$). In addition, rotational barriers in the range 3–20 kcal/mole can be studied by this method (*3*).

### Theory

#### *Line Shape Analysis*

If two groups of chemically equivalent nuclei are exchanged by an intramolecular process, the nmr spectrum is a function of the difference in their resonance frequencies, $\nu_A - \nu_B = \Delta\nu$, and of the rate of exchange, $k$. (A typical value for $\Delta\nu$ is about 10 Hz.) The effects of exchange at several temperatures on the linewidths at $\nu_A$ and $\nu_B$ are shown in Figure 1. At low temperatures the exchange is slow and $k \ll \Delta\nu$. The spectrum thus consists of two sharp singlets at $\nu_A$ and $\nu_B$ (Fig. 1 *A*). At high temperatures the exchange is fast; i.e. $k \gg \Delta\nu$ and a single sharp peak is observed (Fig. 1 *D*). There is also an intermediate temperature range over which the spectrum consists of two significantly broadened overlapping lines (Fig. 1 *B*).

Usually spin-spin and spin-lattice relaxation determine the width of an nmr absorption peak (*7*). Here we are concerned with the additional effect of exchange of two groups of chemically equivalent nuclei on linewidth. The Heisenberg uncertainty principle states that the product of the uncertainty in the measurement of the energy of a particular state, $\Delta E$, and the uncertainty in the lifetime of the state, $\Delta t$, is approximately equal to $\hbar$; i.e

$$\Delta E \Delta t \simeq \hbar \tag{1}$$

Since

$$\Delta E = h\Delta\nu_{1/2} \tag{2}$$

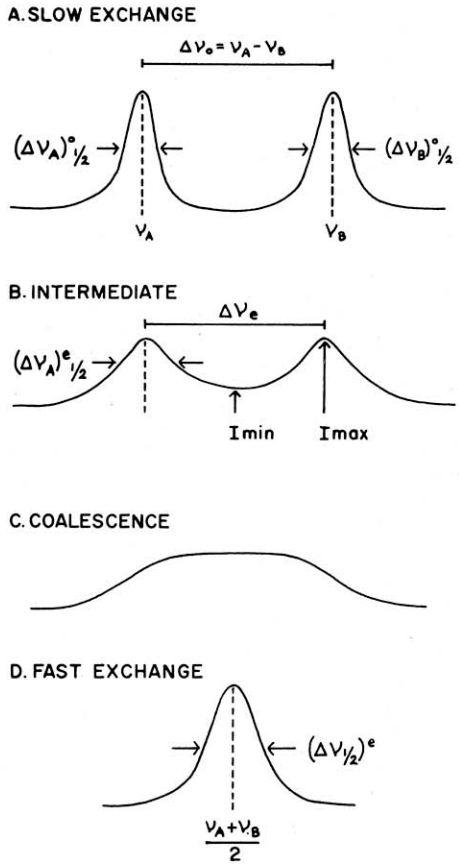



Figure 1. Effect of exchange of chemically equivalent nuclei on nmr line shapes.

$\Delta\nu_{1/2}$, the absorption linewidth for the transition, is inversely proportional to the lifetime of the excited state

$$\Delta\nu_{1/2} = \frac{\Delta E}{h} = \frac{\Delta E \Delta t}{h \Delta t} = \frac{1}{2\pi\Delta t} \tag{3}$$

An exact analysis of the line broadening produced by the exchange process is derived from the Bloch equations (*4*). The Bloch equations describe the motion of the bulk magnetic moment of a sample in the presence of a static field, $H_0$, and a rotating field, $H_1$, perpendicular to $H_0$.

The exact function for the lineshape (*5*) in the case of two equivalent exchanging groups with no coupling is given by

$$g(\nu) = \frac{K\tau(\nu_A - \nu_B)^2}{\left[\frac{1}{2}(\nu_A - \nu_B) - \nu\right]^2 + 4\pi^2\tau^2(\nu_A - \nu)^2(\nu_B - \nu)^2} \tag{4}$$

where $g(\nu)$ is the intensity at the frequency, $\nu$; $K$ is a normalization constant and $\tau = 1/2k$ where $k$ is the rate constant for the exchange. $\tau$, $\nu_A$, and $\nu_B$ are functions of temperature and cannot be determined separately. Computer programs are available in which estimated values for $\tau$, $\nu_A$, and $\nu_B$ are used to generate $g(\nu)$ which is then compared to the experimental spectrum.[1] Values for $\tau$, $\nu_A$, and $\nu_B$ are chosen such that the deviation between the experimental and calculated lineshapes is minimized. Alternatively various approximations can be made which apply over different ranges of exchange rates.

[1] For example, see Program 140 or 165, Quantum Chemistry Program Exchange, Indiana University, Bloomington, Indiana 47401.

*Approximate Methods for Evaluation of Rate Constants (6).*

Direct calculation of the lifetime of a specific spin state from eqn. (4) can be made over a limited temperature range. Beyond a certain temperature, the rate of exchange is so fast that the magnetic environments of the two sets of nuclei are identical and any possible distinction between the two sets of nuclei is lost. Thus we have only one set of spins with a lifetime determined by spin-spin and spin-lattice relaxation mechanisms.

As the temperature is varied from values at which the rate of exchange is low through values of intermediate exchange rates, to rapid exchange, a series of approximations is available for the calculation of lifetimes. Although these approximate methods provide somewhat less accurate results than does eqn. (4), they present the student with a meaningful treatment of the data obtained by an nmr study of a chemical rate process.

*Slow and Intermediate Exchange:* At slow exchange rates the spectrum consists of two lines. In this region $\tau \gg (\nu_A - \nu_B)^{-1}$, and eqn. (4) reduces to

$$g(\nu)_A = g(\nu)_B = \frac{KT_{2A}'}{1 + T_{2A}'^2(\nu_A - \nu)^2} \tag{5}$$

where $T_{2A}'$ is the spin-spin relaxation time. Comparison of eqn. (5) to the exact function shows that the linewidth of the line at $\nu_A$ is

$$(\Delta\nu_A)_{1/2} = \frac{1}{\pi}\left(\frac{1}{T_{2A}'} + \frac{1}{\tau_A}\right) \tag{6}$$

In the absence of exchange the linewidth is $(\Delta\nu_0)_{1/2} = (\pi T_{2A}')^{-1}$. Exchange results in *broadening* equal to $(\pi\tau_A)^{-1}$. A value for $k$ $(= 1/2\tau)$ is determined by comparing linewidths at half height of exchanging peaks to those of peaks recorded at temperatures where the rate of exchange is very small

$$k = \pi[(\Delta\nu_e)_{1/2} - (\Delta\nu_0)_{1/2}] \tag{7}$$

For slow exchange, the rate can also be related to the change in *peak separation.* Equation (8) applies over the limited range where there is extensive overlap between the two separate peaks (but not too close to coalescence, see below)

$$k = \frac{\pi}{\sqrt{2}}(\Delta\nu_0^2 - \Delta\nu_e^2)^{1/2} \tag{8}$$

where $\Delta\nu_i$ is the peak separation in Hz, and the subscripts (i = e or 0) have the previously defined meanings.

A third method applies in the slow exchange region. In the *ratio method,* $k$ is calculated from the ratio of the intensities of the peaks, $I_{max}$, to the intensity midway between the peaks, $I_{min}$, $r = I_{max}/I_{min}$ and

$$k = \frac{\pi\Delta\nu_0}{\sqrt{2}}(r + (r^2 - r)^{1/2})^{-1/2} \tag{9}$$

*Coalescence Temperature:* The coalescence temperature is defined as the temperature at which the appearance of the spectrum changes from that of two separate peaks to that of a single, flat-topped peak (see Fig. 1*C*). At this temperature

$$k = \frac{\pi\Delta\nu_0}{\sqrt{2}} \tag{10}$$

*Fast Exchange:* At temperatures above the coalescence temperature, the spectrum consists of a single peak. In this region $\tau \ll (\nu_A - \nu_B)^{-1}$ and eqn. (4) reduces to

$$g(\nu) = \frac{KT_2'}{1 + \pi T_2'(\nu_A + \nu_B - 2\nu)^2} \tag{11}$$

If the signal is not completely collapsed, i.e., the process is slow enough to contribute to its width but is still well beyond the rate corresponding to separate signals, the following approximation results

$$k = \frac{\pi\Delta\nu_0^2}{2}[(\Delta\nu_e)_{1/2} - (\Delta\nu_0)_{1/2}]^{-1} \tag{12}$$

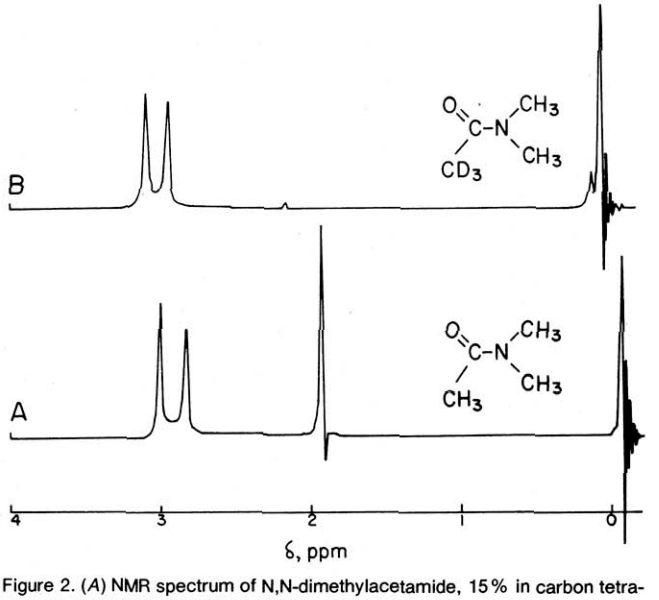



Figure 2. (*A*) NMR spectrum of N,N-dimethylacetamide, 15% in carbon tetrachloride (2% TMS). (*B*) NMR spectrum of acetyl deuterated N,N-dimethylacetamide, 15% in carbon tetrachloride (2% TMS).

## Experimental

A 15 volume percent solution of freshly distilled N,N-dimethylacetamide (NNDMA) is prepared gravimetrically in carbon tetrachloride containing 2% tetramethylsilane (TMS). The sample is transferred to a clean and dry nmr tube, degassed, and permanently sealed. Degassing is required in order to remove paramagnetic oxygen which, if not removed, would result in an additional, indeterminate line broadening factor. To be sure that the sealed nmr tube can withstand exposure to high temperatures, the tube should be immersed in an oil bath and heated to ~160°C.

Any nmr spectrometer equipped with a variable temperature probe may be used for the spectral measurements. A series of spectra is recorded at each temperature until no further change in spectral characteristics (line-width or peak separation) is observed. The resolution of the instrument should be checked at each temperature by recording the methyl resonance of TMS. The temperature is most conveniently determined using either a sample of ethylene glycol (above ambient): $T = 466.4 - 1.705\,(\Delta\nu) - 63.4\,(\Delta\nu/100)^2$ or methyl alcohol (below ambient): $T = 406.0 - 0.551\,(\Delta\nu)$ (8).

Exact peak positions and linewidths are determined using the sideband technique (7). This technique may also be used to calibrate the chart paper. Typical full scale spectra obtained with a Perkin-Elmer R12 nmr spectrometer are shown in Figure 2. Figure 3 shows results at temperatures ranging from 259–368°K. These results were obtained with the spectrometer set on the 50 Hz scale.

The data are divided into three groups corresponding to slow exchange and intermediate exchange, coalescence temperature, and fast exchange. Then eqns. (7) through (12) are used to calculate $k$ (Table 1). Figure 4 shows a plot of log $k$ versus $(T\,(°K))^{-1}$. The slope of this plot yields a value for the activation energy. Using values of $k$ extending over the entire temperature range, 279–485°K, $E_a$ was found to be 14 kcal/

**Table 1. Typical Values for *k***

| $T$ (°K) | $k$ ($s^{-1}$) |
|---|---|
| 279 | 1.45 |
| 288 | 2.35 |
| 308 | 5.95 |
| 325 | 19.8 |
| 331 | 24.1 |
| 334 | 27.8 |
| 348 | 129 |
| 368 | 598 |
| 485 | 805 |

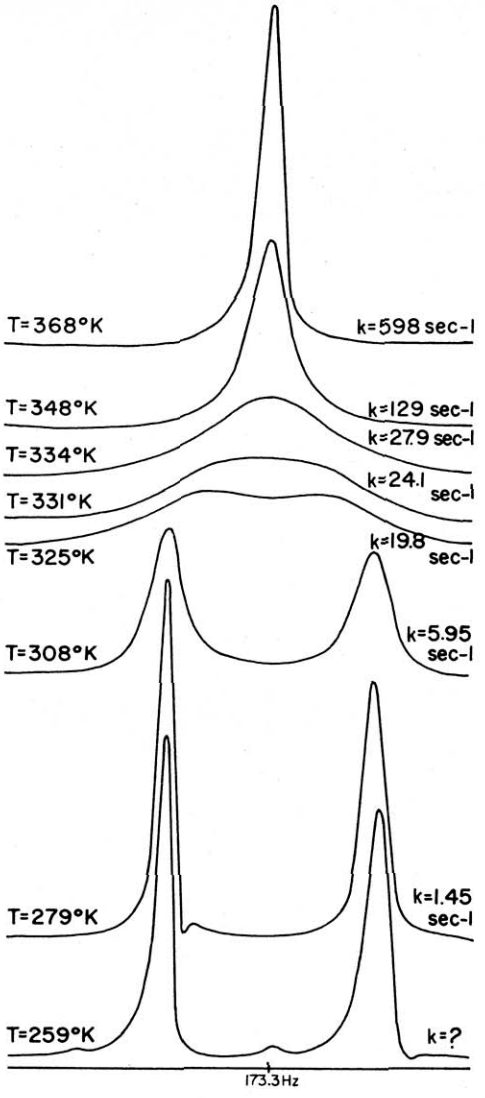



Figure 3. Effect of temperature on line shapes and values for $k$, the exchange rate for the two N-methyl groups.

**Table 2. Comparison to Values of Reeves, et al. (9)**

| | This study | Reeves et al. (9) |
|---|---|---|
| $T_c$, (°K) | 331 | 339 |
| $E_a$ (kcal/mole) | 17(14)[a] | 16.8 |
| $\Delta G^{\ddagger}$ (kcal/mole) | 17 | 17.3 |
| $\Delta H^{\ddagger}$ (kcal/mole) | 16 | 16.3 |
| $\Delta S^{\ddagger}$ (e.u.) | −2.1 | −3.59 |

[a] See Discussion Section.

mole. Eliminating values for $k$ at the two lowest temperatures yielded a value for $E_a$ = 17 kcal/mole, in much better agreement with the 16.8 kcal/mole determined by Reeves et al. (*9*) in an identical study. The quantity, $\Delta G^{\ddagger}$, is obtained from a plot of log $(k/T)$ versus $T^{-1}$. From values for $E_a$ and $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ can be evaluated. See Table 2 for a comparison of the results of this study with the values obtained by Reeves et al. (*9*).

## Discussion

Amides are the simplest model compounds for the peptide bond in proteins. The conformation of the peptide bond plays an important role in determining the backbone structure of proteins (*10*). X-Ray crystallographic results indicate that the trans configuration (*11*) is the predominant form in amides, polypeptides, and proteins. However, recent work has shown

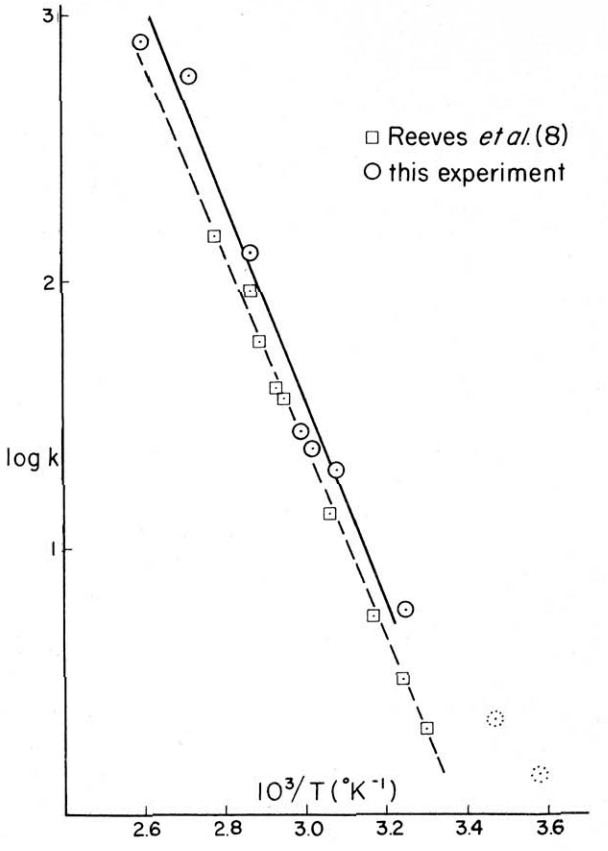



Figure 4. Log $k$ versus $10^3/T$ (°K).

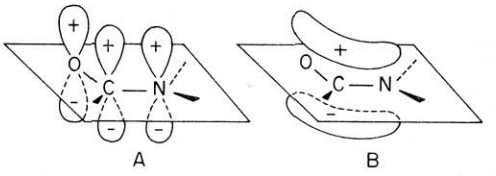
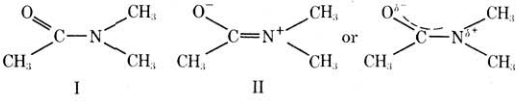



Figure 5. (*A*) Sigma-bonding skeleton for peptide group. (*B*) Pi-bonding molecular orbital for peptide group.

that the cis form does occur in some proteins and polypeptides (*12*).

The planarity of the peptide bond originates from the delocalization of the carbonyl electrons and two resonance structures, (I) and (II), can be drawn




Alternatively, the origin of this rotational barrier can be viewed in terms of molecular orbital theory. After constructing the sigma bonding skeleton, the carbon, nitrogen, and oxygen atoms each have a $p$ orbital "left over." (See Figure 5*A*.) One possible linear combination of these $p$ orbitals leads to a $\pi$ bonding molecular orbital which extends over the three atoms, Figure 5*B*.

If the $-N(CH_3)_2$ moiety rotates freely, we would expect the complete nmr spectrum of NNDMA to consist of two singlets, with an intensity ratio of 2:1 (2 methyls on nitrogen, 1 methyl on the carbonyl carbon). The nmr spectrum shown in Figure 2*A* is thus not consistent with free rotation about the peptide bond. Instead of one peak at 3 ppm and one at 2 ppm, there are two peaks at ~3 ppm in addition to the one at 2 ppm. This is thought to result from the two $-N-CH_3$ groups being in magnetically nonequivalent environments. One methyl group is cis to the carbonyl bond and the other is cis to the acetyl

methyl group. The upfield resonance at ~3 ppm is assigned to the $-NCH_3$ group cis to the acetyl methyl; the downfield resonance at ~3 ppm is assigned to the $-NCH_3$ group cis to the carbonyl bond. The 2 ppm resonance is assigned to the acetyl methyl protons.

The effects of the rotational barrier, i.e. different magnetic environments for the two N-methyl groups, observed at low temperatures (Fig. 3) vanish at higher temperatures. The rate of exchange between the two magnetic environments increases as the temperature is increased. The lifetime of each state thus decreases and hence the absorption peak is broadened. At temperatures below the coalescence temperature few molecules have sufficient energy to overcome the barrier to rotation. However, at temperatures greater than the coalescence temperature, many molecules have sufficient thermal energy to overcome the barrier and therefore rotation occurs. Thus there is no longer a preferred configuration (cis or trans) and the spectrum is the single line characteristic of free rotation about a single bond. Further increases in temperature cause the line to narrow.

Our results are in good agreement with those of Reeves et al. (*9*). One experimental difficulty plagued our attempts to accurately determine $k$ at low temperatures (<288°K). A significant amount of drift was noted as the doublet was recorded at these temperatures, thus introducing an indeterminate uncertainty in both the linewidths and peak separations. Elimination of the two values for $k$ at 279°K and 288°K resulted in marked improvement in the value for $E_a$ which increased from 14 to 17 kcal/mole. The drift could be eliminated by using an instrument provided with a locking mode.

To avoid the effects of coupling between the trans N-methyl group and the acetyl methyl group, linewidth measurements were made on the cis peak only. This coupling effect can be almost completely eliminated by studying the acetyl deuterated analog of NNDMA, because proton-deuterium coupling is markedly smaller than proton-proton coupling (*13*). (Compare the peaks centered at ~3 ppm in Fig. 2*A* and 2*B*.)

## Related Projects

The magnitude of the rotational barrier in NNDMA has been shown to be both solvent and concentration dependent. At high concentrations and in the presence of polar solvents, molecular complex formation leads to values for $E_a$ significantly greater than 17 kcal/mole (*14*).

The scope of this experiment can be broadened by including the synthesis and purification (*15*) of the acetyl deuterated analog of NNDMA. As such it would be an experiment suitable for project-type laboratories currently in vogue. Infrared spectroscopy (*16*) and dielectric studies (*17*) can also supplement the nmr results.

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