

NMR Determination of Internal Rotation Rates and Rotational Energy Barriers

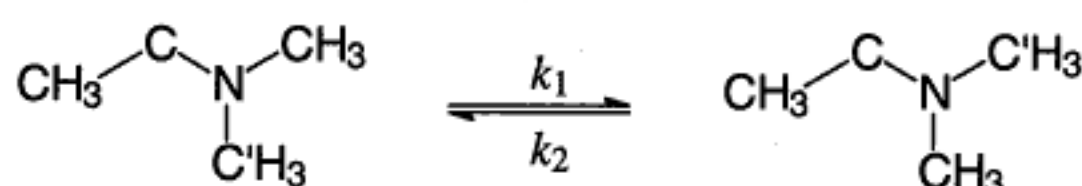
A Physical Chemistry Lab Project

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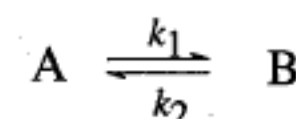
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Variable temperature NMR measurements often have been employed to obtain rates of internal rotation and the corresponding energy barriers to internal rotation for a wide range of structures including substituted ethanes, amides, and metal-coordinated olefins (1, 2). Gasparro and Kolodny (3) describe an NMR experiment that employs standard line-shape analysis techniques to obtain the rate of rotation at several temperatures and the associated energy barrier for *N,N*-dimethylacetamide. We have regularly used a variation of this experiment in a physical chemistry course that includes formal study of both rate processes and NMR spectroscopy. With a chemical shift difference between the two nonequivalent *N*-methyl signals of 0.16 ppm (about 50 Hz for our 300 MHz spectrometer), the spectral appearance is most sensitive to changes in the rate for $k_1 \approx 100 \text{ s}^{-1}$. This occurs about 360–370 K. Although rate constant and free energy of activation data obtained by the students typically are quite respectable, the enthalpy and entropy of activation calculated from the data vary considerably.

The quality of the rate data and student understanding of NMR principles increased substantially by employing an alternative NMR technique, the saturation transfer method, in conjunction with conventional line-shape analysis to expand the temperature range of the experiment (4, 5). For temperatures more than 20° on either side of the coalescence temperature of the two *N*-methyl peaks of *N,N*-dimethylacetamide the estimation of the rate constant by line-shape analysis methods is subject to considerable uncertainty. However, for rate constants of the order of one second ($k_1 \approx 1 \text{ s}^{-1}$), the saturation transfer technique can provide quite accurate rate data. For *N,N*-dimethylacetamide, this is just about the rate of rotation at room temperature. By employing the saturation transfer technique for a sample at room temperature along with conventional line-shape analysis for the same sample at high temperatures, the temperature range over which rate data are acquired is extended from 20–30° to almost 100°, and the accuracy of the enthalpy and entropy of activation determination is, thereby, considerably improved. The saturation transfer experiment also introduces students to an important multipulse technique that can be done in a reasonable time. Finally, extraction of rate constants from the data requires the independent determination of the spin-lattice relaxation time, T_1 , for the amide protons. Students are, thus, introduced to the inversion recovery method for that T_1 determination. The significance of T_1 is magnified by introducing it as part of a larger project that focuses on an important rate process of considerable chemical interest.



Theory



The chemical rate process being considered here can be represented as:

where A and B denote the two sites that are exchanged by the rate process, and k_1 and k_2 , the first-order rate constants of the forward and reverse reactions, respectively, are equal in the case of amide rotation. The NMR energy level diagram for a spin 1/2 nucleus that is undergoing slow chemical exchange on the NMR time scale between two sites, A and B, is shown in Figure 1 (6). In the absence of scalar coupling between the two spins, each nucleus must be in either the α or β spin state, where the label α denotes α spin aligned with the external magnetic field and β denotes a spin aligned against the external field. For both sites A and B at equilibrium, there will be slightly more nuclei in the lower energy α state than in the β state. In Figure 1, the number of spins in the β state at equilib-

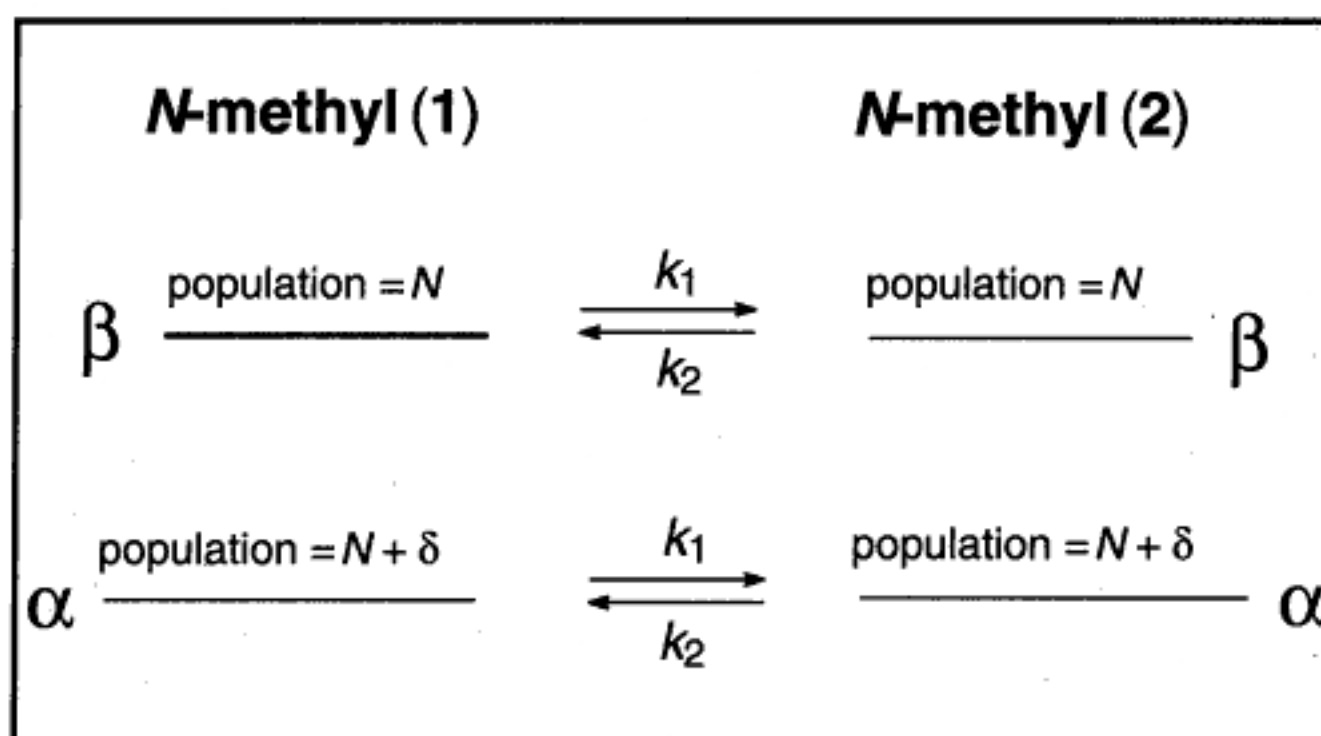


Figure 1. Energy level diagram for protons undergoing chemical exchange between two sites A and B.

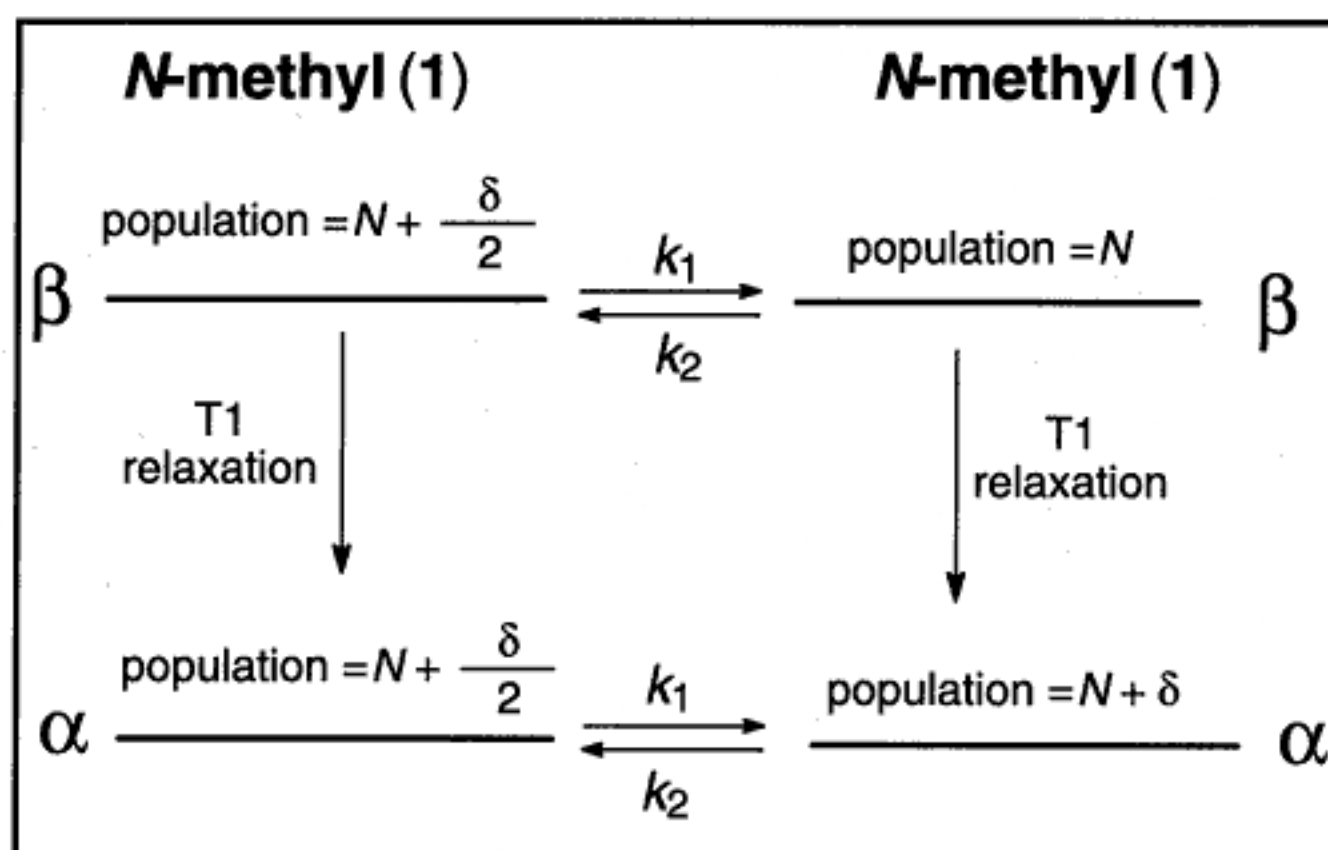


Figure 2. Effect of saturation of nuclei in the A site on the population of spin states for A and B sites.

rium is denoted as N and the number of spins in the α state as $N + \delta$, where δ is a small positive number.

When the internal rotation converts A into B, it is assumed that this chemical reaction occurs without a change in the spin state and that the rate of the reaction is independent of the spin states of the nuclei involved. In other words, the internal rotation can convert A spins that are in the α spin state into B spins also in the α state, but not into B spins in the β state.

By selectively saturating the A transition the populations of the α and β spin states are equalized to yield the new populations shown in Figure 2. A nonequilibrium situation with an excess of A spins in the β state and a deficit of A spins in the α state has now been created. Because exchange is occurring without a change of spin state, the selective saturation of A will lead to an increase in the transfer of spins from the upper level of A to that of B in order to restore the equilibrium situation, and will, likewise, lead to an increase in the transfer of spins from the lower level of B to that of A. The signal that is detected in the NMR experiment, S , is proportional to the difference in the populations of the two spin states; i.e.,

$$S \propto (\text{Number of } \alpha \text{ spins}) - (\text{Number of } \beta \text{ spins}) \quad (1)$$

Because saturation of A leads to an increase of B spins in the β state and a decrease of B spins in the α state, a decrease in the intensity of the B resonance is observed when A is saturated.

At the same time that the chemical exchange process is causing the population distribution of B to approach that of A, spin-lattice relaxation is occurring and B spins in the β state are relaxing back to the lower energy α state. When the rate constants for spin-lattice relaxation, $R1 = 1/T1$, and the exchange process, k_1 , are comparable, the signal that is observed for B, in the presence of saturation of A, will be slightly less than the signal observed when A is not saturated. Solution of the Bloch equations for two spins with equal spin-lattice relaxation rates undergoing chemical exchange yields the following expression for the rate constant:

$$k_1 = \frac{I_0 - I}{I} \cdot R1_B \quad (2)$$

where I and I_0 are, respectively, the intensity of the B resonance with and without saturation of A and $R1_B$ is the spin-lattice relaxation rate constant for spin B.

Care must be taken, though, when measuring these spin-lattice relaxation rates. The values of $R1$ for the two methyl groups in N,N -dimethyl amides differ by about 20% at room temperature and, therefore, the exchange process averages the spin-lattice relaxation over the two sites. A conventional inversion-recovery pulse sequence, therefore, cannot be used to measure $R1_B$. A method for overcoming this difficulty was developed by Mann who suggested that the spin-lattice relaxation rate for spin B should be measured using the inversion-recovery pulse sequence, but with saturation of the A resonance (7). The observed relaxation rate constant in this inversion-recovery experiment, $R1_{obs}$, is then given by:

$$R1_{obs} = R1_B + k_1 \quad (3)$$

When $R1_{obs}$ is measured in this manner the exchange rate constant is given by:

$$k_1 = \frac{I_0 - I}{I} \cdot R1_{obs} \quad (4)$$

A typical $T1 = 1/R1$ for a small organic molecule in a non-degassed sample is around one second and intensity changes of roughly 5% can be measured accurately; i.e., $I = 0.05 I_0$ to $I = 0.95 I_0$. Substitution of these numbers into eq

4 shows that the saturation-transfer experiment can be used to measure conveniently rate constants in the range of $k_1 = 0.05$ to 1.0 s^{-1} .

Experimental Details

Spectrophotometric grade N,N -dimethylacetamide and (methyl sulfoxide)- d_6 were purchased from Aldrich and used without further purification. A 10% solution of the amide in DMSO was prepared gravimetrically and used for all NMR studies. Proton NMR spectra in the temperature range 290 to 365 K were collected with a Bruker AF-300 spectrometer equipped with a B-VT 1000 variable temperature control unit. Analysis of NMR data was done using the Aspect-3000 resident software in the saturation-transfer experiments and free induction decay at each temperature was transferred to a personal computer and analyzed using PCNMR in the lineshape experiments.

In the saturation-transfer studies exchange rates as a function of temperature were measured by saturating the upfield N -methyl resonance and monitoring the change in the intensity of the downfield N -methyl peak. Full saturation was accomplished by irradiating the upfield resonance with low power radio frequency radiation for four seconds prior to data acquisition. The intensity of the downfield N -methyl peak in the absence of saturation of the upfield peak was measured using an identical pulse sequence, but with the irradiation frequency set at the high frequency end of the spectrum well away from any resonances.

The spin-lattice relaxation rate constant for the downfield N -methyl peak was measured using a standard inversion-recovery pulse sequence, but with irradiation of the upfield resonance during the relaxation and recovery delays. Typically, eight NMR spectra were collected in this manner with relaxation delays, t , ranging from 0.25 to 4.0 s and $R1_{obs}$ was determined by performing a nonlinear least squares regression analysis of the intensities of the downfield N -methyl resonance, S , and τ to the equation:

$$S = S_0 \cdot [1 - 2 \cdot \exp(-R1_{obs} \cdot \tau)] \quad (5)$$

with S_0 and $R1_{obs}$ as the free parameters. The spin-lattice relaxation rate constants were found to be temperature dependent and, therefore, a separate $R1_{obs}$ measurement was required at each temperature. Once relaxation rate constants were determined, the rate constants for the internal rotation process were calculated using eq 4.

Rate constants at higher temperatures were determined by first collecting five NMR spectra in the temperature range 340 to 365 K. NMR spectra, $I(\nu)$, were then simulated by taking the imaginary component of the complex lineshape:

$$I(\nu) = \frac{\frac{\alpha i}{k_1} \left[2 + \frac{1}{K_1} (R2^* - 2\pi i \nu) \right]}{\left\{ 1 + \frac{1}{k_1} \left[R2^* - 2\pi i \left(\nu + \frac{\Delta}{2} \right) \right] \right\} \cdot \left\{ 1 + \frac{1}{k_1} \left[R2^* - 2\pi i \left(\nu + \frac{\Delta}{2} \right) \right] \right\}} - 1 \quad (6)$$

where α is a normalization constant, k_1 is the exchange rate constant, Δ is the frequency difference in Hz between the two exchange sites ($\nu_B - \nu_A$) and $R2^*$ is the effective spin-spin relaxation rate constant. Values for ν_A , ν_B , and $R2^*$ were determined from the experimental low temperature NMR spectrum. Simulated lineshapes, $I(\nu)$ versus ν , for different values of the rate constant k_1 were calculated using the computer program MATHCAD (Mathsoft Inc.). These lineshapes then were matched visually to the experimental spectra.

Effect of Temperature on the Relaxation and Internal Rotation Rate Constants for *N,N*-dimethylacetamide

<i>T</i> (K)	<i>R</i> _{1obs} (s ⁻¹)	Rate Constant (s ⁻¹)	Experiment
290	0.395	0.109	saturation transfer
295	0.392	0.144	saturation transfer
300	0.538	0.291	saturation transfer
305	0.758	0.584	saturation transfer
310	1.33	0.930	saturation transfer
340		15.2	lineshape transfer
345		25.8	lineshape transfer
355		58.8	lineshape transfer
360		85.7	lineshape transfer
365		153	lineshape transfer

Eyring Plot

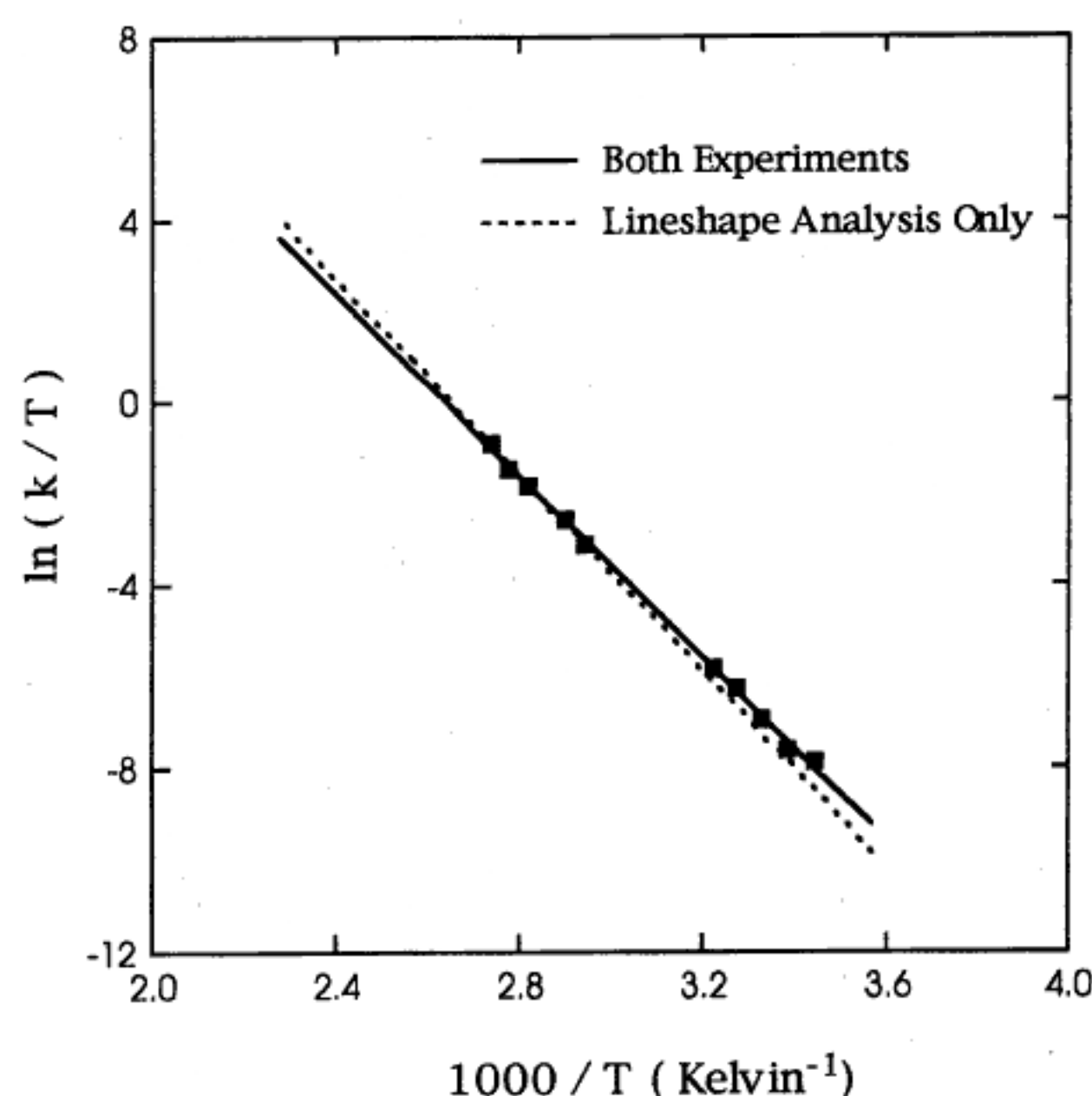


Figure 3. Eyring plot of rate data for internal rotation in *N,N*-dimethylacetamide.

Results

The table summarizes a typical set of student-determined rate constants as a function of temperature and the experiment used to measure them. The enthalpy (ΔH^*) and entropy of activation (ΔS^*) for the internal rotation process can be determined from the Eyring equation:

$$\ln\left(\frac{k_1}{T}\right) = \ln\left(\frac{k_B}{h}\right) - \frac{\Delta H^*}{R \cdot T} + \frac{\Delta S^*}{R} \quad (7)$$

where *T* is Kelvin temperature, and *k_B*, *h*, and *R* are Boltzmann's, Plank's, and the gas constant, respectively.

Figure 3 shows an Eyring plot of the rate data in the table. The solid line represents a linear regression of the entire data set while the dotted line corresponds to fitting only the rate constants measured with the lineshape analysis. The enthalpy and entropy of activation determined by performing both experiments are 82.4 kJ mol⁻¹ and 19.9 J K⁻¹ mol⁻¹, respectively, and agree well with the values reported by Neuman and Jonas ($\Delta H^* = 86.1$ kJ mol⁻¹ and $\Delta S^* = 19.6$ J K⁻¹ mol⁻¹) (8). However, if only the higher temperature lineshape analysis data are fit, the slope of the Eyring plot is steeper, as shown by the dotted line in Figure 3, which leads to larger values for the enthalpy and entropy of activation (88.8 kJ mol⁻¹ and 37.9 J K⁻¹ mol⁻¹, respectively). Therefore, by combining both experiments and extending the temperature range of the experiment from 25 to 75 K considerable improvement in the accuracy of the activation parameters is achieved. This improvement is particularly evident in the entropy of activation that involves a long extrapolation and is, thus, very sensitive to small errors in rate data.

Discussion

Typically, we have assigned a pair of students to work together on the experiment. Two three-hour laboratory periods are sufficient to complete the data collection and a third period is allowed for completion of calculations and preparation of reports. In order to save time we have each pair of students determine the effective spin-lattice relaxation rate constant, *R*_{1obs}, at only one temperature (between 295 and 315 K in 5 K intervals) after doing the saturation transfer experiment at each of four to five temperatures over that range. For *N,N*-dimethylacetamide, we have sometimes asked students to determine the coalescence temperature (and corresponding rate constants) from both proton and ¹³C spectral data. Because the chemical shift difference, *v_B* - *v_A*, in Hertz is greater for the ¹³C signal (90 Hz) than for the proton signal (50 Hz) of the *N*-methyl groups, a higher temperature is required to reach ¹³C coalescence.

Many other systems, including other *N,N*-dimethyl amides could be employed for this project. We, however, have avoided systems that require that the saturation transfer experiments be done below room temperature in order to avoid the additional complications associated with the use of a nitrogen cooling system. Lone pair inversion at the metal-coordinated sulfur of [Pt(CH₃-S-CH₂-CH(CO₂H)-NH₂Cl₂)] interconverts the two diastereomers of this compound at conveniently measurable rates between 300 and 400 K. The rate of lone-pair inversion of amines can be investigated by this technique by controlling the pH and, thereby, the fraction of protonated amine.

The scope of the project can be extended to include a theoretical calculation of the energy barrier to internal rotation. We have employed both molecular mechanics approaches, based on CAChe molecular modeling software and quantum calculations. The latter might include both semiempirical and *ab initio* methods (9).

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