Carbon-13 and Nitrogen-15 Spin–Lattice Relaxation (T_1) and Nuclear Overhauser Enhancement (NOE) Measurements for Acetamide and *N,N*-Dimethylacetamide[1a]

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Abstract: Nitrogen-15 spin–lattice relaxation times (T_1's) and nuclear Overhauser enhancement (NOE) values are found to vary over a range of concentrations for acetamide. Our data indicate that intermolecular amide–amide hydrogen bonds are broken on dilution in water. Carbon-13 spin–lattice relaxation times and nuclear Overhauser enhancement measurements are given for acetamide and *N,N*-dimethylacetamide at 5.3 *M*. There is good agreement between experimental and calculated relaxation rates assuming rapid rotation of the α-methyl group and slow rotation about the amide bond.

The properties of the amide bond have received considerable attention because of its importance in determining secondary and tertiary structure in peptides and proteins. Several NMR studies have been made of amides[2,3] as well as peptides and proteins.[4,5]

Spin–lattice relaxation (T_1) measurements for ^{13}C nuclei have become almost routine in many laboratories because of improvements in NMR instrumentation such as Fourier-transform methods as well as the increased availability of enriched compounds.[6] However, there is much less information on nitrogen-15 relaxation times and nuclear Overhauser (NOE) data,[7] and it appears that the only compound so far reported[7c] with a maximum ^{15}N NOE (-3.93) is aniline.

We present here ^{15}N and ^{13}C T_1 and NOE measurements for acetamide (95.5% ^{15}N enriched) at various concentrations in water and, in addition, ^{13}C relaxation data for *N,N*-dimethylacetamide. It will be shown that there is good agreement between $1/T_{1\mathrm{DD\,(calcd)}}$ and $1/T_{1\mathrm{DD\,(exptl)}}$ for these molecules using current theoretical methods.

Experimental Section

N,N-Dimethylacetamide used in this work was commercial material. Acetamide was recrystallized from acetone and dried under reduced pressure over phosphorus pentoxide. The 95.5% ^{15}N-enriched acetamide which was used only for ^{15}N T_1 measurements was purchased from International Chemical and Nuclear Corp., Irvine, Calif.

Oxygen was removed by bubbling argon gas through the solutions for 10–15 min. Each sample was submitted for metal-impurity analysis by atomic emission methods and was reported to contain no significant paramagnetic impurities. However, because of the known importance of such impurities on ^{13}C relaxation times, we believe that it would be unwise to put great reliance on the T_1 (overall) values. The $T_{1\mathrm{DD}}$ values are much more certain, because they are confirmed by the NOE measurements.

The T_1 and NOE data were obtained with a Brukarian, pulsed FT spectrometer[8] operating at 15.09 MHz for carbon-13 and 6.08 MHz for nitrogen-15 at 30.0 ± 1°. Some spectra were obtained at 25.2 MHz at 31 ± 1° with an FT-equipped Varian XL-100-15 spectrometer for carbon-13.[9]

All ^{13}C and ^{15}N spin-lattice relaxation times were determined by the progressive saturation method of Freeman and Hill.[10] The pulse interval ratio b/a was chosen to equal 4, and only those spectra where $0.65 \geq S_a/S_b \geq 0.52$ were used to evaluate T_1. No less than three sets of measurements were taken for each reported T_1 and NOE. Prior to each set of measurements, calibration of the 90° pulse width was confirmed. For the Brukarian spectrometer, a spectral width of 200 Hz was chosen, giving 2K accumulated data points, while a 1200 Hz spectral width with 8K data points was used on the XL-100-15.[11] The Fourier transform was carried out with 8K time-domain points providing a resolution of 0.05 Hz/point (0.34 for the XL-100-15). The values of S_a and S_b were taken equal to the computer-printed intensities which resulted after the application of an exponential weighting factor (SE) of 0.1.[12] Dynamic nuclear Overhauser enhancements were measured using a gating technique.[6h]

Results and Discussion

A. Nitrogen-15 Results. The results in Table I show a maximum NOE for nitrogen-15 at high concentrations ($\geq$4.5 *M*), which diminishes at lower concentrations. This decrease in NOE with dilution reflects a decrease in the relative importance of the dipolar relaxation mechanism. The contribution of other relaxation times ($T_{1\mathrm{other}}$) can be calculated from the following expression

$$\frac{1}{T_{1\mathrm{obsd}}} = \frac{1}{T_{1\mathrm{DD}}} + \frac{1}{T_{1\mathrm{other}}} \tag{1}$$

where

$$T_{1\mathrm{DD}} = T_{1\mathrm{obsd}}\left(\frac{\eta_{\mathrm{max}}}{\eta_{\mathrm{obsd}}}\right) \tag{2}$$

Because chemical-shift anisotropy is an unlikely mechanism here, one is left with scalar relaxation and spin-rotation as possible mechanisms for the term $1/T_{1\mathrm{other}}$ in eq 1. Rapid proton exchange, which is responsible for scalar relaxation, is unlikely to change much over the concentration range which we have studied, because acetamide is highly solvated even at high concentrations. We assume, therefore, that scalar relaxation is unimportant at low concentrations and, in dilute solutions ($\leq$0.06 *M*) of acetamide, the spin-rotation contribution to the relaxation mechanism is consequently of some importance. However, it is not at all clear what part of the $T_{1\mathrm{other}}$ values are due to effects of paramagnetic ions.

The increase in the magnitude of $T_{1\mathrm{DD}}$ on going to dilute solutions indicates that acetamide is tumbling at a faster rate than at high concentrations. This is reasonable because, at these concentrations, catenation due to hydrogen bonding would be expected whereas, at low concentrations, such bonding is not expected to be as significant because of aqueous solvation.[2]

B. Carbon-13 Results. The results of the carbon-13 and nitrogen-15 T_1 measurements for acetamide in H_2O and D_2O and *N,N*-dimethylacetamide in D_2O at 5.3 *M* concentration are presented in Table II. The T_1 values of the car-

Table I. Variation of ^{15}N Spin–Lattice Relaxation Times (T_1) with Concentration[a,b] for Acetamide

Concn,[c] mol/l.	T_1, sec	$1 + \eta$	T_{1DD}, sec	T_{1SR}, sec[d]
6.0	11.9	−4.1	11.9	>150
5.3	14.2	−4.1	14.2	>150
4.5	14.9	−3.9	15.1	>150
2.3	17.9	−3.7	19.4	>150
0.6	21.6	−2.6	39.6	47.5

[a] Samples were dissolved in H_2O and degassed with argon. [b] D_2O external lock. [c] pH 5.4 at 6.0 *M* and pH 5.1 at 0.6 *M*. [d] Experimental errors are such as to prevent determination of this value when it exceeds 150 sec.

bamide carbons are long relative to the methyl groups in the same molecule, as one might expect for carbons without directly bonded hydrogens. It is, however, noteworthy that the T_1 of the carbamide carbon of acetamide in D_2O is much longer than the same carbon of acetamide in water under the same experimental conditions. The increase in the T_1 value from 37.1 to 72.0 sec results from exchange of deuterium for hydrogen on the amide nitrogen. The amide hydrogens (in H_2O) contribute to the relaxation of the carbamide carbon via the dipole–dipole mechanism and, when these are replaced with deuterium,[13] the relaxation will be less efficient ($\gamma_D/\gamma_H = 0.15$). The effect of this smaller magnetogyric ratio, γ, on the T_{1DD} of a neighboring carbon can be readily seen from eq 3, where N is the number of hy-

$$\frac{1}{T_{1DD}} = N_X \frac{4}{3} \gamma_C^2 \gamma_X^2 S(S+1)\tau_c/r^6 \qquad (3)$$

drogens (or deuteriums) on adjoining carbons or nitrogens, τ_c the effective correlation time, and r the distance from the hydrogen(s) to the carbon. Because the T_{1DD} is dependent on the square of the gyromagnetic constant and the spin quantum number, S, exchange reduces the dipole–dipole contribution by about 0.06.

C. Calculation of $T_{1DD(calcd)}$. The $T_{1DD(exptl)}$ values shown in Table II were obtained from eq 2 using the experimentally determined NOE ($\eta + 1$) for each nucleus listed. The τ_c value which gave the optimum fits to all $1/T_1$ values for each molecule was obtained by varying τ_c until the sum of squared deviations was minimized, using data on carbon-13 and nitrogen-15 nuclei in both water and deuterium oxide. As the methyl group in acetamide is rotating much more rapidly than the overall rotational diffusion, eq 3 must be modified to include the appropriate angle term (see Figure 1) for rapidly rotating groups.[6j,14] Thus, our calculations for acetamide assume very rapid rotation of the methyl group, while internal rotation of the $-NH_2$ group is assumed to be negligibly slow on the τ_c time scale because of the partial double-bond character of the C–N bond. Diffraction data for bond distances and angles for acetamide[15] and urea[16] were used to calculate the various angles and distances required for eq 4. The best τ_c for acetamide was

$$\frac{1}{T_{1DD}} = \frac{N\gamma_C^2\gamma_H^2\hbar^2\tau_c}{r^6}\left(\frac{3\cos^2\theta - 1}{2}\right)^2 \qquad (4)$$

found to be 7.5×10^{-12} sec. The agreement between $1/T_{1DD(exptl)}$ and $1/T_{1DD(calcd)}$[17] using this τ_c value for the methyl carbon and the amide nitrogen is very good (Figure 2), especially in view of the high-order dependence of T_1 on distance, angle, and gyromagnetic ratio. Thus, the assumption that the overall molecular motion may be characterized with a single effective correlation time appears to be unusually good. The agreement between calculated and experimental for the carbamide carbons is also reasonable when it is realized that the reciprocal times or rates are the ones which were fit.

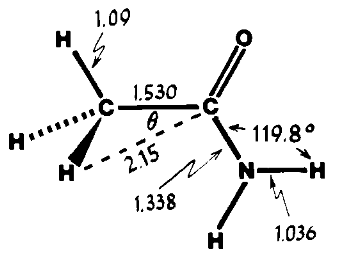

Figure 1. Bond angles and bond lengths for acetamide.

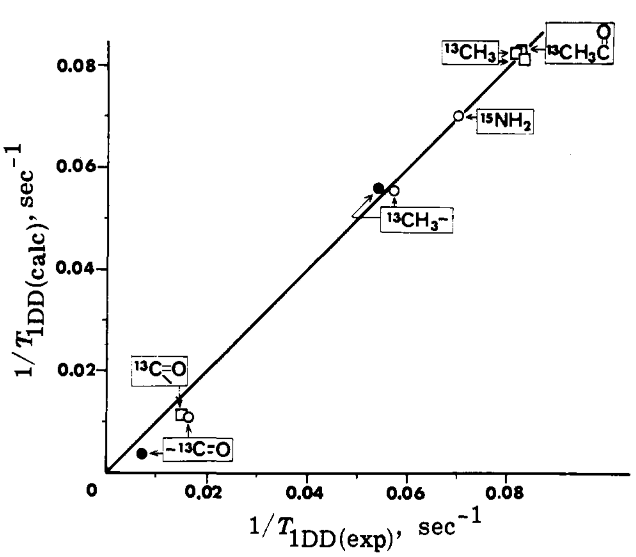

Figure 2. Calculated vs. experimental relaxation rates, $1/T_1$ using the $\tau_{c,eff}$ from Table II; (□) $CH_3CON(CH_3)_2$; (○) CH_3CONH_2; (●) CH_3COND_2.

The agreement in $T_{1DD(exptl)}$ and $T_{1DD(calcd)}$ (Table II) for the three methyl carbons in *N,N*-dimethylacetamide is also good, as also observed in Figure 2. Again the three methyl groups were assumed to be rapidly rotating, while rotation about amide bond was considered to be negligibly slow. The best effective τ_c for this model was found to be 11.1×10^{-12} sec using the same statistical method as for the acetamide calculation and structural data from diffraction measurements on *N*-methylacetamide.[18] The calculation of τ_c for the carbamide carbon of dimethylacetamide included the effect of the methyl groups bound to nitrogen. For this calculation, the three rapidly rotating hydrogens of each methyl were assumed to occupy their average position along the axis of the methyl top and at a distance of $|r_{C-H} \cos 109° \ 28 \ \text{min}|$ from the methyl carbon (see Figure 3). It is necessary to include the hydrogens in such a calculation in order to get reasonable agreement. Neglect of these hydrogens would lead to a τ_c of $\sim 30 \times 10^{-12}$ rad/sec for the amide carbon.

It is interesting to note the similar magnitudes of τ_c for acetamide and *N,N*-dimethylacetamide. While one does not expect the latter to form hydrogen bonds as readily as acetamide, a shorter τ_c is expected; however, this effect is offset by the larger mass, and the τ_c values for both compounds are similar.

The observation of a single effective correlation time for all ^{13}C and ^{15}N nuclear relaxations in these molecules is not so surprising if attention is given to the similarity of both mass and, to a lesser extent, volume of a methyl and oxygen moiety. The similarity of these two substituents will tend to force one of the principal axes of rotational diffusion to lie along the C–N bond bisecting the $O-C-CH_3$ angle, with the remaining two principal axes perpendicular to this bond. Thus, we see that the square of the directional cosines relative to the principal axes of the two N–H bonds and the

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Table II. Spin–Lattice Relaxation Times (T_1) for ^{13}C and ^{15}N in Acetamide and *N,N*-Dimethylacetamide

	T_1, sec	$\eta + 1$	T_1DD(exptl), sec	T_1DD(calcd), sec	$\tau_{c,eff}$
Acetamide (in D_2O)[a]					
$^{13}C{=}O$	72.0	2.0	139	283	7.5×10^{-12} sec
$^{13}CH_3$	12.3	2.3	18.5	17.8	
Acetamide (in H_2O)[a,b]					
$^{13}C{=}O$	37.1	2.2	61.0	94.7	
$^{13}CH_3$	11.0	2.3	17.5	17.8	
$^{15}NH_2$	14.2	−4.1	14.2	14.1	
N,N-Dimethylacetamide (in D_2O)[a]					
$^{13}C{=}O$	44.2	2.3	65.6	89.0	11.1×10^{-12} sec
$^{13}CH_3$	9.6	2.6	12.2	12.0	
$-N^{13}CH_3$	9.5	2.6	12.0	12.0	
$-NCH_3$	9.2	2.5	12.1	12.1	

[a] 5.3 *M*. [b] D_2O external lock.

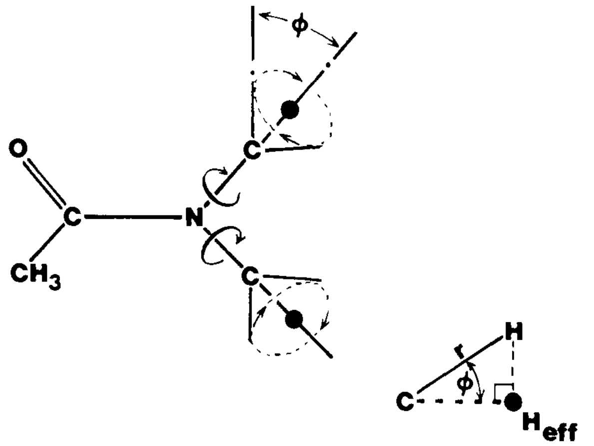

Figure 3. The *N*-methyl groups of *N,N*-dimethylacetamide are represented as rotating about the N–C axis. The effective position for the *N*-methyl hydrogens is indicated by ● and is assumed to lie along the N–C axis at a distance $r_{C-H} \cos \phi$ from the *N*-methyl carbon.

C-CH_3 axis in acetamide and the N-CH_3 axes and the C-CH_3 axes in dimethylacetamide will, in each instance, be nearly, if not exactly equal. Furthermore, the effective correlation times governing relaxation in asymmetric tops depend on the squares of these directional cosines. For rapidly rotating methyl groups, it is the effect of overall rotation on the methyl top axis which is of importance. Thus, one cannot presume overall isotropic diffusional motion, even though a single effective correlation time was found to be sufficient to give a good fit of the data. Whenever the requisite linearly independent internuclear vectors required to reveal anisotropic motion are not available for a molecule, the three rotational diffusion constants required to characterize motion in liquids may be reduced to two or even one effective parameter. However, unless the appropriate vectors are linearly independent, one might conclude that, with just one correlation time, the motion is actually isotropic. Care should be taken to avoid this pitfall when interpreting reported relaxation data. This point is of considerable importance and should not be ignored when drawing conclusions regarding the nature of molecular motions in liquids.

The agreement between calculated and experimental values for the carbamide carbons may, at first blush, be considered at best fair. Such a conclusion would not, however, take proper consideration of the manner in which the τ_c values were obtained. Because a restrained least-squares approach was applied to reciprocal T_1 values or relaxation rates, the errors are actually no greater for the carbamide carbons than for the carbons with shorter T_1's. This feature is illustrated in Figure 2, where $(1/T_1)_{calcd}$ is plotted vs. $(1/T_1)_{exptl}$, and an excellent correlation of nine data points is achieved with only two single adjustable correlation times, one for each molecule. Thus, the scatter of carbamide relaxation rates about the perfect agreement line is really not much greater than those noted for the other carbons. It is true, however, that the shorter T_1 values (or larger reaction rate constants) carry more weight in determining τ_c, because values of $1/T_1$ nearer to zero have little effect on a least-squares fit of τ_c. The weighting here of the shorter T_1's over the longer ones is, in one way, fortunate, because intermolecular effects and intrinsic experimental errors are much larger for the longer T_1 values. The shorter $T_{1(exptl)}$ for carbamide carbons probably indicates some intermolecular relaxation for which no provision is made in the model for relaxation, and this may explain why all three carbamide carbons fall slightly below the line in Figure 2.

Conclusions

It is clear that the studies such as those reported here will be essential before it is possible to completely understand data obtained on more complicated systems, such as peptides[19] and proteins, which have been investigated recently using the carbon-13 T_1 parameter. Furthermore, our data indicate, as would be expected, that different T_1 values may be obtained for carbamide carbons if peptide and protein molecules are dissolved in D_2O rather than H_2O.[20] This warns against excessive interpretation of T_1 data without first obtaining NOE parameters. In addition, use of more sophisticated expressions, such as eq 4 or its more complete antecedent given by Woessner,[14] is dictated if simple correlation times as are found in this work are to have any value. Indiscriminate application of eq 3 to T_1 data becomes nothing more than linear transformation of T_1 values into $\tau_{c,eff}$ values with marginal conceptual benefit. It is seen, however, that careful sorting out of the various motional features can characterize the molecular dynamics.

References and Notes

(1) (a) Supported by the Public Health Service, Research Grant No. GM-11072, from the Division of General Medical Sciences, and by the National Science Foundation; (b) Harkness Fellow of the Commonwealth Fund, New York, 1972–1974; (c) Sherman Fairchild Distinguished Scholar at the California Institute of Technology (on sabbatical leave from the Department of Chemistry, University of Utah, 1973–1974).

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Correlation of ^{13}C Chemical Shifts and CNDO/2 Charge Distributions in Phenylcarbenium Ions and Related Phenyl Substituted Onium Ions[1]

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Abstract: The complete ^{13}C NMR spectra have been obtained for 22 phenylcarbenium ions and related phenyl substituted onium ions. The ^{13}C chemical shifts for these cationic, monosubstituted benzenes are discussed in relation to charge densities calculated for the systems using the CNDO/2 method and in relation to similar data for electronically neutral monosubstituted benzenes. The para carbon shifts are linearly correlated with charge over a range of 45 ppm. The phenylcarbenium ions and phenyl substituted onium ions are treated as successfully in calculations, neglecting the gegenion, as are the electronically neutral benzenes. The para carbon shifts in ions formed by protonation of a heteroatom in a substituent exhibit small deviations from the expected para shifts, which may be due to hydrogen bonding between the ion and solvent. Nonequivalent ortho shifts in several ions indicate an important shielding contribution from the γ-substituent effect at ortho carbons in addition to charge effects. The nonequivalence in ortho shifts arises from slowed rotation about the substituent-ring bond due to significant double bond character. Meta carbon shifts in the cations occur in a narrow range, slightly downfield from meta carbons in electronically neutral benzenes. The shifts for the directly substituted ipso carbons, and also for sp^2 hybridized α carbons, correlate poorly with calculated charge densities, with the deviations from a correlation line showing some regularity related to the type of substituent.

The interpretation and prediction of ^{13}C NMR chemical shifts is an area of much theoretical activity. However, in practice, ^{13}C chemical shifts are frequently used to provide detailed information about structure, bonding, and electron distribution in organic molecules and ions with only cursory reference to theoretical treatments of chemical shifts. In our previous work, we have had considerable success in using ^{13}C spectra as evidence for the existence of stable carbocations in solution and as a probe for determining the pattern of charge distributions in such ions. Now, as part of an investigation into the various possible influences on ^{13}C chemical shifts, we have attempted to determine the extent to which the ^{13}C shift can be used as a quantitative index of charge distribution in phenylcarbenium and phenyl substituted onium ions.

The relationship between ^{13}C NMR chemical shifts in monosubstituted benzenes and the electronic effects of substituents has received considerable attention.[3-11] Particular attention has been given to the para carbon which is shielded by electron-donating substituents and deshielded by electron-withdrawing groups. The para carbon shifts give linear correlations with calculated electronic charge densities and with various chemically derived para substituent constants. Similar electronic effects are observed at ortho carbons, although the correlations with charge densities obtained from molecular orbital calculations are much less satisfactory than for the para position.[5,8-10] It has often been assumed that substituent influences other than charge density perturbations affect the magnetic environment of the ortho carbons.[4,5,11] Least subject to substituent influences are the meta carbons, which absorb over a narrow range; the directly substituted ipso carbons are the most sensitive.[11]

We now report a ^{13}C NMR study of monosubstituted

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