Studies of Chemical Exchange by Nuclear Magnetic Resonance. X. The Inherent C-N Rotational Barriers in Amides, Thioamides, and Amidinium Ions[1,2]

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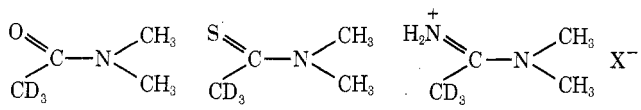
Received September 25, 1973

Activation parameters have been determined for C-N rotation in compounds of the general structure $CD_3C(X)NMe_2$ at low concentrations in nonpolar media. The resulting data follow [X, solvent, concentration (mole per cent], E_a (kilocalories/mole), log A, ΔF^* (25°, kilocalories/mole), ΔS^* (eu)]: O, CCl_4, 1.7, 18.3 ± 0.2, 13.5, 17.4, +1.1; O, isooctane, 2.6, 18.0 ± 0.3, 13.3, 17.3, +0.5; S, decalin, 1.6, 21.1 ± 0.2, 13.4, 20.3, +0.6; $NH_2^+NO_3^-$, 1,1,2,2-tetrachloroethane, 0.4, 24.0 ± 0.3, 14.2, 22.1, +4.6; $NH_2^+Cl^-$, TCE, 0.4, 22.8 ± 0.3, 13.6, 21.7, +1.9. These are compared with data obtained for the same systems in different solvents. Solute-medium interactions are discussed and it is proposed that these new data represent the "inherent" C-N rotational barriers for these systems. In contrast with earlier results, the values of ΔF^* now correlate with values of J (^{13}CH) for the NCH_3 protons.

Activation parameters for rotation about the partial double C-N bond in amides and derivatives are influenced by solute-solute and solute-solvent interactions.[1,3-6] Amides and thioamides exist as self-association dimers in the pure liquids or in high-concentration solutions of noninteracting solvents. In dipolar solvents such as dimethyl sulfoxide, a molecule of amide or thioamide is presumed to associate strongly with a solvent molecule in a similar pairwise dipolar association. However, in a solvent such as formamide, hydrogen-bonding interactions appear to replace the dipolar association complexes. In any event, we and others have shown that the medium has a marked influence on rotational barriers.

Recently, we reported a study of the three systems shown below in the common solvent dimethyl sulfoxide-



1 2 3

d_6.[3] The types of intermolecular interactions of 1 and 2 with the medium were the same as mentioned above, but the experimental data, and common sense, indicated that the amidinium ion 3 interacted with DMSO-d_6 *via* hydrogen bonding. Thus, the results were not directly comparable, even though all three systems were studied in a common solvent. It was necessary to try to analyze the contributions of the different interactions to attempt to compare rotational barriers.

We have now been able to obtain rotational activation parameters for the solutes 1-3 in nonpolar media at low concentrations. The results give a different ordering of the relative rotational barriers for these compounds than previously observed.[3] This order O < S < NH_2^+ conforms to the relative values of the ^{13}CH coupling constants for the NCH_3 protons in 1-3, a correlation which we had proposed early in our studies of the comparative barriers of amides, thioamides, and amidinium salts. We suggest that the data presented here are close approximations to the "inherent" barriers to C-N rotation in these compounds, and this report concludes the series "Studies of Chemical Exchange by Nuclear Magnetic Resonance."

Results and Discussion

The nonexchanging chemical shift ($\delta\nu_\infty$) between the two NCH_3 resonance signals reflects the extent of aggregation of amide molecules in noninteracting media.[7] The concentration dependence of $\delta\nu_\infty$ for DMA-d_3 in isooctane at 5° is

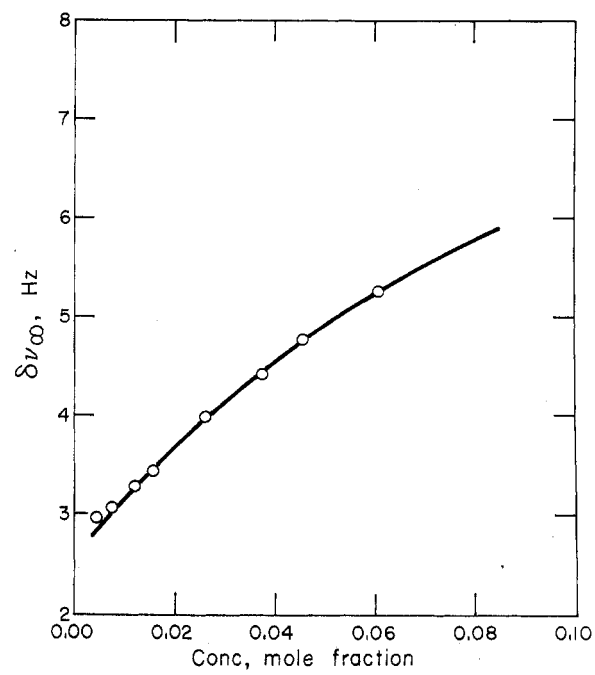


Figure 1. Concentration dependence of the chemical shift ($\delta\nu_\infty$) between the two NCH_3 groups which would exist in the absence of rotation about the C-N bond; solvent, isooctane.

shown in Figure 1 and from these data a dimerization constant of 2.3 (mole fraction)$^{-1}$ was calculated for the equilibrium shown in eq 1.[8] This compares favorably with

$$2\text{DMA-}d_3 \rightleftharpoons (\text{DMA-}d_3)_2 \quad (1)$$

a previous value of 3.8 (mole fraction)$^{-1}$ determined for DMA-d_3 in CCl_4 (37°).[7] From the data in isooctane, it is possible to extract values of $\delta\nu_\infty$ for monomeric and dimeric DMA. The values 2.6 and 17.0 Hz are different from those obtained in CCl_4, which are 7.3 and 13.8 Hz, but this is not unexpected owing to the possible medium effects on the relative magnetic environments of the NCH_3 groups.

Careful kinetic studies of C-N rotation in DMA-d_3 in isooctane (0.026 mole fraction) and carbon tetrachloride (0.017 mole fraction) were carried out. Under these conditions, DMA-d_3 exists primarily, but not exclusively, in the monomeric state (isooctane, 95% monomer; CCl_4, 94% monomer). Lower concentrations would have been desirable, but were not feasible owing to low amplitude of the nmr signals. The activation parameters in these two solvents are reported in Table I (see Figure 2) along with

Table I
Activation Parameters for C–N Rotation in $CD_3C(X)N(CH_3)_2$

X	Solvent	Concn, mol %	E_a, kcal/mol	Log A	ΔF^* (25°), kcal/mol	ΔS^*, eu	Ref
O	CCl_4	1.7	18.3 ± 0.2	13.5	17.4	+1.1	This work
	Isooctane	2.6	18.0 ± 0.3	13.3	17.3	+0.5	This work
	Neat	100.0	19.6 ± 0.3	13.8	18.2	+2.9	*a*
	DMSO-d_6	9.5	20.3 ± 0.3	14.1	18.5	+4.1	*b*
	Formamide	9.8	21.3 ± 0.6	14.2	19.4	+4.4	*a*
	D_2O	2.0	21.0 ± 0.9	13.9	19.5	+3.0	*c*
S	Decalin	1.6	21.1 ± 0.2	13.4	20.3	+0.6	This work
	o-DCB	33.3	(21.0 ± 0.3)	(12.6)	21.3	(−3.0)	*d*
	DMSO-d_6	8.1	25.9 ± 0.9	14.6	23.4	+6.3	*b*
$NH_2^+NO_3^-$	TCE	0.4	24.0 ± 0.3	14.2	22.1	+4.6	This work
	DMSO-d_6	3.1	21.3 ± 0.3	12.7	21.5	−2.6	*b*
$NH_2^+Cl^-$	TCE	0.4	22.8 ± 0.3	13.6	21.7	+1.9	This work
	DMSO-d_6	7.4	22.8 ± 0.7	13.5	21.8	+1.4	*b*

[a] See ref 4. [b] See ref 3. [c] P. A. Temussi, T. Tancredi, and F. Quadrifoglio, *J. Phys. Chem.*, **73**, 4227 (1969). [d] Determined using an approximate analysis method; see ref 10.

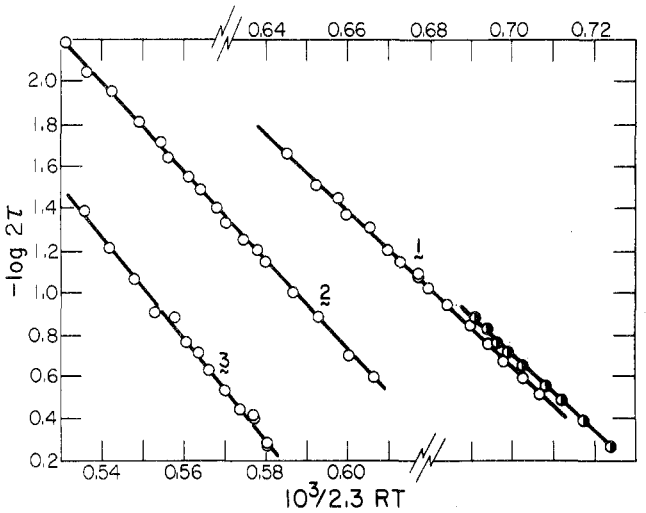


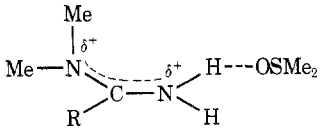
Figure 2. Arrhenius plots of the kinetic data for rotation about the central C–N bond in **1**, ◑, solvent, isooctane; **1**, ○, solvent, CCl_4); **2**, solvent, decalin; **3** (nitrate salt), solvent, 1,1,2,2-tetrachloroethane.

other data for DMA-d_3 under conditions in which it exists primarily as a self-association dimer (neat), associated with an aprotic dipolar solvent (DMSO-d_6), and hydrogen bonded at the carbonyl group (formamide and D_2O). The results clearly demonstrate that the association or hydrogen-bonding interactions substantially increase the rotational barrier (1 and 2 kcal/mol, respectively, in ΔF^*). The major effect of solvent is apparently on E_a, but log A (ΔS^*) also shows the expected change reflecting transition state desolvation.[9]

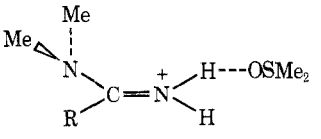
Rotational activation parameters were determined for the thioamide **2** using the solvents decalin and *n*-decane with thioamide concentrations of 0.016 mole fraction. The concentration dependence of $\delta\nu_\infty$ was not determined in either case. However, the low concentrations and large values of $\delta\nu_\infty$ observed strongly indicate, based on an earlier study of DMTA-d_3 in carbon tetrachloride,[7] that DMTA-d_3 is primarily monomeric under these conditions. Extensive kinetic data were accumulated using the solvent decalin and the results of the study are reported in Table I (see Figure 2) along with some other values for comparison. The very limited kinetic data in *n*-decane gave a value of ΔF^* identical with that found using decalin, but were insufficient to provide accurate values for E_a and log A.

A comparison of the results using decalin and DMSO-d_6 shows that dipolar association with dimethyl sulfoxide substantially increases the rotational barrier. Once again the major part of the effect is in E_a but log A does show an increase in the associating medium. A result from another laboratory[10] for **2** in *o*-dichlorobenzene gives a ΔF^* value intermediate between those in DMSO-d_6 and decalin. The use of an approximate line shape analysis method makes the values of E_a and log A from that study suspect.[11] If the data in decalin correspond to the inherent C–N barrier, they indicate that the difference between an amide and thioamide is only about 3 kcal/mol rather than the 5 kcal/mol difference suggested by the data using the solvent DMSO-d_6. It appears that dipolar association with DMSO-d_6 has a much greater effect on the dipolar character of a thioamide than that of an amide.

It was possible to obtain rotational barrier data for the nitrate and chloride salts of *N,N*-dimethylacetamidinium ion (**3**) in 1,1,2,2-tetrachloroethane at very low concentrations (Table I and Figure 2). The behavior of the line widths of the individual NCH_3 signals with temperature indicated that ion pairing existed under these conditions for both salts, but greater effects were observed for the nitrate. Although there are differences between the two salts, there is remarkably little change in ΔF^* in going from the solvent DMSO-d_6 to tetrachloroethane (Table I). We had proposed that DMSO-d_6 was hydrogen bonded to both the rotational ground and transition states (**4a** and **4b**) but that this bonding might be a bit tighter in the latter.[3] The relatively low values for log A (ΔS^*) in DMSO-d_6 were offered as evidence for this. The absence of a solvent effect on ΔF^* for **3** now seems to support the similarity in solvent interactions with **4a** and **4b**. However, the detailed interaction of the anion with the rotational ground and transition states is not known.[12]



4a



4b

Several years ago, we proposed a correlation between J (^{13}CH) for the NCH_3 groups on **1–3** and their C–N rotational barriers.[13] Haake had proposed that values of J (^{13}CH) for methyl groups bonded to nitrogen reflected the amount of positive charge on nitrogen.[14] Since the charge on the NCH_3 nitrogen of amides and related derivatives **5**

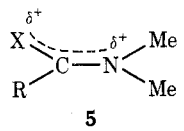


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Table II
Comparison of ΔF^* for C–N Rotation in $CD_3C(X)N(CH_3)_2$ with ^{13}CH Coupling Constants for the NCH_3 Protons[a]

Registry no.	X	ΔF^* (25°), kcal/mol	$J(^{13}CH)$, Hz[b]
44364-33-2	NH	(<17)	135
20255-66-7	O	17.3	138
34302-08-4	S	20.3	140
50600-26-5	NH_2^+	22	141

[a] Values of ΔF^* from Table I except for X = NH, which comes from ref 3. [b] The ^{13}CH coupling constants for NCH_3 protons; see ref 3 and 13.

should depend on the extent of C–N double-bond character and since in turn the rotational barrier should also depend on this, we were disappointed that an inconsistency appeared based on our kinetic data using DMSO-d_6.[3] We are now gratified to be able to report that the rotational barriers determined in the nonpolar solvents at low concentration do correlate with the ^{13}CH coupling constants for the NCH_3 protons (Table II).

Experimental Section

Compounds. Syntheses and properties of all of the compounds have been previously described.[3]

Solvents. Isooctane (spectroquality, Matheson Coleman and Bell), carbon tetrachloride (spectrophotometric grade, Mallinckrodt), decalin (spectrophotometric grade, Aldrich), *n*-decane (99%, gold label grade, Aldrich), and 1,1,2,2-tetrachloroethane (Matheson Coleman and Bell) were used as received in sealed bottles.

Variable-Temperature Spectra, Temperatures, and Line Shape Analyses. The procedures followed were essentially those which we have previously used and described.[1,3] Kinetic data were obtained in all cases by total line shape analysis.[1,3]

References and Notes

(1) Part IX: R. C. Neuman, Jr., and V. Jonas, *J. Org. Chem.*, **39**, 925 (1974).
(2) Support by the U. S. Public Health Service (National Institute of General Medical Sciences) through Grant GM-13342 is gratefully acknowledged.
(3) R. C. Neuman, Jr., and V. Jonas, *J. Phys. Chem.*, **75**, 3532 (1971).
(4) R. C. Neuman, Jr., W. Woolfenden, and V. Jonas, *J. Phys. Chem.*, **73**, 3177 (1969).
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(7) R. C. Neuman, Jr., W. Snider, and V. Jonas, *J. Phys. Chem.*, **72**, 2469 (1968).
(8) Calculations were performed in a manner similar to that described in ref 7.
(9) These results for dimethylacetamide are qualitatively similar to those reported by Calzolari, *et al.*[6]
(10) J. Sandström, *J. Phys. Chem.*, **71**, 2318 (1967).
(11) See ref 1 for a discussion of analysis methods and leading references.
(12) See R. C. Neuman, Jr., and V. Jonas, *J. Phys. Chem.*, **75**, 3550 (1971).
(13) R. C. Neuman, Jr., and L. B. Young, *J. Phys. Chem.*, **69**, 2570 (1965).
(14) P. Haake, W. B. Miller, and D. A. Tysee, *J. Amer. Chem. Soc.*, **86**, 3577 (1964).

Synthesis and Fourier Transform Carbon-13 Nuclear Magnetic Resonance Spectroscopy of New Toxic Polyhalodibenzo-*p*-dioxins

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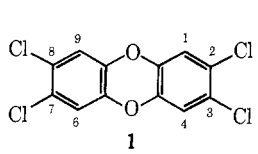
Received October 24, 1073

The extraordinary toxicity and potential environmental significance of certain polyhalodibenzo-*p*-dioxins has led us to carry out regiospecific syntheses of these compounds by condensation of catechol derivatives with various polyhalobenzenes. Electrophilic halogenation of 2,3-dihalodibenzo-*p*-dioxins, available by the above route, leads mainly to 2,3,7,8-tetrahalo derivatives, but these are more cleanly obtained by direct condensation of 4,5-dichlorocatechol with 1,2,4,5-tetrahalobenzenes. Fourier transform ^{13}C spectroscopy is shown to be a useful structural probe in this series. Some structure–activity relations for enzyme induction by polyhalodibenzo-*p*-dioxins are outlined.

The surprisingly high toxicity of certain halogenated dibenzo-*p*-dioxins has been demonstrated in a number of recent investigations.[1] The most thoroughly studied member of this group is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (**1**, TCDD), which has been shown to be the cause of several outbreaks of chloracne among workers in factories which manufacture the herbicide 2,4,5-T (2,4,5-trichlorophenoxyacetic acid).[2] It is now recognized that structure **1** represents perhaps the most lethal small molecule known.[1d] Although present in only trace amounts during the manufacture of 2,4,5-T, the toxicity of this xenobiotic is so extraordinarily high that even these minute quantities constitute a potentially serious health hazard.



1 **2**

The identification of a toxic contaminant in poultry feed, 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin (**2**), as a probable cause of the "chick edema" which has caused widespread loss of chickens in the United States since 1957[3] also demonstrates the environmental significance of certain polyhalogenated dibenzo-*p*-dioxins, apparently formed as by-products in the commercial synthesis of a number of chlorinated phenols. Thus the tetrachloro derivative **1** formed during the manufacture of 2,4,5-trichlorophenol is responsible for the contamination of 2,4,5-T, since the phenol is an intermediate in the manufacture of the herbicide. Because of the widespread use of chlorinated phenols, the extreme potency and environmental persistence of the chlorinated dibenzo-*p*-dioxins which may be present as impurities, and the teratogenic[4] and possible mutagenic effects of these contaminants at sublethal concentrations, further chemical and toxicological characterization of these compounds is urgently needed.

Until recently little was known about the biochemical mechanisms of toxicity for these compounds, and no systematic studies had attempted to relate molecular structure to toxicity or other biological properties in the dibenzo-*p*-dioxin series. In 1973, however, Poland and Glov-