

The Barrier to Internal Rotation in Amides

III. * The Barrier to Internal Rotation, Dipole Moment and Conformation of 1,1-Dimethyl-3-isopropylurea

PETER STILBS

*Division of Physical Chemistry, The Lund Institute of Technology, Chemical Center,
P.O. Box 740, S-220 07 Lund 7, Sweden*

The barrier to internal rotation in the $(\text{CH}_3)_2\text{N}-\text{C}$ amide bond in 1,1-dimethyl-3-isopropylurea (DMIPU) has been determined by proton magnetic resonance (PMR) studies at 60 and 100 MHz. Rate parameters have been evaluated, using complete lineshape treatment of the PMR signals between -60°C and -115°C .

In order to determine the conformation of this trialkylsubstituted urea, its electric dipole moment and the concentration dependence of its molar polarization have been measured, using dielectric methods. The combined PMR and dielectric measurements indicate that DMIPU in solution assumes a planar conformation, in which the carbonyl group and the NH-proton are *trans* to each other.

Attempts to measure the barriers to internal rotation around the amide bond in tetramethylurea, tetramethylthiourea, and tetramethylselenourea¹ by PMR have failed, because they are obviously too low to be measured by this method (ΔG^\ddagger is probably less than about $6.5 \text{ kcal mol}^{-1}$). The signal from the methyl protons in these compounds is a singlet even at -120°C , and the low barriers are attributed to steric repulsion between the methyl groups in the ground state.^{2,3} This interpretation seems correct in view of recent NMR studies of trisubstituted^{3,4} and monosubstituted⁵ thiourea systems, where this kind of steric repulsion is not present, and where slow rotation is observed by PMR.

Here we wish to report a study of a trisubstituted urea: 1,1-dimethyl-3-isopropylurea (DMIPU) (I). Attempts were initially made to study the simpler, and perhaps theoretically more important trimethylurea (II), but were discontinued, mainly because of complications due to overlapping 1- and 3-methyl signals. No significant difference in coalescence temperatures was, however, found in preliminary studies of (I) and (II).

* Part II, see Ref. 9.

Trisubstituted ureas would be expected to exhibit a predominance of the *trans* conformation (IIIa) over the *cis* conformation (IIIb) in solution to minimize the steric interaction mentioned above. To our knowledge, this has never been directly demonstrated. Dielectric measurements have given direct evidence concerning the analogous problem in open chain and cyclic amide systems,⁶⁻⁸ and we have adopted these methods for the DMIPU conformation problem.

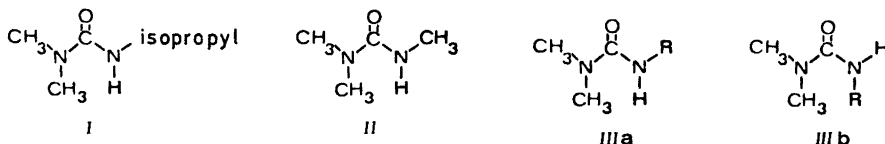


Fig. 1. DMIPU (I), trimethylurea (II), and *trans*- (IIIa) and *cis*- (IIIb) conformations of trisubstituted urea systems.

EXPERIMENTAL

Synthesis. 1,1-Dimethyl-3-isopropylurea was synthesized from isopropylisocyanate (Fluka) and excess anhydrous dimethylamine (Fluka) in sodium-dried benzene. The benzene and excess dimethylamine were evaporated in a Rotavapor (Büchi AG) vacuum distillation apparatus. The crude product showed no impurity signals in PMR. It was recrystallized twice from benzene, and dried *in vacuo* over phosphorus pentoxide at room temperature. The final product was white and had an uncorrected m.p. of 117–118°C. It was stored over phosphorus pentoxide in a desiccator, in view of the fact that trimethylurea has been found to be fairly hygroscopic.

Monodeuterated DMIPU, $(\text{CH}_3)_2\text{N}-\text{CO}-\text{NDCH}(\text{CH}_3)_2$, was prepared by dissolving DMIPU in a large excess of D_2O and by evaporating off the water over phosphorus pentoxide in a vacuum desiccator. The product was then stored with Linde 4A molecular sieves. Its deuteration was checked by PMR of the isopropyl signal at -40°C , where no NH coupling was visible and the CH signal was a binomial heptet, and by PMR in the NH region, where no NH signal was observed.

NMR measurements. An approximately 0.6 M solution of DMIPU in equal volumes of 3-fluorotoluene (Fluka, dried over Linde 4A molecular sieves) and dichloro-fluoro-methane (Frigen 21, Hoechst, used without further treatment) was used in the PMR measurements, for reasons discussed below.

A capillary tube containing equimolar amounts of dimethyl ether (The Matheson Co. Inc., USA) and methanol (BDH, Analar) was placed between teflon spacers in the center of the sample tube. The temperature-dependent PMR shift between the dimethyl ether and hydroxyl signals had been precalibrated, using standard techniques in this laboratory.^{9,10} This capillary mixture was found useful for accurate temperature measurements down to at least -120°C . The hydroxyl 1 : 3 : 3 : 1 quartet is considerably sharper at low temperatures than that observed in, for example, solutions of methanol in Frigen 21.

The main reason for choosing the solvent mixture mentioned above was, that if only CHFCl_2 was used, which is a good solvent for the urea, the sample signals and the dimethyl ether signal were too close to each other due to an unfortunate magnetic susceptibility difference. On the other hand, 3-fluorotoluene, which has a susceptibility that gives a good separation between the dimethylamino- and the capillary signals, is a poor solvent for this urea. A combination of these two solvents was found acceptable.

The NMR measurements were made, using Varian A-60A and HA-100 spectrometers, equipped with variable temperature probes and V-6040 temperature controllers. The HA-100 spectrometer was used in the frequency sweep mode, using the low field CHFCl_2 PMR signal as internal lock signal. The instrumental settings at both 60 and 100 MHz were as follows: scale expansion 1 Hz/cm, sweep rate 0.1 or 0.2 Hz/sec, depending on the linewidth, and an r.f. field well below the saturation level.

At 60 MHz, the chemical shift between the capillary signals was obtained by the usual side band technique, using HP 200 CD Audio Oscillator and an HP 5216 A Electronic frequency counter. At 100 MHz, the shifts were obtained directly from the V 4315 frequency counter of the spectrometer, which monitors the side band frequencies.

Dielectric measurements were made, using a Wissenschaftlich-Technischen Werkstätten Dipolmeter DM 01 (measuring frequency 2 MHz), equipped with a DFL 1 measuring cell. The cell and a Hilger Abbe-type refractometer were thermostated at 25.0°C.

Benzene (BDH Analar, dried over sodium wire and stored over Linde 4A molecular sieves) was used as a solvent for the urea, to make solutions in the range 0–3 wt.%. The chemicals, as well as the solutions, were exposed as little as possible to the atmosphere, to avoid moisture.

The measuring scale of the dipolmeter is linear in ϵ and can be calibrated with solutions of known ϵ . For this purpose, benzene, cyclohexane (BDH Analar, dried over sodium wire and stored over Linde 4A molecular sieves), and dry air were used. Their dielectric constants at 25.0°C were taken to be¹¹ 2.2727, 2.0148, and 1.0006, respectively. The use of dried reagent chemicals as solvents and calibration standards instead of more carefully purified chemicals is sufficient for dipole moment measurements.¹¹

Measurements and calculations

General appearance of the proton NMR spectrum. The dimethylamino signal broadened significantly at about -60°C , to give separate methyl signals below *ca.* -95°C . The exchange broadening effects were accompanied by a rapid increase in natural linewidth of the signals at low temperatures. Moreover, the separated signals differ in linewidth by about 20 %, the low field signal being sharper. This effect has been observed earlier in trisubstituted thioureas, and is suggested⁸ to be due to different spin relaxation conditions. It may also be a long-range spin-spin coupling between the NH proton and one 1-methyl group. We tested the *N*-deuterium substituted compound, using the same solvent mixture, but without the capillary tube. No significant difference in linewidth was observed for the two separated 1-methyl signals in this case.

The substitution of deuterium in this position in DMIPU could remove the broadening difference both by introducing a lower dipolar interaction between the NH and the 1-methyl group closest to it, and by reducing a spin coupling constant by a factor equal to the ratio of the ^2H and ^1H gyromagnetic numbers ($\approx 1/6$).

Double resonance measurements on the undeuterated DMIPU at both $+30^\circ\text{C}$ and at -105°C were performed. No significant effect on the dimethylamino signal(s) was observed in either case, when a strong decoupling field was applied to the NH proton signal.

Theoretical spectra were also calculated, and indicate that at $+30^\circ\text{C}$ any remaining coupling constant must be less than 0.2 Hz, and at -105°C it must be greater than 1 Hz in the broader signal, to be consistent with the observed spectra.

Therefore, it seems reasonable that the observed difference in the linewidth of the two CH_3 signals arises from different relaxation conditions.

Lineshape measurements and calculations. The NMR lineshape in the case studied, equivalent nuclei exchanging between two equally populated sites, depends on the exchange rate, τ , the effective spin-spin relaxation time, T_2^{eff} , and the difference in chemical shift between the two sites, $\delta\nu$. The latter two parameters cannot be evaluated for all values of τ , but must usually be extrapolated or interpolated, and generally depend more or less on temperature. (A discussion of the resulting errors is given in Ref. 9.) To minimize the uncertainty in T_2^{eff} and $\delta\nu$, efforts were made to obtain spectra at both 60 and 100 MHz at the same or at very similar temperatures. Such spectra provide additional information, because τ , T_2 , and $\delta\nu$ (in ppm) must be the same for both spectra. T_2^{eff} depends also on magnetic field inhomogeneities ($1/T_2^{\text{eff}} = 1/T_2 + 1/T_2^{\text{inh}}$), but this will only have a small effect in the present case, because the HA 100 and the A-60A field homogeneities were not found to be very different in this temperature range, and T_2 is comparably short in the system under study.

Theoretical spectra were calculated with a UNIVAC 1108 computer, equipped with a Calcomp paper plotter, according to the theory of Gutowsky *et al.*¹² Calculated and observed spectra were compared visually.

A form of manual iteration procedure for the evaluation of spectral parameters was used. It was assumed that the Eyring equation (1) was valid for this specific rotation.

$$k = \frac{1}{\tau} = \frac{\kappa kT}{h} \exp(-\Delta G^\ddagger/RT) \quad (1)$$

Eqn. (1) can be written in the expanded form (2):

$$\ln\left(\frac{1}{\tau}\right) = -\frac{\Delta H^\ddagger}{RT} + \frac{\Delta S^\ddagger}{R} + \ln\frac{\kappa kT}{h} \quad (2)$$

Now, if ΔS^\ddagger is taken to be zero, as found in most amides, and if $\Delta H^\ddagger + RT$ is taken to be a constant, it is seen from (2) that the complete τ versus temperature relation can be determined, if τ is known for one temperature.

τ at the temperature of coalescence, t_c , is approximately given by $\sqrt{2}/\pi \delta\nu$, where $\delta\nu$ is the frequency separation between the two sites at this temperature. Using approximate values of $\delta\nu$ and t_c , a $\log \tau$ versus $1/T$ diagram was constructed.

From two 60/100 MHz spectra pairs, one in the slow and one in the very fast exchange region, and from the approximate τ -temperature relation, preliminary T_2 -values were evaluated at these temperatures. For interpolation, an exponential dependence of T_2 versus $1/T$ seemed reasonable, and for illustration, the initial relation constructed in this way is given in Fig. 2.

The dotted lines were used when separate peaks were observed, to take into account the fact that the linewidth of the high field signal was greater than that of the low field signal.

Using the exponentially interpolated T_2 -values according to Fig. 2, and the initial τ versus temperature relation, the slow exchange spectra were compared more carefully with calculated spectra to obtain better values of $\delta\nu$ at these temperatures. The relation between temperature and $\delta\nu$ was assumed to be linear, and a least-squares treatment of these $\delta\nu$ values versus temperature was assumed to be valid. With these T_2 and $\delta\nu$ relations, spectra were again calculated with varying τ -values, until no significant deviation between observed and calculated spectra was seen. The τ -values for best agreement were plotted in a $\log(1/\tau)$ versus $1/T$ diagram (Fig. 3).

No significant deviation from linearity, nor any systematic difference between spectra pairs or between 100 and 60 MHz spectra was found. The trial T_2 and $\delta\nu$ functions could therefore be assumed to be essentially correct, and the iteration procedure was complete.

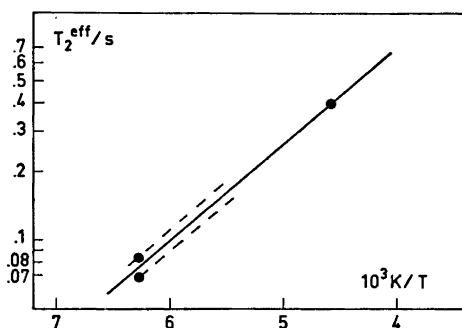


Fig. 2. The initially assumed dependence of T_2^{eff} with temperature.

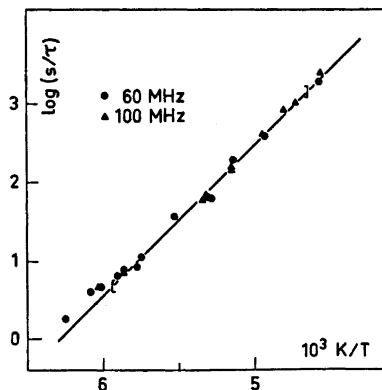


Fig. 3. Arrhenius plot of the kinetic data, obtained from the lineshape study of DMIPU. The solid line is a linear least-squares fit to the points within the brackets.

If any systematic deviations had been observed, the $\delta\nu$ and/or T_2 functions would have to be adjusted, and one or more calculations of τ -values would have to be performed, until the discrepancies disappeared.

The final $\delta\nu$ function was $\delta\nu_t = (0.1325 \pm 0.016)t + (28.7 \pm 1.6)$, where $\delta\nu_t$ is the 100 MHz shift difference in cps at $t^\circ\text{C}$. The final T_2 function was the same as that given in Fig. 2.

Using the data in Fig. 3, values of ΔG^\ddagger , ΔH^\ddagger , and ΔS^\ddagger were evaluated by means of eqn. (2). The Arrhenius activation energy, E_a , was obtained directly from the slope of the line in Fig. 4. The results are given in Table 1.

^a Table 1. Activation parameters with estimated standard deviations.^a

E_a	=	8.8 ± 0.2 kcal mol ⁻¹
ΔH^\ddagger	=	8.2 ± 0.2 kcal mol ⁻¹
ΔG_{298}^\ddagger	=	9.7 ± 0.1 kcal mol ⁻¹
ΔS^\ddagger	=	-4.4 ± 1.0 cal mol ⁻¹ K ⁻¹

^a As discussed in Ref. 9, small systematic errors in the experimental spectral parameters will cause serious errors in E_a , ΔH^\ddagger , and especially in ΔS^\ddagger values. Even under best possible conditions, one cannot determine ΔH^\ddagger and E_a better than within 2%. In the present (in spite of the interpolation checks), relatively ill-conditioned case, it cannot be realistic to believe that the error limits are smaller than 5% in E_a and ΔH^\ddagger , leading to a possible error of at least 50% in ΔS^\ddagger .

Dielectric measurements. Two series of measurements of the dielectric constant, ϵ_{12} , and the refractive index, n_{12} , of benzene solutions of DMIPU were made. No significant deviations were found between the two series, and they have been combined in the calculations.

The dipole moment was calculated, using the Guggenheim method,¹³⁻¹⁵ with formulas from Ref. 15. Calculations by this method make use of the extrapolated slope of the ϵ_{12} and n_{12}^2 versus weight fraction curves at zero concentration of the solute. These parameters, a_ϵ and a_n , are most conveniently evaluated by fitting the refractive index and dielectric data to a polynomial of second degree,¹¹ from which they are given as the coefficient of the first degree term.

This calculation was made by a computer, using the method of least squares, and the following values and standard deviations were found: $a_\epsilon = 12.89 \pm 0.13$ and $a_n = -0.18 \pm 0.07$. The combined result is $(a_\epsilon - a_n) = 13.07 \pm 0.15$, which leads to $\mu = 3.95 \pm 0.03$ Debye units. The limits incorporate only random errors.

Table 2. Measurements data. w_2 = weight fraction of the solute, $\epsilon_{12} = \epsilon$ of solution, n_{12} = refractive index of solution using polychromatic tungsten light. (After these measurements were completed, it came to our attention that light, containing short wavelengths, should be avoided for the determination of dipole moments. Therefore, n_{12} was re-measured for some w_2 -values, using sodium-D light, but the effect on the final result was found to be negligible.)

w_2	1st series		w_2	2nd series	
	ϵ_{12}	n_{12}		ϵ_{12}	n_{12}
0.00297	2.3109	1.4978	0.00032	2.2771	1.4979
0.00343	2.3174	1.4976	0.00087	2.2839	1.4981
0.00504	2.3413	1.4976	0.00236	2.3031	1.4980
0.01237	2.4571	1.4974	0.00669	2.3640	1.4978
0.02963	2.7915	1.4970	0.00942	2.4051	1.4975

Using the theory in Refs. 6 and 7, and the data in Table 2, the molar polarization of the solute, P_{2M} , was obtained as a function of concentration. P_{2M} was calculated from eqn. (3):

$$P_{2M} = \frac{1}{X_2} \left[\left(\frac{\epsilon_{12} - 1}{\epsilon_{12} + 2} \right) \left(\frac{X_1 M_1 + X_2 M_2}{\rho_2} \right) - \left(X_1 \frac{\epsilon_1 - 1}{\epsilon_1 + 2} \frac{M_1}{\rho_1} \right) \right] \quad (3)$$

In this equation, ϵ = measured dielectric constant, X = mol fraction, M = molecular weight, ρ = density, and the subscripts 12, 1, and 2 refer to the solution, solvent, and solute, respectively.

Combining all P_{2M} versus X_2 data, and assuming a linear dependence of these two parameters, a least-squares calculation resulted in $P_{2M} = (314 \pm 4) + (3.2 \pm 0.5) \times 10^3 X_2$ cm³ mol⁻¹. Clearly the molar polarization of the solute DMIPU increases with increasing concentration, but the effect is smaller than for simple amides.^{6,7}

DISCUSSION

The ΔG^\ddagger value obtained for hindered internal rotation around the (CH₃)₂N-CO amide bond in DMIPU (9.7 kcal mol⁻¹) is lower than the corresponding barrier in analogous substituted thiourea derivatives.³⁻⁵ A lowering of the amide barrier is also observed in going from thioamides^{16,17} to amides, and can partly be explained by assuming a larger contribution of polar resonance structures, such as $-(S^- -)C = \overset{+}{N} <$ in the latter.^{4,17,18} This explanation is equally valid for ureas.

The usual problem to decide which dimethylamino signal is which in the slow exchange spectra is of interest, in particular because of the different linewidths at low temperatures. As discussed below, the dielectric measurements indicate that DMIPU assumes the *trans*-conformation (IIIa) in solution. In a methylene chloride or CHFCl₂ solution of 1,1,3-trimethylurea, which is expected to have the same preferred conformation as DMIPU, the 3-methyl PMR at room temperature appears at a higher field than the dimethylamino signal.

For this reason, the high field dimethylamino signal in DMIPU is believed to arise from the methyl group *cis* to the oxygen atom. This assignment is in agreement with the carbonyl shielding model of Karabatsos *et al.*¹⁹ and the measurements of Paulsen and Todt.²⁰

In our search for suitable solvents for the measurements, it was noted that the shift difference of the dimethyl group signals was increased upon the addition of 3-fluorotoluene, most certainly due to the well-known aromatic solvent induced shifts. Even without correcting for this effect, the observed nonexchanging chemical shift is smaller than for trimethylthiourea.³ It has been shown that the carbonyl and thiocarbonyl shielding intensities, as well as their shielding zones, are different in amide systems,^{20,21} which explains the observed difference.

The dipole moment of the molecule was found to be 3.95 Debye units. From bond moment summation,²² a value of 3.3 is calculated for (IIIa), and 2.1 for (IIIb). In these calculations, the following values²² were used: C=O→ = 2.4, C-N→ = 0.4, H-N→ = 1.3, H-C→ = 0.4, H₃C→ = 0.4, and isopropyl→ = 0.4. The latter two values were assigned, using bond moment

summation of HC-moments. Summation of these bond moments results in a good prediction of the experimental dipole moment of 1,3-dimethylurea.²³

The concentration dependence of the molar polarization can be interpreted in terms of intermolecular association.⁶ (IIIb) is expected to associate to dimers (4a), and (IIIa) to larger aggregates or chains (4b). In the former case,

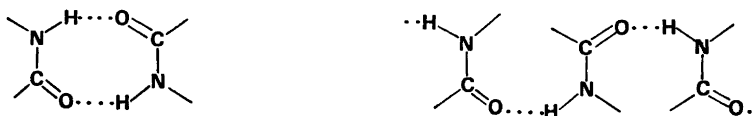


Fig. 4a-b. Associated forms of *cis*- and *trans*-amide systems, according to Refs. 6 and 7.

the increased association due to increased concentration lowers the molar polarization, because the net moment of the dimer is reduced due to partial cancellation of the monomer moments. In 4b, the net moment should stay unchanged, if the moment of the bonded monomer units were the same as for the free unit. Huisgen and Waltz⁶ suggested that the increase in P_{2M} , actually observed for *trans*-amides, is due to an increased participation of the polar form $-(O^-)C=N^+$, an argument which is also applicable to ureas. Another source of polarity is the hydrogen bond itself.

Experimentally it was found for DMIPU that P_{2M} increased with the solute concentration, which, together with the high value of the experimental dipole moment for DMIPU, implies that this molecule assumes the conformation (IIIa) in solution.

Possible changes in the contribution of polar forms are directly related to changes in the C-N double bond character of the ground state and to the barrier to internal rotation. In this case, such effects would increase the $(CH_3)_2CHNH-CO$ -barrier, and possibly also the $(CH_3)_2N-CO$ -barrier (Fig. 5). and the values from the NMR measurements could therefore be higher than the "true" monomer values, because P_{2M} was found to increase with increasing concentration.

Association of DMIPU is obviously occurring even at room temperature, and if large aggregates are formed, this will affect the correlation times, which in turn will affect the spin-lattice and spin-spin relaxation times. This is most

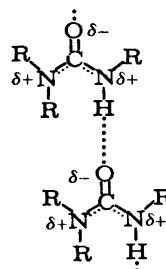


Fig. 5. Schematic picture of induced polar forms in associated trisubstituted urea systems.

likely the explanation for the strong increase in the PMR linewidths at low temperatures, where the association must become very strong due to the lowered T₁S term.

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