Restricted Carbon–Nitrogen Bond Rotation in Some Ureas, Thioureas, and Thiuronium Salts

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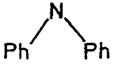
Some *NN*-diaryl-*N'N'*-dimethylureas, their thio-analogues, and their *S*-methylthiuronium salts exhibit a kinetic phenomenon, observable by n.m.r. spectroscopy, which has a free energy of activation, $\Delta G^{\ddagger}_{T_c}$, of between 40 and 70 kJ mol^{-1}. The origin of this process, probably slow rotation about the C–NMe$_2$ bond, is discussed in terms of the variation of $\Delta G^{\ddagger}_{T_c}$ with structure.

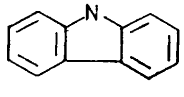
RECENTLY, the phenomenon of restricted rotation about the carbon–nitrogen bond in amides has been reviewed,[1] and the actual value of the barrier to rotation has been found to vary with steric and electronic effects associated with the amide substituents. Since the rotational barrier is commonly in the range 60—100 kJ mol^{-1} the process can be studied conveniently by variable temperature n.m.r. spectroscopy.

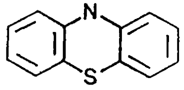
However, comparatively little work has been done on ureas, which, in general, appear to have very low barriers (<40 kJ mol^{-1}), and thus are not amenable to study by n.m.r. spectroscopy. The origin of this low rotational barrier is thought to arise from two complementary effects:[2] first, cross-conjugation, *i.e.* competition between the lone pairs on the nitrogen atoms for conjugation with the carbonyl group, and secondly, a steric inhibition of planarity in the N–CO–N group preventing maximum *p*–π overlap.

Barriers to rotation of the order of 65 kJ mol^{-1} have been observed for some di- and tri-substituted ureas,[3] where at least one of the substituents is a bulky group. The origin of this barrier is attributed to a biphenyl-like rather than an amide-like restriction. Also, Sutherland *et al.*[4] and others[5] have shown that carbamates can exhibit high (*ca.* 65 kJ mol^{-1}) rotational barriers.

We report here that the *NN*-diaryl-*N'N'*-dimethylureas (1a)—(3a) and (4) have rotational barriers which can be observed by n.m.r. spectroscopy. The magnitude and variation with structure of these barriers and those of the thiourea analogues (1b)—(3b) are consistent with the origin of the process being a restricted amide-like rotation. In addition we report


(1)

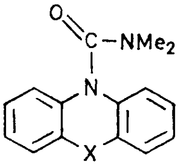

(2)


(3)

a; $R = O{=}\overset{|}{C}{-}NMe_2$

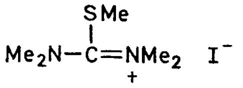
b; $R = S{=}\overset{|}{C}{-}NMe_2$

c; $R = MeS{-}\overset{|}{C}{=}\overset{+}{N}Me_2\ I^-$


(4)

a; $X = \overset{+}{S}{-}\overset{-}{O}$

b; $X = S\begin{smallmatrix}\diagup O\\ \diagdown O\end{smallmatrix}$


(5)

$$Me_2N{-}\overset{\overset{SMe}{|}}{C}{=}\underset{+}{N}Me_2\ I^-$$

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[1] W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, 1970, **70**, 517.

[2] W. E. Stewart and T. H. Siddall, III, *J. Org. Chem.*, 1967, **32**, 3261.

[3] W. E. Stewart and T. H. Siddall, III, *Chem. Comm.*, 1968, 617.

[4] B. J. Price, R. V. Smallman, and I. O. Sutherland, *Chem. Comm.*, 1966, 319.

[5] (*a*) T. M. Valega, *J. Org. Chem.*, 1966, **31**, 1150; (*b*) E. Lustig, W. R. Benson, and N. Duy, *ibid.*, 1967, **32**, 851.

that for the *S*-methylthiuronium iodides (1c)—(3c) and (5) a kinetic phenomenon is observed by n.m.r. spectroscopy. The origin of this may also be restricted amide-like rotation.

RESULTS AND DISCUSSION

The low temperature n.m.r. spectrum of each of the reported compounds shows an equal intensity doublet for the *N*-methyl resonance. These signals coalesce at higher temperatures to a sharp singlet. Tables 1 and 2 summarise the n.m.r. data for these compounds and show the free energy of activation, $\Delta G^{\ddagger}_{T_c}$, at the coalescence temperature, T_c, as calculated by the standard approximation.[6]

TABLE 1

Spectroscopic, kinetic, and thermodynamic parameters for the ureas

Compound	δ(NMe)		Δδ		T_c/K		k_{T_c}/s^{-1}		$\Delta G^{\ddagger}_{T_c}$/kJ mol^{-1}		
	CH_2Cl_2	CH_2Cl_2–CF_3CO_2H	CH_2Cl_2	CH_2Cl_2–CF_3CO_2H	CH_2Cl_2	CH_2Cl_2–CF_3CO_2H	CH_2Cl_2	CH_2Cl_2–CF_3CO_2H	CH_2Cl_2	CH_2Cl_2–CF_3CO_2H	$\nu_{C=O}$/cm^{-1}
(1a)	2·80	2·88	0·38	0·46	197	228	50·0	61·1	41	47	1654
(2a)	3·07	3·17	0·27	0·29	223	258	36·2	38·9	47	55	1680
(3a)	2·76	2·80	0·42	0·57	192	221	55·5	75·6	39	45	1667
(4a)	3·05	3·02	0·40	0·41	253	288	52·8	55·0	53	60	1693
(4b)	3·05	3·10	0·40	0·41	262	282	53·0	54·5	55	59	1697

Δδ = Chemical shift difference at the slow exchange limit. T_c = Coalescence temperature (±5°). k_{T_c} = Rate of exchange at T_c. $\Delta G^{\ddagger}_{T_c}$ = Free energy of activation at T_c (±2 kJ mol^{-1}). $\nu_{C=O}$ = Carbonyl stretching frequency.

TABLE 2

Spectroscopic, kinetic, and thermodynamic parameters for the thioureas and thiuronium salts

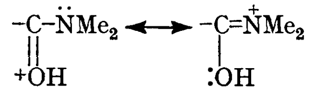
Compound	δ(NMe)	δ(SMe)	Δδ	T_c/K	k_{T_c}/s^{-1}	$\Delta G^{\ddagger}_{T_c}$/kJ mol^{-1}
(1b)	3·19		0·55	239	73·8	49
(2b)	3·36		0·60	308	80·0	64
(3b)	3·32		0·32 *	197	42·3	41
(5)	3·43	2·69	0·12 *	198	15·6	43
(1c)	3·40	2·40	0·73	306	97·6	63
(2c)	3·90 *	2·18	0·64	>313	86·6	>65
(3c)	3·78	2·78	0·75	259	100·0	53

* Approximate values. For key see Table 1.

Discounting the possibility of slow nitrogen inversion in the ureas and thioureas there are two intramolecular processes whose energetics might give rise to the observed phenomenon. First, slow amide-like rotation about the C–NMe$_2$ bond, and secondly, slow rotation about the C–NAr$_2$ bond arising either from steric interaction between the Ar$_2$N and the Me$_2$N groups, or, from amide-like partial double bond character in the Ar$_2$N–C bond. The second process alone, however, would not lead to magnetic non-equivalence for the *N*-methyl groups if rotation about the C–NMe$_2$ bond were still fast. Also, in the phenothiazine compounds (3a and b) and (4) any process such as slow inversion of the roof-like structure of the heterocyclic ring system,[7] or slow nitrogen or sulphoxide inversion could give rise only fortuitously to an equal doublet for the *N*-methyl resonance. Consequently, slow amide-like rotation about the C–NMe$_2$ bond seems the most reasonable explanation of the observations, and qualitatively at least, the variations in $\Delta G^{\ddagger}_{T_c}$ with structure support this tenet.

The Ureas.—The barrier to rotation about the C–NMe$_2$ bond in tetramethylurea has not been observed by n.m.r. spectroscopy, and, consequently, is thought to be very low, but in *NN*-dimethyl-*N'N'*-diphenylurea (1a) a barrier of 41 kJ mol^{-1} is observed (Table 1). This can arise because cross-conjugation between the two nitrogen lone pairs is reduced by overlap of the aromatic π-system with one of them. In the carbazole (2a) where the nitrogen lone pair is *part* of the aromatic system the barrier increases to 47 kJ mol^{-1}. The series of phenothiazines, (3a), (4a), and (4b), shows that the barrier is influenced by substituent effects. As the contribution of the nitrogen lone pair in the ring system to the urea group is decreased by the increased electron-withdrawing power of the sulphoxide and sulphone groups, so the barrier rises from 39 to 55 kJ mol^{-1}. The electron-withdrawing effect at nitrogen of oxidation at sulphur in phenothiazines is indicated by the downfield shift of *N*-methyl resonance by *ca.* 0·4 p.p.m. in 10-methylphenothiazine 5-oxide and 5,5-dioxide relative to the unoxidised heterocycle.

Protonation of amides is thought to occur predominantly on the oxygen atom.[1] As a result, the barrier to rotation about the C–N bond should increase as delocalisation of the positive charge can arise by greater participation of the nitrogen lone pair [process



$$-\underset{\overset{\|}{^{+}OH}}{C}-\ddot{N}Me_2 \longleftrightarrow -\underset{\overset{|}{:OH}}{C}=\overset{+}{N}Me_2 \qquad (1)$$

(1)]. In this work it is seen that addition of a molar excess of trifluoroacetic acid increases the barrier by 4—8 kJ mol^{-1} for all the ureas suggesting that protonation here also occurs on oxygen, and that the observed

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[6] (*a*) J. A. Pople, W. G. Schneider, and H. J. Bernstein, 'High Resolution Nuclear Magnetic Resonance,' McGraw-Hill, New York, 1959, ch. 10; (*b*) S. Glasstone, K. J. Laidler, and H. Eyring, 'The Theory of Rate Processes,' McGraw-Hill, New York, 1941, ch. 1.

[7] C. Bodea and I. Silberg, *Adv. Heterocyclic Chem.*, 1968, **9**, 321.

process is indeed slow rotation about the C–NMe$_2$ bond.* For the phenothiazine 5-oxide (4a) it is possible that protonation could take place on the sulphinyl group since sulphoxides and amides have similar basicities.[8] The u.v. spectrum of the n.m.r. solution, however, remained unchanged after the addition of acid, whereas the spectra of other phenothiazine 5-oxides change markedly upon protonation.[7]

The variation in carbonyl stretching frequency for these ureas also reflects the decrease in cross-conjugation. As the lone pair of the diaryl-substituted nitrogen becomes more a part of an aromatic system, either through direct incorporation *e.g.* in the carbazole (2a), or through substituent effects *e.g.* in (4), so $\nu_{C=O}$ increases. A similar situation is found with carbamates where the carbonyl stretching frequency (1740—1690 cm^{-1}) [9] is generally higher than that in amides, and ureas as a result of the inductive effect of the ester oxygen. Nevertheless, their rotational barriers can also be measured by n.m.r. spectroscopy.[4,5]

The Thioureas.—Thioamides commonly have a rotational barrier about the C–N bond 8—16 kJ mol^{-1} higher than their oxygen analogues,[1] probably because the relatively weak $p\pi$–$d\pi$ carbon–sulphur double bond has a large dipolar contribution. Similarly thioureas might be expected to exhibit increased barriers, and compounds (1b)—(3b), all show an increase over their oxygen equivalents. Siddall and Stewart found a value of 44 kJ mol^{-1} for $\Delta G^{\ddagger}_{T_c}$ in *NN*-dimethyl-*N'*-phenylthiourea [2] which is in close agreement with our values. The phenothiazine compound (3b) does not show such a great increase as the others, and the explanation of this at the present time is unclear.

The Thiuronium Salts.—Protonation of the thioureas generally leads to reaction, but methylation with methyl iodide gives crystalline salts whose n.m.r. spectra show a sharp *S*-methyl singlet at δ *ca.* 2·5. Compounds (1c)—(3c) and (5) are hygroscopic and removal of the last traces of recrystallisation solvent is difficult. Decomposition to methyl iodide and the thiourea also occurs upon warming. Nevertheless, these compounds, too, exhibit a doublet for the *N*-methyl signal at low temperatures. Assuming this process is also slow rotation about the C–NMe$_2$ bond, a barrier increase over the corresponding thioureas is expected and found. The exact barrier for the carbazole derivative (2c) could not be measured since the *N*-methyl doublet was observable at magnet temperature and thermal decomposition occurred in [^{2}H]chloroform, pyridine, and 1-chloronaphthalene before the coalescence temperature was attained. A lower limit of 65 kJ mol^{-1} is estimated.

Although no slowing down of amide-like rotation in tetramethylthiourea is observable, pentamethylthiuronium iodide (5) exhibits a barrier of 43 kJ mol^{-1}. If the increases in the barrier height observed on going from urea to thiourea to thiuronium salt in this case are comparable with those of the other compounds reported a very rough estimate of the amide-like rotational barrier in tetramethylurea is made at 20—30 kJ mol^{-1}.

EXPERIMENTAL

Spectra.—N.m.r. spectra were obtained for 10% w/v or saturated solutions in dichloromethane, except where otherwise stated, on a Varian A60-A spectrometer fitted with the standard variable temperature unit. Temperatures were measured using an external methanol sample and are considered accurate to ±5°. I.r. spectra were recorded using a Perkin-Elmer 621 instrument for 1% w/v solutions in chloroform, and u.v. spectra were recorded on a Unicam SP 800 spectrophotometer.

Syntheses.—The microanalyses and m.p.s of new compounds are given in Table 3.

TABLE 3

Microanalytical and m.p. (b.p.) data

	Found (%)			Required (%)			
Compound	C	H	N	C	H	N	M.p. (b.p.) (°C)
(2a)	75·8	6·1	11·7	75·5	5·9	11·7	64·5—65·5 (196–198 at 0·6 mmHg)
(4a)	62·8	5·05	9·75	62·8	4·9	9·8	156—159
(4b)	59·4	4·8	9·3	59·5	4·6	9·3	208—211
(2b)	70·6	5·5	10·8	70·9	5·5	11·0	102
(3b) *	62·2	5·2	9·1	62·1	5·5	9·1	122—124
(1c)	48·2	4·8	7·0	48·2	4·8	7·05	128—129
(3c)	45·0	4·1	6·7	44·9	4·0	6·55	124—125

* For $C_{15}H_{14}N_2S_2,0{\cdot}5C_2H_5OH$ (confirmed by n.m.r. spectroscopy).

NN-*Dimethyl*-N'N'-*diphenylurea* (1a). Treatment of diphenylcarbamoyl chloride in dry benzene with an excess of anhydrous dimethylamine gave *NN*-dimethyl-*N'N'*-diphenylurea in quantitative yield, m.p. 72—75° (from ethanol) (lit.,[10] 70°).

NN-*Dimethylcarbazole*-9-*carboxamide* (2a). Sodium hydride (50% mineral oil suspension; 1 g) was added cautiously to a stirred solution of carbazole (3·3 g) in dimethylformamide (25 ml). After evolution of hydrogen had ceased (2 h) dimethylcarbamoyl chloride was added to the brown solution and the mixture was stirred overnight. Precipitated sodium chloride was removed by filtration and the filtrate was added to water (150 ml). The resultant turbid mixture was extracted with ether (3 × 30 ml) and the combined extracts were washed with water (100 ml), dried ($MgSO_4$), and evaporated to give a viscous oil which was purified by column chromatography (alumina–chloroform) and subsequent distillation to yield *amide* (2a) (25%).

NN-*Dimethylphenothiazine*-10-*carboxamide* (3a). Phenothiazine-10-carbonyl chloride (50 g) was dissolved in benzene (1 l) and anhydrous dimethylamine was passed in until no further heat was evolved. The solution was stirred

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* A referee suggests that complete proton transfer does not necessarily take place since the changes in the NMe chemical shift between the neutral and acidified solutions are small. There is some evidence (W. E. Stewart, L. Mandelbern, and R. E. Glick, *Biochemistry*, 1967, **61**, 150) that for $CDCl_3$–CF_3CO_2H solutions of amides a molar excess of acid over amide gives rise to complete protonation of the amide on oxygen. We might expect an analogous situation with ureas. In any event, hydrogen bonding could also give rise to the same effect on the rotational barrier about the C–NMe$_2$ bond.

[8] (*a*) D. Landini, G. Modena, G. Scorrano, and F. Taddei, *J. Amer. Chem. Soc.*, 1969, **91**, 6703; (*b*) G. Gatti, A. Levi, V. Lucchini, G. Modena, and G. Scorrano, *Chem. Comm.*, 1973, 92.

[9] D. H. Williams and I. Fleming, 'Spectroscopic Methods in Organic Chemistry,' McGraw-Hill, New York, 1966, ch. 3.

[10] J. Voss, *Annalen*, 1971, **746**, 92.

overnight, washed with 2M-hydrochloric acid and with water, dried ($MgSO_4$) and, after carbon treatment, reduced in volume to *ca.* 50 ml. The crude product was precipitated with light petroleum and recrystallised from benzene to yield the amide (3a) (61%), m.p. 94—96° (lit.,[11] 94—96°) (Found: C, 66·9; H, 5·3; N, 10·4. Calc. for $C_{15}H_{14}N_2OS$: C, 66·6; H, 5·2; N, 10·4%).

NN-*Dimethylphenothiazine*-10-*carboxamide* 5-*oxide* (4a). The amide (3a) (8·5 g) was refluxed for 8 h in ethanol (50 ml) with 33% hydrogen peroxide (11 ml). After removal of the solvent the product was recrystallised from ethanol to yield the 5-*oxide* (4a) (84%).

NN-*Dimethylphenothiazine*-10-*carboxamide* 5,5-*dioxide* (4b). The amide (3a) (8·5 g) was refluxed for 2 h with 33% hydrogen peroxide (20 ml) in acetic acid (50 ml) and allowed to stand overnight. The precipitate was filtered off and recrystallised from ethanol to give the 5,5-*dioxide* (4b) (81%).

NN-*Dimethylphenothiazine*-10-*thiocarboxamide* (3b). Phenothiazine (5 g), *NN*-dimethylthiocarbamoyl chloride [12] (8 g), sodium carbonate (4 g), and copper bronze (0·4 g) were refluxed for 6 h in benzene (150 ml), the apparatus being fitted with a Dean and Stark water-trap. After removal of benzene the viscous oily residue was extracted with ether (500 ml) and the extract dried ($MgSO_4$). Evaporation of the ether gave the *amide* (3b) (28%) which was recrystallised from ethanol.

NN-*Dimethyl*-N′N′-*diphenylthiourea* (1b) and NN-*dimethylcarbazole*-9-*thiocarboxamide* (2b) were prepared in the same manner in yields of 20 and 10%, respectively.

Thiuronium iodides (1c)—(3c) *and* (5). To a solution of the corresponding thiourea (1 g) in dry benzene (2 ml) was added an excess of methyl iodide. The products were isolated by filtration after 0·5 h and were washed with and recrystallised from dry acetone. The salts were hygroscopic and were stored under their solvent of recrystallisation.

Tetramethylthiourea. This, obtained by treatment of *NN*-dimethylthiocarbamoyl chloride [12] with dimethylamine, had m.p. 75—78° (lit.,[13] 78°). The pentamethylthiuronium iodide (5) had m.p. 178—179° (lit.,[13] 180—185°).

We were unable to obtain the thiuronium salt (2c) analytically pure either as the iodide or as the tetrafluoroborate obtained by the action of trimethyloxonium tetrafluoroborate [14] in nitromethane on the precursor (2b).

[3/1317 *Received, 22nd June*, 1973]

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[11] B.P. 781,526 (*Chem. Abs.*, 1958, **52**, 8211d).

[12] R. H. Goshorn, W. W. Levis, jun., E. Jaul, and E. J. Ritter, *Org. Synth.*, Coll. Vol. IV, p. 307.

[13] H. Lecher and C. Heuck, *Annalen*, 1924, **438**, 179 (*Chem. Abs.*, 1924, **18**, 3359).

[14] T. J. Curphey, *Org. Synth.*, 1971, **51**, 142.