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Hindered Internal Rotation of N,N-Dimethylpropylamines[1]

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The N-methyls in 2,3-disubstituted N,N-dimethylpropylamines (I—VIII) have given two peaks with an equal intensity in an acid solution owing to the hindered internal rotation about the C-NMe_2H^+ bond. The energy barriers between two staggered forms have been estimated to be 0.7 (benzylthio)—7(thiocyanato) kcal mole^{-1} from the temperature dependence of the peak separations. The high-field shift and the largest separation of the N-methyls in the benzylthio derivative (I) have been ascribed to an anisotropic effect of the benzene ring. 1,3-Disubstituted 2-N,N-dimethylaminopropanes (IX) and 2-substituted N,N-dimethylethylamines (XII—XV) have shown a single peak for the N-methyls. A restricted rotation about the CH_2-CH bond in 2,N,N-trimethylaminoethyl disulfide (X) has been studied by the temperature dependence of the vicinal coupling constants.

A number of derivatives of N,N-dimethylaminopropane have been prepared[3] to develop an insecticide, 1,3-bis(carbamoylthio)-2-N,N-dimethylaminopropane, in relation to nereistoxin isolated from a marine annelid. Nuclear magnetic resonance (NMR) has been used to determine their structures and to analyze the isomers, 2-aminopropanes and propylamines. It has been noted[3b] that the N-methyls in 2,3-disubstituted N,N-dimethylpropylamines are non-equivalent in acid media. The present paper deals with the further study on the non-equivalence due to the hindered internal rotation about the C-NMe_2H^+ bond.

Many papers on dynamic NMR[4] have accumulated to discuss the restricted motions. For example, the hindered internal rotations about C-N bonds in amides, nitrosoamines, *etc.* have been interpreted by the partially double-bond character. The restricted motions of trialkylamines have been assumed to be the inversion of pyramidal conformations. It has been generally considered[4] that a non-equivalence in NMR depends upon an intrinsic asymmetry, a gradient electromagnetic field, and the restricted intramolecular motion on the NMR time scale.

The non-equivalence of the N-methyls examined in this paper has been interpreted to be due to the steric hindrance of the bulky groups and the asymmetrically staggered conformations about the C-N bonds. The equivalence of the N-methyls in 1,3-disubstituted 2-N,N-dimethylaminopropanes has been ascribed to the symmetrically staggered conformations in spite of the steric hindrance.

Experimental

Samples——All samples (I—XV) were synthesized by Numata, *et al.*[3] Solvents such as deuterium oxide (D_2O), deuterosulfuric acid (D_2SO_4), deuterochloroform ($CDCl_3$), trifluoroacetic acid (CF_3CO_2H), carbon

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[1] This paper was presented at the 9th NMR Symposium in Japan, at Kanazawa, in October, 1970.

[2] Location: *Juso, Higashiyodogawa-ku, Osaka.*

[3] *a*) H. Hagiwara, M. Numata, K. Konishi, and Y. Oka, *Chem. Pharm. Bull.* (Tokyo), **13**, 253 (1965); *b*) M. Numata and H. Hagiwara, *ibid.*, **16**, 311 (1968); *c*) K. Konishi, *Agr. Biol. Chem.*, **32**, 678, 1199 (1968); *d*) H. Hirano, M. Sakai, and M. Numata, *Takeda Kenkyusho Nempo*, **28**, 272 (1969).

[4] *a*) G. Binsch, "Topics in Stereochemistry," Vol. 3, ed. by E.L. Eliel and N.L. Allinger, Interscience Publishers, Inc., New York, N.Y., 1968, pp. 127—191; *b*) T.H. Siddall III and W.E. Stewart, "Progress in NMR Spectroscopy," Vol. 5, ed. by J.W. Emsley, J. Feeney, and L.H. Sutcliffe, Pregamon Press, Oxford, 1969, pp. 33—147; *c*) W.E. Stewart and T.H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970).

tetrachloride (CCl_4) and deuterodimethylsulfoxide (d_6-DMSO) were supplied from Wako Pure Chemical Industries, Ltd.

Measurement of NMR——Varian's A-60, A-60 A and HA-100 (for double resonance) NMR spectrometers were used. Temperature in the probe was measured by chemical shifts of methanol or ethylene glycol. Internal standards to measure chemical shifts were tetramethylsilane (TMS) in CCl_4, $CDCl_3$ and CF_3CO_2D, and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) in D_2O and D_2SO_4.

Assignment by Nuclear Overhauser Effect——The N-methyl peak in the higher field (τ 7.22) for 2,N,N-trimethylaminoethyl disulfide (X) in 1N D_2SO_4 was enhanced by +1.2% on irradiating the C-methyl at τ 8.56, and *vice versa* by +2%. The methine peaks at τ 6.26 was enhanced also by +9.7% on irradiating the vicinal C-methyl. No enhancement of the N-methyl in the lower field and the S-methylene was observed on irradiating the C-methyl. Since these enhancements were small but significant on the 0.95 level, the peak at τ 7.22 was assigned to the N-methyl in the *gaushe* position of the C-methyl.

Rate of Exchange of Ammonium Proton for Deuterium——The N-methyls of N,N-dimethylpropylammonium salts in D_2SO_4 or CF_3CO_2D exhibited initially doublets due to a coupling with the NH^+ proton, which exchanged slowly for deuterium to decouple the doublets. The rate of the exchange determined by intergration of the N-methyl peaks was in first order about the residual NH^+. The rate constants (k) in CF_3CO_2D were given in Table I.

Measurement of Dissociation Constant (pK_a)——The pK_a values of the amines were measured by potentiometric titration on a Radiometer's Titrigraph. Thus, 10 ml of 4 mM aqueous solution of a salt was titrated with 0.1N NaOH at 25°.

2,3-Bis(carbamoylthio)-N,N-dimethylpropylamine (IV) hydrochloride was titrated rapidly at 2° to prevent a decomposition of the carbamoylthio group into the thiol. The first-order rate constants of the decomposition measured by a pH-stat or by a polarograph depended on concentrations of hydroxyl ion.

Result

NMR Parameters of 2,3-Disubstituted N,N-Dimethylpropylamines (I-VIII)

The N-methyls of the free bases (I-VIII) gave a singlet peak in an alkaline solution or in carbon tetrachloride (CCl_4) at 29—50°. The N-methyls of the deuteroammonium salts (I—V and VIII) showed two peaks with an equal height in deuterotrifluoroacetic acid (CF_3CO_2D) or deuterosulfuric acid (D_2SO_4-D_2O). The peak separation (δ) increased to reach a limiting value (δ_0) in a lower temperature (Fig. 1). The chemical shifts (τ or τ') and the δ_0 values of I—VIII are shown in Tables I and II. The multiplets for the propyl moieties were mostly too complicate to analyze apart from 2,3-dichloro-N,N-dimethylpropylamine (III), which could be analyzed as shown in Table I. The multiplets for the HN^+CH_2 were assigned by the variation due to the deuterium exchange of the NH^+. The benzyl methylenes in 2,3-bis(benzylthio)-N,N-dimethylpropylamine (I) gave two peaks and the phenyls showed a converged peak. The phenyls in 3-N,N-dimethylamino-1,2-propanedithiol dibenzoate (II) showed a multiplet.

Average chemical shifts of the N-methyls and the N-methylenes in I—VIII were affected by protonation of the amines. For example, the N-methyls in I shifted from τ 7.90 to τ 7.43

Table I. NMR Parameters of 2,3-Disubstituted N,N-Dimethylpropylamines in Deuterotrifluoroacetic Acid

No.	R_2, R_3	R_2	τ NMe	 1-CH_2	 2-CH	 3-CH_2	 R	δ_0	E_a	log k_0	k	pK_a
I	$SCH_2C_6H_5$	H	7.46	7	6.7	7	6.16 6.20 2.62	42.5	0.7	3.2	2	7.3
II	$SCOC_6H_5$	H	6.75	6.3	6.1	6.3	1.9—2.5	5.5	1	1.8	4	6.5
III	Cl	H	6.82	6.57$^{a)}$ 6.16$^{a)}$	5.44$^{a)}$	6.22$^{a)}$ 6.06$^{a)}$		5.0	1	1.5	1	7.5
IV	$SCONH_2$	H	6.8	6.3	5.8	6.5		2.5	4	2.9	2	7.8
V	SCN	H	6.72	6.1	5.9	6.4		4.1	7	5.5	10	6.1
VIII	SCN	Me	6.63	6.03		6.24	8.06	3.4				

a) J_{AB} 14, J_{AE} 10, J_{BE} 3.5, J_{CD} 12, J_{CE} 7, J_{DE} 4.5 (Hz) for $NCH_AH_BCClH_ECClH_CH_D$, δ_0: spacing of N-methyl peaks at the lowest temperature, Hz at 60MHz, E_a: energy barrier of the rotation of MeN_2-C bond, kcal mole^{-1}, log k_0: intercept of the Arrhenius plot, sec^{-1}, k: rate constant for deuterium exchnage of the NH^+, $\times 10^{-4}$ sec^{-1}, pK_a: dissociation constant of the NH^+

Table II. NMR Parameters of 2,3-Disubstituted N,N-Dimethylpropylamines in 80% Deuterosulfuric Acid

No.	R_2, R_3	R_2	τ'						δ_0
			NMe	1-CH_2	2-CH	3-CH_2	R		
I	$SCH_2C_6H_5$	H	7.86	7	7	7	6.4	2.7	29
II[a]	$SCOC_6H_5$	H	6.95	6.5	6.3	6.5		1.9—2.5	5
III	Cl	H	7.01	6.5	5.6	6.2			5
IV	$SCONH_2$	H	7.00	6.5	6.0	6.5			2
V[a,b]	SCN	H	6.96	6.2	6.0	6.4			0
VI	Cl	Me	6.95	6.44[c]		6.2	8.28		0
VII	$SCONH_2$	Me	7.01	6.0		6.2	8.06		0
VIII[a]	SCN	Me	6.83	6.36		6.36	8.24		2

a) unstable b) in 1N D_2SO_4 c) $\delta_{AB}=9.5$Hz, $J_{AB}=14$Hz

in addition of 1 eq CF_3CO_2H to the CCl_4 solution. On adding 2—3 eq CF_3CO_2H to the CCl_4 solution of I, the sharp singlet broadened and then separated into a doublet (δ 21 Hz at 35°), which collapsed again at 67°. On the CCl_4 solution being saturated with CF_3CO_2H, the N-methyls gave double doublets with $J=5$ Hz and $\delta=39$ Hz at $-40°$, which were also decoupled at about 0° by rapid exchange of the NH^+. The coalescence temperature of the N-methyl peaks depends upon the acidity of the solution: 40° at pH 4 in D_2O or in a mixture of CF_3CO_2H: d_6-DMSO (1: 2) and above 100° in 4.6 N D_2SO_4.

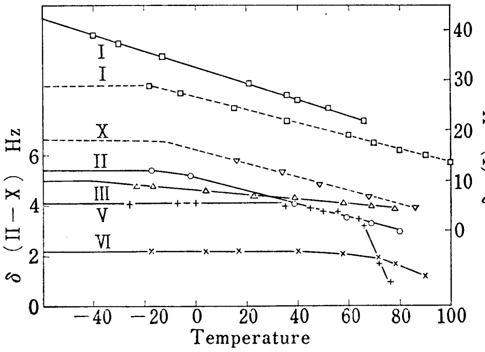


Fig. 1. Temprature Dependence of Spacing of the N-Methyl Peaks (δ) at 60 MHz NMR in CF_3CO_2D (——) or $D_2SO_4-D_2O$(------)

NMR Parameters of 2-Substituted N,N-Dimethylethylamines (X—XV)

The N-methyls in 2,N,N-trimethylaminoethyl disulfide (X) and 2-benzylthio-1,N,N-trimethylethylamine (XI) gave also two peaks in acid D_2O but a single peak in $CDCl_3$. The separation (δ) of N-methyls of X in 1N D_2SO_4 decreased from 5.0 Hz at 35° to 3.9 Hz at 80°. The doublet of the oxalate (XI) with δ 4.9 at 30° in D_2O collapsed to a broad singlet at 50° and changed to a sharp peak at 80°.

The deutero salts of 2-chloro-(XII), 2-thiocyanato-(XIII), 2-disulfide (XIV) and 2-benzylthio-(XV) derivatives of N,N-dime-

Table III. NMR Parameters of 2-Substituted 1-N,N-Dimethylethylamines

No.	2-R	1-R	Solv.	τ'					
				NMe	NCH_2	RCH_2	R		
X[a]	$S)_2$	Me	a	7.18d	6.30m	6.96m	8.60d		
XI[b]	$SCH_2C_6H_5$	Me	a	7.35d	6.78s	7.28d	8.76d	6.21	2.63
XII	Cl	H	a	7.08	6.48	6.1			
			b	7.08	6.58	6.18			
XIII	SCN	H	a	7.08	6.42	6.59			
			b	7.06	6.52	6.70			
XIV	$S)_2$	H	a	7.09	6.42	6.94			
			b	7.12	6.62	7.03			
XV	$SCOC_6H_5$	H	a	7.06	6.66	6.66			
			b	7.07	6.66	6.66			

a: the salts in D_2O b: in 80% D_2SO_4, $J_{NHMe}=5$Hz

a) $J_{MeCH}=6.5$, $J_{AB}=14$, $J_{BC}=7.5$, $J_{AC}=6$, $\delta_0=6.6$Hz, $E_a=1.2$ kcal mole^{-1}, log $k_0=1.8$

b) $J_{MeCH}=J_{CH_2CH}=6.5$, $\delta_{Me}=5$Hz at 30°

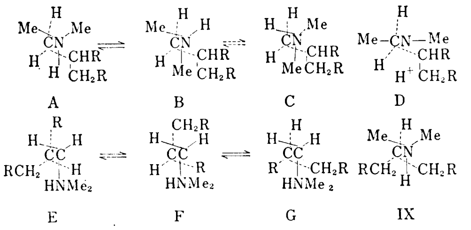
thylethylamine gave a single peak at τ' 7.1 for the N-methyls and A_2B_2-type multiplets for the vicinal methylenes in 0—60% D_2SO_4 at 30—80°. The broader parts of the multiplets at about τ' 6.4—6.7 were assigned to the N-methylenes and the other parts at τ' 6.1 (XII), 6.6 (XIII), 6.7 (XV) and 7.0 (XIV) were due to the 2-methylenes (Table III).

Discussion

Hindrance of Internal Rotation about the C-N Bond

Deutero salts of 2,3-disubstituted N,N-dimethylpropylamines (I—V) and 1-substituted 2,N,N-trimethylethylamines (X, XI) gave two peaks due to the N-methyls in acid media. Coupling of the N-methyls with NH^+ in the protonated amines result in two pairs of doublets. Internal chemical shifts (δ) of the N-methyls decreased in higher temperature (Fig. 1) until a sharp peak remained. These phenomena suggest the hindered internal rotation about the $C\text{-}NMe_2H^+$ bonds. Similar phenomena in N-alkylamides[4)] and N-alkylamino heterocyclic compounds[5)] have been interpreted by the partially double bond character of the $C\text{-}NR_2$ bonds. This character is unlikely in the aliphatic amines examined in this paper. Reasons of the hindrance are assumed to be steric effects of the bulky substituents and the electronic interaction.

It is generally considered[4a)] that amines are pyramidal and ammonium ions are tetrahedral. The amines in the case take the tetrahedral ammonium forms in acid solutions examined. Three staggered rotamers can be drawn in Chart 1, seeing through the $N\text{–}C_{(1)}$ bonds.



R: $SCH_2C_6H_5$(I), $SCOC_6H_5$(II), Cl(III), $SCONH_2$(IV), SCN(V)

Chart 1

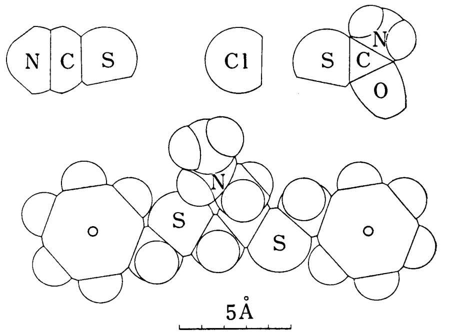


Chart 2

The steric hindrance of the form C will be larger than those of A and B, which are almost same. The methyls of A or B in *trans* and *gaushe* positions against the $C_{(2)}\text{–}C_{(3)}$ group are differently affected by the substituents to show two peaks with different chemical shifts and an equal intensity.

According to a stereo model with Van der Waal's radii, the rotations about the $C\text{-}NMe_2H^+$ bonds in I—V seem to be sterically hindered even in the most extended forms as shown in Chart 2. Most of the other bonds are also restricted, whereas the end groups such as Me-N and $C_6H_5\text{-}CH_2$ are fairly free in the relaxed forms. The high-field shift of the N-methyls in I as well as the largest separation (δ) will be due to the anisotropic effect of the benzene rings faced with the N-methyls and also due to the hindrance by the NH···S hydrogen bond with a 6-membered ring.

The rotational hindrance of the benzoylthio group in II is larger than that of the benzylthio group in I because of the bulkiness, a weak hydrogen bond of NH···OC, and the coplanarity due to conjugation of the benzylthio group. The direction of the group will be restricted

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5) G. Fraenkel and Y. Asahi, *Takeda Kenkyusho Nempo*, **24**, 209 (1965).

near a plane. The rather small spacing (δ) and the regular chemical shift of the N-methyls in II suggest the occupation in node of the anisotropic effect of the benzene rings.

The steric effects of chlorine in III and thiocyanato group in V will be smaller than those of substituents in I and II. In spite of larger steric effect of carbamoylthio group in IV than the thiocyanato, hydrogen bond of the CO···HN with a 7-membered ring may decrease the difference of environment at the N-methyls.

In 2-substituted 1,N,N-trimethylethylamines (X, XI), the rotations about the Me_2NH-CHMeR bonds are also restricted by the steric hindrance of the C-methyl and the N-methyls. The anisotropic effect of the benzylthio group in XI results in a higher field shift of the N-methyls by 0.4 ppm, about a half of 1 ppm in the bis-substituted homologue (I).

Another process for the exchange of the N-methyls is an inversion of the trialkyl ammonium *via* a trigonal intermediate of the free base (Chart 1, D). Dissociation constants of I—V were pK_a about 6—8, so that population of the free bases must be negligible in the extreme acid solutions. The rate constants (k) for deuterium exchange of the NH in I—V were as small as 10^{-4}—10^{-3} sec^{-1} at 35° in deuterotrifluoroacetic acid. The inversion process with the proton exchange can be ruled out by these facts.

It is also unlikely that the optical isomers in the racemic mixtures (I—VIII) give the different chemical shift of the N-methyls in the optically inactive solvents. Diastereoisomeric associations (*dd*, *ll*, and *dl*) of the solutes with the different shifts can be ruled out since the spacings (δ) are independent of the concentrations.

Kinetics of Internal Rotation of the N-C Bonds

In the mean lifetimes (t_A and t_B) of the rotamers A and B being equal and comparable to the reciprocal of the separation (δ) between the N-methyl peaks and transverse relaxation time being large, the mean lifetime, $t=t_At_B/(t_A+t_B)$, can be calculated by Eq. 1.[6]

$$t^{-1} = \sqrt{2}\,\pi\sqrt{\delta_0{}^2-\delta^2} \qquad \text{Eq. 1}$$

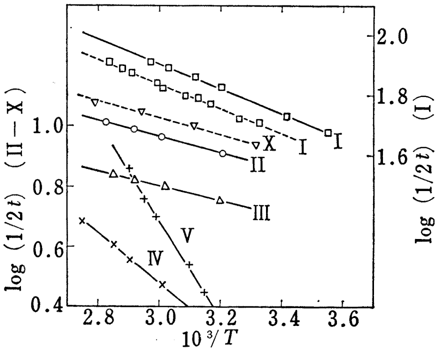

Fig. 2. Arrhenius Plots of the Rates ($1/2t$) of Exchanges between the Rotamers A and B (same symbols as Fig. 1)

A peak separation (δ_0) under a condition of slow exchange was estimated from the value converged at low temperature, or assumed so as to obtain a linear Arrhenius plot, log ($1/2t$) *vs.* $1/T$ (Fig. 2). The energy barriers (E_a) between the rotamers A and B estimated from the slopes of the linear plots were small as shown in Table I. No correlation was observed between the energy (E_a) and the shift (δ_0) probably because the energy (E_a) depends on the steric hindrance of the internal ratotion whereas the shift (δ_0) is related with the anisotropic shielding effect of the substituent. Namely, the carbamoylthio and thiocyanato groups have large steric hindrance to give the large energy (E_a), whereas the large and flexible benzylthio group with a smaller steric hindrance gives the small energy (E_a) although the large anisotropic effect results in the large shift (δ_0).

Equivalence in Symmetrical Isomers

The symmetrical isomers, 1,3-disubstituted 2-N,N-dimethylaminopropanes (IX), gave a single peak for the N-methyls. Therefore, the environments at the methyls will be equal in the most preferable conformation with symmetry even if the internal rotations would be still restricted.

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[6] H.S. Gutowsky and C.H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956).

2-Substituted N,N-dimethylethylamines (XII—XV) showed again a single peak for the N-methyls. In a sterically preferable *trans*-conformation, rotation about the $C_{(1)}$–$C_{(2)}$ bond seems to be unrestricted in the condition examined.

Restriction of Internal Rotation about the C-C Bonds

Among three staggered rotamers E–G about the $C_{(1)}$–$C_{(2)}$ bonds in I—V, the rotamer E with the Me_2NH at a *gaushe* position of the 3-CH_2R will be the most preferable conformation whereas the rotamer G with the crowded substituents must be less stable than the other rotamers E and F. The rotations about the $C_{(1)}$–N bonds being assumed to be free, the N-methyls should give three peaks with different intensities corresponding to the populations of the rotamers E–G. This prediction did not agree with the fact that the N-methyls in I—V gave two peaks with an equal intensity.

The 100 MHz NMR spectrum of 0.3 M X in 1 N D_2SO_4 was analyzed on irradiating the C-methyl at —3°—86°. The two vicinal coupling constants diverged with increasing temperature, from 6.1 to 5.4 and from 7.1 to 7.9 Hz, whereas the geminal coupling constants remained constant 14.5 Hz. The populations of three staggered rotamers about the CH_2–CH bond can be evaluated from the observed vicinal coupling and the proposed values, $J_g=2.60$ and $J_t=13.56$.⁷⁾ The differences of enthalpy (ΔH) and entropy (ΔS) among the ratomers were estimated from the temperature dependence of the equilibrium constants (K) according to the Equation: $R \ln K=-\Delta H/T+\Delta S$. The enthalpy of the rotamer E was lower than those of the rotamers F and G by 1.1 and 0.5 kcal $mole^{-1}$, respectively, to indicate the stability. The entropy of the rotamer E was again lower than those of F and G by 4.3 and 3.1 cal $mole^{-1}$ deg^{-1}, respectively, to suggest the unstability.

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7) K.G.R. Pachler, *Spectrochim. Acta*, **20**, 581 (1964).