

**Conformational Studies of Quaternary Ammonium Ions. Part III.¹
Conformational Analyses of Substituted Piperidinium Ions by ¹H Nuclear
Magnetic Resonance Spectroscopy and Evaluation of the Contribution
of Electrostatic Interaction Energy in Controlling Conformation**

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Conformations of piperidinium and *NN*-dimethylpiperidinium ions having a hydroxy- or acetoxy-group at C-4 or C-3, and of the corresponding free amines in solution have been studied by ¹H n.m.r. spectroscopy. The population of the form with an axial hydroxy- or acetoxy-group of these ammonium ions is larger than that of the corresponding form in the free amines, without exception. The effect of 1,3-diaxial interaction energy and electrostatic interaction energy is discussed and an approximate value for the contribution of the latter in the conformation control of some ammonium ions is estimated.

In previous reports^{1,2} we suggested the importance of two main factors in controlling the conformational behaviour of β -substituted ethyltrimethylammonium ions: van der Waals and electrostatic interactions among the pairs of nonbonded atoms in the molecule. Turning

our attention to cyclic systems, the conformational behaviour of cyclohexanes or piperidines is generally regarded as being controlled mainly by 1,3-diaxial interactions.³ The similarity of the chair form of a cyclohexane ring to that of piperidine and piperidinium

¹ Part II, Y. Terui, preceding paper.

² Y. Terui, M. Ueyama, S. Satoh, and K. Tori, *Tetrahedron*, 1974, **30**, 1465.

³ E. L. Eliel, N. Y. Allinger, and A. Morrison, 'Conformational Analysis,' Interscience, New York, 1965.

ion rings is suggested by the results of X-ray analyses⁴ and the fact that the values of the vicinal coupling constants, J_{aa} , J_{ae} , J_{ea} , and J_{ee} , where a and e represent axial and equatorial, are almost equal in each ring system⁵⁻⁹ (see Figures 1 and 2). Thus, similar conformational free energy differences, ΔG^0 , and/or free

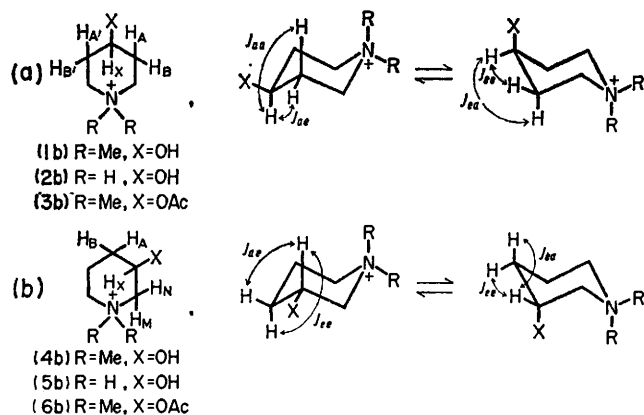


FIGURE 1 Structures and conformation equilibria of (1b)–(6b)

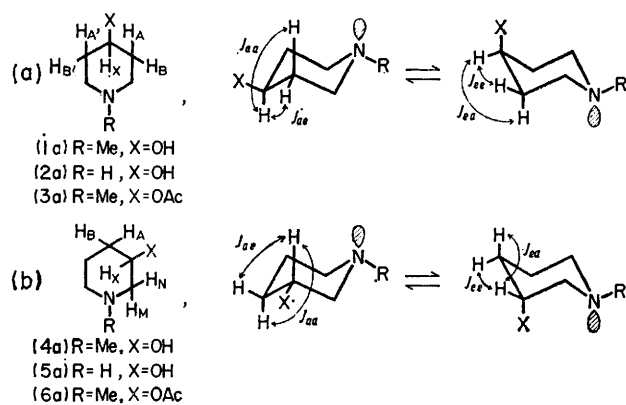


FIGURE 2 Structures and conformation equilibria of (1a)–(6a)

enthalpy differences, ΔH^0 , are anticipated for these molecules when they have the same substituents if 1,3-diaxial interactions are the main factor controlling conformational behaviour.

However, it is expected that the thermodynamic parameters obtained for piperidinium ions possessing a polar but not so bulky substituent differ considerably from those of the corresponding free amines or cyclo-

* The values of ΔG^0 reported for substituted piperidines are very similar to those reported for the corresponding substituted cyclohexanes (see refs. 5–7 and 9). This demonstrates the small contribution of the electrostatic interaction effect in substituted piperidines.

⁴ (a) L. E. Sutton, 'Interatomic Distances,' Chem. Soc. Special Publ., No. 11, 1958, and No. 18, 1965; (b) C. Rérat, *Acta Cryst.*, 1960, **13**, 72; (c) H. S. Yanai and W. N. Lipscomb, *Tetrahedron*, 1959, **6**, 103; (d) W. Fedeli, F. Mazza, and A. Vaciago, *J. Chem. Soc. (B)*, 1970, 1218; (e) M. D. Draper, F. J. Petrachek, M. W. Klohs, R. G. Parker, and J. D. Roberts, *Tetrahedron Letters*, 1970, 4481; (f) F. R. Ahmed, W. H. Barnes, L. D. M. Masironi, *Acta Cryst.*, 1963, **16**, 237; (g) G. Kartha, F. R. Ahmed, and W. H. Barnes, *ibid.*, 1960, **13**, 525.

hexane derivatives, if electrostatic interactions are another important factor in conformation control of the ammonium ions. In addition, we can estimate an approximate value for the contribution of the electrostatic interaction energy by comparison of the observed ΔH^0 and/or ΔG^0 values with those predicted only by considering the 1,3-diaxial interaction energy, because the contribution of electrostatic interaction energy to conformation control in cyclohexanes having one polar and/or one or more nonpolar groups,³ and their piperidine analogues* are considered to be very small except for piperidines with a polar group at C-2, in which the influence of an anomeric effect can be expected. A hydroxy- or acetoxy-group close to the ammonium cationic pole can be anticipated to be very effective in causing electrostatic interactions.^{1,2}

From this standpoint, population analyses of several substituted piperidines (1a–6a) and their quaternary ammonium salts (1b–6b) in solution have been carried out by ¹H n.m.r. spectroscopy.

With the ammonium ions (1b–6b), analyses assuming an equilibrating system between the two chair conformers shown in Figure 1 have been carried out. The possibility of the presence of boat or twisted forms may be ruled out as steric effects (or van der Waals interactions) are too large to permit stabilisation of boat forms of 4-substituted ammonium ions especially those with *N*-methyl groups. In the case of free amines (1a–6a), however, four conformers should be taken into account because of the presence of nitrogen inversion, even if the stable conformations are chair forms.⁵⁻⁸ Chen and LeFèvre reported that, with (1a), the assumptions of a high inversion rate for R (methyl group on nitrogen) and of relatively large free energies for R in the axial conformation make the approximation method assuming the equilibrium system between two conformations with R equatorial shown in Figure 2 possible;⁶ these assumptions were also used for the conformational analysis of derivatives of piperidine having a hydroxy- or acetoxy-group at C-3.⁷ In our population analysis of the free amines, (1a), (3a), (4a), and (6a), these assumptions are made.

For these equilibria, the set of equations (1)–(3) can be obtained, where P_e is the population of the X-equatorial form, P_a is that of the X-axial form, and J_t and J_c are apparent vicinal J values of *cis*- and *trans*-

$$J_t = P_e J_{aa} + P_a J_{ee} \quad (1)$$

$$J_c = P_e J_{ae} + P_a J_{ea} \quad (2)$$

$$P_e + P_a = 1 \quad (3)$$

$$P_e = 1 - P_a = [(J_t + J_c) - (J_{ea} + J_{ee})] / [(J_{aa} + J_{ae}) - (J_{ea} + J_{ee})] \quad (4)$$

⁵ C. Y. Chen and R. J. W. LeFèvre, *Tetrahedron Letters*, 1965, **45**, 4057.

⁶ C. Y. Chen and R. J. W. LeFèvre, *J. Chem. Soc.*, 1965, 3467.

⁷ R. E. Lyle, D. H. McMahon, W. E. Krueger, and C. K. Spicer, *J. Org. Chem.*, 1966, **31**, 4164.

⁸ G. Hite, E. E. Smismann, and R. West, *J. Amer. Chem. Soc.*, 1960, **82**, 1207.

⁹ F. A. L. Anet, *J. Amer. Chem. Soc.*, 1962, **84**, 1054.

protons (J_{AX} and J_{BX} , Figures 1 and 2). Thus, equation (4) can be used to calculate P_e and P_a . Since it is assumed that there are similar chair forms among the piperidine, the piperidinium ion, and the cyclohexane rings and a weak electronegativity effect* of N-1 on J_{AX} and J_{BX} , it is expected that the sets of limiting J values (J_{aa} , J_{ae} , J_{ea} , and J_{ee}) for these systems are almost the same. In the present population analysis, the limiting values employed were J_{aa} 11.2, J_{ae} 4.6, J_{ea} 3.0, and J_{ee} 2.5 Hz; these values were obtained by averaging similar values reported for each limiting J value of these systems.^{5-7,9,10} Thus, we can estimate $P_e(P_a)$ and the conformational free energy difference, ΔG^0 , by equations (5) and (6).

$$P_e = 1 - P_a = [(J_t + J_c) - 5.5]/10.3 \quad (5)$$

$$\Delta G^0 = -RT \ln (P_e/P_a) \quad (6)$$

To the free amines (2a) and (5a), this method is not always applicable, because the assumption of relatively large free energies for the R(hydrogen)-axial conformations is doubtful.¹¹ However, we may calculate the apparent populations, P_e and P_a of (2a) and (5a), which are the sum of the populations of lone-pair-axial and lone-pair-equatorial conformations, by using equation (4), even though the energy differences among these four conformers cannot be directly clarified.

In the case of 4-substituted piperidines and piperidinium ions, we can assume an AA'BB'X spin system [see Figures 1(a) and 2(a)] to obtain an exact value for $(J_{AX} + J_{BX})$ [$= (J_{A'X} + J_{B'X}) = (J_t + J_c)$] if the spectral pattern of H_X is a distinct triplet of triplets.¹² Fortunately, all spectral patterns for H_X of the 4-substituted series appear as clear triplets of triplets. The spectral patterns obtained in heavy water are shown in Figure 3. The n.m.r. parameters, the populations, and the free energy differences obtained are listed in Table 1.

For the 3-substituted derivatives, the determination of $(J_t + J_c)$ values was not simple because of the complexity of the H_X spectral patterns. In the case of ammonium ions, the pattern becomes further complicated by the vicinal ^{14}N - 1H coupling. Therefore, by using the triple or the quadruple resonance $\{H_M, H_N, \text{and/or } ^{14}N\}$ technique, the H_X spectral patterns were recorded to obtain $(J_t + J_c)$ values (see Figure 4). However, in some cases, the determination of exact $(J_t + J_c)$ values was impossible because of the second order patterns of H_X still apparent during spin-decoupling and overlapping of other signals including that of solvent. The predominant form of some of those molecules, however, can be conjectured from the H_X pattern and its half-height band-width, $W_{1/2}$. For example, the H_X patterns of (5b) and (6b) obtained by the quadruple resonance technique are triplet-like; the $W_{1/2}$ values were ca. 9.0 Hz. This value is very

* The very weak electronegativity effect of N-1 is supported by the fact that the spectral patterns and the band-widths of 3-H of tropine derivatives and their ammonium ions or those of pseudotropine derivatives and their ammonium ions are almost the same.

similar to that obtained from the signal of an equatorial proton in a similar spin system, and implies the predominance of the X-axial conformation. If we can assume that this $W_{1/2}$ value is comparable with or slightly larger than the $(J_t + J_c)$ value, an approximate ΔG^0 value or the lower limit of this value can be estimated by analogy with the reported method.¹⁰ The n.m.r. parameters, populations, and the ΔG^0 values obtained are listed in Table 1.

TABLE 1

¹H N.m.r. parameters, populations, and ΔG^0 values of 4- and 3-substituted piperidine derivatives at 30°

Com-pound	Solvent	δ_x	$J_t + J_c$ (Hz)	P_e (%)	P_a (%)	ΔG^0 (kcal mol ⁻¹)
4-Substituted series						
(1a)	D ₂ O	3.68	13.5	77.7	22.3	-0.75 -0.94 (at 40°) ⁵
	CD ₃ OD	3.59	12.8	70.9	29.1	-0.54
	CDCl ₃	3.59	13.0	72.8	27.2	-0.59 -0.82 (at 40°) ⁵
	CCl ₄	3.48	12.7	69.9	30.1	-0.51 -0.60
(2a)	Average					
	D ₂ O	3.68	14.3	(85.4) ^a	(14.6) ^a	
	CD ₃ OD	3.63	13.6	(78.6) ^a	(21.4) ^a	
(3a)	D ₂ O	4.79	11.4	57.3	42.7	-0.18
	CD ₃ OD	4.75	12.1	64.1	35.9	-0.35
	CDCl ₃	4.75	12.5	68.0	32.0	-0.45
	CCl ₄	4.62	12.5	68.0	32.0	-0.45 -0.36
(1b)	Average					
	D ₂ O	4.06	11.5	58.3	41.7	-0.20
	CD ₃ OD	4.02	10.3	46.6	53.4	+0.08
(2b)	D ₂ O	4.50	12.1	64.1	35.9	-0.35
	CD ₃ OD	3.95	10.9	52.4	47.6	-0.06
(3b)	D ₂ O	5.04	8.7	31.1	68.9	+0.48
	CD ₃ OD	5.02	9.3	36.9	63.1	+0.32
3-Substituted series						
(4a)	D ₂ O	3.69	13.8	80.6	19.4	-0.86
	CD ₃ OD	3.65	13.2	74.8	25.2	-0.66
	CCl ₄	3.59	11.2	55.3	44.7	-0.13 -0.25 (at 34°) ⁷
(5a)	D ₂ O	3.61	12.6	(68.9) ^a	(31.1) ^a	
	CD ₃ OD	3.55	12.5	(68.0) ^a	(32.0) ^a	
(6a)	D ₂ O	~4.82				
	CD ₃ OD	~4.82				
	CCl ₄	4.71	11.6	58.3	41.7	-0.20 -0.64 (at 34°) ⁷
(4b)	D ₂ O	4.20	11.2	55.3	44.7	-0.13
	CD ₃ OD	4.16	10.5	48.5	51.5	+0.04
(5b)	D ₂ O	4.65	~9.0 ^b	~34 ^b	~66 ^b	+0.4<
	CD ₃ OD	4.03	~9.0 ^b	~34 ^b	~66 ^b	+0.4<
(6b)	D ₂ O	5.23	~9.0 ^b	~34 ^b	~66 ^b	+0.4<
	CD ₃ OD	5.21	~9.0 ^b	~34 ^b	~66 ^b	+0.4<

^a Apparent population. ^b Estimated from half-height band-width, $W_{1/2}$, by assuming $W_{1/2} \geq (J_t + J_c)$.

Comparison of the results obtained for the free amines (1a), (4a), and (6a) with those reported shows some

¹⁰ H. Booth, *Tetrahedron*, 1964, **20**, 2211.

¹¹ (a) N. Y. Allinger, J. A. Hirsch, and M. A. Miller, *Tetrahedron Letters*, 1967, 3279; (b) J. B. Lambert, P. G. Keske, R. E. Carhart, and A. P. Jovanovich, *J. Amer. Chem. Soc.*, 1967, **89**, 3761; (c) P. G. Brignell, A. R. Katritzky, and P. L. Russel, *J. Chem. Soc. (B)*, 1968, 1459; (d) A. F. Casy, 'P.M.R. Spectroscopy in Medical and Biological Chemistry,' Academic Press, New York, 1971, p. 1628, and references therein.

¹² J. W. Emsley, J. Feeney, and L. H. Sutcliffe, 'High Resolution Nuclear Magnetic Resonance Spectroscopy,' Pergamon Press, Oxford, 1965, vol. 1, pp. 416-423.

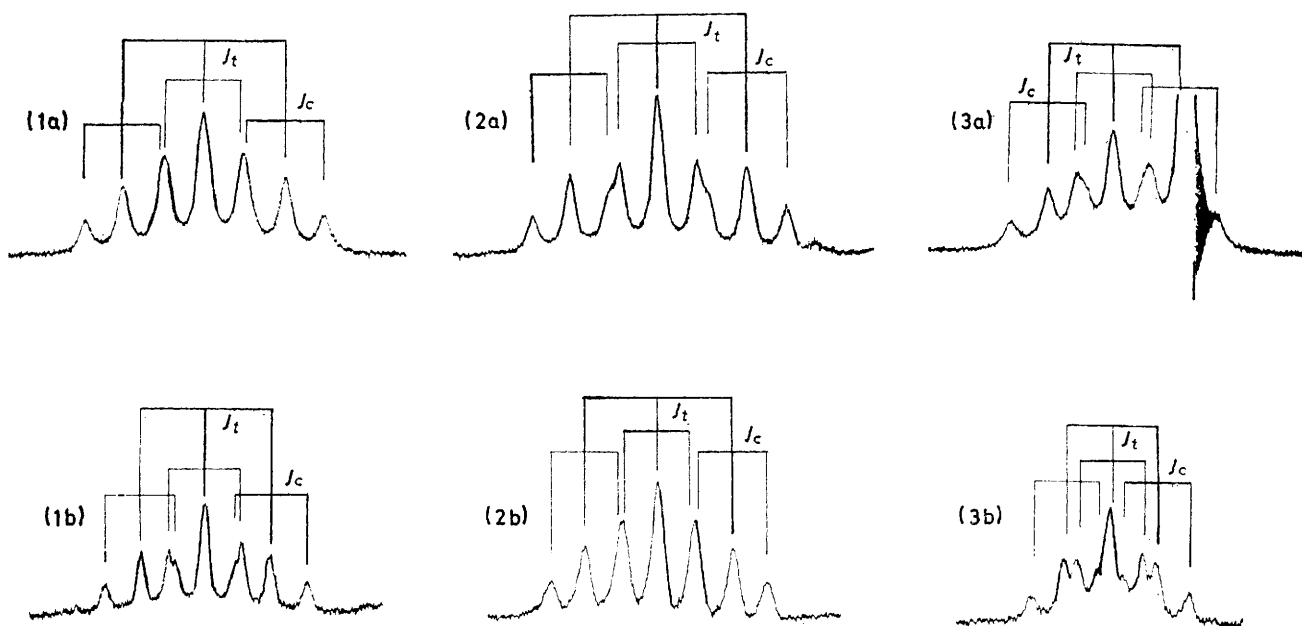


FIGURE 3 4-H Signals in 100 MHz ^1H n.m.r. spectra of 4-substituted piperidine derivatives (1a)—(3a) and (1b)—(3b) in D_2O at 30°

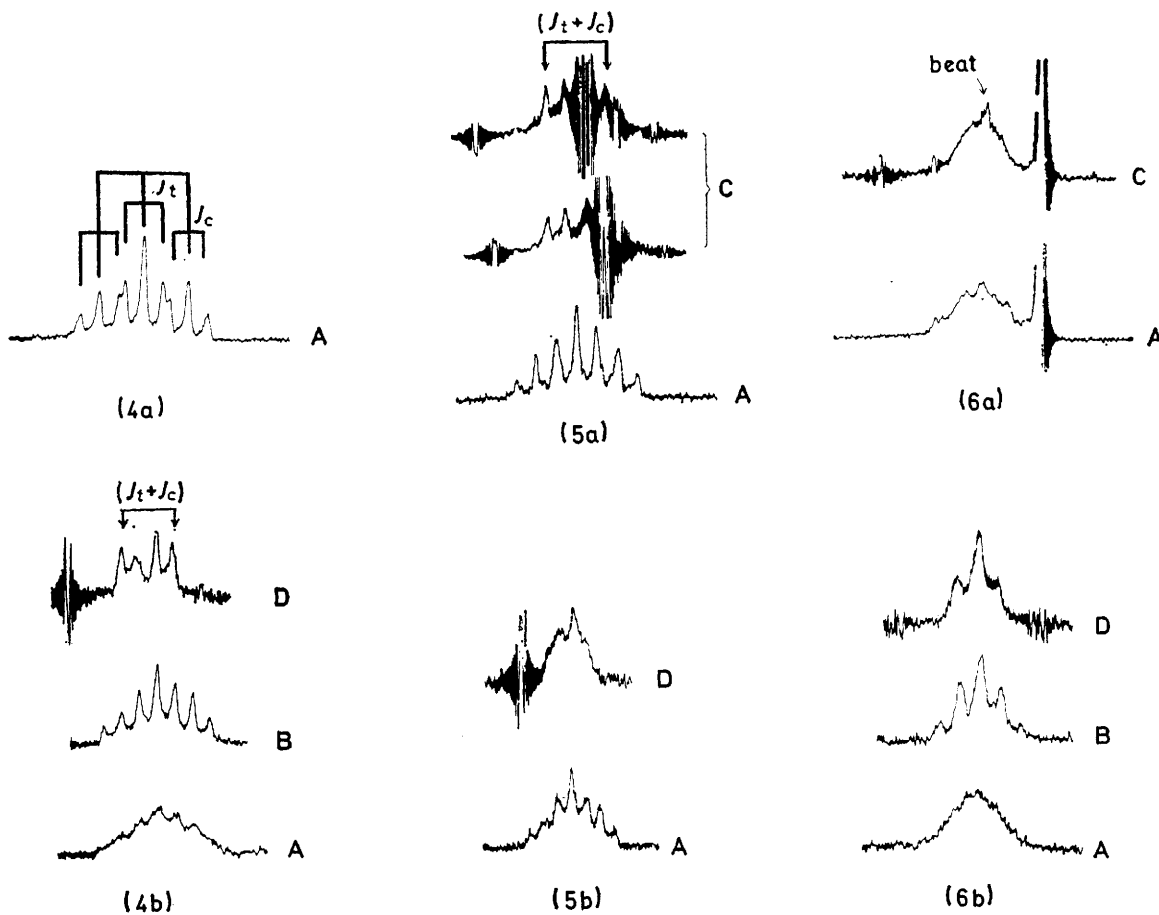


FIGURE 4 3-H Signals in 100 MHz ^1H n.m.r. spectra of 3-substituted piperidine derivatives (4a)—(6a) and (4b)—(6b) in D_2O at 30° : A, normal; B, ^{14}N -decoupled; C, triple resonance spectra (H_M and H_N -decoupled); D, quadruple resonance spectra (^{14}N , H_M , and H_N -decoupled)

differences in spite of using almost the same limiting J values and taking the difference in temperature into consideration. These differences in ΔG^0 may depend on the differences between the methods used (*i.e.*, the methods for determining J_a , J_c , and/or their sum, and the equations used in calculating the populations).

Since the molecules under study have a hydroxy- or acetoxy-group, a considerable solvent dependence of the ΔG^0 values was expected (see Table 1). The range of ΔG^0 values obtained for (1a) is -0.51 to -0.75 kcal mol⁻¹, average -0.60 kcal mol⁻¹; this is in fairly good agreement with the average ΔG^0 for cyclohexanol (-0.7 kcal mol⁻¹).³ The ΔG^0 values obtained for (3a) are in the range -0.18 to -0.45 kcal mol⁻¹, average -0.36 kcal mol⁻¹. This value is rather smaller than that reported for ΔG^0 for 1-acetoxycyclohexane (-0.7 kcal mol⁻¹).³ The reason for this discrepancy is uncertain at present.* The ΔG^0 values for (4a) obtained in D₂O and CD₃OD (-0.86 and -0.66 kcal mol⁻¹, respectively) are very similar to those of (1a). On the other hand, ΔG^0 obtained in CCl₄ differs considerably from the values described above; this can be understood by considering the effect of the hydrogen bonding between the hydroxy-hydrogen and the nitrogen lone-pair as suggested by several workers.^{7,8} In the case of (6a), ΔG^0 was obtained as only -0.20 kcal mol⁻¹ in CCl₄; this value is also rather small for an absolute value, as obtained for (3a), which has the same substituent.*

Although the ΔG^0 values cover a wide range, the preference of the X-equatorial conformation in all the free amines examined was revealed as expected from the 1,3-diaxial interaction effect.

On the other hand, all ΔG^0 values obtained with the ammonium ions (1b)–(6b) differ considerably from those expected on the basis of 1,3-diaxial interaction energies (Table 1). All show an increase in the X-axial forms, particularly those for (3b), (5b), and (6b) in D₂O and CD₃OD.

Insofar as 1,3-diaxial interactions are the main factor controlling their conformational behaviour, similar ΔH^0 and/or ΔG^0 values should be obtained for a 4-substituted free amine and its ammonium ion in the same solvent. With the 3-substituted series, the ammonium ions should demonstrate a greater preference for X-equatorial conformation over the corresponding free amine because of 1,3-diaxial interactions between R and X except for the case where R is hydrogen. Thus, the results clearly indicate that other factors are important in controlling the conformational behaviour of the ammonium ions. We consider that the most important of these is electrostatic interaction as proposed for acetylcholine and choline ions.^{1,2}

On the basis of the considerations described above, we estimated an approximate value for the contribution

* The D₂O solutions of (3a) and (6a) were slightly unclear, possibly indicating a colloidal state, and this phenomenon may affect the relatively small absolute values of ΔG^0 for those molecules. Although ΔG^0 for (6a) in D₂O could not be determined, the absolute value is thought to be small from the band-width (see Figure 2). However, a clear CCl₄ solution of (6a) also gave a similar ΔG^0 value, the reason for which is uncertain at present.

of the electrostatic interaction energy in the conformation control of the ammonium ions by using equation (7), where ΔE_{total} is the total energy difference between an axial and an equatorial form, ΔE_e is the energy difference caused by electrostatic interactions, and ΔE_s is that caused by other factors. It is possible to estimate an approximate value for ΔE_s from the difference of the sum of 1,3-diaxial interaction energies between axial and equatorial forms for the same substituents in similar ring systems. In the case of 4-substituted ammonium ions, ΔE_s can be substituted by the free enthalpy difference ΔH^0 of the corresponding cyclohexane derivative and/or that of the corresponding free amine. Thus, equation (8) can be used to estimate an approximate value of the contribution of electrostatic interactions ΔE_e where ΔH_a^0 is the free enthalpy difference obtained for the ammonium ion, and ΔH_b^0 is that of the corresponding free amine and/or cyclohexane derivative possessing the same substituents X and R.

$$\Delta E_{\text{total}} = \Delta E_e + \Delta E_s \quad (7)$$

$$\begin{aligned} \Delta E_e &= E_e(\text{equatorial}) - E_e(\text{axial}) \\ &= \Delta E_{\text{total}} - \Delta E_s \simeq \Delta H_a^0 - \Delta H_b^0 \quad (8) \end{aligned}$$

To estimate ΔE_e , variable temperature experiments on the 4-substituted free amines and their ammonium ions were performed in D₂O, and the results obtained are listed in Table 2 together with the entropy differences ΔS^0 .

TABLE 2

Compound	ΔH^0 , ΔS^0 , and ΔE_e values of 4-substituted piperidine derivatives (1a), (3a), and (1b)–(3b)		
	ΔS^0 (cal K ⁻¹ mol ⁻¹)	ΔH^0 (kcal mol ⁻¹)	ΔE_e (kcal mol ⁻¹)
(1a)	-1.00	-1.05	
(1b)	-0.39	-0.32	0.73
(2b)	-0.80	-0.59	(0.46) ^a
(3a)	~0	-0.18	
(3b)	+3.4	+1.51	1.69

^a Estimated by using ΔH^0 of (1a) as ΔH_b^0 .

The ΔE_e values estimated for (1b) and (3b) are 0.73 and 1.69 kcal mol⁻¹, respectively. The larger ΔE_e of the latter can be interpreted as a reflection of the presence of two negatively charged oxygen atoms. To estimate the ΔE_e value for (2b), ΔE_s was substituted by ΔH^0 for (1a), because the ΔH^0 or ΔG^0 value for (2a) calculated by using the apparent populations is not always adequate as discussed already. This treatment leads to ΔE_e ca. 0.46 kcal mol⁻¹. These ΔE_e values obtained are never exact. Strictly speaking, even for the free amines (1a), (3a), (4a), and (6a), the two conformers approximation may not always be adequate: a ΔG^0 value of ca. 0.65 kcal mol⁻¹ (at 20° in cyclohexane) has recently been reported for the equilibrium between *N*-methyl-axial and *N*-methyl-equatorial conformers of *N*-methylpiperidine.¹³ However, we can obtain ΔE_e values for (1b) and (2b) similar to the respective values described above, and somewhat larger than the value

¹³ I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Kartzky, and K. A. F. Record, *J.C.S. Perkin II*, 1973, 332.

for (3b), when ΔE_s is estimated from the 1,3-diaxial interaction energies reported for cyclohexane derivatives.³

We have calculated the electrostatic interaction energy E_e for the ammonium ions according to the simplified method described below.

When we calculate E_e by the sum of Coulomb interaction energies among the charges of nonbonded atoms ($E_e = \sum_{i < j} e_i e_j / D r_{ij}$), estimation of the net charge on all the atoms in a molecule and many calculations of the Coulomb interaction energies are required, as noted previously.¹ When we use, however, the approximate model shown in Figure 5, a comparison of the sum of only three interaction energies in the axial form and those in the equatorial form gives an approximate ΔE_e value for the ammonium ions with a hydroxy-group. The following assumptions are made. (a) The charge at the cationic pole is localised at the centre of the pole, *i.e.* a unit positive charge on nitrogen is assumed; (b) the net charge of each atom of the polar substituent δ , δ' , and δ'' (see Figure 5) is estimated by methods such as the use of orbital and group electronegativities,¹

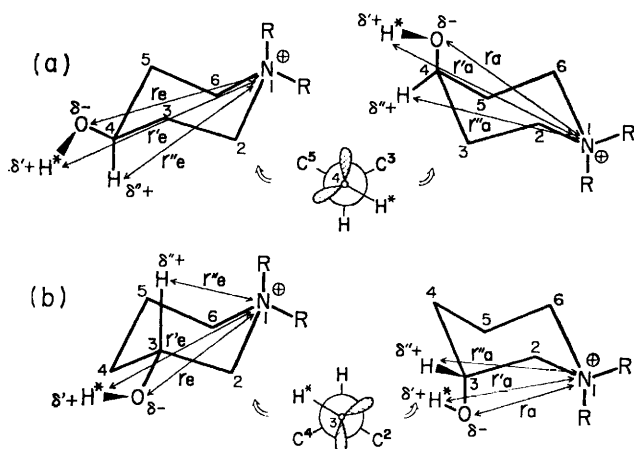


FIGURE 5 Diagrams for the simplified calculation method for the electrostatic interaction energy (see text)

or the use of bond dipole data;¹⁴ (c) the bond lengths, bond angles, and net charges are not altered by ring inversion; (d) the staggered form for the hydroxy-hydrogen atom shown in Figure 5 is assumed, *i.e.* the total conformation energies of both forms are stabilised in both steric and electrostatic senses; and (e) the influence of the sum of electrostatic interaction energies of other charges upon ΔE_e is assumed to be very small.

To estimate net charges in the polar substituent, the method of calculation using orbital and bond electronegativities was applied,* and the estimated charges δ , δ' , and δ'' are listed in Table 3 together with the interatomic distances r_e , r_a , r_e' , r_a' , r_e'' , and r_a'' (see Figure 5) estimated from a molecular model.

* Here, the orbitals H(s), O(20%*s*), and C(*te*) were used and the principle of electronegativity equalisation was applied to the system H—O—C to estimate δ and δ' , and to C—CH(OH)—C to estimate δ'' . The electronegativity of the OH group was calculated by using the orbital electronegativities of H(*s*) and O(20%*s*), in accordance with Huheey's method; see ref. 1 and J. E. Huheey, *J. Phys. Chem.*, 1965, **69**, 3284.

Using these values, ΔE_e of (1b) is given by $(332/D)\{[(-0.30)/4.2 + 0.18/4.8 + 0.10/3.3] - [(-0.30)/3.5 + 0.18/4.2 + 0.10/3.9]\} = 4.51/D$. D is the effective dielectric constant. When $D = 6$ is applied to a D₂O solution of this molecule, a reasonable

TABLE 3

Net charges and interatomic distances in (1b) and (4b)

Compound	Net charges (charge unit)		Interatomic distances (Å)		
	(1b)	δ -0.30	δ' +0.18	r_e 4.2	r_a 3.5
	δ'' +0.10		r_e'' 3.3	r_a'' 3.9	
(4b)	δ -0.30	δ' +0.18	r_e 3.8	r_a 2.9	r_e' 4.4
	δ'' +0.10		r_e'' 3.4	r_a'' 2.8	

value (ΔE_e *ca.* 0.7 kcal mol⁻¹) can be obtained; this value is almost equal to that estimated from the n.m.r. study.

For the distributed charge model of ammonium ions in D₂O, D *ca.* 4 is an adequate, effective dielectric constant.¹ We attempted to apply the present simplified (localised charge) model to some β -substituted ethyltrimethylammonium ions and obtained results similar to those obtained with the distributed charge model,¹ although the effect of electrostatic interaction energy was somewhat emphasised in the simplified method. This means that the present simplified model can be used for conformational analysis of ammonium ions by applying an effective dielectric constant which is somewhat larger than that used for the distributed charge model. Thus, we can regard the above D value as adequate.

This method of calculation gives the same ΔE_e value (0.7 kcal mol⁻¹) for (2b). Since the charge distribution in the cationic pole of (1b) differs from that of (2b), it is natural to obtain somewhat different ΔE_e values for (1b) and (2b). This might be taken to show the limitation of the present simplified method. However, the ΔE_e value estimated (*ca.* 0.5 kcal mol⁻¹) was not exact, and the difference between the ΔE_e value calculated and that estimated is not so large. Therefore, the present simplified method may be applicable when the aim is the estimation of an approximate value.

The same treatment applied to (4b) using the same net charges and the same apparent dielectric constant gave ΔE_e *ca.* 1.2 kcal mol⁻¹. As discussed already, the ΔH^0 value obtained for (4a) cannot be applied to the ΔE_s of the ammonium ion. But, by the application of the average values of 1,3-diaxial interaction energies reported for the CH₃-H, CH₃-OH, and H-OH interactions (0.85, 2.00, and 0.35 kcal mol⁻¹, respectively),³ *ca.* -1.5 kcal mol⁻¹ was assumed as an approximate value of ΔE_s . Therefore, a slightly higher stability of the equatorial form is conjectured in this case, because $\Delta H^0 = (\Delta E_s + \Delta E_e)$ was calculated to be *ca.* -0.3 kcal mol⁻¹. This is essentially in good agreement with the result obtained from the n.m.r. study ($\Delta G^0 = -0.13$ kcal mol⁻¹

¹⁴ (a) M. M. Kreevoy and E. A. Mason, *J. Amer. Chem. Soc.*, 1957, **79**, 4851; (b) T. Ooi, R. A. Scott, G. Vanderkooi, and H. A. Scheraga, *J. Chem. Phys.*, 1967, **46**, 4410.

in D₂O at 30°). By analogy with the calculations of ΔE_e for (1b) and (2b), the calculated ΔE_e value for (5b) is also identical with that for (4b). For (5b), however, ΔE_s ca. -0.7 kcal mol⁻¹ is obtained by the application of the 1,3-diaxial interaction energy because of the lack of *N*-methyl groups; thus $\Delta H^0 = (\Delta E_s + \Delta E_e) \simeq 0.5$ kcal mol⁻¹, in good agreement with the result estimated from n.m.r. analysis ($\Delta G^0 = 0.4$ kcal mol⁻¹ or more in D₂O at 30°).

The simplified calculation method could not be used for (3b) and (6b) because of the difficulty in determining the rotational position of the carbonyl oxygen of the acetoxy-group. However, we may predict the preferred form of these molecules by assuming that the contribution of ΔE_e is approximately double or more that obtained for corresponding alcohols such as (1b) and (4b) because of the presence of the two oxygens having similar negative charges. The validity of this assumption is supported by the comparison of the ΔE_e values listed in Table 3 and the results obtained for acetylcholine ion and choline ion.¹ The application of such ΔE_e values for (3b) and (6b) indicates the clear preference for the axial form, and this is in agreement with the n.m.r. analysis.

Thus, the present method for calculating ΔE_e can be regarded as adequate, although, with the 3-substituted ions, direct comparison of the ΔH^0 value from the n.m.r. study and that calculated could not be achieved because of the difficulty of determining ΔG^0 at various temperatures.

The variable temperature experiments were not performed in other solvents. However, the difference in ΔG^0 between the free amine and its ammonium ion obtained in CD₃OD at 30° is very similar to that obtained in D₂O at 30° in all cases examined. This indicates a similar contribution of the electrostatic interaction effect in both solutions.

Thus the importance of the contribution of electrostatic interactions to conformation control in cyclic ammonium ions has been revealed. We have concluded that electrostatic interactions in conformation control of ammonium ions is of general importance.*

The considerations presented here will be useful in understanding or predicting the conformational behaviour of similar cyclic ammonium ions and their phosphonium analogues, and further, in interpreting their biological activities; for example, the similar strength of the muscalinic effect of (6b) to that of *cis*-*NN*-dimethyl-4-acetoxymethyl-3-acetoxypiperidinium iodide¹⁵ can be explained by their preferred conformations in which the 3-acetoxy-group is axial.

* It has recently been reported that electrostatic interactions are also important in the conformation control of cyclohexanes with polar groups, especially in the vapour phase; see R. J. Abraham and Z. L. Rossetti, *J.C.S. Perkin II*, 1973, 582. A referee has pointed out that this form of electrostatic interaction is very similar to the now discarded dipole-dipole interaction.

¹⁵ N. J. Lewis, K. K. Barker, R. M. Fox, jun., and M. P. Mertes, *J. Medicin. Chem.*, 1973, **16**, 156.

EXPERIMENTAL

¹H *N.m.r.* Measurements.—100 MHz Spectra were recorded on a Varian HA-100 spectrometer in the frequency-swept and homonuclear locked mode at various temperatures. The {¹H} and {¹⁴N} multiple resonance experiments were carried out using two Hewlett-Packard 200 ABR audio-oscillators and an NMR Specialties HD-60B heteronuclear decoupler operating at ca. 7.225 MHz. Tetramethylsilane was used as internal reference for CCl₄, CDCl₃, and CD₃OD solutions, and external reference for D₂O solutions. Sample concentrations were ca. 1M.

Materials.—*N*-Methyl-4-hydroxy- (1a), 4-hydroxy- (2a), *N*-methyl-3-hydroxy- (4a), and 3-hydroxy-piperidine (5a) were used as received from Aldrich. *N*-Methyl-4- (3a) and *N*-methyl-3-acetoxypiperidine (6a) were prepared by acetylation of (1a) and (4a), respectively, by literature procedures.¹⁶

NN-Dimethyl-4-hydroxypiperidinium Iodide (1b).—Methyl iodide (2 ml) was added to (1a) (200 mg) dissolved in methanol (3 ml) and the solution was left for 2 h at room temperature. After removal of the solvent *in vacuo*, the crystalline residue (445 mg) was recrystallised from methanol and then ethanol to give crystals, m.p. 309–311° (decomp.) [lit.,¹⁷ 309–311° (decomp.)].

4-Hydroxypiperidinium Chloride (2b).—Compound (2a) (500 mg) was dissolved in concentrated HCl (5 ml) with ice-cooling. After 30 min, the solution was concentrated to dryness under reduced pressure, and the residual solid (690 mg) was recrystallised from methanol to give hygroscopic crystals, m.p. 154–155° (Found: C, 43.95; H, 8.65; N, 10.0. C₅H₁₂ClNO requires C, 43.65; H, 8.8; N, 10.2%).

NN-Dimethyl-4-acetoxypiperidinium Iodide (3b).—Methyl iodide (2 ml) was added to compound (3a) (200 mg) dissolved in methanol (2 ml). The solvent was evaporated off after 10 h, and the crude product (100%) was recrystallised from ethanol to give needles, m.p. 165–167° (Found: C, 36.3; H, 6.15; N, 4.8. C₉H₁₈INO₂ requires C, 36.15; H, 6.05; N, 4.7%).

NN-Dimethyl-3-hydroxypiperidinium Iodide (4b).—Starting from compound (4a), a quantitative yield of the crude product was obtained as for (1b). Recrystallisation from ethanol gave needles, m.p. ca. 270° (sublimed) (Found: C, 32.55; H, 6.4; N, 5.6. C₇H₁₆INO requires C, 32.7; H, 6.25; N, 5.45%).

3-Hydroxypiperidinium Chloride (5b).—Treatment of compound (5a) with concentrated HCl as described for (2b) gave the crude salt quantitatively. Recrystallisation from methanol gave hygroscopic grains, m.p. ca. 150° (sublimed) (Found: C, 43.4; H, 8.65; N, 10.0. C₅H₁₂ClNO requires C, 43.65; H, 8.8; N, 10.2%).

NN-Dimethyl-3-acetoxypiperidinium Iodide (6b).—Compound (6b) was obtained from (6a) as for (3b), m.p. 171–172° (lit.,¹⁸ 171–172°).

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¹⁶ C. A. Grob, A. Kaiser, and E. Renk, *Helv. Chim. Acta*, 1957, **40**, 2170.

¹⁷ L. E. Craig and D. S. Tarbell, *J. Amer. Chem. Soc.*, 1949, **71**, 465.

¹⁸ J. H. Biel, E. S. Sprengeler, H. A. Leiser, J. Horner, A. Drukker, and H. L. Friedman, *J. Amer. Chem. Soc.*, 1955, **77**, 2250.