

## Conformational Studies of Quaternary Ammonium Ions. Part II.<sup>1</sup> Molecular Mechanical Calculation of Conformation Energies of $\beta$ -Substituted Ethyltrimethylammonium Ions

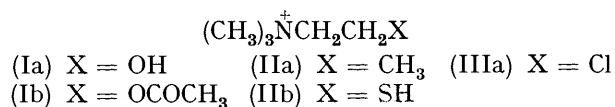
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The results are reported of calculations of the molecular geometries of choline ion, acetylcholine ion, chloro-choline ion, thiocholine ion, and n-propyltrimethylammonium ion, in which electrostatic interaction energy, van der Waals interaction energy, and torsional energy have been taken into account. The results are in good agreement with those of X-ray analysis of crystal structures and n.m.r. analysis in heavy water solutions.

PREVIOUSLY<sup>1</sup> we explained how the results of an n.m.r. study suggested that electrostatic interactions and van der Waals interactions between nonbonded atoms are two important contributors to conformational control in  $\beta$ -substituted ethyltrimethylammonium ions. This suggestion was derived from the assumption that all stable conformers are ideal staggered forms and only two species of conformer, *gauche* and *trans* about  $R^1CH_2-CH_2R^2$ , exist in the system examined. Strictly speaking, however, this assumption is not always correct, because other rotation angles exist besides that of the  $R^1CH_2-CH_2R^2$  bond, all of which exert an influence on the conformational energy, and because the possibility cannot be excluded that in the *gauche*-form about  $R^1CH_2-CH_2R^2$  the dihedral angle between  $R^1$  and  $R^2$  is considerably distorted from an ideal staggered relation by some kind of interaction. Therefore, all rotation angles and the torsional energies influenced by these angles must be considered in order to calculate the conformational energy.

The  $\beta$ -substituted ethyltrimethylammonium ions can roughly be classified into three groups in accordance with conformational behaviour: (i) *gauche*-form preferred, (ii) *trans*-form preferred, and (iii) *gauche*- and *trans*-forms similarly stabilized.<sup>1,2</sup> On the basis of

these experimental data and the considerations described above, we have made molecular mechanical calculations of the conformational energies of several representative molecules, choline ion (Ia), acetylcholine ion (Ib),



n-propyltrimethylammonium ion (IIa), thiocholine ion (IIb), and chloro-choline ion (IIIa) taking into account the electrostatic interactions and van der Waals interactions between nonbonded atoms and the torsional potentials about rotation angles as functions of molecular geometry.

### METHODOLOGY

To calculate approximate conformation energies of  $\beta$ -substituted ethyltrimethylammonium ions equation (1)

$$\begin{aligned} E_{\text{total}} &= E_e + E_v + E_t \\ &= \sum \frac{332e_i e_j}{Dr_{ij}} + \sum (a_{ij}r_{ij}^{-12} - b_{ji}r_{ij}^{-6}) + \\ &\quad \sum \frac{U_k^0}{2} \{1 + \cos(n_k \psi_k)\} \quad (1) \end{aligned}$$

<sup>1</sup> Part I, Y. Terui, M. Ueyama, S. Satoh, and K. Tori, *Tetrahedron*, 1974, **30**, 1465.

<sup>2</sup> (a) C. C. J. Culvenor and N. S. Ham, *Chem. Comm.*, 1966, 537; (b) R. J. Cushley and H. G. Mautner, *Tetrahedron*, 1970, **26**, 2151; (c) P. Partington, J. Feeney, and A. S. V. Burgen, *Mol. Pharmacol.*, 1972, **8**, 269.

is used where  $E_e$ ,  $E_v$ , and  $E_t$  are electrostatic interaction energy, van der Waals interaction energy, and torsional energy respectively,  $r_{ij}$  is the distance between interacting atoms,  $\psi_k$  is the rotation angle, and the other terms are constants. The three energy terms and the geometries of the molecules are discussed in sections 1—4. The methods of determining the main stable conformers and their potentials are described in section 5.

(1) *Electrostatic Interactions*.—Electrostatic interaction energies are calculated by a Coulombic-type potential function where the electric monopole-monopole interactions between electric charges of nonbonded atoms are considered <sup>1,3,4</sup> ( $E_e = \sum 332e_i e_j / Dr_{ij}$ ). The problem is how to estimate the net charges of atoms because of the uncertainty of the dipole model for the C-N bond of the cationic pole, as discussed previously.<sup>1</sup> Hinze and Jaffé have introduced two useful concepts for the definition of the electronegativity of an atom or group: 'orbital electronegativity' and 'bond electronegativity.'<sup>5-7,\*</sup> Applying these concepts, Huheey has suggested a simple method for calculating the electronegativities of groups.<sup>8,9</sup>

To apply this method, we consider various possible constructions for the molecule, each construction consisting of a different combination of components, atoms, or groups. For example, with choline ion (Ia) the following constructions are considered and net charge of each atom can be calculated.

*Construction 1:*  $R^1-O-H$  [ $R^1 = CH_2CH_2N^+(CH_3)_3$ ]. The principle of electronegativity equalization for stabilized

obtained, where the electronegativities are described as  $a + b\delta$  in accordance with Huheey's method.

$$a_H + b_H\delta_H = a_O + b_O\delta_O = a_{R^1} + b_{R^1}\delta_{R^1} \quad (2)$$

$$\delta_H + \delta_O + \delta_{R^1} = 0 \quad (3)$$

*Construction 2:*  $R^2-CH_2-R^3$  [ $R^2 = CH_2N^+(CH_3)_3$ ,  $R^3 = OH$ ].

$$a_H + b_H\delta_H = a_C + b_C\delta_C = a_{R^2} + b_{R^2}\delta_{R^2} = a_{R^3} + b_{R^3}\delta_{R^3} \quad (4)$$

$$2\delta_H + \delta_C + \delta_{R^2} + \delta_{R^3} = 0 \quad (5)$$

*Construction 3:*  $R^4-CH_2-R^5$  [ $R^4 = N^+(CH_3)_3$ ,  $R^5 = CH_2OH$ ].

$$a_H + b_H\delta_H = a_C + b_C\delta_C = a_{R^4} + b_{R^4}\delta_{R^4} = a_{R^5} + b_{R^5}\delta_{R^5} \quad (6)$$

$$2\delta_H + \delta_C + \delta_{R^4} + \delta_{R^5} = 0 \quad (7)$$

*Construction 4:*  $(R^6)_3N^+R^7$  ( $R^6 = CH_3$ ,  $R^7 = CH_2CH_2OH$ ).

$$a_N^+ + b_N^+\delta_N^+ = a_{R^6} + b_{R^6}\delta_{R^6} = a_{R^7} + b_{R^7}\delta_{R^7} \quad (8)$$

$$\delta_N^+ + 3\delta_{R^6} + \delta_{R^7} = 0 \quad (9)$$

*Construction 5:*  $H_3C-R^8$  ( $R^8 = N^+CH_2CH_2OH$ ).

$$a_H + b_H\delta_H = a_C + b_C\delta_C = a_{R^8} + b_{R^8}\delta_{R^8} \quad (10)$$

$$3\delta_H + \delta_C + \delta_{R^8} = 0 \quad (11)$$

From these simultaneous equations, we can calculate the  $\delta$  values of all atoms in the molecule, these values

TABLE I  
Calculated net charges of ions (Ia), (Ib), (IIa), (IIb), and (IIIa) <sup>a</sup>

(Ia) <sup>b</sup>		$H^a = H^b = H^c = H^d = +0.073$ $C^a = +0.010, C^b = C^c = +0.009$ $O = -0.356, N = +0.286^d$
(Ib) <sup>c</sup>		$H^a = H^c = H^d = +0.084, H^b = +0.083$ $C^a = C^c = C^d = C^e = +0.020, C^b = +0.019$ $O^a = -0.396, O^b = -0.383, N = +0.298^d$
(IIa)		$H^a = H^b = H^c = H^d = +0.050$ $C^a = C^b = C^c = C^d = -0.013$ $N = +0.278^d$
(IIb) <sup>e</sup>	$R-S-H^d$	$H^a = H^b = H^c = H^d = +0.054$ $C^a = C^b = C^c = -0.009$ $S = +0.006, N = +0.283$
(IIIa) <sup>f</sup>	$R-Cl$	$H^a = H^b = +0.076, H^c = +0.075$ $C^a = C^b = C^c = +0.012$ $Cl = -0.339, N = +0.294$

<sup>a</sup> In these calculations orbitals C(2s) and H(1s) were used for all carbon atoms and all hydrogen atoms.<sup>8</sup> <sup>b</sup> The orbital O (20% s) was used for the oxygen of the hydroxy-group.<sup>8</sup> <sup>c</sup> The orbital O (26.8% s) was used for the ether oxygen, and orbitals C(2s) and O(2s) were used for the carbon and oxygen of the carbonyl group.<sup>8,9</sup> <sup>d</sup> Modified slightly to make a total charge +1.000. <sup>e</sup> The orbital S (3.7% s;  $a_s = 7.80$  and  $b_s = 10.12$ ) was used because of  $\widehat{CSH} = 95^\circ$  (ref. 8). <sup>f</sup> The orbital Cl(2s) was used.<sup>8</sup>

bonding<sup>6,9</sup> is applied to estimate the net change of each component and the simultaneous equations (2) and (3) are

\* A similar concept has also been proposed by Pilcher and Skinner (*J. Inorg. Nuclear Chem.*, 1962, **24**, 937).

<sup>3</sup> (a) D. Ajo, M. Bossa, A. Damiani, R. Fidenzi, S. Gigli, L. Lanzi, and A. Lapicciarella, *J. Theor. Biol.*, 1972, **34**, 15; (b) Y. Terui, Abstract, The Vth Structural Organic Chemistry Symposium, Nagoya, 1972, p. 28; (c) M. Froimowitz and P. J. Gans, *J. Amer. Chem. Soc.*, 1972, **94**, 8020.

<sup>4</sup> (a) R. A. Scott and H. A. Scheraga, *J. Chem. Phys.*, 1966, **45**, 2091; (b) T. Ooi, R. A. Scott, G. Vanderkooi, and H. A. Scheraga, *ibid.*, 1967, **46**, 4410.

corresponding directly to the net charges on the atoms, except that on the quaternary nitrogen. For the quaternary nitrogen, the orbital  $\widehat{N}(2s)$  is used.<sup>7</sup> This has a positive unit charge and the net charge on this atom is therefore given by  $\delta_N^+ + 1$ . In the present calculations, the

<sup>5</sup> J. Hinze and H. H. Jaffé, *J. Amer. Chem. Soc.*, 1962, **84**, 540.

<sup>6</sup> J. Hinze, M. A. Whitehead, and H. H. Jaffé, *J. Amer. Chem. Soc.*, 1963, **85**, 148.

<sup>7</sup> J. Hinze and H. H. Jaffé, *J. Phys. Chem.*, 1963, **67**, 1501.

<sup>8</sup> J. E. Huheey, *J. Phys. Chem.*, 1965, **69**, 3284.

<sup>9</sup> J. E. Huheey, *J. Phys. Chem.*, 1966, **70**, 2086.

reported values<sup>8,9</sup> of the orbital electronegativities of atoms are used, except for that of quaternary nitrogen; for quaternary nitrogen  $a_N^+ = 23.72$  and  $b_N^+ = 22.16$  are used, these are calculated from the data reported by Hinze and Jaffè<sup>7</sup> in accordance with the method of Huheey.<sup>8</sup> The electronegativities of the groups used here are also calculated using the orbital electronegativities of atoms in accordance with the method of Huheey.<sup>8,9</sup> The results are listed in Table 1 together with those for (Ib), (IIa), (IIb), and (IIIa).

The total charge of each molecule must be unity (+1), and this was found to be so within the error arising from discarding fractions  $< 0.001$  in the absolute charge values calculated. The distribution of positive charge in the cationic pole is also indicated by this method, as shown by MO calculations on acetylcholine ion.<sup>10</sup> The remaining problem is to determine the value of the effective dielectric constant  $D$ . However, as the value of  $D$  is dependent upon the environment in which the molecule exists (in aqueous solution, for example,  $D$  is influenced by interactions between solute and water molecules), and as we lack knowledge of the specific situation in the present case, we cannot determine theoretically the  $D$  values for the ammonium ions described.

We have therefore done calculations for  $D$  1, 2, 4, and  $\infty$ , and compared the results;  $D = 1$  implies the evaluation of an intact  $E_e$  that corresponds to the electrostatic interaction energy in a vacuum,  $D = \infty$  means that the  $E_e$  term is neglected, and  $D = 2$  or 4 requires a half or a quarter contribution of the intact  $E_e$ , respectively; values near these were suggested from conformational analysis of some molecules including (Ib).<sup>3c,4</sup>

If it is possible to assume a similar environment for the ammonium ions and to use a single  $D$  value for them in a given medium, we will be able to obtain results in agreement with those obtained by experiment.

(2) *van der Waals Interactions*.—A Lennard-Jones 6-12 potential function was used for van der Waals interactions of pairs of nonbonded atoms  $i$  and  $j$  [equation (12)]. The

$$E_v = \Sigma(a_{ij}r_{ij}^{-12} - b_{ij}r_{ij}^{-6}) \quad (12)$$

constants  $a_{ij}$  and  $b_{ij}$  used are listed in Table 2.

(3) *Torsional Potentials*.—According to the concept of Scott and Scheraga<sup>11</sup> we express torsional energies as  $n_k$ -fold potential functions,  $E_t = U_k^0 \{1 + \cos(n_k \psi_k)\} / 2$ , where only torsional (*i.e.*, orbital interaction) terms are considered. The values of  $U_k^0$  used for the rotation around C-C, C-CO, C-OH, and C-SH bonds are 2.8, 1.1, 0.9, and 1.2 kcal mol<sup>-1</sup>, respectively,<sup>4,11</sup> and that for the C-N<sup>+</sup> bond is 2.6 kcal mol<sup>-1</sup>, which is assumed to be 3/2 that for the C-N bond in amines in accordance with Pauling's concept.<sup>12</sup> Strictly speaking, the  $U_k^0$  values should be calculated by equation (13), when equation (1) is used for the calculation of conformation energy.  $E_{(R.B.)}^{\text{exp}}$  is the rotational barrier

$$U_k^0 = E_{(R.B.)}^{\text{exp}} - \Delta E_v - \Delta E_e \quad (13)$$

that includes all energy terms and is obtained by experi-

\* For example, calculations showed that the absolute value of  $\Delta E_e$  is  $< 0.01$  for ethane and  $< 0.2$  kcal mol<sup>-1</sup> even for methylammonium ion or methanol. These  $\Delta E_e$  values were calculated by the method described in section 1. Such small values will be within the experimental error in the determination of the rotational barrier. Scott and Scheraga also neglected the  $E_e$  term for the calculation of  $U_k^0$  of ordinary compounds, except for some specific molecules such as perfluoroethane.

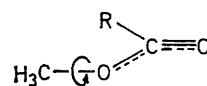
ment,  $\Delta E_v$  is the difference in van der Waals interaction energy between the eclipsed and the staggered form, and  $\Delta E_e$  is the difference in electrostatic interaction energy. The influence of  $E_e$  on  $U_k^0$ , however, is usually very small so  $U_k^0$  values obtained by Scott *et al.*<sup>4,11</sup> can be used as in our calculations.\*

TABLE 2  
Constants for van der Waals potential function<sup>a</sup>

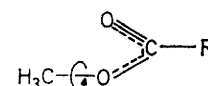
	$10^3 a_{ij}$ (kcal Å <sup>12</sup> mol <sup>-1</sup> )	$b_{ij}$ (kcal Å <sup>6</sup> mol <sup>-1</sup> )
H...H	4.5	47
H...C	38	128
H...O	25	124
H...N	27	125
H...Cl	108	327
H...S	149	409
C...C	286	370
C...O	205	367
C...N	216	366
C...Cl	808	958
C...S	1081	1177
O...N	153	365
N...Cl	613	950
N...S	820	1160

<sup>a</sup> The coefficients  $a_{ij}$  and  $b_{ij}$  for the interactions among H, C, N, and O are cited from ref. 4b and those for the interactions relating to Cl and S were calculated from the reported values of effective number of outer-shell electrons,<sup>4a,11</sup> atomic refractivities (A. I. Vogel, *J. Chem. Soc.*, 1948, 1820, 1833), and van der Waals radii (A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441) in accordance with the same method.<sup>4b,11</sup>

For the estimation of the  $U_k^0$  value of the C-OCRO bond in esters, the rotational barrier,  $E_{(R.B.)}^{\text{exp}}$ , of H<sub>3</sub>C-OCHO<sup>13</sup> was used; the result indicated a higher possibility for *cis*-type rotation in this case.



*cis*-type rotation



*trans*-type rotation

If *trans*-type rotation is assumed,  $\Delta E_v$  turns out to be greater than the value of  $E_{(R.B.)}^{\text{exp}}$  in spite of setting the various bond lengths and bond angles within sensible limits; whereas a normal result (*i.e.*,  $E_{(R.B.)}^{\text{exp}} > \Delta E_v$ , and  $U_k^0 = 0.4$  kcal mol<sup>-1</sup>) is obtained if *cis*-type rotation is assumed. The type of rotation around the C-OCRO bond (*i.e.*, *cis*- or *trans*-type) will depend on R. When R is an alkyl group *trans*-type rotation has been assumed, because of steric requirements, by several authors in calculations of the conformational energy of molecules containing an acetoxy-group.<sup>10,14</sup> However, while torsional energy is considered on the basis of the interaction between orbitals having a 1,3-relationship as suggested by Pauling,<sup>12</sup> we can expect similar  $U_k^0$  values for each rotational type, and the  $U_k^0$  obtained above can therefore be used for C-OCRO rotation. All  $n_k$  values for the present cases are taken as 3 in accordance with the method of Scott and Scheraga.<sup>11</sup>

<sup>10</sup> (a) L. B. Kier, *Mol. Pharmacol.*, 1967, **3**, 487; (b) D. L. Beveridge and R. J. Radna, *J. Amer. Chem. Soc.*, 1972, **93**, 3759; (c) B. Pullman and P. Courrière, *Mol. Pharmacol.*, 1972, **8**, 612.

<sup>11</sup> R. A. Scott and H. A. Scheraga, *J. Chem. Phys.*, 1965, **42**, 2209.

<sup>12</sup> L. Pauling, *Proc. Nat. Acad. Sci. U.S.A.*, 1958, **44**, 211.

<sup>13</sup> R. F. Curl, *J. Chem. Phys.*, 1959, **30**, 1529.

<sup>14</sup> A. M. Liquori, A. Damiani, and J. L. De Coen, *J. Mol. Biol.*, 1968, **33**, 445.

(4) *Geometry and Description of Conformation.*—In our calculations it is assumed that bond lengths and bond angles given are not altered by rotation. The values used are listed in Table 3 and the designations of bond lengths and bond angles used in this Table are shown in Figure 1; the values are obtained by averaging values derived from

method, we can always use  $\psi_5$  independent of the type of substituent if we want to describe the partial conformation of a 1,2-disubstituted ethyl fragment in a series of  $\beta$ -substituted ethyltrimethylammonium ions;  $\psi_4$  and  $\psi_6$  can likewise be used for  $\psi(\text{C}-\text{C}-\text{N}-\text{C}^a)$  and  $\psi(\text{X}_2-\text{X}_1-\text{C}-\text{C})$  respectively.

TABLE 3

Compounds	Bond length (Å)		Bond angle (°)				Others
	$r_3$	Others	$\theta_1$	$\phi_1$	$\theta_2$	$\phi_2$	
(Ia) (X = OH)	1.41	$r(\text{O}-\text{H}) = 0.95$	113.0	108.8	112.0	109.0	$\widehat{\text{COH}} = 104.0$
(Ib) (X = O-C*O*-C**H <sub>3</sub> )	1.47	$r(\text{O}-\text{C}^*) = 1.34$ $r(\text{C}-\text{O}^*) = 1.26$ $r(\text{C}^*-\text{C}^{**}) = 1.52$	113.0	108.8	113.0	108.8	$\widehat{\text{COC}}^* = 111.5$ $\widehat{\text{OC}^*\text{C}^{**}} = 110.0$ $\widehat{\text{OC}^*\text{O}^*} = \widehat{\text{C}^{**}\text{C}^*\text{O}^*} = 125.0$
(IIa) (X = CH <sub>3</sub> )	1.54		113.0	108.8	112.0	109.0	
(IIb) (X = SH)	1.81	$r(\text{S}-\text{H}) = 1.34$	113.0	108.8	113.0	108.8	$\widehat{\text{CSH}} = 95.0$
(IIIa) (X = Cl)	1.76		113.0	108.8	111.0	109.2	

<sup>a</sup> It is assumed that all  $r(\text{C}-\text{H})$  are 1.09, all  $r(\text{C}-\text{N})$  of *N*-methyl groups are 1.52,  $r_1$  is 1.53,  $r_2$  is 1.54 Å, and that all bond angles,  $\widehat{\text{HCH}}$ , of methyl groups and all  $\widehat{\text{CNC}}$  are tetrahedral (see Figure 1). <sup>b</sup> The notations of bond lengths and bond angles are shown in Figure 1.

X-ray data on the molecules used here and some similar compounds.<sup>15, 16</sup>

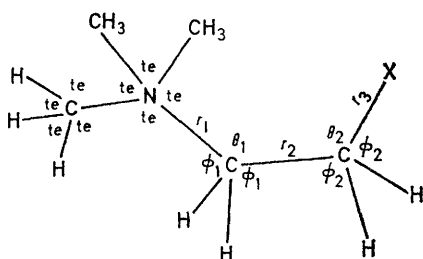


FIGURE 1 Designation of bond lengths and bond angles used in Table 3

There are several ways to describe the conformation of a molecule. Here we use the method of enumerating all rotation angles. As shown in Figure 2, five rotation angles ( $\psi_1, \psi_2, \dots, \psi_5$ ) for ion (IIIa), six ( $\psi_1, \psi_2, \dots, \psi_6$ ) for ions (Ia), (IIa), and (IIb), and eight ( $\psi_1, \psi_2, \dots, \psi_8$ ) for ion (Ib) are needed to describe their total conformations. The rotation angle  $\psi_k$  is defined as follows; looking at the molecule from the terminal atom of a substituent and tracing a path in the direction of extension of the chain as shown in Figure 2,  $\psi_k$  is defined as  $0^\circ$  if vicinal bonds along this path have an eclipsed relation to each other, and is defined as  $a^\circ$  if there is a dihedral angle between these vicinal bonds of  $a^\circ$  in a clockwise direction. To describe rotation angles having three-fold symmetry (*i.e.*,  $\psi_1-\psi_4$  in Figure 2), the smallest of the three possible values obtained as defined above is used (see Figure 2). Distinguishing the methyl carbons as a, b, and c as shown in Figure 2, the dihedral angles  $\psi(\text{C}-\text{N}-\text{C}^a-\text{H}^*)$ ,  $\psi(\text{C}-\text{N}-\text{C}^b-\text{H}^*)$ , and  $\psi(\text{C}-\text{N}-\text{C}^c-\text{H}^*)$  are taken for  $\psi_1, \psi_2$ , and  $\psi_3$  respectively. Further,  $\psi(\text{C}-\text{C}-\text{N}-\text{C}^a)$  is  $\psi_4$ ,  $\psi(\text{X}_1-\text{C}-\text{C}-\text{N})$  is  $\psi_5$ , and  $\psi(\text{X}_2-\text{X}_1-\text{C}-\text{C})$  is  $\psi_6$ . The conformations of (Ia), (IIa), (IIb), and (IIIa) are expressed by enumeration of these values in suffix number order. For the conformation of (Ib) two more rotation angles,  $\psi_7$  and  $\psi_8$ , are added. By this

<sup>15</sup> L. E. Sutton, 'Interatomic Distances,' Chem. Soc. Special Publ., No. 11, 1958.

(5) *Method of Determining the Stable Conformers and their Energies.*—When we use equation (1), the conformational energy is a function of rotation angles only, because the internal distances among pairs of interacting nonbonded atoms are themselves functions of rotation angles. Now, one simple method which can be used to lead to determination of the stable conformers is to classify the substituents of the molecule as follows.

A. The substituent is an atom or a group having cylindrical symmetry and no rotating bonds within itself (*e.g.* halogens, nitrile, isonitrile, *etc.*).

B. The substituent is a group having no cylindrical symmetry and no effective rotating bonds within itself, *i.e.* no rotations which influence the conformation energy (*e.g.* hydroxy, formyl, methyl, *etc.*).

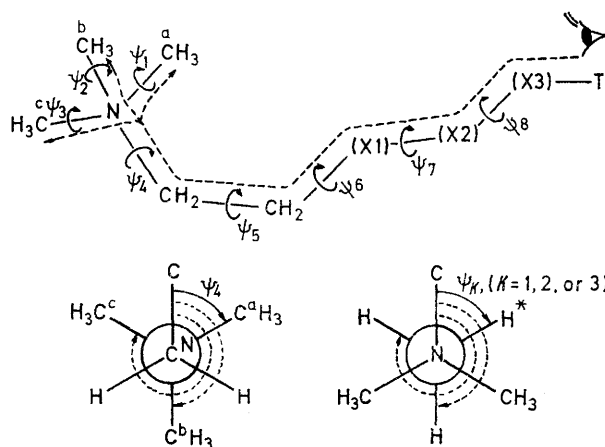


FIGURE 2 Designation of rotation angles

C. The substituent is a group having rotating bonds that influence the conformation energy (*e.g.* acetoxy, *n*-propyl, ethoxy *etc.*).

Roughly speaking, it is sensible to suppose that conformational energy depends mainly on  $\psi_5$  and  $\psi_4$  in A-type

<sup>16</sup> F. G. Canepa, P. Pauling, and H. Sörum, *Nature*, 1966, **210**, 907.

molecules, on  $\psi_5$ ,  $\psi_4$ , and  $\psi_6$  in B-type molecules, and on other rotation angles in addition to  $\psi_4$ ,  $\psi_5$ , and  $\psi_6$  in C-type molecules. The specific natures of A-, B-, and C-types are confirmed by rough pre-calculation on the ammonium ions described and some other typical molecules. Ion (IIIa) is A-type, ions (Ia), (IIa), and (IIb) are B-type, and ion (Ib) is C-type. We can, however, regard ion (Ib) as a B-type molecule if we can assume partial double bond character of the O-CO bond to fix  $\psi_7$ , as has been done by several authors,<sup>10,14</sup> and assume that the contribution of  $\psi_8$  to the

tained. Next, for each low energy region, the converging point of minimum energy as a function of all rotation angles is arrived at by computer calculation using the program STCA-1.\*

#### RESULTS AND DISCUSSION

A FACOM 270-20 computer was used for the calculations. Nonbonded interactions which are independent of rotation angles are not taken into account.

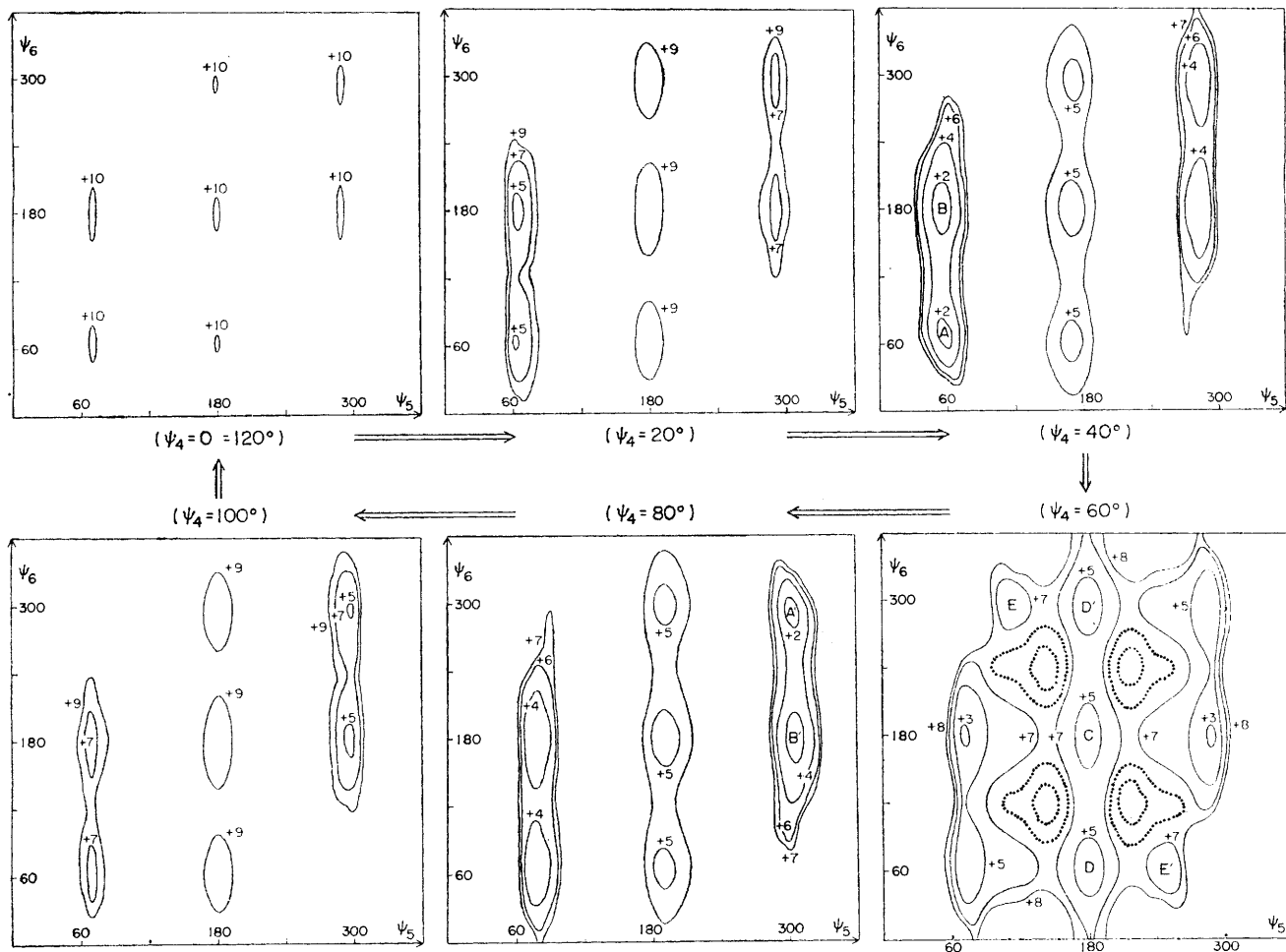


FIGURE 3 Calculated potential energy surface for choline ion with  $D_2$ . The rotation angles  $\psi_1$ — $\psi_3$  are fixed at  $60^\circ$ . The contour lines are in kcal mol<sup>-1</sup>. The extrema expressed by dotted lines are maxima

conformational energy is small. The validity of the latter assumption was confirmed by the results of calculations to determine the stable conformers. In the present paper these assumptions are made so that we can compare our results with those which have been obtained under similar conditions by other workers, although the rotational barrier for the O-CO bond in ion (Ib) is not well defined. Now, we can determine the stable conformers and their energies in the following way. First, outlines of the variations of the potential energy valleys are found from the energy map for  $\psi_4$ ,  $\psi_5$ , and  $\psi_6$ , made by calculating the energies at different values of  $\psi_4$ ,  $\psi_5$ , and  $\psi_6$  by equation (1) (the rotation angles being varied in  $10^\circ$  increments), and main regions of low energy, *i.e.*, the regions of stable conformation, are ascer-

*Choline Ion (Ia).*—To draw up the energy map  $\psi_4$ ,  $\psi_5$ , and  $\psi_6$  were varied in  $10^\circ$  increments holding all other rotation angles constant. A series of two-dimensional energy diagrams ( $\psi_5$  and  $\psi_6$ ) have been drawn for different values of  $\psi_4$ . These are shown in Figure 3, where the diagrams for  $\psi_4 = 10, 30, 50, 70, 90$ , and  $110^\circ$  are omitted.

Because of the three-fold symmetry of  $\psi_4$ , the energy diagrams for  $\psi_5$  and  $\psi_6$  repeat after  $120^\circ$  rotation of  $\psi_4$ . From this energy map we can find seven important

\* Here, procedures for convergency applying the sequential search method by partitioned lattice of rotation angles are carried out.

regions of low energy, A, A', B, B', C, D, and D', and two slightly stabilized regions, E and E'. Symmetry of rotation indicates that A and A', B and B', D and D', and E and E' are equivalent. They are enantiomeric pairs. From several starting points selected freely in each region, calculations were made to arrive at the conformation having minimum energy as a function of all rotation angles including  $\psi_1$ ,  $\psi_2$ , and  $\psi_3$ . Only one converging point was obtained in each region in as far as the final increments of all  $\psi_k$  are limited to  $1^\circ$ .

**Acetylcholine Ion (Ib).**—As described in the Methodology section,  $\psi_7$  is assumed to be  $180^\circ$ , corresponding to the *trans*-type. The energy map for ion (Ib) was obtained as described above, and part of this map is shown in Figure 4. Again, seven important regions of

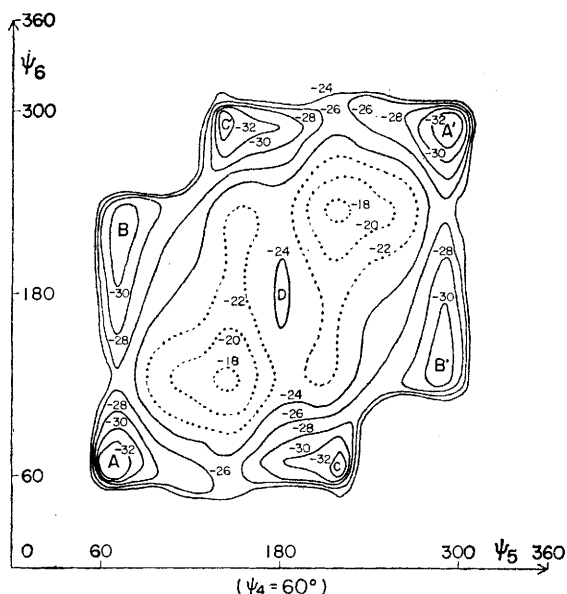


FIGURE 4 Calculated potential energy surface for acetylcholine ion with D 1. The rotation angles  $\psi_1$ — $\psi_3$  and  $\psi_8$ , and  $\psi_7$  are fixed at  $60^\circ$  and  $180^\circ$  respectively. The contour lines are in kcal mol $^{-1}$

low energy, A, A', B, B', C, C', and D, are indicated, where A and A', B and B', and C and C' are enantiomeric pairs.

**n-Propyltrimethylammonium Ion (IIa).**—The same treatment for ion (IIa) reveals the existence of only two important stable conformers, A, B(B'), because both  $\psi_4$  and  $\psi_6$  have three-fold symmetry. A part of the energy map showing this situation is given in Figure 5. A similar result was obtained from an energy diagram for one variable,  $\psi_5$ , as shown in Figure 6, where all other rotation angles are fixed at  $60^\circ$ .

**Thiocholine Ion (IIb).**—By analogy with the method described for choline ion, (Ia), we find four important conformers A(A'), B, C(C'), and D(D') as shown in Figure 7.

**Chlorocholine Ion (IIIa).**—The energy diagram ( $\psi_5$  and  $\psi_4$ ) shows two important conformers A and B(B') and a slightly stabilized conformer C(C') (Figure 8).

When calculations for convergency by varying all rotation angles are made, conformer C(C') gradually

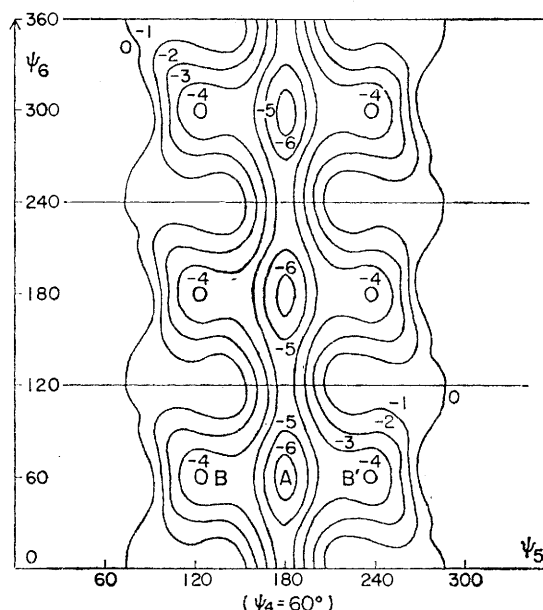


FIGURE 5 Calculated potential energy surface for n-propyltrimethylammonium ion with  $D \infty$ . The rotation angles  $\psi_1$ — $\psi_3$  are fixed at  $60^\circ$ . The spacing of contour lines is 1 kcal mol $^{-1}$

approaches conformer B(B') and finally B and C give an identical convergence point.

The convergence points in the regions of main stable conformers, and the energies of these ions are listed in

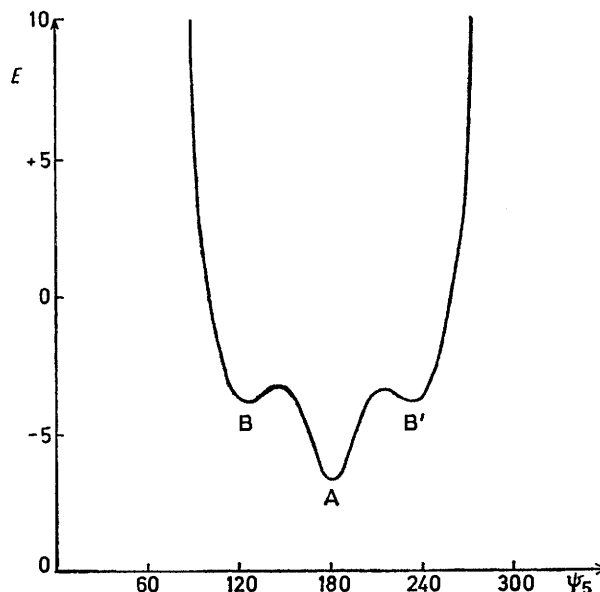


FIGURE 6 Energy diagram of n-propyltrimethylammonium ion for one variable  $\psi_5$ . The rotation angles  $\psi_1$ — $\psi_4$  and  $\psi_6$  are fixed at  $60^\circ$ , and  $D = \infty$

Table 4, where one of the equivalent enantiomers is omitted.

The present calculations show that the most stable

conformation of all ions (examined) is the  $\psi_5$ -*trans*-conformation (*i.e.*,  $\psi_5$  180°) when the  $E_e$  term is neglected. The result of our calculation on ion (Ib), neglecting the  $E_e$  term, is almost identical to that reported by Liquori *et al.*<sup>14</sup> On the other hand the high stability of the  $\psi_5$ -*gauche*-conformation of ions (Ia) and (Ib) and that of the  $\psi_5$ -*trans*-conformation of ions (IIa) and (IIb) are indicated by calculations in which the  $E_e$  term is included,  $D$  being taken as 1, 2, or 4. In addition, a

the  $\psi_5$ -*gauche*- $\psi_6$ -*gauche*-conformation of the organic cation is not altered by the influence of the counter anion even in the crystal state. We cannot decide by the above calculations alone which interpretation is better.

From an n.m.r. study on ion (Ib) in heavy water Culvenor and Ham suggested the predominance of the  $\psi_5$ -*gauche*- $\psi_6$ -*trans*-conformation from consideration of the value of the acylation shift.<sup>2a</sup> If this suggestion is

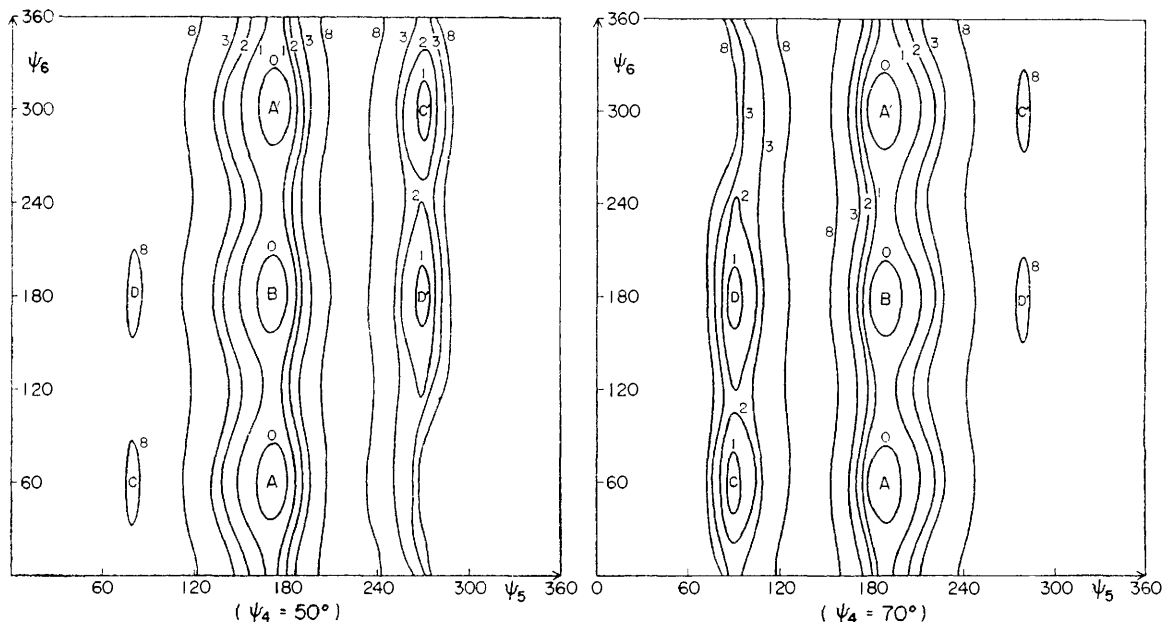


FIGURE 7 Calculated potential energy surface for thiocholine ion with  $D$  4. The rotation angles  $\psi_1$ — $\psi_3$  are fixed at 60°. The contour lines are in kcal mol<sup>-1</sup>

similarity in stability of  $\psi_5$ -*gauche*- and  $\psi_5$ -*trans*-conformations of ion (IIIa) results from the contribution of  $E_e$  ( $D$  4).

The most stable conformation of ion (Ib) given by these calculations is  $\psi_5$ -*gauche*- $\psi_6$ -*gauche*, which corresponds to the conformation in the crystal state.<sup>16</sup> This

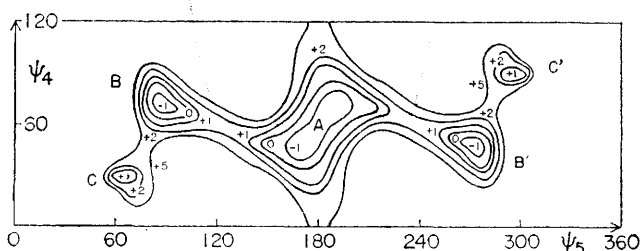


FIGURE 8 Calculated potential energy surface for chlorocholine ion with  $D$  4. The rotation angles  $\psi_1$ — $\psi_3$  are fixed at 60°. The contour levels are in kcal mol<sup>-1</sup>

result, however, seems to be rather accidental because the influence of the counter anion is neglected in our calculations and it will have considerable importance for the crystal structure of the ammonium salt. Another possible explanation of this is that the high stability of

valid, the important effect of solvation around polar sites of a solute has to be considered as a possible cause of the high stability of the  $\psi_5$ -*gauche*- $\psi_6$ -*trans*-conformation, where the repulsion between the solvated cationic pole and the solvated acetoxy-group will be somewhat relieved in the  $\psi_6$ -*trans*-conformation and the attractive force by electrostatic interactions between the cationic pole and ether oxygen will cause retention of the  $\psi_5$ -*gauche*-conformation. However, it will be better to investigate exhaustively the conformational behaviour of ion (Ib) in solution, since the acylation shift alone is not sufficiently strong to prove the  $\psi_5$ -*gauche*- $\psi_6$ -*trans*-conformation.

Although the orientation of the hydrogen of the hydroxy-group of ion (Ia) has not been determined by *X*-ray or n.m.r. analysis, the  $\psi_5$ -*gauche*-conformation in the crystal structure<sup>16</sup> and its predominance in solution<sup>1,2b,c</sup> have been clarified. The result of our calculations including the  $E_e$  term is in good agreement with this.

Calculations on ions (IIa) and (IIb) indicate high stability of the  $\psi_5$ -*trans*-conformation as expected from n.m.r. studies and/or *X*-ray analysis.<sup>1,2b</sup> Since a methyl group is not electronegative, the influence of the  $E_e$

term on conformations of ion (IIa) is expected to be small. The results of calculations with different dielectric constants support this. The preferred  $\psi_5$ -*trans*-conformation was indicated regardless of whether the  $E_s$  term was neglected or not and the energy difference between the  $\psi_5$ -*trans* and  $\psi_5$ -*gauche* conformers did not vary much with the dielectric constants used. In addition, almost constant values were obtained for the

TABLE 4

Main stable conformers of  $\beta$ -substituted ethyltrimethylammonium ions and their energies

Compound (Ia)	D	Con- former <sup>a</sup>	Rotation angles (°) ( $\psi_1, \psi_2, \dots, \psi_n$ )	Relative energy $\Delta E$ (kcal mol <sup>-1</sup> )
1	1	A	(54, 60, 77, 44, 50, 178)	0
		B	(53, 60, 76, 44, 52, 68)	0.77
		C	(52, 60, 68, 60, 180, 180)	6.94
		D	(52, 60, 68, 58, 178, 64)	7.47
	2	A	(52, 60, 76, 46, 57, 180)	0
		C	(52, 60, 77, 47, 57, 64)	0.23
		C	(52, 60, 68, 60, 180, 180)	2.67
		D	(52, 60, 68, 59, 179, 62)	2.90
	4	A	(51, 60, 72, 66, 72, 180)	0
		B	(50, 60, 73, 63, 70, 62)	0.04
		C	(52, 60, 68, 60, 180, 180)	0.82
		D	(52, 60, 68, 60, 180, 62)	0.91
	$\infty$	A	(52, 60, 68, 60, 180, 61)	0
		B	(52, 60, 68, 60, 180, 180)	0.06
		C	(52, 60, 70, 68, 75, 61)	0.75
		D	(52, 60, 69, 68, 76, 181)	0.86
1	1	A	(54, 60, 82, 44, 48, 66, 180, 60)	0
		B	(50, 60, 85, 56, 60, 238, 180, 60)	4.03
		C	(56, 60, 67, 69, 219, 66, 180, 60)	4.32
		D	(52, 60, 68, 60, 180, 180, 180, 60)	14.34
	2	A	(54, 60, 80, 45, 51, 69, 180, 61)	0
		B	(55, 60, 65, 70, 213, 69, 180, 60)	2.56
		C	(53, 60, 73, 43, 55, 201, 180, 60)	2.96
		D	(52, 60, 68, 60, 180, 180, 180, 60)	6.56
	4	A	(53, 60, 79, 46, 54, 71, 180, 60)	0
		B	(52, 60, 65, 69, 196, 73, 180, 60)	1.42
		C	(52, 60, 72, 67, 71, 191, 180, 60)	1.52
		D	(52, 60, 68, 60, 180, 180, 180, 60)	2.97
	$\infty$	A	(52, 60, 68, 60, 180, 180, 180, 60)	0
		B	(51, 60, 68, 62, 183, 75, 180, 60)	0.01
		C	(50, 60, 73, 64, 70, 74, 180, 60)	0.32
		D	(52, 60, 70, 68, 74, 184, 180, 60)	0.35
1	1	A	(52, 60, 68, 60, 180, 60)	0
		B	(53, 60, 65, 68, 98, 59)	3.00
	2	A	(52, 60, 68, 60, 180, 60)	0
		B	(53, 60, 65, 68, 98, 59)	2.60
	4	A	(52, 60, 68, 60, 180, 60)	0
		B	(52, 60, 65, 68, 97, 59)	2.39
	$\infty$	A	(52, 60, 68, 60, 180, 60)	0
		B	(52, 60, 65, 68, 97, 59)	2.19

TABLE 4 (Continued)

Compound	D	Con- former <sup>a</sup>	Rotation angles (°) ( $\psi_1, \psi_2, \dots, \psi_n$ )	Relative energy $\Delta E$ (kcal mol <sup>-1</sup> )
(IIb)	1	A	(52, 60, 68, 60, 180, 180)	0
		B	(52, 60, 68, 59, 179, 62)	0.22
		C	(53, 60, 67, 70, 87, 179)	1.18
		D	(53, 60, 67, 70, 87, 64)	1.38
	2	A	(52, 60, 68, 60, 180, 180)	0
		B	(52, 60, 68, 60, 180, 61)	0.04
		C	(53, 60, 67, 70, 87, 179)	1.28
		D	(53, 60, 67, 70, 87, 61)	1.30
	4	A	(52, 60, 68, 60, 180, 60)	0
		B	(52, 60, 68, 60, 180, 180)	0.05
		C	(53, 60, 67, 70, 87, 60)	1.31
		D	(53, 60, 67, 70, 87, 180)	1.39
$\infty$	A	(52, 60, 68, 60, 180, 59)	0	
	B	(52, 60, 68, 60, 180, 180)	0.15	
	C	(53, 60, 67, 70, 87, 58)	1.36	
	D	(53, 60, 67, 70, 88, 181)	1.53	
(IIIa)	1	A	(50, 60, 71, 67, 80)	0
		B	(52, 60, 68, 60, 180)	4.90
	2	A	(52, 60, 68, 69, 83)	0
		B	(52, 60, 68, 60, 180)	1.56
	4	A	(52, 60, 68, 60, 180)	0
		B	(52, 60, 68, 69, 85)	0.02
	$\infty$	A	(52, 60, 68, 60, 180)	0
		B	(52, 60, 67, 69, 87)	1.53

<sup>a</sup> A, B, C, and D are in decreasing stability order.

sets of rotation angles ( $\psi_1, \psi_2, \dots, \psi_6$ ) for both conformers from calculations at different dielectric constants. With ion (IIb), very similar tendencies were found because of the weak electronegativity of the thiol. The substituents in ions (Ia), (Ib), and (IIIa) are electro-negative and thus it can be expected that electrostatic interactions have much influence on conformation. In fact, considerable variation of the rotation angles of the stable conformers, ( $\psi_1, \psi_2, \dots, \psi_n$ ), and large variations of energy differences among conformers are found, depending on the effective dielectric constant used with those ions. However, the fact that high stability of the  $\psi_5$ -*gauche*-conformations of (Ia and b) and a similar stability of the  $\psi_5$ -*gauche*- and  $\psi_5$ -*trans*-conformations of (IIIa) can be obtained only when the  $E_s$  term is taken into account reveals the importance of the contribution of electrostatic interactions in their conformational control. We can estimate an approximate energy difference between the  $\psi_5$ -*gauche*- and the  $\psi_5$ -*trans*-conformation in solution from the result of n.m.r. population analysis,<sup>1,2</sup> if the system observed can be regarded as an equilibrium between the two conformers. With ions (Ia), (Ib), and (IIb), however, the result of calculations indicated the existence of more than two stable conformers. In this case, evaluation of the free energy difference,  $\Delta G^0$ , by the n.m.r. method assuming a two conformer-system will not be adequate. Even so, we can compare the populations of all ions estimated by the results of calculations with those obtained by n.m.r. analysis, where it is assumed that the population of the *gauche*-form,  $P_g$ , and that of the *trans*-form,  $P_t$ , obtained by the n.m.r. method correspond to the sum of the populations of  $\psi_5$ -*gauche*- and



that of  $\psi_5$ -*trans*-conformations, respectively. The populations of conformers A, B, . . . , N are calculated by equations (14) and (15). Here, energies  $E(A)$ ,  $E(B)$ , . . . ,

$$P_A : P_B : \dots : P_N \\ = e^{-E(A)/RT} : e^{-E(B)/RT} : \dots : e^{-E(N)/RT} \quad (14)$$

$$P_A + P_B + \dots + P_N = 1 \quad (15)$$

and  $E(N)$  are estimated from the result of the present calculations by taking the mixing entropy ( $R \ln \Omega$ ) into consideration.

With ions (IIa) and (IIIa), the present calculations also indicate the validity of the two-conformer approximation. Therefore we can directly compare the energy difference calculated with that obtained by the n.m.r. method for ions (IIa) or (IIIa). N.m.r. population

Surprisingly, the populations calculated for  $D$  4 are, for all ions, in fairly good agreement with those obtained by n.m.r. analyses, although the result for ion (Ib) shows some discrepancy. When we calculated the populations with other  $D$  values, 1, 2, and  $\infty$ , considerable discrepancies resulted between  $P_g(P_t)$  calculated and that obtained by n.m.r. analysis for some ions.

Energy calculations for  $D$  1.8, as suggested by Froimowitz and Gans,<sup>3c</sup> and for  $D$  79, which is the dielectric constant of water, were also attempted, but the results were very similar to those obtained for  $D$  2, and  $\infty$ , respectively.

Thus, we can deduce empirically that an adequate value of effective dielectric constant for the present calculation model of heavy water solution of these

TABLE 5

Comparison of populations of  $\beta$ -substituted ethyltrimethylammonium ions calculated with  $D$  4 and those estimated by n.m.r. analysis<sup>a</sup>

Compound <sup>b</sup>	Conformer ( $\psi_4, \psi_5, \psi_6$ ) <sup>c</sup>	$E(i) = \Delta E - RT \ln \Omega$ (kcal mol <sup>-1</sup> )	$\Omega$	$P_i^{\text{calc.}}$ (%)	$P_i^{\text{obs.}}$ (%) <sup>d</sup>
(Ib)	A (SGG)	0	2	84.7	$P_g \approx 92$ $P_t \approx 8$ $P = 0$
	B (STG)	1.42	2	8.0	
	C (SGT)	1.52	2	7.0	
	D (STT)	3.39	1	0.3	
(Ia)	A (SGT)	0	2	43.8	$P_g \approx 85$ $P_t \approx 15$ $P_g = 89$ $P_t = 11$
	B (SGG)	0.04	2	41.0	
	C (STG)	0.91	2	9.6	
	D (STT)	1.24	1	5.6	
(IIIa)	A (SG)	0	2	66.0	$P_g = 66$ $P_t = 34$ $P_g = 64$ $P_t = 36$
	B (ST)	0.40	1	34.0	
(IIb)	A (STG)	0	2	60.0	$P_t \approx 88$ $P_g \approx 12$ $P_g = 89$ $P_t = 11$
	B (STT)	0.47	1	27.6	
	C (SGG)	1.31	2	6.7	
	D (SGT)	1.39	2	5.7	
(IIa)	A (STS)	0	1	96.3	$P_t \approx 96$ $P_g \approx 4$ $P_t = 93$ $P_g = 7$
	B (SGS)	1.97	2	3.7	

<sup>a</sup> Values for D<sub>2</sub>O solution at 30°. <sup>b</sup>  $\beta$ -Substituent. <sup>c</sup> G, S, and T mean *gauche*, *staggered*, and *trans*, respectively. <sup>d</sup> Values estimated by the method by Abraham and Gatti (see ref. 2c).

analyses showed  $P_g$  ca. 0.04 ( $P_t$  ca. 0.96) for ion (IIa) in heavy water at 30°,\* and  $P_g$  ca. 0.64 ( $P_t$  ca. 0.36) for ion (IIIa); this corresponds to  $\Delta G^0$  (IIa) ca. -1.6 and  $\Delta G^0$  (IIIa) ca. 0.4 kcal mol<sup>-1</sup>, respectively. When we consider the fact that the  $\psi_5$ -*gauche*-conformer has a double probability, a correction of 0.42 kcal mol<sup>-1</sup> ( $RT \ln 2$ ) is needed for these values to compare with the calculated energy difference,  $\Delta E_{\text{total}}$ . Thus, for ion (IIa) ca. 2 kcal mol<sup>-1</sup> of energy difference is estimated by the n.m.r. method and here the  $\psi_5$ -*trans*-form is preferred. The same treatment with ion (IIIa) shows that the energy difference is almost zero.

When we compare the above values with the corresponding values of  $\Delta E_{\text{total}}$  calculated for  $D$  1, 2, 4, or  $\infty$ , fairly good agreement can be found for both ions for  $D$  4. This fact prompted us to compare the populations of all ions for  $D$  4 with those obtained by n.m.r. analyses of heavy water solutions. The results are listed in Table 5.

\* The value of  $P_g(P_t)$  reported previously<sup>1</sup> was that obtained at 50°. The present value was obtained by an examination at 30°.

ammonium ions is ca. 4, although we cannot theoretically rationalize this value at present.

There are some weak points in the present calculation method. First, the specific situation in a crystal field or in solution is not taken into consideration except for the introduction of  $D$  (an effective dielectric constant) into the calculation. Secondly, the method of estimating the net charges, though convenient, does have some problems. As pointed out by Huheey, the method results in the same electronegativity value for a group regardless of the way in which the component atoms of the group are combined.<sup>8</sup> This means that the same value is obtained for the net charge of atom X in molecules R-X and R'-X when R and R' have the same components, even though in different combinations. For example, the net charges of all hydrogen atoms of choline ion are evaluated as +0.073, contrary to the expectation that the hydrogen of the hydroxy-group will be more positively charged than hydrogens attached to the  $\beta$ -carbon. The very slight differences in net charge among the hydrogens or carbons in ions calculated (the net charges should be equal by this method

in so far as we use the same electronegativity for the hydrogens or the carbons) arise from the errors incurred by discarding fractions  $<0.01$  for coefficients  $a$  and  $b$  of the calculated electronegativities of the groups, and fractions  $<0.001$  in the absolute charge unit. For the acetylcholine ion the orbital O(te) was used for the carbonyl oxygen in accordance with Pauling's 'bent  $\sigma$ -bond' concept<sup>17</sup> because a three-fold potential function was employed also for the torsional energy of RCO-CH<sub>3</sub>. If we regard the carbonyl double bond as a bent  $\sigma$ -bond, the carbonyl carbon can be assumed to be almost tetrahedral because the bond angle  $\widehat{OC^*C^{**}}$  is  $110^\circ$  (see Table 3) and therefore the carbonyl oxygen can also be assumed to be almost tetrahedral. This causes the absolute value of the net charge of the carbonyl oxygen ( $-0.383$ ) to be slightly less than that of ether oxygen ( $-0.396$ ).<sup>\*</sup> MO calculations indicate the reverse tendency,<sup>10a,b</sup> except the results of *ab initio* calculations.<sup>10c</sup> The general state of charge distribution calculated for ion (Ib), however, is in good agreement with the results of MO calculations, except for the low charge density of the carbonyl carbon. Strictly speaking, it would be most desirable to use a more accurate representation of the oxygen and carbon orbitals of the

\* When we use the orbitals O(tr) and C(tr) for carbonyl oxygen and carbonyl carbon and use O (26.8% s) for ether oxygen,<sup>7,12</sup> a larger absolute value is obtained for the charge of the carbonyl oxygen ( $-0.457$ ) than for that of the ether oxygen ( $-0.392$ ). The energy calculation using these net charges also gives very high stability for the  $\psi_6$ -gauche-conformer.

† We varied all rotation angles except  $\psi_7$ ; Froimowitz and Gans varied only two angles, and neglected torsional energies. Ajo *et al.* did not give details of the conformations ( $\psi_1, \psi_2, \dots, \psi_6$ ) and fixed angles used.

acetoxy-group, taking the partial double bond character into consideration, and to test the variation of  $E_{\text{total}}$  by the rotation of  $\psi_7$ . There are some other weak points in the present method of calculation, but at least it does confirm the important contributions of electrostatic interactions and van der Waals interactions to the conformation of ammonium ions, especially those having electronegative but not so bulky substituents. Using a similar treatment including the  $E_\sigma$  term, Ajo *et al.* and Froimowitz and Gans have recently calculated the conformation energy of the acetylcholine ion.<sup>3a,c</sup> There are some differences among their results and ours for the stable conformations, their energies, and their stability order. These arise partly from the difference in fixed rotation angles used in the energy calculations,<sup>†</sup> and partly from the use of different parameters (net charges and other constants).

In any case, all workers recognize the importance of the electrostatic interaction effect on the total energy.

The considerations in this paper will also be useful for an understanding of the conformational behaviour of cyclic ammonium ions and their phosphonium ion analogues.

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<sup>17</sup> L. Pauling, 'The Nature of the Chemical Bond,' Cornell University Press, Ithaca, 3rd edn., 1960.