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An *ab initio* Study of the Hydration of Alkylammonium Groups

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Ab initio STO 3G calculations of the electronic structure and interaction energies with water of methyl and ethylammonium ions are reported. It is shown that the calculations predict a preferential attack at the α-group (relative to the nitrogen), in agreement with experimental facts, and that successive ethylation reduces the favorable energy of hydration.

Key words: Hydration of alkylammonium

Introduction

Alkylammonium groups occur frequently in pharmacologically active molecules; well-known examples are the cholinergic and adrenergic drugs. Generally, the nature of the alkyl substituents has a critical influence on the activity of the drug. For instance, in acetylcholine, replacement of the methyl groups of the cationic head by either ethyl groups or hydrogen atoms greatly reduces parasympathomimetic activity [1, 2]. In the adrenergic catecholamines, replacement of a hydrogen atom of the ammonium head by methyl and higher alkyl groups leads to a decrease in *alpha* activity but to an increase in *beta* activity [1, 3]. Similar modifications of the alkyl groups also produce changes in physicochemical properties of alkylammonium ions in aqueous solution. These last changes have often been discussed in terms of the interactions of these ions with the water structure (see e.g. [4–6]).

This paper presents the results of a theoretical study of the electronic properties of methyl and ethyl ammonium ions and of their interactions with water. In particular we wish to examine whether there are significant changes in interaction with water when the methyl groups of a cationic head are replaced by ethyl groups. The calculations have been performed using the SCF *ab initio* method in an STO 3G basis [7]. The program Gaussian 70 [8] was used for the computations. Standard bond lengths were used ($N–C = 1.49$ Å, $C–C = 1.51$ Å, $C–H = 1.09$ Å), and all angles were taken to be tetrahedral.

Results

Atomic Charges of $N(CH_3)_4^+$ *and* $N(C_2H_5)_4^+$

There is some disagreement in the literature about the distribution of charge in alkylammonium groups. PCILO calculations by Pullman and Courrière [9] on acetylcholine, and CNDO calculations by George *et al.* [10] on alkylam-

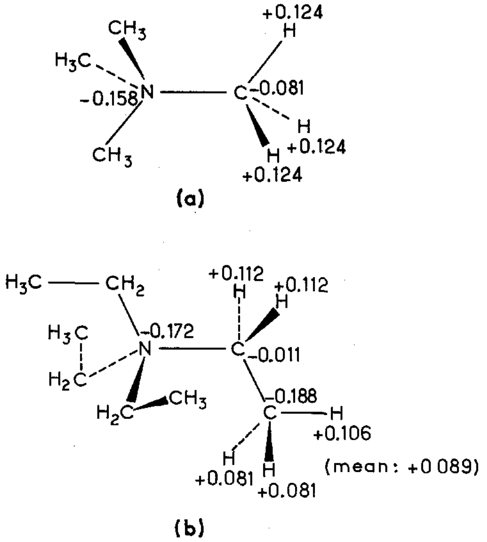

Fig. 1. Atomic charges in a) tetramethylammonium ion and b) tetraethylammonium ion. A positive charge corresponds to a deficiency of electrons

monium, show the positive charge distributed over the hydrogen atoms with the nitrogen and carbon atoms roughly neutral. This presents a picture of the alkylammonium head as a sphere of positive charge, with the nitrogen atom buried in the centre, and has obvious consequences for interaction with nucleophiles. INDO calculations on acetylcholine [11] predict on the contrary that the positive charge rests on the nitrogen atom and adjacent carbon atoms, which suggests different possibilities for attack by nucleophiles such as water.

The net atomic populations obtained by the STO 3G calculations for the tetramethyl and tetraethylammonium ions are shown in Fig. 1. In both ions the nitrogen atom is seen to be negative while the positive charge is located entirely on the hydrogen atoms. This last result clearly disagrees with the INDO predictions but is in accord with the PCILO and CNDO ones.

In the tetraethyl ion, which has more hydrogens, the positive charge is more spread out, but a striking fact is that it is not uniform. Thus the α (methylene) hydrogens are more positive than the β (methyl) ones; $+0.112$ electron units as compared to $+0.089$ (mean value) respectively. Moreover, the α carbons are less negative than the β ones, (-0.011 and -0.188 respectively), thus making the methylene groups *overall* considerably more positive than the terminal methyl groups or the nitrogen atom. These charge distributions, characteristic of ethyl and methyl groups, remain largely unaltered in the mixed ions, thus methyl has very similar atomic charges in $N(CH_3)_4^+$ and in $NCH_3(C_2H_5)_3^+$.

In as far as hydration of alkylammonium ions is a predominantly long-range interaction depending on electrostatic forces, one might hope to predict the site of attack by water, or another nucleophile, from these charge distributions. Thus it seems most likely that such attack would occur at a position α to the nitrogen rather than at this atom itself or at the hydrocarbon chain ends. To definitely

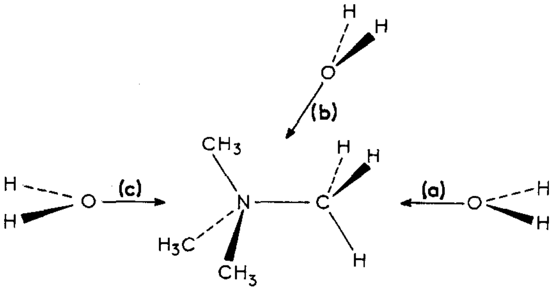

Fig. 2. Paths of approach of a water molecule to a tetramethylammonium ion. (a) direct approach towards a CH_3 group along the prolongation of an NC bond. (b) bisecting approach along the bisectrix of two NC bonds. (c) axial approach on an NC axis [opposite to approach (a)]

establish the preferred hydration sites we have computed the interaction energy of a molecule of water with the alkylammonium ion in different orientations. These calculations are described below.

Hydration of the $N(CH_3)_4^+$ *Ion*

We have calculated the *ab initio* STO 3G energy of the system tetramethylammonium ion + water, as a function of intermolecular separation, for three possible paths of approach shown in Fig. 2.

The *direct* approach of water towards a methyl group along the N–C axis, (a) in Fig. 2, gives a minimum in total energy at C–O separation of 3.1 Å and with an interaction energy (relative to the isolated molecules) of −5.4 kcal/mole. An approach along a bisector of two C–N bonds, (b) in Fig. 2, shows a more favourable interaction (−6.4 kcal/mole at N–O distance of 3.7 Å) possibly because the oxygen atom can interact simultaneously with two sets of positive α-methyl hydrogens. Axial approach along a C–N axis as in (c) in Fig. 2 permits simultaneous interaction with three α groups and is even more favourable. The minimum occurs at N–O separation of 3.4 Å and with an interaction energy of −10.3 kcal. The energy curve for this type of approach is shown in Fig. 3. It is interesting that the exact orientation of the water hydrogens is not found to be very important, leading to differences of less than 0.5 kcal/mole at the minimum.

The above results show a gain in stabilisation when the water molecule can interact with more than one α group. The most favoured hydration site (Fig. 2(c)] permits simultaneous interaction with three α groups, and there are four equivalent sites of this type. Although the sites where water interacts with only two α groups are less favoured, there are six of them, and it is difficult to predict *a priori* which type of fixation will be more effective in the total hydration of $N(CH_3)_4^+$. We have accordingly added further water molecules in equivalent positions up to a maximum of four (which is the limit imposed by the program) and calculated the interaction energy for each complex, relative to the isolated components. These results are shown in Table 1 for both types of interaction and it is clear from the trends observed that even with six water molecules in the bisecting positions the total interaction energy will be less than for the complex with four water molecules in the most favoured axial sites.

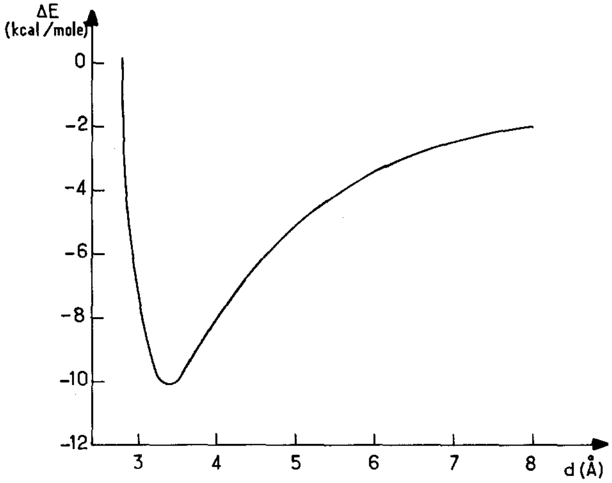

Fig. 3. The calculated stabilization energy for the interaction of tetramethylammonium ion with water as a function of intermolecular separation [water approaches as in Fig. 2, (c)]. ΔE: stabilisation energy; d: N–O distance

Table 1. Calculated energies of interaction of tetramethylammonium ion with water molecules in two different types of site (STO 3G energies in kcal/mole)

Number of water molecules	Energy of interaction	
	(b) (bisectrix)	(c) (axial)
1	− 6.4	−10.3
2	−12.5	−19.2
3	−18.2	−27.6
4	−23.5	−35.3
	...	
	...	

Hydration of the Ethyl-Substituted Ions

The single ethyl group in $(CH_3)_3N\,C_2H_5^+$ offers the choice of α or β attack by water as shown in Fig. 4. The β approach is exactly analogous to case (a) in $N(CH_3)_4^+$ above but yields an interaction energy of (only) −3.4 kcal/mole at a C–O distance of 3.1 Å. The α approach (to the methylene group) is more favourable giving −5.6 kcal/mole at a C–O distance of also 3.1 Å. Thus *within the ethyl group, α attack by water is favoured over β attack.* Between different α positions, an α methylene group and an α methyl group are about equally attractive to water. In connection with these results it is interesting to note that experimental observations of the crystal structures of a number of choline derivatives [12] show the halide counter-ion to be almost always located in the vicinity of an α position on the alkyl substituents of the cationic head.

With regard to the total hydration of $(CH_3)_3N\,C_2H_5^+$, the ethyl group sterically hinders approach to one of the most favoured "axial" sites [Fig. 2(c)] but three

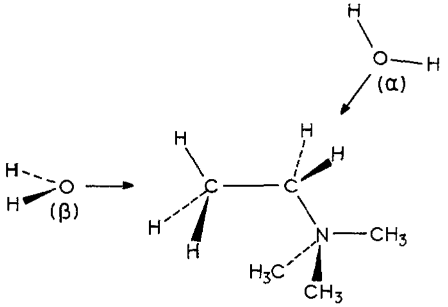

Fig. 4. The monoethyl substituted ion showing approach of water to α and β positions

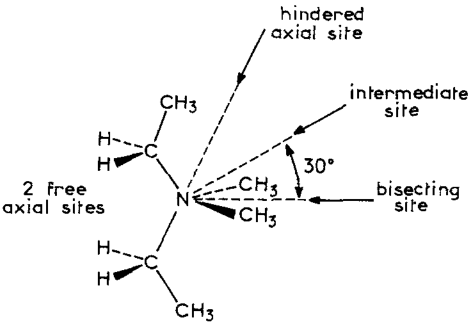

Fig. 5. Types of hydration site considered in the diethyl substituted ion

others are available. With these three occupied, the calculated energy of interaction is -26.7 kcal/mole slightly less than for the first three water molecules in $N(CH_3)_4^+$. The limitations of the program do not permit the addition of one more water molecule, but it is clear that this could only enhance the difference relative to $N(CH_3)_4^+$.

In the diethyl-substituted ion $(CH_3)_2N\,(C_2H_5)_2^+$ the two ethyl groups may be either *syn* or *anti*. In either case two of the "axial" sites are free and two are rather sterically hindered (see Fig. 5). The two water molecules in the hindered sites can occupy intermediate positions nearer to a bisecting type. Indeed the calculation shows a maximum interaction energy with these two molecules lying 30° above and below the plane of the N atom and the two methyl carbons (Fig. 5), with an N–O separation of 3.6 Å. The energies of interaction of one and two water molecules in these positions are given in Table 2 and indicate that the second ethyl substituent brings about slight further decreases relative to the tetramethylammonium ion.

In the triethylsubstituted ion, $CH_3N(C_2H_5)_3^+$, we have calculated the best energy of interaction with one water molecule. This molecule occupies an intermediate site of the type described above and the interaction energy shows again a further reduction (Table 2).

Table 2. Calculated hydration energies of methyl and ethylammonium ions as a function of number of water molecules and degree of ethylation (STO 3G energies in kcal/mole)

Number of water molecules	Energy of interaction NMe_4^+	NMe_3Et^+	$NMe_2Et_2^+$	$NMeEt_3^+$
1	−10.3	− 9.7	− 8.7	−8.2
2	−19.2	−18.4	−16.0	—
3	−27.6	−26.7	—	—
4	−35.3	—	—	—

Conclusions

The present calculations predict a gradual decrease in the magnitude of the hydration energy when the size and number of alkyl groups are increased. This trend is well illustrated by the figures of Table 2 and has two causes:

1) The charge distribution is smoothed out as the size of the alkyl chain increases, so that the positive charge located on the hydrogens becomes less concentrated.

2) Successive ethylation introduces steric hindrances, making the most favoured "axial" sites of $N(CH_3)_4^+$ less and less available.

It is interesting to remark that the order of the trend obtained is parallel to the order of decreasing blocking activity exerted by quaternary ammonium derivatives at the neuro muscular junction [13].

Note Added in Proof: Further calculations show that due to the large positive charges on the hydrogens, direct C–H...O hydrogen bond formation is possible. Thus a water molecule forms such a hydrogen bond of −10 kcal/mole in NMe_4^+; of −9 kcal/mole at an α position in the ethylated ions and of −6 kcal/mole at a β position. The α preference noted above is thus preserved. It seems unlikely that such interactions significantly change the overall hydration described above. Although twelve sites for H-bonding exist in NMe_4^+, they approach each other rather closely and after addition of four water molecules further water molecules introduce such intermolecular repulsions as to reduce rather than increase the total hydration energy which remains always slightly lower than that obtained with water in the axial type of site described above [14].

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