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Ab Initio Molecular Orbital Calculations of Electron Distribution in Tetramethylammonium Ion

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SUMMARY

Ab initio molecular orbital calculations of electron distribution in tetramethylammonium ion and its uncharged isoelectronic analogue, neopentane, have been carried out. Comparison of the two compounds permits a detailed description of the delocalization of the positive charge of tetramethylammonium ion. The van der Waals surface of this ion is found to be characterized by "patches" of positive charge associated with the methyl groups, interspersed with essentially neutral regions. The consequences of this nonspherical charge distribution for interaction with anions have been explored by calculations of the interaction energy of fluoride ion with tetramethylammonium ion and neopentane in several mutual orientations. The lowest-energy orientation is found to be one in which the anion approaches a "face" of the tetrahedral cation (opposite to a C—N bond direction). The origins of this preference and the electron redistribution produced by the interaction with fluoride are discussed. The tetramethylammonium ion is clearly not a featureless positively charged sphere but will have appreciable geometrical specificity in its interaction with a presumed anionic group on the acetylcholine receptor.

INTRODUCTION

Of the factors determining the ability of a drug to form a complex with a receptor, two—the shape of the drug molecule and its charge distribution—appear to be particularly important. Clearly there should be a complementarity between the shape of the drug and that of its binding site so as to minimize repulsive interactions and maximize attractive ones. Similarly, experience in medicinal chemistry has shown that active drugs often bear a net charge which is important for activity. For example, on guinea pig ileum, acetylcholine has 3000 times the potency of its uncharged isoelectronic analogue, 3,3-dimethylbutylacetate (1).

Both shape and charge are, of course, directly related to the electron distribution in the molecule, and are therefore related to one another. For example, the "textbook" description of ionic interactions as isotropic (i.e., nondirectional) is based on a point source model. This is entirely adequate for simple inorganic ions, where the charge distribution is spherically symmetrical (and thus equivalent to a point source at the center of a sphere), but it is unlikely that this will be a satisfactory description for organic ions of more complex shape. Similarly, since the introduction of a net charge into a molecule will lead to a redistribution of electron density, it may be accompanied by a significant change in the shape of the molecule.

To explore these questions as they relate to the specificity of drug-receptor interactions, we have embarked on a detailed study of electron distribution in acetylcholine and related compounds by *ab initio* molecular orbital methods. Although a number of molecular orbital calculations on acetylcholine have been reported (2–7), these have been primarily concerned with the conformation of the molecule, and descriptions of the electron distribution have been confined to Mulliken population analysis (8), whose limitations are well known (9).

In this first paper we describe calculations on the "cationic head" of acetylcholine, TMA[2] (itself an interesting drug), and neopentane. TMA and neopentane contain the same number of electrons but differ in the nuclear charge on the central atom. A comparison of these molecules will thus throw light on the questions of shape and charge distribution discussed above.

METHODS

Ab initio molecular orbital calculations were carried out with the Gaussian 70 program package (10), using 6-31G or STO-3G basis sets as indicated in the text. Idealized tetrahedal geometry (i.e., bond angles set at 109.45°) was used for both TMA and neopentane. Since we wished to calculate the difference in electron distribution between these two molecules, it was necessary to set the N—C and C—C bonds at

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[2] The abbreviation used is: TMA, tetramethylammonium ion.

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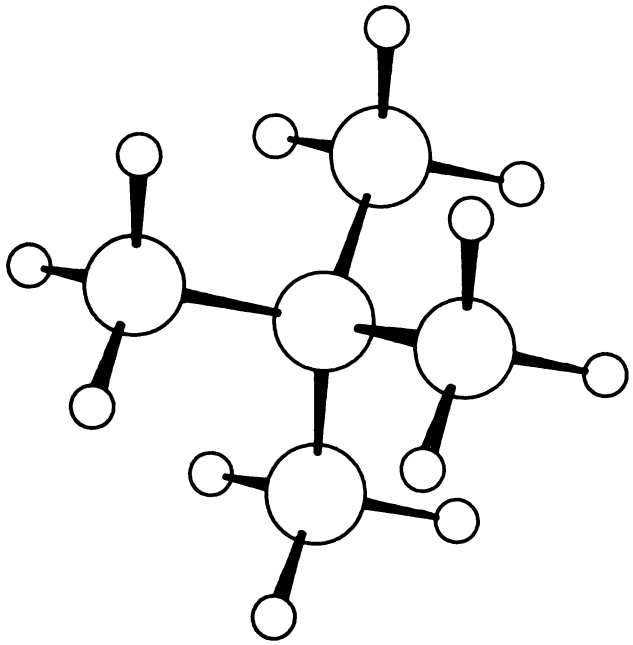

FIG. 1. *Conformation of TMA and neopentane used in the electron density calculations*

equal lengths. The electron density maps shown below were calculated with both of these bonds set equal to the N—C bond length of 1.47 Å. We have confirmed that closely similar results are obtained with both bonds set at the C—C bond length of 1.52 Å. A direct comparison showed that the electron density around the protons of the methyl groups (a part of the molecule of particular interest for the present discussion) was altered by no more than 0.006 $e/Å^3$ when the N—C bond length was altered from 1.47 to 1.52 Å. We conclude that the use of both C—C and N—C bonds set at 1.47 Å has no significant effect on our conclusions. All C—H bond lengths were set at the standard value of 1.09 Å.

The remaining geometrical variable is the torsion angle about the N—C or C—C bonds, determining the mutual orientation of the methyl groups. The conformation used in the calculations is shown in Fig. 1; this is very similar to that seen in the crystal (11, 12), and we have found it to be the lowest energy conformation (STO-3G basis set, fixed bond lengths and angles).

RESULTS AND DISCUSSION

Electron distribution in the isolated molecules. Figure 2A shows the electron distribution in TMA, displayed in a plane which includes the central nitrogen atom, two methyl carbon atoms, and two hydrogen atoms. We have computed the electron density in a series of sections through the molecule, but, because of the tetrehedral symmetry of the molecule, the essential features of the electron distribution can be appreciated from this single section. A corresponding electron density map for neopentane is shown in Fig. 2B. (For discussion of the charge distribution in neopentane, see also ref. 13.)

The primary effect of the increased nuclear charge on the central atom in TMA as compared with neopentane will, of course, be to draw electrons in toward the center of the molecule. This can be seen clearly in Fig. 2, and in the form of an increase in electron density around the nitrogen atom and in the nitrogen-carbon bond of TMA as compared with the corresponding regions of neopentane [note the greater area within the 2.69 $e/Å$ contour (contour *k*) in TMA].

As noted under Introduction, this redistribution of electrons will potentially lead to a change in size and shape of the molecule. The surface of the isolated molecule can usefully be defined by the 0.027 $e/Å^3$ contour

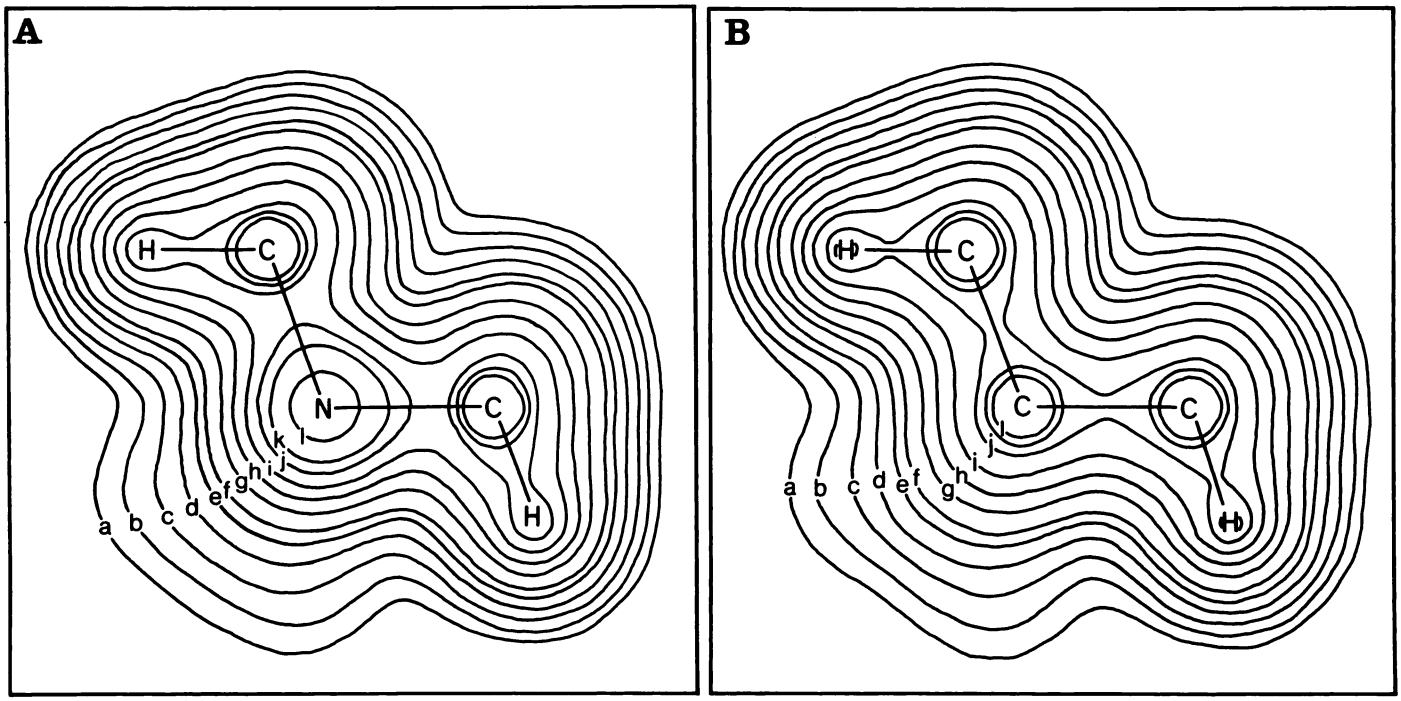

FIG. 2. *Electron density distribution in (A) TMA and (B) neopentane*

The contours are at the following electron density levels: *a*, 0.027; *b*, 0.043; *c*, 0.068; *d*, 0.107; *e*, 0.169; *f*, 0.269; *g*, 0.426, *h*, 0.675; *i*, 1.067; *j*, 1.694; *k*, 2.687; and *l*, 4.26 $e/Å^3$.

TABLE 1

Mulliken population analysis of electron distribution in TMA and neopentane[a]

	TMA	Neopentane	Difference[b]
Central atom (N or C)	7.164	5.961	−1.203
Methyl C	6.078	6.169	+0.091
H	0.877	0.947	+0.070

[a] STO-3G basis set.

[b] Positive sign indicates a deficiency of electrons in TMA.

(*a* in Fig. 2A and B) (14). (When two neutral molecules approach one another, significant electron-electron repulsion is first evident when the two 0.027 $e/Å^3$ contours overlap; this definition corresponds closely to the traditional van der Waals radii.) On this basis, the charge in TMA leads to a decrease of 0.08 Å, or 2.6%, in the radius of the molecule along the C—N bond direction, although there is no change in the radius along the bisector of the C—N—C angle. In this case, therefore, there is some change in size and shape arising from the introduction of the positive charge, but it is, for practical purposes, negligible. This remains true when we include the further decrease of 1.6% in the radius measured along the C—N bond due to the 0.05 Å difference between C—C and C—N bond lengths. Neopentane and TMA are thus essentially isosteric, confirming that the difference in charge is the important difference between them.

The distribution of this charge within the molecule will obviously be an important determinant of the interactions between TMA and other molecules, including a receptor. The over-all pattern of electron distribution (and hence of charge delocalization) can be evaluated in an approximate manner by Mulliken population analysis (8) of TMA and neopentane. The results of this analysis are given in Table 1; the results for TMA are essentially identical with those previously calculated, using the same basis set, for TMA (15) and acetylcholine (6). The Mulliken analysis suggests that all of the net positive charge of TMA is delocalized on to the methyl groups, predominantly onto the hydrogens, leaving the nitrogen atom, paradoxically, with a net negative charge of 0.2 *e*. This unexpected result for the nitrogen atom arises from weaknesses in the Mulliken procedure (see ref. 9), notably the fact that the overlap population is divided equally between adjacent atoms—clearly an unrealistic procedure when polarization is present (see below). A number of improved procedures for associating electron populations with specific atoms have been proposed (see refs. 9 and 16), one of which consists of integrating the electron population within a sphere of covalent radius centered on the atom of interest (17). Using this procedure, Marchington *et al.* (15) calculated that the electron population associated with the nitrogen of TMA was about 0.76 electron greater than for the central carbon of neopentane, giving a net positive charge of 0.24 *e* on the nitrogen. This is undoubtedly a more realistic value than that given by the Mulliken procedure, but the essential point, that there is extensive delocalization of the positive charge onto the methyl groups, remains qualitatively true.

To examine this delocalization in more detail, we have calculated a difference electron density map between TMA and neopentane, shown in Fig. 3. It is clear from this difference map that the flow of electrons in toward the nitrogen in TMA is not spherically symmetrical. Rather, as expected, it occurs by polarization along the bonds (or, more precisely, polarization from one orbital to another). The main features of the difference map can readily be understood in terms of this polarization (see also ref. 18). First, the N—C bonds of TMA are clearly more polarized than the equivalent C—C bonds of neopentane. The buildup of electron density around the positively charged nitrogen is accompanied by a decrease in electron density at the other end of the N—C bond as the electrons are polarized from the carbon *sp* hybrid orbital to that of the nitrogen. There is also a decrease in electron density on the opposite side of the carbon atom, corresponding to the "tail" of the *sp* orbital involved in bonding to the nitrogen, which forms a rather pear-shaped lobe extending in the direction opposite to that of the C—N bond. Second, there is a similar polarization of electrons along the C—H bonds of TMA toward the central nitrogen atom. Thus there is a decrease in electron density around the hydrogen atom, accompanied by an increase at the carbon end of the C—H bond, and, again, in a lobe extending on the far side of the carbon atom.

It is clear from the difference electron density map that the net result of these shifts in electron distribution in TMA relative to neopentane is a distinctly nonspherical distribution of the delocalized positive charge. The

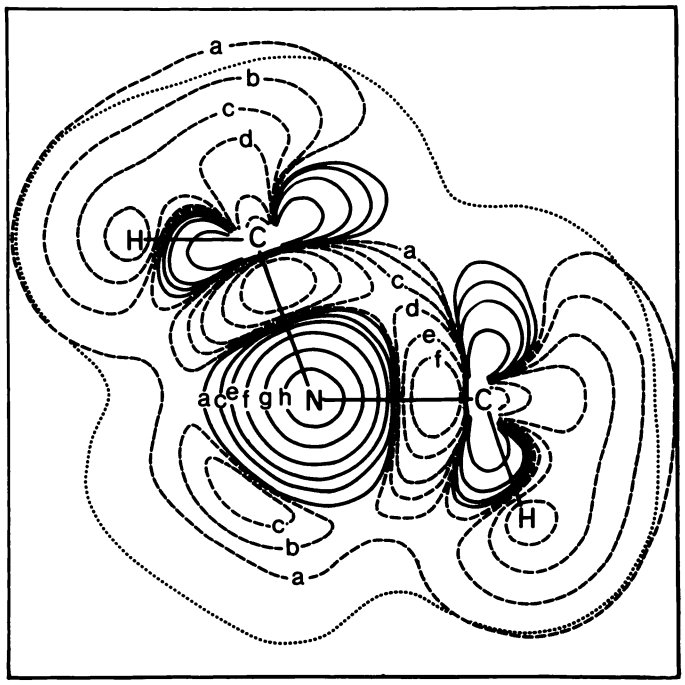

FIG. 3. *Difference electron density map of TMA minus neopentane* *Solid contours* indicate regions where the electron density is higher in TMA than in neopentane; *dashed contours*, regions where the electron density is lower in TMA than in neopentane. In both cases, the contours are at the following difference electron density levels: *a*, 0.004; *b*, 0.011; *c*, 0.024; *d*, 0.068; *e*, 0.101; *f*, 0.236; *g*, 0.425; and *h*, 1.08 e/Å³. The *dotted line* indicates the van der Waals' surface of TMA.

positive charge (electron deficiency) is very much localized to the methyl groups, and if we relate this to the van der Waals surface of the molecule, we clearly have four tetrahedrally disposed patches of positive charge, interspersed with essentially neutral regions.

We now need to consider what influence, if any, this uneven distribution of charge will have on the interaction of TMA with an anion.

Interaction with fluoride. To investigate this point, we have studied the interaction of TMA with fluoride ion; to identify the effects of the charge in TMA we have carried out parallel calculations on the neopentane-fluoride ion system.

Considering the tetrahedral symmetry of TMA and neopentane, one would expect there to be three low-energy directions of approach for an anion: toward a vertex, an edge, or a face of the tetrahedron. As can be seen from Fig. 4, these correspond, respectively, to approaches toward a single methyl group (along a C—N bond), between two methyl groups, and between three methyl groups (diametrically opposite the "vertex" approach).

The interaction energies between TMA and fluoride and between neopentane and fluoride as the anion approaches along each of these three directions are shown in Fig. 5A and B. The absolute interaction energies will have limited significance, since the calculations were carried out with a minimal basis set incorporating no correction for basis set superposition error and no configuration interaction calculations. However, the relative energies are likely to be semiquantitatively correct; some support for this comes from the observation that the difference in interaction energy between TMA-fluoride and neopentane-fluoride is, at sufficiently large distances,[3] closely comparable to that given by the simple Coulomb equation (see Fig. 5C).

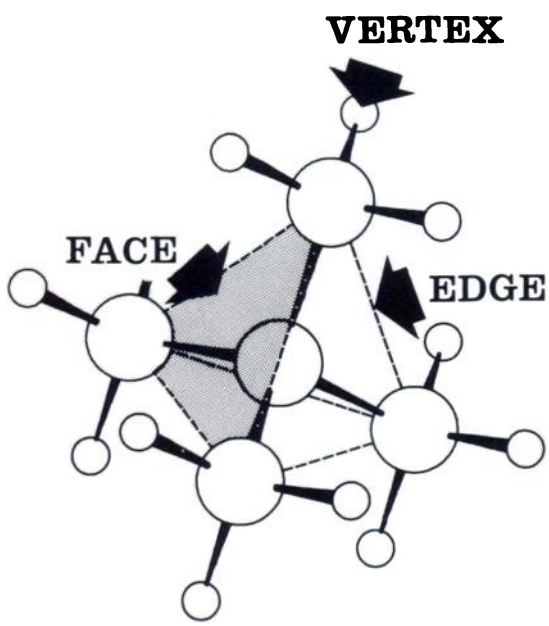

FIG. 4. *Three low-energy directions of approach of fluoride ion to TMA or neopentane: toward a vertex, an edge, or a face of the tetrahedral molecule*

For clarity, one face of the tetrahedron has been *shaded*.

Figure 5A, for neopentane-fluoride, shows that, as expected from the electron density map (Fig. 2), steric repulsion becomes apparant at progressively greater distances as one goes from the face to the edge to the vertex approach. No minima were observed for the vertex or edge approaches (since dispersion interactions are not reproduced in the absence of configuration interaction calculations), but a relatively shallow minimum was found at ~2.7 Å for the face approach, presumably arising from charge-induced dipole interactions.

In the case of the TMA-fluoride interaction (Fig. 5B), clear minima are observed for all three approaches. Comparison of Fig. 5A and B confirms that the positions of these minima are determined primarily by the steric interactions—they range from ~2.5 Å for the face approach to ~3.3 Å for the "vertex" approach. The deepest minimum is that for the face approach, followed by the vertex and then the edge approach, the latter two being very similar in energy. There is thus no direct correlation between interaction energy and closeness of approach to the central atom.

The contribution to the interaction energy from the charge on TMA can be assessed by calculating the difference in interaction energies between the TMA-fluoride and neopentane-fluoride systems. This is shown in Fig. 5C as a function of the distance between the anion and the central atom. The largest contribution is seen for the vertex approach, i.e., when the fluoride approaches one of the methyl groups, identified in the electron density difference map (Fig. 3) as the sites of the "patches" of positive charge on the surface of TMA. As noted above, it is appropriate to take the distance in the simple Coulomb equation as that to the center of the molecule only for a spherically symmetrical charge distribution. Since for the vertex approach a major contribution to the interaction energy comes from the delocalized positive charge on the methyl group, the electrostatic contribution for this approach does not follow the Coulomb equation with this choice of distance (Fig. 5C). When the fluoride approaches a face of the tetrahedron, it is reasonably close to three methyl groups and their associated "patches" of positive charge, and can also approach relatively closely to the central nitrogen, in the neighborhood of which is a substantial part of the positive charge. For both face and edge approaches, where the charge on the central atom makes a substantial contribution, the electrostatic contribution follows the Coulomb equation reasonably closely for $r \geq 2.6$ Å. The face approach involves almost as large an electrostatic contribution as the vertex approach at the distances corresponding to the energy minima for TMA-fluoride, the differences in interaction energy between TMA-fluoride and neopentane-fluoride being −143 kcal/mole for the vertex approach and −135 kcal/mole for the face approach. The fact that the face approach is associated with a significantly greater over-all interaction energy than the vertex

[3] For the "face" and "edge" approaches, $r \geq 2.6$ Å; a similar comparison could not be made for the vertex approach, since calculations on the neopentane-fluoride system failed to converge for $r > 3.5$ Å.

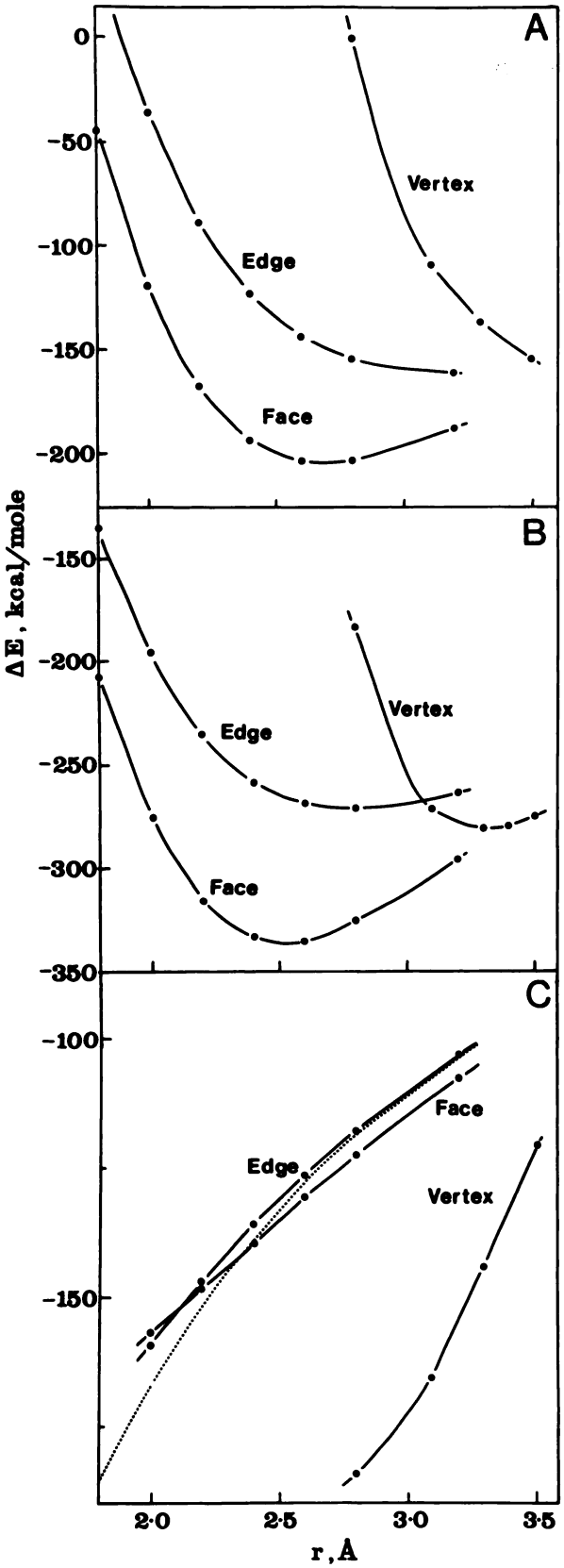

FIG. 5. *Energy of interaction of fluoride ion with (A) neopentane and (B) TMA for the three directions of approach defined in Fig. 4, as a function of r, the distance between the fluoride ion and the central atom (N or C)*

The interaction energy for TMA is defined as $\Delta E_{F\text{-}TMA^+} = E_{F\text{-}TMA^+} - (E_{TMA^+} + E_{F^-})$ and similarly for neopentane. In C, the difference in interaction energy between the fluoride-TMA and fluoride-neopentane systems (i.e., $\Delta E_{F\text{-}TMA} - \Delta E_{F\text{-}neopentane}$) is shown. The *dotted line* represents the result expected for the interaction between two point charges (the Coulomb equation).

approach must thus be ascribed to interactions present in both the TMA and neopentane systems—that is, to charge-induced dipole interactions.

Figure 6A and B shows (in the same section through the molecules as used in Figs. 2 and 3) the changes in electron distribution associated with bringing a fluoride ion up to TMA and neopentane along the face approach to the minimal energy position in each case (2.5 Å for TMA and 2.7 Å for neopentane). The general features of the redistribution of electrons are very similar for both molecules, since electrons are of course polarized away from the anion. As discussed above in connection with Fig. 3, this polarization takes place along bonds, in this case along the C—H bonds nearest the anion (one of which appears in the sections of Fig. 6) and along the C—C or N—C bond which points directly away from the anion. The dipoles thus induced along these bonds will contribute to the interaction energy.

Two differences between TMA and neopentane are apparent. First, the effect on the electron distribution of the fluoride ions is quite different; this can be ascribed in part to the slightly different position of the fluoride ion and in part to the effects of the "positive patches" associated with the two symmetry-related methyl groups which do not appear in this section. Second, the redistribution of electrons produced by the fluoride is somewhat greater in TMA than in neopentane; that is, the C—H and C—N bonds of TMA are rather more polarizable than the corresponding bonds of neopentane.

It is also interesting to note that the approach of fluoride to a face of the molecule leads to a significant increase in the electron density around the methyl group forming the opposite vertex. The "patch" of positive charge associated with this group is thus somewhat decreased. This will tend to weaken the interaction with a second anion approaching from the opposite side of the molecule.

Comparison with experiment. Two very recent surveys of crystallographic data on $R\text{-}CH_2N^+(CH_3)_3$ compounds (19, 20) show that the preferred mutual orientations of the quaternary nitrogen "head-group" and simple halide anions indicated by the present *in vacuo* calculations are in fact observed in practice. In an analysis of 34 structures, Rosenfield and Murray-Rust (20) noted a clear clustering of the anions (Cl^-, Br^-, I^-) about the approaches to the faces of the tetrahedron (specifically those faces not sterically hindered by the *R* group), with a secondary clustering about the vertices. Our calculations show that these orientational preferences are determined not simply by packing considerations but also by the electron distribution in the TMA group itself.

CONCLUSIONS

The detailed calculations of electron density distribution in TMA presented here confirm that there is a substantial delocalization of the positive charge onto the

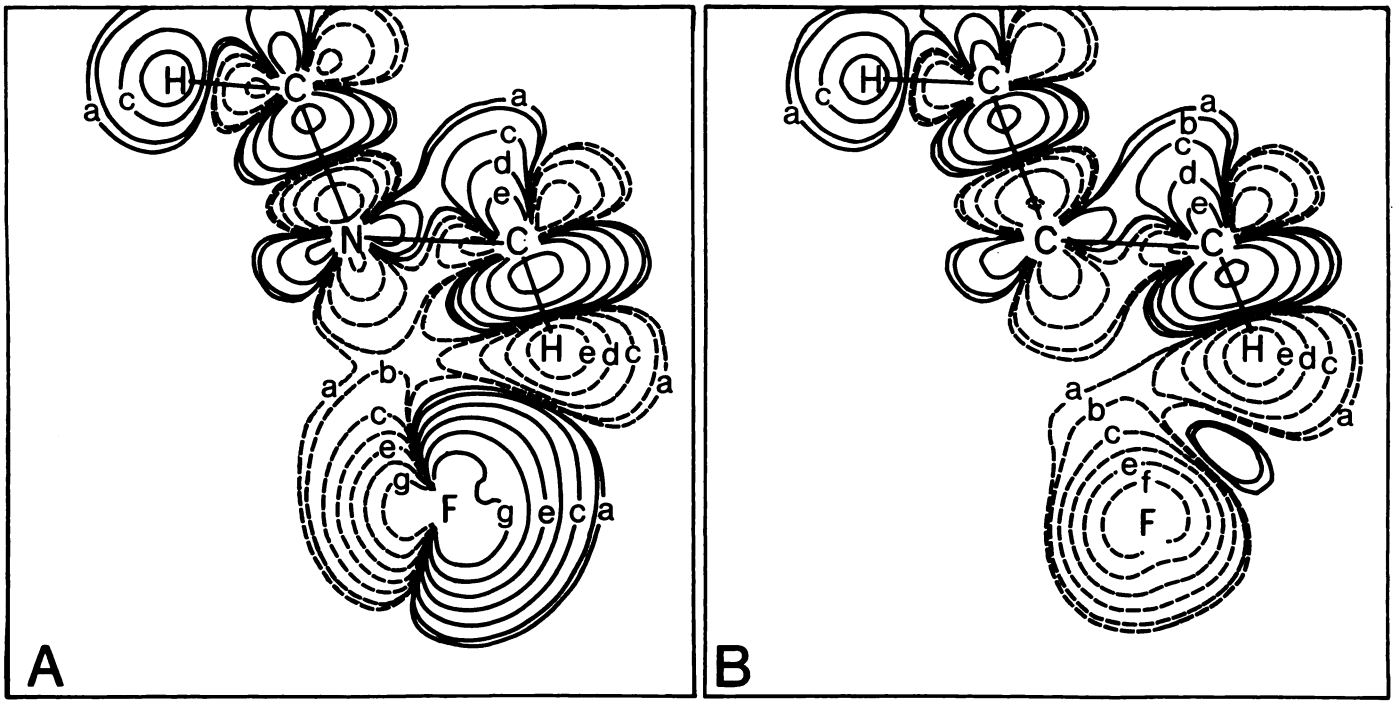

FIG. 6. *Changes in electron density produced by bringing a fluoride ion to its mimimal energy position with respect to (A) TMA or (B) neopentane*

In both cases the fluoride is approaching a face of the tetrahedron, in A at 2.5 Å and in B at 2.7 Å from the central atom. *Solid contours* indicate regions where the interaction produces an increase in electron density; *dashed contours*, regions where it produces a decrease. In both cases the contours are at the following difference electron density levels: *a*, 0.0047; *b*, 0.0068; *c*, 0.017; *d*, 0.043; *e*, 0.107; *f*, 0.269; *g*, 0.675 $e/Å^3$.

hydrogen atoms. However, since this positive charge is localized to the methyl groups, there are regions of the surface of the molecule which are effectively neutral. (This feature of the molecule, of course, is not brought out by the simple Mulliken approach.) As a result of this and of the contribution of charge-induced dipole interactions, there is a favored orientation of the TMA molecule with respect to an anion. This will also be true for the "cationic head" of acetylcholine (in unpublished calculations, we have found that the electron distribution around the *N*-methyl groups of alkyltrimethylammonium ions is essentially identical to that in TMA). From the point of view of its interaction with the receptor, it is clearly not satisfactory to regard this part of the acetylcholine molecule as a featureless, positively charged sphere. It will have specific orientational requirements for interaction with the presumed anionic group on the receptor. Since this anionic group is most likely to be a carboxylate group which (unlike fluoride) has its own orientational preferences for interaction with cations, the interaction of the "cationic head" of acetylcholine with the receptor is likely to have appreciable geometrical specificity.

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