Ab initio SCF STUDY OF THE EFFECT OF Na^+ AND K^+ IONS AND WATER ON THE LOCAL ANAESTHETIC–PHOSPHOLIPID INTERACTION

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For gaining insight into the interactions of local anaesthetics with phospholipids, *ab initio* molecular orbital calculations were performed using trimethylamine and phosphate as model substances. The $(OH)_2OPO^- \cdots H^+N(CH_3)_3$ interaction was found comparable in strength to the $(OH)_2OPO^- \cdots M^+$ (M = Na, K) interaction and considerably stronger than the $(OH)_2OMPO \cdots H_2O$ interaction. This suggests that a major role of local anaesthetics may consist in their disturbing the $P—O \cdots H_2O$ hydrogen bonds. Such interference may be one of the possible types of interaction between local anaesthetics and the biophase, leading to a measurable pharmacological effect.

Local anaesthetics are known to suppress electric excitation of biological cells by interfering into the normal activity of ionic channels. The result of this interference is reversible blocking of the action potential in excitable membranes[1]. The sites of the effect of anaesthetics in the membranes, however, have not been definitely identified. It is supposed that the effect of local anaesthetics consists either in their binding to specific receptors in the nerve membrane[2–6] or in an overall disturbance of the membrane structure[7,8].

The principal components of membranes are phospholipids and lipoproteins. Thus, it is of importance to gain insight into interactions between these biopolymers and compounds exhibiting local anaesthetic effects. Various physico-chemical methods have been used for this purpose[9–13], these, however, fail to provide data of the equilibrium geometry and energy of the local anaesthetic–membrane interaction considered. Such data, on the other hand, can be gained by theoretical chemical treatment. In this connection, the possible interactions between local anaesthetics and the association sites of biomembranes were studied by us previously using quantum chemical methods[14–19]. The present work is concerned with the relation of the effect of Na^+ and K^+ ions and water to the interaction between an ionized amine and the phosphate anion, modelling the local anaesthetic–phospholipid interaction.

CALCULATIONS

The *ab initio* SCF method was employed for the calculation of the equilibrium geometries, interaction energies and electronic structures of the complexes studied (Fig. 1). The MINI-1 basis[20,21], which has been applied with success to the study of neutral and ionic molecular complexes[19,22,23], was used.

For establishing the relative stability of the systems studied (Fig. 1), geometric optimization was performed, minimizing the parameter R and, for the hydrogen bonded complex *VII*, the angle α.

The interaction energy ΔE_{AB} was determined as the difference between the energies of the optimized structures E_A, E_B and E_{AB},

$$\Delta E_{AB} = (E_A + E_B) - E_{AB} . \qquad (1)$$

The superposition error, typical for bases of the minimal type, was determined by using the Boys–Bernardi counterpoise correction[24]. The MINI-1 optimized structures[19] of $H_2PO_4^-$ and $(CH_3)_3NH^+$ served as the input geometries for the monomers. The MINI-1 optimized O—H bond length of 95·44 pm and H—O—H angle of 108·303° were entered for water. Calculations were performed by employing programs GAUSSIAN 80 and GAUSSIAN 82 (refs[25,26]).

RESULTS AND DISCUSSION

The calculated geometries and bonding energies of the systems (Fig. 1) are given in Table I. The last column contains interaction energies corrected for the superposition error (BSSE). The effect of this correction, determined in the potential energy minimum, is highest (about 17%) for neutral hydrogen bonds (complexes *V* and *VI*), somewhat lower (10%) for the ionic systems *I*–*IV*, and lowest (below 5%) for complex *VII*, representing the $NH^+\cdots O^-$ hydrogen bond. Although the absolute values of the correction of the basis set were calculated in different ways for the systems treated, the relative stability order of the complexes remains unaltered by the correction (Table I).

In a membrane, the PO_4^- groups of phospholipids are shielded by small cations[27]. Interactions of this kind are represented by complexes *I*–*IV*. Our *ab initio* calculations indicate that a sodium cation is bonded to the phosphate anion more strongly than a potassium cation. In both cases the bifurcated complexes, where the cation interacts with both oxygen atoms, emerge as somewhat stronger. The results agree with the calculations[28,29] where different basis sets were employed.

The recent Monte Carlo study[30] of hydration of phospholipids has shown that the O(*3*) oxygen in the PO_4^- group is strongly bonded to an Na^+ cation whereas the O(*2*) oxygen is hydrated by a molecule of water. This led us to study complexes *V* and *VI* as well (Fig. 1). The hydrogen bonding of water is somewhat stronger in

complex *VI* involving a potassium cation than in complex *V* involving a sodium cation (Table I); in both complexes, however, the hydrogen bonds are considerably stronger than in the water dimer (20·1 kJ mol^{-1}, MINI-1 basis[22]).

TABLE I

Optimized geometries and interaction energies of complexes studied

Complex		*R* pm	*r*[a] pm	*α* deg	Δ*E* kJ mol^{-1}	Δ*E* (BSSE) kJ mol^{-1}
I	$(OH)_2OPO^- \cdots Na^+$[b]	195	—	—	543·1	492·1
II	$(OH)_2OPO^- \cdots K^+$[b]	235	—	—	441·4	405·8
III	$(OH)_2PO_2^- \cdots Na^+$[c]	261	—	—	558·5	498·6
IV	$(OH)_2PO_2^- \cdots K^+$[c]	306	—	—	474·5	432·4
V	$(OH)_2ONaPO \cdots H_2O$	270	95	—	41·3	34·1
VI	$(OH)_2OKPO \cdots H_2O$	271	95	—	45·1	37·6
VIIa	$(OH)_2OPO^- \cdots H^+N(CH_3)_3$[d]	237	107	157·0	458·9	438·3
VIIb	$(OH)_2OPOH \cdots N(CH_3)_3$	237	105	157·0	502·1	481·5

[a] Bond length between hydrogen bonding proton and atom to which it is bonded according to the formula; [b] linear; [c] bifurcated; [d] this complex is no true minimum but it decomposes without any energy barrier to *VIIb* (ref.[19]).

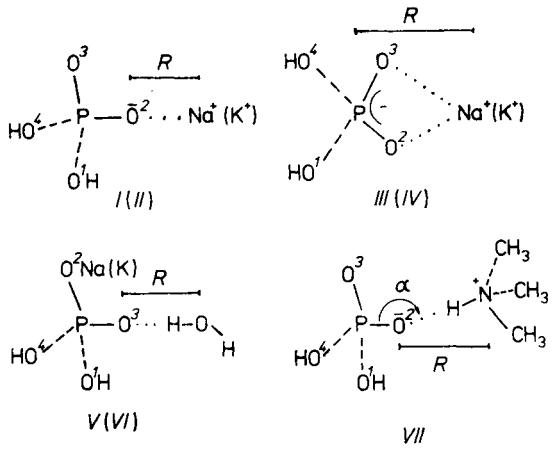

FIG. 1

Molecular structure of complexes studied. Definition of the intermolecular parameters *R* and *α* is indicated

It is supposed that local anaesthetics affect the normal activity of nerve cells either directly, by interacting with sodium channels[4,6,7], or indirectly, by bonding to phospholipids in the membrane[8,31]. Interaction of a negatively charged phosphate group of a phospholipid with an ionized amino group of an anaesthetic is modelled by complex *VII*. The interaction energy of this complex is very high (438·3 kJ mol^{-1}). However, *ab initio* calculations of the proton transfer[19] have shown that in this system, proton is transferred to phosphate without any energy barrier. It follows from a comparison with complexes *I*–*IV* that the complex of the ionized amino group with $H_2PO_4^-$ is weaker than the $H_2PO_4^-\cdots Na^+$ complex but stronger than the $H_2PO_4^-\cdots K^+$ complex (Table I). Hence, during their interaction with phospholipids, local anaesthetics must compete with small cations, present in vivo and forming strong bonds to phosphate groups. Water, solvating phosphate groups in phospholipids particularly at the outer surface of the membrane, forms considerably weaker

TABLE II

Gross atomic charges (q) and amount of charge transfer (CT) in complexes studied

Parameter	Value for complex							
	I	*II*	*III*	*IV*	*V*	*VI*	*VIIa*	*VIIb*
				Phosphate group				
q_P	1·38	1·36	1·27	1·29	1·40	1·38	1·40	1·47
$q_{O(1)}$	−0·73	−0·74	−0·70	−0·72	−0·72	−0·73	−0·72	−0·70
$q_{O(2)}$	−0·86	−0·84	−0·74	−0·75	−0·85	−0·82	−0·84	−0·83
$q_{O(3)}$	−0·67	−0·68	−0·74	−0·75	−0·71	−0·72	−0·68	−0·64
$q_{O(4)}$	−0·73	−0·73	−0·70	−0·72	−0·72	−0·73	−0·72	−0·70
$\sum q_H$	0·72	0·70	0·72	0·72	0·72	0·73	0·72	1·26
q	−0·89	−0·93	−0·89	−0·93	−0·88	−0·89	−0·84	−0·14
q_M	0·89	0·93	0·89	0·93	0·91	0·95	—	—
				Water				
q_O	—	—	—	—	−0·76	−0·76	—	—
$\sum q_H$	—	—	—	—	0·73	0·70	—	—
				Amine				
q_H	—	—	—	—	—	—	0·50	—
q_N	—	—	—	—	—	—	−0·47	−0·43
q_C	—	—	—	—	—	—	−0·66	−0·69
$\sum q_H$	—	—	—	—	—	—	0·93	0·88
CT	0·1	0·06	0·1	0·06	0·03	0·06	0·16	0·14

hydrogen bonds with the phosphate oxygen. Then, ionized local anaesthetics will be capable of breaking down particularly the P—O···H—OH hydrogen bonds and forming new phosphate–local anaesthetic hydrogen bonds.

These conclusions were inferred from energy data. Actually, calculated interaction energies can only serve as a qualitative index of the possible interference of local anaesthetics with phospholipids. Quantitative results can, ideally, be obtained by analysis using the free enthalpy of the systems, including the entropy effect. However, the high difference in the stability of the phosphate–water and phosphate–trimethylamine complexes suggests that the order of stability of these systems will remain unaltered by the entropic contribution.

Electron distribution was also examined to seek whether electrostatic interactions predominate in the complexes or whether charge transfer is also involved. The gross atomic charges obtained by the Mulliken population analysis are given in Table II. The data can serve as a measure of the electron transfer from the anion to the cation, or from the proton acceptor to the proton donor.

As to the ionic complexes *I*–*IV*, the amount of charge transfer is nearly one-half higher in the complexes with Na^+ than in those with K^+. Also, Na^+ forms stronger complexes with $H_2PO_4^-$ than K^+ does (Table I). The two ions accept only little of a negative charge (0·06 – 0·1 e). Thus, the bonding of the two cations to phosphate will be apparently completely ionic in nature. The gross atomic charges and amounts of CT are virtually independent of whether the structure of the complexes is linear or bifurcated (Table II).

Water in complexes *V* and *VI*, in comparison to systems *I* and *III*, has a relatively small effect on the charge distribution in the $(HO)_2PO_2M$ (M = Na, K) subsystem. Only a very small amount of charge (0·03 – 0·06 e) is transferred to water.

Proton transfer in the P—O^-···H^+—N hydrogen bond (complexes *VIIa,b*, Table II) appears in a charge redistribution at the atoms H, N, O, and P participating in the hydrogen bond. Proton transfer is associated with a change in the direction of the charge transfer: while this direction is from phosphate to amine in *VIIa*, it is opposite in *VIIb*.

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