QUANTUM CHEMICAL STUDY OF PHENYLCARBAMATES POSSESSING LOCAL ANAESTHETIC ACTIVITY. EFFECT OF HYDRATION ON STABLE CONFORMATIONS OF 1-[2-(2-METHOXYPHENYLCARBAMOYLOXY)ETHYL]PIPERIDINE AND ITS CATION

Milan REMKO[a] and Ivan SEKERKA[b]

[a] *Department of Pharmaceutical Chemistry and*
[b] *Chemical Institute, Comenius University, 832 32 Bratislava*

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The PCILO quantum chemical method was applied to the study of 1-[2-(2-methoxyphenylcarbamoyloxy)ethyl]piperidine (B), its cation (BH^+), and hydrofluoride (BHF). For B and BH^+, their principal hydration sites were established. Conformation maps of the hydrated molecules were plotted based on the "supermolecule" concept and compared with those of the isolated species. As compared to the nonhydrated molecules, the hydrated B and BH^+ have a considerably smaller tendency to assume one preferred conformation. The preferred conformation of isolated molecule of BHF as obtained by the PCILO calculation agrees well with crystal structure data of the structurally related heptacaine hydrochloride.

A number of compounds exhibiting pronounced local anaesthetic activity such as diperodone or heptacaine possess the 1-[2-(phenylcarbamoyloxy)ethyl]piperidine structure arrangement[1,2]. These phenylcarbamate local anaesthetics can be characterized by the general scheme: Aromatic part–polar group–connecting chain-amino group. For gaining insight into the mechanism of their local anaesthetic activity,we have subjected a number of them to a detailed physico-chemical study[3-14], and as a result, suggested a bonding model for carbamate type local anaesthetics[15].

This work, which is a continuation of our quantum chemical studies of carbamate type local anaesthetics[3-9], is concerned with the effect of hydration on the stable conformations of 1-[2-(2-methoxyphenylcarbamoyloxy)ethyl]piperidine, which is a simpler model for the local anaesthetic heptacaine[2], with the OC_7H_{15} group replaced by an OCH_3 group. Since the unprotonated substances are very low soluble in water, solubility in water being a prerequisite for the transportation of drugs to the place of their action[16], water soluble salts of local anaesthetics are used in practice. With regard to this, the 1-[2-(2-methoxyphenylcarbamoyloxy)ethyl]piperidine cation and its hydrofluoride are also treated in this work.

CALCULATIONS

The PCILO quantum chemical method[17] was applied to the calculation of the stable conformations and hydration energies of 1-[2-(2-methoxyphenylcarbamoyloxy)ethyl]piperidine (B), its cation (BH^+), and hydrofluoride (BHF). A schematic diagram of the molecules, along with the torsional angles, is shown in Fig. 1. For the study of the conformational structure of these molecules, the two-dimensional conformation maps were calculated, *viz.* as a function of the torsional angles α_4 and α_5 for fixed angles α_1, α_2, α_3, and α_6. The torsional angles were defined following the convention suggested by Klyne and Prelog[18]. The presentation of the results on the conformation maps is limited to the 20 kJ mol^{-1} isoenergy interval above the global minimum.

The effect of hydration on the stable conformations of B and BH^+ was studied in terms of the supermolecule concept[19]. First, the monohydration of the local anaesthetic and its cation was investigated. Molecules of water were located in suitable sites in the vicinity of polar groups of the substances where hydrogen bonding is feasible (Fig. 2). The energy of the X—H···Y hydrogen bonds, E_{HB}, was calculated as the difference between the total energy of the isolated monomers and the total energy of the hydrogen bonded complex,

$$E_{HB} = E_{X-H} + E_Y - E_{MIN} . \qquad (1)$$

The geometry of the complex was optimized with respect to the H···Y (Y = O, N) distance and angle φ. The hydration was examined for conformers where all of the heavy atoms, except those in the piperidine ring, lie in a plane (Fig. 2). The geometry of the N^+—H···F^- hydrogen bond in BHF was minimized with respect to the H···F distance; its energy was calculated as

$$E_{HB} = E_{BH^+} + E_{F^-} - E_{MIN} . \qquad (2)$$

For water, the experimental geometry data[20] were employed. Since no experimental X-ray diffraction data were available for B or BH^+, the starting geometry was set up using those for heptacaine hydrochloride[21].

RESULTS AND DISCUSSION

Interaction with Water

The PCILO calculations were first applied to the hydration of the polar groups in the drug B and its cation BH^+. With regard to the fact that long-range electrostatic

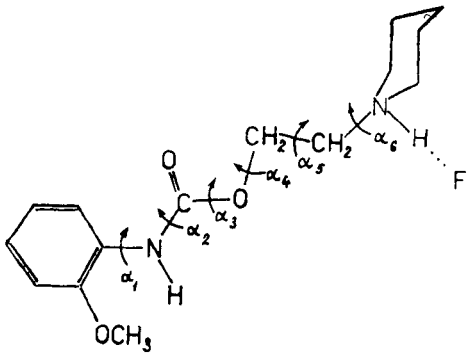

FIG. 1

Torsional angles in the compounds studied. The form shown has $\alpha_1 = \alpha_2 = \alpha_3 = \alpha_4 = \alpha_5 = \alpha_6 = 0°$

interactions predominate in the hydration of polar and charged molecules, the *ab initio* calculated[6,22] charge distributions of B and BH^+ were used for predicting their attack sites; and for determining conclusively the preferred hydration sites, the interaction energies of association of the two substances with a water molecule located in selected interaction sites were calculated (Fig. 2).

The results of our calculations of the relative stability of the various hydrogen bonded complexes are given in Table I. Of the hydrated polar groups of the base B, the carbonyl group forms the strongest hydrogen bond with water. The energies of the next four hydrogen bonds studied (Fig. 2) are lower than the hydrogen bond energy in the water dimer. As to the protonated form BH^+, the strongest hydrogen bond with water, with an energy of 32·7 kJ mol^{-1}, is formed by the cationic part of the substance. Of the polar groups bonded to the hydrophobic part of BH^+, the carbonyl group oxygen suits best to hydration.

For comparing the strength of the interaction with water for the protonated and unprotonated drug species, the average hydrogen bonding energies E_A were calculated for the two of them as

$$E_A = (1/n) \sum E_{HB} , \qquad (3)$$

where the summation of the hydrogen bond energies E_{HB} is performed over all the n hydrogen bonds. The values obtained are 18·6 kJ mol^{-1} for BH^+ and 15·4 kJ mol^{-1} for B. The former value is higher than that for the water dimer (Table I) and hence, the protonated base can be assumed to be able to disturb the water–water hydrogen bonds. For B, on the other hand, the E_A value is lower than the hydrogen bond energy in the water dimer, which suggests that in the base–water system, water–water hydrogen bonds will preferentially be present.

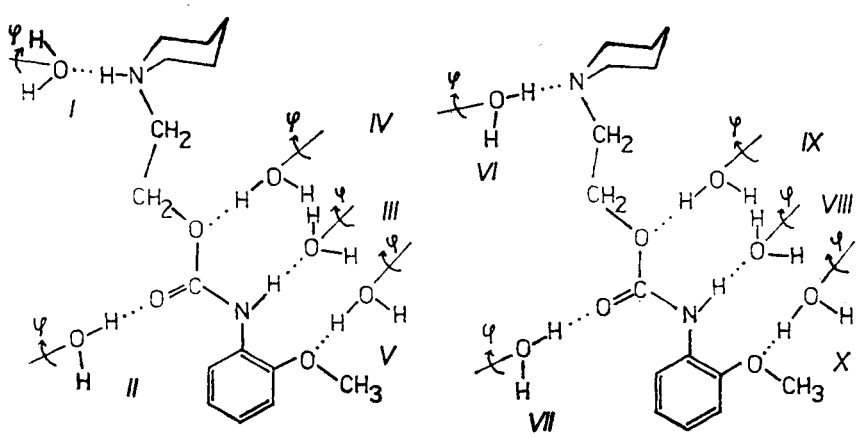

FIG. 2

Molecular arrangement of the systems studied

Conformational Analysis

The PCILO energy surfaces for BHF, B, and BH^+ are shown in Figs 3–5, respectively. The conformation energy maps were plotted as functions of torsional angles α_4 and α_5 using fixed values of α_1 obtained from *ab initio* calculations for methyl 2-methoxyphenylcarbamate[7], *viz.* $\alpha_1 = 0°$, and α_2, α_3, and α_6 obtained from X-ray diffraction data of heptacaine hydrochloride[21].

The conformation energy map of BHF (Fig. 3) is characterized by a rather large area with relative energies (*i.e.*, above the global energy minimum) lower than 20 kJ mol^{-1}. Two equivalent minima, corresponding to the most stable conformers, lie at $\alpha_4 = 0°$, $\alpha_5 = \pm 120°$ with the anticlinal alignment of the O—C—C—N fragment. The next minimum, at 8·8 kJ mol^{-1}, corresponds to the conformer with the *trans* alignment of the O—C—C—N fragment, and the third value corresponds to two conformers with $\alpha_4 = \pm 90°$ and $\alpha_5 = 0°$ (Fig. 3). The calculated populations at 310·2 K for these stable conformations are in the ratio of 96 : 3 : 1. Thus, a single most stable conformation should predominate in the BHF crystal. A single predominating conformation also has been established theoretically based on PCILO calculations of the conformation energy map for lidocaine hydrofluoride[23]. The conformation map of BHF shows that the energetically allowed regions, *i.e.* those within the 5 kJ mol^{-1} limit, are rather narrow, comprising as little as 5% of the α_4, α_5 surface. This surface represents the conformationally stable region and involves the most stable minimum I.

TABLE I

PCILO calculated equilibrium hydrogen bonding distances and energies. The angle φ was 0° in all cases (Fig. 2)

System	Hydrogen bond	$R_{X\cdots Y}$ nm	E_{HB} kJ mol^{-1}
I	N^+—H···O	0·262	32·7
II	O—H···O	0·266	20·0
III	N—H···O	0·261	16·9
IV	O—H···O	0·271	11·4
V	O—H···O	0·271	12·0
VI	O—H···N	0·276	17·1
VII	O—H···O	0·261	21·9
VIII	N—H···O	0·268	15·6
IX	O—H···O	0·271	12·1
X	O—H···O	0·271	9·1
$(H_2O)_2$	O—H···O	0·253	18·0

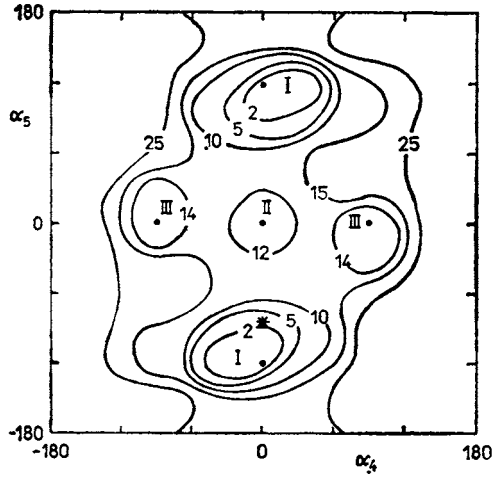

FIG. 3

PCILO energy surface for 1-[2-(2-methoxyphenylcarbamoyloxy)ethyl]piperidinium fluoride. The isoenergy curves are in kJ mol^{-1} with respect to the global minimum which is taken as energy zero. The energy minima are labelled I through III. The value labelled with an asterisk is the experimental value found for heptacaine hydrochloride

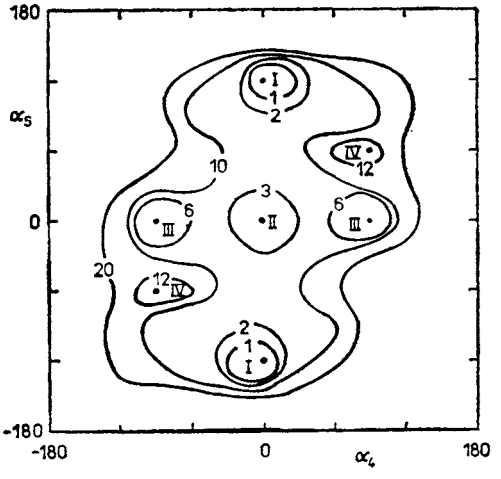

FIG. 4

PCILO energy surface for hydrated 1-[2-(2-methoxyphenylcarbamoyloxy)ethyl]piperidine. The isoenergy curves are as in Fig. 3. The energy minima are labelled I through IV

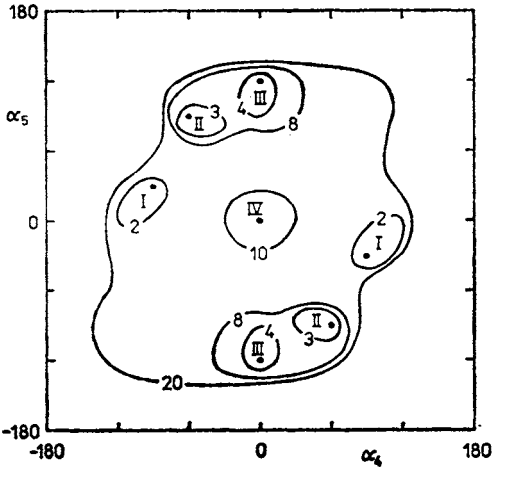

FIG. 5

PCILO energy surface for hydrated 1-[2-(2-methoxyphenylcarbamoyloxy)ethyl]piperidine cation. The isoenergy curves are as in Fig. 3. The energy minima are labelled I through IV

Our theoretical torsional angles α_4 and α_5 for BHF were compared with the X-ray data for the structurally related heptacaine hydrochloride[21] and were found to be in a reasonable agreement (Fig. 3). The PCILO energy of the N^+—H···F^- intermolecular hydrogen bond in BHF, calculated based on Eq. (*2*), is very high, *viz.* 378·9 kJ mol^{-1} for the equilibrium $R_{F...H}$ distance of 0·170 nm.

For investigating the effect of hydration on the stable conformations of the base B and its cation BH^+, their first solvation layers were constructed. Simultaneous occupation of several hydration centres of the lipophilic parts of the substances poses a problem because, *e.g.*, the interaction sites for the hydration of the carbamate and methoxy groups are so near to each other that simultaneous occupation of both of them by molecules of water is hindered by the mutual repulsion of the latter. With regard to this, and also to the fact that the hydrogen bonds formed by the ether oxygens of the methoxy and carbamate groups of the drug are considerably weaker than those formed by the NH—C=O group (Table II), the former association sites were disregarded in our treatment. The effect of hydration was studied for B: $(H_2O)_3$ and BH^+: $(H_2O)_3$ "supermolecules" where the water molecules are located in the PCILO optimized positions about the amide NH and C=O groups and the amino group of the substance.

The energy map of the base B (Fig. 4) displays several minima within the 20 kJ . . mol^{-1} energy region. The lowest corresponds to two conformers with $\alpha_4 = 0°$, $\alpha_5 = \pm 120°$ with the anticlinal conformation of the O—C—C—N fragment. The next minimum, 0·4 kJ mol^{-1} less stable, is found for $\alpha_4 = 0°$, $\alpha_5 = 0°$, hence, for the planar arrangement of the O—C—C—N fragment. The third and fourth minima correspond each to two conformers with nonplanar arrangements of the O—C—C—N fragment. Based on the calculated energies (Table II), the equilibrium distribution of these conformers at 310·2 K was calculated to be in the ratio 51 : 43 : 5 : 1. Comparison of this ratio with that calculated based on the data in ref.[6] for the most stable conformers of the isolated base, *viz.* 65 : 22 : 13, indicates that in water the population of the most stable conformation will decrease; in dilute aqueous solutions the base will occur predominantly as a mixture of two anticlinal and the *trans* arrangements of the O—C—C—N fragment.

As to the BH^+ cation, the energy map of the isolated molecule exhibits a very limited region of stable conformations. The most stable conformation is stabilized by the N^+—H···O=C intramolecular hydrogen bond[6]. In aqueous solutions the situation is different. Hydration of the functional groups involved is a hindrance to the above hydrogen bond formation. The energy surface of the hydrated cation (Fig. 5) is characterized by the occurrence of large areas of stable conformations. Instead of a single, deep minimum obtained for the isolated species[6], several shallow statistically significant minima are found for the hydrated cation. This is also reflected by the calculated populations of the most stable conformers, which are 91 : 9 for the isolated and 52 : 28 : 16 : 4 for the hydrated cations. Two equivalent minima,

corresponding to the most stable conformers, are found for $\alpha_4 = 90°$, $\alpha_5 = -30°$ and $\alpha_4 = -90°$, $\alpha_5 = 30°$. The second and third minima, corresponding to nonplanar arrangements of the O—C—C—N chain, also lie within the energetically favourable region of 5 kJ mol^{-1} (Table II). The planar *trans* conformer (minimum IV, Fig. 5) is 6·3 kJ mol^{-1} less stable.

Comparing the energy maps of BHF, B, and BH^+ (Figs 3–5) we find that although the 20 kJ mol^{-1} regions examined assume roughly the same area in the three cases, the salt of the drug in the crystalline state occurs in a single prevailing conformation

TABLE II

PCILO calculated lowest energy minima and C=O···N interatomic distances for the stable conformations of hydrated 1-[2-(2-methoxyphenylcarbamoyloxy)ethyl]piperidine B, its hydrated cation BH^+, and hydrofluoride BHF

Minimum	α_4 deg	α_5 deg	ΔE kJ mol^{-1}	$R_{CO\cdots N}$ nm
		BHF		
I	0	120	0	0·485
I	0	−120	0	0·485
II	0	0	8·8	0·514
III	90	0	12·6	0·431
III	−90	0	12·6	0·431
		B: $(H_2O)_3$		
I	0	120	0	0·485
I	0	−120	0	0·485
II	0	0	0·4	0·514
III	90	0	6·3	0·431
III	−90	0	6·3	0·431
IV	−90	−60	13·4	0·469
IV	90	60	13·4	0·469
		BH^+: $(H_2O)_3$		
I	90	−30	0	0·390
I	−90	30	0	0·390
II	60	−90	1·7	0·385
II	−60	90	1·7	0·385
III	0	120	2·9	0·485
III	0	−120	2·9	0·485
IV	0	0	6·3	0·514

whereas the base and cation in dilute aqueous solutions will exist at least in two stable equilibrium conformations.

Although we are aware that our approach cannot account for the behaviour of the local anaesthetic in solution in its completeness, the results obtained for the hydrated B and BH^+ species indicate that solvent has a marked effect on the molecular conformation. A greater effect of hydration on the overall conformational situation was observed for the water-soluble cation which in the isolated state occurs predominantly in a single conformation; this is changed completely by the hydration. As a tool for assessing whether the solvent effect on the stable conformations might affect the possible drug–receptor interactions, the interatomic distances between the carbonyl oxygen and the basic nitrogen atoms are presented in Table II. According to the frequently used receptor mapping concept[24], atoms of the drug with lone electron pairs are likely to bond to the receptor. Table II shows that for both the hydrofluoride BHF and base B, the O···N distance in the most stable conformers is near 0·48 nm, for the hydrated cation this distance is somewhat shorter, *viz.* 0·39 nm. Thus, hydration may cause both the cation and the base to be able to interact with similar receptors.

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