CONFORMATIONAL STRUCTURE OF THE LOCAL ANAESTHETIC LIDOCAINE, ITS CATION, AND HYDROFLUORIDE

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Received October 11th, 1985

The PCILO quantum chemical method was applied to the conformational analysis of the local anaesthetic lidocaine (2-diethylaminoacet-2′,6′-dimethylanilide), its cation and hydrofluoride. The stable conformations, proton affinity, and the hydrogen bonding energy of the lidocaine ion pair were determined. The results are compared with published data and discussed in terms of the present theories of the mechanism accounting for the activity of these drugs.

Lidocaine (2-diethylaminoacet-2′,6′-dimethylanilide) exhibits marked local anaesthetic and antiarrhythmic activity[1]. In the clinical practice, its hydrochloride is employed. Although it is known that the site of action of local anaesthetics is nerve membranes, the mechanism of activity of these drugs is not quite clear. Several theories have been proposed to explain the molecular mechanism of the effect of local anaesthetics on nerve membranes[2,3]. Some authors assume that local anaesthetics interact specifically with phospholipids[4–8], other researchers suggest that the drugs act on the protein sites of the nerve membrane[9–11]. Newer theories suppose that the effect of local anaesthetics consists in their bonding to specific receptors in the nerve membrane[12–14]. According to Hille[14], the lipid-soluble form of the anaesthetic (base) comes to the receptor and leaves it through the hydrophobic region of the membrane, while the charged, less lipid-soluble form of the anaesthetic (cation) interacts with the receptor situated in the channel (Fig. 1). Interaction of local anaesthetics with a specific site in the sodium channel is also assumed by Posma and Catterall[15]. It is supposed that also local anaesthetic antiarrhythmics can interact with sodium channels in a similar manner[16,17].

From among the multitude of factors that affect the pharmacological activity (drug transport through the membrane, atomic, steric, and electronic structure determining the location of the drug at a suitable site in the biophase and its subsequent pathway leading to the measurable pharmacological response), only the atomic, steric, and electronic structures of local anaesthetics have been so far studied by quantum chemical methods because of theoretical difficulties[18–27], and moreover, more or less extensive simplifications have been used. Various models of lidocaine have been examined using the PCILO (refs[18,19]) or *ab initio* SCF (refs[23,24,26]) approaches. The local anaesthetic–lipid and lipoprotein interactions have been studied on model complexes in refs[22,23,26].

The present paper gives the results of a conformational study of the clinically used local anaesthetic lidocaine, its protonated form and its hydrofluoride. The calculations were performed with a view to gaining insight into the conformational aspect of drugs of this kind, particularly the mutual geometric arrangement of the aromatic and amino groups which are the lipophilic and hydrohilic centres, respectively, of the

substance. The results of calculations of the proton affinity and hydrogen bonding energy are also discussed.

CALCULATION METHOD

The stable conformations of lidocaine, its cation and hydrofluoride were sought by means of the PCILO quantum chemical method[28]. A diagram of the compounds, along with the relevant torsional angles, is shown in Fig. 2. The two-dimensional conformation maps were calculated and plotted as functions of the torsional angles γ and δ for fixed angles α and β; 30° steps in the torsional angles were made. The torsional angles were defined following the convention proposed by Klyne and Prelog[29]. The presentation of the results on the conformation maps is limited to the 20 kJ mol^{-1} isoenergy interval above the global minimum.

The proton affinity was also calculated for lidocaine. The proton affinity of a base LA is the negative ΔE value of the exothermic reaction

$$LA + H^+ \rightarrow LAH^+ , \qquad (A)$$

i.e., the difference between the energies of the neutral and protonated species,

$$\Delta E = E_{LA} - E_{LAH^+} . \qquad (1)$$

The energy of the $N^{(+)}—H\cdots F^{(-)}$ hydrogen bonding in lidocaine hydrofluoride, 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_{MIN}),

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

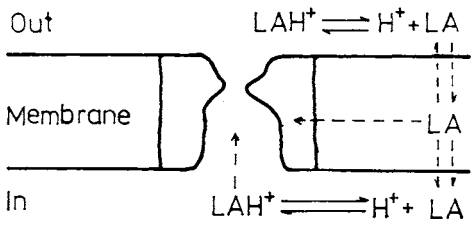

FIG. 1

Diagram of the motion of local anaesthetic (LA) through the membrane phase and to the receptor

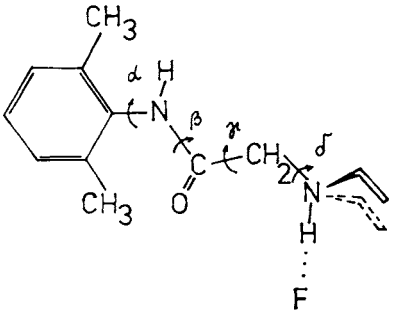

FIG. 2

Torsional angles in the compounds studied. The form shown has $\alpha = \beta = \gamma = \delta = 0°$

The geometry of the hydrogen-bonded complex was optimized with respect to the H···F distance.

All theoretical calculations were performed for the experimental geometry. X-ray data for lidocaine are available[30] but they cannot be regarded as reliable[30], and so, those for lidocaine bis-(*p*-nitrophenyl)phosphate[31] were employed. The value of 0·107 nm, obtained by optimization by the PCILO method, was used for the $N^{(+)}$—H distance in the cation and hydrofluoride.

RESULTS

Conformational Analysis

The knowledge of the torsional angles α, β, γ, and δ (Fig. 2) is prerequisite for obtaining information on the stereochemical arrangement of the lipophilic and hydrophilic groups. Since in the PCILO method there is an arbitrariness as to the choice of a suitable zero order wave function with respect to the existence of two Kekule structures, we used data obtained by other methods for the torsional angles α and β. For α, we took the value of 60°, obtained by *ab initio* calculations[24] for 2,6-dimethylacetanilide, a simpler model of lidocaine. As to the amide group, we considered the *trans* isomer ($\beta = 0°$), which was experimentally found to be the more stable[31,32].

The conformational flexibility of lidocaine was examined using the PCILO conformation maps. The PCILO energy surfaces calculated for lidocaine, its cation and hydrofluoride are shown in Figs 3–5, respectively. The isoenergy curves are in kJ mol^{-1} with respect to the global minimum regarded as the energy zero.

The energy map of lidocaine (Fig. 3) is characterized by the occurrence of a wide region of stable conformations. A total of six minima (Table I) were found on the conformation map within the 20 kJ mol^{-1} energy region covering about 40% of the total energy surface. The calculated population ratios for the six stable conformations (at 310·16 K) are 34 : 31 : 21 : 7 : 6 : 1. The minima I and II are nearly energy-equivalent. While minimum I corresponds to the conformer with the *cis* arrangement of the carbonyl oxygen atom and the amino nitrogen atom, for minimum II the conformation is stabilized by NH···N type intramolecular hydrogen bonding. This hydrogen bonding, formed by the amino group and the hydrogen atom of the anilide group, was also observed in the infrared spectra of lidociane in CCl_4 solution[32,33] as well as in the crystalline state[30]. Minima V and VI also pertain to conformers where the formation of NH···N intramolecular hydrogen bonding is feasible. The N···N interatomic distances calculated for the hydrogen bonding-stabilized conformers II, V, and VI are 0·293, 0·265, and 0·293 nm, respectively, which agree well with the experimental value[30] of 0·268 nm.

As compared to lidocaine, the region with stable conformations in the energy map of the lidocaine cation (Fig. 4) is considerably narrower. A total of three minima were

found in the conformation map within the 20 kJ mol^{-1} range (Table I); this range makes up only 17% of the whole energy map. Similarly as for lidocaine, the most stable conformer is that with the *cis* arrangement of the carbonyl oxygen and amino nitrogen atoms. The carbonyl group and the $N^{(+)}$—H group then are in the *trans* arrangement, so that $N^{(+)}$—H···O=C type intramolecular hydrogen bonding does

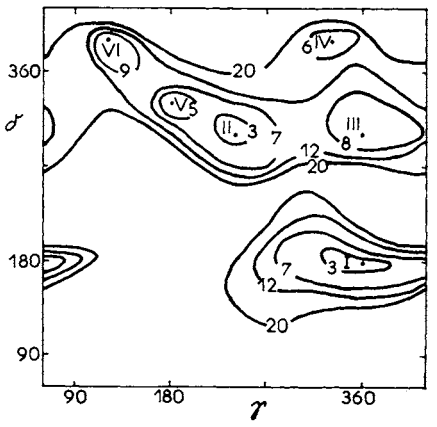

FIG. 3

PCILO energy surface for lidocaine. The isoenergy curves are in kJ mol^{-1} with respect to the global minimum which is taken as the energy zero

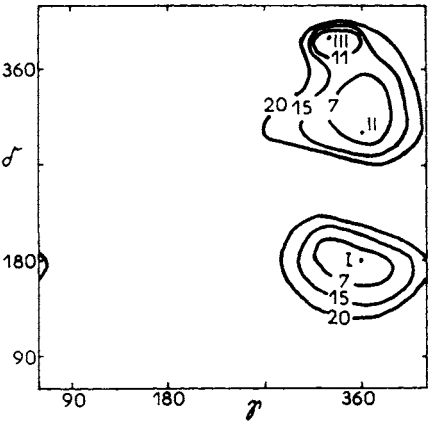

FIG. 4

PCILO energy surface for lidocaine cation. The isoenergy curves are as in Fig. 3

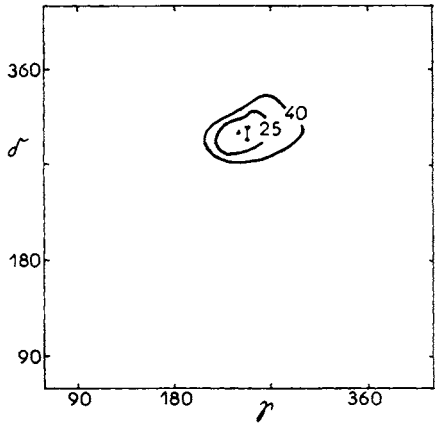

FIG. 5

PCILO energy surface for lidocaine hydrofluoride. The isoenergy curves are as in Fig. 3

not occur in this conformer; it does occur, however, in the second and third most stable conformers. The equilibrium distribution of the three conformations, based on the calculated energies, is 71 : 26 : 3.

The energy map of the lidocaine cation with the fluorine counter-ion in the PCILO-optimized position (Fig. 5) exhibits only one minimum within the 20 kJ mol^{-1} energy range (Table I). The existence of ion pairs in lidocaine salts has been confirmed by spectroscopic[34] and X-ray diffractometric[31,35,36] evidence. The ion pairs can also be assumed to exist in concentrated solutions and, particularly, in nonaqueous media such as lipids. In this case, the calculation can reflect the actual conformational situation. In the most stable conformation with torsional angles $\gamma = 240°$ and $\delta = 300°$, the fluorine anion is engaged in bifurcated hydrogen bonding, *viz.*, with the hydrogen atom of the $N^{(+)}$—H group and that of the amide group. The carbonyl oxygen atom and the basic nitrogen atom are in a mutual anticlinal conformation.

TABLE I

The PCILO-calculated lowest energy minima and C=O···N interatomic distances for the stable conformations of lidocaine, its cation and hydrofluoride

Minimum	γ deg	δ deg	ΔE kJ mol^{-1}	C=O···N distance nm
		Lidocaine		
I	360 (0)	180	0	0·277
II	240	300	0·3	0·343
III	360 (0)	300	1·2	0·277
IV	330	390	4·1	0·284
V	180	330	4·3	0·363
VI	120	390	7·9	0·343
		Lidocaine cation		
I	360 (0)	180	0	0·277
II	360 (0)	300	2·5	0·277
III	330	390	8·4	0·284
		Lidocaine hydrofluoride		
I	240	300	0	0·343

Proton Affinity and Hydrogen Bonding

At physiological pH, lidocaine can occur in positively charged or uncharged forms. The protonation site is the amino group. The protonation–deprotonation equilibrium is characterized by the experimental pK_a value (in aqueous system); this quantity, however, is not proportional to the electron density at the nitrogen atom of the base. A quantity which is related to the electron densities at nitrogen atoms is the proton affinity in the gaseous state[37]. For lidocaine, the experimental value is unknown; we calculated it therefore theoretically by the PCILO method (Eq. (*1*)) and for the PCILO-optimized geometry of the base and lidocaine cation, obtained a value of 1 418·8 kJ mol^{-1}; this is somewhat higher than the value obtained similarly for trimethylamine[38], *viz.* 1 372·2 kJ mol^{-1}.

The energy of the $N^{(+)}$—$H\cdots F^{(-)}$ type intermolecular hydrogen bond in lidocaine hydrofluoride, calculated from Eq. (*2*), is very high, 292·0 kJ mol^{-1}, with the equilibrium $R_{F\ldots H}$ distance 0·185 nm.

DISCUSSION

A comparison of the PCILO-calculated conformation maps (Figs 3–5) for the rotation about the torsional angles γ and δ defining the mutual arrangement of the lidocaine lipophilic and hydrophilic centres shows that considerable differences exist between the conformation flexibility of lidocaine, its cation and salt. Whereas the unprotonated base exhibits a fairly high steric flexibility, for the salt only one conformer is stable. Table I gives the interatomic distances between the oxygen atom and the basic nitrogen atom. According to the frequently employed receptor mapping approach[39], atoms of the drug with lone electron pairs are likely to bond to the receptor. The comparison of the $R_{N\ldots O}$ interatomic distances for lidocaine base, cation and hydrofluoride, however, does not allow unique conclusions concerning the receptor topology to be drawn. While for lidocaine the distances are, due to the high flexibility, about 0·28 nm and 0·35 nm, for the protonated form they are nearly identical, about 0·28 nm, in all the stable conformers. The $O\cdots N$ distance in the single stable conformation of the lidocaine salt was calculated to be 0·35 nm.

From the fact that for some stable conformations of lidocaine the $R_{O\ldots N}$ distances are the same as for the cation, it might be inferred that the base and the cation can interact with the same receptor. Present pharmacological studies, however, indicate that the biologically active form is the cation which blocks the sodium channels from the internal side of the membrane. Thus, it is likely that owing to its high conformational flexibility, the hydrophobic lidocaine base, which tends to separate from the outer aqueous phase on the interface[40], can penetrate through the lipid part of the membrane, as suggested by Hille[14]. The conformationally more rigid protonated lidocaine form then acts on the ionic channel. The conformational rigidity increases further due to the hydrogen bonding interaction of the cation with the counter-ion.

In addition to the conformational study, important information on the possible interactions of lidocaine with the biophase can be derived from the atomic population analysis and calculations of molecular electrostatic potentials. Since the results of atomic population analysis obtained by semiempirical methods and by *ab initio* calculations[25,41] differ considerably, particularly for the hetero atoms and hydrogen atoms, and also the wave functions obtained from semiempirical calculations generally do not suit to the calculation of electrostatic potentials of aromatic compounds[42], we do not report the PCILO atomic population data for lidocaine. Discussion of the possible types of interaction of this anaesthetic with the nerve membrane based on *ab initio* SCF calculations has been presented in our earlier papers[23,24,26].

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Translated by P. Adámek.