CONFORMATIONAL STRUCTURE OF THE ANTIARRHYTHMIC MEXILETINE, ITS CATION AND HYDROCHLORIDE

Milan REMKO[a] and Martin MACKOV[b]

[a] *Department of Pharmaceutical Chemistry, Comenius University, 832 32 Bratislava*
[b] *Drug Research Institute, 900 01 Modra*

Received January 26, 1990
Accepted March 28, 1990

The PCILO and MNDO quantum chemical methods were applied to the conformational analysis of antiarrhythmic mexiletine (1-(2,6-dimethylphenoxy)-2-aminopropane, its cation and hydrochloride. The stable conformations, proton affinity, and the hydrogen bonding energy of the mexiletine ion pair were determined.

Mexiletine (1-(2,6-dimethylphenoxy)-2-aminopropane) is an established antiarrhythmic agent belonging to the Ib category[1]. It also exhibits considerable local anaesthetic activity[2]. Chemical features that are essential for nonspecific activity of those local anaesthetic-like antiarrhythmics are the same as for the local anaesthetic efficiency[3]. It is known that the class Ib antiarrhythmics contain certain structural elements in suitable positions (the aromatic part, polar group, connecting chain and amine group) which are requirements for activity[4]. Their main antiarrhythmic effect seems to be due to a blockade of the sodium channels[5,6]. However, the nature of this membrane-stabilizing effect is not well understood. The interaction of antiarrhythmics with artificial membranes was investigated experimentally in works[7,8]. The interactions between models of antiarrhythmics and local anaesthetics and polar groups of membranes were also studied theoretically (refs[9,10]).

One of the most important factors determining pharmacological activity is the electronic and spatial structure which governs the fit of the drug to a suitable portion of the biophase, the receptor. In this connection, in our foregoing works[11,12] the spatial and electronic structures of the local anaesthetic-like antiarrhythmics lidocaine and tocainide were investigated. The present paper gives the results of a conformational study of the clinically used antiarrhythmic mexiletine. Since the unprotonated substances are very low soluble in water, water soluble salts of antiarrhythmics are used in practice. Within regard of this, the mexiletine cation and its hydrochloride are also treated in this work.

THEORETICAL

The stable conformations of mexiletine, its cation and hydrochloride were sought by means of the PCILO (ref.[13]) and MNDO (ref.[14]) quantum chemical methods. A diagram of the compounds, along with the relevant dihedral angles, is shown in Fig. 1. For the study of the conformational structure of mexiletine (B), its cation (BH^+) and hydrochloride (BHCl), the two-dimensional conformational maps werre calculated and plotted as functions of the torsion angles γ and δ. The conformational maps were computed by means of the PCILO method. Since we are dealing with aromatic compounds there is some ambiguity in the choice of the appropriate zeroth-order wave function with respect to the existence of two Kekulé structures. The pilot calculations were therefore also performed by means of the MNDO method.

The proton affinity of mexiletine was calculated as the negative value of the differences E_p between the total energies of base B and its cation BH^+,

$$E_p = E_B - E_{BH^+}, \qquad (1)$$

for the exothermic reaction

$$B + H^+ \rightarrow BH^+. \qquad (A)$$

The energy of the hydrogen bond (E_{HB}) of the $N^+—H\cdots Cl^-$ type in the mexiletine hydrochloride was determined as the difference between the total energy of the isolated monomers and the total energy of the hydrogen-bonded complex (E_{min})

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

The geometry of this hydrogen-bonded complex was optimized with respect to the $N\cdots Cl$ distance.

Since the X-ray data for mexiletine are not available, we used for conformational map calculations of BH^+ and BHCl the partially optimized geometry of the mexiletine. For the optimization of the internal parameters of mexiletine the PCILO method was used as it was adopted[15,16] for the optimization of geometry through internal geometrical parameters. The required accuracy during the optimization

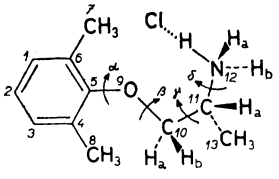

FIG. 1

Numbering of atoms and dihedral angles in the compounds studied. The form shown has $\alpha = \beta = \gamma = \delta = 0°$

of the geometry was 0·1 pm for the bond lengths, 0·01° for the bond angles and 0·1° for the dihedral angles.

RESULTS AND DISCUSSION

Conformational Analysis

First we studied, by means of the MNDO method, the energy curve of rotation around the C_{arom}—O bond (α angle, Fig. 1) for mexiletine. The energy curve shows two minima (at 90° and 270°) and two maxima (at 0° and 180°). The energy barrier is very high (170 kJ mol^{-1}). As our PCILO calculations have shown, the C—O—C—C fragment favors the *trans* form. We considered this trans conformation ($\beta = 0°$, Fig. 1) in all calculations. From the conformational point of view the most interesting is the mutual orientation of the ether and amine groups of mexiletine, its cation and hydrochloride. The conformational structure of those species was investigated on the conformational maps. The PCILO energy surfaces for the base, its cation and hydrochloride are shown in Figs 2–4.

The energy map of mexiletine (Fig. 2) is characterized by the occurence of a vide region of stable conformations. A total of nine minima has been found on the conformation map within the 20 kJ mol^{-1} energy region. In order to gain the information about the mutual arrangements of the aromatic ring (representing the hydrophobic centre) and the amine group (the hydrophilic part of drug), we carried out the optimization of geometry of nine stable conformers of mexiletine, as determined from the PCILO calculations of energy map of mexiletine (Fig. 2) using the standard geometry. The results of our calculations including energy minimization of mexiletine are given in Table I. The optimized values of selected bond lengths of the C—O—C—C—N moiety are practically the same in all nine stable conformers. Similarly, the valence angles of this fragment do not change noticeably upon optimization. Of the four dihedral angles chosen for the geometry optimization, the dihedral angles α and β, which determine the rotation of benzene ring and ether group, respectively, do not show any important variation in the nine conformers under study. The optimum values of the dihedral angle α are close to 90°, a minimum value calculated by the MNDO method. The CO—CC fragment is in a more stable *trans* form ($\beta = 0-5°$). The other two dihedral angles γ and δ change dramatically upon energy minimization. The net result of the energy minimization of those nine stable conformers of mexiletine is a considerable change in the energy and the order of conformers stability. As our PCILO geometry optimizations of mexiletine have shown, the most stable conformer is that with the values of dihedral angles $\alpha = 94·3°$, $\beta = 0·4°$, $\gamma = 57·6°$ and $\delta = -61·0°$. The heavy atoms of the C—O—C—C—N fragment are not coplanar. The conformation about the OC—CN bond is gauche. This conformer is stabilized by the intramolecular hydrogen bond ($R_{O\cdots H}$ = 239 pm,

$R_{O\cdots N}$ = 277 pm) formed by the NH group hydrogen and the oxygen atom. Existence of such type of intramolecular hydrogen bond has been found[17] in the 2-methoxyethylamine simpler model of mexiletine. As microwave measurements have shown[17], the molecule exists in a gauche form with an intramolecular hydrogen bond of the N—H···O type. The determined hydrogen bond parameters ($R_{N\cdots O}$ = 292 pm and $R_{O\cdots H}$ = 254 pm) are close to our PCILO values calculated for the most stable conformer of mexiletine. The second most stable conformer of mexiletine (dihedral angles α = 93·8°, β = 0·1°, γ = 178·6° and δ = 77·0°, respectively) corresponds to the all-*trans* arrangement of the C—O—C—C—N fragment. In this conformer the

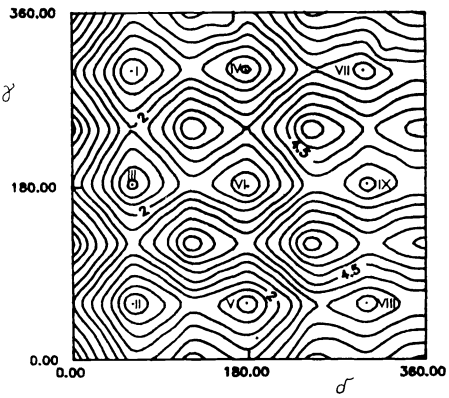

FIG. 2

PCILO energy surface for mexiletine. The isoenergy curves are in kJ mol^{-1} with respect to the global minimum which is taken as the energy zero. Contours: 0 (0·5) 6·5 kJ mol^{-1}

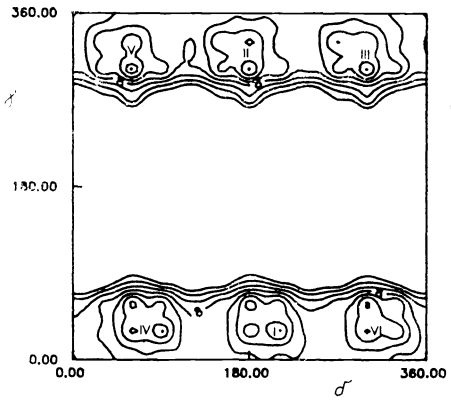

FIG. 3

PCILO energy surface for mexiletine cation. The isoenergy curves are as in Fig. 2. Contours: 0 (2) 15 kJ mol^{-1}

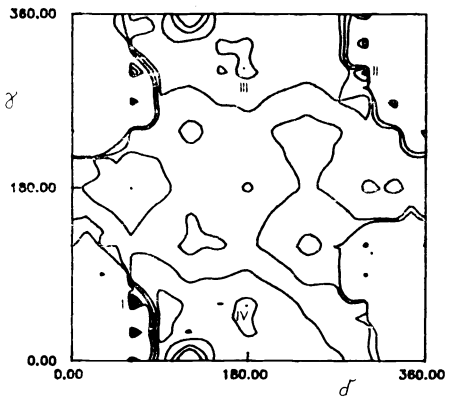

FIG. 4

PCILO energy surface for mexiletine hydrochloride. The isoenergy curves are as in Fig. 2. Contours: 0 (2·5) 10 kJ mol^{-1}

existence of intramolecular hydrogen bond of the NH···O type for stereochemical reasons is excluded. Equally stable is the third minimum (Table I). Substantially less stable are rest six minima. The calculated population ratios (at 310·16 K) for the most stable conformations of the mexiletine are 30 : 22 : 22 : 10 : 6 : 4 : 3 : 2 : 1.

The energy map of the ionized mexiletine (Fig. 3) shows six minima (Table I). All those stable conformations are stabilized by the internal hydrogen bonding NH···O. The found $R_{O\cdots H}$ lengths were in the range of 192–242 pm, which is less

TABLE I

The PCILO-calculated lowest energy minima and O···N interatomic distances for the stable conformations of mexiletine, its cation and hydrochloride

Minimum	γ, °	δ, °	ΔE kJ mol^{-1}	O···N distance pm
		Mexiletine[a]		
I	300·0 (57·6)	60·0 (+ 61·0)	0·0 (0·0)	290·0 (277·0)
II	60·0 (178·6)	60·0 (77·0)	0·5 (0·9)	290·0 (363·0)
III	180·0 (298·9)	60·0 (76·0)	1·7 (0·9)	370·4 (280·0)
IV	300·0 (293·3)	180·0 (304·1)	2·6 (4·6)	290·0 (285·0)
V	60·0 (296·1)	180·0 (178·9)	2·6 (4·7)	290·0 (291·0)
VI	180·0 (55·0)	180·0 (181·0)	4·2 (5·3)	370·4 (283·0)
VII	300·0 (180·9)	300·0 (287·2)	9·4 (5·6)	290·0 (367·0)
VIII	60·0 (54·4)	300·0 (316·0)	11·6 (7·8)	290·0 (274·0)
IX	180·0 (174·5)	300·0 (316·0)	11·9 (8·1)	370·4 (362·0)
		Mexiletine cation		
I	30·0	210·0	0·0	254·3
II	300·0	180·0	0·2	278·5
III	300·0	300·0	0·3	278·5
IV	30·0	90·0	0·7	254·3
V	300·0	60·0	0·9	278·5
VI	30·0	300·0	1·8	254·3
		Mexiletine hydrochloride		
I	60·0	60·0	0·0	278·5
II	300·0	300·0	4·1	278·5
III	300·0	180·0	7·0	278·5
IV	60·0	180·0	7·4	278·5

[a] Minima gained by the PCILO optimization of geometry of the mexiletine are in the parentheses. Their energy order is different from those substracted from the conformational energy map (Fig. 2).

than the sum of the van der Waals radii (260 pm) of the oxygen and hydrogen atoms. The calculated populations of these six stable conformers of the cation are: 21 : 20 : : 18 : 16 : 15 : 10.

The energy map of the mexiletine cation with the chlorine counter-ion in the PCILO optimized position (Fig. 4) exibits four energy minima within the 20 kJ mol^{-1} energy range (Table I). The ion pairs can be assumed to exist in concentrated solutions, and particularly, in nonaqueous media such as lipids. In this case, the calculation may reflect the actual conformational situation. The most stable minimum lies at $\gamma = 60°$ and $\delta = 60°$ with the gauche alignment of the OC–NH fragment and is stabilized by the intramolecular hydrogen bond of the NH···O type. As the calculated populations (76 : 15 : 5 : 4) at 310·17 K show, the most stable conformation should predominate in crystal.

The stereochemical drawings of the PCILO most stable conformers of mexiletine, its cation and hydrochloride are shown in Fig. 5. This figure shows that in the stable conformers of the mexiletine species studied both oxygen and nitrogen atoms lie at the same half-plane of the plane defined by the O—C—C—C fragment. This is obviously due to the strong hydrogen bonding between the NH and O atoms. We propose that the mexiletine conformation shown in Fig. 5 approximates the intristic conformation of the mexiletine base as it exists in solution in non-polar solvents. However, with respect to the high population ratio of the second and third most stable conformers, several conformers of mexiletine may coexist. It is known[18] that complexation may change the conformation. The calculations of mexiletine hydrochloride indicate that no such changes are likely in this case. The most stable conformations (Fig. 5) of mexiletine and its salt have been found to be very similar.

According to the frequently used receptor mapping concept[19], atoms of the drug with lone electron pairs are likely to bond to the receptor. These are the oxygen and nitrogen atoms in mexiletine and their distances in lowest energy conformations are

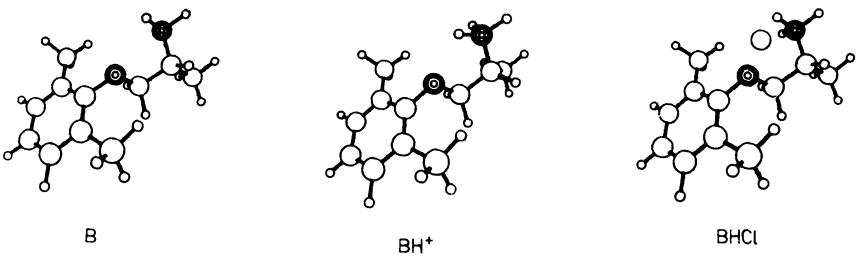

FIG. 5

Views of the minimum energy conformations of mexiletine (B), its cation (BH^+) and hydrochloride (BHCl)

listed in Table I. Owing to a high flexibility of mexiletine, the N···O distance is close to 280 or 360 pm. In stable conformations of the cation and hydrochloride the N···O lengths were calculated at about 255 and 279 pm. Almost the same distribution of the O···N distances has been found from the PCILO calculations for lidocaine[11] and tocainide[12], drugs belonging to the Ib class of the category of antiarrhythmics. Therefore all, lidocaine, tocainide and mexiletine, may interact with the structurally similar receptors, as it was discussed in our recent work[11].

Proton Affinity and Hydrogen Bonding

Mexiletine is practically completely protonated[8,20] (98% charged species) at pH of a physiological medium. However, the experimental gas phase proton affinity has not yet been known. For that reason the theoretical proton affinities, E_p, (Eq. (*1*)) have been also computed by means of the PCILO and MNDO methods. The PCILO calculated proton affinity is very high (1 413·6 kJ mol^{-1}). A similar value (1 340·4 kJ . . mol^{-1}) was found, also from the PCILO calculations, for the protonation of tocainide[12]. The MNDO method, on the other hand, yielded substantially lower value of 636·6 kJ mol^{-1}, calculated using the geometry of the PCILO most stable conformers of B and BH^+. The comparison of *ab initio* and PCILO calculated proton affinities for tocainide[12] inidcated that the PCILO values are rather overestimated. On the other hand, the MNDO proton affinity is very low and it seems that this method seriously underestimates the stability of cations. The value of 1 021·1 kJ . . mol^{-1} has been determined[21] from the ab initio calculations of the protonation of methylamine, which may be considered as a simpler model of the mexiletine amine group.

The intermolecular hydrogen bond $NH^+\cdots Cl^-$ in mexiletine hydrochloride has been investigated by the PCILO method. The equilibrium N···Cl distance was computed to be 223·6 pm. The energy of this hydrogen bond, with respect to its ionic character, is very high (335·7 kJ mol^{-1}).

Charge Distribution

In Table II we present the calculated PCILO and MNDO net charges on the atoms of mexiletine, its cation BH^+ and hydrochloride BHCl. The net charges were calculated for the most stable PCILO conformations of these compounds. The net atomic charges obtained from MNDO were compared with those obtained from PCILO to check the consistency of the electron distribution from the two semiempirical methods. Despite of fact that the absolute values of the net charges calculated by the MNDO method are different from those calculated by the PCILO method, the general trends in electron density changes upon protonation of mexiletine are described equally by the two methods.

One of the most significant regions of the species investigated is the amine group, which can interact with the anionic sites of the membrane[3]. In B and BHCl (Table II) the amine group has total negative charge. On the other hand, a larger part of the positive charge of the cation mexiletine is localized on the $-NH_3^+$ group (0·673e (PCILO)/0·743e (MNDO)). The ether oxygen bears a considerable negative charge

TABLE II

Gross atomic charges (in e) for the mexiletine (B), its cation (BH^+), and hydrochloride (BHCl) [PCILO/MNDO]

Atom	B	BH^+	BHCl
C(1)	−0·033/−0·031	−0·026/−0·015	−0·036/−0·035
H—C(1)	−0·011/ 0·061	0·004/ 0·079	−0·009/ 0·062
C(2)	0·004/−0·065	0·027/−0·033	0·015/−0·055
H—C(2)	−0·010/ 0·061	0·007/ 0·082	−0·006/ 0·064
C(3)	0·012/−0·028	0·021/−0·014	0·017/−0·024
H—C(3)	−0·010/ 0·062	0·004/ 0·079	−0·002/ 0·071
C(4)	−0·050/−0·109	−0·054/−0·108	−0·053/−0·090
C(5)	0·156/ 0·093	0·149/ 0·053	0·154/ 0·070
C(6)	0·045/−0·118	0·048/−0·106	0·042/−0·118
C(7)	−0·016/ 0·082	−0·014/ 0·078	−0·014/ 0·084
H—C(7)	0·009/−0·004	−0·012/ 0·020	−0·004/ 0·001
H—C(7)	0·001/ 0·010	0·009/ 0·008	0·002/ 0·007
H—C(7)	0·004/−0·002	0·016/−0·014	0·006/−0·013
C(8)	−0·016/ 0·081	−0·015/ 0·080	−0·016/ 0·064
H—C(8)	0·013/−0·006	−0·023/ 0·023	0·002/ 0·009
H—C(8)	0·003/ 0·007	0·022/−0·021	0·006/ 0·043
H—C(8)	0·002/ 0·011	0·016/−0·001	0·037/−0·004
O(9)	−0·215/−0·255	−0·229/−0·295	−0·209/−0·268
C(10)	0·177/ 0·155	0·153/ 0·109	0·143/ 0·152
H—C(10)	−0·035/ 0·003	−0·005/ 0·029	0·017/ 0·044
H—C(10)	−0·041/−0·010	0·016/ 0·054	−0·005/ 0·007
C(11)	0·119/ 0·026	0·102/−0·031	0·112/−0·005
H—C(11)	−0·050/−0·014	0 031/ 0·097	0·008/ 0·049
N(12)	−0·141/−0·260	0·005/ 0·003	−0·057/−0·046
H—N(12)	0·040/ 0·091	0·244/ 0·270	0·194/ 0·193
H—N(12)	0·054/ 0·111	0·218/ 0·236	0·209/ 0·223
H—N(12)	—	0·206/ 0·234	0·248/ 0·292
C(13)	−0·017/ 0·039	−0·030/ 0·003	−0·032/ 0·003
H—C(13)	0·003/ 0·001	0·027/ 0·026	−0·014/ 0·012
H—C(13)	0·006/ 0·011	0·026/ 0·023	0·060/ 0·065
H—C(13)	−0·002/−0·002	0·059/ 0·064	0·037/ 0·036
Cl	—	—	−0·884/−0·910

in all mexiletine species. The highest value was found for the ionized mexiletine. Hence the ether group may act as a proton acceptor in the hydrogen bonding with the biophase. The aromatic ring does not carry significant net charge (Table II). However, the electrostatic potentials computed from the *ab initio* wave functions of the "double zeta" quality for aromatic parts of the structurally related anaesthetics and antiarrhythmics have shown[22], that the aromatic part possesses a large area of negative potentials resulting from the superposition of the electronegative atoms of the substituents and electrons of the benzene ring. Hence this part of drug may serve as an electron-donor site in the drug – receptor interaction. On the other hand, the existence of strong intermolecular hydrogen bonds between ionized amine and ether group of antiarrhythmic and polar groups present in the biomembrane was confirmed by the *ab initio* calculations in our foregoing works[9,10].

REFERENCES

1. Vaughan Williams E. M.: Adv. Drug. Res. *9*, 69 (1974).
2. Pottage A.: Am. J. Cardiol. *52*, 24c (1983).
3. Wolff M. E. (Ed.): *Burgers Medicinal Chemistry*, Part III, p. 87. J. Wiley, New York 1981.
4. Morgan P. H., Mathison I. W.: J. Pharm. Sci. *65*, 467 (1976).
5. Catterall W. A.: Mol. Pharmacol. *20*, 356 (1981).
6. Hau J., Derhsam G. H., O'Connell D. P.: J. Electrocardiolog *22*, 81 (1989).
7. Villalogna F. A., Phillips E. W.: J. Pharm. Sci. *68*, 314 (1979).
8. Voigt W., Mannhold R., Limberg J., Blaschke G.: J. Pharm. Sci. *77*, 1018 (1988).
9. Remko M., Scheiner S.: J. Pharm. Sci. *77*, 304 (1988).
10. Remko M., Schiener S.: J. Pharm. Sci., in press.
11. Remko M.: Collect. Czech. Chem. Commun. *51*, 2063 (1986).
12. Remko M.: Chem. Papers *43*, 267 (1989).
13. Diner P., Malrieu J. P., Jordan F., Gilbert M.: Theor. Chim. Acta *15*, 100 (1969).
14. Dewar M. J. S., Thiel W.: J. Am. Chem. Soc. *99*, 4899 (1977).
15. Powell M. J. D.: Comput. J. *7*, 155 (1964).
16. Zanqwill V. I.: Comput. J. *10*, 293 (1967).
17. Caminati W., Wilson E. B.: J. Mol. Spectrosc. *81*, 356 (1980).
18. Pullman B.: Adv. Quantum Chem. *10*, 251 (1977).
19. Kier L. B.: *Molecular Orbital Theory in Drug Research*, p. 162. Academic Press, New York 1971.
20. Johansson P. A.: Acta Pharm. Suec. *19*, 137 (1982).
21. Remko M.: J. Mol. Struct., THEOCHEM *201*, 287 (1989).
22. Remko M., VanDuijnen P. T.: J. Mol. Struct., THEOCHEM *105*, 1 (1983).

Translted by the author (M.R.).