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Theoretical study of mexiletine and its interaction with cationic and anionic receptor sites

Milan Remko *, Martin Smieško, Adriána Beňová

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University, Odbojarov 10, SK-832 32 Bratislava, Slovakia

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Abstract

Theoretical methods are applied to study the antiarrhythmic (AA) mexiletine (1-(2,6-dimethylphenoxy)-2-aminopropane). The AM1 method is used to construct a three-centre binding model for this drug. This model consists of an amine nitrogen atom that is protonated to a higher degree at physiological pH, flat hydrophobic regions of aromatic rings and additional functional groups with lone electron pairs of oxygen. Based on these ideas, a model for the binding of mexiletine at the transmembrane protein was constructed. An ab initio SCF method was used to study the two-component mexiletine–receptor binding site composed of acetate (Glu^-, Asp^-) and protonated methylamine (Lys^+, Arg^+). The binding of mexiletine to the receptor may be understood by considering a two-step process of recognition and binding of AA to its receptor. Within this model the mexiletine cation is recognised in the first step and bonded to the negatively-charged part of the receptor. In a subsequent step, the interaction between the amide oxygen and cationic amine group of the membrane protein may follow.

Keywords: Mexiletine; Antiarrhythmic–receptor interaction; Theoretical calculations

1. Introduction

Mexiletine (1-(2,6-dimethylphenoxy)-2-aminopropane) is a class IB antiarrhythmic (AA) drug used in the treatment of ventricular arrhythmias [1,2]. Chemically, mexiletine is a congener of lidocaine — a powerful AA drug that has a similar chemical structure. Thus, the mode of action of lidocaine and mexiletine should be the same. It is believed that these drugs exert their clinically important action by blocking voltage-gated Na^+ channels of the cardiac cells [2–6]. The mode of action of drugs that block the fast Na^+ channel is not known. Recent studies support the idea that the Na^+ channel blocking AAs react with specific receptors of cardiac cell membrane proteins [2,7]. Ion channels acting as pharmacological receptors possess manifold drug binding sites [4,8]. At normal heart rates, the drugs produce little or no block. As the heart rate increases, the degree of block increases. This so-called 'use-dependent block' is caused either by changes in receptor affinity or by a possible access to the receptor, sometimes both [9,10]. Despite a great deal of pharmacological evidence for AA binding sites at or in ionic channels, none of them have been identified using the techniques of molecular biology. The absence of experimental structural data of membrane-bound receptors presents a challenge to the application of molecular modelling methods in order to obtain an insight into the recognition and binding processes.

In this paper we have used the results of large-scale theoretical quantum chemical investigations [11–13] of the interaction of associative groups of membrane-active drugs (represented by simple models such as an amine, amide, ether and ester group) with both cationic and anionic groups of membrane (formate, phosphate, amino and amide groups, respectively) as a first step in an explicit modelling of the AA–anionic receptor site interaction. The effect of the medium and Na^+ and K^+ ions on the equilibrium geometry and interaction energy of the AA–carboxylate complexes was also investigated [14–16]. Based on these results, and in order to elucidate structure–function correlation, we applied the methods of theoretical chemistry to the explicit modelling of the mexiletine–receptor site interaction. We

* Corresponding author. Tel.: +421-7-5025 9360; fax: +421-7-5557 2065.

E-mail address: remko@pharm.uniba.sk (M. Remko)

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investigated intermolecular hydrogen bonds formed between neutral and protonated mexiletine and the polar acetate and methylamine groups. A binding model should be constructed and the general AA receptor site proposed and theoretically modelled. The results of molecular modelling studies of mexiletine and lidocaine were compared and the results discussed with the present theories of action of these sodium channel blocking AAs.

2. Theoretical section

Molecular modelling studies were carried out by means of the HYPERCHEM 5.02 [17], MOLGEN 4.0 [18] and CHEM-X [19] computer programs. An ab initio SCF method was employed for the determination of the interaction energies and equilibrium geometries of the mexiletine–ionic complex loci of membrane protein (Fig. 1). The split-valence 3-21G basis set [20] was used. As has been shown previously [12,14,15], this basis set reproduces the general trends of the relative stability of various hydrogen-bonded species, for which we are primarily interested, qualitatively well. The intermolecular parameters (r, r', R, α, α' and β) of the complexes given in Fig. 1 were energy optimised, keeping the internal geometries of each subunit fixed at their monomer structures. The bridging proton was held within the H-bond axis. The initial geometry for the AA was obtained from the X-ray structure of mexiletine hydrochloride [21]; for the conversion of the X-ray coordinates of AA to internal coordinates the MOLGEN 4.0 program was used. The ionic receptor binding sites were represented by the acetate anion and the methylamine cation. The 3-21G optimised geometry of these was taken from Refs. [15,22]. In H-bonded complexes the bridging proton was held within the H-bond axis and the energy of the intermolecular com-

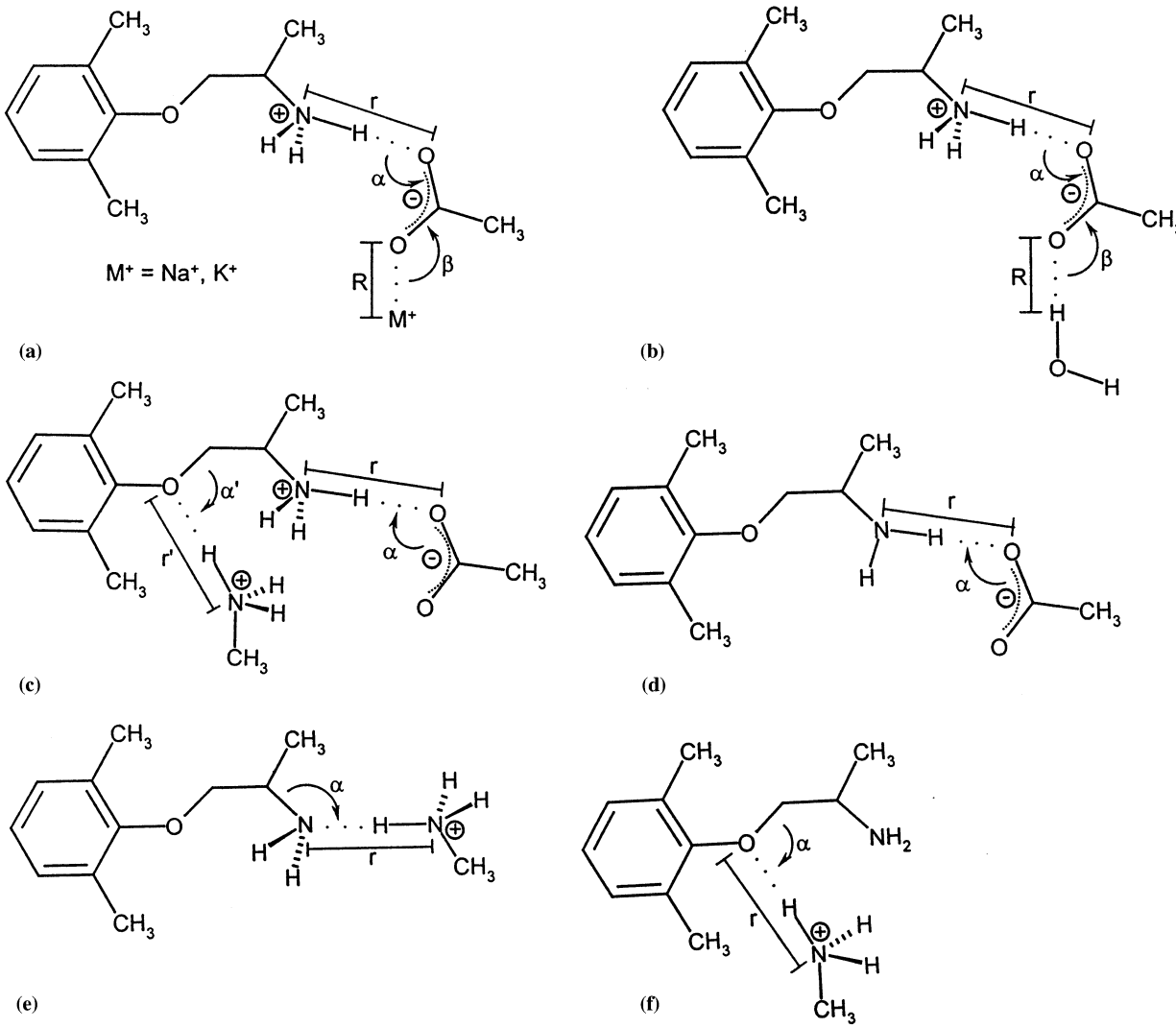

Fig. 1. Molecular structure and definition of intermolecular parameters r, r', R, α, α' and β for the systems studied.

plexes (ΔE_{AB}) was determined as the difference between the total energy of the isolated molecules and that of the complex (E_{AB}):

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

Complex **6** consists of the optimised complex **1** and the ionised methylamine. The r' and α' parameters were optimised. In complex **7** the position of the acetate group was reoptimised (r and α parameters (Fig. 1)) at the constant (optimal) position of the methylamine cation.

The energies of the ion- and water-coordinated complexes (Fig. 1) are:

$$E_{AB}(I) = E_{(IA\cdots B)} - (E_{IA} + E_B) \quad (2)$$

where E_{IA} is the total energy of the optimised anion–cation (Na^+, K^+) or anion–water systems. The quantity 'net stabilisation energy' (E_{NS}) was determined by subtracting the H-bond energy of the free complex from the respective $E_{AB}(I)$ values of the ternary complex I–A···B.

$$E_{NS} = E_{AB}(I) - E_{AB} \quad (3)$$

The basis set superposition error was determined and corrected using the Boys–Bernardi method [23]. All ab initio calculations were performed by the GAUSSIAN-98 program [24].

3. Results and discussion

3.1. Geometry

Chemically, mexiletine is a derivative of lidocaine. Despite their structural similarities, mexiletine exhibits significantly greater inhibitory potency on the in vitro activity of the cytochrome P4501A1 isozyme [25]. Deluca et al. [26] observed a stronger potency of *R*-(−)- versus *S*-(+)-enantiomers of mexiletine on sodium currents of adult skeletal muscle fibres in frogs. Thus, the structural factors could have a primary effect in modulating the activity of these AAs and the receptor of mexiletine shows stereochemical selectivity corresponding to both chiral locations [2]. Theoretical calculations have therefore been carried out to identify all low-energy conformations (arbitrarily taken as < 40 kJ/mol above the global minimum) that could conceivably be involved in binding at the receptor (Fig. 2). For the determination of the minimum energy conformations, the conformational search module of the CHEM-X program was used. The resulting MM2 structures were finally reoptimised using the quantum chemical AM1 method [27]. The presence of two methyl groups in positions 2 and 6 in benzene results, for reasons of stereochemistry, in the most stable nonplanar conformers (torsion angle φ_1, Table 1). Thus, these drugs

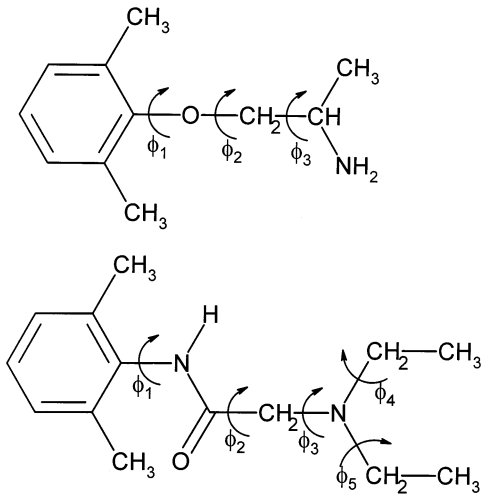

Fig. 2. Definition of torsion angles used in conformational energy calculations.

exhibit a certain steric stability, i.e. mexiletine and lidocaine could access the same hydrophobic pocket of the receptor. Examination of the lowest energy conformations for mexiletine found from the energy calculations showed two main types of conformations (both for *R*- and *S*-mexiletine, Table 1), which differ in the orientation of the amino group. For *S*-(+)-mexiletine, the first, more stable type has the amino group oriented towards the phenyl ring (torsion angle $\varphi_3 = 67.6°$). The second type represents an extended conformation of the side chain (torsion angle $\varphi_3 = 164.5°$). For each conformation of *S*-(+)-mexiletine there is also a mirror image conformation of the same energy obtained from the enantiomer (Fig. 3). The optimised structures of mexiletine and lidocaine were also used to investigate a presumed basic receptor feature. The amine nitrogen atom, the oxygen atom and the phenyl ring were recognised as functional groups for receptor binding [13,16]. Table 1 contains the computed N···O distances connecting the non-bonding nitrogen and oxygen atoms. The N···O distance is in mexiletine close to 0.29 or 0.36 nm. Almost the same distribution of the O···N distance has been found (Table 1) for the stable conformation of the lidocaine (about 0.35 nm). Thus, lidocaine and mexiletine may interact with the structurally similar receptors.

3.2. Modelling of mexiletine–receptor interactions

The previously discussed binding model allows some limited conclusions on the structure and properties of a receptor. Based on these ideas we constructed a model for the binding of mexiletine to the transmembrane protein receptor (Fig. 4). The primary interactions involve the aromatic ring, the protonated or unprotonated amine nitrogen and the ether oxygen. As might

Table 1
Torsion angles (Fig. 2) and relative energies of the stable conformers of mexiletine and lidocaine

Drug	φ_1 (°)	φ_2 (°)	φ_3 (°)	φ_4 (°)	φ_5 (°)	φ_6 (°)	ΔE (kJ/mol)	$R_{N\cdots O}$ (nm)
S-(+)-Mexiletine	93.7	−176.5	67.6				0	0.291
	99.7	177.4	164.5				7.5	0.365
R-(−)-Mexiletine	98.6	175.1	−68.3				0	0.291
	86.9	−178.1	−164.2				7.5	0.365
Lidocaine	119.8	−176.2	52.4	−157.7	74.3	−154.9	0	0.350

be expected, modelling of mexiletine [13,16], as well as the crystal structure of mexiletine hydrochloride [21], indicate that the aromatic ring is likely to occupy a region that is not coplanar with the side chain plane containing the –O–CH_2–C–NH_2 atoms. The site that is occupied by the phenyl substituent is therefore depicted as an out-of-plane lipophilic pocket. The methyl group of the amine region of the drug could pose as a steric constraint for the favourable hydrogen bond (Fig. 4) formed by the amine group. The lipophilic pocket and the steric inhibitions certainly play an important part in the accommodation of mexiletine on the receptor surface. The molecule is then 'recognised' by the receptor and bound to its surface by means of H-bonds (Fig. 4). The higher biological activity [26] of the *R*-(−)-enantiomer of mexiletine could be explained by the presence of a stereospecific hydrophobic interaction centre of the receptor, which forms a hydrophobic bond with the *R*-(−)-mexiletine. In the case of the less active *S*-(+)-mexiletine this stereospecific interaction is not possible (Fig. 4).

We have simulated the interactions between mexiletine and its biological host model. This receptor binding site model is based on the optimised interactions of two polar regions of mexiletine and its cation (the amine nitrogen and the ether oxygen atoms) with a hypothetical two-component receptor model consisting of an anionic site (modelled by the acetate anion) and a cationic receptor (modelled by the cation of methylamine). These ionised groups are commonly present in acidic (Glu, Asp) and basic (Lys, Arg) residues of amino acids of cardiac membrane proteins. The optimised geometry and interaction energy of the systems studied are shown in Table 2.

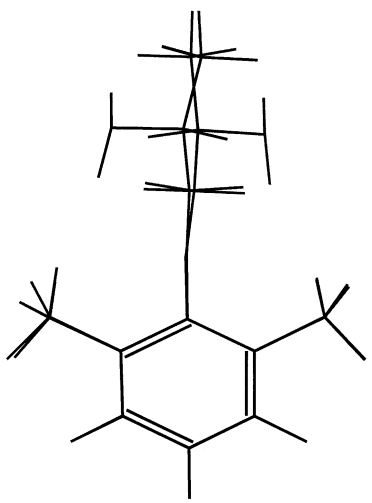

Fig. 3. Superimposition of the most stable *R*- and *S*-enantiomers of mexiletine.

In physiological solutions at neutral pH, the amine groups of various AAs are almost completely protonated [28]. Complex **1** combines the cation of mexiletine with the negatively charged $CH_3CO_2^-$. The calculated energy of interaction is, as expected, very large for this type of calculation [14,15]. The ion-pair complex **1** is very strong with an interaction energy of −498.3 kJ/mol. A second category of the complexes investigated involves the systems coordinated by Na^+ and K^+ cations. These cations serve as counterions which are commonly present in excitable cells [29]. The interaction of cations with the acetate group of the isolated system **1** results in considerable changes in H-bond geometries and interaction energies (Table 2). Coordination of Na^+ and K^+ to the carboxyl oxygen produces an 'opening' of hydrogen-bonded structures characterised by a considerably wider H-bond angle α (Table 2). This arrangement is a result of minimisation of mutual repulsion of metal cations and hydrogens of the amino part of mexiletine. The ion approach a carboxyl group in *anti* arrangement (systems **2**, **3**). The net effect of ion coordination on the energy of the $NH^+\cdots{}^-O$ hydrogen bond is a considerable reduction of the H-bond energy in comparison with the isolated systems. In order to visualise the specific effects of Na^+ and K^+ on the stability of the isolated complex **1** we also computed net stabilisation energies (E_{NS}), which describe the influence of ions on the strength of H-bonds (Table 2). Positive E_{NS} values correspond to a destabilised hydrogen bond. The natrium cation produces slightly larger destabilisation than K^+. The large destabilisation effect of Na^+ and K^+ ions on the strength of the $NH^+\cdots{}^-O$ hydrogen bond indicates that these ions can cause a considerable weakening of mexiletine–carboxylate bond. Thus, the interaction of external Na^+ and K^+ ions on channel-modifying AAs bound to their receptor may be one of the factors which govern the direct dissociation of

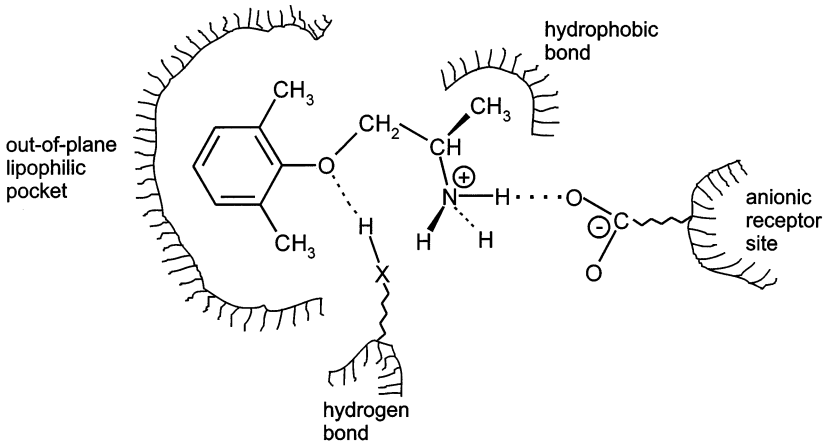

Fig. 4. A model of the binding of mexiletine with the receptor.

charged drugs from the AA binding site. Water, which may solvate carboxylate groups in lipoproteins, particularly at the outer surface of the membrane, may also play an important role in the recognition and stabilisation of the interaction between a ligand and its site. Complex **4** contains the mexiletine–$NH^+\cdots{}^-OCOCH_3$ system hydrated by a water molecule. However, the placing of water on the oxygen of CH_3COO^- that does not interact directly with the bridging hydrogen of the charged mexiletine resulted in slight destabilisation of the system **1** only (Table 2). In order to study the influence of the surrounding medium on the stability of the mexiletine–acetate complex **1** (Table 2) we also investigated the environmental effects. The calculations were carried out using the SCRF formalism of Wong et al. [30]. The placing of the isolated complex **1** (Table 2) into a spherical cavity within a dielectric medium of the Onsager model of solvation does not represent the realistic situation in the biological medium; it seems helpful in revealing the main role of the solvent in intermolecular electrostatic interactions. Water ($\varepsilon = 78.5$) has a remarkable effect on the geometry of the mexiletine–$NH^+\cdots{}^-OCOCH_3$ complex, resulting in an opening of the N–$H^+\cdots{}^-$O–C bond (Table 2). The interaction energy of complex **1** decreases upon solvation. Accordingly, the presence of solvent results in a net destabilisation of system **1**.

The binding of AAs to the receptor may, however, be understood by considering a two-step process of recognition and binding of AAs to their receptors [13]. Within this model the mexiletine cation is recognised in the first step and bonded at the negatively charged $-CO_2^-$ part of the receptor. In a subsequent step the interaction between the ether oxygen and positively charged $-NH^+$ group of the membrane protein may follow. Complex **6** (Table 2) represents such a possibility for a two-centre interaction. This complex contains as a subsystem the optimised complex **1**. The $>O\cdots{}^+HN$ H-bond energy is high and neg-

Table 2
Ab initio SCF optimised geometries and interaction energies of the complexes studied (Fig. 1)

	Complex	$r(r')_{N\cdots O(N)}$ (nm)	$\alpha(\alpha')$ (°)	$R_{O\cdots Me+}$ (nm)	β (°)	ΔE_{AB} [a] (kJ/mol)	E_{NS} (kJ/mol)
1	Mexiletine$NH^+\cdots{}^-OCOCH_3$	0.2510	98.7			−498.3	
2	[Mexiletine$NH^+\cdots{}^-OCOCH_3$]Na^+	0.2528	155.3	0.1974	172.5	−201.3	297.0
3	[Mexiletine$NH^+\cdots{}^-OCOCH_3$]K^+	0.2513	147.7	0.2392	166.3	−222.2	276.1
4	[Mexiletine$NH^+\cdots{}^-OCOCH_3$]H_2O	0.2519	101.4	0.2729	116.8	−460.4	37.9
5	[Mexiletine$NH^+\cdots{}^-OCOCH_3$]solv [b]	0.2529	115.3			−480.3	
6	[Mexiletine$NH^+{}^-OCOCH_3$]$O\cdots{}^+H$–NH_2CH_3	0.2925	140.4			−31.3	
7	Mexiletine$NH^+\cdots{}^-OCOCH_3(^+HNH_2CH_3)$	0.2485	95.9			−760.4	
8	Mexiletine$NH^+\cdots{}^-OCOCH_3$	0.2826	131.2			−41.0	
9	Mexiletine$N\cdots{}^+H$–NH_2CH_3	0.2727	114.8			−120.0	
10	Mexiletine$O\cdots{}^+H$–NH_2CH_3	0.2784	134.5			−71.9	

[a] Binding energy corrected for the basis set superposition error.
[b] Binding energy calculated using an Onsager model reaction field calculation ($\varepsilon = 78.5$).

ative due to the charge on amine. The considerable energetic contribution (− 31.3 kJ/mol) of this H-bond to the stability of the drug–receptor complex supports the hypothesis [13] about a stepwise interaction of AAs. The creation of a second H-bond (by means of ether oxygen) in system **6** (Table 2) could produce some effect on the strength of the mexiletine–$NH^{+}\cdots{}^{-}OCOCH_3$ interaction. The optimisation of the mexiletine–$NH^{+}\cdots{}^{-}O$ H-bond in system **7** leads to a 'shorter' H-bond with much higher H-bond stabilisation (− 760.4 kJ/mol) in comparison with system **1**. The anchoring of the mexiletine cation at a second (cationic) receptor site results in a substantial net effect (about 45%) for the energy of the mexiletine–$NH^{+}\cdots{}^{-}OCOH$ bond. The two H-bonds in systems **6** and **7** can be termed as 'cooperative'.

In order to study the possible interaction of neutral mexiletine with the associative site of the membrane we also investigated complexes **8–10** (Table 2). A basic mexiletine could reach a receptor via hydrophobic pathways [28]. Complex **8** pairs the base of mexiletine with the acetate group of the receptor. The interaction energy of this complex is about 12 times lower than the value computed for system **1**. Thus, the anionic receptor site will preferentially recognise and bind the charged mexiletine. There are two possibilities for docking the base of mexiletine at the $-NH_3^+$ receptor site, namely by the oxygen and amine nitrogen atoms (complexes **9** and **10**). The energy of the $N\cdots{}^{+}HN$ hydrogen bond was computed to be about twice as large as that for the $>O\cdots{}^{+}HN$ bond. A cationic receptor site will, in recognition and binding of the mexiletine base, prefer the interaction by means of its amine nitrogen.

4. Conclusions

The results of the theoretical calculations of the interaction of mexiletine with both anionic and cationic associative sites of cardiac membranes led to the following conclusions:

1. The strongest interaction is of the ion-pair type and occurs between the cationic NH^+ group of mexiletine and anionic–CO_2^- moiety. The coordination of Na^+ and K^+ ions to this system considerably reduces the strength of the $O^{-}\cdots{}^{+}HN$ hydrogen bond.
2. The effects of a solvating medium (within the direct reaction field theory) are changes in the geometry and a reduction of the interaction energy.
3. A cationic receptor site will, in recognition and binding of the mexiletine base, prefer the interaction by means of its amine nitrogen.
4. The large difference between the stabilisation energy of cationic and neutral mexiletine with association sites of receptor models indicates that complex formation with the protonated AAs is favoured. The binding of AAs to the receptor may be understood by considering a two-step process of recognition and binding of AA to its receptor. Within this model the mexiletine cation is recognised in the first step and bonded at the negatively charged part of the receptor. In a subsequent step the interaction between the polar oxygen region of mexiletine and the $-NH_3^+$ group of the membrane protein may follow.

The simple models used to model mexiletine–receptor interactions cannot adequately represent all facets of real AA–receptor complexes. The consideration of more realistic receptor models, in combination with the application of sophisticated methods for predicting ligand binding Gibbs energies [31,32], could further improve our understanding of the mechanism of action of AAs and help to design more selective and safe AA drugs.

Acknowledgements

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