Theoretical Study on the Local Anaesthetic-Receptor Interaction

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Received 20 November 1996

Theoretical methods are applied to study the local anaesthetics (LAs) procaine, 2-chloroprocaine, tetracaine, benzocaine, DI-MAPA, procainamide, lidocaine, tocainide, mepivacaine, ropivacaine, bupivacaine, etidocaine, W36017, and prilocaine. The AM1 method is used to construct a three-centre pharmacophore model for both ester and amide types of LAs. This model consists of an amine nitrogen atom that is protonated to a higher degree at physiological pH, a flat hydrophobic region of aromatic ring, and an additional functional group containing oxygen with lone electron pairs. Based on these ideas a model for the binding of the lidocaine at the transmembrane protein was constructed. *Ab initio* SCF method was used to study two-component lidocaine receptor binding site composed of formate (Glu^-, Asp^-) and protonated methylamine (Lys^+ Arg^+). The binding of LAs to the receptor may be understood by considering a two-step process of recognition and binding of LA to its receptor. Within this model the lidocaine cation is in the first step recognized and bonded at the negatively charged part of the receptor. In a subsequent step the interaction between the amide oxygen and cationic amine group of membrane protein may follow.

Local anaesthetics (LAs) are a class of similar compounds that reversibly block peripheral and central nerve pathways following regional administration [1, 2]. On the basis of the LA-cell membrane interactions several theories of LA action were developed [3], among them two are the most cited in the literature. The first theory is based on the proposal [4] that a LA causes a perturbation in the membrane structure by interacting with its lipid and/or protein components (the primary is nonspecific hydrophobic binding between the agent and phospholipid and/or lipoprotein of the membrane). The second and current hypothesis [2, 5, 6] suggests the existence of specific receptors at or within sodium channels. LAs interfere, according to that theory, with sodium channels in a much more specific way that it is possible to consider a receptor-mediated action. Clinically useful LAs (beside benzocaine) are secondary or tertiary amines prevailingly protonized at pH of physiological medium. Only a small fraction of the dose of any LA applied remains in the uncharged form. But this uncharged (basic) form of LA plays important role since it is believed that the drug can reach its site of action only in the form of the uncharged amine. Once LA has reached its site of action, the cationic form is supposed to be the active form of the molecule [2, 3].

Considering the chemical structures of LAs there are several loci on the channel where LA is likely to bind. However, none of these have been definitely identified using the techniques of molecular biology. The absence of three-dimensional structural data for transmembrane receptors presents a challenge to the application of molecular modelling methods to obtain insights into the recognition and binding process. Moreover, these methods may be used to establish pharmacophore models for the required anaesthetic effect. These pharmacophore models then allow limited conclusions to be drawn on the structure and properties of a receptor. The results of theoretical modelling [7—14] of interactions of associative sites of LAs with polar groups (as carboxylate, phosphate, amine, amide) of membranes have been used to identify molecular determinants of recognition and binding process. The effect of medium on the equilibrium geometry and interaction energy of the LA-carboxylate complexes was also investigated [14].

Based on these results, and in order to elucidate structure-function correlation, we applied the methods of theoretical chemistry to a group of fourteen clinically useful LAs of the procaine and lidocaine types (Fig. 1). A pharmacophore model should be constructed and the general LA receptor site proposed and theoretically modelled.

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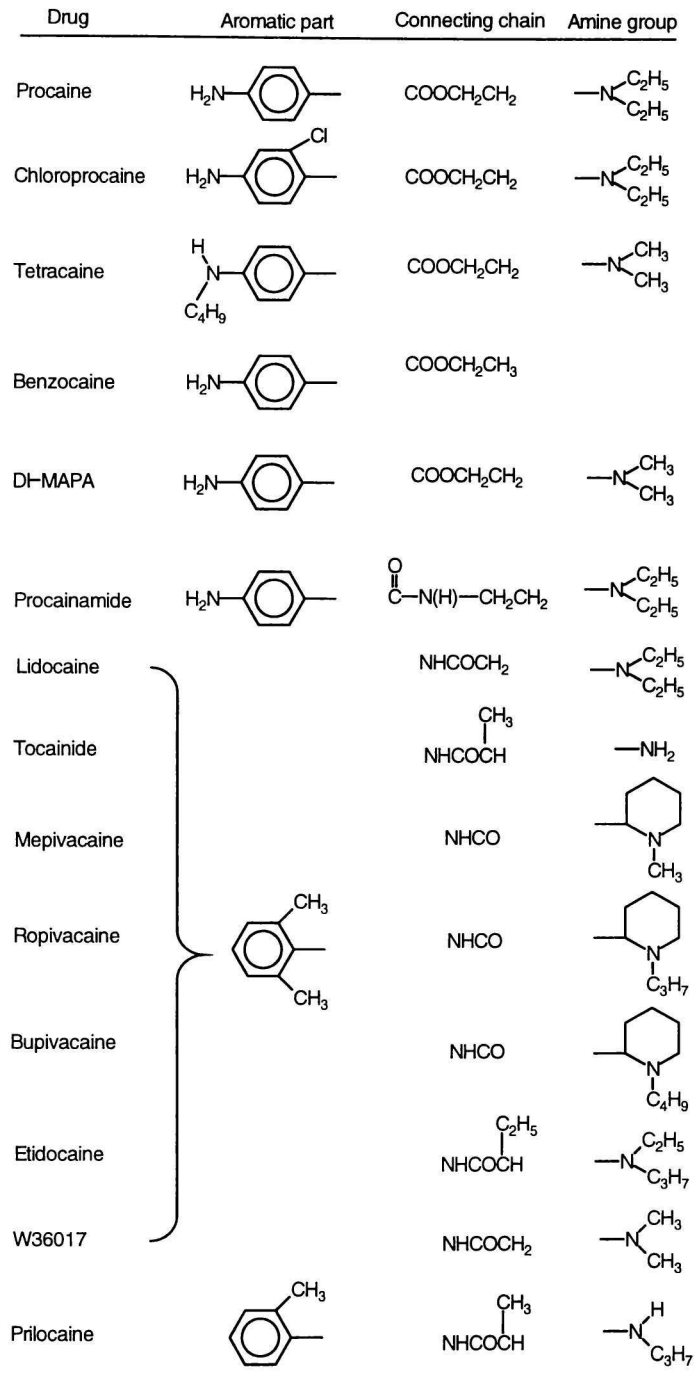


Fig. 1. Molecular structure of the local anaesthetics investigated.

THEORETICAL

The geometry of procaine, 2-chloroprocaine, tetracaine, benzocaine, DI-MAPA, procainamide, lidocaine, tocainide, mepivacaine, ropivacaine, bupivacaine, etidocaine, W36017, and prilocaine (Fig. 1) and their ionized species were fully energy-optimized using the quantum-chemical AM1 method [15]. The molecular modelling studies were carried out by means of the MOLGEN 4.0 [16]. The proton affinity (PA) of basic drugs (B) was computed using eqn (*1*).

$$\mathrm{PA} = \Delta H^{\circ}_{\mathrm{f},T}(\mathrm{H}^{+},\mathrm{g}) + \Delta H^{\circ}_{\mathrm{f},T}(\mathrm{B},\mathrm{g}) - \Delta H^{\circ}_{\mathrm{f},T}(\mathrm{BH}^{+},\mathrm{g}) \quad (1)$$

$\Delta H^{\circ}_{\mathrm{f},T}$ represents the heat of formation of the species stated between parentheses. It was computed using the AM1 method. For $\Delta H^{\circ}_{\mathrm{f,298\ K}}$ (H^{+}, g), the experimental value 1537.1 kJ mol^{-1} is taken [17].

Table 1. The 3-21G Optimized Geometries and Energies of HCO_2^- and $CH_3NH_3^+$ [a]

HCO_2^-	$CH_3NH_3^+$ [b]
r(CO) = 0.1248; r(CH) = 0.1125	r(CN) = 0.1547; r(NH) = 0.1018; r(CH) = 0.1077
<HCO = 114.6	<HNC = 110.7; <HCN = 107 7
E_{tot} = −187 104632	E_{tot} = −95.059342

a) Bond lengths r/nm, bond angles </° and energies E_{tot}/(2625.5 kJ mol^{-1});
b) C_{3v} structure of the CH_3 and NH_3 groups.

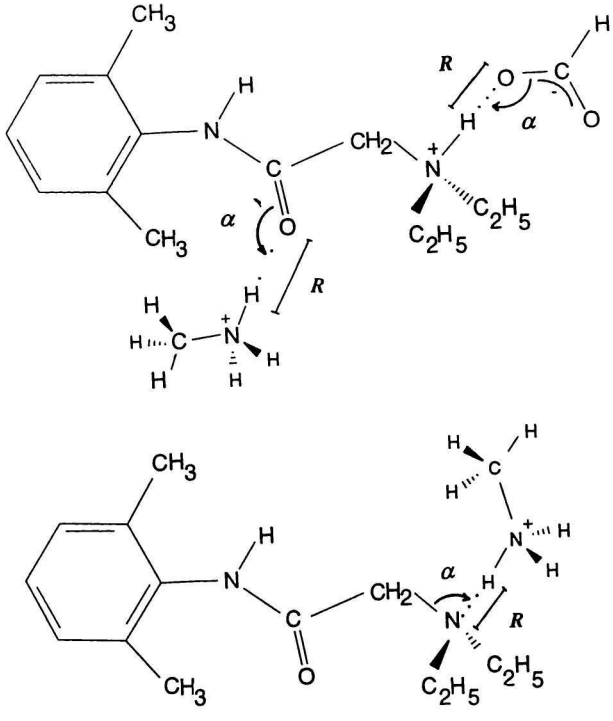


Fig. 2. Molecular structure and definition of intermolecular parameters R and α of the systems studied.

Ab initio SCF method was employed for the determination of the interaction energies and geometries of the complexes lidocaine—ionic loci of membrane protein (Fig. 2). The split-valence 3-21G basis set [18] was used. As has been shown previously [12, 19, 20] this basis set reproduces qualitatively well general trends of the relative stability of various hydrogen-bonded species, in which we are primarily interested. The intermolecular parameters R and α of the complexes given in Fig. 2 were energy-optimized, 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 LA was taken from the X-ray structure of lidocaine chloride [21], for the conversion of the X-ray coordinates of LA to internal coordinates the program MOLGEN 4.0 was used. The ionic receptor binding sites were represented by the formate anion and the methylammonium cation. The 3-21G optimized geometry of these species is shown in Table 1. The hydrogen bond energy ΔE was determined as the difference between the total energy of the model complex (E_{AB}) and that of the isolated molecules.

$$\Delta E = E_{AB} - (E_A + E_B) \qquad (2)$$

The superposition error was taken into account using the Boys—Bernardi method [22]. The quantum-chemical calculations were performed using the HyperChem 4.5 [23] and GAUSSIAN92 [24] programs.

RESULTS AND DISCUSSION

Physicochemical Properties of Local Anaesthetics Studied

Several molecular factors (lipophilicity, pK_a, molecular size, molecular conformation) influence the binding and unbinding of LAs at the specific site within the excitable membrane. These physicochemical factors are often related to anaesthetic potency and action [1—3]. Their individual importance and relationship to the physiological activity has been intensively investigated experimentally [25—28], but not yet well understood. The theoretical determination of these parameters has a great advantage in the fact that all values are computed in a uniform way, and thus do not suffer of he well known shortcomings of experiments [29, 30]. Table 2 presents the computed log P, molar refraction, dipole moments, and proton affinities together with the known experimental data. The partition coefficient, log P is one of the most frequently used "bulk parameters" correlated with LA activity. The computed log P values (n-octanol/water), using the hydrophobic atomic parameters defined by *Crippen* [31], span a rather broad interval (1—4). Procainamide, DI-MAPA, benzocaine, and tocainide show the highest hydrophilicity. The comparison of computed and experimentally determined [28] log P (in n-octanol:buffer) for neutral bases shows (Table 2) that the theoretical values in most cases well match the experimental ones. The "outliers" are tetracaine, mepivacaine, and ropivacaine. Mepivacaine and ropivacaine differ from bupivacaine in the number of CH_2 groups of the piperidine alkyl chain only (two and one CH_2 groups less in mepivacaine and ropivacaine, respectively, Fig. 1). The experiment, however, shows that these two LAs are substantially less lipophilic (the difference in log P between bupivacaine and mepivacaine (ropivacaine) is 0.81 and 1.74). This indicates

Table 2. Computed Partition Coefficient, P, Molar Refraction, MR, Dipole Moment, μ, Proton Affinity, PA, Torsion Angle, Φ, Interatomic Distances, A, B, C, and Available Experimental Data of Drugs Under Study

Compound	log P		MR		μ	PA	Φ/°	A(C$_1$ ·O)/nm		B(N· ·O)/nm		C(C$_1$ ·N)/nm	
	calc.	exp.[a]	calc.	Ref. [33]	D	kJ mol^{-1}		B	BH$^+$	B	BH$^+$	B	BH$^+$
Procaine	1.73	1.90	70.01	67.68	3.75	935.2	3.8	0.243	0.244	0.493	0.492	0.523	0.525
											0.497		0.521[b]
2-Chloroprocaine	2.29	2.85	74.62	72.51	4.19	947.3	9.5	0.242	0.242	0.486	0.491	0.533	0.527
Tetracaine	2.59	3.55	78.78	77.17	4.41	913.8	2.9	0.243	0.244	0.495	0.497	0.524	0.525
Benzocaine	1.39	1.90	47.15	45.29	3.21	876.7	4.5						
DI-MAPA	1.05		60.41		3.50	909.0	4.5	0.243	0.244	0.495	0.497	0.523	0.525
Procainamide	1.05	0.86	71.98		4.26	967.0	25.6	0.239	0.240	0.485	0.376	0.596	0.538
Lidocaine	2.41	2.48	73.93	70.73	2.25	916.9	66.0	0.287	0.288	0.290	0.282	0.504	0.499
											0.297[b]		0.485[b]
Tocainide	1.33		58.78		2.78	895.0	59.4	0.288	0.291	0.280	0.267	0.497	0.493
Mepivacaine	2.62	1.95	75.94	73.33	2.71	916.0	63.3	0.286	0.288	0.345	0.306	0.446	0.472
Ropivacaine	3.44	2.88	85.34		2.46	936.0	67.4	0.285	0.287	0.346	0.297	0.447	0.481
Bupivacaine	3.86	3.41	89.94		2.94	946.0	70.0	0.284	0.286	0.342	0.302	0.443	0.474
Etidocaine	3.87	3.69	87.62		2.42	938.9	67.0	0.287	0.288	0.288	0.281	0.497	0.497
W36017	1.73		64.33		2.18	908.6	65.8	0.287	0.289	0.289	0.282	0.501	0.501
Prilocaine	2.18	2.11	67.28		2.58	910.5	3.2	0.295	0.296	0.282	0.270	0.500	0.498

a) Ref. [1]; *b*) X-Ray data for procaine chloride [42] and lidocaine chloride [21].

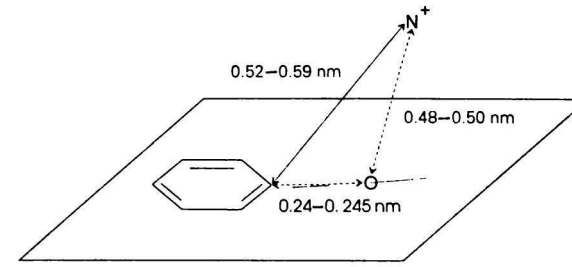
a strong nonadditivity of the NC_nH_{2n+1} ($n = 1, 3, 4$) structural parts of these drugs with respect to this property. The experimentally determined log P values could be influenced to a large extent by solvation forces. *Leo* [32] has recently shown that discrepancies between calculated and experimental partition coefficients can be caused, among other factors, also by an overlap of hydrocarbon chains. If we apply this hypothesis to the observed differences in log P for mepivacaine, ropivacaine, and bupivacaine, the largest discrepancy between theory and experiment (due to the possible folding of C_4H_9 side chain) should be exhibited by bupivacaine. Since this is not the case (Table 2), the lower experimental log P for mepivacaine and ropivacaine should probably be ascribed to the not well known solvation forces acting on the solute, and/or to some uncertainties of the theoretical as well as the experimental methods used.

The other computed "one dimensional" parameter, molar refraction, represents dispersion interaction. Higher values are found with amide drugs (Table 2). The theoretically computed values are in excellent agreement with the molar refractions of some LAs reported by *Abe et al.* [33]. The prime candidate for the interaction with the polar loci in transmembrane receptors is the amine group of the drug. At physiological pH this group can be present in its protonated and unprotonated forms. Table 2 contains the AM1 computed proton affinities using fully optimized geometries of base and cation. The aromatic amine benzocaine has the lowest proton affinity. Generally, tertiary amine LAs exhibit highest basicities (Table 2).

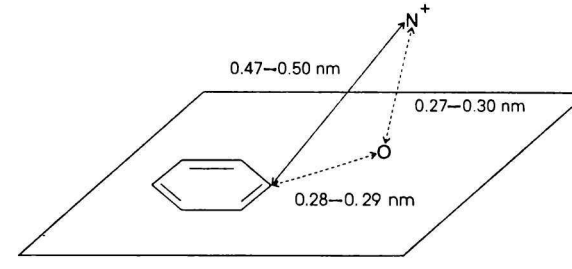
The results of the QSAR investigations of a series of LAs [34] show that the structural factors have a primary effect in modulating the activity. According to *Courtney* [27] the steric hindrance might unfavour the amides compared to ester-linked compounds, because of their hindered rotation out of the 2,6-dimethylsubstituted ring plane. This could prevent the ring itself from interacting with a lipophilic binding site [27, 34]. The AM1 computed optimal values for the torsion angle Φ of the rotation of ester and amide groups of LAs out of the benzene ring plane are reported in Table 2. The presence of two methyl groups in the positions 2 and 6 on benzene results, due to the stereochemical reasons, in the most stable nonplanar conformers. In seven LAs of the lidocaine type the torsion angle Φ lies within a relatively narrow interval of 60°—70° Thus these drugs exhibit a certain steric stability, *i.e.* tocainide, lidocaine, mepivacaine, ropivacaine, bupivacaine, etidocaine, and W36017 could access the same hydrophobic pocket of the receptor. In the absence of the steric hindrance, in procaine, benzocaine, tetracaine, and DI-MAPA the benzene and ester groups are practically coplanar (Table 2). The repulsion between electronegative oxygen and chlorine atoms in 2-chloroprocaine results in a slightly bent conformation ($\Phi = 9.5°$). The AM1 computed optimal torsion angles Φ reproduce very well the available experimental data. The X-ray data [35] show that the carbonyl group is tilted out of the phenyl plane by 2.5—7.5° in salts of procaine. A similar value of $\Phi = 9.4°$ was determined [36] for benzocaine bis-4-nitrophenylphosphate. The amide group of lidocaine in different crystal environments forms an angle Φ with the phenyl ring of 64°, 71° , and 66°, respectively [37].

The AM1 optimized structures of basic drugs and their cations were also used to investigate a presumed basic receptor feature. The quantum-chemical calculations of conformational energy maps [38—41] reveal the presence of several stable conformations in ba-

sic and protonized LAs. Without taking into account any environment, the most stable conformations correspond to bent structures stabilized by intramolecular hydrogen bonds [38—41]. Among the several binding possibilities of these drugs to the receptor the strongest interaction is that of ion pair type [8—14]. The actual, biologically active conformation may be better represented by structures observed in the ion pairs of salts of some anaesthetics. Therefore, the thermodynamically stable X-ray structures of procaine [42] and lidocaine [21] chlorides were considered as starting geometries for the AM1 energy optimizations of drugs in this study. As functional groups for receptor binding the amine nitrogen atom, the carbonyl oxygen atom and the phenyl ring were recognized [7—14]. Table 2 contains the computed distances A, B, and C connecting the nonbonding nitrogen, oxygen, and carbon atom C-1 of the phenyl ring. The analysis of these separations among the common functional groups of LAs reveals that they are within certain narrow intervals. Based on this analysis a model for the local anaesthetic pharmacophore was developed (Fig. 3), both for procaine and lidocaine type LAs. This pharmacophore model can be defined as an amine nitrogen atom, mostly protonated at physiological pH, plus a flat hydrophobic region of an aromatic ring. An additional functional group with lone electron pairs acting as hydrogen bond acceptor (the carbonyl oxygen) is also present. This polar group causes an increase of binding energy to the receptor [14], which may result in enhanced potency. It is apparent that the interatomic separations between amine and oxygen atoms are very different for these two groups of drugs (0.48—0.50 nm, procaine LAs and 0.27—0.30 nm, lidocaine LAs). This suggests that the binding sites for the ester and amide types of LAs should be different.



LAs of the Procaine type



LAs of the Lidocaine type

Fig. 3. Proposed pharmacophore models for the ester (procaine) and amide (lidocaine) types of LAs.

Modelling the Anaesthetic-Receptor Interactions

The previously discussed pharmacophore models allow some limited conclusions on the structure and properties of a receptor. Based on these ideas we constructed a model for the binding of lidocaine, the most frequently used drug, to the transmembrane protein receptor (Fig. 4). The primary interactions involve the aromatic ring, the protonated or unprotonated amine nitrogen, the amide oxygen, and the hydrophobic alkyl chain of the amine moiety. According to *ab initio* SCF calculations [43] the aromatic part of both ester and amide LAs exhibits large regions of negative electrostatic potentials, serving thus as an electron donor site. As might be expected, modelling of LAs of the lidocaine type (Table 2) as well as the crystal structure of lidocaine chloride [21] indicates that the aromatic ring is likely to occupy a region that is not coplanar with the side chain plane containing the –N(H)–C(O)–C– atoms. The site that is occupied by the phenyl substituent is therefore depicted as an out-of-plane lipophilic pocket. The aliphatic alkane and/or cycloalkane part 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 for the accommodation of LA on the receptor surface. The molecule is then "recognized" by the receptor and bound to its surface by means of H bonds (Fig. 4).

We have simulated the interactions between LA and its biological host model. This receptor binding site model is based on the optimized interactions of two polar regions of lidocaine and its cation (the amine nitrogen and the amide oxygen atoms) with a hypothetical two-component receptor model consisting of an anionic site (modelled by the formate anion) and a cationic receptor (modelled by the methylammonium cation). These ionized groups are commonly present in acidic (Glu, Asp) and basic (Lys, Arg) residues of amino acids of membrane proteins. The optimized intermolecular parameters and interaction energy of the systems studied are shown in Table 3. The complexes *I* and *II* combine the cation of lidocaine with the negatively charged HCO_2^- and cation of methylamine. Our calculated interaction energies are very large, as expected for this type of complexes [12—14]. The ion-pair complex *I* is very strong with an interaction energy of -467.7 kJ mol^{-1} However, the pairing of the protonated lidocaine with the cationic site in complex

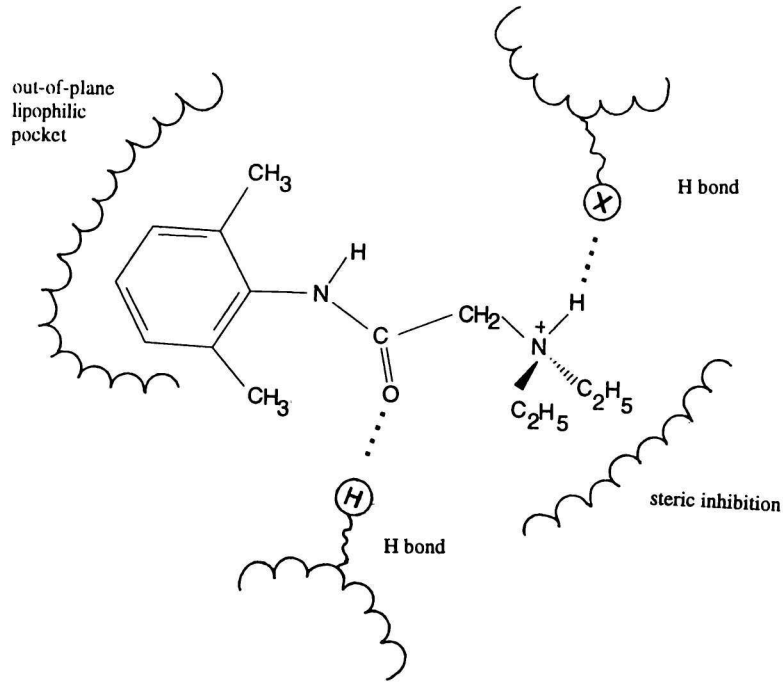


Fig. 4. Model of the binding of a local anaesthetic to the receptor.

Table 3. The 3-21G *ab initio* Optimized Geometries and Interaction Energies

No.	System	$R_{X\cdots H}$	α/°	ΔE	ΔE (BSSE)[a]
		nm		kJ mol^{-1}	kJ mol^{-1}
I	Lidocaine NH^+ $\cdot^-OCOH$	0.1479	133.9	−530.3	−467.7
II	Lidocaine $NH^+(C{=}O\cdot\ \cdot^+H{-}NH_2CH_3)$	0.1803	164.4	114.1	128.1
III	Lidocaine $NH^+HCOO^-(C{=}O\cdot\ \cdot^+H{-}H_2CH_3)$	0.1642	170.4	−93.5	−77.7
IV	Lidocaine $NH^+\cdot\ \cdot^-OCOH(CH_3NH_3^+)$	0.1440	132.6	−742.9	−677.5
V	Lidocaine $(C{=}O\cdot\ \cdot^+H{-}NH_2CH_3)$	0.1584	172.6	−148.1	−130.9
VI	Lidocaine $(N\cdot\ \cdot^+H{-}NH_2CH_3)$	0.1758	103.4	−98.4	−77.9

a) Interaction energies corrected for basis set superposition error.

II results in a positive interaction energy, *i.e.* this complex is not stable. This means that the charged lidocaine cannot be recognized and bonded by the positively charged receptor site. The binding of LAs to the receptor may, however, be understood by considering a two-step process of recognition and binding of LAs to their receptors [13, 14]. Within this model the lidocaine cation is in the first step recognized and bonded to the negatively charged $-CO_2^-$ part of the receptor. In a subsequent step the interaction between the amide oxygen and positively charged $-NH^+$ group of the membrane protein may follow. The complex *III* (Table 3) represents such a possibility for two-centre interaction. This complex contains as a subsystem the optimized complex *I*. The $C{=}O\cdot\ \cdot^+HN$ H bond energy is, due to the charge on amine, high and negative. The considerable energetic contribution (−77.7 kJ mol^{-1}) of this H bond to the stability of the drug—receptor complex supports the hypothesis [14] about a stepwise interaction of LAs. The creation of a second H bond (by means of the amide oxygen atoms) in system *III* (Table 3) could produce some effect on the strength of the NH^+ $\cdot^-OCOH$ interaction. The optimization of the $NH^+\cdot\ \cdot^-O$ H bond in system *IV* leads to a "shorter" H bond with much higher H bond stabilization (−677.5 kJ mol^{-1}) in comparison with system *I*. The anchoring of the lidocaine cation at a second (cationic) receptor site results in a substantial net effect (about 45 %) for the energy of the $NH^+\cdot\ \cdot^-OCOH$ bond. The two H bonds in systems *III* and *IV* can be termed as "cooperative"

Besides charged lidocaine we also studied the interaction of its neutral base with the cationic receptor site (systems *V* and *VI*, Table 3). A basic LA could reach a receptor *via* hydrophobic pathways [6]. There are two possibilities how to dock the lidocaine base at the $-NH_3^+$ receptor site, namely by the oxygen and the amine nitrogen atoms. The energy of the $C{=}O\cdot\ \cdot^+HN$

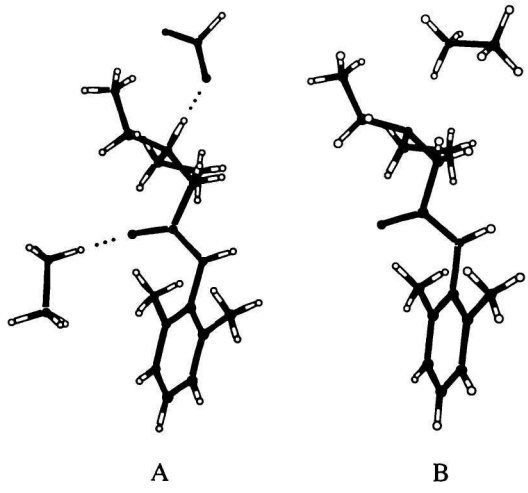


Fig. 5. Molecular representation of the optimized complexes. A – lidocaine ($NH^{+}-OCOH)CH_3NH_3^+$, B – lidocaine $CH_3NH_3^+(N\cdots{}^+HN)$.

H bond was computed about twice as large as that of the $N\cdots{}^+HN$ bond. A cationic receptor site will, in recognition and binding of the lidocaine base, prefer the interaction by means of its amide oxygen. The interaction energy was evaluated, for reasons of computational limitations, at the frozen geometries of each subunit. This may have some influence on the absolute values of computed interaction energies. Selected optimized complexes of Table 3 are depicted in Fig. 5. These pictures clearly show the optimal orientation of the hydrophobic methyl group of the receptor towards the aromatic ring of LA, enabling a favourable hydrophobic interaction.

CONCLUSION

The molecular modelling methods are used to the recognition of functional groups of LAs for receptor binding. Based on this analysis a model for the local anaesthetic pharmacophore is developed, both for ester and amide type LAs. This model consists of an amine nitrogen atom that is protonated to a higher degree at physiological pH, a flat hydrophobic region of aromatic ring, and an additional functional group containing oxygen with lone electron pairs. The large differences in stabilization energies of cationic and neutral lidocaine with association sites of receptor models indicate that complex formation with the protonated LAs is favoured. The binding of LAs to the receptor may be understood by considering a two-step process of recognition and binding of LA to its receptor. Within this model the lidocaine cation is in the first step recognized and bonded to the negatively charged part of the receptor. In a subsequent step the interaction between the polar oxygen region of lidocaine and the $-NH_3^+$ group of the membrane protein may follow.

Acknowledgements. Support of this work from the Austrian Federal Ministry for Science and Research (Grant No. 45.423.1-1V/B3a/97), from the Slovak Ministry of Education (Grant No. 1224/97), and from EC Program COPERNICUS (Grant No. ERB3512PL941009) is gratefully acknowledged.

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Translated by M. Remko