Ab initio and PCILO investigations of the antiarrhythmic tocainide, its cation and hydrochloride

M. REMKO

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University, CS-832 32 Bratislava

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Dedicated to Academician V Kellö, in honour of his 70th birthday

The quantum-chemical PCILO and *ab initio* SCF methods (STO-3G basis) were applied to the conformational analysis of antiarrhythmic tocainide (2-amino-2′,6′-propionoxilidine) (B) and its cation (BH^+). For B the conformation with N—H···N hydrogen bond, corresponding to the mutual *cis* arrangement of both nitrogen atoms of —N—CO—CH—N— fragment, has been found to be most stable. On the other hand, for BH^+ the most stable conformation is stabilized by the bifurcated intramolecular hydrogen bond of the N^+—H···O=C type formed by two protons of $-NH_3^+$ group of drug and carbonyl oxygen. The proton affinity was determined by means of *ab initio* SCF (STO-3G and MINI-1 bases, respectively) and PCILO methods. The STO-3G calculated energy of intermolecular hydrogen bond N^+—H···Cl^- in the tocainide hydrochloride is very high (507.8 kJ mol^{-1}). The gross atomic charges resulting from the STO-3G *ab initio* calculations for B, BH^+, and BHCl were compared.

Для конформационного анализа антиарритмического препарата токаинида (2-амино-2′,6′-пропионоксилидина) (B) и его катиона (BH^+) применены квантово-химический метод PCILO и *ab initio* метод ССП с базисным набором STO-3G. Для B наиболее устойчивой является конформация с водородной связью N—H···N, что отвечает взаимному *цис*-расположению обоих атомов азота в фрагменте —N—CO—CH—N—. С другой стороны, наиболее устойчивая конформация для BH^+ стабилизируется двойной внутримолекулярной водородной связью типа N^+—H···O=C, образуемой двумя протонами группы NH_3^+ и карбонильным кислородом молекулы препарата. Сродство протонов было определено с помощью *ab initio* метода ССП (базисные наборы STO-3G или MINI-1) и метода PCILO. Вычисленное с использованием базиса STO-3G значение энергии межмолекулярной водородной связи N^+—H···Cl^- в гидрохлориде токаинида очень высоко (507,8 кДж $моль^{-1}$). Проводится сопоставление величин полных атомных зарядов, полученных с помощью *ab initio* вычислений с базисом STO-3G для B, BH^+ и BHCl.

Tocainide (2-amino-2′,6′-propionoxilidine) exhibits considerable antiarrhythmic activity [1—3]. In the clinical practice, its hydrochloride is used. Tocainide is structurally related to the local anesthetic antiarrhythmic lidocaine. Tocainide, in contrast to lidocaine, acts also on oral administration and its time of action is substantially longer, which is of considerable practical importance by treatment of the initial stage of heart attack.

The chemical features that seem to be essential for nonspecific antiarrhythmic activity are the same as for the local anesthetic efficiency [4]. Tocainide, similarly as other local anesthetic antiarrhythmics, can be characterized by the general scheme: lipophilic (aromatic) part—connecting chain—amino group (ionized at pH of physiological medium).

By the investigations of antiarrhythmics on a molecular level using quantum-chemical methods we obtain information about stable conformations and electron distribution of the drugs. On the basis of them we are in a position to deduce something about the nature of the receptor. From this point of view the results of the quantum-chemical calculations on the tocainide (B), its cation (BH^+) and hydrochloride (BHCl) are presented in this paper. The particular attention was paid to the mutual geometrical arrangement of the aromatic and amino groups of B and BH^+ (representing the lipophilic and hydrophilic centres, respectively) with respect to each other. The conformational study of the structurally related lidocaine was carried out in our foregoing paper [5].

Calculation method

The knowledge of the torsion angles α, β, γ, and δ (Fig. 1) is prerequisite for obtaining information on the stereochemical arrangement of the lipophilic and hydrophilic groups. For the study of the conformational structure of tocainide (B) and its cation (BH^+), the two-dimensional conformational maps were calculated and plotted as functions of the

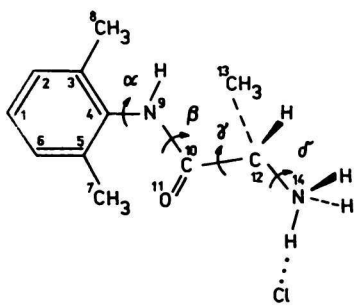

Fig. 1. Numbering of atoms and torsion angles in the compounds studied. The form shown has $\alpha = \beta = \gamma = \delta = 0°$.

torsion angles γ and δ. The conformational maps were computed by means of the PCILO method [6]. Because by its application to the study of aromatic compounds there is some ambiguity by choosing the appropriate zeroth-order wave function with respect to the existence of two Kekulé structures, the initial computations were also performed by means of the *ab initio* SCF (STO-3G basis) method. The calculations were carried out with 30° steps in the torsion angles. The torsion angles were defined following the convention proposed by *Klyne* and *Prelog* [7]. The presentation of the results on the conformational maps is limited to the 25 kJ mol^{-1} isoenergetic interval above the global minimum.

The proton affinity of tocainide was also computed. The proton affinity of the base B is the negative ΔE value for the exothermal reaction

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

ΔE is the energy difference between the B and BH^+ species

$$\Delta E = E_B - E_{BH+} \qquad (1)$$

where E_B is the energy of base.

The energy of the hydrogen bond (E_{HB}) of the N^+—H···Cl^- type in the tocainide 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})

$$E_{HB} = (E_{BH+} + E_{Cl-}) - E_{mi} \qquad (2)$$

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

Since the X-ray data for tocainide are not available, we used, similarly as in the case of lidocaine [5], as starting geometry the experimental data of the lidocaine bis(*p*-nitrophenyl) phosphate [8]. For N—H distances of the neutral as well as ionized amino group of the tocainide we considered the STO-3G optimized value for CH_3NH_2 equal to 0.1033 nm [9].

Results and discussion

Conformational analysis

At first we investigated the mutual stereochemical arrangement of aromatic and amide groups in the tocainide (rotation around the C_{arom}—N bond). Fig. 2 illustrates the *ab initio* STO-3G calculated potential energy curve for a rotation of the angle α. Since both 2 and 6 positions of the aromatic ring are substituted by the methyl groups aromatic and amide parts are not coplanar. Two equivalent minima were found at $\alpha = 60°$ and 300°, respectively. Besides the high-energy regions (about 0° and 180°, respectively) of the planar conformers this curve, however, also contains large, flat regions of the minima. The energy changes at $\alpha = 60°$ to 120° and $\alpha = 240°$ to 300°, respectively, were calculated

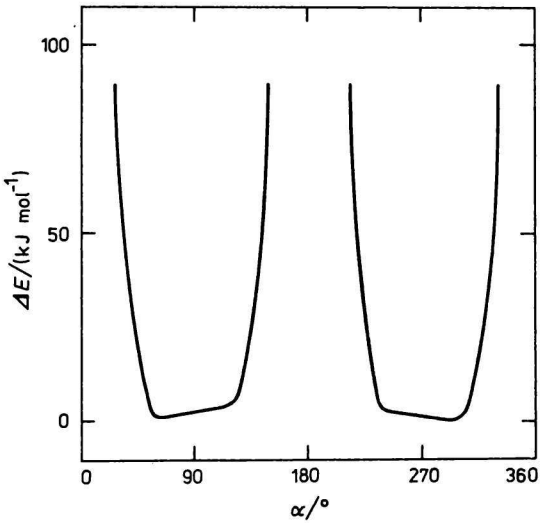

Fig. 2. Ab initio (STO-3G basis) potential energy curve for the rotation of the angle α in tocainide.

less than 3 kJ mol^{-1} Hence practically free rotation is possible by those values of the angle α. The experimental X-ray values for the torsion angle α in the structurally related salts of lidocaine [8, 10, 11] are from the interval 64—71.5°

As the amide group exists in the more stable *trans* form [8, 10, 11] we considered in all calculations the *trans* isomer ($\beta = 0°$, Fig. 1). From the conformational point of view the most interesting is the mutual orientation of the carbonyl and amino groups of tocainide and its cation. That orientation may be influenced by the intramolecular hydrogen bond. This possibility was, at first, studied on the potential energy curves of the rotation of —NH_2 and —NH_3^+ groups, respectively (torsion angle δ). The potential energy curves were computed, for reasons of comparison, by means of both *ab initio* SCF (STO-3G basis) and PCILO methods. Fig. 3 shows the results of computations for the tocainide. The *ab initio* curve has its absolute minimum at $\delta = 180°$ It corresponds to the bifurcated hydrogen bond in which both protons are equally distant ($R_{O\cdots H} = 0.272$ nm) from the carbonyl oxygen. The second minimum (by 24.3 kJ mol^{-1} less stable) corresponds to the *gauche* conformation ($\delta = 60°$). In this conformer one hydrogen of the —NH_2 group is connected *via* intramolecular hydrogen bond N—H···O=C ($R_{O\cdots H-1} = 0.272$ nm; $R_{O\cdots H-2} = 0.379$ nm). The PCILO curve shows, like the *ab initio* calculation, the global minimum at $\delta = 180°$ and a local minimum ($\delta = 60°$). Besides of these two minima still one minimum is present ($\delta = 300°$) on the PCILO curve (practically energetically equivalent with the global minimum). This minimum was not found on the similar *ab initio* curve (Fig. 3).

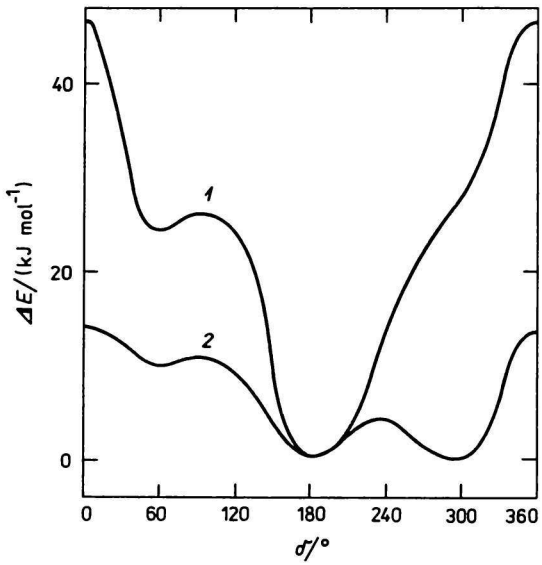

Fig. 3. Potential energy curve for the rotation of the angle δ in tocainide. *1. Ab initio* calculation; *2.* PCILO calculation.

Similar *ab initio* and PCILO calculations for the rotation of the $-NH_3^+$ group of the ionized form BH^+ are presented in Fig. 4. Three energetically equivalent minima (at $\delta = 60°$, 180°, and 300°, respectively) and maxima (at $\delta = 0°$, 120°, and 240°, respectively) were computed by both methods. All minima are stabilized by the bifurcated intramolecular hydrogen bonds formed always with two protons of the $-NH_3^+$ group and the carbonyl oxygen ($R_{O\cdots H} = 0.272$ nm). The higher rotational barriers were computed using the *ab initio* method.

The calculations of the conformational energy maps (γ, δ) for B and BH^+ were carried out in order to gain a deeper information about stable conforma-

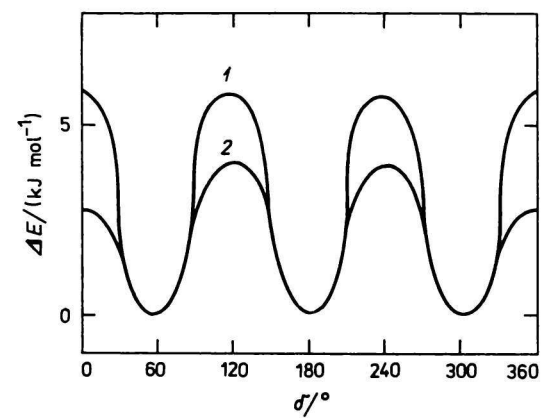

Fig. 4. Potential energy curve for the rotation of the angle δ in cation of tocainide. *1. Ab initio* calculation; *2.* PCILO calculation.

tions of the —CO—CH—NH_2 fragment. For the generation of the conformational maps, with respect to the considerable saving of the computer time by PCILO calculations as compared with the *ab initio* ones, the PCILO method has been applied only.

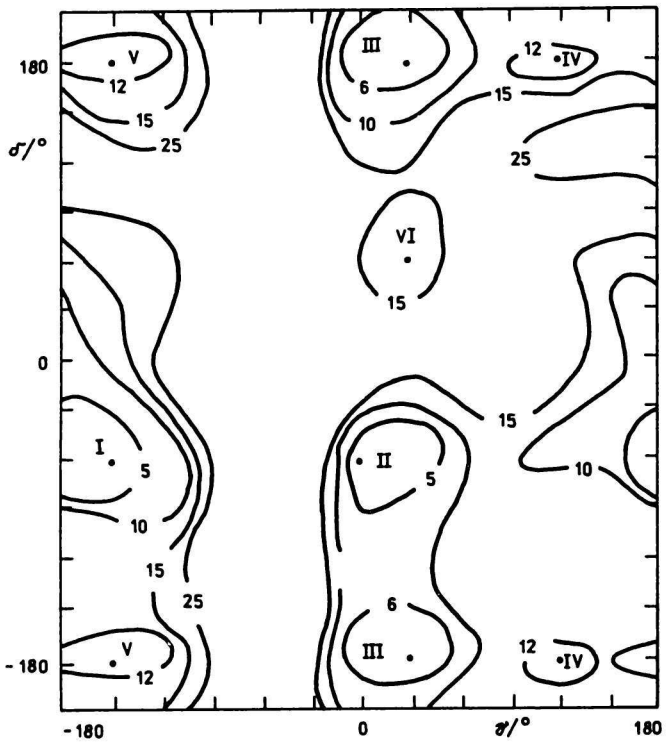

Fig. 5. PCILO energy surface for tocainide. The isoenergy curves are in kJ mol^{-1} with respect to the global minimum which is taken as the energy zero.

The energy map of tocainide (Fig. 5) is characterized by the occurrence of a wide region of stable conformations. A total of six minima (Table 1) has been found on the conformational map within the 25 kJ mol^{-1} energy region covering about 60% of the total energy surface. The minimum found at $\gamma = -150°$ and $\delta = -60°$ corresponds to the most stable conformer. This minimum is stabilized by the intramolecular hydrogen bond ($R_{N\cdots H} = 0.224$ nm) formed by the >NH group of the amide and the amine nitrogen atom. The second and third minima were found somewhat less stable (3.8 and 4.2 kJ mol^{-1}, respectively). They correspond to the *cis* arrangement of the carbonyl oxygen and amine nitrogen and are stabilized by the intramolecular hydrogen bond N—H···O=C.

Table 1

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

Minimum	γ/°	δ/°	ΔE / kJ mol^{-1}	C=O···N distance / nm
		Tocainide		
I	− 150	− 60	0	0.358
II	0	− 60	3.8	0.277
III	30	180	4.2	0.283
IV	120	180	9.6	0.343
V	− 150	180	10.1	0.358
VI	30	60	12.6	0.283
		Tocainide cation		
I	0	− 60	0	0.277
	0	60	0	0.277
	0	180	0	0.277

The fourth and fifth minima correspond to the conformers with a possibility to create the intramolecular hydrogen bonds of the N—H···N type, in which the amine nitrogen atom acts as a proton acceptor. On the other hand, the sixth minimum is again stabilized by the intramolecular interaction between the carbonyl oxygen and amine nitrogen. The calculated population ratios (at 310.16 K) for the most stable conformations of the tocainide are 68 : 16 : 13 : 2 : 1.

The energy map of ionized tocainide (Fig. 6) shows within the 25 kJ mol^{-1} energy region three energetically equivalent minima (Table 1) calculated at $\gamma = 0°$, $\delta = -60°$; $\gamma = 0°$, $\delta = 60°$ and $\gamma = 0°$, $\delta = 180°$, respectively. All those minima are stabilized by the bifurcated intramolecular hydrogen bonds of the C=O···H—N^+ type.

In comparison with the conformational energy map of tocainide (Fig. 5) the region with stable conformations in the energy map of tocainide cation (Fig. 6) is considerably narrower. The 25 kJ mol^{-1} relative energy range makes up only about 30 % of the whole energy map. While the base exhibits a fairly higher steric flexibility, in the case of the cation the only conformer, threefold degenerated, is conformationally stable. Table 1 gives the interatomic distances between the oxygen atoms and the basic nitrogen atom. According to the frequently used receptor mapping approach [12], atoms of the drug with lone electron pairs are likely to bound to the receptor. In the case of tocainide those distances, due to its high flexibility, are situated in the vicinity of 0.28 nm and

0.35 nm, respectively. The N···O length in the single stable conformation of cation was calculated to be 0.28 nm. Almost the same distribution of the O···N distances has been found from the PCILO calculations [5] of the structurally related lidocaine and its cation. Therefore both tocainide and lidocaine should interact with the structurally similar receptors. With respect to the common structural features of tocainide and lidocaine both drugs may interact with the biological membrane in the similar way, as it was discussed in our recent work [5].

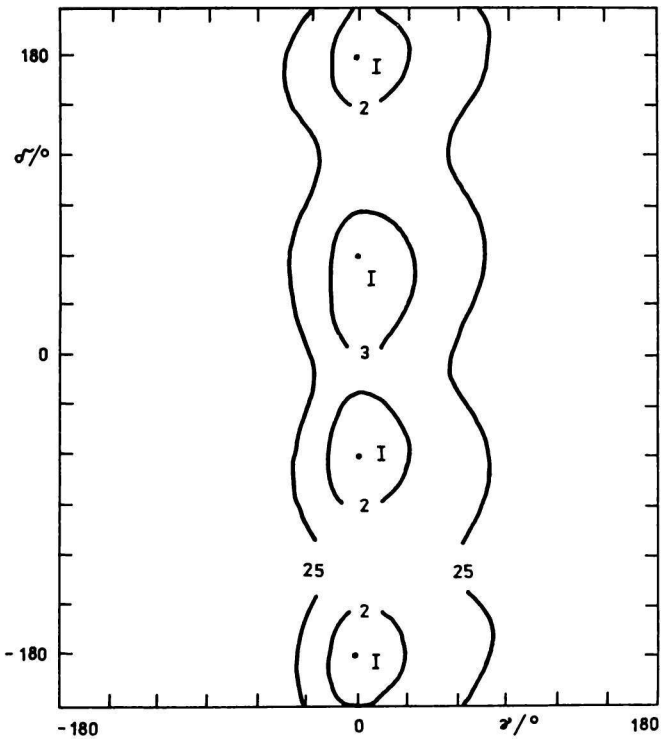

Fig. 6. PCILO energy surface for tocainide cation. The isoenergy curves are as in Fig. 5.

In contrast to lidocaine the amino group of which is diethyl-substituted and hence this group may act as a proton acceptor only, the tocainide —NH_2 group (base) acts as a proton donor and also as a proton acceptor. Similarly, the —NH_3^+ group of the ionized tocainide is a triple proton donor site. A substantially higher hydrogen bonding capacity of the hydrophilic part of the tocainide, in comparison with the related group of lidocaine, may cause that tocainide is bound much easier to the corresponding receptor. Different conditions for the hydrogen bonding interaction of tocainide and lidocaine may be one of the factors of their different pharmacological activity.

Proton affinity and hydrogen bonding

At pH of physiological medium tocainide can occur in its ionized and nonionized form. For that reason the theoretical proton affinities ΔE (eqn (*1*)) have been also calculated by means of PCILO and *ab initio* methods. The calculations of total energies for B and BH^+ were first performed with the same geometry. The PCILO calculations were also performed with the PCILO optimized geometry of B and BH^+ obtained from the calculations of conformational maps. Using the same geometry for B and BH^+ we determined the proton affinity equal to 979.8 kJ mol^{-1} (MINI-1 basis [13, 14]), 1138.8 kJ mol^{-1} (STO-3G basis), and 1342.3 kJ mol^{-1} (PCILO). The value of 1340.4 kJ mol^{-1} was obtained using the PCILO minimized geometry of B and BH^+ From the three methods applied the MINI-1 *ab initio* calculation yielded the lowest proton affinity. In both cases studied the PCILO proton affinities are higher than the *ab initio* values, which is not surprising because it is well known that the semiempirical methods overestimate the stability of cations [15]. Of the minimal bases used the MINI-1 proton affinity is about 14 % lower than the STO-3G value. The value 972.8 kJ mol^{-1} has been found for the protonation of the trimethylamine [16] (MINI-1 basis), which is close to the experimental proton affinity 944.4 kJ mol^{-1} [17]. Hence, with respect to the known fact that the MINI-1 proton affinities are far superior to the STO-3G proton affinities [16, 18], we may conclude that our MINI-1 proton affinity is more reliable (its value represents the electronic contribution to the proton affinity only) and closer to the experimental vapour phase proton affinity of tocainide which is till now not known.

The intermolecular hydrogen bond N^+—H···Cl^- in the tocainide hydrochloride has been investigated by means of the *ab initio* method (STO-3G basis). The equilibrium N···Cl distance was computed at 0.263 nm. The energy of this hydrogen bond, with respect to its ionic character, is very high (569.9 kJ mol^{-1}). After the correction of the basis set superposition error by the *Boys* and *Bernardi* counterpoise procedure [19] the value 507.8 kJ mol^{-1} was obtained.

Charge distribution

Table 2 shows the STO-3G gross atomic charges for tocainide (B), its cation (BH^+), and hydrochloride (BHCl). The largest positive and negative charges were found on the heteroatoms of polar groups. Both the nitrogen and oxygen atoms of the amide group in B carry considerable negative charge. This charge is lowered in BH^+ by protonation. Similarly, the net negative charge on the nitrogen atom of the amino group decreases upon protonation (Table 2). The

Table 2

Gross atomic charges (in $10^3 e$) for the tocainide (B), its cation (BH^+), and hydrochloride (BHCl)

Atom	B	BH^+	BHCl
C-1	− 79	− 66	− 75
H—C-1	82	98	86
C-2	− 97	− 92	− 96
H—C-2	81	92	83
C-3	44	46	45
C-4	100	93	101
C-5	35	41	40
C-6	− 98	− 90	− 95
H—C-6	79	92	83
C-7	− 314	− 314	− 314
H—C-7	107	120	110
H—C-7	103	104	100
H—C-7	111	105	118
C-8	− 321	− 321	− 321
H—C-8	104	118	108
H—C-8	126	111	123
H—C-8	104	101	100
N-9	− 394	− 380	− 389
H—N-9	214	223	213
C-10	309	324	326
O-11	− 297	− 270	− 251
C-12	− 13	18	20
H—C-12	105	138	128
C-13	− 308	− 318	− 318
H—C-13	96	142	120
H—C-13	114	116	107
H—C-13	100	138	116
N-14	− 384	− 346	− 363
H—N-14	151	327	326
H—N-14	150	331	263
H—N-14	—	334	266
Cl	—	—	− 743

net negative charge on both nitrogen atoms increases and on the oxygen decreases in the hydrochloride in comparison with the cation. Hydrogens of the polar amide and amino groups carry in all cases significant positive charges. As our conformational analysis has shown, these atoms are more or less bound *via* hydrogen bonds.

Some information about charge distribution, besides the atom population analysis, can be also obtained from the charges on particular functional groups.

The aromatic part carries positive charge (0.157, 0.238, and 0.196 *e* for B, BH^+, and BHCl, respectively). The polar —NH—CO— group possesses in all cases a negative charge. Totally this part of drug, with the exception of B, is something electropositive (− 0.011, 0.135, and 0.095 *e* for B, BH^+, and BHCl, respectively). The electrostatic potentials computed from the *ab initio* wave functions of the "double-zeta" quality for the simpler model of tocainide — 2,6-dimethylacetanilide [20] in planes parallel with the aromatic ring plane have shown, however, that the aromatic part possesses a large area of negative potentials resulting from the superposition of the nitrogen and oxygen atoms of the substituents and electrons of the benzene ring. Hence this part of drug can serve as an electron-donor site in the drug—receptor interaction.

Amino group has total negative charge in B and BHCl (Table 2). On the other hand, the larger part of the positive charge in the cation of tocainide is localized on the $-NH_3^+$ group (0.646 *e*). From three investigated species of the drug the amino group with largest positive charge (in ionized tocainide) will have the largest capacity for the creation of the intermolecular hydrogen bonds, *e.g.* with the proton acceptor groups of the biological membrane. The energy decomposition analysis of *Umeyama* and *Morokuma* [21] within the *ab initio* theory showed that the electrostatic stabilization is the most important component of the hydrogen bond energy.

The existence of strong intermolecular hydrogen bonds between ionized amine and polar groups present in the biomembrane was confirmed by the *ab initio* and PCILO calculations in our foregoing works [16, 22—25].

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