Quantum chemical investigations of intermolecular hydrogen bonds formed by phenylcarbamates and *N*-methylacetamide

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Dedicated to Associate Professor Dr. J. Krätsmár-Šmogrovič, in honour of his 60th birthday

The quantum chemical PCILO method has been used to determine equilibrium geometries and hydrogen bond energies of the 1-[2-(2-methoxyphenylcarbamoyloxy)ethyl]piperidine (B) and its cation (BH^+)—*N*-methylacetamide systems which represent the models for the local anaesthetic—lipoprotein part of the nerve membrane interactions. According to our calculations of the complexes local anaesthetic—*N*-methylacetamide it is the N^+—H group of the cationic form of drug which forms the strongest hydrogen bond with the carbonyl group of the *N*-methylacetamide. This group is able to interrupt the N—H ... O=C interpeptide hydrogen bond. The possible consequences of this on the mechanism of action of local anaesthetics are briefly discussed.

Использован квантово-химический метод PCILO для определения равновесной геометрии и энергий водородной связи в системах 1-[2-(2-метоксифенилкарбамоилокси)этил]пиперидина (B) или его катиона (BH^+) с *N*-метилацетамидом, которые представляют собой модели для изучения взаимодействия местный анестетик—липопротеиновая часть нервной мембраны. В соответствии с нашими расчетами комплексов местный анестетик—*N*-метилацетамид, самую прочную водородную связь с карбонильной группой *N*-метилацетамида образует N^+—H группа катионной формы медикамента. Эта группа способна нарушить N—H ... O=C межпептидную водородную связь. Коротко обсуждаются возможные последствия такого нарушения на механизм действия местных анестетиков.

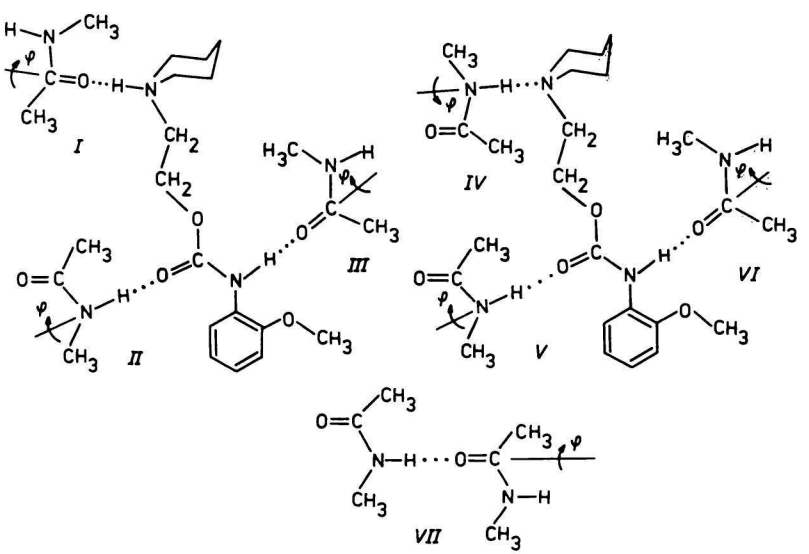
The biological tests have shown [1—6] that basic esters of the phenylcarbamic acid exhibit considerable local anaesthetic and antiarythmic activities (heptacaine, pentacaine, karbisocaine). These compounds can be characterized by the general scheme: aromatic part—polar group—connecting chain—amino group. So they possess several polar groups which are able to form intermolecular hydrogen bonds. The ability of polar groups of methyl esters of the phenylcarbamic acid to form intermolecular hydrogen bonds with such com-

pounds as water, *N*-methylacetamide, *N*,*N*-dimethylacetamide, and phenol has been proved by the PCILO method [7, 8].

The aim of this work, which is a continuation of our investigations of intermolecular interactions of local anaesthetics of the carbamate type, was a theoretical study of intermolecular hydrogen bonds formed by 1-[2-(2-methoxyphenylcarbamoyloxy)ethyl]piperidine and its cation with *N*-methylacetamide. The 1-[2-(2-methoxyphenylcarbamoyloxy)ethyl]piperidine and its cation are simpler models of the local anaesthetic heptacaine [2] and its chloride in which the 2-heptyloxy group was substituted by the 2-methoxy group. The *N*-methylacetamide represents the model of the associative site in the lipoprotein part of membrane.

Calculation method

The investigated hydrogen-bonded complexes local anaesthetic—*N*-methylacetamide are shown in Scheme 1. With respect to the fact that the results of *ab initio* SCF calculations of hydrogen bonds using the minimal basis set seem to be completely unsatisfactory [9, 10] and *ab initio* calculations using larger basis sets are for such large systems [11] extremely time-consuming, we decided to use the semiempirical PCILO method [12]. This method, despite of some shortcomings by the studies of hydrogen bonds with full geometry optimaliza-



Scheme 1

tion [13], well describes the X—H ... Y hydrogen-bonded complexes in which the only optimized distances were R_{X-H} and $R_{X\cdots H\cdots Y}$ bonds [14].

The geometry of the complexes studied (Scheme 1) was optimalized with respect to the following parameters: 1. the length $R_{O\cdots H}$; 2. the torsional angle φ. In all cases studied the X—H ... Y hydrogen bonding was assumed linear (Scheme 1).

The hydrogen bond energy E_{HB} was defined as the difference between total energy of the hydrogen-bonded complex and total energy of the isolated molecules

$$E_{HB} = -(E(R_{min}) - E(R_{\infty})) \qquad (1)$$

A zero value of the torsional angle φ corresponds to the complexes (Scheme 1) in which the planes of the anaesthetic (defined by the plane in which lie all heavy atoms excluding the piperidine ring) and the *N*-methylacetamide are coplanar.

The interaction energies were computed using the monosolvation model of the supermolecular approach.

The calculations were performed with experimental geometry of the *N*--methylacetamide [15]. Because X-ray data for the 1-[2-(2-methoxyphenylcarbamoyloxy)ethyl]piperidine (B) and its cation (BH^+) are not known, we used as starting geometry the experimental data of heptacaine chloride [16]. For O—C—C—N fragment *trans* arrangement was considered, which is together with the *gauche* conformer the most stable as calculated by the PCILO method for B [11].

Results and discussion

According to the mechanism of action of local anaesthetics proposed by *Hille* [17] lipoprotein in sodium channel is the specific site of interaction of anaesthetics. However, the experimental structural data on the type of this noncovalent interaction do not exist, because the molecular structure and exact composition of membrane proteins are not known so far. It is assumed that local anaesthetics can, with respect to their hydrogen bonding ability, interact with associative sites of biophase [8, 18—20].

α-Helical structure of proteins contains C=O ... H—N colinear hydrogen bonds. The oligomers of a simple realistic model peptidic bond—*N*-methylacetamide were recently studied theoretically [21]. By these investigations it was shown that such compounds as water, methanol, and phenol act as breakers of interpeptidic hydrogen bonds [21]. With the aim to determine whether or not local anaesthetics can interrupt hydrogen-bonded chain of peptidic bonds in the protein secondary structure we studied the model complexes local anaesthetic

Table 1

PCILO calculated equilibrium geometry and hydrogen bond energy of the systems local anaesthetic—*N*-methylacetamide (Scheme 1)

System	$R_{X...Y}$/nm	φ/°	E_{HB}/(kJ mol^{-1})
I	0.255	90	68.3
II	0.277	90	9.3
III	0.266	90	18.5
IV	0.372	90	3.8
V	0.277	90	18.8
VI	0.271	90	12.5
VII	0.277	90	19.8

—*N*-methylacetamide (Scheme 1). The results of the PCILO calculations of these systems are given in Table 1. With respect to the fact that the energies of hydrogen bonds formed by ether oxygens of the methoxy and carbamate groups of the local anaesthetic are substantially lower than of those formed by the —NH—CO— group [7], we studied only the interaction of the *N*-methylacetamide with amino group and —NH—CO— group of B and BH^+, respectively.

The comparison of the interaction energies of the systems *I*—*VII* (Table 1) shows that the cationic head of protonized local anaesthetic (system *I*, Scheme 1) forms the strongest hydrogen bond with the *N*-methylacetamide. This hydrogen bond is fairly strong ($E = 68.3$ kJ mol^{-1}) because of the positive charge on the local anaesthetic. On the other hand, the amino group of B (system *IV*, Scheme 1) forms, for reasons of stereochemistry, with the *N*-methylacetamide very weak complex of the van der Waals type.

In all the systems local anaesthetic—*N*-methylacetamide studied, the complexes in which the amide group plane was perpendicularly oriented to the local anaesthetic plane ($\varphi = 90°$) were found to be the most stable. Except the system *I* the hydrogen bond energies are lower by comparison with the hydrogen bond energy of the *N*-methylacetamide dimer (system *VII*, Scheme 1). From this fact we may conclude that while neutral local anaesthetic is not capable to interrupt the interpeptide hydrogen bonds, the cationic head of BH^+ forms with the *N*-methylacetamide fairly strong hydrogen bond. Thus BH^+ can act as breaker of N—H...O=C bonds similar to those present in the α-helix of proteins. This finding is in agreement with the facts that inside of the nerve cell it is the protonized form of anaesthetic which takes part in the blocking of nerve conduction [22].

Our calculations of the hydrogen bonding ability of the carbamate type local anaesthetic polar groups indirectly confirmed experimentally [23, 24] and theoretically [25] found out facts that the polar groups bound to the aromatic ring

act mainly as a source of additional electrons to the negative potential regions of the benzene ring, which causes an increase of the electron donor-acceptor properties of these molecules in comparison with the unsubstituted benzene. These parts of local anaesthetics form charge-transfer complexes with suitable electron acceptors [23, 24].

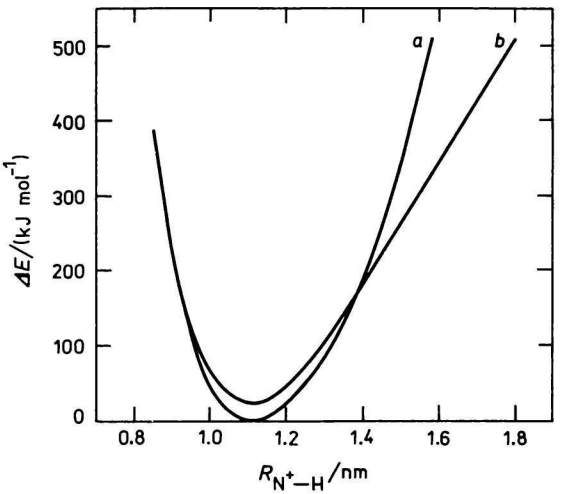


Fig. 1. Proton potential functions for the proton transfer in the system *I* (Scheme 1). *a*) $R_{O...N} = 0.255$ nm; *b*) $R_{O...N} = 0.30$ nm.

Fig. 1 presents the results of the calculations of the proton potential function for proton transfer between proton donor and proton acceptor at fixed geometries and intermolecular distances. Curve denoted by *a* in Fig. 1 was calculated at the equilibrium $R_{O...N}$ length, curve denoted by *b* at somewhat longer $R_{O...N} = 0.3$ nm distance. The potential curves with the single-minimum were found for the system under study at both $R_{O...N}$ distances corresponding to a "simple" hydrogen-bonded complex. Proton transfer, on the contrary to the model hydrogen-bonded complex N^+—H...O^-—P of the local anaesthetic—phospholipid interaction [20], was not observed.

In conclusion we may say that the interpeptide hydrogen bond of lipoprotein (modelled by the dimer of the *N*-methylacetamide) is able to perturb cationic NH^+ group of the protonized form of local anaesthetic. It is therefore probable that local anaesthetics, through their hydrogen bonding ability, could act as perturbers of these hydrogen bonds, which eventually leads to conformational changes of the macromolecules forming the membrane and so disturbs the conduction system of the nerve cell.

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