MO STUDY OF MOLECULAR ASSOCIATION OF LOCAL ANAESTHETICS OF CARBAMATE TYPE

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The quantum-chemical PCILO method has been used to study of molecular association of piperidinoethyl alkoxyphenylcarbamates. The self-association of this type of compounds has been studied with methyl phenylcarbamate as a simple model. The PCILO calculations indicate the open dimer with N—H...O=C hydrogen bond to be the most stable complex. Moreover, the PCILO method has been used for study of intermolecular hydrogen bonds formed between oxygen and nitrogen atoms of —NH—COO— group of the title compounds and N-methylacetamide, N,N-dimethylacetamide, and phenol. The calculations have shown that the most stable hydrogen bonds are formed by carbonyl oxygen atom. Somewhat weaker hydrogen bonds are formed by N—H group. The weakest hydrogen bonds are formed by methoxyl oxygen atom of the —NH—COO— part of the drug.

It was proved experimentally[1-3] that carbamates show local anaesthetic, antiarythmic and spasmolytic activites. Piperidinoethyl alkoxyphenylcarbamates[4] exhibit considerable local anaesthetic activity which is increased with increasing alkoxy substitution, reaching its maximum in the case of 2-heptyloxy derivatives (heptakain).

The molecular mechanism by which local anaesthetics block reversibly the conductivity of nerves is not known yet. The local anaesthetics are presumed to interact with membrane phospholipids[5-9]. Importance of hydrogen bonds in the interaction of local anaesthetics with receptors was stressed in refs[10,11]. Formation of hydrogen bonds with association sites of a biological membrane can affect its permeability and perturb the nervous system[11].

Quantum-chemical studies of stable conformations and electron distribution of local anaesthetics and their models were carried out by semiempirical (PCILO, INDO) methods[12-14] as well as by the *ab initio* method[15]. The present communication deals with hydrogen-bonding properties of carbamate group —NH—COO—, studying both the self-association and interaction of —NH—COO— part of the drug with the association sites of membrane. The calculations were carried out with simpler models (methyl phenylcarbamate and 2-methoxyphenylcarbamate) instead of real drugs, since the *ab initio* calculations[15] of electron distribution showed that the other parts of the drug molecule do not affect significantly the electron distribution of the parts involved in the models. The following molecules were considered

as models of association sites of membrane: N-methylacetamide, N,N-dimethylacetamide, and phenol.

CALCULATION METHOD

The interaction energies, E_{HB}, and equilibrium geometries of hydrogen bonds type N—H···O=C, O···H—N, and O—H···O=C were calculated by the quantum-chemical PCILO method[16]. Linear arrangement was considered in calculations of X—H···Y (X,Y = N,O). The geometry of the studied complexes was optimized with respect to $R_{O...H}$ distance (Figs 1—3). The hydrogen bond energy E_{HB} was defined as difference between total energy of the isolated molecules (E_∞) and total energy of the hydrogen-bonded complex (E_{min}).

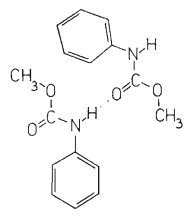
$$E_{HB} = E_{min} - E_\infty . \qquad (1)$$

Due to existence of several classical resonance structures in the case of aromatic and heteroaromatic compounds, choice of suitable wave function of zero order within the PCILO formalism (fully localized description of the molecule as the zero order approximation) is rather arbitrary. Practical criteria were suggested[17,18] to overcome these difficulties. As in our previous papers[13,14,19] we have used the criterion by Diner and coworkers[17], taking the wave function with the best energy as the starting one.

The calculations were carried out with experimental geometry of the monomers[20] using the Siemens 4004/150 computer in Computer Centre, Comenius University, and the QCPE No 220 program[21].

RESULTS AND DISCUSSION

The title local anaesthetics contain two or more strongly associative groups and tend to self-association. The self-association of anaesthetics of carbamate type was studied



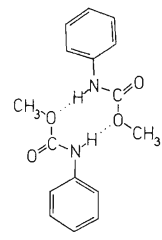


FIG. 1

The PCILO equilibrium geometries, hydrogen bond energies and dipole moments of the open and the cyclic dimers of methyl phenylcarbamate

$R_{O...H}$ = 0·167 nm
E_{HB} = 24·1 kJ mol^{-1}
μ = 12·24 . 10^{-30} C m

$R_{O...H}$ = 0·185 nm
E_{HB} = 20·0 kJ mol^{-1}
μ = 3·27 . 10^{-30} C m

on a simple model – methyl phenylcarbamate whose most stable conformer[14] (torsion angles CC—NC = 35°, CN—CO = 10°) calculated by the PCILO method can form two types of dimers (Fig. 1): (*i*) an open dimer *I* with a N—H···O=C hydrogen bond and (*ii*) a cyclic dimer *II* with two N—H···O hydrogen bonds. By the PCILO calculations the most stable dimer is *I* with the hydrogen bond energy of 24.1 kJ mol^{-1}. Energy of the two N—H···O hydrogen bonds of *II* dimer has a value of 20.0 kJ mol^{-1} at the equilibrium distance $R_{O...H}$ = 0·185 nm. Hence the *II* dimer is less stable than *I*. The relatively large value of interaction energy of *I* dimer indicates that methyl phenylcarbamate forms linear hydrogen bonds in the dimer or in higher n-mers, which is analogous to simple amides[22].

The hydrogen bond interaction between polar groups of local anaesthetics and association sites of biological membranes is presumed[23,10,11] to be one of possible interaction type drug – membrane receptor. We studied this type of interaction between local anaesthetics of carbamate type (represented by methyl 2-methoxyphenylcarbamate as a simple model) and association sites of membrane (represented by N-methylacetamide, N,N-dimethylacetamide, and phenol as simple models).

Fig. 2 represents possible hydrogen-bonded complexes of the PCILO most stable conformer[13] of methyl *o*-methoxyphenylcarbamate with N-methylacetamide and N,N-dimethylacetamide. With respect to steric hindrance, two types of dimers were optimized: (*a*) those with carbamate and amidic groups lying in the same plane and (*b*) those in which the plane of carbamate group is perpendicular to the plane

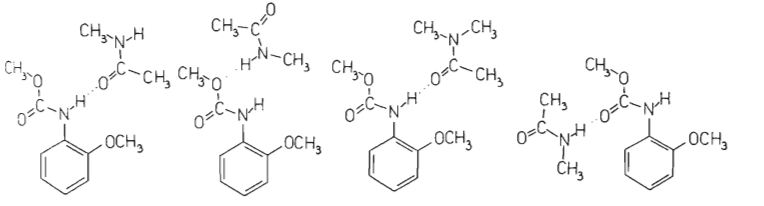


FIG. 2

The PCILO equilibrium geometries, hydrogen bond energies and dipole moments of the systems of methyl 2-methoxyphenylcarbamate and N-methyl- or N,N-dimethylacetamide

$R_{O...H}$ = 0·165 nm
E_{HB} = 19·8 kJ mol^{-1}
μ = 17·0 . 10^{-30} C m

$R_{O...H}$ = 0·170 nm
E_{HB} = 20·2 kJ mol^{-1}
μ = 16·27 . 10^{-30} C m

$R_{O...H}$ = 0·185 nm
E_{HB} = 10·5 kJ mol^{-1}
μ = 11·47 . 10^{-30} C m

$R_{O...H}$ = 0·160 nm
E_{HB} = 20·6 kJ mol^{-1}
μ = 15·97 . 10^{-30} C m

of the amide. In the case of *III* and *V* dimers the dimers type (*a*) are more stable (Fig. 2). On the contrary, for the *IV* and *VI* dimers, the type (*b*) was found to be more stable. The strongest hydrogen bond is that formed by oxygen atom of the carbonyl group. A somewhat weaker hydrogen bond is formed by N—H group. Out of the polar groups studied, the weakest hydrogen bonds are formed by oxygen atom of the methoxy group.

Fig. 3 presents analogous results of the hetero-association of the local anaesthetic model with phenol which represents a model of polar group in side chain of membrane protein. The complexes given in Fig. 3 have perpendicular orientation of phenol molecule to the plane of carbamate group, which increases their stability sterically as compared with planar orientation. In analogy with N-methyl- and N,N-dimethyl-acetamides, phenol forms the strongest hydrogen bond with carbonyl oxygen atom of —NH—COO— group (complex *VIII*). A somewhat lower hydrogen bond energy was found with the N—H group (Fig. 3). The weakest hydrogen bond is O—H···O in the *IX* dimer with the interaction energy of 13·6 kJ mol^{-1}.

Our PCILO calculations showed that carbamate group of methyl 2-methoxyphenyl-carbamate can form hydrogen bonds of various stability with polar groups of the lipoprotein models. The strongest ones should be the hydrogene bonds formed by carbonyl oxygen atoms. Somewhat less stable hydrogen bonds are formed by N—H group. The weakest hydrogen bonds are formed by methoxyl oxygen atom of the —NH—COO— part of the drug. The authors arrived at similar conclusions[13] also in a study of hydratation of —NH—COO— group of methyl 2-methoxyphenyl-carbamate.

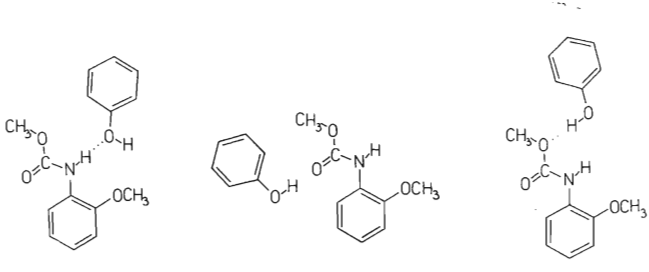


FIG. 3

The PCILO equilibrium geometries, hydrogen bond energies and dipole moments of the system methyl 2-methoxyphenylcarbamate–phenol

$R_{O...H}$ = 0·170 nm	$R_{O...H}$ = 0·165 nm	$R_{O...H}$ = 0·175 nm
E_{HB} = 16·3 kJ mol^{-1}	E_{HB} = 22·0 kJ mol^{-1}	E_{HB} = 13·3 kJ mol^{-1}
μ = 11·91 . 10^{-30} C m	μ = 11·20 . 10^{-3} C m	μ = 6·37 . 10^{-30} C m

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