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Quantum-Mechanical Study of the Conformational Properties of Drugs with Local Anesthetic Action

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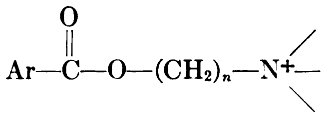
SUMMARY

Quantum-mechanical calculations have been performed, by the method of perturbative configuration interaction using localized orbitals, on the conformational properties of models for local anesthetics belonging to the class of esters of the general formula

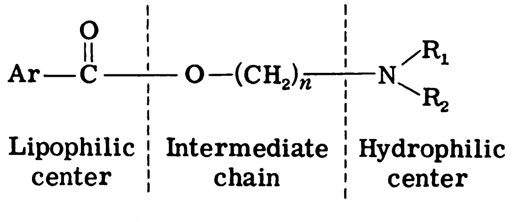


$$\mathrm{Ar{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}(CH_2)_n{-}N^{+}\!\!\lessgtr}$$

for $n = 1, 2, 3$, and for the anilide drug lidocaine. The results indicate that in spite of the different numbers of intermediate carbons, the distances between the carbonyl and amino groups of the esters are similar in some of their stable conformations. This suggests that they may react with the same receptor.

INTRODUCTION

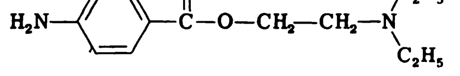
Among the large number of synthetic molecules exhibiting local anesthetic action, an important group is formed of esters represented by the general formula (1–3)



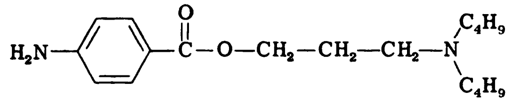
$$\mathrm{Ar{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}(CH_2)_n{-}N\begin{matrix}R_1\\R_2\end{matrix}}$$

The most common compounds of this series contain two CH_2 groups between the esteratic oxygen and the amino nitrogen (e.g., procaine, I), but a number of active compounds contain three such groups (e.g., butacaine, II) while some contain only 1 saturated carbon atom in the main chain (e.g., amyleine, III). Another related group of local anesthetics is formed of anilides, a typical example of which is lidocaine (IV).

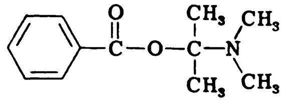
The local anesthetics are related chemically to cholinergic drugs. It is frequently considered (2, 3) that the electronic characteristics and, in particular, the charge distributions on the carbonyl bond are important in the action of local anesthetics. On the other hand, although it is essential for their activity that a balance exist between the lipophilic and the hydrophilic parts of the molecule, only slight steric complementarity is needed between these drugs and their re-



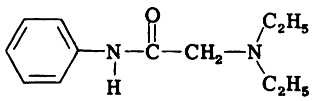
I. Procaine



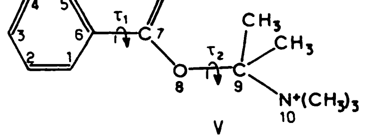
II. Butacaine

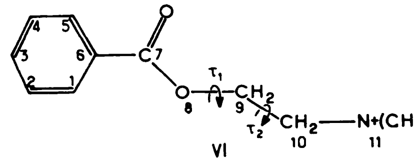


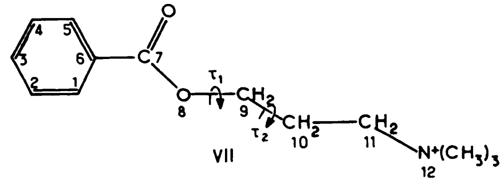
III. Amyleine

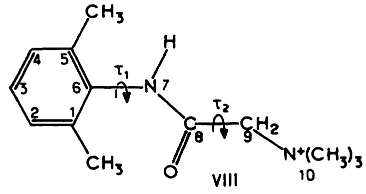


IV. Lidocaine







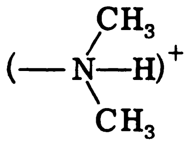


ceptors, and there exists in this respect a relatively large degree of freedom.

The aim of the present study was to gain more knowledge about the conformational aspects of local anesthetics, in particular the geometrical arrangement of the lipophilic and hydrophilic centers with respect to each other. Maps of the conformational energy have heen constructed to indicate its variation as a function of rotations about the appropriate torsion angles. Although it is obvious that such a study of molecules in a vacuum is not necessarily related directly to their pharmacological activity, numerous examples have shown that at least some degree of correlation between the two may reasonably be expected.

The investigation has been carried out on the model compounds V–VIII. The molecules were considered in their ionized forms because, although identification of the active form of the drugs was for some time controversial (2, 4), recent evidence seems to favor the cationic form as the active one. This evidence springs in particular from the studies of Narahashi, Yamada, and Frazier (5–7), who used intracellular perfusion techniques to investigate the potency of local anesthetics with low and high pK_a values when applied outside or inside the nerve membrane at different pH values. Studies with tertiary local anesthetics have clearly demonstrated that these compounds block the action potential from inside the nerve membrane in charged forms. Moreover, complementary experiments with quaternary compounds, which might be anticipated to be more effective from the inside than from the outside of the nerve membrane as their permanent charges generally impair their penetration through nerve membranes, led to similar conclusions. Altogether these strongly support the hypothesis that local anesthetics in their charged form block the action potential from inside the nerve membrane.

For reasons of computational simplification our calculations have been carried out on quaternary ammonium forms, with a terminal $—N^+(CH_3)_3$ grouping. There is no doubt that virtually identical results would be obtained for a



$$\left(\text{—}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{N}}\text{—}H\right)^+$$

grouping.

METHODS

The method utilized is that of perturbative configuration interaction using localized orbitals (PCILO) (8), which recently was used successfully for the study of a number of conformational problems in biochemistry and pharmacology (9–11) and was employed previously in the study of acetylcholine and its agonists (12).

This method belongs to the all valence electrons procedures and therefore the σ- and π-electrons are considered simultaneously. It takes into account interelectronic repulsions and goes beyond the self-consistent field approximation in the calculation of the ground state energy by incorporating part of the correlation energy. Its fundamental idea is to choose a set of reasonable bonding and antibonding orbitals localized on the chemical bonds. Such a set may be constructed on the basis of hybridized atomic orbitals (χ_i), the bond orbitals being obtained as linear combinations of distinct hybrids taken two by two, each bonding orbital Φ_i being associated with an orthogonal antibonding orbital Φ_i^*:

$$\Phi_i = = C_{i1}\chi_{i1} + C_{i2}\chi_{i2}$$

$$\Phi_i^* = C_{i2}\chi_{i1} - C_{i1}\chi_{i2}$$

A localized orbital representing a lone pair is described by a single hybrid orbital.

The bonding orbitals are then used to construct a fully localized Slater determinant. This determinant represents the zero-order wave function for the ground state of the system. The antibonding orbitals are utilized to build the excited states, and a configuration interaction matrix is constructed on this basis. Then the lowest eigenvalue and eigenstate, i.e., the energy and the wave function of the ground state of the system, are obtained by a Rayleigh-Schrödinger perturbation expansion truncated after the third order.

As a technical simplification, the principal

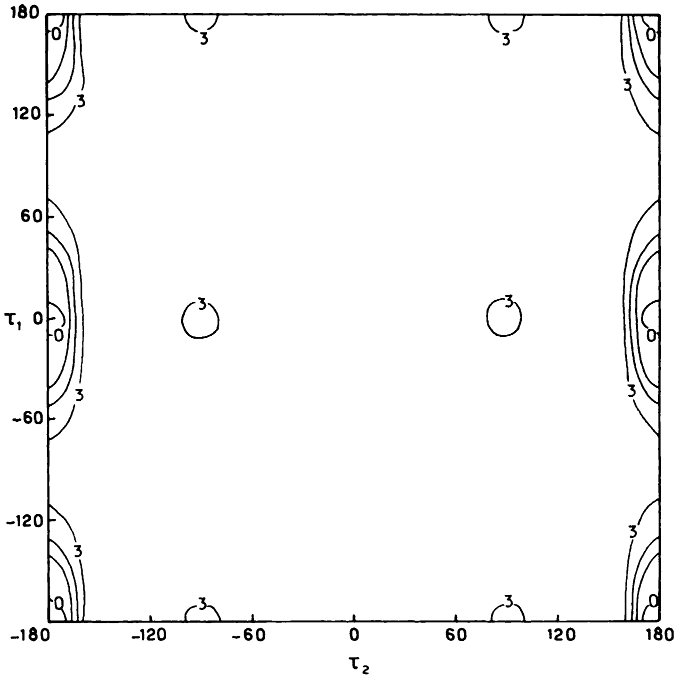


FIG. 1. *Conformational energy map of compound V*

Isoenergy curves, in kilocalories per mole, with respect to the global minimum, taken as zero energy.

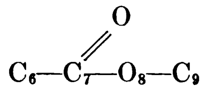
working hypothesis of the CNDO/2 procedure have been retained, in particular the hypothesis of complete neglect of differential overlap as well as the general parametrization of this procedure (13, 14).

More details about the method are to be found in the original papers (8). A larger summary is presented in ref. 9.

Standard values of bond lengths and angles have been utilized as geometrical input data. The torsion angles taken into account for the construction of the conformational energy maps are indicated in formulae V–VIII. (The torsion angle τ of the bonded atoms A—B—C—D is the angle between the planes ABC and BCD. Viewed from the direction of A, τ is positive for clockwise and negative for counterclockwise rotations. The value $\tau = 0°$ corresponds to the planar-*cis* arrangement of the bonds AB and CD.) In all cases the N^+H_3 group was fixed in a staggered position in accordance with previous results (12, 15). The rotations about the torsion angles τ_1 and τ_2 were carried out with 30° increments.

RESULTS

Compound V. The two torsion angles considered are τ_1 (C_1—C_6—C_7—O_8) and τ_2 (C_7—O_8—C_9—N_{10}). The group



$C_6—C_7(=O)—O_8—C_9$

was considered to be planar, as indicated by a previous study of cholinergic drugs (12). The conformational energy map presented in Fig. 1 shows very limited zones of stability. There is a net preference for the conformation corresponding to $\tau_1 = 0°$, $\tau_2 = 180°$ (or the identical one, $\tau_1 = 180°$, $\tau_2 = 180°$), which represents the global minimun. It corresponds to a planar backbone (the esteric group coplanar with the aromatic ring), the carbonyl group, and the quaternary ammonium group, which are *trans* with respect to one another.

Compound VI. The torsion angles considered in this compound are τ_1 (C_7—O_8—C_9—C_{10}) and τ_2 (O_8—C_9—C_{10}—N_{11}). The part of

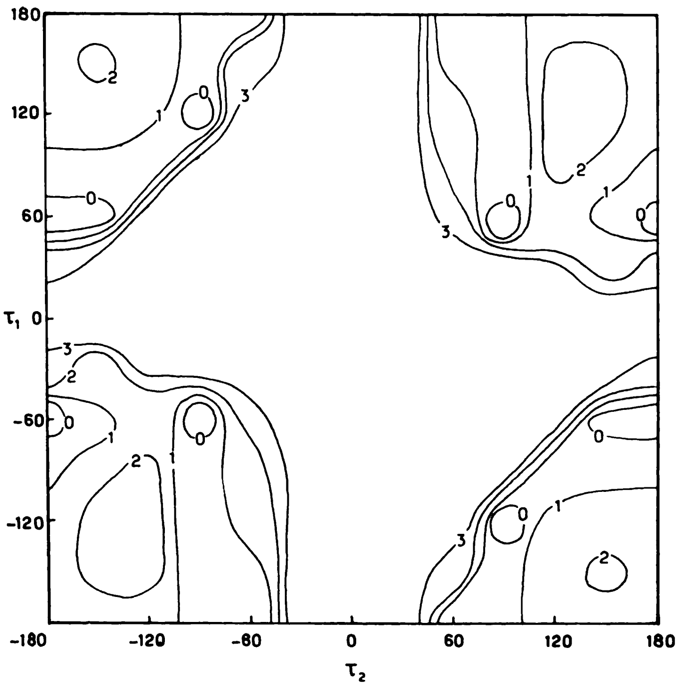
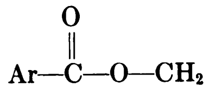


FIG. 2. *Conformational energy map of compound VI*
Isoenergy curves, in kilocalories per mole, with respect to the global minimum, taken as zero energy.

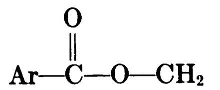
the molecule involving



$$\mathrm{Ar{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}CH_2}$$

was taken to be planar on the basis of the results for compound V. The conformational energy map (Fig. 2) shows that lengthening of the backbone has produced an increase in the available conformational possibilities. There are three practically equivalent global minima, located at $\tau_1 = 60°$, $\tau_2 = -150°$, at $\tau_1 = 120°$, $\tau_2 = -90°$, and at $\tau_1 = -60°$, $\tau_2 = -90°$, as well as the symmetrical ones.

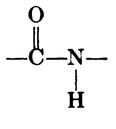
Compound VII. The torsion angles considered are τ_1 (C_7—O_8—C_9—C_{10}) and τ_2 (O_8—C_9—C_{10}—C_{11}). The molecular fragment



$$\mathrm{Ar{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}CH_2}$$

was again considered planar, as in compound VI, and the fragment CH_2—CH_2—CH_2—$N^+(CH_3)_3$ was fixed in a *trans* arrangement so as to minimize steric hindrance. The conformational energy map (Fig. 3) shows a further increase in the allowed conformational space (within the fixed limit of 3 kcal/mole above the minimum). There are two practically equivalent global minima, at $\tau_1 = -90°$, $\tau_2 = 60°$, and at $\tau_1 = 60°$, $\tau_2 = 60°$, in addition to the symmetrical ones.

Compound VIII. In this compound the peptide linkage



$$\mathrm{{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\underset{\underset{\displaystyle H}{|}}{N}{-}}$$

has been considered planar, in accordance with numerous theoretical and experimental results (16). (The torsion angles taken into account are τ_1 (C_1—C_6—N_7—C_8) and τ_2 (N_7—C_8—C_9—N_{10}). The resulting conformational map is shown in Fig. 4. The available space is rather restricted. There is a global minimum at $\tau_1 = 60°$, $\tau_2 = 180°$ (and a symmetrical one at $\tau_1 = 120°$, $\tau_2 = 180°$). In this molecule the two methyl groups, *ortho* with respect to the chain, prevent coplanarity between the aromatic ring and that chain.

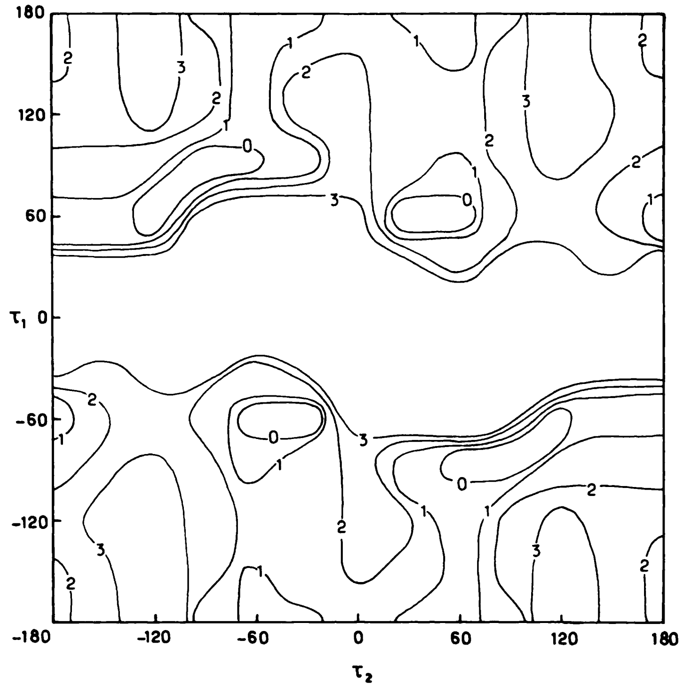


FIG. 3. *Conformational energy map of compound VII*
Isoenergy curves, in kilocalories per mole, with respect to the global minimum, taken as zero energy.

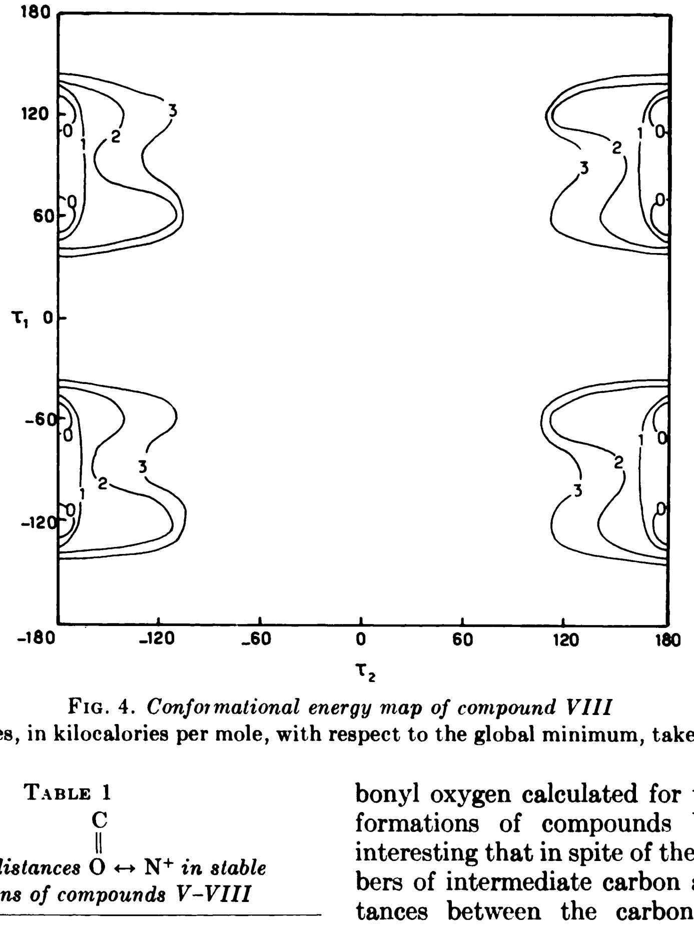


FIG. 4. *Conformational energy map of compound VIII*
Isoenergy curves, in kilocalories per mole, with respect to the global minimum, taken as zero energy.

TABLE 1

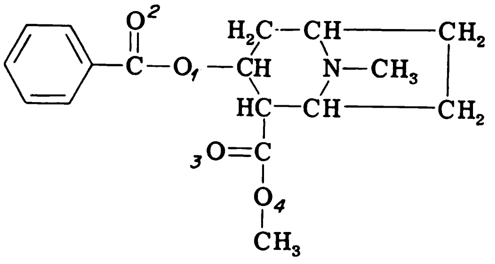
Interatomic distances $\overset{\overset{\displaystyle C}{\|}}{O} \leftrightarrow N^+$ *in stable conformations of compounds V–VIII*

Compound	Distance
	A
V	4.19
VI	3.60 (1st minimum)
	3.81 (2nd minimum)
	4.10 (3rd minimum)
VII	4.24 (1st minimum)
	5.53 (2nd minimum)
VIII	2.62

DISCUSSION AND CONCLUSIONS

Because the carbonyl and amino groups are generally considered particularly important for the manifestation of local anesthetic activity in drugs of the type considered here (probably being involved in interactions with receptors), we have centered our attention on the relative geometrical arrangement of these two groupings. Table 1 indicates the distance between the N^+ atom and the carbonyl oxygen calculated for the stable conformations of compounds V–VIII. It is interesting that in spite of the different numbers of intermediate carbon atoms, the distances between the carbonyl and amino groups of compounds V, VI, and VII, are similar in some of their stable conformations: in the vicinity of 4.1–4.2 A. It is obviously the flexibility of the longer chains which is responsible. It therefore seems possible that in spite of their apparent differences in structure these compounds may easily present similar steric arrangements for interactions with the same receptor. Of course, the present calculations, carried out for compounds in a vacuum, in no way demonstrate this possibility, although they favor it.

Compounds V–VII are related to cocaine (IX). We have therefore calculated the different N^+—O distances corresponding to the crystalline form of this compound, following the X-ray results of Gabe and Barnes (17). While the distance N^+—O_2 is 5.37 A and thus is larger than the corresponding distances in compounds V–VII, the distances N^+—O_3 and N^+—O_1, equal to 4.07 and 4.15 A, re-



IX. Cocaine

CH

spectively, are of the same order of magnitude. It is possible, therefore, that the amino and carbonyl groups occupy similar relative positions in cocaine and the ester local anesthetics.

In the anilide (VIII), the theoretical distance between the N^+ atom and the carbonyl oxygen is only 2.6 A, and thus is significantly smaller than in the ester compounds. The distance between the N^+ atom and the peptidic nitrogen is 3.66 A. It seems too risky to draw any conclusions about the possible differences in the mode of action of these two types of anesthetics from this isolated result.

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