MOLECULAR ORBITAL STUDIES ON SEVERAL MOLECULES WHICH INTERACT WITH THE γ-AMINOBUTYRIC ACID

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PCILO and CNDO/2 computations for γ-aminobutyric acid choline ester(GABACh)-ion and nipecotic acid(piperidine-3-carboxylic acid) have been done using X-ray determined crystal geometry as input data. The conformations of GABACh-ion have been studied as a function of τ_1 and τ_2 of the GABA moiety, keeping the conformation of the choline-moiety at the crystallographic form. The results show preference for the *gauche-trans* and *trans-trans* forms with respect to τ_1 and τ_2. The conformations of nipecotic acid have been studied with τ, the torsion angle for carboxylate group. The results in both cases corroborate with NMR studies.

The extensive studies strongly advocate that γ-aminobutyric acid (GABA) acts as an inhibitory transmitter at certain synapses in the mammalian central nervous system. Structure-activity correlations of many GABA analogues implicate both the intramolecular distance between the zwitterionic centres and the rotational freedom of the molecule act as important factors governing the synaptic activity of these substances[1]. It seems to be of interest to study theoretically the conformations and molecular structures of GABA-complex and GABA analogue which can interact with the GABA receptors. The present work deals with the conformational study on GABAC (γ-aminobutyric acid choline ester) and nipecotic acid (piperidine--3-carboxylic acid).

The biological activity of GABAC has been studied and it has been concluded[2,3] that the compound possesses weak GABA-like activity and negligible acetylcholine--like activity. GABA has a less potent GABA-like activity on primary afferent fibres which is entirelly resistant to choline esterase inhibitors. These results suggest that GABAC can interact with the GABA receptors on primary afferents. Cellular uptake may terminate the post-synaptic action of the inhibitory transmitter GABA in the mammalian central nervous system and thus inhibitors of GABA uptake have considerable pharmacological and neurochemical interest. The nipecotic acid is a powerful inhibitor of the uptake of the GABA by slices of rate cerebral cortex.

RESULTS AND DISCUSSION

The present theoretical study of the conformations and electronic structures of GABAC and nipecotic acid have been performed by the all-valence electrons

methods PCILO and CNDO/2. PCILO method has been used for complete conformational analysis of the molecules *in vacuo*; and the electronic structures of the experimental conformations (determined by X-ray method) have been calculated by the CNDO/2 method. Theoretical studies[4] especially on the effect of a solvent (water) on the relative stability of different conformers of GABA also seem to indicate that a number of conformations with relatively small mutual energy differences are possible. The conformation of the choline moiety as known from crystallographic and theoretical[5] results are generally *gauche-gauche* and *gauche-trans* with respect to ϕ_2 and ϕ_3 (Fig. 1).

Choline moiety of GABAC-ion possesses negligible acetylcholine-like activity. The crystal structures of GABAC as diiodide and tartarate have already been solved[6]. The conformations of GABA moieties are different in the two crystal structures but the conformations of the choline moieties are approximately the same. The protonated molecule of GABAC possesses the important torsion angles denoted $\tau_0 - \tau_3$ for the GABA-moiety (Fig. 1). τ_1 and τ_2 being essential and $\phi_1 - \phi_4$ for the choline-moiety, ϕ_2 and ϕ_3 being important. ϕ_1 and ϕ_4 are generally *trans*, *e.g.* $\phi_1 = \phi_4 = 180°$, ϕ_2 is usually 60°, but ϕ_2 (180°) and ϕ_3 (60°) conformation has never been observed. In this work, the conformational study as a function of two torsion angles τ_1 and τ_2 was made by PCILO method[7], and the CNDO/2 procedure[8] has been used to compute the electronic densities of the different atoms.

The PCILO conformational energy map of the protonated GABACh is shown (Fig. 2) as a function of τ_1 and τ_2. It is evident from the map that the global energy minimum corresponds to the extended form at $\tau_1 = -150°$, $\tau_2 = 180°$, followed by a secondary minimum at $\tau_1 = 90°$, $\tau_2 = 180°$ representing a *gauche-trans* form. The totally extended conformation ($\tau_1 = \tau_2 = 180°$) is only 1·5 kcal mol^{-1} higher than the global minimum. There is a local minimum at $\tau_1 = -150°$ and $\tau_2 = -150°$ only 0·5 kcal mol^{-1} above the global minimum. Stable conformations of the

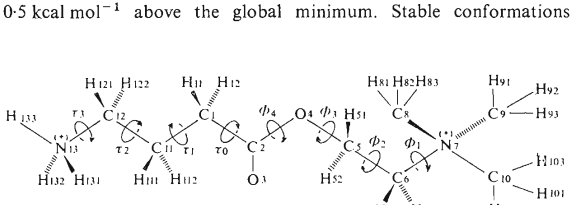


FIG. 1

The (nonstandard) atomic numbering system used for GABACh-ion. Definition of torsion angles: $\tau_0 = \tau(O_4—C_2—C_1—C_{11})$, $\tau_1 = \tau(C_2—C_1—C_{11}—C_{12})$, $\tau_2 = \tau(C_1—C_{11}—C_{12}—N_{13})$, $\tau_3 = \tau(C_{11}—C_{12}—N_{13}—H)$, $\phi_1 = \phi(C_5—C_6—N_7—C_{10})$, $\phi_2 = \phi(\phi_4—C_5—C_6—N_7)$, $\phi_3 = \phi(C_2—O_4—C_5—C_6)$, $\phi_4 = \phi(C_1—C_2—O_4—C_5)$

GABACh-ion corroborate with the recent NMR study on the aqueous solutions of GABA by Ham[9]. The most abundant conformation of the GABA-moiety a *gauche--trans* one with respect to τ_1 and τ_2, obviously corresponds to the stable conformation at $\tau_1 = 90°$, $\tau_2 = 180°$ of the present work. Finally, the *gauche-gauche* conformations common in isolated GABA-molecule are high energy ones in GABAC-ion. This situation may be due to the fact that the two ends of the ion are similarly charged and interactions would be greater in the folded GABA-moiety.

The GABA molecule has considerable flexibility and the ability to adopt different conformational modes may well be essential to its physiological activity.

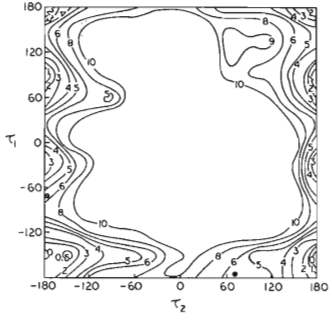


FIG. 2

PCILO conformational energy map of GABACh-ion with the geometrical input data from [σ]. Isoenergy curves in kcal/mol with respect to the global energy minimum taken as energy zero. ● X-Ray crystallographic conformations

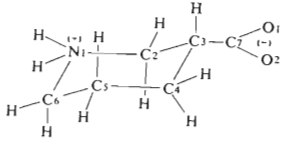


FIG. 3

The atomic numbering used for carbon, nitrogen and oxygen atoms of nitrecotic acid; torsion angle $\tau(C_2—C_3—C_7—O_1)$

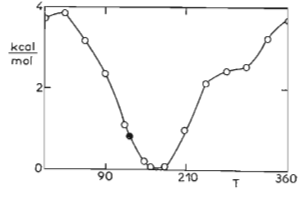
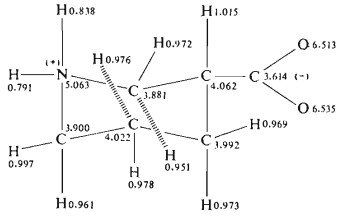


FIG. 4

Plot of calculated energy in kcal/mol with respect to the lowest energy conformation against the torsion angle (τ). X-Ray crystallographic conformation

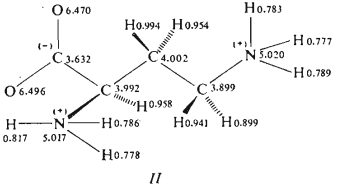
Compared to the GABA molecule, nipecotic acid is a relatively bulky and inflexible molecule. None the less, studies with radioactive nipecotic acid indicate that GABA and nipecotic acid can be counter-transported in brain slices *via* the same mobile carrier and that nipecotic acid appears to have a higher affinity than GABA for this carrier[10]. From experimental evidence it is observed that the piperidine ring of nipecotic acid is in the chair form with the carboxylate group in an equatorial position[11].

The theoretical study of the energy changes for the rotation of the carboxylate group with respect to the piperidine ring of nipecotic acid has been performed by PCILO method. The minimum energy for the chair form of nipecotic acid (Fig. 3) with respect to the torsion angle $\tau(C_2–C_3–C_7–O_1)$ is obtained at $\tau = 160°$, but the experimental value is $\tau = 127{\cdot}6$. The relative energy changes for the variation of $\tau(C_2–C_3–C_7–O_1)$ is shown in Fig. 4. It is evident that the energy varies within a short range for rotation around $C_3–C_7$ bond and the energy variation is almost negligible in the range $\tau = 155°$ to $\tau = 185°$.



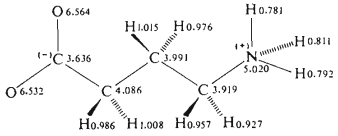
I

The CNDO/2 gross atomic populations (GAP's) for the crystallographic conformations of the molecules nipecotic acid zwitter ion *I*, protonated 2,4-diaminobutyric acid (*II*), GABA zwitter ion* *III* and GABACh-ion *IV* are shown below.



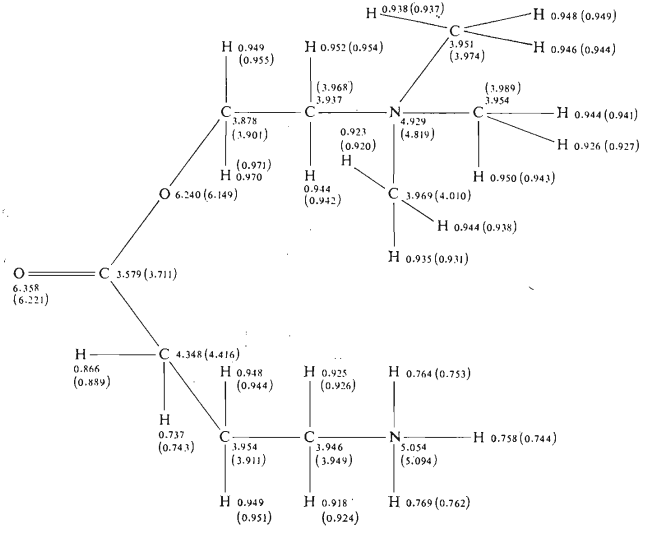
II

* The CNDO/2 conformational analysis has been performed[12] but GAP's for crystallographic conformation are not presented.



III

The electron distribution on the N^+ of *I* to *III* may be compared. It may be noted that GAP on N^+ in case of nipecotic acid(*I*) is higher than in the cases of open chain molecules *II* and *III*. It is known that the highly ionic interaction between the cationic head N^+ and some corresponding anionic receptor site is a preliminary and fundamental qualification for the binding of the amino acid to the receptor. The conformation of *I* is quite different from the open chain compounds as N^+ in (*I*) is connected with two hydrophobic branches whereas in *II* and *III* the two ionic ends are separated by a single hydrophobic branch.



IV

The GAP's of the GABAC-ion (protonated form) are represented in *IV* for the diiodide crystallographic structure[6] only. The GAP's obtained by PCILO method are also indicated within the parentheses. The GAP (5·054) on $^{(+)}NH_3$ of GABAC ion is comparable to GAP (5·06) on N^+ of nipecotic acid. The N^+ atoms are the most active points for biological and pharmacological activities of the protonated molecules.

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