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An *ab initio* SCF Molecular Orbital Study on the Conformation of Serotonin and Bufotenine*

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Ab initio SCF molecular orbital computations on the conformation of cationic serotonin and bufotenine indicate a preference for a perpendicular, or nearly so, arrangement of the ethylamine side chain with respect to the ring. The planar extended forms observed, among others, in the crystals of cationic indolealkylamines do not represent intrinsically stable conformations of these molecules. Their occurrence must be attributed to the effect of environmental forces.

Key words: Serotonin – Bufotenine

It has been shown recently in our laboratory [1] that molecular orbital computations with the PCILO (Perturbative Configuration Interaction using Localized Orbitals) method account satisfactorily for the essential conformational properties of indolealkylamines, in crystals and in solution, provided that these molecules are divided into groups corresponding to their occurence as neutral or ionic species with an amino or dimethylamino terminal group. An interesting exception to this agreement is offered, however, by the existence in the crystalline state of *planar* extended structures observed (among other) for the cationic species of serotonin (*I* with $R_1{=}R_2{=}R_3{=}H$) and 5-methoxy-N,N-dimethyltryptamine (*I* with $R_1{=}R_2{=}R_3{=}CH_3$), which do not correspond to any energy minimum on the conformational energy maps.

In order to explore this point further and to ascertain whether this disagreement could be due to the approximations inherent in a semi-empirical treatment, we have reevaluated the conformational properties of serotonin and bufotenine (*I*, $R_1{=}R_2{=}CH_3$, $R_3{=}H$) by the *ab initio* SCF method. This last molecule is considered as representing 5-methoxy-N,N-dimethyltryptamine. The computations have been carried out using an extension, performed in our laboratory, of the program Gaussian 70 [2] to 105 orbitals (we shall call the extended program: Gaussian 105), in an STO-3G basis [3]. The procedure has been applied recently with very satisfactory results to the study of the conformational properties of acetylcholine [4, 5] and histamine [6].

Another problem which we also wished to settle by these refined computations concerns the disagreement between PCILO and EHT results with respect to the preferred conformation of cationic serotonin: both methods predict the preferred conformation to have the ethylamino side chain perpen-

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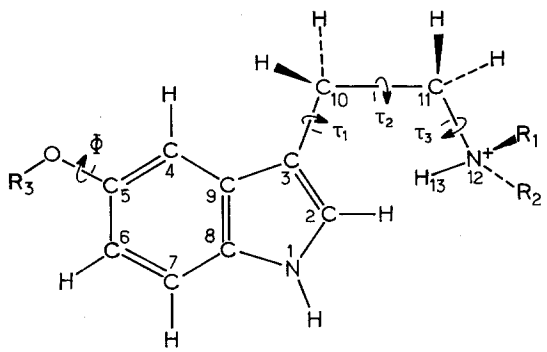
dicular to the indole ring but the conformation should be *gauche* following PCILO [1, 7] and *trans* following EHT [8, 9].

The computations have been performed only for limited parts of the conformational energy maps, relevant to the problems under discussion. In these parts they have been carried out as a function of the two essential torsion angles τ_1 and τ_2 at 30° intervals. We recall that the torsion angle τ of the bonded atoms A—B—C—D is the angle between the planes ABC and BCD; viewed from A, τ is positive for a clockwise rotation of the far end with respect to the near one, with $\tau = 0°$ corresponding to the cis-planar arrangement of the bonds AB and CD. In our study $\tau_1 = \tau(C_2—C_3—C_{10}—C_{11})$, $\tau_2 = \tau(C_3—C_{10}—C_{11}—N^+_{12})$ and $\tau_3 = \tau(C_{10}—C_{11}—N^+_{12}—H_3)$. The drawing of I corresponds to $\tau_1 = \tau_2 = \tau_3 = 0°$.



I

In the study of serotonin the cationic head was considered staggered ($\tau_3 = 60°$). τ_3 was also assumed to be 60° for bufotenine, this value being close to the value 52° observed in the crystal of 5-methoxy-N,N-dimethyltryptamine [10].

The results for serotonin are indicated in Fig. 1. The global energy minimum ($\tau_1 = 90°$, $\tau_2 = 60°$) and the next local energy minimum ($\tau_1 = 120°$, $\tau_2 = -60°$), 1.4 kcal/mole above the global one, correspond to *gauche* forms with the side chain perpendicular or nearly so to the ring. There is a local energy minimum at $\tau_1 = 110°$, $\tau_2 = 180°$, 2.6 kcal/mole above the global one, corresponding to an extended form. The *ab initio* computation confirms thus the PCILO results about the preference of cationic serotonin for a *gauche* form. (There is, however, an inversion of the energies of the two *gauche* forms with respect to the indications of PCILO). The planar extended conformation ($\tau_1 = 0°$, $\tau_2 = 180°$) is 7.2 kcal/mole above the global one and does not correspond to an energy minimum. The result is again very similar to that obtained by PCILO. It seems therefore necessary to admit that the nearly planar extended conformation ($\tau_1 = 13°$, $\tau_2 = 173°$) assumed by serotonin in complex with creatinine sulphate [11] must be due to crystal packing forces.

The results for bufotenine are indicated in Figs. 2a and 2b. Both curves refer to the same global energy minimum at $\tau_1 = 120°$, $\tau_2 = -60°$. There is a close local energy minimum, only 0,8 kcal/mole above the global one, at $\tau_1 = 120°$, $\tau_2 = 180°$ corresponding to an extended form. The PCILO results

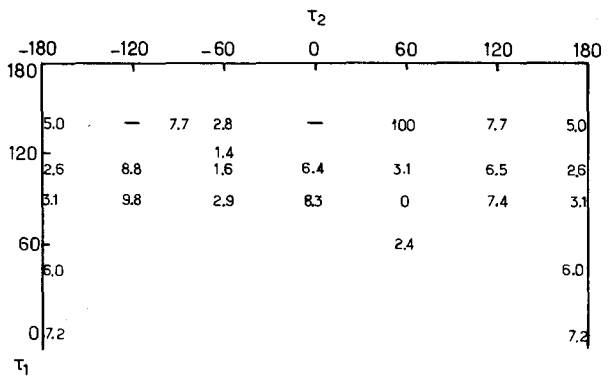


Fig. 1. *Ab initio* conformational energy map for cationic serotonin. Energies in kcal/mole with respect to the global energy minimum taken as energy zero

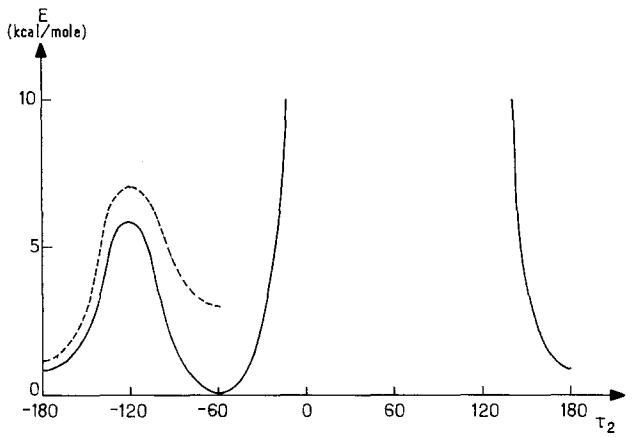


Fig. 2a. *Ab initio* conformational energy of cationic bufotenine as a function of τ_2, for ——— $\tau_1 = 120°$ and – – – $\tau_1 = 90°$. Energies in kcal/mole with respect to the global energy minimum taken as energy zero

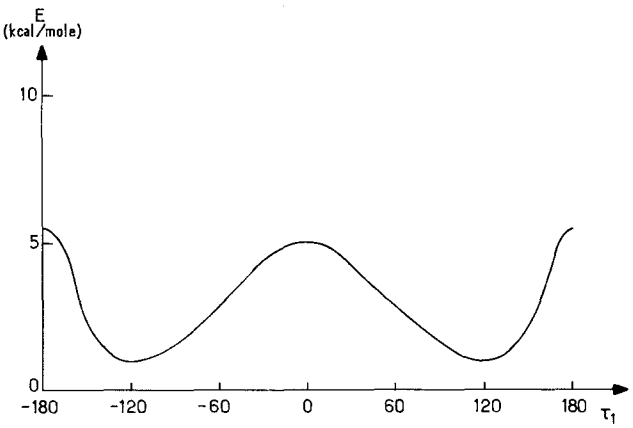


Fig. 2b. *Ab initio* conformational energy of cationic bufotenine as a function of τ_1 for $\tau_2 = 180°$. Energies in kcal/mole with respect to the global energy minimum (Fig. 2a) taken as energy zero

indicated a reverse order between these two minima, with the *trans* form 0.5 kcal/mole more stable than the *gauche* one. Whatever be the case the *ab initio* results confirm that the molecule prefers a conformation with a strongly inclined orientation of the side chain with respect to the ring. A planar extended conformation ($\tau_1 = 0°$, $\tau_2 = 180°$) would correspond to a high energy region, over 5 kcal/mole above the global minimum and is not associated with any local energy minimum, in agreement again with the PCILO results. The nearly planar, extended conformation ($\tau_1 = 17°$, $\tau_2 = 179°$) observed in the crystal of 5-methoxy-N,N-dimethyltryptamine [10] must therefore be ascribed again to the action of packing forces.

Altogether the *ab initio* computations confirm the essentials of the PCILO results. The planar extended forms observed (among others) in the crystals of some cationic indolealkylamines do not represent intrinsically stable conformations of these molecules. Their occurrence must be attributed to the effect of environmental forces. We are trying presently to elucidate the nature of these effects.

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