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# Conformational Analysis of 5-Hydroxytryptamine and Its Cation: $\Psi$, $\Phi$-Energy Contour Diagram by the INDO Molecular Orbital Method

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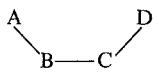
Complete conformational energy contour diagrams of 5-hydroxytryptamine and its cationic form have been obtained by the semi-empirical LCAO-MO-SCF method of the INDO level of approximation. The most stable conformation of the neutral form is when $\Psi$ is approximately 90° (or 270°) and $\Phi$ is near 60° (*l-gauche*) and 300° (*r-gauche*). The higher stability of the *gauche* conformations over the *trans* form probably results from protic hydrogen-$\pi$-base interaction. The calculated stabilization energy is approximately 1 Kcal/mole. The quantum mechanical calculation of the $\Psi$, $\Phi$ energy diagram is in qualitative agreement with the $\Psi$, $\Phi$ interatomic distance diagram in the evaluation of the range of conformational degrees of freedom. Calculations on the 5-hydroxytryptamine cation show that the stabilization energy due to proton-$\pi$-interaction appears to be exaggerated because the counter-anion is neglected in the calculation. In the neutral species the hydrogen-$\pi$-base interaction does not seem to be charge-transfer type, while there is a strong indication that in the cationic form the charge-transfer type of interaction is significant.

Vollständige Diagramme der Konformationsenergie von 5-Hydroxytryptamin und seiner kationischen Form wurden mit Hilfe der LCAO-MO-SCF-Methode in der INDO-Näherung berechnet. Die stabilste Konformation des neutralen Moleküls liegt vor, wenn $\Psi$ annähernd 90° (oder 270°) und $\Phi$ annähernd 60° (*l-gauche*) sowie 300° (*r-gauche*) groß sind. Die größere Stabilität der *gauche*-Konformationen gegenüber der *trans*-Form rührt vermutlich von einer Wechselwirkung zwischen positiv geladenem Wasserstoff und $\pi$-Base her. Die berechnete Stabilisierungsenergie beträgt annähernd 1 kcal/Mol. Das quantenmechanisch berechnete $\Psi$, $\Phi$-Energiediagramm stimmt qualitativ mit dem $\Psi$, $\Phi$-Diagramm der Atomabstände überein, wenn man den Bereich stabiler Konformationen untersucht. Die Ergebnisse der Berechnungen am Kation des 5-Hydroxytryptamins zeigen, daß die Stabilisierungsenergie auf Grund der Proton-$\pi$-Wechselwirkung überhöht zu sein scheint, da das entsprechende Anion bei der Berechnung vernachlässigt wird. Im neutralen Molekül scheint die Wasserstoff-$\pi$-Wechselwirkung nicht auf Ladungsübertragung zurückzuführen zu sein, während diese Art der Wechselwirkung für das Kation wesentlich ist.

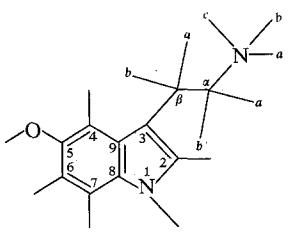
Emploi de la méthode LCAO MO SCF dans l'approximation INDO pour le calcul des diagrammes d'énergie conformationelle de la 5-hydroxytryptamine et de sa forme cationique. La conformation la plus stable pour la forme neutre correspond approximativement à $\Psi = 90°$ (ou 270°) et $\Phi = 60°$ (*l-gauche*) et 300° (*r-gauche*). La plus grande stabilité des conformations *gauches* par rapport à la forme *trans* résulte probablement de l'interaction entre hydrogène positif et base $\pi$. L'énergie de stabilisation calculée est d'environ 1 Kcal/mole. Le calcul par la mécanique quantique du diagramme d'énergie $\Psi$, $\Phi$ est en accord qualitatif avec le diagramme $\Psi$, $\Phi$ des distances interatomiques en ce qui concerne les zones de conformations permises. Les calculs sur le cation de la 5-hydroxytryptamine montrent que l'énergie de stabilisation due à l'interaction proton-électrons $\pi$ est exagérée si l'on néglige l'anion correspondant dans le calcul. Dans l'espèce neutre l'interaction hydrogène-$\pi$ ne semble pas être du type transfert de charge, alors que cela semble être le cas dans la forme cationique.

In a butane-like molecule (I), when A and D are substituted by heteroatoms or aromatic rings, the conformational stability of the molecule is not easily predicted by simple stereochemical models. Obtaining the conformational energy of such a molecule requires more sophisticated methods.



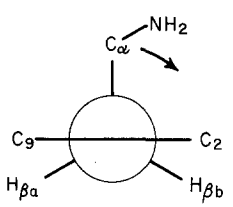

(I)

The $\beta$-arylethylamines, where A is substituted by an amino group and D by an aromatic ring, comprise the overwhelming majority of the biogenic amines. 5-Hydroxytryptamine (II), known as serotonin [1] is one of the important and interesting molecules in this category.

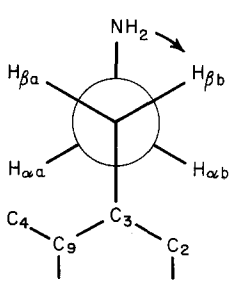



(II)

It appears that more precise information about 5-hydroxytryptamine could be obtained by a) calculation of the degrees of conformational freedom resulting from rotation of the two single bonds ($\Psi$ = dihedral angle $C_9-C_3-C_\beta-C_\alpha$ and $\Phi$ = dihedral angle $C_3-C_\beta-C_\alpha-N_{amino}$) (Fig. 1), and b) estimation of the molecular




A. Rotational Axis = Ψ ($C_9-C_3-C_\beta-C_\alpha$)




B. Rotational Axis = Φ ($C_3-C_\beta-C_\alpha-N$)

Fig. 1. Newman projection of 5-Hydroxytryptamine. Arrows indicate the Rotational Direction

stability, which is due to both intramolecular hydrogen-$\pi$ interaction and the repulsive forces resulting from steric hinderence. In guinea pig ileum two types of 5-hydroxytryptamine receptors have been proposed, one associated with the muscle fibre and the other with the neural tissue [2–6]. It is probable that 5-hydroxytryptamine assumes different stereochemical orientations for the different biological receptors. Kier [7] found, using the extended Hückel molecular orbital method, that 5-hydroxytryptamine exists in one stable conformation and has concluded that in this conformation the molecule is fairly rigid. This rigid structure, according to his calculation, is where $\Psi$ is 90° and $\Phi = 180°$. In Kier's study $\Phi$ was rotated every 90°. This calculation did not take into account the accepted stereochemical fact that staggered conformations are energetically stable. Because of the possibility that partial resolution of the conformation energy may lead to the wrong conclusion, a complete $\Psi$, $\Phi$-energy map is required to obtain the conformational degrees of freedom.

The INDO (Intermediate Neglect of Differential Overlap) molecular orbital method was employed in these calculations. This method has been shown to be good in predicting relative energies and charge densities, and is described elsewhere in detail [8].

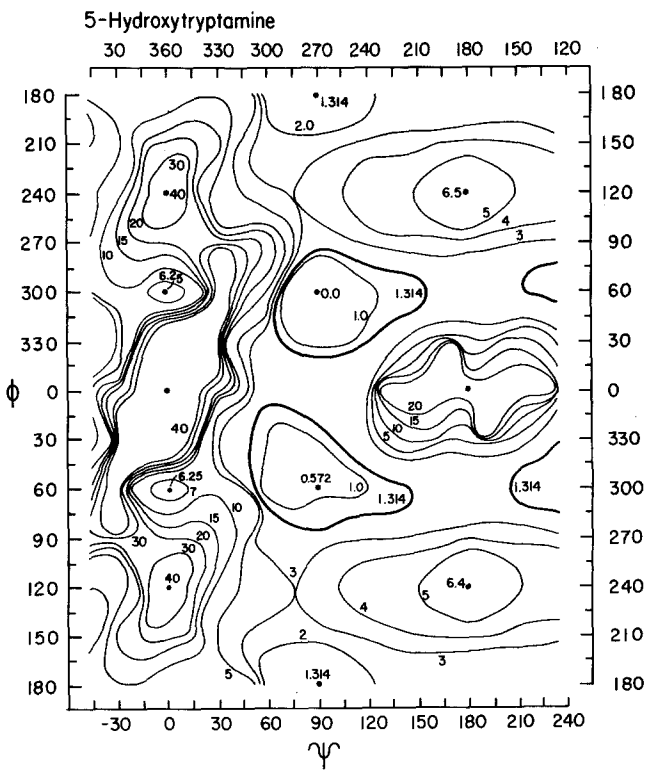



Fig. 2. $\Psi$, $\Phi$ Energy Contour Diagram of 5-Hydroxytryptamine given in Kcal/mole. The lowest conformation ($\Psi = 90°$, $\Phi = 300°$) has been set arbitrary to 0.0 Kcal/mole, and the heavy lines indicate the same energy level as the *trans* conformation ($\Psi = 90°$, $\Phi = 180°$)

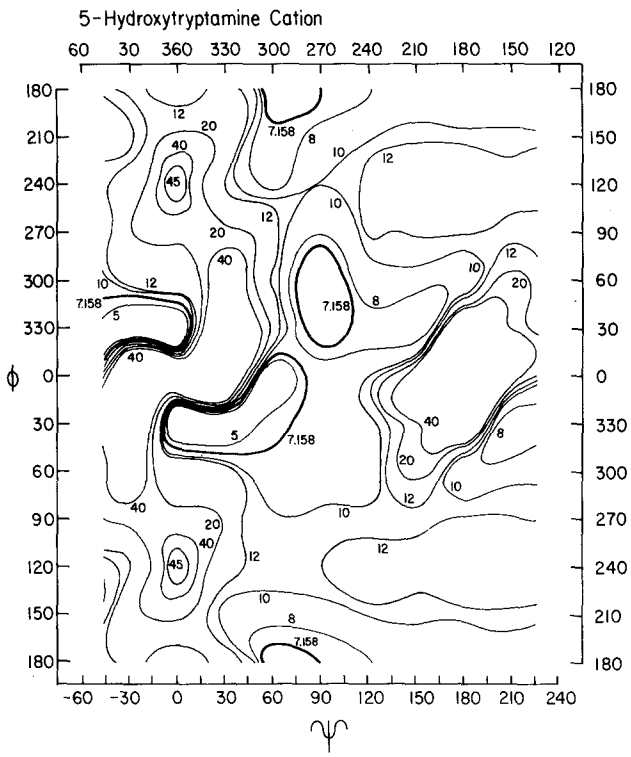



Fig. 3. $\Psi$, $\Phi$ Energy Contour Diagram of 5-Hydroxytryptamine cation given in Kcal/mole. The lowest conformation ($\Psi = 60°$, $\Phi = 0°$) has been set arbitrary to 0.0 Kcal/mole, and the heavy lines indicate the same energy level as the *trans* conformation ($\Psi = 90°$, $\Phi = 180°$)

The standard geometry [9] of 5-hydroxytryptamine was assumed and the calculations were performed by simultaneously rotating $\Psi$ and $\Phi$ energy 30° in a clockwise manner (Fig. 1) and when necessary by rotating $\Psi$ and $\Phi$ every 15°. $\Psi$, $\Phi$-energy contour maps of 5-hydroxytryptamine and its cationic form are given in Figs. 2 and 3, respectively. Fig. 2 shows that the most stable conformation of 5-hydroxytryptamine exists where $\Psi$ is approximately 90° and $\Phi$ is near 60 (1-*gauche*), 180 (*trans*) and 300 (r-*gauche*) degrees. This is in excellent agreement with the stereochemical model, where the staggered conformations are expected to be energetically favorable. When $\Psi$ is fixed at 90° and energy calculations carried out at $\Phi = 60°$ and 300°, the molecule is more stable than that calculated for $\Phi = 180°$ by 0.742 and 1.314 Kcal/Mole, respectively. The latter conformation ($\Psi = 90°$, $\Phi = 180°$) should show the least interaction between non-bonded atoms, and is therefore classically most stable. It is apparent that at $\Psi = 90°$, and $\Phi = 60°$ and 300°, this molecule is stabilized by the intramolecular interaction between the amino hydrogen and $\pi$-electron of the indole ring similar to that previously described for $\pi$-protic hydrogen type of interaction [10–12]. This interaction does not seem to be charge-transfer type, although over-all electronic density change is observed between *trans*-conformation ($\Psi = 90°$; $\Phi = 180°$) and r-*gauche* conformation ($\Psi = 90°$; $\Phi = 300°$) as shown in Tables 1 and 2. Providing that the

Table. 1. *Total charge densities of the 5-hydroxytryptamine and its cation of two different conformations. Atomic numbers are referred to the compound II*

| Atomic number | Neutral | | Cation | |
|---|---|---|---|---|
| | $\Psi = 90, \Phi = 180$ | $\Psi = 90, \Phi = 300$ | $\Psi = 90, \Phi = 180$ | $\Psi = 60, \Phi = 0$ |
| $N_1$ | −0.1075 | −0.1076 | −0.0949 | −0.0961 |
| $C_2$ | 0.0686 | 0.0677 | 0.0935 | 0.1024 |
| $C_3$ | −0.0499 | −0.0475 | −0.0677 | −0.0981 |
| $C_4$ | −0.0613 | −0.0613 | −0.0689 | −0.1018 |
| $C_5$ | 0.2111 | 0.2108 | 0.2263 | 0.2375 |
| $C_6$ | −0.0540 | −0.0540 | −0.0465 | −0.0500 |
| $C_7$ | 0.0077 | 0.0074 | 0.0179 | 0.0280 |
| $C_8$ | 0.0736 | 0.0730 | 0.0781 | 0.0791 |
| $C_9$ | 0.0283 | 0.0275 | 0.0264 | 0.0042 |
| $C_\beta$ | 0.0509 | 0.0518 | 0.0565 | 0.0460 |
| $C_\alpha$ | 0.1758 | 0.1778 | 0.1166 | 0.1289 |
| N | −0.2396 | −0.2373 | 0.0504 | 0.0101 |
| $H_1$ | 0.0960 | 0.0960 | 0.1182 | 0.1258 |
| $H_2$ | −0.0139 | −0.0138 | −0.0074 | 0.0075 |
| $H_4$ | −0.0118 | −0.0087 | −0.0226 | −0.0238 |
| $O_5$ | −0.2996 | −0.2992 | −0.2952 | −0.2911 |
| $H_5$ | 0.1606 | 0.1605 | 0.1747 | 0.1838 |
| $H_6$ | −0.0136 | −0.0135 | 0.0033 | 0.0125 |
| $H_7$ | −0.0276 | −0.0276 | −0.0111 | −0.0020 |
| $H_{\beta a}$ | −0.0258 | −0.0236 | −0.0069 | 0.0145 |
| $H_{\beta b}$ | −0.0285 | −0.0336 | −0.0142 | 0.0074 |
| $H_{\alpha a}$ | −0.0411 | −0.0455 | 0.0359 | 0.0298 |
| $H_{\alpha b}$ | −0.0585 | −0.0620 | 0.0319 | 0.0254 |
| $H_{Na}$ | 0.0754 | 0.0769 | 0.1949 | 0.1862 |
| $H_{Nb}$ | 0.0846 | 0.0857 | 0.2061 | 0.1977 |
| $H_{Nc}$ | | | 0.2047 | 0.2362 |

Table 2. *π-electron densities of the 5-hydroxytryptamine and its cation of two different conformations. Atomic numbers are referred to the compound II*

| Atomic numbers | Neutral | | Cation | |
|---|---|---|---|---|
| | $\Psi = 90, \Phi = 180$ | $\Psi = 90, \Phi = 300$ | $\Psi = 90, \Phi = 180$ | $\Psi = 60, \Phi = 0$ |
| $N_1$ | 1.6883 | 1.6886 | 1.6632 | 1.6614 |
| $C_2$ | 1.0572 | 1.0580 | 1.0219 | 1.0086 |
| $C_3$ | 1.1001 | 1.0989 | 1.1606 | 1.1626 |
| $C_4$ | 1.0857 | 1.0839 | 1.1030 | 1.1248 |
| $C_5$ | 0.9739 | 0.9742 | 0.9553 | 0.9426 |
| $C_6$ | 1.0751 | 1.0747 | 1.0602 | 1.0614 |
| $C_7$ | 1.0236 | 1.0241 | 1.0087 | 0.9859 |
| $C_8$ | 1.0614 | 1.0619 | 1.0675 | 1.0689 |
| $C_9$ | 1.0147 | 1.0144 | 1.0222 | 1.0202 |
| Total | 10.0800 | 10.0787 | 10.0626 | 10.0364 |

conformation showing least interaction is $\Psi = 90°$ and $\Phi = 180°$, stabilization due to intramolecular interactions are shown enclosed within the heavy lines in Figs. 2 and 3. Outside the enclosed heavy lines repulsive interactions predominate between the non-bonded atoms of the molecule. Particularly in the vacinity of $\Psi = 0°$ the energy of the molecule is highly unfavorable, even though our calculation of the energy barriers are exaggerated due in part to neglect of the equilibrium geometry (optimization of bond angles and bond lengths) and also to the inherent limitations of the INDO level of approximation. The energy contour surface diagram of 5-hydroxytryptamine is in qualitative agreement with the interatomic distance maps shown in Figs. 4, 5 and 6. While the two dimensional interatomic distance maps are useful in qualitatively evaluating the range of the conformational freedom, the quantum mechanical calculation of the conformational energy leads to more precise information concerning the nature and the magnitude of this energy.

The results obtained for the 5-hydroxytryptamine cation seem of interest, because the shape of its contour diagram, and also its relative energy differences are quite different from those of the corresponding neutral species. The most stable conformation of the cation is that where $\Psi = 60°$ and $\Phi = 0°$, and it is 7.158 Kcal/mole more stable than the least interacting conformation ($\Psi = 90°$ and $\Phi = 180°$). The stabilization energy of 7.158 Kcal/Mole seems to be highly exaggerated as compared to the neutral species. Similarly, an exaggerated stabilization of energy for the histamine and its cation has been observed [13]. The high stabilization energy of the protonated form of 5-hydroxytryptamine is probably due to electrostatic forces resulting from the high positive charges on the amine hydrogens. In contrast to the neutral species, a significant charge-transfer has

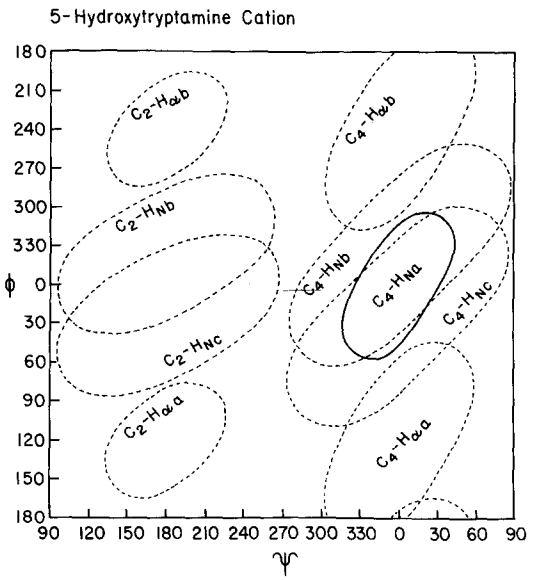



Fig. 4. $\Psi$, $\Phi$-Interatomic Distance Map. Inside the circle, the interatomic distance is smaller than the Van der Waal's distance

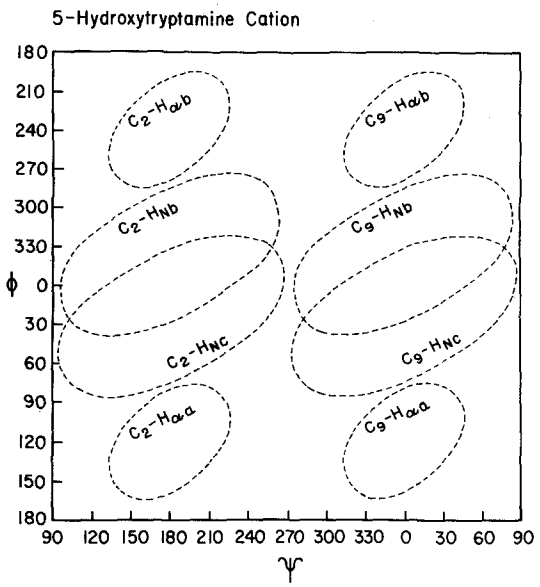



Fig. 5. $\Psi$, $\Phi$-Interatomic Distance Map. Inside the circle, the interatomic distance is smaller than the Van der Waal's distance

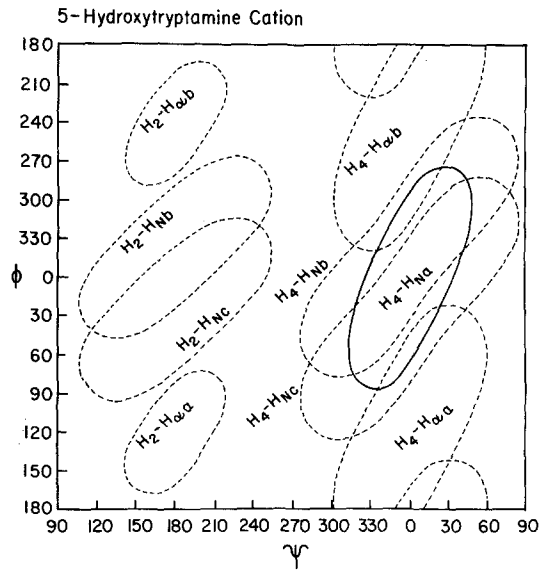



Fig. 6. $\Psi$, $\Phi$-Interatomic Distance Map. Inside the circle, the interatomic distance is smaller than the Van der Waal's distance

been observed in the protonated form, for example, total charge density of the ammonium ion, $q_{NH_3^+}$, of the $\Psi = 90$, $\Phi = 180$ – conformation is 0.6561, and that of the $\Psi = 60$, $\Phi = 0$ – conformation is 0.6302. Similar difference in the total $\pi$-electron density of the indole ring of the above two different conformations has been noticed (Table 1 and 2). Actually, the ammonium ion is balanced by the surrounding counteranion. Calculations on the cationic form neglect this situation [7] and the relative magnitude of the stabilization energy appears to be less reliable.

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