Theoretical Study of 5-HTP. Potential New Drug Resulting from the Complexation of 5-HTP with ATP

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ABSTRACT

5-HTP (5-Hydroxytryptophan), is the precursor of the neurotransmitter serotonin. Molecular parameters (interatomic distances and angles, total atomic charge, dipole moments) of 5-HTP (5-Hydroxytryptophan) and ATP (Adenosine triphosphate), and of their possible complex, including its heat of formation, have been computed in an *ab initio* study involving DFT calculations. The 6-31G* basis set and the B3LYP functional were employed. The aim of this study is to emphasize by DFT calculation the possible existence of a complex between ATP and 5-HTP that may have the properties of a new drug. A Natural Bond Orbital analysis description offers supplementary details for the structure of the molecular units and their interaction.

Keywords: ATP; 5-HTP; Density Functional Theory (DFT); NBO

1. Introduction

5-HTP (5-Hydroxytryptophan), is itself the precursor of the neurotransmitter serotonin. In one study, when normal, healthy humans were deprived of L-tryptophan, a rapid lowering of mood occurred, similar to that of depressed individuals [1]. In another study, depression occurred when supplies of serotonin were depleted [2]. Also, when normal, healthy humans were given 5-HTP, mood-elevation characteristics developed similar to those that occur when antidepressants are taken [3-5]. Indeed, 5-HTP has become very popular with the public for just this reason: people feel better when they use it.

The special carrier of energy in human organism is the molecule adenosine triphosphate, or ATP.

ATP consists of adenosine composed of an adenine ring and a ribose sugar and three phosphate groups (triphosphate).

Adenosine 5'-triphosphate (ATP) is a multifunctional nucleotide, discovered in 1929 by Lohmann [4] and proposed as the main energy carrier in the cell by Lipmann in 1941 [5] nowadays being notoriously known as the "molecular currency" of the intracellular energy transfer [6]. It is produced during the processes of photosynthesis and cellular respiration, being subsequently used as energy source in a multitude of cellular processes including biosynthetic reactions, motility and cell division.

The discussed molecules are presented in **Scheme 1**.

The advances made in various areas of chemistry with the help of the supramolecular paradigm emphasize the importance of a theoretical analysis of intermolecular interactions in relevant couples of weakly bound bio-
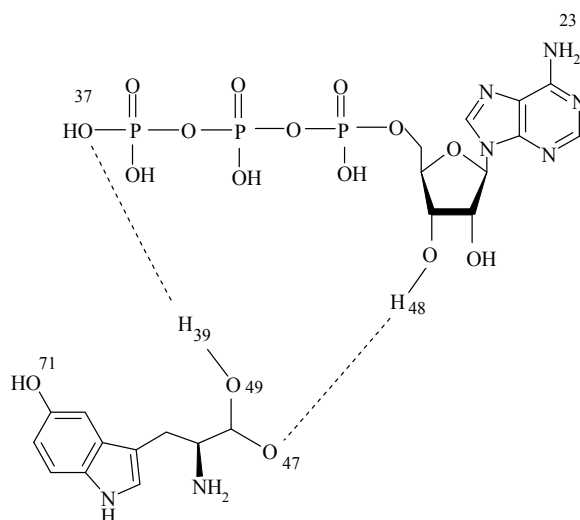
Scheme 1. Structure and the numbering of selected atoms in the ATP-5-HTP complex.

logically active molecules. The present paper targets such a goal by characterizing 5-HTP and the nucleotide ATP, as well as their association in a complex.

The electronic structure of a possible complex DHEA with serotonine and a complex DHEA with ATP has been described by the authors [7-9].

2. Methods

The initial input for 5-HTP and for ATP were obtained from a molecular mechanics calculation (MM⁺ force field) [10]. The molecular geometries were optimized without any constraints.

The *ab initio* calculations were carried out using the Gaussian 09 program [11]. The geometries of ATP, 5-HTP and of their complex were optimized at the 3-21G* level, starting from an INDO guess. A stationary point was found. At this point, a refinement was carried out by a single point at the B3LYP/6-31G* level [12].

In the last part of this paper, an analysis of the molecular wave function performed in terms of localized electron-pair bonding units using the NBO program is given [13,14]. This analysis is deemed very important to understand the various interactions involving each component of the complex under study.

Computed HOMO and LUMO orbitals were drawn with the Gview-09 program [15].

The structure and the numbering of selected atoms in the ATP-5-HTP complex are shown in **Scheme 1**.

3. Results and Discussion

3.1. Structure and Bonding in the Molecular Units and Their Intermolecular Complex

The formation of the ATP-5-HTP complex is analyzed in terms of geometry, charge and energy parameters. Finding the absolute minimum for a complex is a nontrivial question, given the subtle balance of the intra- and intermolecular factors. The different nature of the overall molecular constitution of the two biomolecules, ATP and 5-HTP which possesses essentially a planar p-conjugated core, practically precludes a significant association of the p-p stacking type. The strongest association involves hydrogen bonds. There are several possible patterns for hydrogen bonding (O-H...O, O-H...N, involving the various heteroatom combinations). The supramolecular association presented here is the optimal one due to the supplementary stabilization resulting from the alignment of the dipoles on the molecular constituents. The bonding associations O(37)...H(39) and O(47)...H(48) have a regular length for the given type, 1.38415 Å and 1.51651 Å respectively. The geometry of association is further characterized by O_{37}....H_{39}-O_{49} angle and O_{47}...$H_{48}O_{15}$ angle values (168.192 and 149.386 respectively). It should be noted that the atoms O_{37}...H_{39}-O_{49} of hydrogen bond are

almost collinear, which suggests that this interaction is the dominant one in the association.

DFT results can be credited with a higher confidence in the quantitative respects because of their treatment of correlation effects. On the other hand, it is acknowledged that the regular DFT functionals face intrinsic problems in the long-range regime [10].

Table 1 shows that atom O_{47} from 5-HTP acquires the largest negative charge in B3LYP calculations. A larger positive increase of the charge is noted for the bridge hydrogen, H_{39}. It is also interesting to note that the inductive effect produces a positive charge increase on atom H_{48} from the outer O-H bond of the intermolecular association region.

The effect of the association with ATP is then an activation of 5-HTP induced by this electronic distribution change. The resulting activation mechanism of 5-HTP would then be due to a potentially significant structural rearrangement as shown by the data in **Table 1**. In 5-HTP, the HOMO and LUMO orbitals are seen as pure π orbitals. The frontier orbitals from 5-HTP lose their almost pure π-nature, and acquire a hybrid character in the complex. This reveals a subtle influence of the electronegativity factors involved in the donor-acceptor interactions that is accounted for in the frame of the DFT approach.

3.2. Frontier Molecular Orbitals

The highest molecular orbitals (HOMO) and the lowest-lying unoccupied molecular orbitals (LUMO) are named as frontier molecular orbitals FMO) [16-18].

The FMOs play an important role in spectra and chemical reactions [18]. The HOMO-1, HOMO, LUMO and LUMO + 1 orbitals distributions computed at the B3LYP/6-31G (d. p) level for the title molecule are illustrated in **Figure 1**. The HOMO and LUMO are localized on almost the whole molecule of 5-HTP (**Table 2** and **Figure 1**). HOMO-1 and LUMO + 1 orbitals are localized on the adenine part of adenosine molecule from ATP.

Since the HOMO-LUMO energy separation has been used as a simple indicator of kinetic stability it can be said that the molecules complex which has:

$$m_{HOMO} - m_{LUMO} = 7.5638 \text{ eV}$$

it seems to be implies in a high kinetic stability and low chemical reactivity [19].

The dipole moment appearing as a result of the formation of the complex (**Table 2**).

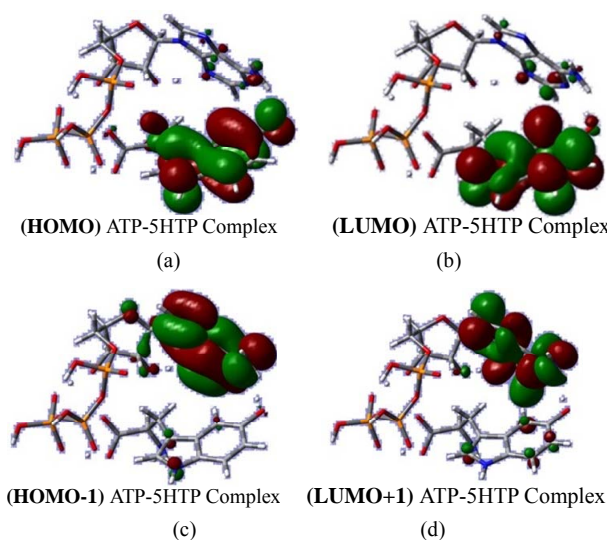### 3.3. NBO Analysis of the Complex by B3LYP Calculations

The natural bond orbital (NBO) method [13,14] offers supplementary structural information. The NBO analysis automatically identifies two molecular units correspond-

Table 1. Total atomic charge on selected atoms in the molecular components and in the association complex, from DFT Mulliken population (B3LYP) analysis.

	Frag.	Compl.	Var.		Frag.	Compl.	Var.
AT.	ATP	ATP-5-HTP	ΔQ	AT.	5-HTP	ATP-5-HTP	ΔQ
O_{37}	−0.700	−0.735	−0.034	**O_{49}**	−0.560	−0.547	0.018
H_{38}	0.411	0.426	0.015	O_{47}	−0.391	−0.645	−0.254
H_{48}	0.449	0.496	0.046	H_{39}	0.376	0.478	0.102

Table 2. Reactivity parameters calculated at B3LYP/6-31G* level.

Method	Reactivity parameter	ATP	5HTP	ATP-5HTP	DEassoc = $E_{AB} − E_A − E_B$ (au)
B3LYP/6-31G* at the HF optimized geometry	Total energy (au)	−2665.517	−761.343	−3427.1	−0.2631
	HOMO (au)	−0.206	−0.201	−0.1899	
	HOMO-1	−0.247	−0.211	−0.1992	
	LUMO (au)	−0.086	−0.015	−0.0881	
	LUMO + 1	−0.093	−0.006	−0.0488	
	μ(D)	7.54	3.489	6.376	

(HOMO) ATP-5HTP Complex

(a)

(LUMO) ATP-5HTP Complex

(b)

(HOMO-1) ATP-5HTP Complex

(c)

(LUMO+1) ATP-5HTP Complex

(d)

Figure 1. Frontier orbitals in the complex, from DFT calculations.

ing to the ATP and 5-HTP molecules. The perturbation donor-acceptor analysis of the NBO method offers information about intermolecular interactions. A look at the corresponding data shows that the most important intermolecular donor-acceptor contact occurs between an antibonding NBO function (NBO no. 176. LP (3) O_{37}/ 456. BD* (1) O_{49}-H_{39} of the O-H group and the lone pair of O(37), corresponding to an energy of 70.99 Kcal/ mol.

Though B3LYP in this study is the following: in the NLMO calculations there are a contribution to 174. (2.00000) 95.8636% LP (1) O_{37} and 182. (2.00000) 93.0824% LP (2) O_{47} that contain 0.945% H_{39} s(100.00%) and 2.798% H_{48} s(100.00%), respectively.

The simplest analysis consists in checking the composition of the natural hybrid orbitals (NHO), which may reveal details about differential hybridization, *i.e.* sometimes rather important deviations from the usual sp^2 (s:p = 33%:67%) or sp^3 (s:p = 25%:75%) compositions.

Particularly interesting are the hybrid orbitals associated with the intermolecular hydrogen bond formed by the sequence of atoms O(37).......H(39)-O(49). The hybrids along BD (1) P_{32}-O_{37} bond has the following compositions: (28.54%) P 32 and (71.46%) O_{37} but exists also a contribution of H_{39} of 0.083% (the hydrogen from the bond) in NLMO analysis. The NBO analysis shows that the hybrid composition is not so standard, and is in fact better characterized by an sp^2 differential hybridization.

The lone pair devoted to the H(39)...O(37) hydrogen bond has the nonstandard composition s(17.02%) p 4.87 (82.98%) which practically suggests an sp^3 character.

The hybrids along the H_{39}-O_{49} and H_{48}-O_{15} bonds have the following compositions s(39.47%) p 1.53 (60.53%) and s(28.60%) p 2.50 (71.40%) respectively.

The first one has an sp character and the last one has an sp^3 character.

The heterogeneous nature of the bond is measured by the 71.46% participation of the oxygen hybrid orbitals in the P-O bond. Similarly in the O-H bond described, the oxygen hybrid orbital percentage is 81.63%.

This one emphasizes the presences of the H bonds in the complex.

4. Conclusions

From these calculations, it appears the possibility of forming an association complex between ATP and 5-HTP, emphasized by the B3LYP calculations.

The NBO analysis reveals several nonstandard hybrid compositions and the associated donor-acceptor pertur-

bative schemes support the idea of a moderate strength hydrogen bond, cumulated with electrostatic effects, leading to a firmly bound molecular complex.

The present theoretical study on the electronic changes brought about by complexation leads to the hypothesis that an enhancement in the biological action of 5-HTP and/or ATP could result from their interaction. This hypothesis should now be reinforced by the experimental observation of an interaction between those two molecules.

The role of ATP (adenosine triphosphate acid) that is the major as a source of energy in the human organism. associated to 5-HTP, a precursor in the synthesis of serotonine, may lead to the design of a new very useful drug.

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