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Structural and vibrational investigations of a neurotransmitter molecule: Serotonin (5-hydroxy tryptamine)

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ABSTRACT

Structural and vibrational studies have been carried out for the most stable conformer of serotonin (5-HT) at the DFT/B3LYP/6-311++G** level using the Gaussian 09 software. In light of the computed vibrational parameters the observed IR and Raman frequencies have been analyzed. To help assign the vibrational fundamentals the GAR2PED software has been used to compute PEDs. Several of the fundamentals are drastically changed in going from indole to serotonin. The two NH bonds of the NH_2 group are slightly different possibly due to bonding of the two H atoms of the NH_2 group with different atoms. The rocking and wagging modes of the NH_2 groups show mixing with the other modes while the remaining four modes are pure group modes. The Kekule phenyl ring stretching mode is found to remain almost unchanged. The HOMO-LUMO energy gap supports to pharmacological active property of the serotonin molecule. The HOMO and LUMO study suggests the existence of charge transfer within the molecule. The NBO analysis has been carried out to gather information regarding the proper and improper hydrogen bonds.

1. Introduction

In normal and pathological conditions, interaction between two amines in brain is an interesting and challenging research field. Serotonin (5-hydroxytraptamine or 5-HT) is an important monoamine neurotransmitter molecule. It plays a key role in the day-by-day behavior and physiological states of human body [1,2]. This molecule is involved in the regulation of stress, pain, sense, aggression, the body temperature, blood pressure, smooth muscle functions in cardiovascular and gastrointestinal tissues, sleep, mood, appetite, anger, and sexuality [3–7]. The total serotonin to be detected in the enterochromaffin cells in the gut is approximately 90% in human body, where it is accustomed to regulate intestinal movements [8]. Specific distribution of receptors on a single cell is another component which can affect the response of 5-HT. Small serotonin level or irregular 5-HT receptor functionalities conceived lead to depression, aggressive behavior, obsessive-compulsive disorders [9], migraine, bipolar disorder, anxiety, and the borderline personality disorder [10]. Irregularities in numerous serotonergic brainstems are believed to play role in sudden infant death syndrome [11]. Different receptor subtypes may present distinct affinities and thus respond to low or high concentrations of the neurotransmitter. In addition, a receptor, which is a component of an ion channel [12] plays faster than one which is connected to a channel via an intermediate molecule [13]. The receptors coupled to the synthesis of second messenger molecules [14,15] act as ionic conductances indirectly [16] and induce changes in the target cells. The conformational flexibility of the ethylamine side chain in neurotransmitter molecules, originating mainly from rotations about C–N and two C–C bonds is responsible for the drug-receptor interaction and molecular recognition [17]. At the physiological pH values, 5-HT occurs in its protonated form serotonin H^+ [18,19] with strong preference for protonation at the amino terminal in ethylamine side chain. The high affinity-binding site of serotonin receptors is required for the strong interaction between the positively charged amino group of the serotonin H^+ and the recognition site, by intermolecular cation-π interactions [17,19–21]. The binding of protonated serotonin to a receptor induces a conformational change, leading to the activation of signal transduction. Therefore, in order to interpret these processes at the molecular level and to affirm the drug design of targeting serotonergic systems, it is of prime interest to investigate possible conformations of an isolated serotonin molecule and its protonated form, as well as their interaction with the environment [17].

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To investigate the relationship between their pharmacological activities and conformational isomers of serotonin, X-ray crystallographic and theoretical methods have been investigated extensively [22–25]. LeGreve et al. [26] have studied the ultraviolet and IR spectra of single conformation of neutral serotonin in the gas phase. Mouric and Emson [24] have carried out theoretical conformational study of serotonin and assigned calculated frequencies for the conformers only in the region 2800–3000 cm^{-1}. The experimental and theoretical SERS spectra of 5-HT were investigated by Song et al. [27] who have observed 27 frequencies in normal Raman spectrum of solid and 21 frequencies in SERS spectrum. The earlier data on Raman spectrum by Song et al. [27] are limited to only 27 observed fundamentals out of the total 69 fundamentals. They also carried out theoretical calculation at the b3lyp/6–31++G level using the Gaussian 05 package. Yang and Gao [28] have compared performance of different DFT methods for only 19 modes of the 5-HT molecule. The conformational landscape of protonated serotonin H^+ has been investigated in gas phase and aqueous solution with full geometry optimization [29]. Bayari et al. [30] have investigated vibrational IR spectrum of 5-HT and observed only 49 fundamentals. These authors have assigned only 58 modes out of the total 69 modes based on theoretical calculation. In order to analyze the 49 experimental IR bands Bayari et al. carried out theoretical calculation at the b3lyp/6-31G* level using the Gaussian 03 package, however, they assigned only 58 fundamentals above 400 cm^{-1}. Neither Song et al. [27] nor Bayari et al. [30] carried out PEDs' calculations for the normal modes. In the present work, we found 12 fundamentals below 400 cm^{-1}. Thus, both the studies reported earlier [27,30] seem to be incomplete.

No work appears to have been reported on the complete vibrational assignment for the lowest energy conformer of 5-HT and therefore, investigation of the complete vibrational spectrum of the 5-HT molecule seems to be of prime importance. In the present paper, we have investigated theoretically the optimized molecular geometries, and fundamental vibrational modes along with their IR intensities, Raman activities and depolarization ratios of the Raman bands of the lowest energy conformer at the B3LYP/6–311++G(d, p) level. We have also calculated the potential energy distributions (PEDs) for the normal modes of 5-HT to make more reliable assignments. Moreover, we have also investigated experimentally the IR and Raman spectra of 5-HT and presented complete vibrational assignments of the observed spectra and correlated the calculated and observed frequencies. We have observed 44 IR and 49 Raman bands. APT and Mulliken atomic charges were also computed. Change in the electron density (ED) in the antibonding orbitals and energies have been computed by the natural bond orbital (NBO) analysis method to provide definite proof of stabilization of the serotonin molecule.

2. Experimental and computational details

The compound serotonin purchased from the Sigma Aldrich Company (purity ≥ 98%) was used for the experimental investigation without any further purification. The compound is white crystalline solid at room temperature.

The room temperature FTIR spectrum of the compound was measured in ATR mode in the spectral range 400–4000 cm^{-1} on a Perkin Elmer FT-IR/FTR frontier spectrometer using the experimental parameters:

Mode- ATR mode, Source- MIR, Detector- MIRTGS, Resolution ~2 cm^{-1}

The Raman spectrum of serotonin was recorded on a Jobin Yvon HORIBA HR 800 Raman spectrometer in the range 50–4000 cm^{-1} using the wavelength 4881 A^0 of an Ar^+ laser for exciting the sample. In recording the Raman spectrum, the following parameters were used:

Laser spot size – 1 μm, Power at the sample: <10 mW, Integration time – 10 s, One window covers – 800 cm^{-1}, Slit-width fixed at the entrance of laser – 200 μm, Resolution –2 cm^{-1}, Accuracy of measurements – 2 cm^{-1}.

For the most stable conformer of 5-HT (serotonin), the optimized molecular geometry has been computed at the B3LYP/6–311++G(d, p) level using the Gaussian 09 package [31] and molecular visualization program [32]. With this optimized geometry, computations have been made for the bond lengths, bond angles, vibrational frequencies with their IR intensities, Raman scattering activities, and depolarization ratio of the Raman bands. To propose reliable vibrational assignments potential energy distribution (PED) for each mode has been computed using the GAR2PED software [33].

LeGreve et al. [26] have proposed eight conformational isomers of serotonin while the same authors [34] have suggested that serotonin exist in 13 conformations. Cabezas et al. [35] have found only three conformers from microwave spectroscopy. To resolve the discrepancy in the number of conformers in serotonin, we have thoroughly investigated the problem using DFT computations. For the serotonin molecule 16 conformers arise due to different orientations of the hydroxyl group (–OH) and ethylamine side chain. For the optimization of the minimum energy conformer of the 5-HT molecule, the following method has been adopted. Initially, the indole ring was optimized by taking different orientations of the CH_3 group at the position 17 with respect to the indole ring. Out of the two possible conformers the lower energy conformer was taken and another methyl group at the position 20 was added and structures with two possible orientations of the NH_3 group were optimized and an –OH group was added to site C_4 and the complete molecular structure was optimized. In this way, the optimized geometric structure for the lowest energy conformer of the serotonin molecule is obtained without any constraint. For the present study the lowest energy conformer is considered. The geometry of the lowest energy conformer Fig. 1 was optimized. The vibrational mode assignment has been made on the basis of the PEDs computed. The observed IR and Raman frequencies modes have

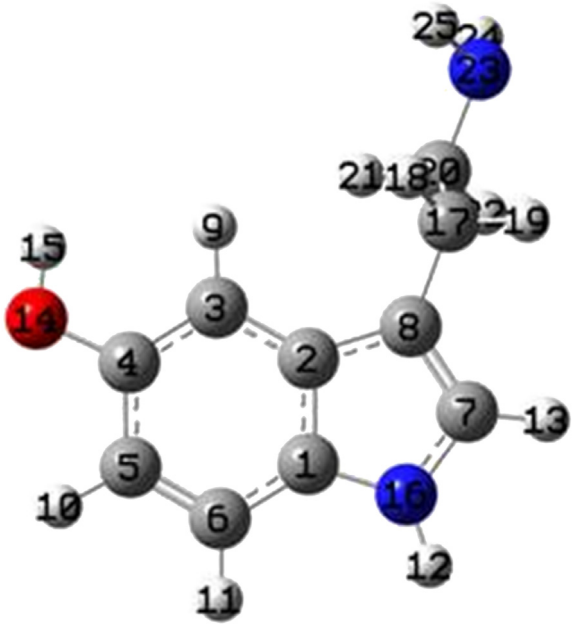

Fig. 1. Atomic numbering scheme of lowest energy conformer of Serotonin.