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Conformational study of octopamine in gas phase and effect of hydrochloride

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ABSTRACT

This work deals with the molecular modeling and vibrational spectra of all the twenty conformers of an important biomolecule octopamine which have been investigated using the DFT/B3LYP level of theory in combination with the 6-31++g(d,p) as a suitable basis set. The experimental FTIR and FTRaman spectra of octopamine neurotransmitter were recorded in the spectral region 400–4000 cm^{-1} and 50–4000 cm^{-1} respectively and correlated with the calculated spectra of the most stable conformer. The effect of hydrochloride on the important geometrical parameters of most stable conformer of octopamine was also studied. The normal coordinate analysis was performed to scale the theoretical frequencies and to calculate potential energy distributions for precise normal mode assignment. Most of the frequencies were in good agreement with experimental one. However, some have been modified. Natural bond orbital analysis was performed in order to confirm the stability of electronic structure of octopamine molecule. HOMO-LUMO analysis for all the twenty conformers was also performed to give the transition profile and to study the chemical reactivity of octopamine.

1. Introduction

The neurotransmitters are chemical messengers that transmit message between two nerve-cells. The conformational analysis and vibrational spectra of neurotransmitters can give deep insight about their behaviour in human and animals. The monoamine octopamine is one of the most abundant biogenic amine in the nervous systems of invertebrates. Octopamine is synthesized from the amino acid tyrosine which is substrate for the catecholamines dopamine, noradrenaline and adrenaline by decarboxylation to give tyramine which is subsequently hydroxylated to octopamine. Octopamine can be detected in nervous tissue by a specific radioenzymatic assay by high-pressure liquid chromatography with electrochemical detection [1]. Octopamine plays a role in mediating various behaviours including flying, egglaying, jumping, and aggression as well as sleep in insects, spiders and crustaceans. In insects, octopamine plays a major role in learning and memory. For example, octopamine can substitute for the appetitive (reward) reinforcement used in olfactory conditioning in insects. Blocking octopaminergic signaling abolishes appetitive learning, and optogenetic activation of octopaminergic neurons triggers appetitive learning in Drosophila larvae [2].

Our present investigation is important because there is no previous theoretical investigation regarding vibrational dynamics (IR and Raman) of octopamine molecule available. However, conformation analysis of octopamine and synephrine neurotransmitters was reported by Cabezas et al. [3] in which the eight stable conformational structures of octopamine were reported using theoretical computations at MP2/6-311++g(d,p) level. Moreover, Ishiuchi et al. also predicted four conformers of octopamine while eight conformers of m-octopamine in their study [4]. In present study, we have found twenty conformational structures of octopamine. The conformational and vibrational spectroscopic study on closely related molecules (tyramine and dopamine) of octopamine has been reported by number of authors using different level of theories [5–10]. Makara et al. predicted nine conformers of tyramine by ab initio calculations at B3LYP/aug-cc-pVDZ level of theory [5].

Four stable gauche conformers and a free jet microwave study of tyramine were reported by Melandri and Maris [6]. The vibrational spectra (IR and Raman) of tyramine and dopamine hydrochloride in gas phase were predicted by Siddiqui et al. [7]. Richardson et al. reported seven conformational structures of tyramine by using ab initio calculations at MP2/6-31G** level of theory [8]. Moreover, Lugutschenkov et al. reported infrared spectrum of protonated dopamine at B3LYP and MP2 level of theory using cc-pVDZ basis set [9]. The vibrational spectrum of dopamine and adrenaline were also reported by Gunasekaran et al. [10]. More recent, we reported possible number of conformers and vibrational spectra of tyramine [11] and dopamine [12]. In addition to this, we also reported the effect of HCl environment of geometrical parameters of tyramine [11] and dopamine [12]. Now, we are extending our same work for octopamine molecule

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with the aim to find out possible number of conformers and to study the effect of HCl environment on its geometrical parameters and vibrational spectra. Therefore, we must be able to explore their important biological properties in our future study.

In our present study, the twenty stable conformers as mentioned above have been found and the vibrational spectra of all the conformers of octopamine have studied using DFT/B3LYP/6-31++g(d, p) level of theory. The effect of protonation on octopamine in the most stable form has also been reported. The change in electron density in bonding and anti-bonding orbitals and second order perturbation energies are calculated by NBO analysis which shows that octopamine in all the conformers is stable. The orbital energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are also calculated.

2. Experimental Details

The white solid octopamine was purchased from Sigma Aldrich Chemical Co. (USA) and it was used as such without further purification. The FTIR spectrum of octopamine molecule was recorded on a JASCO FTIR-5300 spectrometer in spectral range 4000–400 cm^{-1} while FTRaman spectrum was recorded on Renishaw inVia Raman spectrometer in the range 4000–50 cm^{-1} respectively. The parameters which were used during the recording of FTIR spectrum: scans-200, spectral resolution-4 cm^{-1}, gain-50.

The following parameters were used during recording FTRaman spectrum of octopamine:

Resolution-1 cm^{-1}, Power at the sample-500 mW, PMT voltage-800 V, Slit-width at the entrance-320 μm, Time constant-0.7 s, Accuracy of the measurements ±2 cm^{-1}, LASER radiation-785 nm.

3. Calculation Details

The optimized geometrical parameters (bond lengths/angles) and vibrational frequencies with the IR intensities and Raman activities were obtained using the density functional theory (DFT) including exchange functional B3LYP with the 6-31++g(d,p) as suitable basis set at the platform of Gaussian 09 software [12].

The optimized geometrical parameters corresponding to the minimum on the potential energy surface have obtained by solving self-consistent field (SCF) equation iteratively. Harmonic vibrational frequencies were calculated using analytic second order derivatives to confirm the convergence to minima on the potential surface and to evaluate the zero-point vibrational energies. The potential energy distributions (PEDs) have also calculated to make a conspicuous assignment as animation available in GaussView [13] is not a guarantee for correct normal mode assignment. For the subsequent normal coordinate analysis (NCA), the force fields obtained in the Cartesian coordinates and dipole derivatives with respect to atomic displacements were extracted from the archive section of the Gaussian 09 output and transformed to a suitably defined set of internal coordinates by means of a modified version of the MOLVIB program [14,15]. The Raman activities were converted into Raman intensities using the following empirical relation [16,17].

$$I = \frac{f(\upsilon_0 - \upsilon_i)^4 S_i}{\upsilon_i \left[1 - \exp\left(-\frac{hc\upsilon_i}{kT}\right)\right]}$$

where, υ_0 is the exciting frequency (in cm^{-1}); υ_i is the vibrational wavenumber of the i^{th} normal mode; h, c and k are the universal constants and f ($=10^{-13}$) is the suitably chosen common scaling factor for all the peak intensities.

Natural bond orbital (NBO) calculations have been performed to study about inter and intra molecular interactions which take part within the molecule. NBO analysis gives the most accurate possible natural Lewis structure of orbital. Interaction between both filled and virtual orbital spaces information correctly explained by the NBO analysis, it could enhance the analysis of intra and inter–molecular interactions. The interaction between filled and anti-bonding orbital's represent the deviation of the molecule from the Lewis structure and can be used as the measure of delocalization. This noncovalent bonding–antibonding interaction can be quantitatively described in terms of the second order perturbation interaction energy $E^{(2)}$ [18–21]. This energy can be deduced from the second–order perturbation approach [22].

$$E^{(2)} = \Delta E_{ij} = q_i \frac{F_{ij}^2}{\varepsilon_j - \varepsilon_i}$$

where q_i is the i^{th} donor orbital occupancy, ε_i and ε_j are the diagonal elements (orbital energies) and F_{ij} is the off diagonal NBO Fock Matrix element.

4. Results and Discussions

4.1. Molecular Structure

In present study, twenty conformational structures (abbreviated as OP_i, $i = 1, 2 \ldots 20$) of isolated octopamine molecule have been ratified by performing tedious potential energy scanning. A local minima corresponding to each conformational structure was obtained on potential energy surface (PES). In addition, each structure has positive vibrational frequencies. All the conformers have been divided into gauche (in which NH_2 group of side chain is heeling towards the ring) and Anti (in which NH_2 group of side chain is away from the ring) conformations. The gauche structures have further subdivided into trans (OP1 to OP8) and cis (OP11–OP18) structures. Both the cis and trans structures are different in the orientation of the OH group of aromatic ring. This classification is shown in Fig. 1. The gauche structures were found having strong $lpNH_2 \ldots \pi$ interaction between the lone pair electrons of N atom of NH_2 group of side chain and π electron system of aromatic ring than anti structures [3]. The four structures (OP8, OP9, OP18 and OP19) of octopamine demonstrate an extra O—H…N type interaction. These interactions play an important role in the stability of octopamine neurotransmitter. Cabezas et al. [3] reported eight conformers (AGa1, AGb1, AGa2, AGb2, GGa1, GGb1, GGa2 and GGb2) of octopamine using MP2/6-311++G(d,p) level of theory in which six structures (AGa1, AGb1, GGa1, GGb1, GGa2 and GGb2) were supported by our calculations while two structures having name AGa2 and AGb2 were not found admittable with our calculations. This discrepancy in result is attributed to the use of two different theories.

The relative energy of all the conformers is listed in Table 1(a)–(b). The OP20 conformer was found having global minimum. Therefore, it was considered as the most preferred structure energetically than the rest conformers of octopamine. Besides OP20, the conformer OP10 has also low energy value. Thus OP10 and OP20 is the most stable pair of conformer. The reason of low energy in OP10 and OP20 is attributed to the weak $lpNH_2 \ldots \pi$ interaction which is due to extended ethylamine side chain. The conformer (OP20) of octopamine was also reported as the most stable conformer in previous reported study [3]. Therefore, our study is strongly supported by previous reported literature for octopamine.

The important optimized geometrical parameters of all the twenty conformers of octopamine at DFT/B3LYP along with the values of these parameters for octopamine cation [26] are collected in Table 1 (a)–(b). Fig. 2 shows the structure of most stable conformer (OP20) of octopamine in hydrochloride with atomic labeling. Both the two bond lengths (N20-H21 and N20-H22) of amine group present at the end of ethylamine side chain are 1.016 Å for the most preferred conformer (OP20) of octopamine in our present study. These two bond lengths