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Structural confirmation and spectroscopic study of a biomolecule: Norepinephrine

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ABSTRACT

The present work deals with the conformational and vibrational spectroscopic study of an important bio-molecule named norepinephrine in gas phase. The FTIR and FTRaman spectrum of norepinephrine in amorphous form were recorded in wavenumber range 4000–400 cm^{-1} and 4000–50 cm^{-1} respectively. We have investigated twenty-seven stable conformational structures of norepinephrine molecule. All the calculations have been done using Density Functional Theory with exchange functional B3LYP incorporated with the 6-31++G (d, p) basis set. The effect of hydrochloride on different bond lengths, bond angles and dihedral angles in the most stable conformer has also been studied. The total potential energy distribution for both the most stable conformer and the most stable conformer in hydrochloride was performed with the help Normal coordinate analysis method. Most of the calculated vibrational frequencies are in good agreement with the experimental frequencies. The natural bond orbital analysis was also performed to ensure the stability of electronic structures of norepinephrine. To know chemical reactivity of norepinephrine molecule we have calculated the energy gap between HOMO and LUMO orbitals and it has found above 5 eV in all the conformers.

1. Introduction

Norepinephrine (NP) belongs to catecholamine neurotransmitter family which has important role in treatment of hypertension, bronchial asthma, organic heart disease, cardiac surgery and myocardial infarction [1]. Its synthesis starts from tyrosine and then stores in the vesicles of the presynaptic region of the neuromuscular junction. It is released with exocytosis to the synaptic cleft, and is transported by passive diffusion to the postsynaptic membrane where it activates R- and α-adrenergic receptors which lead to the propagation of a nerve impulse. Norepinephrine neurotransmitter is also used to increase blood pressure during socks [2]. Norepinephrine has strong influences on attention and response activities within the brain. Norepinephrine also underlies the fight to flight responses, directly increasing heart rate, triggering the release of glucose from energy stores, and increasing blood flow to skeletal muscle. Norepinephrine can also suppress neuroinflammation when released diffusely in the brain from the *locus coeruleus* [3].

During the articles survey, we found few articles [2,4–6] dealing with structural analysis of the title molecule. However, no theoretical investigation regarding vibrational behaviour of norepinephrine molecule has been done so far. Some works are also available on closely related molecules (tyramine and dopamine) of norepinephrine neurotransmitter [7–10]. Nagy and co-workers [2] reported twelve conformational structures of norepinephrine molecule in their study. Lee et al. [4] also reported an assignment regarding conformational study of noradrenaline. The relaxed potential energy profiles for interconversion between the conformers in the two most stable noradrenaline families (AG1 and GG1, each containing four members) have been reported by T. V. Mourik et al. [5] at the B3LYP/6-31 þ G* level of theory. Moreover, A.M. Andersen [6] also reported the assignment concerning electronic structure study of noradrenaline molecule. Makara et al. reported a note on conformational analysis of tyramine molecule using B3LYP/aug-cc-pVDZ level of theory [7]. A literature on conformational study of tyramine was reported by Melandri and Maris and four stable structures were predicted in this literature [8]. Siddiqui et al. reported a detailed spectroscopic analysis on vibrational spectra (IR and Raman) of tyramine and dopamine hydrochloride in gas phase [9]. Moreover, the infrared spectrum of dopamine in protonated form has been reported using B3LYP/cc-pVDZ and MP2/cc-pVDZ theories [10]. The interaction between dopamine and water molecule was reported by Zhai et al. [11].

Our theoretical investigation for norepinephrine molecule is very much useful as no experimental data on vibrational spectra (IR and Raman) of norepinephrine molecule is available so far. Recently, we have reported our work regarding conformational and vibrational study of tyramine neurotransmitter [12] where we focused on vibrational behaviour and effect of hydrogen bond in HCl on different geometrical parameters of tyramine. Now we are extending the same study considering norepinephrine as target molecule. In present study,

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total twenty-seven conformational structures of norepinephrine molecule has been found using DFT/B3LYP/6-31++G(d, p) level of theory. In addition to this, the vibrational dynamics for all the conformers have been studied. The effect of hydrochloride (HCl) on the geometry of the most stable structure of norepinephrine has also reported. Using NBO analysis, we calculated change in electron density of bonding as well as antibonding orbitals and second order perturbation energies to find out about the stability of norepinephrine molecule. The orbital energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are also calculated.

2. Experimental Details

The norepinephrine was purchased from Sigma-Aldrich Chemical Co. (USA). It was present in white solid form. We used it as such without any further purification during recording of the FTIR and FTRaman spectrum.

The FTIR spectrum was recorded on JASCO FTIR-5300 spectrometer in range 4000–400 cm^{-1} with 200 scans, 4 cm^{-1} spectral resolution, 50 gain while FTRaman spectrum was recorded on Renishaw inVia Raman spectrometer in range 4000–50 cm^{-1} with following parameters.

Resolution 1 cm^{-1}; power at the sample 500–600 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 source 785 nm.

3. Calculation Details

Theoretical computations for norepinephrine molecule were done at DFT/B3LYP level of theory available in Gaussian09 software [13]. We consumed 6-31++G(d, p) as standard basis set during our calculations. The self-consistent field (SCF) equation was solved iteratively to get the optimized geometries whose energies were found minimal on the potential energy surface. Analytic second order derivatives were used to calculate the harmonic vibrational frequencies so as to determine the zero-point vibrational energies and confirming the minima on the potential energy surface. The potential energy distributions (PEDs) calculation was also performed to make important assignment of normal modes as animation available in GaussView.

For the subsequent normal coordinate analysis (NCA), the Cartesian coordinates and dipole derivatives with respect to atomic displacements were taken from the output file of Gaussian09 and transformed to a suitably defined set of internal coordinates by means of a modified version of the MOLVIB program [14,15]. The Gaussian calculated Raman activities for norepinephrine were converted into Raman intensities with the help of following relation of Raman scattering theory [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 ith 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 also performed at NBO 3.1 program available in Gaussian09 software at DFT/B3LYP level to perform second order perturbation analysis between filled and virtual orbitals which measures the intermolecular hyper-conjugation. The second order perturbation interaction energy $E^{(2)}$ was deduced by second order perturbation approach [18–22].

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

where q_i is the ith 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.

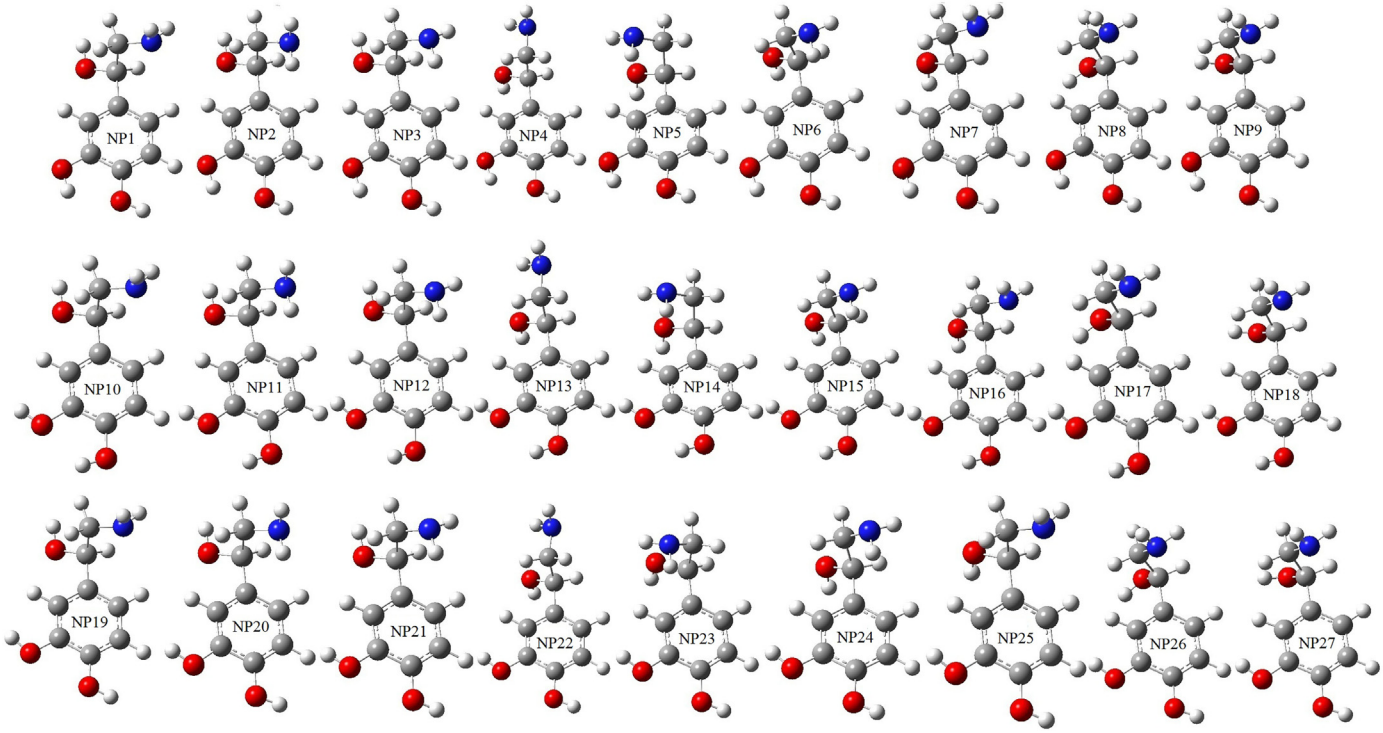

Fig. 1. Optimized structures of different conformers of norepinephrine.