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# Molecular modeling and spectroscopic investigation of a neurotransmitter: Epinephrine

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ABSTRACT

The investigation of possible number of conformational structures of gas phase epinephrine molecule has been performed using tedious potential energy scanning with respect to different dihedrals. All the theoretical computations were carried through first principles Density Functional Theory (DFT) method. While calculating optimized geometrical parameters and vibrational frequencies the 6-31++G(d, p) was consumed as a standard basis set. The FTIR and FTRaman spectra for epinephrine molecules were also recorded in the spectral region 400–4000 $cm^{-1}$ and 50–4000 $cm^{-1}$ respectively and correlated with the theoretical spectra of most preferred structure of epinephrine. The potential energy distribution was also computed using the normal coordinate analysis method to understand the vibrational dynamics of the epinephrine. The neutral bond orbital (NBO) analysis was performed for epinephrine and epinephrine hydrochloride to check out the stabilization of predicted electronic structures. The investigation regarding the strength and effect of N···H hydrogen bond in hydrochloride was also performed. The HOMO-LUMO energy gap was calculated to predict the chemical reactivity of molecule.



## 1. Introduction

Epinephrine is an important neurotransmitter which allows the transmission of message (in the form of signal) between two nerve cells. The conformational investigation of epinephrine can provide deep insights about their important biological activities. Epinephrine belongs to harmone, neurotransmitter and medication. It is produced in central nervous system by the certain neurons and adrenal glands [1]. Epinephrine has important roles in fight to fight responses by increasing the level of pupil dilation and blood sugar [2,3]. It is commonly found in animals and some single cell organism [4,5]. It is used in the treatment of anaphylaxis and superficial bleeding. It can be used in the treatment of asthma also [6]. Abnormal use of epinephrine may lead some side effects as shakiness, anxiety and sweating. Epinephrine neurotransmitter is synthesized in the medulla of the adrenal gland in an enzymatic pathway that converts the amino acid tyrosine into a series of intermediates and ultimately, epinephrine [7]. Together with norepinephrine, these two agents (epinephrine + norepinephrine) exert their actions through the adrenergic receptors a subfamily of 7-trans-membrane G-protein-coupled receptors [8]. Like dopamine and tyramine, epinephrine also belongs to group of monoamines called as catecholamines [9].

Few important researches [8–16] concerning structural confirmation and vibrational spectra of epinephrine and its closely coincidental molecules (dopamine and tyramine) have been reported at different levels of theories by a number of workers. Carcabal and co-workers performed conformational analysis of epinephrine and reported its sixteen different preferred structures at B3LYP/6-31G*, MP2/6-31 + G* and MP2/aug-cc-pVDZ levels [8]. The authors used mass selected ultraviolet and infrared holeburn spectroscopy following laser ablation of target compound into pulsed supersonic argon jet [8]. The vibrational spectra (IR and Raman) of epinephrine was reported by Gunasekaran et al. [9]. However, the authors performed the optimization only on one conformational structure of title molecule in their study [9]. Melandri and Maris reported four gauche structures of tyramine molecule [10]. All the four conformational structures were identified at MP2/6-31G* level of theory [10]. In a LIF excitation spectrum of tyramine molecule, six different origin bands were assigned corresponding to six different conformers of tyramine by Martinez et al. [11]. Six gauche-trans and three anti conformational structure were invented by Yoon et al. for tyramine molecule using MP2/6-31G* level of theory [12]. Makara et al. identified nine conformer

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of tyramine during structural modeling study at B3LYP/aug-cc-pVDZ level of theory [13]. The FTIR, Raman and UV–Visible spectra of dopamine molecule was also reported by Barreto et al. [14] and Singh et al. [15]. Moreover, in a theoretical investigation seven conformational structures of dopamine molecules in gas phase were predicted by Jha et al. [16]. In addition, the authors also reported the vibrational assignment of the most preferred structure of dopamine in their paper [16]. Siddiqui et al. [17] also reported the assignment regarding structural modeling and vibrational spectra of protonated tyramine and protonated dopamine neurotransmitter.

More recent, we have reported the spectroscopic investigation and vibrational dynamics of tyramine [18] and dopamine [19] in gas phase where we predicted possible number of conformers of both the tyramine and dopamine molecules. In addition to this, we also tried to report the effect of hydrogen bond on the structural parameters of these molecules in HCl. The present investigation is the extension of the same study which was performed for the tyramine [18] and dopamine [19]. However, the target compound is now epinephrine neurotransmitter. Clearly the aim of present investigation is to corroborate possible number of conformers and to study the effects of hydrochloride (HCl) on the structural parameters and vibrational spectra of different conformers of epinephrine. In addition to this, the electronic density of bonding and antibonding orbitals and hyper-conjugative energies in the most stable conformer and most stable conformer in HCl were computed through NBO method to assure the stability of the electronic structures of epinephrine. The chemical reactivity of the epinephrine was explored by energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO).

## 2. Experimental details

Fine epinephrine was purchased from Sigma Aldrich Chemical Co. (USA) which was present in white solid form. The FTIR and FTRaman spectrum of epinephrine was recorded without any further purification in compound.

The FTIR spectrum of epinephrine was recorded on JASCO FTIR-5300 spectrometer in spectral range of 4000-400 $cm^{-1}$ at instrumental facility centre (Banaras Hindu University). The parameters which were used during recording of spectrum were - 200 scans, 4 $cm^{-1}$ spectral resolutions, 50 gain.

The FTRaman spectrum of epinephrine was recorded on Renishaw inVia Raman spectrometer in spectral range of 4000-50 $cm^{-1}$ at National Physics Laboratory (Dehli) with the 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

The *ab initio* calculations for the epinephrine molecule were carried through well known DFT/B3LYP level available in Gaussian 09 software [20]. The 6-31++g(d,p) was used as canonical basis set during whole computations. 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 distribution (PEDs) was calculated to make crucial assignment of vibrational modes as animation available in GaussView.

For the normal coordinate analysis (NCA), the Cartesian coordinates and dipole derivatives were extracted from output file of Gaussian09 and transformed to a suitably defined set of internal coordinates (given in supplementary Table S1) by means of a modified version of the MOLVIB program [21,22]. The Gaussian calculated Raman activities for title molecule were converted into Raman intensities with the help of following relation of Raman scattering theory [23,24].

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

Where, $\upsilon_0$ is the exciting frequency (in $cm^{-1}$); $\upsilon_i$ 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 been performed at NBO 3.1 program available in Gaussian2009 software at DFT/B3LYP level to understand 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 [25–29].

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

Where $q_i$ is the $i^{th}$donor orbital occupancy, $\varepsilon_i$ and $\varepsilon_j$ 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

Carcabal and co-workers [8] reported sixteen different conformers of epinephrine molecule by using the combination of DFT and *ab initio* calculations at B3LYP/6-31 + G*, MP2/6-31 + G* and MP2/aug-cc-pVDZ levels of theory. However, in our present investigation we have found twenty one possible conformers of epinephrine molecule using DFT/B3LYP/6-31++G(d, p) level of theory. The optimized structures of all the possible conformers of epinephrine molecule have been shown in Fig. 1. All the twenty one optimized structures of title molecule presented in Fig. 1 were confirmed by performing the one dimensional potential energy scanning on the epinephrine molecule. During potential energy scanning of the title molecule the side chain was rotated about the bonds C12–N17 (N–CH3 group rotation), C10–C12 (CH2 group rotation) and C10–O15 (OH group rotation) with a step size of $10^0$ up to $360^0$ to confirm its possible conformations. In addition to this, the orientation of hydroxyl groups (OH) relative to ring was also considered. Therefore, the five bonds (C12–N17, C10–C12, C10–O15, C6–O23 and C1–O25) are there in epinephrine molecule which confirms its possible conformations. Each structure was found with positive vibrational frequency which predicts that all the structures should exist. We have divided all the conformers into two groups (gauche and anti) on the basis of side chain. The gauche structures (EPi, i = 1, 3, …, 21 except 2, 9 and 16) are those in which side chain is in folded form while in anti structures (EP9i, i = 2, 9 and 16) side chain is in extended form.

In the gauche structures, there is interaction between π electron system of ring and lone pair electrons of nitrogen atom of N–$CH_3$ group which is clearly due to the folded form of side chain. Moreover, some of the conformers of epinephrine demonstrate O–H···N