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Interpretation of IR and Raman spectra of dopamine neurotransmitter and effect of hydrogen bond in HCl

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ABSTRACT

The potential energy scanning with respect to the different dihedral angles were performed to search possible numbers of dopamine (neutral) conformers and further, fifteen conformers of dopamine were identified on the basis of energy minima. Vibrational frequencies were calculated for all the conformers of dopamine. Density functional theory was employed to carry out all the computations. The exchange correlation functional B3LYP and the basis set 6−31++G(d,p) were included in DFT calculation. The FTIR and FT-Raman spectra of dopamine hydrochloride were also recorded in the spectral region 400 −4000 cm^{-1} and 50−4000 cm^{-1} respectively. The normal coordinate analysis was also performed to scale DFT calculated force constants and to calculate potential energy distributions. The detailed vibrational spectral analysis and the assignments of the bands, done on the best-fit basis comparison of the experimentally obtained and theoretically calculated IR and Raman spectra, match quite well indicating DFT calculations as very accurate source of normal mode assignments. The interaction of the most stable conformer of dopamine with HCl was also studied to know the effect of hydrogen bond on its geometry and dynamics. The stability of the dopamine in isolated and protonated forms arising from hyperconjugative interactions was also analyzed by natural bond orbital analysis.

1. Introduction

Dopamine is a neurotransmitter that serves as a chemical messenger in the nervous system and permits individual neurons to communicate with each other. The dopamine neurotransmitter belongs to the class of compounds known as monoamines, and more specifically to a subclass of chemicals called catecholamines. Dopamine can act either as an inhibitory mechanism or an excitatory mechanism in the nervous system, depending on the location of dopamine neurons, and the receiving characteristics of the next neuron in the chain [1]. The dopamine system is involved in neural functions including locomotion, movement, reward, cognition and endocrine regulations [2].

Several important diseases of the nervous system are associated with dysfunctions of the dopamine system, and some of the key medications used to treat them work by altering the effects of dopamine. Parkinson's disease, a degenerative condition causing tremor and motor impairment, is caused by a loss of dopamine-secreting neurons in an area of the midbrain called the substantia nigra. Its metabolic precursor L-DOPA can be manufactured, and in its pure form marketed as Levodopa is the most widely used treatment for the condition. There is evidence that schizophrenia involves altered levels of dopamine activity, and most antipsychotic drugs used to treat this are dopamine antagonists which reduce dopamine activity [3]. Dopamine gets synthesized from the amino acid L-tyrosine, in the body. It is of immense biological significance, being the immediate precursor of the neurotransmitter hormone noradrenaline. In certain organs, dopamine can reach relatively high local concentrations especially, in the central nervous system where it probably has a function of its own. Dopamine affects brain process that control movement, emotional response and ability to experience pleasure and pain. Regulation of dopamine plays a crucial role in our mental and physical health [4].

Dopamine has been studied in isolated neutral and protonated forms and also in interacting form with different solvents from both the structural and vibrational points of view to develop simple and sensitive methods for the direct determination of it [5–9]. Structural conformations and Infrared spectrum of protonated dopamine was reported by Lugutschenkov et al. [5]. They performed quantum chemical calculations for protonated dopamine at B3LYP

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and MP2 level of theory using cc-pVDZ basis set to obtain possible conformers. They predicted two *gauche* conformers of doapmineH + energetically strong in the gas phase and could not identify any *trans* configuration of dopamineH+ in the IRMPD spectrum [5]. Moreover, Siddiqui et al. reported the molecular structures and vibrational dynamics of tyramine and dopamine hydrochloride [4]. They considered only one of the *trans* configurations of both the tyramine and dopamine which is not acceptable spectroscopically in gas phase rather they might be a stable solution in condensed phase [4].

The vibrational spectra (FTIR and FTRaman) of dopamine and adrenaline have been reported by Gunasekaran et al. [6] and interestingly, they also considered the *trans* conformer and /performed normal coordinate analysis to assign normal modes of 28 observed bands only. Zhai et al. studied the interactions, including the interaction sites and nature between dopamine hydrochloride with water and N,N-dimethyl formamide (DMF) by cyclic voltammetry, DFT calculations, nuclear magnetic resonance and atoms in molecules (AIM) analysis [7,8]. They observed that hydrogen bonding between dopamine and water/DMF is the strongest in *gauche* conformer of dopamine. *Ab initio* calculations at HF, DFT and MP2 have been employed for dopamine that showed minimal relative stability for stretched *trans*, folded *gauche* and folded *gauche* + conformers of dopamine neutral base in isolated state [9]. The structural and spectral analysis of 3-metoxytyramine has also been reported earlier which is an important metabolite of dopamine [10].

At physiological pH values, i.e. at pH = 7.4 for human blood, dopamine and other catecholamines occur in their protonated form with protonation occurring at the terminal amino group of the alkylamine side chain [5]. Therefore, most of the researchers considered protonated form of dopamine in their study. However, to understand the neurological behaviour of dopamine, the exact structure and numbers of stable conformers of dopamine in neutral form must also be known which is actually lacking at present. Keeping this all in mind, we have planned to present a theoretical study containing molecular modeling, investigation of possible numbers of stable conformers, vibrational dynamics and electronic structure of dopamine in isolated neutral form. We have also included dopamine hydrochloride to study the N..H hydrogen bond effect prior to the protonation of dopamine which might form exact basis for the dopamine crystals.

2. Experimental details

Dopamine hydrochloride was purchased from sigma aldrich chemical co. (USA) and it was used without further purification. The FTIR spectrum of dopamine hydrochloride was recorded in the spectral range 4000–400 cm^{-1} on a JASCO FTIR-5300 spectrometer. The following parameters were used: scans = 200, spectral resolution = 4 cm^{-1}, gain = 50.

FT-Raman spectrum of dopamine hydrochloride was recorded in salt form on Renishaw inVia Raman spectrometer in spectral range 4000–50 cm^{-1}. The following parameters were used during the recording of Raman spectrum:

Resolution = 1 cm^{-1}; power at the sample = 500–600 MW; PMT voltage = 800 V; slit-width at the entrance = 320 μm; time constant = 0.7s; accuracy of the measurements ± 2 cm^{-1}, LASER source = 785 nm.

3. Calculation details

All the theoretical calculations like potential energy scanning, structure optimization, vibrational frequencies and electronic structures were done by employing density functional theory (DFT) available in Gaussian 09 software [11]. DFT has an exact form for dynamic electron correlation but approximates exchange correlation [12]. B3LYP is generally faster than most post Hartree-Fock techniques and usually yields comparable results. It is also fairly robust for a DFT method. B3 is Becke's 3 parameter exchange correlation functional which uses 3 parameters to mix in the exact Hartree-Fock exchange correlation and LYP is the Lee, Yang and Parr correlation functionals that recovers dynamic electron correlation [13–15]. The B3LYP exchange functional and 6–31++G(d,p) basis set were included in present DFT calculations.

The optimized geometrical structures corresponding to the minima on the potential energy surface have been obtained by solving self-consistent field (SCF) equation iteratively. Harmonic vibrational frequencies were calculated using analytical second order derivatives to confirm the convergence to minima on the potential surface and to evaluate the zero-point vibrational energies. 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 (calculated scale factors are given in supplementary Table S1) by means of a modified version of the MOLVIB program [16,17]. The Gaussian calculated Raman activities (S_i) were converted into Raman intensities (I_i) using the following relation [18,19] -

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

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 is the suitably chosen common scaling factor for all the peak intensities.

Natural bond orbital (NBO) calculations have been performed to understand various second order perturbation analysis. NBO analysis gives the most accurate possible natural Lewis structure of orbital. The interaction between both the filled and virtual orbital spaces is correctly explained by the NBO analysis, which could enhance the analysis of intra and inter–molecular interactions. The interaction between filled and antibonding 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 $E^{(2)}$ [20–23]. This energy represents the estimate of the off–diagonal NBO Fock Matrix elements. It can be deduced from the second–order perturbation approach [24]-

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

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

To investigate the possible numbers of conformers of neutral dopamine, we have performed one dimensional potential energy scanning (PES) with respect to the dihedral angles of ethylamine side chain (CH_2NH_2 and NH_2) and OH groups individually. The full scanning was performed with a step size of 10^0 to complete a