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Conformational study of neutral histamine monomer and their vibrational spectra

V. Mukherjee *, T. Yadav

SUIIT, Sambalpur University, Sambalpur, 768019, Odisha, India

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ABSTRACT

Molecular modeling and potential energy scanning of histamine molecule, which is an important neurotransmitter, with respect to the dihedral angle of methylamine side chain have done which prefer three different conformers of histamine monomer. We have calculated molecular structures and vibrational spectra with IR and Raman intensities of these conformers using Density Functional Theory (DFT) with the exchange functional B3LYP incorporated with the basis set 6-31++G(d,p) and Hartree-Fock (HF) with the same basis set. We have also employed normal coordinate analysis (NCA) to scale the theoretical frequencies and to calculate potential energy distributions (PEDs) for the conspicuous assignments. Normal modes assignments of some of the vibrational frequencies of all the three conformers are in good agreement with the earlier reported experimental frequencies of histamine whereas others have modified. The standard deviations between the theoretical and experimental frequencies fall in the region 13–20 cm^{-1} for the three conformers. NBO analyses of histamine conformers were also performed. The net charge transfers from ethylamine side chain to the imidazole ring. The intensive interactions between bonding and anti-bonding orbitals are found in imidazole ring. The HOMO-LUMO energy gap is nearly 5.50 eV.

1. Introduction

Biogenic amine histamine (2-aminoethyl imidazole) is an organic molecule involved in several defense mechanisms of the body [1]. Histamine is an organic nitrogenous compound involved in local immune responses as well as regulating physiological function in the gut and acting as a neurotransmitter [2]. Histamine is widely distributed in both vegetal and animal kingdoms, from unicellular to superior organism. The biological activity of histamine is related with specific receptors on the cell membranes, having different responses depending on the receptor. The interaction with the receptors stimulates muscle contraction, vasodilatation, drop in blood pressure, etc. [1]. Histamine is, in fact, one of the most toxic and most commonly found biogenic ammine in foods. Foods that may concentrations of histamine include fish, fish products, tormented meat, vegetables, dairy products and alcoholic beverages [3]. The neutral histamine molecule is composed of an imidazole ring and an aminoethyl side-chain, both of which have the possibility of accepting a proton if the pH of the medium is acidic enough. At physiological pH (around 7.4), only the side-chain is protonated, as deduced from the two pH values of histamine, namely 5.8 and 9.4, so histamine is largely a monocation (96%) [4].

In previous studies, the attention was paid to the cationic species of histamine, which were studied from both the structural and the vibrational point of views. Vibrational spectra for solid and solved samples, including deuterated derivatives, in combination with quantum mechanical calculations were performed [1]. The vibrational spectra of histamine dication had been studied earlier in which the vibrational spectra of histamine dication have scarcely been revised, and the Raman spectrum in solid state has not been reported [4].

Few works have been found regarding vibrational dynamics of histamine in monomeric form, its receptors and interaction between other legends [5–14]. FT-Raman and QM/MM study of the interaction between histamine and DNA was reported [5]. The experimental results were used to build an intercalating and two minor groove models of DNA–histamine interaction. Only the minor groove models successfully passed the theoretical protocols, thus obtaining minimal energy structures for both of them. The smaller deviations were obtained for the model in which the contacts were ammonium group with guanine-N3 and imidazole group with guanine-N2. Interestingly, this model involve the two DNA strands while the other minor groove model was intra-strand, which agrees with the increasing of the melting temperature since a double helix is stabilized by inter-strand binders, as the biogenic polyamines [5]. The infrared spectrum of protonated histamine ($histamineH^+$) was also reported by Lagutschenkov et al. [14]. They concluded that the preferred protonation site of the histamine in the gas phase is at the imidazole ring and not at the ethylamine side chain and hence, histamine differs from all other related neurotransmitters. The crystal structure of 2-(1H-imidazol-4-yl)-ethanaminium chloride was reported recently [15]. This molecular salt, $C5H10N3^+ \cdot Cl^-$, was obtained as

* Corresponding author.
E-mail addresses: vishwajeet10@gmail.com, vmukherjee@suiit.ac.in (V. Mukherjee).

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by product in the attempted synthesis of a histamine derivative. The terminal amino group of the starting material was protonated. The molecular geometries of this molecule were considered in the present study for the comparison purpose.

In this paper, we have reported three different stable conformers of histamine (H1, H2 and H3). We have calculated molecular structures and vibrational spectra with IR and Raman intensities of histamine in all the three conformers using Density Functional Theory (DFT) incorporated with the basis B3LYP/6-31++G(d,p) and Hartree-Fock (HF) with the same basis set. We have also employed normal coordinate analysis (NCA) to scale the theoretical frequencies and to calculate potential energy distributions (PEDs). The change in electron density (ED) in the antibonding orbitals and second order perturbation energies $E^{(2)}$ are calculated by natural bond orbital (NBO) analysis to give clear evidence of stabilization of the conformers of histamine. The orbital energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are also calculated to analyze the transition profile of histamine.

2. Calculation details

The quantum chemical calculations were performed at the DFT/B3LYP and HF levels of theory supplemented with the standard 6-31++G(d,p) basis set at the Gaussian 03 program [16] to calculate bond lengths, bond angles and vibrational frequencies with the IR intensities and Raman scattering activities in the different conformers of the histamine molecule. The optimized geometries corresponding to the minimum on the potential energy surface have obtained by solving self consistent field (SCF) equation iteratively. Harmonic vibrational frequencies was calculated using analytic second order derivatives to confirm the convergence to minima on the potential energy surface and to evaluate the zero-point vibrational energies without imposing any molecular symmetry constraints. All the vibrational frequencies thus calculated are real for all the three histamine conformers.

The potential energy distributions (PEDs) have also calculated to make a conspicuous assignment as animation available in GaussView [16] 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 03 output and transformed to a suitably defined set of internal coordinates which by means of a modified version of the MOLVIB program [17,18]. To reproduce the Raman spectra, Gaussian calculated Raman activities were converted in corresponding Raman intensities using the empirical relation of Raman scattering theory [19,20].

Natural bond orbital (NBO) analyses have also performed which transforms the canonical delocalized Hartree-Fock (HF) MOs into localized orbitals that are closely tied to chemical bonding concepts. This process involves sequential transformation of non orthogonal Atomic Orbital's (AOs) to the sets of Natural Atomic Orbital's (NAOs), Natural Hybrid Orbital's (NHOs) and NBOs. NBO analysis gives the accurate possible natural Lewis structure of orbital because all orbitals are mathematically chosen to include the highest possible percentage of the electron density. 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 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 $E^{(2)}$ [21–24]. This energy represents the estimate of the off-diagonal NBO Fock Matrix elements. It can be deduced from the second–order perturbation approach [25]:

$$E^{(2)} = \Delta E_{ij} = q_i \frac{F_{ij}^2}{\varepsilon_j - \varepsilon_i} \quad (1)$$

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.

3. Results and discussions

3.1. Molecular structure

We have performed potential energy surface (PES) scanning of histamine with respect to the ethylamine side chain ($CH_2CH_2NH_2$) which is shown in Fig. 1. The full scanning was performed with step size of 5°. PES scanning reveals that there exist three different conformers of histamine (H1, H2 and H3) with respect to the ethylamine side chain ($CH_2CH_2NH_2$). The dihedral angles are 111.54°, −11.99° and −126.75° at DFT and 113.46°, −5.60° and −124.05° at HF respectively. This angle was reported at 93.03^0 for $C_5H_{10}N_3^+ \cdot Cl^-$ which is close to that in H1. Ramirez et al. also reported this angle at −78.17° which is also close to that in H1 if taken counter clockwise [1]. The optimized molecular structures of all the three conformers of histamine are shown in a Fig. 2. The relative energy (kcal/mol) of H1, H2 and H3 conformers are 0.753, 0 and 2.573 respectively with respect to H2, which reveals that H3 is the most stable conformer of histamine than other two. In most of the earlier works the structure H1 of histamine has been confirmed while in present work we have also found two more conformers of histamine (H2 and H3) whose molecular energy is very close to that of H1. The global minimum energy is also found in H3 conformer. In the third conformer (H2), all the atoms except hydrogen atoms are almost in same plane, therefore, the hydrogen bonding between amine group and imidazole ring will have less possibility. The zero point vibrational energy (ZPVE) is 91.11 kcal/mol, 90.99 kcal/mol and 91.33 kcal/mol for H1, H2 and H3 conformers of histamine respectively.

Optimized bond lengths, bond angles and dihedral angles in different conformers of histamine at the DFT/B3LYP/6-31++G(d,p) level and HF/6-31++G(d,p) level along with experimental values of these parameters of 2-(1H-imidazol-4-yl)-ethanaminium chloride ($C_5H_{10}N_3^+ \cdot Cl^-$) [15] are collected in Table 1. The DFT and HF values are slightly different as HF calculation does not include electron-electron interaction term. Therefore, we have discussed only DFT results. The bond lengths of the bonds N15–H16 and N15–H17 in H3

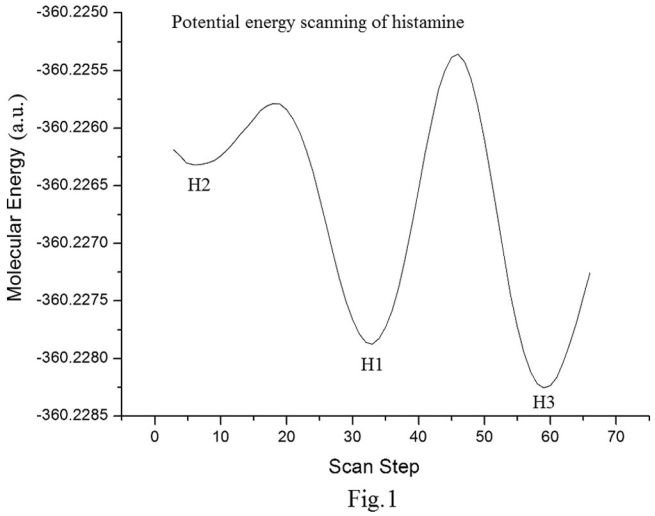

Fig. 1. Potential energy surface (PES) of histamine.