EXECUTIVE SUMMARY: UGC RESEARCH PROJECT [41-880/2012 (SR)]

'Conformational properties, Spectroscopy, and Photochemistry of the Isolated Neurotransmitters in the Biological Environment'

Principal Investigator: Dr VIPIN BAHADUR SINGH

Neurotransmitters Dopamine and Serotonin are central power drivers for multiple brain functions, including voluntary movement**, behavior, cognition, emotion, reward, motivation, learning, mood, and sleep.** Low serotonin/dopamine levels or **dysfunctions are considered to lead to neuropsychiatric disorders such as Parkinson's disease, schizophrenia, bipolar disorder, depression, addiction, aggressive behavior, anxiety, etc.** The more precise knowledge of the flexible conformation and spectroscopy of such ethylamino **neurotransmitters provide an understanding of these highly specific and intricate neurobiological mechanisms at the molecular level. In the present research project,** we have re**investigated** the lowest energy structures and computational IR, Raman, and UV spectra of these **neurotransmitters, Dopamine, and Serotonin,** including Histamine, 2-Phenylethylamine, and similar biomolecules: Melatonin, Glutamic acid, Glycine, caffeine, theophylline **in the gas phase/aqueous solution using high-level first-principle calculations.**

The twenty-three lowest energy structures of neutral Serotonin and most stable forms of protonated Serotonin have been investigated. The MP2, CC2, and DFT calculations predict that the Gph-out/anti conformation of neutral Serotonin is the most stable, which agrees with the experiment. The OH bending fundamental's intensity provides a useful diagnostic for the 5-OH anti and syn conformations. The infrared alkyl CH stretch fundamentals are assigned, which are found to be the most sensitive to conformational changes due to the ethylamine side chain in neutral Serotonin. **The computed hydrogen bond geometries of the observed Serotonin-Water complex: $Sero_1$-$(H2O)_1$ and $Sero_1$-$(H2O)_2$ are found in remarkable agreement with the experiment** (See Fg. 1)**. The $Sero_1$-$(H2O)_2$ complex involving the Gph(out) conformation is used to form a strong water dimer bridge to the 5-OH with a binding energy of 104 KJ/Mol.** The low-lying excited states of each observed conformer of Serotonin show the coexistence of the blue and redshift of the vertical excitation energies of the ^1L_b (ππ*) and the ^1L_a (ππ*) state upon forming a complex with water. **The lowest excited state (^1L_b) of the most stable $Sero_1$-$(H2O)_1$ structure shows a significant shift of 1.15 Å of water molecule towards the 5-OH group due to S0-S1 electronic excitation.** The MP2 and DFT studies of various lowest energy structures of Protonated Serotonin provide more physical insight in interpreting the experimental IRMPD spectra and their conformational preferences in the aqueous solution. **The strength of intra-molecular Cation (NH3+)- π interaction in the lowest**

energy, g-1, and g+1, gauche conformers is found very high, and solvated cation NH_3^+ retains their attractive character in the aqueous solution.

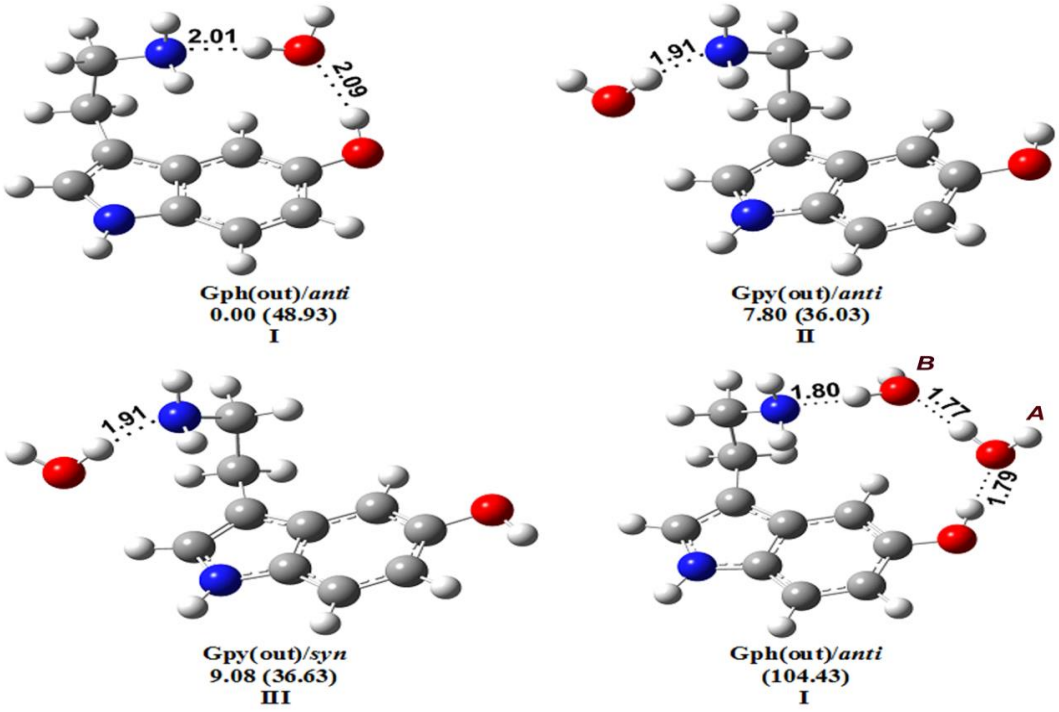
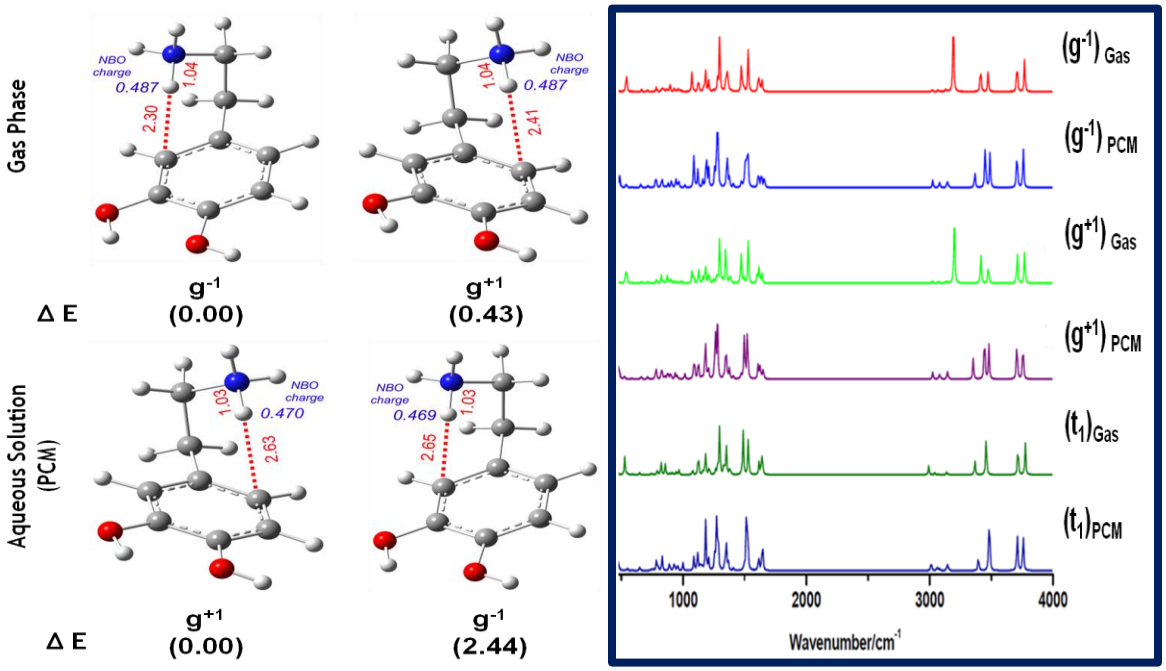


Fig. 1 Computed optimized structures, relative energies and binding energies (in parenthesis) (in kJ/mol) for the observed SERO-$(H_2O)_1$ [**I-III**] and SERO-$(H_2O)_2$ [**I**] clusters at MP2/6-311++G(d,p) level of theory.

The twenty lowest energy (isolated) structures of neutral dopamine and nine lowest energy forms of protonated dopamine (DAH+) are re**investigated by MP2 and DFT/DFT-D3 methods,** employing a higher basis set in both gas and aqueous phases**. The gauche conformers, GIa ('non up' structure)), and GIIa & GIIc ('up' structures) are predicted to be the most stable conformers of neutral dopamine in the gas and aqueous phase, respectively.** Computed fundamental mode vibrations due to the OH, NH2, aromatic CH, and alkyl CH stretching modes of each conformer are assigned well. The two hydroxyl stretching modes' frequency and intensity are almost unchanged in all the conformers of neutral DA; however, wavenumbers of NH stretching modes for the 'up' conformer from the 'non up' conformer were found shifted to be about 8-10 cm^{-1}**. Interestingly the symmetric CH2 (alkyl CH) stretching vibrations were appreciably changed by 62-68 cm^{-1} for the 'up' conformers from the 'non up'** conformers. **In biological environment,** the **trans-isomer t1 of the protonated Dopamine (DAH^+) is higher in energy than most stable gauche isomer g+1 by 6.4 and 5.7 kJ/mol** at the MP2 and B3LYP-D3 levels of theory, respectively. The gauche (g) conformers of protonated **Serotonin and Dopamine are stabilized by**

cation−π interactions; this interaction's strength is higher in Serotonin. The dispersion corrected DFT evaluation of anharmonicity allows us to confirm most experimental IRMPD frequencies and suggest many new interpretations. Conformer specific MP2/aug-cc-pVDZ frequencies computed for the first time are consonant with the intense Raman band observed at 750 cm^{-1} indicating that the trans conformer t1 might be favorable in the bulk liquid and solid phases. The aqueous-phase gauche population ratio of DAH+ is estimated to be more than 80%. **The solvated cation NH_3^+ retains its attractive character, supporting NH3+- π interaction in the active states' of dopamine receptors.** Present Raman spectroscopic analysis in conjunction with previous studies expect that all three conformers of DAH^+, g-1, g+1, and t1, **might coexist in the conformational equilibrium of extracellular fluid of synaptic cleft between neuron cells and may exhibit population redistribution upon a change in pH, in different physiological conditions.** A more precise experimental **measurement for the population distribution of gauche and trans conformers in the synaptic cleft's physiological conditions and at the dopamine receptors might be required to figure out the underpinnings of dysfunction in dopamine neurotransmission.**

Fig 2. *Left side* (a) Optimized structures of the DAH^+ isomers $\mathbf{g^{-1}}$ and $\mathbf{g^{+1}}$ in the gas phase and in aqueous solution (PCM). *Right side* (b) Computed IR spectra of the DAH^+ isomers $\mathbf{g^{-1}}$ **(g-1),** $\mathbf{g^{+1}}$ **(g+1)** and $\mathbf{t_1}$ **(t1)** in the gas phase and in aqueous solution (PCM)



The precise determination of **spectral signatures and structural motifs of the stable conformers of the Melatonin, neutral and protonated Histamine and 2-phenyl ethylamine, Monomers, and dimers of Glycine, Glutamic acids, etc. provide many valuable results.** The MP2, CC2, and DFT (using M06-2X, ωB97X-D functionals) predict that the Gph (trans-in)/anti (C) is the most stable conformer of the neutral melatonin, which is in agreement with the experiment. The amide NH stretch fundamental is found to provide the most evident basis of a distinction between the five most stable melatonin conformations**. The second-lowest singlet excited state ^1L_a ($^1\pi\pi^*$) is located about 2807 cm^{-1} above the ^1L_b state in the melatonin B**. MP2/aug-cc-pVDZ optimization yields the gauche conformer 1G-IVa (A)/g1 to be the global minimum on the potential in the aqueous solution, with the energy gap of 3.95 kJ mol-1 and 6.68 kJ mol-1 to the related 3G-Ic (B) and 3G-Vc (D)/g3 isomers respectively of the neutral histamine. **The 1G-IVa (A)/g1 conformation of neutral histamine forming complex with a water molecule based on MP2/aug-cc-pVDZ level optimization shows that the water bound to the Nτ atom of imidazole ring is the most stable of the three hydrogen bonding possibilities**. A particular feature of protonated histamine (histamine H$^+$) involves the possibility of several gauche isomers to form intra-molecular NH(+)···N hydrogen bonds, which lead to additional stabilization concerning the corresponding trans isomers in the gas phase. Computed fundamental mode vibrations due to alkyl CH stretching modes of histamineH+ are well predicted between 3013 - 3081 cm^{-1}. The highest occupied molecular orbital (HOMO) of Dopamine and Histamine is also found to be a π-orbital. Its electron density is localized mainly on the C-C fragments of the aromatic ring. **The lowest singlet excited state of these species is of ππ* character**. The **CC2 and B3LYP-TDDFT approach more accurately characterize the low-lying excited states of caffeine and theophylline**.

Paper Published in Peer Reviewed International Journals:

1. Spectroscopic signatures and the cation- π interaction in conformational preferences of the neurotransmitter dopamine in aqueous solution.Vipin Bahadur Singh, ACS Chem NeuroScence (accepted) 2020. I.F: 4.4; DOI: https://dx.doi.org/10.1021/acschemneuro.0c00597

2. Spectroscopic signatures and structural motifs in isolated and hydrated serotonin: a computational study;S K Srivastava and Vipin Bahadur Singh, RSC Adv 5, 28141 -28157 (2015). Citation 6, I.F: 3.1

3. Spectroscopic signatures and structural motifs in isolated and hydrated theophylline: a computational study, Vipin Bahadur Singh, RSC Adv 5, 11433 -11444 (2015). Citation 8, I.F: 3.1

4. Spectroscopic signatures and structural motifs in isolated and hydrated caffeine: a computational study; Vipin Bahadur Singh, RSC Adv 4, 58116- 58126 (2014). Citation 5, I.F: 3.1

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