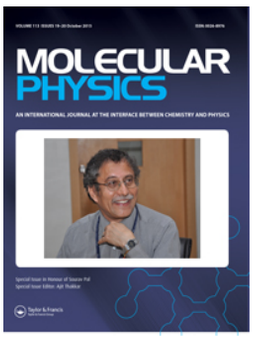

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INVITED ARTICLE

Relative stabilities and the spectral signatures of stacked and hydrogen-bonded dimers of serotonin

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The O–H···N hydrogen-bonded dimer of serotonin is shown to be more stable than the stacked dimer in its ground electronic state, by using the Møller–Plesset second-order perturbation theory (MP2) and the 6–31g** basis set. The vertical excitation energy for the lowest $\pi \rightarrow \pi^*$ transition for the monomer as well as the dimer is predicted by time-dependent density functional theory. The experimentally observed red shift of excitation wavelength on oligomerisation is explained in terms of the change in the HOMO–LUMO energy gap due to complex formation. The impact of dimer formation on the proton magnetic resonance spectrum of serotonin monomer is also examined.

Keywords: serotonin dimer; conformer stability; hydrogen bond and stacking; absorption maxima; proton NMR chemical shift

1. Introduction

Serotonin (5-hydrxoytryptamine) is a neurotransmitter of immense biological importance [1]. It plays a vital role in the regulation of mood, sleep and appetite [2–4]. It plays a key role in heart disease and asthma [3] as well. Imbalances of serotonin in the body can result in migraine, depression and exhaustion. Hence, the study of the most stable monomer of serotonin and its oligomers has been of interest in the past few decades.

Serotonin in its monomeric form is expected to react with the receptors in the postsynaptic cell [5]. It is present in hundreds of millimoles/litre concentration in neurotransmitter vesicles. At this high concentration, serotonin is thought to undergo oligomerisation. Mourik and Emson [6] explored the conformational landscape of serotonin at the density functional theory (DFT) level using the B3LYP functional and the $6-31+G^*$ basis set by varying the three dihedral angles and the position of the OH group. The three dihedral angles define the position of the side chain, amino group and the orientation of the amino group lone pair. They assigned the vibrational frequencies for all twenty three conformers. There has been a controversy in the literature regarding the orientation of the side chain of serotonin. While there are studies that show that the side chain prefers to be out of plane of the molecule, some semi-empirical studies on tryptamine derivatives [7] and melatonin [8] show a preference for the side chain to be in the plane of the molecule. The conformational flexibility of the ethyl amine side chain plays a vital role in its binding to receptor sites and is important in drug design. The structure and vibrational spectra of serotonin have been investigated by Bayari et al. [9] by molecular mechanics, semi-empirical (PM3), Hartree–Fock (HF) and DFT methods. The resonant two photon ionisation (R2PI), laser-induced fluorescence (LIF), UV–UV hole-burning and resonant ion-dip infrared (RIDIR) spectra of isolated serotonin cooled in a supersonic expansion have been studied by LeGreve et al. [10]

Maiti and co-workers investigated the fluorescence and the proton nuclear magnetic resonance (NMR) spectrum of serotonin at intravesicular concentrations [11]. They investigated the spectra of serotonin at different concentrations and found that the monomer exhibits two absorption peaks (270 and 340 nm) [12]. An excitation scan at larger concentrations, where oligomers are expected to be formed, shows a considerable red shift in the vertical excitation wavelength maxima. This helps in the multiphoton imaging of the serotonin vesicle and is important in recognition of the oligomers in cell conditions [13,14]. Therefore, in the present work a detailed investigation of the structure and stability of serotonin monomer and dimer has been undertaken. A time-dependent density functional theoretic (TDDFT) [15,16] study has been carried out to examine the vertical excitation of serotonin monomer and dimer in their ground electronic states. A detailed investigation involving

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the orbital energies accounts for the observed red shift of the absorption maximum.

2. Methodology

The ground electronic state geometry of the monomer and different configurations of the dimer, stacked conformer A with the OH groups anti-parallel to each other, conformer B with a hydrogen bond between the pyrrole N and H of the amino group and conformer C with a hydrogen bond between the pyrrole N and H of the hydroxyl group was optimised at the Møller–Plesset second-order perturbation theory (MP2/6–31g(d, p)) level using the 6–31G(d, p) basis set. The moderate-sized basis set was chosen to keep the calculations manageable with the available computational resources. Frequency calculations at the same level of theory with the same basis set were not possible for the dimer. The stabilisation energy (ΔE_s) of the dimer is defined as $\Delta E_s = E_{\text{dimer}} - 2E_{\text{monomer}}$. The resulting ΔE_s values were corrected for basis set superposition error counterpoise correction using the counterpoise method of Boys and Bernardi [17]. Vertical excitation energy values for the monomer and the dimer were calculated using the TDDFT methodology for the MP2/6–31g(d, p) optimised geometry. All MP2 and TDDFT calculations were carried out using the GAUSSIAN 03 suite of programmes [18]. For visualisation purposes, GaussView was used [19].

Proton NMR shielding tensors (σ) were calculated using the Gauge Independent Atomic Orbital (GIAO) method [20] at the same level of theory as mentioned above. A recent study [21] has made it clear that changes in chemical shift can be predicted reliably in a basis set independent fashion. Therefore, a medium size basis set like 6–31G(d, p) is considered adequate to predict the chemical shift values for larger systems with a reasonable accuracy. The ^{1}H NMR shielding tensor of the reference compound tetramethylsilane (TMS) was also calculated at the same level of theory (MP2/6–31G (d, p)) using the GIAO method. The proton chemical shift was computed by taking the difference between the isotropic shielding value for the proton in TMS and that in the compound under investigation.

3. Results and discussion

3.1. Molecular electrostatic potential map

The most stable geometry of the ground electronic state of serotonin monomer along with the molecular electrostatic potential (MEP) map obtained with the self-consistent-field (SCF) electron density with an isosurface value of 0.01 e/au^3 is plotted in Figure 1. The blue colour denotes regions of strong positive potential and the red colour denotes regions of negative potential. The yellow colour represents an intermediate potential. It becomes obvious that serotonin dimer may not prefer a T-shaped geometry as the central part of the molecule shows a weak electrostatic potential.

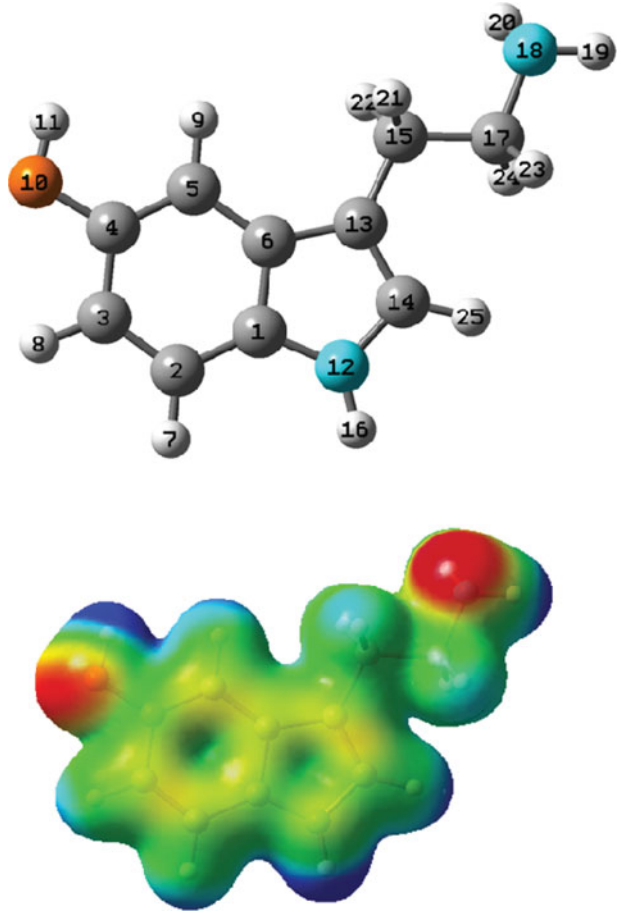

Figure 1. The most stable geometry of the ground electronic state of serotonin monomer at the MP2/6–31g** level of theory along with the molecular electrostatic potential map from total MP2 density mapped with the SCF electron density (isosurface value = 0.01 e/au^3). The red and blue regions indicate the negative and positive parts of the electrostatic potential, respectively, while the yellow and green regions show an intermediate potential.

An attempt to form a T-shaped dimer geometry with two H atoms of the NH_2 group of one serotonin molecule pointing towards the benzene ring of the other ended up in a more stable in-plane hydrogen-bonded geometry. The MEP map of serotonin explains its tendency to form a hydrogen-bonded dimer in which the N atom of the amino group behaves as an acceptor and the pyrrole nitrogen or the hydroxyl oxygen acts as the donor.

3.2. Monomer

Selected geometrical parameters of serotonin monomer are listed and compared with the experimental results in the supplementary Table 1 (ESI). The bond length values for indole N–H and C-O are overestimated by 0.095 Å and 0.007 Å, respectively while the O–H bond length is underestimated by 0.045 Å. The theoretically computed bond angles are close to the experimental values. The dihedral plane

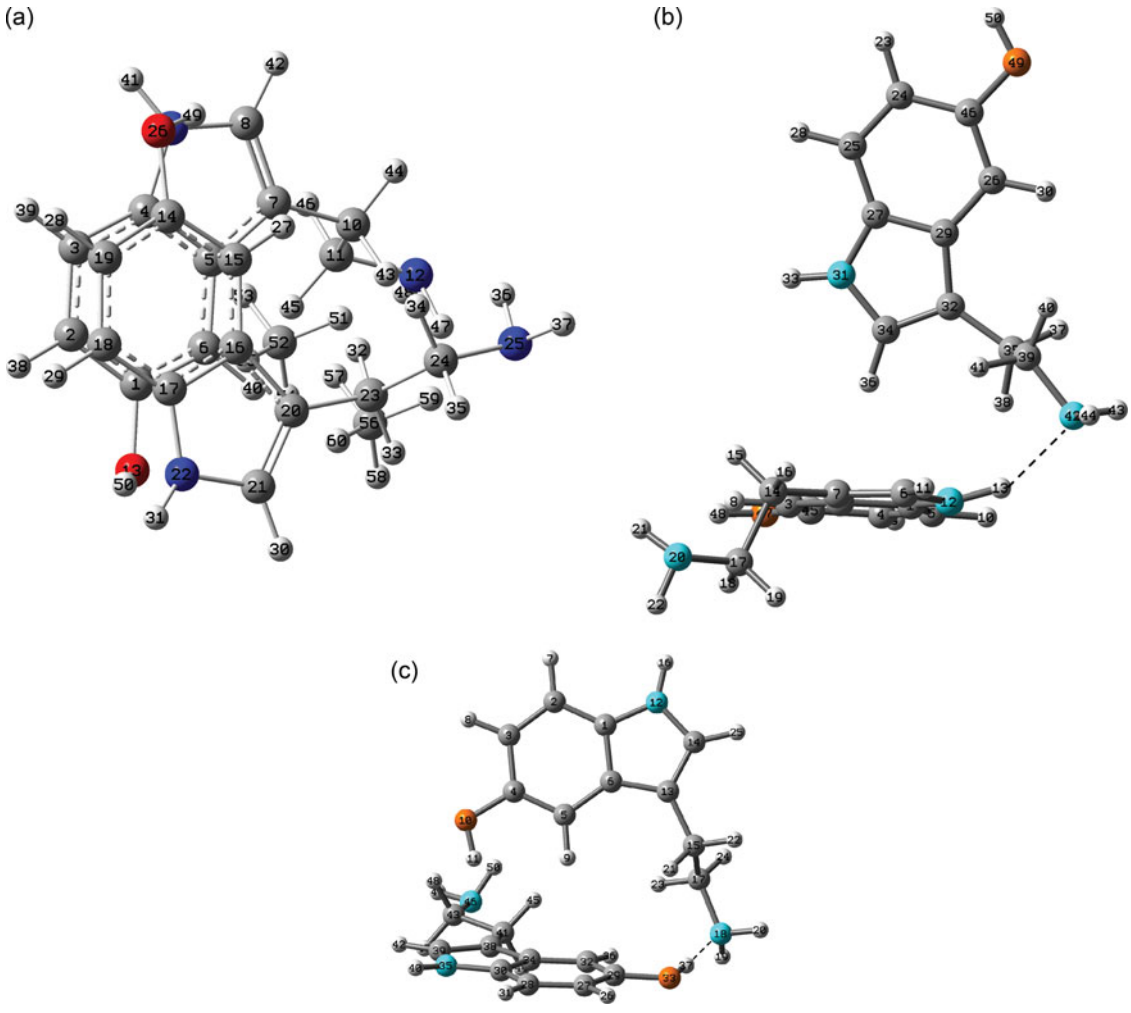

Figure 2. Optimised geometry of (a) the stacked dimer A in which the benzene rings are slipped from each other and the two hydroxyl groups are antiparallel to each other, (b) the T-shaped hydrogen-bonded dimer B, where the pyrrole NH makes a hydrogen bond with the amine NH_2, and (c) the T-shaped hydrogen-bonded dimer C, where the hydroxyl OH makes a hydrogen bond with the amine NH_2. The numbering in this figure is different from that in Figure 1.

($D_{C13C15C17N18}$), which determines the position of the amino group and $D_{C6C13C15C17}$ (°), which determines the position of the side chain are also very close to the experimentally obtained values. The crystal structure of serotonin picrate monohydrate reveals the dihedral angle ($D_{C13C15C17N18}$) to be –67° [9]. An analysis of the potential energy curve for this dihedral angle shows that serotonin can be crystallised in different conformations. The ethyl amine side chain is in an extended transplanar conformation. The all positive vibrational frequencies of the structure were an added evidence for the geometry to be a true minimum.

3.3. Dimer

The MEP map for serotonin monomer shows that the H atom of the pyrrole N–H and the hydrogen atom of O–H are electropositive, while the O atom of the O–H and the N atom of the amino group are negative sites. Hydrogen-bonded dimers involving N–H (pyrrole)···NH_2 (amino) (B) and O–H···NH_2 (amino) (C) were considered along with the stacked dimer geometry (A). The optimised geometry of different dimers is shown in Figure 2.

3.3.1. Dimer A

Efforts to optimise the geometry of serotonin dimer, keeping the O–H groups in the two monomers parallel to each other in a stacked configuration was not successful because of the unfavourable interaction between the dipole moment vectors. The other stacked geometry, where the two OH groups are anti-parallel to each other showed a very slow rate of convergence due to the shallow potential energy surface. In the stable configuration, the monomers are slipped from each other. The distance between the centres of the two benzene rings is 3.40 Å and the centre-to-centre line makes an angle of 81.92° with C14. Furthermore, the monomers

are not exactly parallel to each other; they are a bit tilted, making an angle of ∼27°. The striking feature of this conformer is the non-planarity of the hydrogen atom of the O–H group with respect to the plane of the benzene ring as it makes a weak hydrogen bond with the N atom of the pyrrole ring. This is confirmed by a ∼0.003 Å increase in the O–H bond length in the dimer when compared to the monomer. The $\angle C_{14}O_{26}H_{49}$ is 106.56° and $\angle C_1O_{13}H_{50}$ is 106.36°. The $\angle O_{26}H_{49}\cdots N_9$ is 131.39° and $\angle O_{13}H_{50}\cdots N_{22}$ is 146.07°. The $H_{49}\cdots N_9$ and $H_{50}\cdots N_{22}$ distances are 2.42 and 2.43 Å, respectively. Conformer A is found to be stable by 5.10 kcal/mole relative to the monomer.

3.3.2. *Dimer B*

The MEP of serotonin suggests the possibility of formation of a dimer with the pyrrole NH···N (amine) hydrogen bond. The BSSE corrected stabilisation energy of such a structure (conformer B) is found to be 10.41 kcal/mole. Clearly, the hydrogen-bonded dimer B is more stable than the stacked dimer A, at least in the gas phase. The conformer B has a nearly T-shaped geometry with a hydrogen bond between the pyrrole NH and the amine NH_2 ($N_{12}H_{13}$ and N_{42}). The NH···N distance is 2.003 Å and the ∠NH···N is 149.85°. The pyrrole H atom goes out of plane with an angle of 124.68° ($\angle C_1N_{12}H_{13}$). The bond length of N_{12}–H_{13} increases by ∼0.02 Å in going from the monomer to the dimer indicating the formation of a hydrogen bond. The H_{36} atom faces towards the benzene ring and the $C_{34}H_{36}\cdots R$ distance is 2.45 Å with an angle of 158.18°. Therefore, a weak CH···π interaction can be considered to exist in this structure.

3.3.3. *Dimer C*

Another hydrogen-bonded dimer (C) was found to be stable with a hydrogen bond between the OH in one monomer and the NH_2 group in the other ($O_{33}H_{37}$ and N_{18}). It has a T-shaped geometry. The OH···N distance is 1.826 Å and ∠OH···N is 171.46°. The $O_{33}H_{37}$ bond length increases by 0.025 Å, while the $O_{10}H_{11}$ distance shows an increase of 0.008 Å suggesting a weak interaction. The H atom of the hydroxyl group is nearly in the molecular plane. The H_9 and H_{11} atoms face towards the benzene and the pyrrole rings with $H_9\cdots R$ and $H_{11}\cdots R$ distances of 3.16 Å and 2.53 Å, respectively. The corresponding angles are 165.96° and 170.37°. Therefore, two weak interactions exist in this conformer. The stabilisation energy for the conformer C is −16.13 kcal/mole, the largest among the three conformers considered.

3.4. *Vertical excitation energy*

Serotonin monomer is known to have an absorption maximum at 270 nm. Maiti and co-workers examined the excitation wavelengths at different concentrations of serotonin.

Table 1. Vertical excitation wavelength computed by the TDDFT/B3LYP method using the 6–31g** basis set for the serotonin monomer and three different conformers of the dimer A, B and C.

System	Excited states	Excitation wavelength (nm) TDDFT/B3LYP	Absorption maximum (nm)	Oscillator strength (f)
Monomer	S_1	285.6	270 [11]	0.0562
	S_2	268.4		0.0882
Dimer A	S_1	317.8		0.0008
	S_2	294.9		0.0445
	S_3	285.3		0.0157
Dimer B	S_1	294.8		0.0043
	S_2	291.3		0.0197
	S_3	288.8		0.0643
Dimer C	S_1	293.9 nm		0.0713
	S_2	290.1 nm		0.0249
	S_3	288.5 nm		0.0211

At higher concentrations, where serotonin is expected to form oligomers a new excitation peak at ∼340 nm has been located [12]. This red shift in the vertical excitation wavelength with an increase in the concentration due to possible oligomerisation has been rationalised from a molecular orbital energy analysis. The red shift in the absorption peak becomes an important signature of the oligomers in the UV region.

The optimised geometry of the monomer was used to calculate the excitation wavelength by the TDDFT method using the B3LYP functional. The first excited state (S_1) of serotonin arises from the HOMO → LUMO ($\pi \rightarrow \pi^*$) excitation. The computed vertical excitation wavelength is in reasonable agreement with the experimentally observed value as illustrated in Table 1.

A TDDFT calculation for the stacked dimer indicates that the absorption maximum is red shifted in going from the monomer to the dimer. That the hydrogen-bonded dimer also exhibits a red shift in the vertical excitation wavelength can be explained by the change in the HOMO–LUMO energy gap. The doubly degenerate HOMO of the monomer splits into two due to the monomer-monomer interaction while forming the dimer. The HOMO of the dimer shows a destabilisation effect, while the LUMO shows a negligible stabilisation effect. Therefore, there is a decrease in the HOMO–LUMO energy gap on dimer formation.

HF calculations are known to overestimate the HOMO–LUMO energy gap. However, they can provide an insight into the factors influencing the energy gap. The energy difference between the HOMO and the LUMO in the monomer of serotonin is 10.94 eV. This decreases to 10.36 eV in dimer A and 10.62 eV and 10.71 eV in dimers B and C, respectively. The decrease is clearly the largest for the stacked dimer A. This decrease in the HOMO–LUMO energy gap is expected to be more pronounced in the solution phase

due to the stabilisation of the LUMO by solvation. This decrease in the LUMO energy level will cause the absorption peak to shift to a longer wave length and the resulting red shift in the absorption maximum can help in detecting the oligomers at higher concentrations.

3.5. NMR analysis

The effect of stacking interaction and the CH$\cdots\pi$ interaction on the ^{1}H NMR spectra of aromatic systems has been investigated both theoretically [22] and experimentally [23].

3.5.1. Serotonin monomer

The serotonin molecule contains five aromatic protons, four aliphatic protons, two aliphatic amine protons and one aromatic hydroxyl proton as shown in Figure 3. The proton NMR isotropic shielding tensor of TMS is computed to be 31.95 ppm at the MP2/6–31G(d, p) level of theory. In comparison, the computed chemical shift values of aromatic protons lie in the range 7.40–6.78 ppm. The aromatic –NH proton and the -OH proton labelled as '4H' and '9H' in Figure 3 show peaks at 7.40 and 3.49 ppm, respectively. Four alkyl protons (–CH_2) and two aliphatic amine (–NH_2) protons are found to lie in the lower chemical shift value region, i.e. 2.59–3.17 ppm and 0.22–0.79 ppm, respectively. The proton NMR isotropic chemical shift values are listed in Table 2. In an experimental NMR spectrum recorded by Nag *et al*. [11], only seven protons gave a clear signature.

3.5.2. Serotonin dimer

As discussed earlier, three conformers have been considered for the dimer, of which one is stacked and other two are hydrogen bonded. In the stacked dimer (A) of serotonin, the –NH proton (proton 4) is shifted upfield by ~0.47 ppm. The isotropic proton chemical shift values of the stacked serotonin dimer are listed in Table 2. The aromatic protons (2, 3 and 5) are upfield shifted, i.e. lower chemical shift values but the proton in the pyrrole ring (proton 1) is downfield shifted (larger chemical shift value). Changes in the chemical shift values are relatively more for the aromatic protons attached to the benzene ring than for the protons in the pyrrole ring. This could be explained on the basis of the benzene parts being stacked over each other and showing upfield shifts. The alkyl proton '6H' shows a downfield shift, whereas the '7H' proton shows an upfield shift.

In the hydrogen-bonded dimer B, the 4H proton (pyrrole –NH) of one serotonin shows a downfield shift with $\Delta\sigma = 4.71$ ppm. The amine protons of the other serotonin moiety show an increment with $\Delta\sigma = 0.73$ and 0.34 ppm. The 1H proton of the latter moiety is involved in the NH$\cdots\pi$ interaction and is upfield shifted with $\Delta\sigma = 2.64$ ppm. Interestingly, the aromatic and alkyl protons of one serotonin moiety move to larger chemical shift values, whereas the

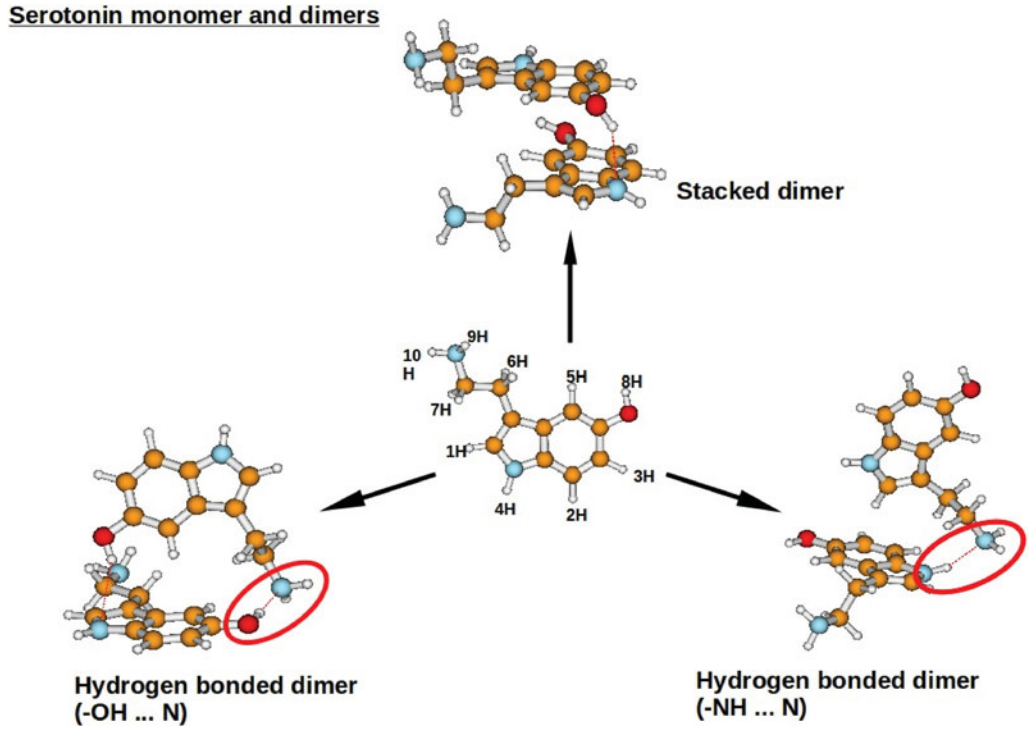

Figure 3. Labelling of protons in the optimised geometry of serotonin monomer and the dimer. The numbering in this figure is different from that in Figures 1 and 2.

Table 2. Values of proton chemical shift (δ) for serotonin monomer and three different conformers of the dimer.

	Aromatic					Alkyl		Hydroxyl	NH2	
Protons	1H	4H	2H	3H	5H	6H	7H	8H	9H	10H
Monomer	**6.78**	**7.39**	**7.31**	**7.16**	**6.94**	2.98, 2.59 **2.79**	3.05, 3.17 **3.11**	**3.49**	**0.22**	**0.79**
Dimer A	Aromatic					Alkyl		Hydroxyl	NH2	
Protons	1H	4H	2H	3H	5H	6H	7H	8H	9H	10H
Moiety 1	6.94	6.73	7.1	6.92	4.98	2.64, 2.94	2.82, 2.29	3.68	0.26	0.63
Moiety 2	7.1	7.1	6.74	5.79	7.16	2.97, 3.30	3.31, 2.42	2.43	0.41	0.73
Averaged Chemical Shift	**7.02**	**6.92**	**6.92**	**6.35**	**6.07**	2.81, 2.97 **2.89**	3.07, 2.36 **2.72**	**3.06**	**0.34**	**0.68**
Dimer B	Aromatic					Alkyl		Hydroxyl	NH2	
Protons	1H	4H	2H	3H	5H	6H	7H	8H	9H	10H
Moiety 1	7.06	12.1	7.73	7.27	7.07	2.61, 2.84	3.16, 2.41	3.53	0.2	0.68
Moiety 2	4.14	6.87	6.98	6.44	7.17	2.62, 2.66	3.29, 1.81	3.21	0.95	1.13
Averaged Chemical Shift	**5.6**	**9.48**	**7.36**	**6.86**	**7.12**	2.62, 2.75 **2.69**	3.23, 2.11 **2.67**	**3.37**	**0.58**	**0.91**
Dimer C	Aromatic					Alkyl		Hydroxyl	NH2	
Protons	1H	4H	2H	3H	5H	6H	7H	8H	9H	10H
Moiety 1	6.86	7.25	7.13	6.91	6.92	3.38, 2.52	3.53, 2.81	4.26	1.53	1.04
Moiety 2	7.07	7.66	7.44	7.33	7.57	3.02, 2.71	2.97, 3.54	10.78	0.64	0.01
Averaged Chemical Shift	**6.96**	**7.46**	**7.29**	**7.12**	**7.25**	3.20, 2.62 **2.91**	3.25, 3.18 **3.22**	**7.52**	**1.09**	**0.53**

Note: The numbers in bold font refer to average values, when there are more than one proton of the same label.

same protons in the other moiety move to lower chemical shift values. Chemical shift values for the individual moieties and the average chemical shift values are reported in Table 2.

In the hydrogen-bonded dimer C, a significant downfield shift occurs for the aromatic hydroxyl proton ($\Delta\sigma$ = 7.29 ppm) of one moiety and the aliphatic –NH_2 proton of the other moiety ($\Delta\sigma$ = 1.31 and 0.25 ppm). As pointed out earlier, the proton involved in hydrogen bonding exhibits a larger chemical shift. The isotropic proton chemical shift values are listed in Table 3. Comparing the average chemical shift values reported in Table 2 for alkyl protons with those of the monomer, a significant increment in the chemical shift values is observed in the dimer. The 5H proton of one moiety participates in a CH$\cdots\pi$ interaction. As a result, the 5H proton and other aromatic protons of the same moiety are upfield shifted. It is worth mentioning that except for the 1H and 5H protons, the variation in the average chemical shift values of the aromatic protons is nearly zero in conformer C. Computed ^{1}H NMR spectra for serotonin monomer and dimers are shown in Figure 4.

The experimentally observed chemical shift values for moderate to large concentrations of serotonin [11] suggest the presence of the dimer and larger oligomers. To compare with the experimental result, one needs to consider thermal averaging, i.e. Boltzmann distribution of all the conformers for a particular system. Understandably, the lowest energy conformer makes the maximum contribution toward the observed NMR spectrum. The average chemical shift of a system with three conformers can be defined as

$$\delta_{\text{avg}} = [\delta 1 + \delta 2 \exp(-\Delta E_2/k_B T) + \delta 3 \exp(-\Delta E_3/k_B T)]/[1 + \exp(-\Delta E_2/k_B T) + \exp(-\Delta E_3/k_B T)], \quad (1)$$

Table 3. ^{1}H NMR chemical shift (δ) values (in ppm) for the different conformers (A, B and C) of the dimer and the Boltzmann weighted average chemical shift values computed at 298 K at the MP2/6–31G (d, p) level of theory.

	δ1(C)	δ2 (B)	δ3 (A)	δ_{avg}
1H	6.96	5.6	7.02	6.96
2H	7.29	7.36	6.92	7.29
3H	7.12	6.86	6.35	7.12
4H	7.46	9.48	6.92	7.46
5H	7.25	7.12	6.07	7.25
6H	2.91	2.69	2.89	2.91
7H	3.22	2.67	2.72	3.22
8H	7.52	3.37	3.06	7.52
9H	1.09	0.58	0.34	1.09
10H	0.53	0.91	0.68	0.53

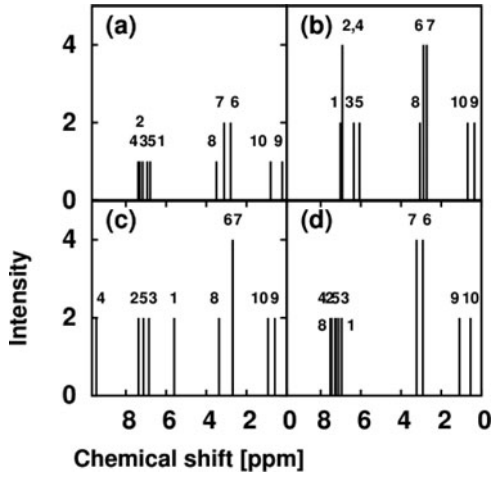

Figure 4. Computed ^{1}H NMR spectra for (a) serotonin monomer, (b) stacked dimer A, and (c) –NH···N– hydrogen-bonded dimer B and (d) –OH···N– hydrogen-bonded dimer C.

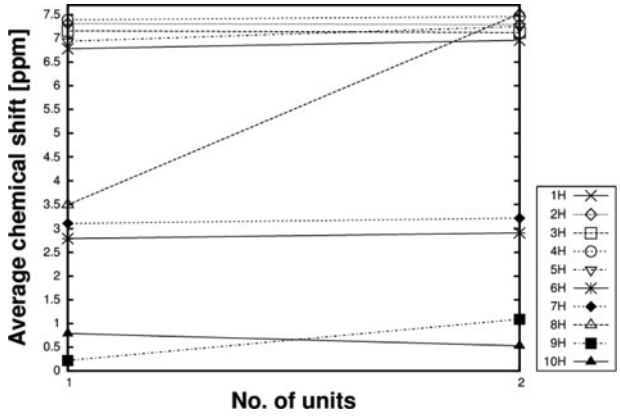

Figure 5. Variation in the Boltzmann averaged proton NMR chemical shift values in going from the monomer to the dimer of serotonin.

where $\delta 1$, $\delta 2$ and $\delta 3$ are the average chemical shift values of the conformers C, B and A, respectively, and ΔE_2 and ΔE_3 are the relative energy values for the dimers B and A, relative to the most stable dimer C. The average chemical shift values estimated at room temperature (298 K) for serotonin are listed in Table 3. It becomes clear that the average values are dominated by the conformer C.

The variation of the average chemical shift values in going from the monomer to the dimer is illustrated in Figure 5. This is a qualitative way to illustrate the effect of concentration of serotonin on its chemical shift values. It can be assumed reasonably well that with an increase in concentration, the % of dimers and larger oligomers would increase. As shown in Figure 5, protons 2H, 3H and 10H move to lower chemical shift values (upfield shifted) and others move to larger chemical shift values (downfield shifted) on dimer formation. The extent of variation in the chemical shift values is not the same for the ten different protons of serotonin. As a matter of fact, there is a crossover in the chemical shift values for certain protons in going from the monomer to the dimer. Although, experimentally, all protons 1H–7H are known to be upfield shifted, the selective formation of the stacked conformer was inferred at higher concentrations [11].

The difference between the theoretical results reported in this paper and the experimental results could also arise from the fact that our calculations pertain to molecules in the gas phase, while the experiments were carried out in solution phase.

3.6. *Energy analysis*

The stacked dimer of serotonin is found to be energetically less stable than the hydrogen-bonded dimers (Table 4). The energy of a system computed at the MP2 level of theory is generally expressed as a sum of the HF and correlation energies. The stabilisation energy can also be decomposed along these two factors. Therefore, we obtain

$$\Delta E = \Delta E^{\mathrm{HF}} + \Delta E^{\mathrm{COR}}. \qquad (2)$$

The first term in the right-hand side of Equation (2) involves Columbic interaction, induction and exchange energy terms, while the second term can be decomposed into intra-system and intersystem correlation energies and a small coupling term. The intra-system correlation energy adds a correction factor to the Columbic and exchange energies and is important if the dipole moment values for the monomer at the HF and the correlated level differ considerably. The intersystem term corresponds to dispersion energy [24]. Serotonin monomer has almost

Table 4. Energy decomposition analysis for serotonin monomer and the conformers A, B and C of the dimer.

System	Dipole moment(D)	ΔE(kcal/mole)	ΔE^{HF} (kcal/mole)	ΔE^{COR} (kcal/mole)
Monomer	3.40(HF), 3.39(MP2)			
	3.39 (MP2)			
Dimer A	1.74 (MP2)	−5.10 (−14.30)	12.55 (8.36)	−17.66 (−22.66)
N−H···N (B)	1.43(MP2)	−10.41 (−16.11)	−0.175 (−2.50)	−10.23 (−13.60)
O−H···N (C)	3.15(MP2)	−16.13 (−25.40)	−3.81 (−7.97)	−12.32 (−17.44)

Note: The values in parentheses are without BSSE corrections.

identical dipole moment values at the HF and MP2 levels of theory (Table 4). Therefore, the ΔE^{COR} value can be a measure of the dispersion energy of the system.

An energy decomposition analysis indicates clearly that the stacked dimer is stabilised due to correlation energy. Dispersion energy plays a very important role in all the dimers. The hydrogen-bonded dimers have a HF stabilisation energy that originates from purely electrostatic interactions or the classical hydrogen bonding. Dimer C has a stronger hydrogen bond than the dimer B. In addition to the classical hydrogen bond, a weak CH$\cdots\pi$ and a OH$\cdots\pi$ type interactions also exist in the dimer C. They also contribute to the ΔE^{HF} term.

4. Summary and conclusion

Experimental studies had suggested possible formation of oligomers of serotonin in solution state at large concentrations [11]. From the upfield shift of the observed chemical shift, stacking interaction between monomers was suggested [25]. In the theoretical NMR study that pertains to molecules in the gas phase, we have observed both upfield and downfield shifts of protons. In addition to that, a crossover and overlapping of the proton signals are also observed in going from the monomer to the dimer. The present study shows that the hydrogen-bonded conformers are much more stable than the stacked geometry. TDDFT calculations predict the absorption maximum for the monomer nearly quantitatively and suggest that it would undergo a red shift on dimer formation.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Supplemental data

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References

[1] D.E. Nichols and C.D. Nichols, Chem. Rev. **108**, 1614 (2008).
[2] W.J. McEntee and T.H. Crook, Psychopharmacology (berl). **103**, 143 (1991).
[3] S.S. Al-Zahrani, M.Y. Ho, D.N.V. Martinez, M.L. Cabera, C.M. Bradshaw, and E. Szabadi, Psychopharmacology (berl). **127**, 346 (1996).
[4] J.R. Copper, F.E. Bloom, and R.H. Roth, *The Biochemical Basis of Neuropharmacology* (Oxford University Press, New York, 1996).
[5] M.A. Bunin and R.M. Wightman, Trends Neurosci. **22**, 377 (1999).
[6] T. van Mourik and L.E.V. Emson, Phys. Chem. Chem. Phys. **4**, 5863 (2002).
[7] M.M. Hamed, R.H. Abu-Eittah, Z. Mobarak, and M.M. Abdou, Int. J. Quantum Chem. **44**, 379 (1992).
[8] G.M. Florio, R.A. Christie, K.D. Jordan, and T.S. Zwier, J. Am. Chem. Soc. **124**, 10236 (2002).
[9] S. Bayari, S. Saglam, and H.F. Ustundag, J. Mol. Struct. (THEOCHEM). **726**, 225 (2005).
[10] T.A. LeGreve, E.E. Baquero, and T.S. Zwier, J. Am. Chem. Soc. **129**, 4028 (2007).
[11] S. Nag, J. Balaji, P.K. Madhu, and S. Maiti, Biophys. J. **94**, 4145 (2008).
[12] S.K. Kaushalya, S. Nag, J. Balaji, and S. Maiti, Proc. of SPIE. **6860**, 68601C (2008).
[13] J. Balaji, R. Desai, S.K. Kaushalya, M.J. Eaton, and S. Maiti, J. Neurochem. **95**, 1217 (2005).
[14] S.K. Kaushalya, R. Desai, S. Arumugam, H. Ghosh, J. Balaji, and S. Maiti, J. Neurosci. Res. **86**, 3469 (2008).
[15] R. Bauernschmitt and R. Ahlrichs, Chem. Phys. Lett. **256**, 454 (1996).
[16] R.E. Stratmann, G. Scuseria, and M.J. Frisch, J. Chem. Phys. **109**, 8218 (1998).
[17] S.F. Boys and F. Bernardi, Mol. Phys. **19**, 553 (1970).
[18] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, and J.A. Pople, *Gaussian 03, Revision B.05* (Gaussian, Inc., Pittsburgh, PA, 2003).
[19] R. Dennington, T. Keith, and J. Millam, *GaussView, Version 5* (Semichem Inc., Shawnee Mission, KS, 2009).
[20] R. Ditchfield, Mol. Phys. **29**, 789 (1974).
[21] J.A. Platts and K. Gkionis, Phys. Chem. Chem. Phys. **11**, 10331 (2009).
[22] M. Majumder and N. Sathyamurthy, Theor. Chem. Acc. **131**, 1092 (2012).
[23] A. Mitra, P.J. Seaton, R.A. Assarpour, and T. Williamson, Tetrahedron. **54**, 15489 (1998).
[24] P. Hobza and J. Šponer, Chem. Rev. **99**, 3247 (1999).
[25] P.R. Mitchell and H. Sigel, Eur. J. Biochem. **88**, 149 (1978).