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Theoretical study of the hydrogen-bonded complexes serotonin–water/hydrogen peroxide

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Abstract Eight H-bonded complexes between serotonin (5-hydroxy-tryptamine) and water/hydrogen peroxide were studied at the B3LYP and HF levels of theory, using the 6-31+G(d) basis set. A thermodynamic analysis was performed in order to find the most stable complex. The calculated bonding parameters showed that the most stable H-bonded complex is formed between serotonin and hydrogen peroxide by means of the intermolecular H-bond $-H_2N...H-OOH$.

Keywords Ab initio calculations · Density functional calculations · Hydrogen-bonds · 5-Hydroxy-tryptamine · Serotonin

Introduction

5-Hydroxy-tryptamine, usually known as serotonin, is a monoamine neurotransmitter, which is synthesized in serotonergic neurons in the central nervous system and enterochromaffin cells in the gastrointestinal tract [1]. Serotonin plays an important role in the biochemistry of depression, anxiety, bipolar disorder, and sexuality. It is also involved in controlling appetite, behavior, emotions, mood, sleep, and body temperature [2]. Serotonin is synthesized in the human body from tryptophan by various enzymes and released from the terminal boutons of serotonergic neurons into the neuronal synapse. There it is free to diffuse into the active serotonin receptors located on the dendrites of adjacent neurons.

The biologically active conformation of serotonin in living organisms is determined by intermolecular inter-

actions as well as interactions with its environment (water). However, the question of the most stable conformation of serotonin is still unsolved. For example, it has been found that protonated serotonin molecules prefer a strongly inclined orientation of the side chain with respect to the indole ring [3]. Isolated serotonin molecules have a completely different configuration [2]. The interest in conformational studies is fueled to some degree by the growing accuracy of quantum-chemical calculations on large molecules with more than one moving part of the molecule. A great number of theoretical papers treating the conformational landscapes of serotonin and tryptamine have been published [2, 4–8]. However, there is no information on the most appropriate conformation of the side chain for H-bonding with water and other small protic molecules. It has been shown (by B3LYP/6-31+G(d) calculations) that the *anti* orientation of the OH group (with respect to the indole NH group) is more realistic than the *syn* [2]. For the purposes of our study, we chose the conformer that has the maximum number of proton donating and accepting sites for H-bonding with water (and hydrogen peroxide). Although hydrogen peroxide is normally a very strong reagent, and should be far too reactive to participate in H-bonding, it was chosen here as a small protic molecule to compare with water.

The purpose of the current study is to explain the forces supporting the H-bonded complexes formed between serotonin and water/hydrogen peroxide in order to explain the ability of serotonin to form heavily hydrated clusters with water in living organisms.

The calculations were performed at the B3LYP [9, 10] and HF levels of theory. The 6-31+G(d) [11] basis set was used in locating the low-lying minima of the H-bonded systems. It has been reported that the combination B3LYP/6-31+G(d) yields fair agreement with experimental parameters of flexible molecules [6, 7, 12–15]. Furthermore, the B3LYP optimized geometries and energies of such flexible (adrenaline and noradrenaline) molecules are very similar to those found with the more expensive MP2 method [2]. It has been established [16]

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that higher order electron correlation corrections for H-bonding energies are usually small. There is no guarantee that the higher order terms are negligible, but there is a substantial degree of compensation of errors for H-bonding [17]. Therefore, we chose to carry out this investigation with the B3LYP functional which gives reasonable accuracy for the structural parameters.

Spöner and Hobza [18] have shown that diffuse polarization functions do not provide a significant improvement for H-bonding. However, these functions are essential for studying the stacking in aggregate structures like dimers, etc. This has been deduced from a theoretical study of several DNA base pairs. The authors report that the larger 6-311G(2d,p) basis set has no influence on the stabilization energies of the base pairs. There is an indication that diffuse functions contribute to the dispersion energy in the case of H-bonded systems [18]. A detailed description of the basis sets and the correlation energy is also given in the work of Handy and Cohen [19].

Materials and methods

Becke's hybrid three-parameter functional [11] and restricted Hartree–Fock method (HF) implemented in the Gaussian 98 program package [20] were used for studying all monomers and dimers (complexes). Both methods in combination with 6-31+G(d) basis functions were used for geometry optimizations of the molecular systems examined. Further, frequency calculations were carried out to prove that the resulting stationary points are real minima and to check the intermolecular vibrations in the H-bonded complexes. The bonding energy ΔE_b for each supersystem (complex) was estimated according to the equation [21, 22]:

$$\Delta E_b = E_{SS} - (E'_S + E'_{W/HP}),$$

where E_{SS} is the energy of the supersystem; E'_S and $E'_{W/HP}$ are the energies of the monomers (serotonin and water/hydrogen peroxide) calculated with “ghost” orbitals of the other monomer involved in the supersystem. The BSSE was evaluated using the counterpoise method [21, 23–26]:

$$\Delta(\text{BSSE}) = \sum_i^n (E_{m_i} - E'_{m_i}),$$

where E_{m_i} are the energies of the individual monomers frozen in their aggregate geometries (single-point) [27]. The serotonin–water/hydrogen peroxide interaction energy (ΔE_{int}) was calculated as the difference between the energies of the complex and isolated serotonin and water/hydrogen peroxide molecules. The difference between the energies of the complex and the deformed configurations of serotonin and water/hydrogen peroxide in the complex (ΔE) was found by single-point calculations of the monomers in their configurations, as in the corresponding supersystem.

Results and discussions

The theoretical study of the serotonin conformational landscape discussed in Ref. [2] did reveal the full picture on the rotation of the serotonin OH group. In the current paper, scan calculations were performed at the B3LYP/6-31+G(d) level to visualize the profile of the rotational energy curve, shown in Fig. 1.

The energy curve is symmetric with two in average deep minima (for the stable *anti* orientation of the OH group) and one shallow minimum corresponding to the *syn* orientation of the OH group. The rotation occurs with comparatively low-energy barrier of about 14.8 kJ mol⁻¹, as the energy difference of the two minima is about 7.6 kJ mol⁻¹.

Eight possible H-bonded systems of serotonin with water/hydrogen peroxide were fully optimized at both theoretical levels (B3LYP and HF). The B3LYP conformations are shown in Fig. 2.

The intermolecular H-bonding between the water oxygen atom and the H atom of the serotonin OH group leads to the formation of the SER-W1 supersystem. This intermolecular H-bond is determined as “medium” [28]. Like the length, the energy of the H-bond also depends on the angle O...H–O, which is predicted to be 172.3° by both methods. It should be mentioned that this kind of H-bonding does not change the dihedral angle $\angle\text{H}(11)\text{O}(10)\text{C}(1)\text{C}(2)$ drastically, since this change is only 0.3° compared to the serotonin monomer.

The formation of the supersystem SER-HP1 causes an increase in the dihedral angle $\angle\text{H}(25)\text{O}(24)\text{O}(22)\text{H}(23)$ by 1.3° according to the B3LYP calculations. The two monomers are bound by a weak (Y...H > 1.9 Å [28]) H-bond, which is 0.081 Å longer than in the SER-W1 supersystem.

The SER-W2 and SER-HP2 supersystems exhibit a hydrogen bond between OH oxygen atom from serotonin and one of the hydrogens from water or hydrogen peroxide. Here, a longer intermolecular H-bond is formed between water and serotonin: 0.075 (B3LYP)

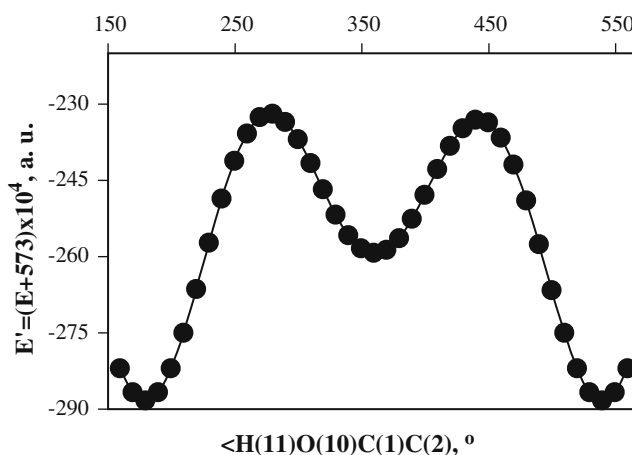
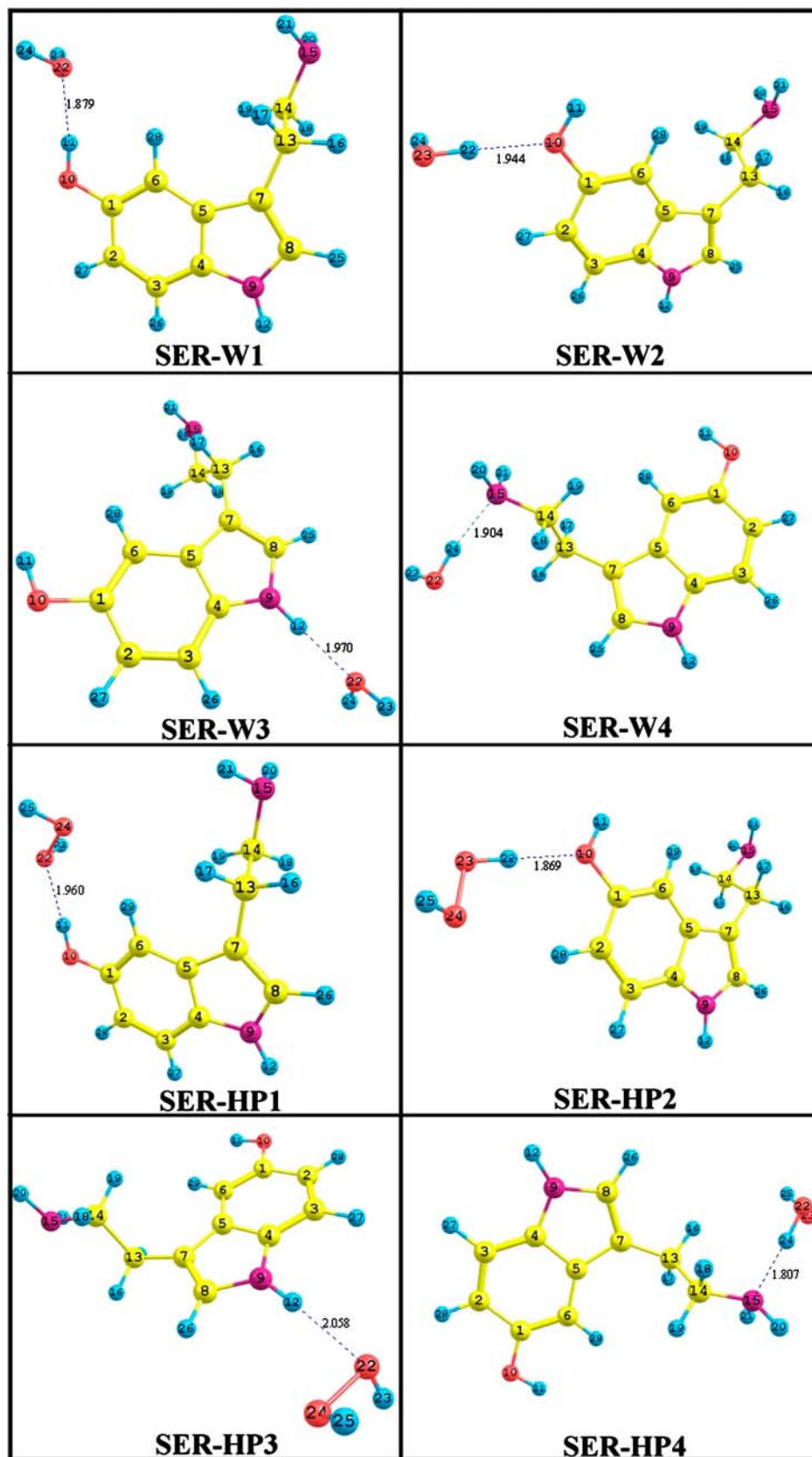


Fig. 1 Energy curve of the OH-rotation in the serotonin molecule

Fig. 2 Optimized structures [B3LYP/6-31+G(d)] of the H-bonded supersystems



and 0.088 Å (HF). Obviously, the complexation with the OH group of serotonin is strongest for the supersystem SER-HP2, which should be the most stable of the

complexes examined so far. The dihedral angle in hydrogen peroxide deviates by 8.3° (B3LYP) from its equilibrium value. In other words, the formation of H-

bonds between the hydrogen atom of hydrogen peroxide and the oxygen atom of the serotonin OH group causes partial *cis*-isomerization of the hydrogen peroxide molecule.

The monomers in the supersystems SER-W3 and SER-HP3 are held together by weak hydrogen bonds (longer than 1.9 Å). A shorter, stronger intramolecular H-bond is found in the SER-W3 supersystem than in the SER-HP3 one. However, the dihedral angle $\angle\text{H}(25)\text{O}(24)\text{O}(22)\text{H}(23)$ is 1.5° smaller than in the equilibrium structure of hydrogen peroxide.

Both methods showed that the shortest intermolecular H-bonds are found in the supersystems SER-W4 and SER-HP4, and thus these complexes should be the most stable. Moreover, the dihedral angle $\angle\text{H}(25)\text{O}(24)\text{O}(22)\text{H}(23)$ in the SER-HP4 supersystem is closest to the equilibrium dihedral angle in the free hydrogen peroxide monomer (118.1° B3LYP and 115.3° HF), with differences of only 0.7° (B3LYP) and 0.9° (HF). It was found (B3LYP) that the HOH bond angle of the water monomer in the SER-W2 supersystem is closest to its equilibrium value (in the free water monomer).

Several important structural parameters of the supersystems, obtained at the two theoretical levels, are listed in Table 1.

The data show that none of the parameters is very sensitive with respect to H-bonding, which leads to the conclusion that complex formation is not connected with drastic steric changes in the nonbonded monomers.

Thermodynamic parameters of complex formation

The energies, ZP-corrected energies of the supersystems and several thermodynamic parameters of complex formation are shown in Table 2.

Comparing the energies, both methods predicted that the supersystems SER-W4 and SER-HP4 are the most stable aggregates. High-energy supersystems are formed between the water hydrogen and the serotonin oxygen atom, and between the hydrogen peroxide oxygen and the serotonin hydrogen atom bound to the N atom of the pyrrol residue.

The B3LYP thermodynamic data (Table 2) show that all the formation of all the complexes entails a positive change of the standard Gibbs free energy. One exception is the formation of the SER-HP4 supersystem, which is thermodynamically favorable (B3LYP). The remaining complexations have a positive change of the Gibbs free energy, which means that these processes are disfavored as long as $|\Delta H| < |T\Delta S|$; in other words they are favored by increasing temperature. The not very large positive values of ΔG_{298}° indicate low-equilibrium constants (smaller than 1), showing equilibria is the gas phase shifted toward the free monomers. Only for the formation of the supersystem SER-HP4 is the equilibrium shifted toward the aggregate structure (the supersystem). The low-absolute values of ΔG_{298}° for dimers indicate that aggregation occurs, although it is entropically disfavored.

All complexations are favored enthalpically. These findings are in agreement with reported thermodynamic

Table 1 Selected structural parameters of the supersystems

	SER-W1		SER-W2		SER-W3		SER-W4	
	1	2	1	2	1	2	1	2
H...O	1.879	1.980	1.944	2.063	1.970	2.072	1.904	2.067
O(10)C(1)	1.373	1.355	1.389	1.368	1.382	1.363	1.380	1.361
H(11)O(10)	0.979	0.952	0.970	0.947	0.969	0.947	0.969	0.947
N(9)H(12)	1.008	0.993	1.008	0.993	1.016	0.997	1.009	0.993
C(14)N(15)	1.471	1.457	1.469	1.456	1.470	1.457	1.479	1.464
HOH ^{water}	105.7	106.6	105.3	106.1	106.0	106.7	106.0	106.7
N(15)H(20)H(21)	106.8	107.0	106.9	107.1	106.8	107.1	106.5	106.6
H(11)O(10)C(1)C(2)	179.3	179.1	174.9	173.3	179.5	179.4	179.3	179.1
H(12)N(9)C(4)C(5)	177.9	177.8	178.1	179.3	179.3	178.8	178.8	178.6
N(15)C(14)C(13)C(7)	179.6	179.0	-178.7	179.9	-179.3	179.6	-179.8	-179.3
	SER-HP1		SER-HP2		SER-HP3		SER-HP4	
	1	2	1	2	1	2	1	2
H...O	1.960	2.070	1.869	1.975	2.058	2.180	1.807	1.971
O(10)C(1)	1.392	1.357	1.392	1.371	1.382	1.362	1.379	1.360
H(11)O(10)	0.976	0.950	0.970	0.947	0.969	0.947	0.970	0.947
N(9)H(12)	1.008	0.993	1.009	0.993	1.014	0.995	1.009	0.993
C(14)N(15)	1.471	1.457	1.469	1.456	1.470	1.457	1.478	1.463
N(15)H(20)H(21)	106.8	107.0	106.9	107.1	106.8	107.1	106.6	106.6
HOOH ^{hydrogen peroxide}	119.4	114.1	112.0	109.8	116.6	113.9	118.8	114.4
H(11)O(10)C(1)C(2)	-179.1	-179.6	-178.8	179.0	179.6	179.5	179.4	179.3
H(12)N(9)C(4)C(5)	177.8	177.3	178.9	178.7	178.0	178.1	178.8	178.7
N(15)C(14)C(13)C(7)	-179.6	178.3	-178.8	179.9	-179.2	179.6	-172.2	-174.6

1 B3LYP/6-31 + G(d), 2 HF/6-31 + G(d)

Table 2 Energies (E) and zero-point energies (E^0) of the supersystems, and thermodynamic parameters of the complex formations, all in kJ mol^{-1} (K in Pa^{-1})

	E		E^0					
	1	2	1	2	1	2	1	2
SER-W1	-649.463851	-645.456855	-649.232052	-645.208168				
SER-W2	-649.460544	-645.453996	-649.229372	-645.205626				
SER-W3	-649.462084	-645.455440	-649.231174	-645.207521				
SER-W4	-649.466071	-645.457318	-649.233883	-645.208216				
SER-HP1	-724.586255	-720.208098	-724.586255	-719.953994				
SER-HP2	-724.588055	-720.209386	-724.352123	-719.955123				
SER-HP3	-724.584883	-720.207005	-724.349424	-719.953355				
SER-HP4	-724.593826	-720.212401	-724.357197	-719.957547				

	ΔG_{298}°		ΔH_{298}°		$T\Delta S_{298}^{\circ}$		K	
	1	2	1	2	1	2	1	2
SER-W1	7.4	9.3	-24.9	-21.5	-32.3	-30.8	0.0504	0.0234
SER-W2	9.7	13.7	-17.2	-14.6	-26.9	-28.3	0.0199	0.0040
SER-W3	6.6	8.2	-21.3	-18.7	-27.9	-26.9	0.0697	0.0365
SER-W4	2.7	8.8	-30.7	-22.3	-33.4	-31.1	0.3363	0.0287
SER-HP1	15.4	14.8	-18.4	-16.6	-33.8	-31.4	0.0020	0.0025
SER-HP2	10.2	13.1	-23.4	-19.9	-33.6	-33.0	0.0163	0.0051
SER-HP3	13.6	13.1	-15.7	-14.4	-29.3	-27.5	0.0041	0.0051
SER-HP4	-3.4	6.0	-37.9	-27.0	-34.5	-43.0	3.9445	0.0888

1 B3LYP/6-31 + G(d), 2 HF/6-31 + G(d)

data on similar H-bonded supersystems composed of guanine and water/methanol [29, 30]. Complexation leading to the formation of supersystem SER-HP4 has the largest negative entropy change. The reason may be the larger number of steric effects accompanying this complexation.

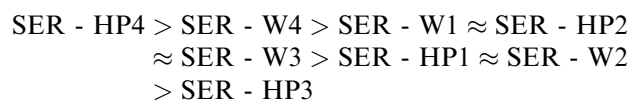
This thermodynamic analysis showed that the most stable supersystem should be SER-HP4, not only because it contains the shortest intermolecular H-bond. Similarly, the complex SER-W4 is the most stable among all water-serotonin supersystems. In general, the water supersystems are more stable than the hydrogen peroxide containing ones. The high stability of the supersystems SER-W4 and SER-HP4 is not found in the other conformers of serotonin [2]. The reason is the large steric effects and the hindrance between H-bonded molecule, amino group, and the indole ring. Furthermore, in this serotonin conformer the electron pairs of the N atom from the amino group are exposed to H-bonding to a greater extent.

Hydrogen-bonding energies and energy properties of the supersystems

All bonding parameters together with the relative SP energies of the monomers, frozen in their aggregate geometry from the relevant supersystem are listed in Table 3.

The results in Table 3 show that the absolute value of the bonding energy (ΔE_b) is the largest for the supersystem SER-HP4. Therefore, this supersystem is the most stable. This confirms the negative ΔG_{298}° value and

relates with the shortest intermolecular H-bonds in this aggregate. The SER-W4 supersystem exhibits the same features. The bonding and interaction energies (summarized in Table 3) are large enough to make it possible for each complex formation to reach the *syn* orientation of the serotonin OH group. According to the bonding-energy values (B3LYP) the following stability pattern is established for the complexes of serotonin with water and hydrogen peroxide:



The small difference between ΔE_{int} and ΔE shows that complexation is accompanied by insignificant changes in the monomer geometries during the formation of supersystems (especially for SER-W4 and SER-HP4).

The changes of BSSEs are comparatively low as compared to the bonding and interaction energies. For example, they are 16–26% of bonding energies, and 13–19% of interaction energies (B3LYP).

The SP calculations of the serotonin monomer (frozen in its geometry in the supersystem) revealed that the serotonin monomer in SER-HP4 is much less favorable than in the supersystem SER-HP3 (taken as a base for comparison). In other words, the high stability of the supersystems SER-HP4 and SER-W4 is not a consequence of the high stability of the serotonin “single-point” geometry in the supersystems.

Single-point calculations with the B3LYP optimized structures of the monomers and dimers were carried out

Table 3 Serotonin–water/hydrogen peroxide interaction energies and their components (kJ mol⁻¹)

	$E_{m_i} \times 10^2$				$E' \times 10^2$			
	SER		W/HP		SER		W/HP	
	1	2	1	2	1	2	1	2
SER-W1	28	11	0 ^c	0 ^e	120	56	0 ⁱ	0 ^k
SER-W2	19	17	8	3	162	129	209	94
SER-W3	11	9	1	0 ^e	172	116	63	58
SER-W4	15	21	93	25	1	31	309	157
SER-HP1	12	5	2	2	80	32	51	105
SER-HP2	29	20	34	17	121	91	0 ^j	0 ^l
SER-HP3	0 ^a	0 ^b	0 ^d	0 ^f	156	102	109	118
SER-HP4	71	59	165	44	0 ^g	0 ^h	202	45

	ΔE_b		ΔE_{int}		ΔE		$\Delta(\text{BSSE})$	
	1	2	1	2	1	2	1	2
SER-W1	-24.55	-21.55	-32.69	-29.16	-30.74	-26.42	6.19	4.87
SER-W2	-18.38	-15.72	-24.01	-21.66	-22.05	-19.01	3.68	3.30
SER-W3	-21.06	-19.01	-28.05	-25.45	-25.94	-22.68	4.88	3.67
SER-W4	-32.27	-24.09	-38.52	-30.38	-37.37	-27.98	5.10	3.89
SER-HP1	-18.63	-16.75	-25.52	-23.54	-23.44	-20.78	4.81	4.02
SER-HP2	-23.25	19.68	-30.25	-26.92	-28.66	-24.46	5.41	4.79
SER-HP3	-16.36	-14.71	-21.92	-20.67	-19.70	-17.84	3.34	3.13
SER-HP4	-39.21	-27.13	-45.40	-34.83	-45.53	-33.05	6.31	5.92

I B3LYP/6-31+G(d), 2 HF/6-31+G(d) The absolute energy:

^a -573.029678

^b -569.429093

^c -76.422569

^d -151.547700

^e -76.017739

^f -150.771114

^g -573.030557

^h -569.429737

ⁱ -76.424400

^j -151.549102

^k -76.019121

^l -150.772500 a.u.

was taken as conventional zero

at the MP2 level of theory and the same basis set. The calculated bonding parameters and BSSEs are given in Table 4.

The data show that the second-order Møller–Plesset perturbation theory method give the same stability pattern (according to bonding parameters) despite the higher values of ΔE_b , ΔE_{int} , ΔE , and $\Delta(\text{BSSE})$ versus those predicted at the HF and B3LYP levels. Obviously

the B3LYP and MP2 methods give the same stability order for the supersystems.

Vibrational frequencies

The experimental spectrum of serotonin in the gas phase is not known and a direct comparison between

Table 4 Serotonin–water/hydrogen peroxide interaction energies and their components (kJ mol⁻¹) found at the MP2/6-31+G(d) level

	$E_{m_i} \times 10^2$		$E' \times 10^2$		ΔE_b	ΔE_{int}	ΔE	$\Delta(\text{BSSE})$
	SER	W/HP	SER	W/HP				
SER-W1	39	0 ^b	377	0 ^c	-25.38	-43.09	-37.85	12.47
SER-W2	24	6	416	328	-18.89	-32.93	-27.60	8.71
SER-W3	6	2	413	100	-23.32	-39.68	-34.13	10.81
SER-W4	33	80	99	438	-30.52	-46.62	-42.13	11.61
SER-HP1	30	5	271	30	-21.89	-38.63	-33.97	12.08
SER-HP2	31	11	270	0 ^f	-24.97	-42.02	-37.44	12.46
SER-HP3	0 ^a	0 ^c	367	133	-20.14	-34.88	-29.88	9.74
SER-HP4	100	108	0 ^d	179	-37.31	-55.27	-52.35	15.03

The absolute energy:

^a -571.233422

^b -76.209773^c -151.145108

^d -571.235907

^e -76.213330

^f -151.148238 a.u.

was taken as conventional zero

Table 5 Vibrational frequencies (cm^{-1}) of the H-bonded complexes and their IR intensities (km mol^{-1})

SER-W1		SER-W2		SER-W3		SER-W4		Exp. ^a	Assignment
1	2	1	2	1	2	1	2		
3852/84	4177/116	3827/159	4171/207	3860/84	4183/119	3812/62	4152/131	–	$\nu_{\text{as}}\text{OH}_{\text{Wat}}$
3735/15	4065/15	3672/326	4048/198	3742/15	4069/41	3403/760	3929/419	–	$\nu_{\text{s}}\text{OH}_{\text{Wat}}$
3672/61	3926/99	3670/87	3923/104	3558/34	3862/451	3670/70	3924/89	3524	νNH
3593/594	4029/460	3764/49	4115/81	3758/579	4119/66	3758/37	4118/69	–	νOH
3559/0	3811/1	3563/0	3814/1	3560/2	3811/1	3552/2	3801/3	3405	$\nu_{\text{as}}\text{NH}_2$
3472/1	3728/0	3475/1	3730/0	3472/1	3728/0	3468/2	3721/1	3337	$\nu_{\text{s}}\text{NH}_2$
3255/2	3425/4	3259/1	3429/3	3254/3	3424/5	3261/0	3430/2	–	$\nu\text{C}_8\text{H}$
3211/12	3387/15	3215/2	3391/5	3212/11	3388/14	3216/8	3391/11	–	$\nu\text{C}_{2/3}\text{H}$
3185/6	3361/8	3167/19	3343/20	3161/25	3337/25	3162/26	3339/24	–	$\nu\text{C}_6\text{H}$
3181/20	3356/18	3190/11	3363/10	3187/13	3362/10	3186/12	3361/11	–	$\nu\text{C}_{2/3}\text{H}$
3084/43	3253/58	3086/37	3255/52	3083/40	3252/55	3099/21	3267/36	–	νCH_2
3068/21	3233/24	3071/21	3237/24	3067/22	3234/26	3084/9	3250/14	–	νCH_2
3006/37	3179/30	3008/35	3179/32	3003/41	3174/33	3007/26	3182/45	–	νCH_2
2981/64	3167/74	2971/72	3159/79	2973/70	3161/80	3005/73	3173/61	–	νCH_2
1695/40	1839/47	1697/40	1839/47	1695/40	1839/47	1684/39	1829/39	–	δNH_2
1677/96	1806/136	1689/75	1828/21	1674/86	1802/127	1713/57	1843/101	–	$\delta\text{HOH}/\text{O}_{\text{Wat}}$
1674/60	1824/63	1678/39	1826/145	1677/50	1826/54	1676/40	1826/54	–	νCC_{ph}
1639/29	1789/33	1636/37	1785/40	1635/33	1785/40	1637/35	1787/33	–	$\nu\text{CC}_{\text{ph.py}}$
1597/5	1735/9	1596/4	1735/9	1592/4	1730/13	1595/4	1734/9	–	νCC_{py}
1536/4	1662/3	1535/3	1662/2	1535/6	1662/3	1537/3	1663/2	–	δCH_2
1531/96	1653/130	1533/85	1654/124	1536/61	1660/85	1529/83	1652/123	–	νCC_{ph}
1509/57	1628/8	1508/10	1628/10	1510/68	1628/7	1512/6	1632/18	–	δCH_2
1505/33	1571/19	1503/58	1571/19	1506/24	1570/16	1504/63	1573/14	–	δCH_2
163/3	149/3	136/5	120/2	143/57	126/2	209/3	187/4	–	ν_{i}

SER-HP1		SER-HP2		SER-HP3		SER-HP4		Exp. ^a	Assignment
1	2	1	2	1	2	1	2		
3701/52	4079/106	3566/646	4024/514	3701/61	4081/121	3191/1171	3838/711	–	$\nu_{\text{as}}\text{OH}_{\text{HP}}$
3706/58	4083/23	3711/28	4094/57	3704/36	4083/58	3715/19	4095/40	–	$\nu_{\text{s}}\text{OH}_{\text{HP}}$
3671/55	3926/99	3670/70	3924/103	3592/469	3896/348	3670/71	3924/105	3524	νNH
3654/440	4070/368	3767/48	4114/81	3758/35	4118/67	3758/38	4118/71	–	νOH
3559/0	3811/1	3562/0	3814/1	3559/0	3812/1	3557/4	3803/6	3405	$\nu_{\text{as}}\text{NH}_2$
3472/1	3728/0	3475/1	3730/0	3472/1	3728/0	3475/0	3724/3	3337	$\nu_{\text{s}}\text{NH}_2$
3255/2	3426/4	3259/2	3429/3	3258/2	3430/3	3260/1	3428/3	–	$\nu\text{C}_8\text{H}$
3212/11	3387/14	3215/3	3396/1	3213/10	3389/13	3217/7	3392/10	–	$\nu\text{C}_{2/3}\text{H}$
3187/2	3363/5	3166/19	3342/20	3160/25	3337/25	3163/21	3340/22	–	$\nu\text{C}_6\text{H}$
3182/17	3356/16	3190/12	3364/12	3185/13	3361/11	3188/14	3362/11	–	$\nu\text{C}_{2/3}\text{H}$
3084/43	3253/60	3086/37	3255/52	3083/39	3253/54	3095/21	3264/43	–	νCH_2
3067/21	3233/24	3071/20	3237/24	3068/22	3234/25	3078/17	3246/23	–	νCH_2
3010/35	3181/30	3008/36	3178/32	3003/40	3174/33	3012/47	3186/35	–	νCH_2
2980/64	3168/72	2972/72	3159/79	2974/69	3160/80	3009/64	3179/64	–	νCH_2
1696/39	1839/46	1697/40	1839/47	1695/40	1839/47	1688/41	1830/52	–	δNH_2
1467/1	1625/1	1527/9	1670/16	1458/2	1622/1	1600/26	1716/12	–	$\delta\text{HOH}/\text{O}_{\text{HP}}$
1674/45	1825/58	1678/34	1827/49	1676/38	1826/55	1677/42	1826/55	–	νCC_{ph}
1639/32	1789/34	1636/36	1786/38	1636/37	1785/41	1637/34	1787/38	–	$\nu\text{CC}_{\text{ph.py}}$
1596/5	1736/9	1596/5	1736/10	1593/4	1730/12	1595/6	1734/9	–	νCC_{py}
1535/3	1662/3	1535/32	1662/2	1536/4	1662/3	1539/3	1665/3	–	δCH_2
1530/80	1653/121	1535/60	1655/117	1535/68	1656/99	1530/83	1652/122	–	νCC_{ph}
1510/38	1628/8	1508/11	1635/53	1510/52	1638/75	1511/8	1628/9	–	δCH_2
1506/51	1570/19	1503/58	1628/11	1506/34	1628/8	1505/61	1583/11	–	δCH_2
156/3	122/4	105/4	155/2	121/4	100/4	268/24	219/17	–	ν_{i}

1 B3LYP/6-31 + G(d), 2 HF/6-31 + G(d)

^a Experimental frequencies of the tryptamine taken from Ref. [6]. All frequencies are not scaled with any scaling factor. The scaling factor for the B3LYP/6-31 + G(d) resulted calculations is 0.9603 [6]

experimental and theoretical harmonic frequencies is possible only if the experimental spectrum of tryptamine [6] is used as a pattern. The only difference between tryptamine and serotonin is the OH-group attached to the indole ring in the latter. A detailed

study of the vibration spectra of the serotonin conformers has been made in Refs. [2, 6], at the B3LYP/6-31 + G(d) level.

The calculated vibrational spectra (B3LYP/6-31 + G(d)) of all supersystems are given in Fig. 3.

The most intensive bands are restricted in the interval 3191–3672 cm^{-1} and give OH and NH stretching vibrations of the intermolecular H-bonds. Furthermore, the lowest frequencies for these vibrations were found for the SER-W4 and SER-HP4 supersystems (3403 and 3191 cm^{-1}) and thus the intermolecular H-bonds in these complexes have higher energies compared with those in the remaining supersystems.

Several vibrational frequencies in the range over 1500 cm^{-1} and in the low-frequency region (intermolecular vibrations, ν_i) are listed in Table 5.

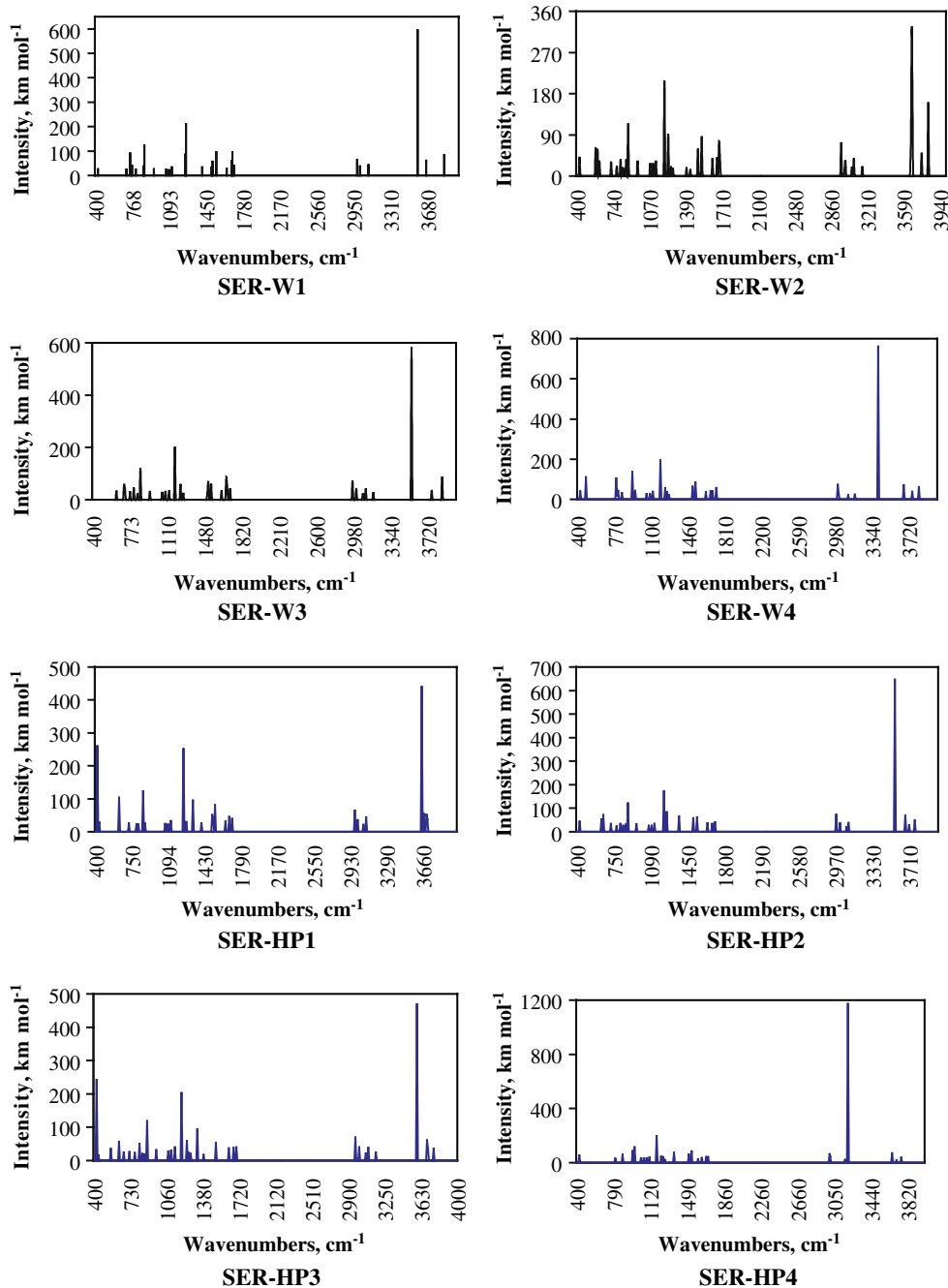
The values from Table 5 are in good agreement with the experimental frequencies of tryptamine

discussed in Ref. [6]. For example, the bands in the 2800–3000 cm^{-1} region have been assigned to the alkyl CH stretching modes of the ethylamine side chain [6]. Calculated values for these vibrations (B3LYP) are restricted within the interval 2971–3099 cm^{-1} or 2853–2976 cm^{-1} , as the later is corrected with scaling factor of 0.9603 [6].

Aromatic CH stretches are observed between 3000 and 3125 cm^{-1} [6] and calculated here in the interval 3182–3217 cm^{-1} (3056–3089 cm^{-1} scaled by 0.9603).

The H-bonding between the water/hydrogen peroxide oxygen atom and the H(11) atom leads to a large decrease (103 cm^{-1} in SER-HP1 and 164 cm^{-1} in SER-

Fig. 3 Vibration (IR) spectra of the H-bonded supersystems between serotonin and water/hydrogen peroxide. All spectra are calculated at the B3LYP/6-31+G(d) level as the frequencies are not scaled with any scaling factor



W1) in the frequency of the OH stretching vibration in serotonin. However, H-bonding between O(10) and the water/hydrogen peroxide hydrogen atom leads to an increase in ν_{OH} of 7 cm^{-1} for the SER-W2 supersystem and 10 cm^{-1} for SER-HP2. The formation of the supersystems SER-W3 and SER-HP3 causes a distinct decrease in ν_{NH} (114 and 80 cm^{-1} , respectively) compared to the serotonin monomer in the gas phase. In addition, the formation of the most stable supersystems SER-W4 and SER-HP4 causes an insignificant decrease in the frequencies of the $\nu_{\text{as/s}}\text{NH}_2$ vibrations—about 5 cm^{-1} .

In the low-frequency region one vibrational eigenvalue corresponding to intermolecular vibration (ν_i) was found for each supersystem.

Conclusions

We report results (B3LYP and HF with the 6-31+G(d) basis set) for the comparative stabilities of possible H-bonded complexes between serotonin (an important neurotransmitter) and water/hydrogen peroxide. The initial study of the rotation of the serotonin OH group reveals that rotation occurs with a comparatively low-energy barrier of about 14.8 kJ mol^{-1} (B3LYP). In agreement with recent results for the orientation of the OH group [6] we found that the *anti* OH-orientation is more favorable than the *syn*-one (7.6 kJ mol^{-1}).

According to the results concerning the structures of the supersystems and their formations, the following major conclusions can be made:

1. Complexation between the serotonin amino group and the hydrogen atom of water or hydrogen peroxide leads to the formation of the shortest intermolecular H-bonds.
2. Only the formation of the SER-HP4 supersystem is thermodynamically favored ($\Delta G_{298}^{\circ} < 0$). All other complex formations have positive ΔG_{298}° values. Therefore, these processes are likely to occur at high temperature, if $|\Delta H| < |T\Delta S|$. Thus, from a thermodynamic point of view the complex SER-HP4 is most stable. The complex SER-W4 is the most stable among all water-serotonin supersystems.
3. Analysis of the bonding parameters reconfirms that the supersystem SER-HP4 is the most stable one, followed by the complex SER-W4. It was established that the bonding and interaction energies overlap the energy barrier of the *syn-anti* rotation of the serotonin OH group. In other words, during the complexation *syn-anti* rotation is expected.

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References

1. Rang HP, Dale MM, Ritter JM, Moore PK (2003) Pharmacology, 5th edn. Edinburgh, Churchill Livingstone, ISBN 0-443-07145-4
2. van Mourik T, Emson LE (2002) Phys Chem Chem Phys 4:5863–5871
3. Port GNJ, Pullman B (1974) Theor Chim Acta 33:275–278
4. Neto JDDaM, de Alencastro RB (1993) Int J Quant Chem Quantum Biol Symp 20:107–112
5. Kang S, Cho M-H (1971) Theor Chim Acta 22:176–178
6. Carney JR, Zwier TS (2000) J Phys Chem A 104:8677–8688
7. Carney JR, Zwier TS (2001) Chem Phys Lett 341:77–85
8. Kang S, Johnson CL, Green JP (1973) J Mol Struct 15:453–457
9. Lee C, Yang W, Parr RG (1988) Phys Rev B 37:785–793
10. Frisch MJ, Pople JA, Binkley JS (1984) J Chem Phys 80:3265–3269
11. Becke AD (1993) J Chem Phys 98:5648–5652
12. Graham RJ, Kroemer RT, Mons M, Robertson EG, Snoek LC, Simons JP (1999) J Phys Chem A 103:9706–9711
13. Snoek LC, Robertson EG, Kroemer RT, Simons JP (2000) Chem Phys Lett 321:49–56
14. Butz P, Kroemer RT, MacLeod NA, Simons JP (2001) J Phys Chem A 105:1050–1056
15. Butz P, Kroemer RT, MacLeod NA, Simons JP (2001) J Phys Chem A 105:544–551
16. Hobza P, Spöner J (1996) J Mol Struct THEOCHEM 388:115–120
17. Spöner J, Jurecka P, Hobza P (2004) J Am Chem Soc 126:10142–10151
18. Spöner J, Hobza P (2000) J Phys Chem A 104:4592–4597
19. Handy NC, Cohen AJ (2001) Mol Phys 99:403–412
20. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA Jr, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson JA, Ayala PY, Cui Q, Morokuma K, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Gonzalez G, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, Pople JA (1998) Gaussian 98, Revision A.3. Gaussian Inc., Pittsburgh, PA
21. Boys SF, Bernadi F (1970) Mol Phys 19:553–558
22. Hobza P, Zahradnik R (1989) Intermolecular complexes. Mir Press, Moscow, p 36
23. Meunier A, Levy B, Bertier G (1973) Theor Chim Acta 29:49–55
24. Mayer I, Surjan PR (1992) Chem Phys Lett 191:497–499
25. Turi L, Dannenberg JJ (1993) J Phys Chem 97:2488–2490
26. Simon S, Duran M, Dannenberg JJ (1999) J Phys Chem A 103:1640–1643
27. Dykstra CE (1988) Ab initio Calculation of the Structure and Properties of Molecules. Elsevier, Amsterdam, p 68
28. Cleland WW, Kreevoy MM (1994) Science 264:1887–1890
29. Delchev VB, Mikosch H (2004) Monatsh Chem 135:1373–1387
30. Shishkin OV, Sukhanov OS, Gorb L, Leszczynski L (2002) Phys Chem Chem Phys 4:5359–5364