Quantum chemical study of hydrogen-bonded complexes of serine with water and H₂O₂

GEETANJALI CHOPRA, NEHA CHOPRA and DAMANJIT KAUR*

Department of Chemistry, Guru Nanak Dev University, Amritsar, Punjab 143 005, India

E-mail: damanjit32@yahoo.co.in; geetanjali012345@gmail.com; nehaomnamah@gmail.com

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Abstract. The hydrogen bonded complexes of serine with water and with H₂O₂ (HP) have been completely investigated in the present study using second-order Møller-Plesset perturbation theory (MP2) and density functional theory (DFT) in order to determine their geometries, stabilization energies, vibrational frequencies and electronic characteristics. The stabilization energies (ΔE_{BSSE}) span a range of -2.76 to -12.46 kcal/mol for 1:1 serine–water complexes and -4.54 to -12.73 kcal/mol for 1:1 serine–HP complexes. The ΔE_{BSSE} values suggest that serine–HP complexes are more stable than serine–water complexes. For all the structures, complex formation results in elongation of N–H, O–H bonds and shortening of C–H bonds thereby showing the red-shift and blue-shift for the respective bonds. The structural, vibrational and electronic features are in accordance with the fact that HP is a better proton donor and water a better proton acceptor. The excellent relationship is obtained for the variation of ΔE_{BSSE} values with the sum of the ρ values and the sum of laplacian at the BCPs for the HBs. The $E^{(2)}$ values are also in concordance with the calculated ΔE_{BSSE} values.

Keywords. Hydrogen bonding; serine–water; serine–HP; blue-shift; red-shift; MP2; DFT.

1. Introduction

Serine, a nonessential amino acid, is important in metabolism involving biosynthesis of purines and pyrimidines. It plays an important role in the catalytic activity of many enzymes. It is a component of brain proteins, nerve sheaths and is important in the formation of cell membranes. Over the past few years, the conformational behaviour of serine has been the subject of many theoretical^{1–11} as well as experimental studies.^{5–11}

The hydrogen bond (HB) is an extremely important molecular interaction as it is inherently present in many biological systems and plays a crucial role in a number of biochemical reactions. HBs formed by protein–water interactions play a vital role in protein folding and dynamics. The direct study of these interactions is extremely difficult due to the complexity of the protein macromolecule.^{12,13} The nature of hydrogen bonding between water and serine^{14–16} can explain the role of water in various bioprocesses wherein making and breaking of HBs is important.

Hydrogen bonding of hydrogen peroxide (HP) to serine has attracted the attention due to its importance in various biological processes.^{17–30} HP functions as a physiological effector in essential cellular processes. It has been recognized to play a metabolic and regulatory role in the initiation of proliferation and direction to immune cells. Although the high concentration of HP can lead to cell damage, low concentration can be used for utilizing its signalling characteristics in several biological processes. The research findings highlight that biological effects of HP are initiated with the formation of HBs between HP and molecules of biological interest. A few quantum chemical calculations have been carried out on the interaction of HP with glycine,^{31,32} serine,³³ uracil,³⁴ adenine,³⁵ cytosine,³⁶ urea³⁷ and phenol.³⁸ Moreover, theoretical research has been conducted on HP binding with water,^{39,40} hydrogen halides,⁴¹ methyl halides,⁴² noble gases,⁴³ NH₂NO,⁴⁴ OCS, CS₂,⁴⁵ TCBQ⁴⁶ and several ions, e.g., Li⁺, Na⁺, F[−], Cl[−], Br[−].⁴⁷ However, to the best of our knowledge, very few studies have been performed on the interaction between amino acid and HP despite having an indispensable role of HP in biological systems.

*For correspondence

In the present work, the four most stable conformers with a relative energy difference smaller than $1.05 \text{ kcal mol}^{-1}$ are selected out of 85 unique conformers of serine. Serine can be both proton acceptor (O and N) as well as donor (O-H, N-H and C-H). The main focus of this work is to study the hydrogen bonding of the first four lowest energy conformers of serine with water and with HP through 1:1 complex formation. The energetic, structural, topological and electronic factors affecting the stability of hydrogen-bonded complexes of 1:1 serine–water and 1:1 serine–HP have been analyzed and compared. The HB donor and acceptor abilities of the various sites of serine are compared in case of 1:1 serine–water and 1:1 serine–HP complexes.

2. Computational methods

The geometries of the first four most stable serine conformers and their corresponding hydrogen-bonded complexes with water and with HP were optimized using second order Møller-Plesset perturbation theory (MP2) with aug-cc-pVDZ basis set. For comparison purposes, the density functional theory calculations at B3LYP level were also performed using same basis set. The basis set chosen is the aug-cc-pVDZ as it represents the best compromise between computational accuracy and computational cost for complexes studied in the present paper. The stability of each complex was examined by the harmonic vibrational frequency calculations at the same theoretical levels mentioned above. All the calculations for the monomers and the complexes were carried out using Gaussian 09 software.⁴⁸ The stabilization energy was estimated as difference of the energy of the complex and the sum of the energies of the separated monomers. The stabilization energy was corrected for basis set superposition error (BSSE) by employing Boys-Bernardi counterpoise correction.⁴⁹ Natural atomic charges, second order delocalization energies ($E^{(2)}$) and charge transfer (CT) values were evaluated at B3LYP/aug-cc-pVDZ level using Natural Bond Orbital (NBO) program implemented in the Gaussian 09 software package.⁵⁰ The topological and energetic properties at the bond critical points (BCPs) of the hydrogen-bonded complexes were computed at MP2/aug-cc-pVDZ level by using Bader's theory of atoms in molecules (AIM) which employs AIM2000 software.^{51,52} In order to understand the physical nature of intermolecular interactions, the Symmetry Adapted Perturbation Theory (SAPT) analysis was performed at the MP2/aug-cc-pVDZ level with the use of GAMESS package linked to the SAPT2012.2 code.^{53–55} The distortion energy which estimates the relaxation of monomers upon complexation, was computed using eq. (1):

$$E_{\text{Dis}} = (E_{\text{M1}} + E_{\text{M2}}) - (E_{\text{M1,Dis}} + E_{\text{M2,Dis}}) \quad (1)$$

where, E_{M1} and E_{M2} are energies of individual monomeric units in gas phase and $E_{\text{M1,Dis}}$ and $E_{\text{M2,Dis}}$ are single

point energies obtained for the distorted isolated monomer geometry upon complexation.

3. Results and Discussion

3.1 Conformational stability

In the present study, we have selected the four lowest energy serine conformers labeled as **I**, **II**, **III** and **IV** (Figure 1) out of 85 conformers reported in literature.¹ Conformer **I** possess a *trans*-COOH, allowing a strong intra-molecular HB ($\text{N} \cdots \text{H}-\text{O}$) to be formed between the hydroxyl (O-H) group of the carboxylic moiety and non-bonding electron pair at the nitrogen atom. Also, a weaker intra-molecular HB ($\text{N}-\text{H} \cdots \text{O}$) is established between one of the amino H atoms and the 'O' atom of the side chain $-\text{CH}_2\text{OH}$. On the contrary, conformer **II** has the $-\text{COOH}$ group in a *cis*-configuration, with two weak intra-molecular HBs. The amino H atom shows an interaction with the 'O' atom of the carbonyl group ($\text{N}-\text{H} \cdots \text{O}=\text{C}$) and second HB is established between the O-H (proton donor) of the side chain $-\text{CH}_2\text{OH}$ and the non-bonding electron pair at the N atom ($\text{O}-\text{H} \cdots \text{N}$). In spite of different orientation of O-H group due to C4-C8 rotation in conformer **II** relative to **I**, the relative energy difference is only 0.16 kcal/mol . Both the conformers reflect the presence of two intra-molecular HBs each. The intra-molecular interactions involved are $\text{N5}-\text{H10} \cdots \text{O13}$, $\text{O3}-\text{H6} \cdots \text{N5}$ and $\text{N5}-\text{H10} \cdots \text{O1}$, $\text{O13}-\text{H14} \cdots \text{N5}$, respectively, in the two. The difference in strength of these HBs along with expected difference in steric interaction results in comparable stability of the two. The conformers **III** and **IV** are rotameric forms of **I** with respect to rotation around C2-C4 and C4-C8 bonds, respectively, also indicate the presence of two intra-molecular HBs. Experimental studies based on matrix isolation IR spectroscopy^{5,11} and combination of laser ablation with Fourier transform microwave spectroscopy (LA-MB-FTMS)⁹ have demonstrated the presence of these four conformers (**I**, **II**, **III** and **IV**) of serine.

3.2 Hydrogen-bonded complexes of 1:1 serine–water and serine–HP

3.2a Stabilization energies: Twenty two stable hydrogen bonded complexes of the four selected conformers of the serine with water in 1:1 ratio have been optimized at the B3LYP/aug-cc-pVDZ (**L1**) and MP2/aug-cc-pVDZ (**L2**) theoretical levels. Nineteen complexes of serine with HP have also been optimized

Figure 1. Optimized geometries and relative energies (MP2/aug-cc-pVDZ) of the four most stable conformers of serine. (the dashed line represents intra-molecular hydrogen bond).

at the same levels mentioned above, which exactly correspond to the optimized complexes of serine–water in terms of proton donor and acceptor sites. Figure 2 shows the optimized structures of 1:1 serine–water and 1:1 serine–HP complexes at **L2** level. Table 1 summarizes the stabilization energies (ΔE_{BSSE}) for serine–water and serine–HP complexes. It is apparent from the table that ΔE_{BSSE} values are computed to be within a range of -2.76 to -12.46 kcal/mol for 1:1 serine–water complexes while it lies in the range of -4.54 to -12.73 kcal/mol for serine–HP complexes at **L2** theoretical level. Each serine–HP complex is found to be more stable than its corresponding serine–water complex as apparent from ΔE_{BSSE} values. The **L2** method yields

the stronger binding than that at **L1** theoretical level. This is understandable as the DFT methods do not fully account for the weak interactions. The hydrogen-bonded complexes involving hydroxyl (O–H) and N of serine acting as HB donor and acceptor respectively towards water/HP are labeled as **A/A'**. The main chain O–H is engaged as HB donor in the complexes **I-A**, **I-A'**, **IV-A**, **IV-A'** while side chain O–H is involved as HB donor in the complexes **II-A**, **II-A'**, **III-A**, **III-A'**. Insignificant variation in ΔE_{BSSE} values is observed, whether main chain O–H or side chain O–H is involved as HB donor. In all the complexes labeled as **A** or **A'**, one of the intra-molecular HB with N as HB acceptor is replaced by intermolecular HB with water or HP respectively.

Figure 2. Optimized geometries (MP2/aug-cc-pVDZ) for 1:1 hydrogen bonded complexes of serine–water and serine–HP. (the dashed — — — line represents intermolecular and represents intra-molecular hydrogen bond).

The N–H and carbonyl oxygen of serine are acting as HB donor and acceptor, respectively, towards water in complexes marked as **B** (except **I–B**) and towards HP in complexes marked as **B'** (except **I–B'**). All the

intra-molecular HBs present in conformers of serine remain intact in the **B/B'** complexes. It is observed that the stabilization in **IV–B** and **IV–B'** is also contributed by additional unconventional C–H $\cdots$ O_{water/HP}

Table 1. Stabilization energies (ΔE_{BSSE} in kcal/mol) at B3LYP/aug-cc-pVDZ (**L1**), MP2/aug-cc-pVDZ (**L2**) levels and distortion energies (E_{Dis}) at **L2** level for 1:1 hydrogen bonded complexes of serine–water and serine–HP.

Serine–water				Serine–HP			
Complexes	$\Delta E_{\text{BSSE}}(-\text{ve})$		E_{Dis}	Complexes	$\Delta E_{\text{BSSE}}(-\text{ve})$		E_{Dis}
	L1	L2			L1	L2	
I-A	12.37	12.46	6.04	I-A'	11.75	12.73	6.00
II-A	9.61	9.75	2.57	II-A'	10.24	10.77	2.83
III-A	10.00	10.25	2.53	III-A'	11.14	12.24	3.01
IV-A	9.51	9.52	6.54	IV-A'	9.91	10.48	6.82
I-B	3.76	4.50	0.12	I-B'	3.27	4.54	0.10
II-B	5.45	5.86	0.47	II-B'	6.82	7.36	0.31
III-B	5.71	6.25	0.68	III-B'	6.76	7.72	0.96
IV-B	4.35	6.32	0.47	IV-B'	5.96	8.33	0.80
I-C	10.11	10.55	1.02	I-C'	10.85	11.58	1.57
II-C	9.57	9.68	0.60	II-C'	11.37	11.47	0.83
III-C	9.72	9.85	0.61	II-C ₁ '	9.11	9.19	0.57
				III-C'	11.04	11.83	0.92
				III-C ₁ '	9.18	9.23	0.58
II-D	5.81	6.76	0.38	II-D'	7.30	8.51	0.54
III-D	2.73	3.98	0.14	III-D'	3.32	4.96	0.22
IV-D	6.49	7.55	0.23	IV-D'	7.82	9.29	0.37
III-E	5.20	5.63	0.21	III-E'	6.61	7.43	0.34
IV-F	4.67	6.53	0.27	IV-F'	4.62	6.84	0.27
IV-G	3.91	4.85	0.64	IV-G'	6.53	7.84	0.16
I-H	6.29	6.89	0.51				
II-I	1.96	2.76	0.20				
II-J	5.03	5.45	0.61				
IV-K	4.23	5.04	0.14				
IV-L	3.89	4.18	0.10				

HB, C-H being part of side chain group $-\text{CH}_2\text{OH}$ of serine. Both **I-B** and **I-B'** involve single $\text{N5-H9} \cdots \text{O15}$ intermolecular interaction and the ΔE_{BSSE} values for both of these complexes are lower relative to the other complexes that come under the category of **B/B'**. The ΔE_{BSSE} values lie in the range of -9.52 to -12.46 kcal/mol and -10.48 to -12.73 kcal/mol for **A** and **A'** complexes, respectively, while the values lie in the range of -4.50 to -6.32 kcal/mol and -4.54 to -8.33 kcal/mol for **B** and **B'** complexes, respectively. The difference in ΔE_{BSSE} for **A/A'** complexes in relative to **B/B'** complexes can be rationalized in terms of difference in strength of intermolecular HBs. The HBs $\text{N} \cdots \text{H-O}_{\text{water/HP}}$ and $\text{water/HP} \cdots \text{H-O}$ involved in **A/A'** complexes are stronger as compared to HBs $\text{C} = \text{O} \cdots \text{H-O}_{\text{water/HP}}$ and $\text{water/HP} \cdots \text{H-N}$ involved in **B/B'** complexes. The O-H and carbonyl oxygen of serine are acting as HB donor and acceptor respectively towards water in complexes marked with **C** and towards HP in complexes labeled with **C'** or **C₁'**. The side chain O-H is involved as HB donor in complexes **I-C**, **I-C'**, while main chain O-H is engaged as HB donor

in complexes **II-C**, **II-C'**, **II-C₁'**, **III-C**, **III-C'** and **III-C₁'**. The ΔE_{BSSE} values are comparable for complexes involving either main chain O-H or side chain O-H as HB donor. Furthermore, both O atoms of HP are involved in the hydrogen bonding interaction with serine in **II-C'** and **III-C'** complexes leading to the formation of seven-membered ring structure while in complexes **II-C₁'** and **III-C₁'**, one of the O-H groups of HP acts as proton donor as well as proton acceptor resulting in the formation of six-membered ring structure. The ΔE_{BSSE} values for **II-C₁'**, **III-C₁'** complexes are found to be smaller than **II-C'**, **III-C'** complexes. This can be accounted for by a large departure from linearity being 35.71° and 35.30° for $\text{C} = \text{O} \cdots \text{H-O}_{\text{water/HP}}$ hydrogen bonding interaction in the six-membered ring structures of **II-C₁'** and **III-C₁'** complexes respectively. The high ΔE_{BSSE} values associated with these complexes are next in stability to **A/A'** complexes which is understandable in terms of anticipated positions of lone pairs present on N and O atoms of serine in the two cases respectively. The C-H and 'O' of O-H group of serine are acting as HB donor and acceptor respectively

towards water in complexes marked with suffix **D** and towards HP in complexes marked with **D'**. The presence of unconventional intermolecular HB C-H...O in complexes labeled as **D/D'** results in relatively lower ΔE_{BSSE} values. The complexes **II-D**, **II-D'**, **IV-D**, **IV-D'** involve 'O' of side chain -CH₂OH as HB acceptor while 'O' of main chain O-H is engaged as HB acceptor in complexes **III-D**, **III-D'**. The higher ΔE_{BSSE} values for **II-D** (−6.76 kcal/mol), **II-D'** (−8.51 kcal/mol), **IV-D** (−7.55 kcal/mol) and **IV-D'** (−9.29 kcal/mol) in comparison to **III-D** (−3.98 kcal/mol) and **III-D'** (−4.96 kcal/mol) complexes indicate the fact that the tendency of side chain O-H of serine to act as HB acceptor is relatively better as compared to the main chain O-H. This is also reflected from the difference in ΔE_{BSSE} values of **II-I** and **III-E/E'** complexes. The complex **II-I** involve 'O' of main chain O-H as HB acceptor towards water along with little contribution from C-H...O_{water} interaction resulting in ΔE_{BSSE} value of mere −2.76 kcal/mol, while 'O' being part of side chain -CH₂OH is playing the role of HB acceptor towards water in **III-E** and towards HP in **III-E'** resulting in relatively higher ΔE_{BSSE} values of −5.63 kcal/mol and −7.43 kcal/mol, respectively. The N-H and 'O' of main chain O-H of serine are acting as HB donor and acceptor respectively towards water in **IV-F** complex with ΔE_{BSSE} value of −6.53 kcal/mol and towards HP in **IV-F'** complex resulting in ΔE_{BSSE} value of −6.84 kcal/mol, with higher contribution from N-H...O_{water/HP} HB interaction to ΔE_{BSSE} . It is obvious as the second HB interaction (main chain O-H) O...H-O_{water/HP} will be relatively weak due to poor tendency of 'O' of main chain O-H to act as HB acceptor. The C-H and carbonyl oxygen of serine are acting as HB donor and acceptor, respectively, towards water in **IV-G** complex and towards HP in **IV-G'** complex, but there is formation of one extra bond in **IV-G'** complex in which side chain O-H is also engaged as HB acceptor towards HP. Due to the formation of this extra bond, the complex **IV-G'** is about 2.99 kcal/mol more stabilized as compared to **IV-G**. The difference in ΔE_{BSSE} values of corresponding complexes of water and HP varies from 0.04 to 2.99 kcal/mol. The smallest difference is between **I-B** and **I-B'** and largest between **IV-G** and **IV-G'**.

It is worth noting that except **A/A'** complexes, the intra-molecular HBs in serine conformers remain preserved upon complex formation which is reflected by the geometrical parameters (Table S43 in Supplementary Information) and the low distortion energy (E_{Dis}) values associated with the complex formation (Table 1). The intra-molecular HB N5...H6-O3 in **I-A/A'**, **IV-A/A'** and N5...H14-O13 in **II-A/A'**, **III-A/A'** gets disrupted during complex formation. In these

complexes, water/HP gets inserted into intra-molecular HB upon complexation resulting in the loss of intra-molecular hydrogen bonding interaction and thus the complex formation is accompanied by high E_{Dis} values. The E_{Dis} values in complexes **I-A** (6.04 kcal/mol), **I-A'** (6.00 kcal/mol), **II-A** (2.57 kcal/mol), **II-A'** (2.83 kcal/mol), **III-A** (2.53 kcal/mol), **III-A'** (3.01 kcal/mol), **IV-A** (6.54 kcal/mol), **IV-A'** (6.82 kcal/mol) reflect that serine molecular plane is significantly deformed in these complexes and the actual stabilization is much higher in comparison to computed ΔE_{BSSE} values. Though these complexes undergo high deformation, these are compensated by high stabilizations with strong intermolecular HBs. It is quite interesting to note that there is the simultaneous formation of intra-molecular HB O1...H14-O13 in complexes **I-A** and **I-A'** to compensate the loss of intra-molecular HB N5...H6-O3, thus the intra-molecular HB O1...H14-O13 also contributes to the relatively higher ΔE_{BSSE} values associated with **I-A** and **I-A'** complexes.

It is found that the ΔE_{BSSE} associated with serine–water and serine–HP complex formation has three contributing components: (i) distortion energy, (ii) interaction energy due to the formation of intermolecular HBs, and (iii) loss of intra-molecular HB interaction energy. Though the third component is difficult to separate from the distortion energy component but it is important when water or HP molecule acts as a shield for intra-molecular hydrogen bonding without deformation of the molecule.

3.2b Geometries and Vibrational frequencies: The intermolecular HB distances and angles for serine–water and serine–HP complexes at **L2** level are displayed in Table 2. The change in bond length (Δd in Å) and shifts of stretching frequencies ($\Delta \nu$ in cm^{−1}) of the HB donor group upon complex formation relative to monomers are incorporated in Table 3. The HB distance values for complexes **I-A/I-A'** are the minimal which indicate that HBs are very strong, therefore the stabilization energy must be the largest and the complexes **I-A/I-A'** are the most stable amongst the series of serine–water/HP complexes. The N...H-O_{water/HP} HB distance range is found to lie in 1.840–1.904 Å/1.720–1.756 Å in complexes categorized as **A/A'** while the HB distance range of N-H...O_{water/HP} lies in 2.069–2.439 Å/2.073–2.446 Å in complexes labeled as **B/B'**. The higher strength of former HBs in relative to the latter indicates that the tendency of 'N' of amino group to act as HB acceptor is better than the HB donor ability of N-H of amino group of serine which can be justified in terms of basic nature of amino nitrogen. The N...H-O_{HP} HBs

Table 2. Intermolecular hydrogen bond distances (r, Å) and angles (θ , °) for 1:1 hydrogen bonded complexes of serine–water and serine–HP at MP2/aug-cc-pVDZ level.

Serine–water				Serine–HP			
Complexes	Hydrogen bond distances (r, Å)	Hydrogen bond angles (θ, °)		Complexes	Hydrogen bond distances (r, Å)	Hydrogen bond angles (θ, °)	
I-A	H16...N5	1.840	148.13	I-A'	H16...N5	1.720	N5...H16-O15
	H6...O15	1.725	170.45		H6...O15	1.758	O15...H6-O3
	H15...N5	1.874	158.77		H15...N5	1.740	N5...H15-O16
II-A	H14...O16	1.865	162.67	II-A'	H14...O16	1.915	O16...H14-O13
	H15...N5	1.867	162.16		H15...N5	1.735	N5...H15-O16
III-A	H14...O16	1.865	161.18	III-A'	H14...O16	1.927	O16...H14-O13
IV-A	H16...N5	1.904	144.30	IV-A'	H16...N5	1.756	N5...H16-O15
	H6...O15	1.752	173.78		H6...O15	1.790	O15...H6-O3
	H9...O15	2.165	143.92		H9...O15	2.173	O15...H9-N5
I-B	H16...O1	2.019	149.69	I-B'	H15...O1	1.888	O1...H15-O16
II-B	H9...O15	2.205	139.62	II-B'	H9...O17	2.354	O17...H9-N5
	H16...O1	1.955	150.24		H15...O1	1.859	O1...H15-O16
III-B	H9...O15	2.069	166.77	III-B'	H9...O17	2.073	O17...H9-N5
	H15...O1	2.376	131.00		H15...O1	1.940	O1...H15-O16
IV-B	H10...O16	2.439	127.86	IV-B'	H10...O17	2.446	O17...H10-N5
	H11...O16	2.532	128.44		H11...O16	2.580	O16...H11-C8
	H17...O1	1.903	153.31		H15...O1	1.771	O1...H15-O16
I-C	H14...O15	1.858	159.31	I-C'	H14...O17	1.892	O17...H14-O13
II-C	H16...O1	2.019	135.23	II-C'	H17...O1	1.792	O1...H17-O16
	H6...O15	1.766	158.77		H6...O15	1.751	O15...H6-O3
III-C	H16...O1	2.012	136.21	II-C ₁ '	H16...O1	1.874	O1...H16-O15
	H6...O15	1.764	159.38		H6...O15	1.851	O15...H6-O3
					H17...O1	1.791	O1...H17-O16
II-D	H15...O13	1.887	156.44	III-C ₁ '	H16...O1	1.869	O1...H16-O15
	H7...O16	2.389	129.68		H6...O15	1.852	O15...H6-O3
III-D	H15...O3	2.065	149.80	II-D'	H15...O13	1.798	O13...H15-O16
	H7...O16	2.464	125.29		H7...O17	2.409	O17...H7-C4
					H15...O3	2.056	O3...H15-O16
				III-D'	H7...O16	2.590	O16...H7-C4
					H7...O17	2.503	O17...H7-C4

Table 2. (contd.)

Serine–water				Serine–HP			
Complexes	Hydrogen bond distances (r, Å)	Hydrogen bond angles (θ , °)	Complexes	Hydrogen bond distances (r, Å)	Hydrogen bond angles (θ , °)	Complexes	Hydrogen bond distances (r, Å)
IV-D	H17...O13 H7...O15	1.901 2.363		O13...H17-O15 O15...H7-C4	151.33 128.41	IV-D'	H18...O13 H7...O17
III-E	H15...O13	1.899		O13...H15-O16	157.77	III-E'	H12...O15
IV-F	H15...O3 H10...O16	2.323 2.285		O3...H15-O16 O16...H10-N5	121.11 126.51	IV-F'	H15...O13 H15...O3
IV-G	H15...O1 H7...O16	2.144 2.408		O1...H15-O16 O16...H7-C4	138.80 128.50	IV-G'	H10...O17 H15...O1
I-H	H15...O1 H7...O16 H11...O16	1.928 2.579 2.552		O1...H15-O16 O16...H7-C4 O16...H11-C8	155.31 112.30 121.45		H18...O13
II-I	H15...O3 H11...O16	2.058 2.476		O3...H15-O16 O16...H11-C8	154.85 154.95		
II-J	H15...O13	1.900		O13...H15-O16	157.71		
IV-K	H9...O15	2.139		O15...H9-N5	145.36		
IV-L	H15...O1	2.076		O1...H15-O16	161.41		

Table 3. Change in bond length (Δd , Å) and shifts of stretching frequencies ($\Delta\nu$ in cm^{-1}) of the HB donor group upon complex formation for 1:1 hydrogen bonded complexes of serine–water and serine–HP at MP2/aug-cc-pVDZ level.

Complexes	Serine–water				Serine–HP			
	Serine		Water		Complexes		Serine	
	HB donor	Δd	HB donor	Δd		$\Delta\nu$	HB donor	Δd
I-A	O3-H6	+0.004	O15-H16	+0.024	I-A'	–308.62	O3-H6	+0.001
II-A	O13-H14	+0.005	O16-H15	+0.021	II-A'	–318.94	O13-H14	+0.003
III-A	O13-H14	+0.004	O16-H15	+0.020	III-A'	–334.46	O13-H14	+0.001
IV-A	O3-H6	+0.002	O15-H16	+0.017	IV-A'	–230.02	O3-H6	+0.001
I-B	N5-H9	+0.002			I-B'		N5-H9	+0.002
II-B	N5-H9	+0.002	O15-H16	+0.005	II-B'	–53.10	N5-H9	+0.001
III-B	N5-H9	+0.004	O15-H16	+0.007	III-B'	–53.19	N5-H9	+0.001
IV-B	N5-H10	+0.001	O16-H15	+0.003	IV-B'	–38.17	N5-H10	+0.001
	C8-H11	–0.005					C8-H11	–0.005
I-C	O13-H14	+0.009	O15-H17	+0.009	I-C'	–80.48	O13-H14	+0.006
II-C	O3-H6	+0.018	O15-H16	+0.010	II-C'	–87.91	O3-H6	+0.019
					II-C₁'		O3-H6	+0.014
III-C	O3-H6	+0.018	O15-H16	+0.010	III-C'	–92.18	O3-H6	+0.019
					III-C₁'		O3-H6	+0.014
II-D	C4-H7	–0.001	O16-H15	+0.011	II-D'	–144.97	C4-H7	–0.002
III-D	C4-H7	–0.002	O16-H15	+0.004	III-D'	–36.32	C4-H7	–0.003
							C4-H7	–0.003
IV-D	C4-H7	–0.001	O15-H17	+0.011	IV-D'	–152.42	C4-H7	–0.001
							C8-H12	–0.003
III-E			O16-H15	+0.009	III-E'	–117.51		
IV-F	N5-H10	+0.001	O16-H15	+0.003	IV-F'	–33.98	N5-H10	+0.001
IV-G	C4-H7	–0.002	O16-H15	+0.004	IV-G'	–32.75	C4-H7	–0.001
I-H	C8-H11	–0.003	O16-H15	+0.009		–93.80		
	C4-H7	–0.002						
II-I	C8-H11	–0.001	O16-H15	+0.002		–23.27		
II-J			O16-H15	+0.009		–117.38		
IV-K	N5-H9	+0.002						
IV-L			O16-H15	+0.002		–33.34		

are comparatively stronger and more linear in serine–HP complexes **I-A'** (1.720 Å, 157.80°), **II-A'** (1.740 Å, 168.38°), **III-A'** (1.735 Å, 167.94°), **IV-A'** (1.756 Å, 156.60°) in relative to the $\text{N} \cdots \text{H}-\text{O}_{\text{water}}$ HBs in the corresponding serine–water complexes **I-A** (1.840 Å, 148.13°), **II-A** (1.874 Å, 158.77°), **III-A** (1.867 Å, 162.16°), **IV-A** (1.904 Å, 144.30°), owing to the fact that HP is a better HB donor than water. On the other hand, the $\text{water} \text{O} \cdots \text{H}-\text{O}$ HBs are slightly stronger and more linear in serine–water complexes **I-A** (1.725 Å, 170.45°), **II-A** (1.865 Å, 162.67°), **III-A** (1.865 Å, 161.18°), **IV-A** (1.752 Å, 173.78°) in comparison to the $\text{HP} \text{O} \cdots \text{H}-\text{O}$ distances in the corresponding serine–HP complexes **I-A'** (1.758 Å, 168.04°), **II-A'** (1.915 Å, 160.06°), **III-A'** (1.927 Å, 155.13°), **IV-A'** (1.790 Å, 166.85°), on account of the fact that water is marginally better HB acceptor as compared to HP. The $\text{C}-\text{H} \cdots \text{O}$ bond distance range between 2.363–2.579 Å and 2.409–2.590 Å for serine–water and serine–HP complexes respectively, which agrees well with established range of $\text{C}-\text{H} \cdots \text{O}$ HB lengths. On the basis of geometrical parameters, a strength sequence of the HBs from the strongest to the weakest is anticipated to be $\text{water} \text{O} \cdots \text{H}-\text{O}$ (1.725–1.865 Å) > $\text{N} \cdots \text{H}-\text{O}_{\text{water}}$ (1.840–1.904 Å) > $\text{O} \cdots \text{H}-\text{O}_{\text{water}}$ (1.887–2.376 Å) > $\text{N}-\text{H} \cdots \text{O}_{\text{water}}$ (2.069–2.439 Å) > $\text{C}-\text{H} \cdots \text{O}_{\text{water}}$ (2.363–2.579 Å) for serine–water complexes. On the other hand, the relative bond strengths in serine–HP complexes follow $\text{N} \cdots \text{H}-\text{O}_{\text{HP}}$ (1.720–1.756 Å) > $\text{HP} \text{O} \cdots \text{H}-\text{O}$ (1.745–1.927 Å) > $\text{O} \cdots \text{H}-\text{O}_{\text{HP}}$ (1.771–2.316 Å) > $\text{N}-\text{H} \cdots \text{O}_{\text{HP}}$ (2.073–2.446 Å) > $\text{C}-\text{H} \cdots \text{O}_{\text{HP}}$ (2.409–2.590 Å) trend. The differences between the geometrical and vibrational properties of the serine–water and serine–HP complexes can be rationalized as a function of the proton donor and acceptor abilities of water and HP. As expected from the pK_{a} (acid dissociation constant) values of HP (11.6) and water (15.7), HP is a better proton donor than water. Furthermore, the gas phase proton affinities of water and HP determined experimentally are 697 and 678 kJ/mol while the values for OH^- and HO_2^- anions are equal to 1635 and 1573 kJ/mol, respectively,⁵⁶ showing that HP is a much better proton donor and water a better proton acceptor. The single crystal X-ray diffraction of various natural amino acid perhydrates and hydrates has led to the conclusion that donor HBs formed by HP are significantly stronger than those formed by water molecules.⁵⁷ Thus, in the present paper, the higher stability found for each serine–HP complex relative to its corresponding serine–water complex can be attributed to the significantly higher strength of HBs $\text{X} \cdots \text{H}-\text{O}_{\text{HP}}$ (where X = HB acceptor site of serine) as compared to $\text{X} \cdots \text{H}-\text{O}_{\text{water}}$ HBs. Traditionally, it is considered that red shifts in the O–H (acting as HB donor) stretching

frequency have been one of the main fingerprints of HBs as the formation of a HB weakens the O–H single bond. In all the optimized complexes, the O–H bond acting as HB donor is elongated upon complex formation accompanied by a red shift in the stretching frequency. In fact, the large shifts appear in the O–H_{HP} stretching frequencies of **I-A'** (−563.51 cm^{-1}), **II-A'** (−528.82 cm^{-1}), **III-A'** (−577.94 cm^{-1}), **IV-A'** (−463.31 cm^{-1}) and comparatively smaller shifts appear in the O–H_{water} stretching frequencies of **I-A** (−308.62 cm^{-1}), **II-A** (−318.94 cm^{-1}), **III-A** (−334.46 cm^{-1}), **IV-A** (−230.02 cm^{-1}) corroborate that HP is a remarkable proton donor in comparison to water. The higher acidity of the O–H bond of HP is also demonstrated by the larger elongations of the bonded O–H groups which comprise between 0.003–0.035 Å (for O–H_{HP}) in the serine–HP complexes and between 0.002–0.024 Å (for O–H_{water}) in the serine–water complexes. The values of $\Delta \nu$ for O–H_{HP} bond and O–H_{water} bond lie in the range −50.43 to −577.94 cm^{-1} and −23.27 to −334.46 cm^{-1} , respectively, for serine–HP and serine–water complexes. Gong X *et al.* also observed red-shift in the frequencies of H_2O sym stretch and asym stretch mode in serine–water complexes.¹⁵ Maximum shift in O–H_{serine} stretching frequency is reflected when main chain O–H of serine acts as HB donor towards water/HP in complexes **II-C** (−270.16 cm^{-1}), **II-C'** (−268.35 cm^{-1}), **II-C₁'** (−243.36 cm^{-1}), **III-C** (−280.04 cm^{-1}), **III-C'** (−282.06 cm^{-1}), **III-C₁'** (−246.97 cm^{-1}). The N–H stretching vibrations exhibit red shift which spans a range of −4.11 to −29.59 cm^{-1} and −1.92 to −10.09 cm^{-1} for serine–water and serine–HP complexes respectively. Gong X *et al.*, have also inferred the same.¹⁵ Blue shift in $\Delta \nu_{\text{C}-\text{H}}$ is reflected along with contraction of C–H bond length in complexes involving C–H as HB donor. The decrease in C–H bond length ranges between 0.001–0.005 Å and the stretching frequency shifts for this bond lie in the range +5.89 to +52.05 cm^{-1} and +8.93 to +52.58 cm^{-1} for serine–water and serine–HP complexes under study. This is as expected for $\text{C}-\text{H} \cdots \text{O}$ being weak bonds in nature. A perfect linear correlation between the O–H bond elongation (Δd) and the red shift ($\Delta \nu$) is found with R values 0.956 and 0.986 for serine–water and serine–HP complexes respectively as shown in Figures 3 (a) and (b).

Surveying the calculated geometrical parameters (Tables S1–S42 in Supplementary Information), the significant contraction or elongation of C2=O1, C2–O3, C4–N5 bonds of serine is observed upon complexation with water/HP. The carbonyl group C2=O1 is elongated in all the complexes where it is involved in hydrogen bonding, the maximum elongation of 0.010 Å to 0.013 Å is observed in complexes **II-C**, **II-C'**, **II-C₁'**,

Figure 3. (a) A plot of the correlation between the bond elongation Δd (O-H) and the frequency shifts $\Delta \nu$ of the serine–water complexes at MP2/aug-cc-pVDZ level. (b) A plot of the correlation between the bond elongation Δd (O-H) and the frequency shifts $\Delta \nu$ of the serine–HP complexes at MP2/aug-cc-pVDZ level.

III-C, III-C', III-C₁'. Maximum shortening of 0.018 Å to 0.024 Å is also seen in the C2-O3 bond of these complexes due to the formation of HB weakening the C=O bond. The complex formation induces an elongation of 0.002 Å to 0.010 Å in the C4-N5 bond of **A/A'** complexes having N involved as HB acceptor. On the other hand, the contraction of 0.001 Å to 0.006 Å in the C4-N5 bond of **B/B'**, **F/F'** complexes is observed where N-H acts as HB donor.

3.2c AIM analysis: The nature of bonding between atoms can be characterized by the value of ρ and the sign of the laplacian $\nabla^2\rho$ of the electron density at the bond critical point (BCP). Large ρ values together with negative $\nabla^2\rho$ values represent shared electron interactions. In contrast, low ρ values along with positive $\nabla^2\rho$ values reflect closed-shell interactions. The topological and energy properties at the bond critical points (BCPs) for 1:1 hydrogen bonded complexes of serine–water and serine–HP evaluated at **L2** level are summarized in Table 4. The calculated laplacian ($\nabla^2\rho$) at the corresponding BCPs are all positive, suggesting that the

intermolecular HBs formed between serine and water and between serine and HP should be predominantly closed-shell interactions. According to the criteria proposed by Popelier, the electron density ρ at the BCPs is in the range of 0.002–0.040 au and laplacian $\nabla^2\rho$ of the electron density at the BCPs lie in the range of 0.024–0.139 au for HB.⁵⁸ The ρ values at HB BCPs for serine–water and serine–HP complexes fall in the range 0.008–0.039 au and 0.008–0.050 au, respectively. The former values conform to the range suggested by Popelier while latter values in the serine–HP complexes for hydrogen bonding interactions extend out of the expected range of values. Similarly the $\nabla^2\rho$ values at HB BCPs lie in the range of 0.032–0.156 au and 0.032–0.152 au for serine–water and serine–HP complexes, respectively. The energy parameters like the total energy density (H_C) and its two components, the local kinetic energy density (G_C) and the local potential energy density (V_C) are also calculated. The $\nabla^2\rho$ and H_C values are estimators of the nature of interaction, if $\nabla^2\rho > 0$ and $H_C > 0$, then the interaction is “closed shell” type but if $\nabla^2\rho > 0$ and $H_C < 0$, then the interactions in the complexes are partly covalent in nature. In addition, the ratio $-G_C/V_C$, is a measure of balance between positive kinetic energy density, G_C and negative potential energy, V_C ; if $-G_C/V_C > 1$, then the interaction is closed-shell non-covalent one, if it is between 0.5 and 1, then partly covalent type but if it is even less than 0.5, then it is shared covalent interactions. Thus, from the analysis of Table 4, it is clear that both $\nabla^2\rho$ and H_C values are greater than zero except $N \cdots H-O_{HP}$ interactions in case of serine–HP complexes, therefore all the interactions except $N \cdots H-O_{HP}$ display the characteristics of closed-shell interaction. The $N \cdots H-O_{HP}$ interactions in case of serine–HP complexes are partly covalent in nature. This is also supported from the ratio $-G_C/V_C$, which is less than 1 for $N \cdots H-O_{HP}$ interactions. Several reports in literature indicate that ρ is a good estimate of strength of HB, larger ρ at the BCP indicates stronger bond. The higher ρ values for $N \cdots H-O_{HP}$ interactions in **I-A'**, **II-A'**, **III-A'**, **IV-A'** relative to $N \cdots H-O_{water}$ interaction in **I-A**, **II-A**, **III-A**, **IV-A** is due to the fact that HP is a much better HB donor than water. In contrast, the slightly higher ρ values for $_{water}O \cdots H-O$ in **I-A**, **II-A**, **III-A**, **IV-A** relative to $_{HP}O \cdots H-O$ in **I-A'**, **II-A'**, **III-A'**, **IV-A'** is due to the reason that water is marginally better HB acceptor in comparison to HP. For serine–water complexes, the order of ρ values for HBs $_{water}O \cdots H-O$ (0.028–0.039 au) $>$ $N \cdots H-O_{water}$ (0.033–0.037 au) $>$ $O \cdots H-O_{water}$ (0.012–0.027 au) $>$ $N-H \cdots O_{water}$ (0.010–0.017 au) $>$ $C-H \cdots O_{water}$ (0.008–0.011 au) agrees well with the HB strength decreasing in the same order. On the other hand, the electron density

Table 4. The topological and energy properties at the bond critical points (BCPs) for 1:1 hydrogen bonded complexes of serine–water and serine–HP evaluated at MP2/aug-cc-pVDZ level using AIM analysis (all the values are in au).

Serine–water complexes								Serine–HP complexes							
	Hydrogen bond	ρ	$\nabla^2\rho$	G_C	V_C	H_C	$-G_C/V_C$		Hydrogen bond	ρ	$\nabla^2\rho$	G_C	V_C	H_C	$-G_C/V_C$
I-A	N5...H16-O15	0.037	0.124	0.030	-0.029	0.0011	1.03	I-A'	N5...H16-O15	0.050	0.144	0.040	-0.044	-0.0041	0.90
	O15...H6-O3	0.039	0.156	0.037	-0.035	0.0022	1.06		O15...H6-O3	0.036	0.148	0.034	-0.032	0.0026	1.06
II-A	N5...H15-O16	0.034	0.116	0.027	-0.024	0.0021	1.12	II-A'	N5...H15-O16	0.047	0.140	0.037	-0.040	-0.0025	0.92
	O16...H14-O13	0.028	0.116	0.026	-0.022	0.0033	1.18		O16...H14-O13	0.025	0.104	0.023	-0.020	0.0028	1.15
III-A	N5...H15-O16	0.034	0.116	0.027	-0.025	0.0019	1.08	III-A'	N5...H15-O16	0.048	0.136	0.037	-0.040	-0.0031	0.92
	O16...H14-O13	0.028	0.116	0.026	-0.022	0.0032	1.18		O16...H14-O13	0.025	0.100	0.023	-0.020	0.0024	1.15
IV-A	N5...H16-O15	0.033	0.112	0.026	-0.025	0.0015	1.04	IV-A'	N5...H16-O15	0.046	0.140	0.037	-0.039	-0.0022	0.95
	O15...H6-O3	0.035	0.144	0.034	-0.031	0.0028	1.10		O15...H6-O3	0.033	0.136	0.031	-0.028	0.0032	1.11
I-B	O15...H9-N5	0.015	0.056	0.013	-0.012	0.0010	1.08	I-B'	O15...H9-N5	0.015	0.052	0.012	-0.012	0.0008	1.00
II-B	O1...H16-O15	0.019	0.076	0.017	-0.015	0.0020	1.13	II-B'	O1...H15-O16	0.025	0.104	0.023	-0.020	0.0030	1.15
	O15...H9-N5	0.014	0.048	0.012	-0.011	0.0005	1.09		O17...H9-N5	0.010	0.044	0.010	-0.009	0.0010	1.11
III-B	O1...H16-O15	0.021	0.088	0.020	-0.017	0.0027	1.18	III-B'	O1...H15-O16	0.026	0.116	0.024	-0.020	0.0043	1.20
	O15...H9-N5	0.017	0.060	0.014	-0.012	0.0013	1.17		O17...H9-N5	0.017	0.068	0.015	-0.013	0.0016	1.15
IV-B	O1...H15-O16	0.012	0.044	0.010	-0.009	0.0009	1.11	IV-B'	O1...H15-O16	0.023	0.088	0.020	-0.018	0.0021	1.11
	O16...H10-N5	0.010	0.036	0.008	-0.008	0.0006	1.00		O17...H10-N5	0.009	0.036	0.008	-0.008	0.0009	1.00
I-C	O16...H11-C8	0.008	0.032	0.007	-0.006	0.0009	1.17	I-C'	O16...H11-C8	0.008	0.032	0.007	-0.006	0.0009	1.17
	O1...H17-O15	0.024	0.100	0.022	-0.019	0.0031	1.16		O1...H15-O16	0.032	0.140	0.031	-0.027	0.0044	1.15
II-C	O15...H14-O13	0.028	0.116	0.026	-0.022	0.0034	1.18	II-C'	O17...H14-O13	0.025	0.108	0.023	-0.019	0.0038	1.21
	O1...H16-O15	0.022	0.080	0.019	-0.018	0.0007	1.05		O1...H17-O16	0.033	0.132	0.030	-0.027	0.0032	1.11
III-C	O15...H6-O3	0.034	0.144	0.032	-0.029	0.0031	1.10	II-C₁'	O15...H6-O3	0.036	0.148	0.034	-0.031	0.0030	1.10
									O1...H16-O15	0.029	0.112	0.026	-0.024	0.0016	1.08
III-C	O1...H16-O15	0.022	0.080	0.019	-0.019	0.0008	1.00	III-C'	O15...H6-O3	0.029	0.120	0.027	-0.024	0.0028	1.12
	O15...H6-O3	0.035	0.144	0.033	-0.030	0.0029	1.10		O1...H17-O16	0.033	0.136	0.030	-0.027	0.0032	1.11
II-D								III-C₁'	O15...H6-O3	0.037	0.152	0.035	-0.032	0.0028	1.09
									O1...H16-O15	0.030	0.112	0.026	-0.025	0.0016	1.04
II-D	O13...H15-O16	0.027	0.112	0.025	-0.022	0.0029	1.14	II-D'	O15...H6-O3	0.029	0.120	0.027	-0.024	0.0028	1.12
	O16...H7-C4	0.010	0.040	0.009	-0.008	0.0009	1.12		O13...H15-O16	0.034	0.136	0.031	-0.028	0.0027	1.11
								O17...H7-C4	0.009	0.040	0.009	-0.008	0.0011	1.12

Figure 4. (a) A plot of the stabilization energies ΔE_{BSSE} of the serine–water complexes versus electron density ρ at the BCP at MP2/aug-cc-pVDZ level. (b) A plot of the stabilization energies ΔE_{BSSE} of the serine–HP complexes versus electron density ρ at the BCP at MP2/aug-cc-pVDZ level.

values at the BCPs are 0.046–0.050 au, 0.025–0.037 au, 0.013–0.034 au, 0.009–0.017 au and 0.008–0.010 au for $N \cdots H-O_{HP}$, $HP O \cdots H-O$, $O \cdots H-O_{HP}$, $N-H \cdots O_{HP}$, $C-H \cdots O_{HP}$ HBs, respectively, in case of serine–HP complexes which is also consistent with the HB length order which is found to be same. It is also observed that the ρ and $\nabla^2 \rho$ values for the non-conventional $C-H \cdots O$ HBs in the complexes are seen to be relatively much smaller range which indicates them to be weak HBs. Figures 4 (a) and (b) depict the good correlation between the sum of ρ values and ΔE_{BSSE} values for serine–water and serine–HP complexes with R values 0.926 and 0.905, respectively. Also there exists a linear relationship between ΔE_{BSSE} values and sum of $\nabla^2 \rho$ values for both serine–water and serine–HP complexes with R values 0.934 and 0.902, respectively, as shown in Figures 5 (a) and (b).

3.2d NBO analysis: NBO method gives useful information about the atomic charges, which reflects

Figure 5. (a) A plot of the stabilization energies ΔE_{BSSE} of the serine–water complexes versus laplacian of electron density $\sigma^2 \rho$ at the BCP at MP2/aug-cc-pVDZ level. (b) A plot of the stabilization energies ΔE_{BSSE} of the serine–HP complexes versus laplacian of electron density $\sigma^2 \rho$ at the BCP at MP2/aug-cc-pVDZ level.

the relative importance of electrostatic interactions associated with the complexes. Table 5 presents the values of NPA atomic charges on atoms involved in hydrogen bonding evaluated at L1 level utilizing NBO analysis. As clear from Figure 6, the atomic charges on various HB acceptor sites of serine follow the order $N5 (-0.918 \text{ to } -0.938 \text{ e}) >_{\text{side chain O-H}} O13 (-0.770 \text{ to } -0.780 \text{ e}) >_{\text{main chain O-H}} O3 (-0.715 \text{ to } -0.722 \text{ e}) > O1 (-0.629 \text{ to } -0.638 \text{ e})$ which reflect that nitrogen is the most electron dense site of serine, hence it can act as a better HB acceptor in relative to hydroxyl oxygen as well as carbonyl oxygen. The above said order also infers that ‘O’ of side chain $-CH_2OH$ of serine is better HB acceptor as compared to the main chain hydroxyl oxygen due to higher electron density present on the ‘O’ atom of side chain in relative to that of main chain O-H. Significant deshielding of the H atom involved in unconventional $C-H \cdots O$ HBs has been observed. However, the atomic charge on H atom involved in unconventional HB donor C-H group is quite low but the electrostatic

Table 5. Atomic charges (e), the amount of charge transfer (CT in e) and second order delocalization energies ($E^{(2)}$ in kcal/mol) associated with orbital interactions obtained from NBO analysis for 1:1 hydrogen bonded complexes of serine–water and serine–HP at B3LYP/aug-cc-pVDZ level.

Serine–water					Serine–HP				
Complexes	Atomic Charges	CT	Orbital interactions	E ⁽²⁾	Complexes	Atomic Charges	CT	Orbital interactions	E ⁽²⁾
I-A	q _{N5} (q _{H16})	+0.002	n _{N5} → σ [*] _{H16–O15}	20.42	I-A'	q _{N5} (q _{H16})	−0.918(0.502)	n _{N5} → σ [*] _{H16–O15}	31.14
	q _{O15} (q _{H6})	−1.001(0.528)	n _{O15} → σ [*] _{H6–O3}	25.54		q _{O15} (q _{H6})	−0.536(0.519)	n _{O15} → σ [*] _{H6–O3}	20.63
II-A	q _{N5} (q _{H15})	+0.003	n _{N5} → σ [*] _{H15–O16}	14.22	II-A'	q _{N5} (q _{H15})	−0.914(0.496)	n _{N5} → σ [*] _{H15–O16}	29.50
	q _{O16} (q _{H14})	−1.003(0.512)	n _{O16} → σ [*] _{H14–O13}	18.21		q _{O16} (q _{H14})	−0.533(0.502)	n _{O16} → σ [*] _{H14–O13}	10.55
III-A	q _{N5} (q _{H15})	+0.002	n _{N5} → σ [*] _{H15–O16}	14.26	III-A'	q _{N5} (q _{H15})	−0.927(0.495)	n _{N5} → σ [*] _{H15–O16}	30.93
	q _{O16} (q _{H14})	−1.004(0.512)	n _{O16} → σ [*] _{H14–O13}	18.71		q _{O16} (q _{H14})	−0.531(0.504)	n _{O16} → σ [*] _{H14–O13}	9.88
IV-A	q _{N5} (q _{H16})	+0.009	n _{N5} → σ [*] _{H16–O15}	11.67	IV-A'	q _{N5} (q _{H16})	−0.923(0.499)	n _{N5} → σ [*] _{H16–O15}	28.54
	q _{O15} (q _{H6})	−0.991(0.529)	n _{O15} → σ [*] _{H6–O3}	18.67		q _{O15} (q _{H6})	−0.528(0.518)	n _{O15} → σ [*] _{H6–O3}	18.32
I-B	q _{O15} (q _{H9})	+0.013	n _{O15} → σ [*] _{H9–N5}	5.76	I-B'	q _{O15} (q _{H9})	−0.539(0.408)	n _{O15} → σ [*] _{H9–N5}	4.44
	q _{O1} (q _{H16})	−0.666(0.504)	n _{O1} → σ [*] _{H16–O15}	5.32		q _{O1} (q _{H15})	−0.670(0.501)	n _{O1} → σ [*] _{H15–O16}	12.62
II-B	q _{O15} (q _{H9})	−0.997(0.415)	n _{O15} → σ [*] _{H9–N5}	1.62	II-B'	q _{O17} (q _{H9})	−0.500(0.412)	n _{O17} → σ [*] _{H9–N5}	2.40
	q _{O1} (q _{H16})	−0.662(0.508)	n _{O1} → σ [*] _{H16–O15}	6.51		q _{O1} (q _{H15})	−0.666(0.502)	n _{O1} → σ [*] _{H15–O16}	11.52
III-B	q _{O15} (q _{H9})	−0.988(0.421)	n _{O15} → σ [*] _{H9–N5}	5.61	III-B'	q _{O17} (q _{H9})	−0.485(0.413)	n _{O17} → σ [*] _{H9–N5}	5.86
	q _{O1} (q _{H15})	−0.657(0.498)	n _{O1} → σ [*] _{H15–O16}	1.74		q _{O1} (q _{H15})	−0.680(0.489)	n _{O1} → σ [*] _{H15–O16}	9.89
IV-B	q _{O16} (q _{H10})	−0.981(0.408)	n _{O16} → σ [*] _{H10–N5}	7.76	IV-B'	q _{O17} (q _{H10})	−0.500(0.401)	n _{O17} → σ [*] _{H10–N5}	4.39
	q _{O16} (q _{H11})	−0.981(0.201)	n _{O16} → σ [*] _{H11–C8}	1.89		q _{O16} (q _{H11})	−0.473(0.204)	n _{O16} → σ [*] _{H11–C8}	2.21
I-C	q _{O1} (q _{H17})	+0.016	n _{O1} → σ [*] _{H17–O15}	9.77	I-C'	q _{O1} (q _{H15})	−0.677(0.507)	n _{O1} → σ [*] _{H15–O16}	24.85
	q _{O15} (q _{H14})	−0.993(0.521)	n _{O15} → σ [*] _{H14–O13}	19.33		q _{O17} (q _{H14})	−0.511(0.516)	n _{O17} → σ [*] _{H14–O13}	19.47
II-C	q _{O1} (q _{H16})	+0.025	n _{O1} → σ [*] _{H16–O15}	7.52	II-C'	q _{O1} (q _{H17})	−0.682(0.496)	n _{O1} → σ [*] _{H17–O16}	19.09
	q _{O15} (q _{H6})	−0.987(0.530)	n _{O15} → σ [*] _{H6–O3}	21.04		q _{O15} (q _{H6})	−0.506(0.521)	n _{O15} → σ [*] _{H6–O3}	22.67
III-C	q _{O1} (q _{H16})	+0.027	n _{O1} → σ [*] _{H16–O15}	7.42	III-C'	q _{O15} (q _{H6})	−0.677(0.504)	n _{O1} → σ [*] _{H16–O15}	13.36
	q _{O15} (q _{H6})	−0.985(0.531)	n _{O15} → σ [*] _{H6–O3}	21.81		q _{O15} (q _{H6})	−0.509(0.520)	n _{O15} → σ [*] _{H6–O3}	15.54
II-D	q _{O13} (q _{H15})	−0.788(0.498)	n _{O13} → σ [*] _{H15–O16}	10.49	II-D'	q _{O13} (q _{H15})	−0.788(0.487)	n _{O13} → σ [*] _{H15–O16}	16.94
	q _{O16} (q _{H7})	−0.999(0.272)	n _{O16} → σ [*] _{H7–C4}	0.87		q _{O17} (q _{H7})	−0.496(0.273)	n _{O17} → σ [*] _{H7–C4}	2.43

Table 5. (contd.)

Serine–water						Serine–HP			
Complexes	Atomic Charges	CT	Orbital interactions	E ⁽²⁾	Complexes	Atomic Charges	CT	Orbital interactions	E ⁽²⁾
III-D	qO3(qH15) qO16(qH7)	−0.746(0.493) −0.979(0.258)	no3 → σ [*] _{H15-O16} no16 → σ [*] _{H7-C4}	3.19 0.70	III-D'	qO3(qH15) qO16(qH7)	−0.750(0.488) −0.486(0.251)	no3 → σ [*] _{H15-O16} no16 → σ [*] _{H7-C4}	6.93 0.20
IV-D	qO13(qH17) qO15(qH7)	−0.794(0.502) −1.002(0.279)	no13 → σ [*] _{H17-O15} no15 → σ [*] _{H7-C4}	9.61 1.56	IV-D'	qO13(qH18) qO17(qH7)	−0.792(0.490) −0.496(0.271)	no13 → σ [*] _{H18-O17} no17 → σ [*] _{H7-C4}	0.22 16.71
III-E	qO13(qH15)	−0.794(0.497)	no13 → σ [*] _{H15-O16}	10.13	III-E'	qO15(qH12)	−0.499(0.223)	no15 → σ [*] _{H12-C8}	0.68 0.58
IV-F	qO3(qH15) qO16(qH10)	−0.736(0.497) −0.983(0.415)	no3 → σ [*] _{H15-O16} no16 → σ [*] _{H10-N5}	2.72 7.35	IV-F'	qO13(qH15) qO3(qH15)	−0.795(0.488) −0.746(0.487)	no13 → σ [*] _{H15-O16} no3 → σ [*] _{H15-O16}	16.00 3.99
IV-G	qO1(qH15) qO16(qH7)	−0.676(0.498) −0.984(0.277)	no1 → σ [*] _{H15-O16} no16 → σ [*] _{H7-C4}	1.03 1.07	IV-G'	qO17(qH10) qO1(qH15)	−0.497(0.409) −0.672(0.485)	no17 → σ [*] _{H10-N5} no1 → σ [*] _{H15-O16}	1.01 3.84
I-H	qO1(qH15) qO16(qH7)	−0.662(0.504) −1.001(0.267)	no1 → σ [*] _{H15-O16} no16 → σ [*] _{H7-C4}	9.35 0.06		qO17(qH7)	−0.498(0.272)	no17 → σ [*] _{H7-C4}	2.00
II-I	qO16(qH11) qO3(qH15)	−1.001(0.231) −0.747(0.40)	no16 → σ [*] _{H11-C8} no3 → σ [*] _{H15-O16}	1.14 3.50		qO13(qH18)	−0.780(0.484)	no13 → σ [*] _{H18-O17}	8.66
II-J	qO16(qH11)	−0.972(0.226)	no16 → σ [*] _{H11-C8}	1.01					
IV-K	qO13(qH15)	−0.790(0.497)	no13 → σ [*] _{H15-O16}	11.09					
IV-L	qO15(qH9)	−0.973(0.428)	no15 → σ [*] _{H9-N5}	6.12					
	qO1(qH15)	−0.660(0.498)	no1 → σ [*] _{H15-O16}	6.09

Figure 6. Natural atomic charges (e) calculated at B3LYP/aug-cc-pVDZ level for the conformers of serine using NBO analysis.

contribution remains significant as HB acceptor atom O has high electron density. The atomic charge on 'O' atom of water lies in range -0.972 to -1.004 e, while this value on 'O' atom of HP is nearly half i.e., -0.473 to -0.539 e which indicates that the electrostatic component in HBs with water as HB acceptor is higher in relative to HBs with HP as HB acceptor. The second order perturbation energies $E^{(2)}$ associated with electron delocalization between HB donor and acceptor orbital are also listed in Table 5. The $E^{(2)}$ values reflect the stabilization resulting from electron delocalization involving the two monomeric units, hence adding to small covalent character. The charge transfer delocalization $n_{N5} \rightarrow \sigma^*_{H16-O15}$ favoring the HB strength for the most stabilized **I-A'** complex in serine–HP complexes has $E^{(2)}$

value 31.14 kcal/mol which is the highest among all the complexes under study. This reflects that the strong HB interaction results when HP acts as HB donor to amino nitrogen of serine. On the other hand, in case of serine–water complexes, the strong HB interaction results when water acts as HB acceptor to main chain hydroxyl group of serine with orbital interaction $n_{O15} \rightarrow \sigma^*_{H6-O3}$ having $E^{(2)}$ value 25.54 kcal/mol. The $E^{(2)}$ values for $n_N \rightarrow \sigma^*_{H-O(HP)}$ interaction in **I-A'** (31.14 kcal/mol), **II-A'** (29.50 kcal/mol), **III-A'** (30.93 kcal/mol), **IV-A'** (28.54 kcal/mol) are significantly higher in relative to $E^{(2)}$ values for $n_N \rightarrow \sigma^*_{H-O(water)}$ in **I-A** (20.42 kcal/mol), **II-A** (14.22 kcal/mol), **III-A** (14.26 kcal/mol), **IV-A** (11.67 kcal/mol), thus the $E^{(2)}$ values for $n_N \rightarrow \sigma^*_{H-O}$ interactions indicate that electron delocalization resulting in

imparting covalent character to the intermolecular HBs are stronger in serine–HP complexes in comparison to serine–water complexes. This can be rationalized on the basis of better HB donor ability of HP as compared to water which is in accordance with relative acidic and basic character of water and HP. The $E^{(2)}$ values for $n_{O(\text{water})} \rightarrow \sigma^*_{\text{H-O}}$ interaction in **A** complexes are higher in relative to $E^{(2)}$ values for $n_{O(\text{HP})} \rightarrow \sigma^*_{\text{H-O}}$ interaction in **A'** complexes which is due to the fact that water is better hydrogen bond acceptor than HP. Comparison of $E^{(2)}$ values of all the complexes under study suggests that N of serine is a better HB acceptor in relative to hydroxyl oxygen as well as carbonyl oxygen which is in close agreement with NBO charge analysis and higher basicity of N. The analysis of $E^{(2)}$ values also indicate towards the better HB acceptor ability of 'O' of side chain O–H relative to that of main chain O–H and the same is inferred by atomic charge analysis. It is observed that the complexes **II-C**, **II-C'**, **II-C₁'**, **III-C**, **III-C'**, **III-C₁'**, where water/HP binds to –COOH unit of serine forming a hydrogen-bonded closed ring structure, exhibit a remarkable resonance-assisted hydrogen bonding (RAHB) mechanism. In these complexes, the $E^{(2)}$ value for $n_{O1} \rightarrow \sigma^*_{\text{C2-O3}}$ orbital interaction decreases with simultaneous increase in $E^{(2)}$ value for $n_{O3} \rightarrow \sigma^*_{\text{C2-O1}}$ orbital interaction upon complexation with water/HP. In the literature, it has been shown that the six-membered ring of glycine–HP complex where HP binds to –COOH unit of glycine, exhibit strong RAHB mechanism.³¹ In the present study, both seven-membered (**II-C'**, **III-C'**) as well as six-membered serine–HP complexes (**II-C₁'**, **III-C₁'**) exhibit strong resonance-assisted hydrogen bonding (RAHB) mechanism. It is well-known that RAHB mechanism enhances the HB strength.

NBO analysis also provides a convenient basis for investigating charge transfer (CT) during complex formation. Table 5 illustrates the values of net CT from HP to serine for serine–HP complexes and from water to serine for serine–water complexes under study at **L1** level. These values have been evaluated utilizing the computed natural charges. The complexes marked as **A/A'** involve HBs with both serine and water/HP acting as HB donor and acceptor, the CT occurs from serine to water/HP and vice-versa. The net CT values of **A** complexes being positive indicate that CT from water to serine is higher than that from serine to water, i.e., serine moiety attracts electronic charge from water. Contrary to this, the CT values are negative in the corresponding complexes marked as **A'**, indicating that HP attracts electronic charge from serine. This is also supported by $E^{(2)}$ values associated with orbital interactions that strengthen the respective HBs. The $E^{(2)}$ values

Figure 7. (a) A plot of the stabilization energies ΔE_{BSSE} of the serine–water complexes versus second order delocalization energies $E^{(2)}$ obtained from NBO analysis at B3LYP/aug-cc-pVDZ level. (b) A plot of the stabilization energies ΔE_{BSSE} of the serine–HP complexes versus second order delocalization energies $E^{(2)}$ obtained from NBO analysis at B3LYP/aug-cc-pVDZ level.

also reflect that higher stabilization is associated with electron delocalization from serine to HP relative to that in case of serine to water. Figures 7 (a) and (b) show a good linear relationship between ΔE_{BSSE} values and $E^{(2)}$ values with R 0.956 and 0.941 for serine–water and serine–HP complexes, respectively. This highlights the importance of orbital interactions in the strength of HBs.

3.2e SAPT analysis: Symmetry-adapted perturbation theory (SAPT) developed by Jeziorski *et al.*, is a very useful method to explore the nature of intermolecular interactions stabilizing the complexes. The method decomposes the stabilization energy (E_{int}) resulting from the intermolecular interactions into energy components having a clear physical meaning, like electrostatic (E_{els}), induced (E_{ind}), dispersion (E_{disp}) and exchange (E_{exch}) interactions, etc. The SAPT components for the serine–water and serine–HP complexes at **L2** level are summarized in Table 6. The electrostatic, induced and dispersion are the main

Table 6. SAPT components (kcal/mol) of the stabilization energy for 1:1 hydrogen bonded complexes of serine–water and serine–HP at MP2/aug-cc-pVDZ level.

Serine–water complexes							Serine–HP complexes						
	E_{els}	E_{ind}	E_{disp}	E_{exc}	$\delta E_{int,r}^{HF}$	E_{int}		E_{els}	E_{ind}	E_{disp}	E_{exc}	$\delta E_{int,r}^{HF}$	E_{int}
I-A	−24.66	−10.92	−4.72	33.04	−5.46	−12.72	I-A'	−21.51	−13.47	−7.11	34.61	−6.01	−13.49
II-A	−19.05	−8.07	−4.52	26.42	−3.93	−9.15	II-A'	−17.20	−9.93	−6.99	28.43	−4.84	−10.53
III-A	−20.83	−8.69	−4.96	29.17	−4.02	−9.33	III-A'	−20.06	−11.64	−8.02	33.78	−5.75	−11.69
IV-A	−17.96	−7.32	−4.36	24.60	−3.96	−9.00	IV-A'	−16.46	−10.13	−5.88	26.54	−4.95	−10.88
I-B	−9.32	−3.44	−2.95	11.87	−1.98	−5.82	I-B'	−8.42	−4.30	−5.19	14.78	−2.01	−5.14
II-B	−11.66	−4.55	−4.10	18.06	−2.83	−5.08	II-B'	−10.77	−6.11	−6.18	19.18	−3.25	−7.13
III-B	−12.29	−5.16	−4.07	17.89	−2.97	−6.60	III-B'	−11.92	−6.95	−7.05	21.02	−3.13	−8.03
IV-B	−12.86	−5.20	−3.99	18.19	−2.07	−5.93	IV-B'	−12.36	−7.09	−6.73	22.46	−4.16	−7.88
I-C	−21.22	−9.26	−6.42	30.57	−4.37	−10.70	I-C'	−18.47	−11.44	−8.34	32.05	−5.87	−12.07
II-C	−17.91	−7.86	−5.43	26.36	−4.21	−9.05	II-C'	−20.15	−12.36	−9.25	35.70	−6.31	−12.37
							II-C₁'	−19.03	−10.60	−8.27	33.78	−5.92	−10.04
III-C	−18.78	−8.33	−5.67	28.07	−4.54	−9.25	III-C'	−20.19	−12.35	−9.33	35.91	−6.72	−12.68
							III-C₁'	−19.17	−10.70	−8.21	33.62	−5.79	−10.25
II-D	−13.46	−5.78	−4.75	20.07	−3.82	−7.74	II-D'	−13.17	−8.13	−8.37	25.52	−3.83	−7.98
III-D	−9.08	−3.55	−3.59	13.91	−2.23	−4.54	III-D'	−7.86	−4.43	−5.57	14.97	−2.28	−5.17
IV-D	−14.48	−6.12	−5.12	21.64	−3.75	−7.83	IV-D'	−13.73	−8.29	−8.69	26.27	−4.07	−8.51
III-E	−12.47	−5.14	−4.16	18.93	−2.75	−5.59	III-E'	−13.04	−7.51	−7.07	25.17	−4.21	−6.66
IV-F	−12.85	−5.17	−4.06	17.57	−2.32	−6.83	IV-F'	−12.08	−6.03	−6.59	21.50	−3.12	−6.32
IV-G	−9.56	−3.56	−3.83	15.16	−2.69	−4.48	IV-G'	−12.45	−6.89	−6.65	20.65	−2.92	−8.26
I-H	−13.92	−5.81	−4.99	20.61	−3.27	−7.38							
II-I	−6.12	−2.40	−2.33	8.31	−0.71	−3.25							
II-J	−10.40	−4.37	−3.44	15.08	−1.70	−4.83							
IV-K	−10.08	−4.09	−3.30	14.51	−1.82	−4.78							
IV-L	−9.51	−3.85	−3.24	13.72	−1.39	−4.27							

stabilizing components. The sum of all the three attractive components, electrostatic, induced and dispersion, overrides the repulsive exchange component, thus indicating the stability of complexes. The $\delta E_{int,r}^{HF}$ component is found to be stabilizing in all complexes. The largest attractive SAPT component is electrostatic that accounts for 56–61% and 44–51% of the total attractive interactions in serine–water and serine–HP complexes, respectively, dominating over other two stabilizing components. The second most important attractive component is induced component and its percentage contribution in serine–water and serine–HP complexes is 21–27% and 24–32%, respectively, thus the intermolecular interactions are largely influenced by polarization caused by electron cloud and nuclear charges. The dispersion component is playing the least role in the stability of complexes and contributes about 11.7–22.6% and 17–31% to the total stabilization energy in the serine–water and serine–HP complexes, respectively, suggesting the relative importance of induction energy over the dispersion energy. The analysis of SAPT components suggests that induced and dispersion components strongly contribute to the overall stabilization of serine–HP complexes relative to serine–water complexes. But the percentage

stability due to the electrostatic component is higher in serine–water complexes relative to that in serine–HP complexes.

4. Conclusions

A comparative study on serine–water and serine–hydrogen peroxide (HP) hydrogen-bonded complexes has been carried out. The ΔE_{BSSE} values for serine–water complexes fall in the range −2.76 to −12.46 kcal/mol while for serine–HP complexes, the range is −4.54 to −12.73 kcal/mol at MP2/aug-cc-pVDZ level. Analysis of geometrical parameters, NBO analysis, SAPT analysis along with red/blue shift infers the following conclusions:

- 1) The most stable complexes **I-A** and **I-A'** among the series of serine–water and serine–HP complexes, respectively, possess two similar intermolecular hydrogen bonding interactions with common HB donor and acceptor atoms. The $O-H \cdots O_{water}$ is the most stabilizing interaction in **I-A** complex followed by $N \cdots H-O_{water}$, whereas reverse happens in the case of **I-A'** complex with $N \cdots H-O_{HP}$ being the strongest interaction followed by $O-H \cdots O_{HP}$. This

is due to the fact that water is a better proton acceptor and HP a better proton donor.

- 2) Six complexes **II-C**, **II-C'**, **II-C₁'**, **III-C**, **III-C'**, **III-C₁'** where water/HP is bonded to the -COOH unit of serine, exhibit remarkable RAHB mechanism which is well known to enhance HB strength.
- 3) The magnitude of red-shift in the stretching frequency of O-H_{HP} bond (-50.43 to -577.94 cm⁻¹) is significantly higher than that of O-H_{water} (-23.27 to -334.46 cm⁻¹). This is due to the fact that HP is a better proton donor than water and has been explained on the basis of the difference in acidity of water and HP.
- 4) The energy decomposition analysis with the utilization of SAPT method indicates that electrostatic interactions play a dominant role in stabilizing all the complexes under study. The contribution of the electrostatic component is higher in serine–water complexes relative to serine–HP complexes, while dispersion component comparatively small contributor is in the reverse order.
- 5) The covalent character in the HBs gained by electron density shift from HB acceptor to the donor is higher in serine–HP complexes relative to serine–water complexes as suggested by NBO and SAPT studies.

Supplementary Information (SI)

Table S1 includes the optimized parameters for the four lowest energy conformers of serine at **L1** and **L2** theoretical levels. Tables S2–S42 include the optimized parameters for the serine–water and serine–HP complexes at the same theoretical levels mentioned above. Table S43 incorporates the intra-molecular HB distances in serine conformers and in 1:1 hydrogen bonded complexes of serine–water and serine–HP at **L2** level. Supplementary information is available at www.ias.ac.in/chemsci.

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Conflict of Interest The authors declare that they have no conflict of interest.

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