

Density functional theory, natural bond orbital and quantum theory of atoms in molecule analyses on the hydrogen bonding interactions in tryptophan-water complexes

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Abstract. The tryptophan-water (Trp-H₂O) complexes formed by hydrogen bonding interactions were investigated at the ω B97XD/6-311++G(d,p) level. Five Trp-H₂O complexes possessing various types of hydrogen bonds (H-bonds) were characterized by geometries, energies, vibrational frequencies. The nature of the H-bonds were characterized by the natural bond orbital (NBO) and the quantum theory of atoms in molecule (QTAIM) analyses as well. The intramolecular H-bond formed between the amino and carboxyl oxygen atom of tryptophan was retained in most of the complexes, and the cooperativity between the intra and intermolecular H-bonds exist in some complexes. The intramolecular H-bond and some intermolecular H-bonds are strong and have partial covalent character. The H-bonds formed between carboxyl and oxygen/nitrogen atoms are stronger than other H-bonds. The H-bonds involving methylene of tryptophan as H-donor are weak H-bonds. For all complexes, ΔE_{ele} and ΔE_{ex} makes major contributions to the total interaction energy (ΔE_{MP2}), while ΔE_{disp} is the smallest component of the interaction energy. Both hydrogen bonding interaction and structural deformation play important roles in the relative stabilities of the complexes. Regardless of strong H-bonds, the stabilities of some complexes are weakened by the serious structural deformations.

Keywords. Natural bond orbital (NBO); quantum theory of atoms in molecule (QTAIM); localized molecular orbital energy decomposition analysis (LMO-EDA); tryptophan; hydrogen bond.

1. Introduction

Tryptophan (Trp) is a kind of essential amino acid for humans and animals. Moreover, Trp has served as a useful probe of its local environment in proteins since the emission wavelength and excited-state lifetime depend on its environment. Trp is the only one amino acid which has both a complex structure and physiological and biochemical function in various amino acids.^{1,2} Trp was studied experimentally and theoretically in the ground and excited state^{3,4} because of its large absorption in the UV and its use as conformational fluorescence label in proteins. Most of the theoretical and experimental studies reported so far are devoted to the Trp and its various conformers. Levy and coworkers studied the UV spectroscopy of jet-cooled Trp and identified six different conformations in the resonantly enhanced two-photo ionization spectrum.⁵ Five of the six conformers were confirmed nicely by the high-resolution vibronic spectra of Trp in 0.38 K cold helium droplets.⁶ Compagnon *et al.* measured the permanent

electric dipole of tryptophan isolated in a molecular beam at 85 K,⁷ which gave different results from that of the Levy group. A systematic and extensive conformational search for the gas-phase tryptophan has been performed by Huang and Lin,⁸ and the results support the conclusion drawn by Compagnon *et al.* that only one dominant isomer existed in the molecular beam at 85 K and add further evidence that the supersonic jet expansion or embedding helium droplets did not produce an equilibrium distribution. Recently, the photochemistry of the neutral and zwitterionic form with two water molecules were analysed with *ab initio* methods.⁹

In general, zwitterionic forms of amino acids are stabilized in the crystalline state and in a solution. On the other hand, the neutral form of amino acids is also found in the gas phase and low-temperature inert matrixes, which has stimulated extensive investigation of the transformation of Trp from the neutral form to the zwitterionic form. As previous researches have reported, eight or more water molecules may be necessary to render the zwitterionic structures of tryptophan-water (Trp-H₂O) complexes.⁹ The conformational picture of such Trp-H₂O complexes is

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considerably complicated and the calculation would be prohibitively expensive. However, the Trp-H₂O complexes may serve as a useful model system for the exploration of tryptophan-water complexes that are characteristic for hydrated zwitterionic Trp. Preliminary knowledge of these mechanisms will certainly be helpful for the future exploration of the nature of Trp in larger complexes. In this paper, the structures of Trp-H₂O complexes formed by the hydrogen bonding interaction between Trp and water was studied. The energetic, vibrational frequencies of H-bonds were investigated. The quantum theory of atoms in molecules (QTAIM)^{10–12} and natural bond orbital (NBO)¹³ analyses were also carried out to study the nature of H-bonds in Trp-H₂O complexes.

2. Computational details

All DFT calculations were performed with the Gaussian09¹⁴ with the default convergence criteria without any constraint on the geometry. The ω B97XD functional¹⁵ with the 6–311++G(d,p) basis set^{16,17} was used to investigate the electronic structure of the Trp-H₂O systems. The ω B97XD functional includes empirical dispersion and can better treat hydrogen bonding and van der Waals interactions than conventional DFT. In the beginning, the geometries of the isolated Trp and water monomers were fully optimized. The complexes were constructed starting from the most stable Trp and water monomers. All complexes were also fully optimized at the same level. The harmonic vibrational frequencies were calculated with analytic second derivatives at the same level, which confirm the structures as minima and enable the evaluation of zero-point vibrational energies (ZPVE). To take into account the effects of the basis set superposition error (BSSE), the counterpoise (CP) correction¹⁸ which was implemented in order to ensure that complexes and monomers are being computed with a consistent basis set. Finally, the interaction energies were calculated based on the ZPVE and BSSE corrections. In order to analyse the properties of the H-bond interactions in complexes, the QTAIM analyses were carried out using the wave functions obtained at ω B97XD at 6–311++G(d,p) level by the software AIM2000,¹⁹ the bond critical point (BCP) of H-bonds and its electron density topologic information can help us to evaluate the nature of H-bond. To understand the nature of hydrogen bonding interaction in complexes, the localized molecular orbital energy decomposition analysis (LMOEDA)²⁰ were carried out using the Gamess electronic structure program code.²¹

3. Results and discussion

The proton transfer reaction mechanism in Trp moiety of Trp-H₂O complex has been studied.²² In this work, the Trp and water monomers were optimized at the ω B97XD/6–311++G(d,p) level and the molecular graphs were presented in figure 1. As shown in figure 1, Trp can offer several possible proton donor/acceptor sites to form H-bond. The hydroxyl or amino groups of Trp can donate proton to form H-bond. Moreover, the methylene of Trp also acts as a H-donor in some complexes. The oxygen atom of carbonyl is the major H-acceptor of Trp, and the nitrogen atom of amino can act as H-acceptor to form intramolecular H-bond in some complexes.

3.1 Structures

In this article, different complexes were taken into account to analyse various types of H-bonds. All molecular graphs of optimized Trp-H₂O complexes were shown in figure 2, and the structural parameters of H-bonds were listed in table 1. The vibrational frequency calculations confirmed that all optimized complexes have no imaginary frequencies and are stable structures. According to the QTAIM, both inter and intramolecular H-bonds can be characterized by the BCPs between H-donor (X–H) and H-acceptor (Y). Therefore, the existence of BCP and the electron density topological properties of BCP can be used to study the nature of H-bond. Ring critical point (RCP) can also be found when a ring structure was formed due to multiple H-bonds. There are two RCPs related with the benzene and indolyl rings of Trp, which have no relationship with H-bonds (figure 1). As shown in

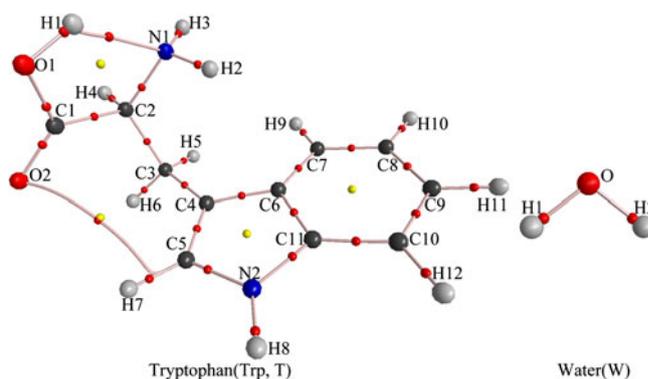


Figure 1. Molecular graphs of free Trp monomer. Large circles correspond to attractors attributed to atomic positions: gray, H; blue, N; black, C; red, O. Small circles are attributed to critical points: red, bond critical point; yellow, ring critical point.

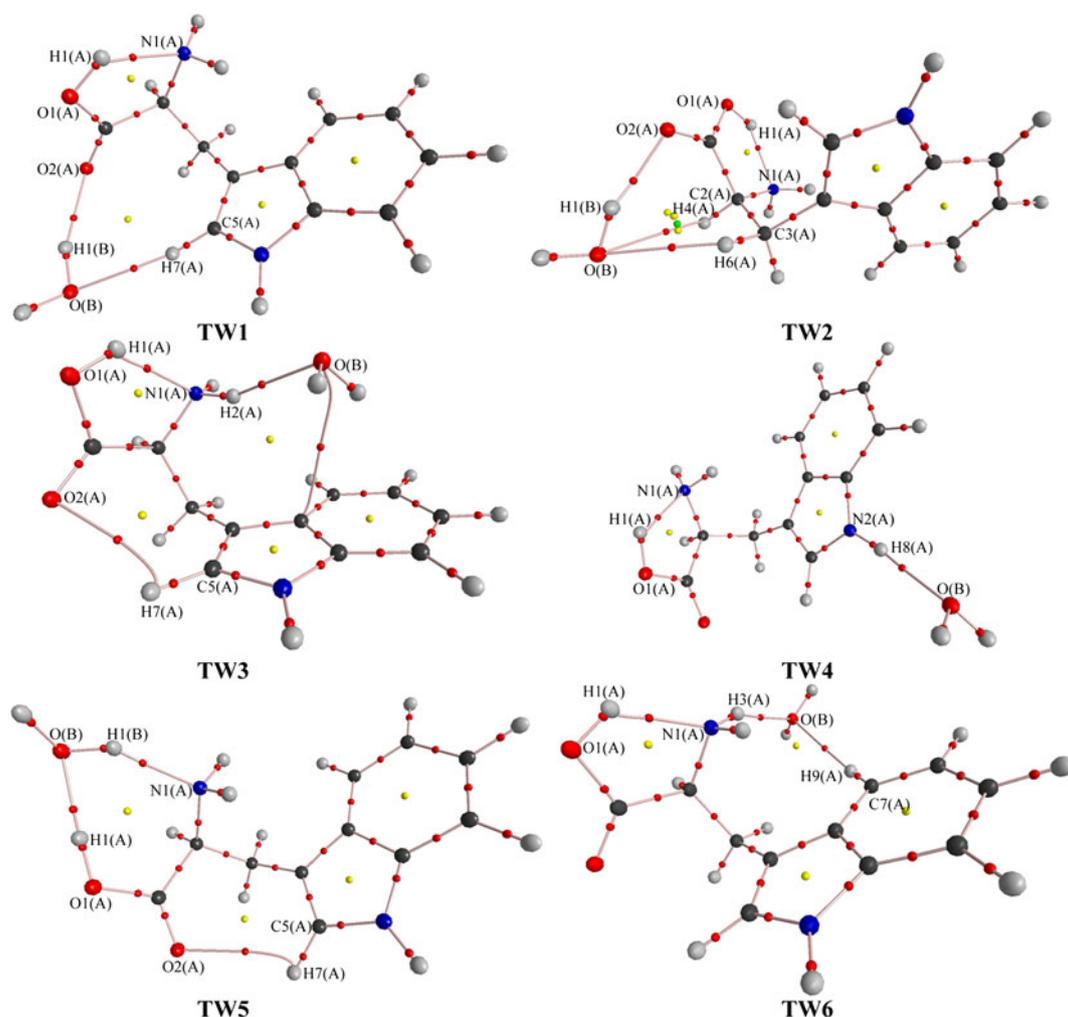


Figure 2. Molecular graphs of Trp-H₂O complexes. Large circles correspond to attractors attributed to atomic positions: gray, H; blue, N; black, C; red, O. Small circles are attributed to critical points: red, bond critical point; yellow, ring critical point.

figure 1, due to the intramolecular O1H1^T...N1^T H-bond in Trp monomer, a ring structure was formed and can be characterized by the BCP and corresponding RCP on the basis of QTAIM. Such intramolecular O1H1^T...N1^T H-bond are retained in all Trp-H₂O complexes except **TW5**. The cleavage of the intramolecular O1H1^T...N1^T H-bond in **TW5** indicates that the serious structural deformation occurred in **TW5** than other complexes. The new intramolecular C5H7^T...O2^T H-bond seems to be formed in **TW3** and **TW5**, respectively. In addition, one cage structure was formed by multiple H-bonds in **TW2** and is characterized by cage critical point (CCP).

As shown in figure 2, only one intermolecular H-bond was formed between Trp and water in **TW3** and **TW4**, respectively. However, because the distance between the centre of benzene ring and the proton of the hydroxyl of water in **TW3** is about 2.520 Å, an π H-bond seems to be formed between the benzene ring

and water molecule. When one water molecule is above the benzene ring, there is a tendency to form π H-bond between them because the sucking–electron ability of benzene is very strong. Unfortunately, neither QTAIM nor NBO analyses can give direct evidence for such π H-bond. For the other complexes (**TW1**, **TW2** and **TW5**), multiple intermolecular H-bonds can be found, respectively.

Structural parameters of H-bonds can provide some rough information on the nature of H-bonds. It is well known that the H-bond formation is connected with the elongation of the proton donating X-H bond (except of the special case of so-called blue-shifted H-bonds) as well as the shortening of H...Y bond. The shorter H...Y bond or the longer X-H bond is, the stronger the interaction is, and vice versa. As shown in table 1, the H-bonds taking methylene as H–donor are very weak, which can be seen from the almost unchanged ΔR_{X-H} and longer R_{H-Y} than about 2.2 Å. The other

Table 1. Structural parameters (bond lengths in Å, angles in degree) of H-bonds in Trp-H₂O complexes calculated at the ω B97XD/6-311++G(d,p) level.

Complex	H-bond ^a	R_{X-H}	ΔR_{X-H}^b	$R_{H...Y}$	$\delta R_{H...Y}$	$\angle X-H...Y$
TW1	OH1 ^W ...O2 ^T	0.968	0.011	1.891	0.829	158.8
	C5H7 ^T ...O ^W	1.082	0.002	2.246	0.474	163.9
	O1H1 ^T ...N1 ^T	0.984	0.004	1.859	0.891	126.7
TW2	OH1 ^W ...O2 ^T	0.969	0.012	1.893	0.827	158.9
	C3H6 ^T ...O ^W	1.090	-0.001	2.553	0.167	126.3
	C2H4 ^T ...O ^W	1.094	-0.002	2.674	0.046	112.6
	O1H1 ^T ...N1 ^T	0.984	0.004	1.851	0.899	127.1
TW3	N1H2 ^T ...O ^W	1.020	0.004	2.114	0.606	160.4
	C5H7 ^T ...O2 ^T	1.080	0.000	2.645	0.075	113.2
	O1H1 ^T ...N1 ^T	0.982	0.002	1.877	0.873	125.5
TW4	N2H8 ^T ...O ^W	1.014	0.010	1.924	0.796	174.3
	O1H1 ^T ...N1 ^T	0.980	0.000	1.880	0.870	126.1
TW5	O1H1 ^T ...O ^W	0.982	0.002	1.742	0.978	175.2
	OH1 ^W ...N1 ^T	0.982	0.025	1.839	0.911	149.3
	C5H7 ^T ...O2 ^T	1.079	-0.001	2.532	0.188	110.2
	N1H3 ^T ...O ^W	1.015	0.004	2.135	0.585	158.4
TW6	C7H9 ^T ...O ^W	1.086	0.000	2.666	0.054	156.5
	O1H1 ^T ...N1 ^T	0.981	0.001	1.885	0.865	125.6
	O1H1 ^T ...N1 ^T	0.980		1.888	0.862	125.7
Tryptophan	N1H2	1.016				
	N1H3	1.011				
	N2H8	1.004				
	C3H6	1.091				
	C2H4	1.096				
	C5H7	1.080				
H ₂ O	OH	0.957				

^aSuperscript "T" denote Trp and "W" denote H₂O

^b $\Delta R_{X-H} = R_{X-H}(\text{complexes}) - R_{X-H}(\text{free monomer})$

H-bonds involving the hydroxyl or amino as H-donor have positive ΔR_{X-H} values and are red-shifted H-bonds. The largest ΔR_{X-H} (0.025 Å) is found in the OH1^W...N1^T H-bond of **TW5**, which indicates that it seems to be the strongest intermolecular H-bond. It is worth noting that another intermolecular H-bond (O1H1^T...O^W) in **TW5** is also very strong although its ΔR_{X-H} (0.002 Å) is very small, moreover, and the intramolecular O1H1^T...N1^T H-bond was destroyed by the formation of such intermolecular H-bonds, which lead to a smaller ΔR_{X-H} of the O1H1^T...O^W H-bond compared to that of the O1H1^T...N1^T H-bond. The shortest $R_{H...Y}$ (1.742 and 1.839 Å) of the two H-bonds in **TW5** further confirms that they are the two strongest intermolecular H-bonds among all Trp-H₂O complexes. However, such strong hydrogen bonding interactions in **TW5** does not mean it is the most stable complex since the cleavage of the intramolecular O1H1^T...N1^T H-bond results in serious structural deformation which will be further discussed later.

The shorter H...Y bond means the stronger hydrogen bonding interaction. However, such a relationship is

only a rough one, even if $R_{H...Y}$ concern similar species immersed into similar environments. In other words, if the considered sample of X-H...Y systems is homogeneous. The estimation of H-bond strength directly on the basis of $R_{H...Y}$ is not possible for a heterogeneous sample if H-bonds differ in the type of H-donor and/or H-acceptor. In view of the above difficulties, a H-bond parameter $\delta R_{H...Y}$ which allow one to unify interactions to estimate their strength even if different pairs of atoms is defined as²³

$$\delta R_{H...Y} = R_H^{\text{vdW}} + R_Y^{\text{vdW}} - R_{H...Y} \quad (1)$$

where R_H^{vdW} and R_Y^{vdW} are van der Waals radii of H and Y atoms given by Bondi,²⁴ respectively, $R_{H...Y}$ is the distance between H-donor and H-acceptor. As shown in table 1, the $\delta R_{H...Y}$ of the intramolecular O1H1^T...N1^T H-bond in all Trp-H₂O complexes except **TW5** is larger than that of Trp monomer, which indicates that the intramolecular O1H1^T...N1^T H-bond was strengthened in complexes. The maximum of $\delta R_{H...Y}$ is 0.978 Å of the intermolecular O1H1^T...O^W H-bond in **TW5**, which seems to be the strongest H-bond. Of course,

another intermolecular H-bond in **TW5**, $\text{OH1}^{\text{W}} \cdots \text{N1}^{\text{T}}$, is the second strongest H-bond due to the second largest $\delta R_{\text{H}\cdots\text{Y}}$ (0.911 Å). It is worth noting that the $\delta R_{\text{H}\cdots\text{Y}}$ of the H-bonds taking methylene as H-donor is small, which implies that the $R_{\text{H}\cdots\text{Y}}$ is close to the sum of van der Waals radii of H and Y atoms. Therefore, from a structural viewpoint, the interaction between the methylene and Y atom is very weak and is the mixture of hydrogen bonding interaction and van der Waals interaction.

3.2 Vibrational frequencies

The harmonic vibrational frequencies and their shifts of H-bonds in Trp-H₂O complexes and monomers calculated at the $\omega\text{B97XD}/6\text{-}311++\text{G(d,p)}$ level were listed in table 2. The red shifts in the X–H stretching vibrational frequency have been traditionally considered one of the main fingerprints of H-bonds, assuming that formation of an H-bond weakens an X–H single bond. The larger the shift value is, the stronger the H-bond is. However, it is not easy to calculate the shifts of X–H stretching vibrational modes if it mixes with other vibrational modes. For example, the intramolecular $\text{O1H1}^{\text{T}} \cdots \text{N1}^{\text{T}}$ H-bond in Trp monomer lead to the mixture of the O–H stretching with symmetric NH_2 stretching vibration modes, which are calculated to be 3556.2 and 3536.5 cm^{-1} , respectively. Similar things also happened in Trp-H₂O complexes, so many $\Delta v_{\text{X-H}}$ values may be given for one H-bond. As shown in table 2, the largest red-shifted values (about 380 ~ 490 cm^{-1}) are found in the $\text{OH1}^{\text{W}} \cdots \text{N1}^{\text{T}}$ and $\text{O1H1}^{\text{T}} \cdots \text{O}^{\text{W}}$ H-bonds in **TW5**, which shows that the two H-bonds are the strongest red-shifted ones. The $\text{OH1}^{\text{W}} \cdots \text{O2}^{\text{T}}$ (**TW1** and **TW2**) and $\text{N2H8}^{\text{T}} \cdots \text{O}^{\text{W}}$ (**TW4**) H-bonds have larger red-shifted values of about 140 ~ 180 cm^{-1} , while other red-shifted H-bonds are tens of wavenumbers shift values. The $\text{C5H7}^{\text{T}} \cdots \text{O}^{\text{W}}$ H-bond in **TW1**, is a red-shifted H-bond with negative $\Delta v_{\text{X-H}}$ of 28.6 cm^{-1} , while other H-bonds involving methylene are blue-shifted ones because of the positive shifts. Moreover, these H-bonds usually are weak since their shifts are small. In addition, the smaller $\Delta v_{\text{X-H}}$ values of the intramolecular $\text{O1H1}^{\text{T}} \cdots \text{N1}^{\text{T}}$ H-bond do not mean that it is weak. On the contrary, it can be seen from the negative $\Delta v_{\text{X-H}}$ values that the intramolecular $\text{O1H1}^{\text{T}} \cdots \text{N1}^{\text{T}}$ H-bond was strengthened during the formation process of Trp-H₂O complex.

3.3 QTAIM analyses

To quantitatively study the nature of H-bond, the QTAIM analysis has been carried out to deepen the nature of the H-bond interactions. QTAIM has

been proved to be a powerful tool and technique to investigate hydrogen bonding interactions.^{23,25–29} For example, the characteristics of critical points provide additional information on the nature of interactions. The topological criteria of the existence of hydrogen bonding were proposed by Koch and Popelier.³⁰ According to the criteria, H-bonds should have a relatively high value of the electron density at the $\text{H} \cdots \text{Y}$ BCP (ρ_b), in the range 0.002–0.034 a.u., and the Laplacian of the electron density at $\text{H} \cdots \text{Y}$ BCP ($\nabla^2 \rho_b$) should be within the 0.024–0.139 a.u.³¹ Therefore, both ρ_b and $\nabla^2 \rho_b$ at the $\text{H} \cdots \text{Y}$ BCP are good measures of the strength of H-bond. Moreover, the criteria provide a basis to distinguish hydrogen bonding interactions from van der Waals interactions and have been proved to be valid for standard and nonconventional H-bonds.

The other characteristics may be applied to describe the considered BCP and further the atom-atom interaction. There are well-known relationships resulting from the Virial theorem between energetic topological parameters and the Laplacian of electron density at BCP

$$(1/4) \nabla^2 \rho_b = 2G_b + V_b \quad (2)$$

$$H_b = G_b + V_b, \quad (3)$$

where G_b , V_b and H_b are the kinetic, potential, and total electron energy densities at critical point, respectively. G_b is a positive value, whereas V_b is a negative one. The sign of H_b depends on which contribution, potential or kinetic, will locally prevail on the BCP. The Laplacian is negative if the modulus of the potential energy outweighs two times the kinetic energy, which implies the covalent character of interaction, and it may concern covalent bonds as well as very strong H-bonds. If the modulus of the potential energy only one time outweighs the kinetic energy, the Laplacian is positive, but H_b is negative, which implies the partial covalent character of interaction and concerns strong H-bonds.^{32,33} Moreover, the $\nabla^2 \rho_b$ at the BCP is low and positive, which is typical of closed-shell interactions. Therefore, the following criterion of strength was proposed by Popelier:³⁰ for weak and medium in strength H-bonds, $\nabla^2 \rho_b > 0$ and $H_b > 0$; for strong H-bonds, $\nabla^2 \rho_b > 0$ and $H_b < 0$; for very strong H-bonds, $\nabla^2 \rho_b < 0$ and $H_b < 0$. This classification shows that weak H-bonds eventually merge with (weaker) van der Waals interactions whereas strong H-bonds merge, at the other end of the continuum, with covalent and polar bonds. The electronic topological properties at $\text{H} \cdots \text{Y}$ BCPs of H-bonds including electron density (ρ_b), the Laplacian of the electron density ($\nabla^2 \rho_b$), kinetic energy density (G_b), potential energy density (V_b) and total electron

Table 2. The X–H stretching vibrational frequencies (strength) of H-bonds in both Trp–H₂O complexes and monomers.

Complex	H-bond	ν_{X-H}^a	$\Delta\nu_{X-H}$
TW1	OH1 ^W ...O2 ^T	3973.7 (89, as)	–37.7
		3753.5 (312, s)	–148.5
	C5H7 ^T ...O ^W	3243.6 (68)	–28.6
TW2	O1H1 ^T ...N1 ^T	3541.2 (31, s) ^b , 3495.9 (318, s) ^b	–15.0, –40.6
	OH1 ^W ...O2 ^T	3972.7 (97, as)	–38.7
		3720.8(372, s)	–181.2
TW3	C3H6 ^T ...O ^W	3147.0 (1, as)	14.6
		3090.7 (9, s) ^c , 3080.2 (14, s) ^c	11.6, 12.2
	C2H4 ^T ...O ^W	3090.7 (9, s) ^c , 3080.2 (14, s) ^c	11.6
TW4	O1H1 ^T ...N1 ^T	3488.4 (303)	–67.8, –48.1 ^f
	N1H2 ^T ...O ^W	3644.3 (30, as)	–1.0
		3517.2 (210, s), 3482.5 (187, s)	–39.0, –54.0
TW5	C5H7 ^T ...O2 ^T	3283.4 (2)	11.2
		3517.2 (210, s) ^b , 3482.5 (187, s) ^b	–39.0, –54.0
	N2H8 ^T ...O ^W	3578.5 (685)	–140.3
TW6	O1H1 ^T ...N1 ^T	3544.6 (81, s) ^b , 3526.3 (204, s) ^b	–11.6, –10.2
		3523.5 (834, s) ^d , 3515.7 (648, s) ^d	–32.7, –20.8 ^g
	O1H1 ^T ...O ^W	3419.7 (276, s) ^e	–482.4
H ₂ O	OH1 ^W ...N1 ^T	3523.5 (834, as)	–487.9
		3523.5 (834, s) ^d , 3515.7 (648, s) ^d	–386.3, –482.4 ^g
	C5H7 ^T ...O2 ^T	3283.9 (3)	11.7
Tryptophan	N1H3 ^T ...O ^W	3596.8 (84, as)	–48.5
		3536.1 (88, s) ^b , 3515.0 (244, s) ^b	–20.1, –21.5
	C7H9 ^T ...O ^W	3198.4 (18) ^h , 3188.7 (2) ^h , 3179.2 (1) ^h	–8.2, –6.2, –5.5
Tryptophan	O1H1 ^T ...N1 ^T	3536.1 (88, s) ^b , 3515.0 (244, s) ^b	–20.1, –21.5
		OH	4011.4 (62, as)
	OH	3902.0 (12, s)	
		O1H1	3556.2 (172, s) ^b , 3536.5 (105, s) ^b
	N1H2	3645.3 (27, as)	
	N2H8	3556.2 (172, s) ^b , 3536.5 (105, s) ^b	
		3718.7 (88)	
	C3H6	3132.4 (5, as)	
C7H9	3079.1 (35, s) ^c , 3068.0 (13, s) ^c		
	3206.6 (23) ^h , 3194.9 (2) ^h , 3184.7 (6) ^h		
	3079.1 (35, s) ^c , 3068.0 (13, s) ^c		
C2H4	3272.2 (1)		

^aAll frequencies are in cm^{–1} and the strength are in km·mol^{–1}. “as” denotes the asymmetric stretching vibration mode, and “s” denotes the symmetric stretching vibration mode

^bThe mixture exists between the symmetric NH₂ stretching and the O1H1 stretching vibration mode

^cThe mixture exists between the symmetric CH₂ (H5C3H6) stretching vibration mode and the C2H4 stretching vibration mode

^dThe mixture exists between the symmetric NH₂ stretching vibration mode and the O1H1 (Trp, T) as well as OH1 (water, W) stretching vibration modes

^eThe mixture exists between the O1H1 (Trp, T) stretching vibration mode and the OH1 (water, W) stretching vibration modes

^f–67.8 and –48.1 are the $\Delta\nu_{X-H}$ values compared to the asymmetric and symmetric H–O–H stretching vibration mode of free water molecule, respectively

^g–32.7 and –20.8 are the $\Delta\nu_{X-H}$ values compared to the O1H1 (Trp, T) stretching vibration mode, while –386.3 and –482.4 are the $\Delta\nu_{X-H}$ values compared to the OH (water, W) stretching vibration mode

^hThe mixture exists among several C–H stretching vibration modes of benzene ring

energy density (H_b) of all complexes were listed in table 3.

As shown in table 3, the intramolecular O1H1^T...N1^T H-bond in all the Trp–H₂O complexes except TW5

is the strongest H-bond since it have negative H_b and positive $\nabla^2\rho_b$ values. Moreover, the value of ρ_b is beyond the upper-limits of the range, which indicates that a partial covalent character is attributed to the

Table 3. Electron density (ρ_b), Laplacian of the electron density ($\nabla^2\rho_b$), kinetic energy density (G_b), potential energy density (V_b) and total electron energy density (H_b) in a.u. at BCPs of H-bonds in both Trp-H₂O complexes and Trp monomer by QTAIM analysis.

Complex	H-bond	ρ_b	$\nabla^2\rho_b$	V_b	G_b	H_b
TW1	OH1 ^W ...O2 ^T	0.02518	0.10199	-0.01982	0.02266	0.00284
	C5H7 ^T ...O ^W	0.01347	0.04649	-0.00808	0.00985	0.00177
	O1H1 ^T ...N1 ^T	0.04030	0.11332	-0.03515	0.03174	-0.00341
TW2	OH1 ^W ...O2 ^T	0.02724	0.10036	-0.02110	0.02310	0.00199
	C3H6 ^T ...O ^W	0.00757	0.02890	-0.00486	0.00604	0.00118
	C2H4 ^T ...O ^W	0.00665	0.02459	-0.00425	0.00520	0.00095
TW3	O1H1 ^T ...N1 ^T	0.04111	0.11416	-0.03611	0.03233	-0.00379
	N1H2 ^T ...O ^W	0.01830	0.06262	-0.01194	0.01380	0.00186
	C5H7 ^T ...O2 ^T	0.00739	0.02623	-0.00449	0.00552	0.00103
TW4	O1H1 ^T ...N1 ^T	0.03857	0.11228	-0.03332	0.03070	-0.00263
	N2H8 ^T ...O ^W	0.02505	0.09665	-0.01922	0.02169	0.00247
	O1H1 ^T ...N1 ^T	0.03831	0.11228	-0.03304	0.03055	-0.00249
TW5	O1H1 ^T ...O ^W	0.03986	0.12730	-0.03581	0.03382	-0.00199
	OH1 ^W ...N1 ^T	0.04022	0.10450	-0.03347	0.02980	-0.00367
	C5H7 ^T ...O2 ^T	0.00950	0.03458	-0.00607	0.00736	0.00129
TW6	N1H3 ^T ...O ^W	0.01668	0.06166	-0.01116	0.01329	0.00213
	C7H9 ^T ...O ^W	0.00638	0.01961	-0.00370	0.00430	0.00060
	O1H1 ^T ...N1 ^T	0.03773	0.11162	-0.03241	0.03016	-0.00226
Tryptophan	O1H1 ^T ...N1 ^T	0.03771	0.11163	-0.03236	0.03013	-0.00223

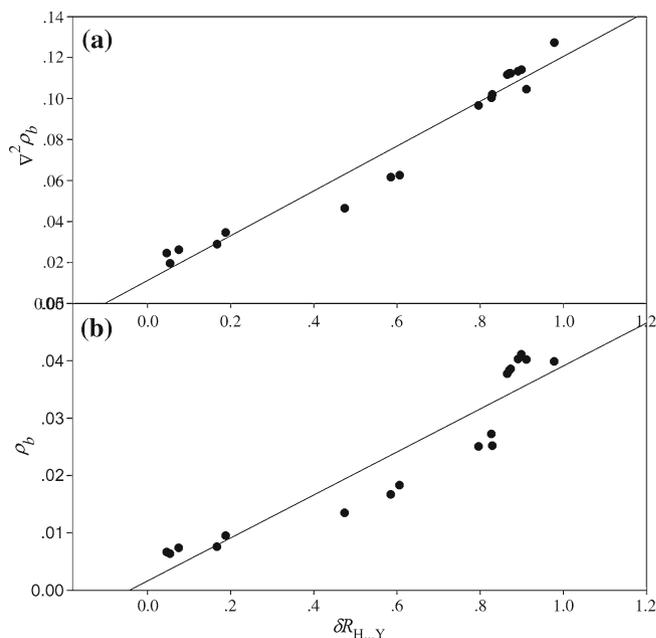
intramolecular O1H1^T...N1^T H-bond. The strength of the intramolecular O1H1^T...N1^T H-bond in Trp-H₂O complexes can also be learnt from the larger ρ_b and $\nabla^2\rho_b$ as well as more negative H_b compared to those of Trp monomer. Similarly, due to the negative H_b (-0.00367 and -0.00199 a.u.) and positive $\nabla^2\rho_b$ (0.10450 and 0.12730 a.u.), the OH1^W...N1^T and O1H1^T...O^W H-bonds in **TW5** are the two strongest intermolecular H-bonds among all Trp-H₂O complexes. Moreover, a partial covalent character is attributed to them since their ρ_b values (0.04022 and 0.03986 a.u.) are beyond the upper-limits of the range. For the other H-bonds, both ρ_b and $\nabla^2\rho_b$ fall in the ranges proposed by Popelier, moreover, the H_b values are positive, which indicates that these H-bonds are of weak or medium strengths. Especially, for the H-bonds taking methylene as H-donor, both ρ_b and $\nabla^2\rho_b$ are close to the lower-limit of criteria proposed by Popelier, which shows that they are very weak and are regarded as the mixture of hydrogen bonding interaction and van der Waals interaction. Therefore, for such extreme case, the existence of BCP is not the unique criterion to verify weak H-bond, and other methods (such as NBO) should be applied to investigate the nature of such interaction. Another embarrassment is that no direct QTAIM evidence can be found for π H-bond formed between the benzene ring and the hydroxyl of water moiety in **TW3**.

To understand the relationship between $\delta R_{H...Y}$ and topological parameters of QTAIM ($\rho_b \sim \delta R_{H...Y}$ and

$\nabla^2\rho_b \sim \delta R_{H...Y}$) were shown in figure 3, and the linear relationships between them can be expressed as

$$\nabla^2\rho_b = 0.0113 + 0.1094\delta R_{H...Y} \quad r = 0.9784 \quad (4)$$

$$\rho_b = 0.0016 + 0.0375\delta R_{H...Y} \quad r = 0.9357 \quad (5)$$

**Figure 3.** Correlation between $\delta R_{H...Y}$ and H-bond parameters of QTAIM. (a) $\delta R_{H...Y} \sim \nabla^2\rho_b$; (b) $\delta R_{H...Y} \sim \rho_b$.

It can be learnt that ρ_b is a linearly correlate to $\delta R_{H...Y}$ substantially, while a better linear relationship exists between $\nabla^2 \rho_b$ and $\delta R_{H...Y}$.

3.4 NBO and energy decomposition analyses

Generally, a certain amount of charge transfer (CT) from the H-acceptor to the H-donor is one of the characteristics attributed to H-bond, which lead to a rearrangement of electron density within each part of the molecule. Although QTAIM analysis can provide relevant information on the strength of H-bonds in Trp-H₂O complexes, it cannot provide information on the CT. The NBO method¹³ shows that for typical hydrogen bonding, a two-electron $n_B \rightarrow \sigma_{XH}^*$ intermolecular donor-acceptor interaction exists where electron density from the lone pair n_B of the H-acceptor delocalizes into the unfilled σ_{AH}^* anti-bonding orbital of the H-donor. The $n_B \rightarrow \sigma_{XH}^*$ orbital overlap is characteristic for hydrogen bonding interaction. The hydrogen bond formation leads to an increase of the occupancy of the σ_{XH}^* antibond orbital and hence the weakening and lengthening of the X-H bond. This leads to the red-shifted ν_{X-H} stretching frequency. Therefore, electron delocalization or CT effects between n_B and σ_{XH}^* may be estimated by second-order perturbation theory:

$$E(2) = -2 \frac{\langle n_B | F | \sigma_{XH}^* \rangle^2}{\varepsilon(\sigma_{XH}^*) - \varepsilon(n_B)}, \quad (6)$$

where $\langle n_B | F | \sigma_{XH}^* \rangle$ is the Fock matrix element between the n_B and σ_{XH}^* orbitals, $\varepsilon(\sigma_{XH}^*) - \varepsilon(n_B)$ is the orbital energy difference (the difference of diagonal Fock matrix element).³⁴ It is worth mentioning that the CT and the corresponding lowering of energy are attributed to hydrogen bonding interactions. In other words, the

second-perturbation energies $E(2)$ lowering is responsible for the orbital interaction of H-bond, the larger $E(2)$ values correspond to stronger CT interaction occurred in the H-bond.

The result of NBO analysis was listed in table 4. As shown in table 4, the O atom involved as H-acceptor has two branches: one has 'sp' hybrid characteristics, and the other one has 'p' hybrid characteristics; they correspond to two $E(2)$ values, respectively. On the contrary, the N atom involved as H-acceptor shows 'sp' characteristics. The sum of $E(2)$ value of 59.51 kcal·mol⁻¹ in the N2H8^T...O^W H-bond of **TW4** is the largest, which indicates the strongest CT interaction is responsible for the H-bond. Similarly, strong CT interaction in the O1H1^T...O^W H-bond of **TW5** is also confirmed by the larger sum of $E(2)$ value of 51.31 kcal·mol⁻¹. Moreover, such strong CT effects in the N2H8^T...O^W (**TW4**) and O1H1^T...O^W (**TW5**) H-bond further confirm the partial covalent character of these H-bonds, which is consistent with above discussion. For other H-bonds except the OH1^W...O2^T H-bond in **TW2**, due to the smaller $E(2)$ less than about 10.0 kcal·mol⁻¹, weaker CT interaction occurred in them. Especially, no $E(2)$ values were found for the C5H7^T...O2^T H-bond in **TW3** and **TW5**, respectively, which indicates that the major contribution to such H-bond comes from non-CT interaction rather than CT interaction.

The $E(2)$ values of intramolecular O1H1^T...N1^T H-bond in some complexes (**TW1**, **TW2** and **TW3**) are significantly larger than that of Trp monomer, which shows that stronger CT effect occurred in these complexes due to the intermolecular H-bond. In other words, there exists a certain cooperative effects between the intramolecular O1H1^T...N1^T H-bond and intermolecular H-bonds in these complexes (**TW1**, **TW2** and **TW3**). There are structural evidences for such cooperativity. The positive ΔR_{X-H} values of the

Table 4. The second-perturbation energies $E(2)$ (in kcal·mol⁻¹) of H-bonds in both Trp-H₂O complexes obtained by NBO analysis.

Complex	H-bond	$E(2)^a$	Complex	H-bond	$E(2)^a$
TW1	OH1 ^W ...O2 ^T	3.66(1.34)	TW4	N2H8 ^T ...O ^W	8.04 (51.47)
	C5H7 ^T ...O ^W	0.59 (4.45)		O1H1 ^T ...N1 ^T	3.63
	O1H1 ^T ...N1 ^T	15.62		TW5	O1H1 ^T ...O ^W
TW2	OH1 ^W ...O2 ^T	9.12(7.79)	TW6	OH1 ^W ...N1 ^T	8.27
	C3H6 ^T ...O ^W	9.63 (0.17)		N1H3 ^T ...O ^W	2.15
	C2H4 ^T ...O ^W	0.81 (1.77)		C7H9 ^T ...O ^W	1.53 (8.72)
	O1H1 ^T ...N1 ^T	17.44		O1H1 ^T ...N1 ^T	13.48
TW3	N1H2 ^T ...O ^W	0.23(7.01)	Tryptophan	O1H1 ^T ...N1 ^T	2.13
	O1H1 ^T ...N1 ^T	12.93			

^aThe values are O 'sp' hybrid branch to form the H-bond; those in the parentheses are O 'p' hybrid branch. The lone pair of N atom is mainly of 'p' character. See discussion in the text.

Table 5. The LMO–EDA results of Trp–H₂O complexes at the MP2/6–311++G(d,p) level.^a

Complex	ΔE_{ele}	ΔE_{ex}	ΔE_{rep}	ΔE_{pol}	ΔE_{disp}	ΔE_{MP2}
TW1	−13.58(41%)	−14.64(45%)	26.07	−3.98(12%)	−0.53(2%)	−6.67
TW2	−13.06(40%)	−14.75(45%)	26.27	−3.74(12%)	−0.91(3%)	−6.19
TW3	−9.95(32%)	−14.88(48%)	25.37	−2.64(9%)	−3.26(11%)	−5.36
TW4	−9.79(42%)	−9.63(41%)	17.52	−2.76(12%)	−1.14(5%)	−5.81
TW5	−29.21(35%)	−39.67(47%)	73.63	−12.04(14%)	−3.12(4%)	−10.41
TW6	−6.96(40%)	−8.03(46%)	13.72	−1.64(9%)	−0.95(5%)	−3.86

^aAll energy are in kcal·mol^{−1} except the total energy (in Hartree)

intramolecular O1H1^T...N1^T H-bond in some complexes (**TW1**, **TW2** and **TW3**) implies that it was the strengthened due to the cooperativity between the intra- and inter-molecular H-bonds. On the contrary, without such cooperativity, the $E(2)$ of the intramolecular O1H1^T...N1^T H-bond in **TW4** has a small change compared to that of Trp monomer since the intermolecular H-bond is away from the side chain of Trp, which can be seen from the unchanged $\Delta R_{\text{X-H}}$ as well.

To explore the nature of hydrogen bonding interaction, an LMO–EDA²⁰ calculations with the MP2 method was carried out, and the results were listed in table 5. In LMO–EDA, total interaction energy ΔE_{MP2} is decomposed into five terms:

$$\Delta E_{\text{MP2}} = \Delta E_{\text{ele}} + \Delta E_{\text{ex}} + \Delta E_{\text{rep}} + \Delta E_{\text{pol}} + \Delta E_{\text{disp}}, \quad (7)$$

where ΔE_{ele} is the electrostatic energy, ΔE_{ex} is the exchange energy, ΔE_{rep} is the repulsion energy, ΔE_{pol} is the polarization energy and ΔE_{disp} is the dispersion energy. As shown in table 5, the total interaction energy (ΔE_{MP2}) between Trp and H₂O is in the range of about $-3.86 \sim -10.41$ kcal·mol^{−1}. The ΔE_{MP2} (-10.41 kcal·mol^{−1}) of **TW5** is the largest among all complexes. However, the cleavage of the intramolecular O1H1^T...N1^T H-bond led to the serious structural deformation, which does not favour the stability of **TW5**. The largest stabilizing force in **TW5** is the exchange interaction of -39.67 kcal·mol^{−1}, which is counteracted simultaneously by the repulsion energy of -73.637 kcal·mol^{−1}, so the exchange-repulsion energy is unfavourable for the stability of **TW5**. The second largest stabilizing force is the electrostatic energy of about -29.21 kcal·mol^{−1}. Although the polarization energy of -12.04 kcal·mol^{−1} in **TW5** is the largest among all complexes, ΔE_{pol} makes a minor contribution to the total interaction energy between Trp and H₂O. Similar trends were found in other Trp–H₂O complexes except **TW5**, ΔE_{ele} and ΔE_{ex} makes major contributions to the total interaction energy (ΔE_{MP2}) of complexes, while ΔE_{disp} is the smallest component of the interaction energy.

4. Conclusions

In this paper, we studied the geometries, energies and IR characteristics of the H-bonds of Trp–H₂O complexes at the ω B97XD/6–311++G(d,p) level. The intramolecular O1H1^T...N1^T H-bond are retained in all complexes except **TW5**, and the cooperativity between the intra- and intermolecular H-bonds exist in **TW1**, **TW2** and **TW3**, respectively. The intramolecular O1H1^T...N1^T H-bond and the intermolecular H-bonds (OH1^W...N1^T and O1H1^T...O^W) in **TW5** are strong and have partial covalent character. The H-bonds involving methylene of Trp as H-donors are weak ones, especially the C5H7^T...O2^T H-bond in **TW3** and **TW5** are derived from non-CT interaction since no CT evidence provided by NBO analyses. There exists an π H-bond in **TW3** which involves the benzene ring as the H-acceptor. Unfortunately, no direct NBO or QTAIM evidences confirm to such π H-bond. For all complexes, ΔE_{ele} and ΔE_{ex} makes major contributions to the total interaction energy (ΔE_{MP2}), while ΔE_{disp} is the smallest component of the interaction energy. Both hydrogen bonding interaction and structural deformation play important roles in the relative stabilities of the complexes. Regardless of strong H-bond, the stability of **TW5** is weakened by the serious structural deformation. In conclusion, the variety of the hydrogen bonding motifs that occur in the studied complexes may be helpful to further understand the hydrogen bonding interactions between Trp and other small organic molecules.

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