Density Functional Theory and Topological Analysis on the Hydrogen Bonding Interactions in Cysteine-Thymine Complexes

ZHENGGUO HUANG, LEI YU, YUMEI DAI

Tianjin Key Laboratory of Structure and Performance for Functional Molecules, College of Chemistry, Tianjin Normal University, Tianjin 300387, People's Republic of China

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ABSTRACT: Hydrogen bonding interactions between amino acids and nucleic acid bases constitute the most important interactions responsible for the specificity of protein binding. In this study, complexes formed by hydrogen bonding interactions between cysteine and thymine have been studied by density functional theory. The relevant geometries, energies, and IR characteristics of hydrogen bonds (H-bonds) have been systematically investigated. The quantum theory of atoms in molecule and natural bond orbital analysis have also been applied to understand the nature of the hydrogen bonding interactions in complexes. More than 10 kinds of H-bonds including intra- and intermolecular H-bonds have been found in complexes. Most of intermolecular H-bonds involve O (or N) atom as H-acceptor, whereas the H-bonds involving C or S atom usually are weaker than other ones. Both the strength of H-bonds and the structural deformation are responsible for the stability of complexes. Because of the serious deformation, the complex involving the strongest H-bond is not the most stable structures. Relationships between H-bond length (ΔR_{X-H}) , frequency shifts (Δv) , and the electron density (ρ_b) and its Laplace $(\nabla^2 \rho_b)$ at bond critical points have also been investigated. © 2010 Wiley Periodicals, Inc. Int J Quantum Chem 111: 3915-3927, 2011

Key words: hydrogen bond; QTAIM; DFT; NBO

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Introduction

ydrogen bonding interactions between amino acids and nucleic acid bases constitute the most important interactions responsible for the specificity of protein binding [1–3]. Moreover, some reviews regarding the evolution of the genetic code [4, 5] have highlighted the relevance of specific interactions between amino acids and their codon or anticodon nucleotides. Therefore, quantitative studies on these interactions are very useful for the interpretation of a number of biological processes in physicochemical terms. However, such biological systems are so large that no current quantum chemical method is within reach for the study of them even with the most powerful computing capabilities. An alternative approach is quantitative studies on simplified model systems at a currently viable computational level. Some theoretical researches on nucleobase-amino acid complexes have been reported for uracil (or thymine) with glycine, alanine leucine, or cysteine [6-14] and with the hydrophilic side chains of asparagines [15]. These studies may provide some basic information about intrinsic affinities for hydrogen bonds (H-bonds) in the complexes, which are essential for understanding its biological function. Even in such simplified model systems, the hydrogen bonding interactions are also very complex because more than one proton donor and acceptor sites can be found in almost all nucleobase or amino acid molecule. Besides, it is sensible to ascribe the fundamental nature of hydrogen bonding interactions, hydrogen-bonded complexes must be considered carefully using a reliable theoretical model. MP2 method is deemed to be a reliable method for description of hydrogen bonding interactions. However, MP2 approach is not a cost-effective approach for the computation of such biomolecular systems even with a medium-size basis set. Density functional theory (DFT) has been accepted by the ab initio quantum chemistry community as a cost-effective approach for description of hydrogen bonding interactions. Many studies have shown that molecular structures and vibrational frequencies calculated by DFT methods are more reliable than MP2 methods [14, 16–18].

Generally, the formation of H-bond can be estimated by the structural parameters (e.g., hydrogen bond length and bond angle), and the strength of H-bond also can be determined by the enlarging or shortening of H-bond length. However, the structural parameters cannot provide sufficient information to accurately describe the nature of hydrogen bonding interactions in biological system. Therefore, a scientific method for description of hydrogen bonding interactions is highly desirable. The quantum theory of atoms in molecules (QTAIM) and natural bond orbital (NBO) analysis have proved to be very useful tools in describing electron densities in various systems and in extending the understanding of H-bond [19-21]. According to QTAIM, the presence of a bond critical point (BCP) between two atoms is a universal indicator of bonded interactions and the electron density (ρ_b) at BCP point is related to the bond strength or bond order. Therefore, the existence of BCP and the topological properties of electron density ρ_b can be used to study the nature of H-bond. Especially, according to QTAIM, Koch and Popelier [22] proposed a set of criteria for the existence of H-bonds. The criteria provide a basis to distinguish these interactions from van der Waals interactions and have been proved to be valid for standard and nonconventional H-bonds.

The formation of H-bond implies that a certain amount of electronic charge is transferred from the H-acceptor to the H-donor, and a rearrangement of electron density within each part of molecule is occurred. Electron delocalization or charge transfer (CT) effects can be identified from the presence of off-diagonal elements of the Fock matrix in the NBO basis [23]. The interaction between filled and lone pair electrons and antibonding orbitals represents the deviation of the molecule from the Lewis structure and can be used as a measure of delocalization because of H-bond in this work. The strength of these delocalization interactions, E(2), is estimated by second-order perturbation theory:

$$E(2) = -n_{\sigma} \frac{\langle \sigma | F | \sigma^* \rangle^2}{\varepsilon_{\sigma^*} - \varepsilon_{\sigma}} = -n_{\sigma} \frac{F_{ij}^2}{\Delta \varepsilon}$$
(1)

where F_{ij} is the Fock matrix element between the NBO *i* (σ) and *j* (σ^*), ε_{σ} and ε_{σ^*} are the energies of σ and σ^* NBOs, and n_{σ} is the population (a lone pair in the H-bond)[23].

In this article, we mainly discuss the structures and hydrogen bonding interactions of the cysteine-thymine complexes (Cys-Thy) by DFT, and QTAIM and NBO analyses are carried out to study the nature of H-bonds.

Computational Details

The three-parameter hybrid functional according to Becke with additional correlation corrections because of Lee et al. [24, 25] was used (B3LYP) with 6-311++G(d, p) basis set [26, 27]. First, the structures of cysteine and thymine monomers were fully optimized. The Cys-Thy complexes were constructed starting from the most stable cysteine and thymine monomers. All complexes were also fully optimized at the same level. To take into account the effects of the basis set superposition error, the counterpoise method [28] was implemented in each step of the iterative process of geometry optimization in an integrated way to ensure that complex and monomer are being computed with a consistent basis set. The harmonic vibrational frequencies were calculated with analytic second derivatives at the same level confirmed the structures as minima and enabled the evaluation of zero-point vibrational energies (ZPVE). All ZPVE and frequencies were unscaled. The interaction energies were calculated based on the ZPVE and basis set superposition error correction. Finally, QTAIM and NBO analyses were carried out to investigate the nature of hydrogen bonding interactions in complexes. In this article, the quantum chemical calculations and NBO analysis were performed using the Gaussian03 suite of programs [29], and QTAIM analysis were carried out with the software AIM2000 [30].

Results and Discussion

Recently, conformers of cysteine have been studied by different research groups [31-34]. In this work, the properties of isolated cysteine and thymine were well reproduced at the B3LYP/ 6-311++G (d, p) level. The optimized conformers of cysteine (A) and thymine (B) were presented in Figure 1. Cysteine and thymine molecules can offer several possible donor and acceptor sites to form H-bond, respectively. As shown in Figure 1, the H-donor sites of cysteine may occur on hydroxyl (OH, O2), amino (NH₂, N), thiol group (SH, S), and even β -carbon, whereas carbonyl (CO, O1), amino (NH₂, N), thiol group (SH, S) as H-acceptor. Thymine, another monomer, could offer carbonyl group (O2 and O4) as H-acceptor, whereas amino group (N1 and N3) and C-H group as H-donor. Therefore, more than 20 kinds of H-bonds can be found in Cys-Thy complexes. All optimized complexes were presented in Figure 2, and the structural parameters of Hbonds were listed in Table I.

STRUCTURES

The vibrational frequency calculations confirmed that all optimized complexes have no imaginary frequencies and are stable structures. The existence of H-bond can be characterized by BCP between the donor (X-H) and acceptor



FIGURE 1. Molecular graphs of free cysteine and thymine monomers. Large circles correspond to attractors attributed to atomic positions: gray, H; blue, N; black, C; red, O; yellow, S. Small circles are attributed to critical points: red, BCP; green, RCP. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



FIGURE 2. Molecular graphs of Cys-Thy complexes. Large circles correspond to attractors attributed to atomic positions: gray, H; blue, N; black, C; red, O; yellow, S. Small circles are attributed to critical points: red, BCP; green, RCP. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE I

The structural parameters of intermolecular H-bonds in Cys-Thy complexes calculated at	
B3LYP/6-311++G(d,p) level.	

Complex	H-bond	R _{X-H}	ΔR_{X-H}	R _{HY}	δR _{HY}	∠X-H…Y
CON1	N1 ^B H…O1 ^A	1.022	0.013	1.881	0.839	170.100
	S4 ^A H…O2 ^B	1.356	0.007	2.119	0.601	173.200
CON2	N1 ^B H…O1 ^A	1.022	0.013	1.884	0.836	173.500
	C6 ^A H…O2 ^B	1.096	-0.001	2.340	0.380	141.300
CON3	N1 ^B H…O2 ^A	1.016	0.007	2.082	0.638	160.100
	C6 ^A H…O2 ^B	1.096	-0.001	2.483	0.237	131.300
CON4	N1 ^B H…O2 ^A	1.016	0.007	2.023	0.697	146.000
	O2 ^A H…O2 ^B	0.989	0.005	2.288	0.432	118.500
CON5	N3 ^B H…O1 ^A	1.025	0.012	1.928	0.792	166.700
	S4 ^A H…O4 ^B	1.356	0.006	2.122	0.598	171.000
CON6	N3 ^B H…O1 ^A	1.025	0.012	1.937	0.783	164.700
	S4 ^A H…O2 ^B	1.355	0.006	2.135	0.585	171.100
CON7	N1 ^B H…O2 ^A	1.014	0.005	2.090	0.630	163.700
	C5 ^B H…O1 ^A	1.084	0.000	2.574	0.146	141.100
CON8	N3 ^A H1…O2 ^B	1.020	0.005	2.085	0.635	154.600
	N1 ^B H…S4 ^A	1.018	0.009	2.514	0.486	170.000
CON9	O2 ^A H…O4 ^B	0.987	0.004	1.751	0.969	163.000
	N3 ^B H…N3 ^A	1.037	0.025	1.928	0.822	169.300
CON10	O2 ^A H…O2 ^B	0.985	0.002	1.768	0.952	162.500
	N3 ^B H…N3 ^A	1.036	0.023	1.939	0.811	169.300
CON11	C7 ^A H…O2 ^B	1.091	-0.001	2.399	0.321	149.100
	N1 ^B H…S4 ^A	1.017	0.008	2.529	0.471	162.500
CON12	N3 ^A H2…O4 ^B	1.017	0.004	2.084	0.636	166.700
CON13	N3 ^B H…O2 ^A	1.019	0.006	2.104	0.616	167.100
	S4 ^A H…O4 ^B	1.354	0.005	2.164	0.556	168.100
CON14	N3 ^A H2…O4 ^B	1.016	0.003	2.101	0.619	162.000
CON15	N3 ^A H1…O4 ^B	1.020	0.005	2.114	0.606	152.000
	N3 ^B H…S4 ^A	1.020	0.008	2.556	0.444	171.500
CON16	N3 ^B H…O2 ^A	1.019	0.006	2.114	0.606	164.900
	S4 ^A H…O2 ^B	1.354	0.004	2.178	0.542	166.400
CON17	N3 ^B H…O2 ^A	1.019	0.006	2.138	0.582	141.800
	O2 ^A H…O2 ^B	0.986	0.003	2.215	0.505	121.600
CON18	N3 ^A H2…O4 ^B	1.015	0.002	2.133	0.587	154.100
CON19	N3 ^A H1…O2 ^B	1.020	0.005	2.126	0.594	152.100
	N3 ^B H…S4 ^A	1.020	0.007	2.572	0.428	170.400
CON20	C7 ^A H…O4 ^B	1.091	-0.001	2.405	0.315	148.600
	N3 ^B H…S4 ^A	1.019	0.007	2.608	0.392	157.900
CON21	S4 ^A H…O4 ^B	1.355	0.006	2.118	0.602	175.800
	C6 ^B H1…O2 ^A	1.093	0.000	2.811	-0.091	154.200
CON22	N3 ^A H1…O4 ^B	1.019	0.004	2.191	0.529	144.700
	C6 ^B H1···S4 ^A	1.093	0.000	3.346	-0.346	156.100
CON23	O2 ^A H…O4 ^B	0.976	-0.007	1.875	0.845	163.600
	N3 ^A H2…O4 ^B	1.012	0.000	2.200	0.520	155.200
	C6 ^B H2···O2 ^A	1.092	-0.001	2.751	-0.031	121.300

groups (Y). The coexistences of several H-bonds maybe result in the formation of ring structures characterized by ring critical point (RCP). In addition, the heterocyclic structure of thymine moiety characterized by a RCP has no relationship with H-bond. The distance between BCP and corresponding RCP can also be used as a criterion to estimate the structural stability of the H-bond. The union between these two critical points represents bond cleavage and consequent ring opening [35]. As shown in Figures 1 and 2, the intramolecular O2^AH···N3^A H-bond in isolated cysteine lead to the formation of a five-membered ring characterized by a RCP, and it is also stable in most of complexes except **CON9**, **CON10**, and **CON23**. Some other intramolecular H-bonds can be found in Cys-Thy complexes. For example, the intramolecular S4^AH···O1^A H-bond is involved in **CON8**, **CON9**, **CON10**, and **CON23**, respectively, whereas intramolecular N3^AH···S4^A H-bond exists in **CON1**, **CON5**, **CON6**, **CON13**, **CON16**, and **CON21**, respectively.

Besides above intramolecular H-bonds, different intermolecular H-bonds can be found in complexes. Only one intermolecular H-bond is involved in CON12, CON14, and CON18, respectively. The bifurcation H-bonds in CON23 lead to the formations of two ring structures characterized by two RCPs, respectively. Another peculiar case is CON21 in which two RCPs are derived from two ring structures formed by two intermolecular H-bonds and O2^A-C7^BO4 bond, respectively. Except above complexes, the rest of complexes involve two intermolecular H-bonds. Moreover, the rings formed by intermolecular Hbonds usually are larger than those formed by intramolecular H-bonds. Major rings are eight- or nine-membered rings, whereas the rings formed by intramolecular H-bonds usually are six- and five-membered rings.

During the process of the formation of X-H…Y H-bond, electrons transfer happened between X-H and Y group result in the shortening of H…Y bond length. The shorter H…Y bond length is, the stronger the interaction is, and vice versa. The H…Y bond length of $O2^{A}$ H… $O4^{B}$ (1.751 Å, **CON9**) and O2^AH···O2^B (1.768 Å, CON10) H-bonds are the shortest ones, which indicate that the strength of the two H-bonds should be the strongest. However, the intramolecular O2^AH···N3^A H-bond of cysteine moiety has been destroyed in CON9 and CON10, which reduce the stability of complex. On the contrary, although the H…Y bond lengths in both N1^BH...O1^A and S4^AH...O2^B H-bonds of CON1 are not the shortest ones, the corresponding ΔR_{X-H} values are smaller than those in **CON9** and CON10 as well, CON1 is more stable than CON9 and CON10 because the former has a small deformation. Therefore, both the strength of H-bond and the deformation are important factor for the stability of complexes. Similar condition also happened in CON23, in which the stronger O2^AH···O4^B H-bond in favor of the enhancement

of stability of complex, whereas the serious deformation reduce the stability.

QTAIM ANALYSIS

The QTAIM was used here to deepen the nature of the hydrogen bonding interactions. The electronic topological properties at H…Y BCPs of intermolecular H-bonds including electron density (ρ_b), the Laplacian of the electron density ($\nabla^2 \rho_b$), and the electron energy density (H_b) of all complexes were listed in Table II.

Electron Density

It was indicated very often that the electron density at the H…Y BCP (ρ_b) is a good measure of Hbond strength. The shorter H...Y distance corresponds to the stronger H-bond and in consequence is characterized by the greater electron density at the corresponding H…Y BCP. Two quantitative criteria proposed by Koch and Popelier usually are used to characterize the strength of a H-bond: ρ_b and its Laplacian ($\nabla^2 \rho_b$), in the range of 0.002– 0.035 and 0.024-0.139 a.u.[20], respectively, which is markedly lower than for a covalent bond. As shown in Table II, for all complexes, most of ρ_b values are within this range. The ρ_b values of $O2^{A}H...O4^{B}$ (0.038, **CON9**) and $O2^{A}H...O2^{B}$ (0.036, CON10) H-bond are excess of the range, which indicates that a partial covalent character is attributed to the H-bonds. Generally, the ρ_b decreases as a result of the lengthening of the corresponding bond. The opposite occurs when the bond length shorten. As pointed out by Galvez et al. [36], the linear behavior between the density and the Hbond length is only held in the neighborhood of equilibrium, whereas the density ρ_b decays exponentially in the long range. Because of different atoms as H-acceptor in different H-bonds, H--Y bond distance cannot be used directly, so a H-bond parameter, δR [37], is defined as

$$\delta R = R_{\rm H}^{\rm vDW} + R_{\rm Y}^{\rm vDW} - R_{\rm H\cdots Y}$$
(2)

where $R_{\rm H}^{\rm vDW}$ and $R_{\rm Y}^{\rm vDW}$ are van der Waals radii of H and Y atoms given by Bondi [38], respectively. To understand the nature of H-bond with the density properties at BCPs, a linear regression analysis between the logarithmic plot $\ln \rho_b$ and δR was carried out, the fitted curve was shown in Figure 3, and a good linear relationship can be expressed as

$$\ln \rho_h = -5.1686 + 1.8483\delta R \quad r = 0.9864 \quad (3)$$

TABLE I	
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Electron density (ρ_b), laplacian of electron density ($\nabla^2 \rho_b$), potential energy density (V_b), Lagrangian form of kinetic energy density (G_b), and total energy density (H_b) at BCPs of intermolecular H-bonds in Cys-Thy complexes optimized at B3LYP/6-311++G(d, p) level.

$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Complexes	H-bonds	ρь	$\bigtriangledown^2 \rho_b$	Vb	G _b	H _b
$ \begin{array}{c} {\rm S4}^{\rm AH} {\rm IO2}^{\rm B} \\ {\rm CON2} \\ {\rm N1}^{\rm BH} {\rm IO1}^{\rm A} \\ {\rm 0.02692} \\ {\rm 0.0294} \\ {\rm 0.002965} \\ {\rm 0.002655} \\ {\rm 0.00260} \\ {\rm 0.000860} \\ {\rm 0.00140} \\ {\rm CON3} \\ {\rm N1}^{\rm BH} {\rmO2}^{\rm A} \\ {\rm 0.01121} \\ {\rm 0.00988} \\ {\rm 0.001720} \\ {\rm 0.000657} \\ {\rm 0.000550} \\ {\rm 0.00657} \\ {\rm 0.00170} \\ {\rm 0.000550} \\ {\rm 0.000570} \\ {\rm 0.00167} \\ {\rm 0.000570} \\ {\rm 0.000510} \\ {\rm 0.000570} \\ {\rm 0.000510} \\ {\rm 0.000520} \\ {\rm 0.000510} \\ {\rm 0.000520} \\ {\rm 0.000570} \\ {\rm 0.000570$	CON1	N1 ^B H…O1 ^A	0.02719	0.10157	-0.02093	0.02316	0.00223
$\begin{array}{c c} {\rm CON2} & {\rm N1}^{\rm PH} {\rmO2}^{\rm R} & 0.0292 \\ {\rm C6}^{\rm AH} {\rmO2}^{\rm B} & 0.01211 \\ 0.03998 & -0.00720 \\ {\rm CON3} & {\rm N1}^{\rm BH} {\rmO2}^{\rm B} & 0.00910 \\ {\rm CON3} & {\rm C6}^{\rm AH} {\rmO2}^{\rm B} \\ 0.00910 \\ 0.03058 \\ -0.00550 \\ {\rm O2}^{\rm AH} {\rmO2}^{\rm B} \\ 0.00218 \\ {\rm O2}^{\rm AH} {\rmO2}^{\rm B} \\ 0.011828 \\ 0.07895 \\ -0.01408 \\ 0.01408 \\ 0.01691 \\ 0.00283 \\ 0.00255 \\ {\rm CON5} \\ {\rm N3}^{\rm BH} {\rmO1}^{\rm A} \\ 0.0241 \\ 0.02211 \\ 0.0224 \\ -0.00980 \\ 0.01231 \\ 0.00255 \\ {\rm CON5} \\ {\rm N3}^{\rm BH} {\rmO1}^{\rm A} \\ 0.02421 \\ 0.09154 \\ -0.01779 \\ 0.00980 \\ 0.01231 \\ 0.00254 \\ -0.00980 \\ 0.01231 \\ 0.00254 \\ 0.00254 \\ -0.00980 \\ 0.01231 \\ 0.00254 \\ 0.00254 \\ -0.00981 \\ 0.01155 \\ 0.00244 \\ 0.00254 \\ -0.00981 \\ 0.01155 \\ 0.00244 \\ -0.00173 \\ -0.00951 \\ 0.01195 \\ 0.00264 \\ -0.00173 \\ -0.00251 \\ 0.00179 \\ -0.00951 \\ 0.01195 \\ 0.00264 \\ -0.00173 \\ -0.00251 \\ 0.00179 \\ 0.00261 \\ -0.00118 \\ 0.00261 \\ -0.00170 \\ -0.00118 \\ 0.00261 \\ -0.00118 \\ 0.00261 \\ -0.00118 \\ 0.00261 \\ -0.00118 \\ 0.00261 \\ -0.00118 \\ 0.00261 \\ -0.00118 \\ 0.00261 \\ -0.00118 \\ 0.00261 \\ -0.00120 \\ 0.00123 \\ -0.00120 \\ -0.00118 \\ 0.00261 \\ -0.00120 \\ 0.00124 \\ -0.00120 \\ -0.00114 \\ 0.00241 \\ -0.00120 \\ -0.00114 \\ 0.00241 \\ -0.00120 \\ -0.00128 \\ -0.00218 \\ -0.00128 \\ -0.00218 \\ -0.00137 \\ -0.00137 \\ -0.00218 \\ -0.00218 \\ -0.00218 \\ -0.00218 \\ -0.00218 \\ -0.00137 \\ -0.00137 \\ -0.00137 \\ -0.00218 \\ -0.00218 \\ -0.00218 \\ -0.00128 \\ -0.00218 \\ -0.00137 \\ -0.00137 \\ -0.00138$		S4 ^A H…O2 ^B	0.01690	0.05963	-0.01001	0.01246	0.00245
$\begin{array}{c} {\rm CoN3} & {\rm N1}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & {\rm 0.01211} & {\rm 0.03988} & -{\rm 0.00720} & {\rm 0.00860} & {\rm 0.00140} \\ {\rm CON3} & {\rm N1}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & {\rm 0.09510} & {\rm 0.00550} & {\rm 0.00657} & {\rm 0.00141} & {\rm 0.00218} \\ {\rm CoN4} & {\rm N1}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & {\rm 0.09140} & {\rm 0.03355} & -{\rm 0.01408} & {\rm 0.01651} & {\rm 0.00283} \\ {\rm CoN5} & {\rm N3}^{\rm B}{\rm H}-{\rm O1}^{\rm A} & {\rm 0.02421} & {\rm 0.09154} & -{\rm 0.01779} & {\rm 0.02034} & {\rm 0.00255} \\ {\rm S4}^{\rm A}{\rm H}-{\rm O4}^{\rm B} & {\rm 0.01651} & {\rm 0.05926} & -{\rm 0.00897} & {\rm 0.01231} & {\rm 0.00261} \\ {\rm CON5} & {\rm N3}^{\rm B}{\rm H}-{\rm O1}^{\rm A} & {\rm 0.02421} & {\rm 0.09154} & -{\rm 0.01779} & {\rm 0.02034} & {\rm 0.00255} \\ {\rm S4}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & {\rm 0.01667} & {\rm 0.05753} & -{\rm 0.00890} & {\rm 0.01231} & {\rm 0.00261} \\ {\rm CON7} & {\rm N1}^{\rm B}{\rm H}-{\rm O2}^{\rm A} & {\rm 0.01690} & {\rm 0.06556} & -{\rm 0.01118} & {\rm 0.01195} & {\rm 0.00244} \\ {\rm CON7} & {\rm N1}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & {\rm 0.01690} & {\rm 0.06556} & -{\rm 0.01118} & {\rm 0.01379} & {\rm 0.00261} \\ {\rm CON8} & {\rm N3}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & {\rm 0.01820} & {\rm 0.06761} & -{\rm 0.01208} & {\rm 0.01449} & {\rm 0.00214} \\ {\rm M1}^{\rm B}{\rm H}-{\rm S4}^{\rm A} & {\rm 0.01504} & {\rm 0.03789} & -{\rm 0.00701} & {\rm 0.00824} & {\rm 0.00126} \\ \\ {\rm CON9} & {\rm 02}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & {\rm 0.03808} & {\rm 0.12466} & -{\rm 0.03334} & {\rm 0.03225} & -{\rm 0.00109} \\ {\rm N3}^{\rm B}{\rm H}-{\rm N3}^{\rm A} & {\rm 0.03205} & {\rm 0.08237} & -{\rm 0.02246} & {\rm 0.02133} & -{\rm 0.00126} \\ \\ {\rm CON10} & {\rm C0}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & {\rm 0.01699} & {\rm 0.03397} & -{\rm 0.00672} & {\rm 0.00735} & {\rm 0.00115} \\ \\ {\rm CON11} & {\rm C7}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & {\rm 0.01699} & {\rm 0.03397} & -{\rm 0.00672} & {\rm 0.00735} & {\rm 0.00115} \\ \\ {\rm CON12} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm A} & {\rm 0.01447} & {\rm 0.03701} & -{\rm 0.00672} & {\rm 0.00799} & {\rm 0.00126} \\ \\ {\rm CON13} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm A} & {\rm 0.01699} & {\rm 0.03397} & -{\rm 0.00672} & {\rm 0.00735} & {\rm 0.00115} \\ \\ {\rm CON14} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & {\rm 0.016161} & {\rm 0.01330} & -{\rm 0.01037} & {\rm 0.002275} \\ \\ {\rm CO$	CON2	N1 ^B H…O1 ^A	0.02692	0.10094	-0.02065	0.02294	0.00229
$\begin{array}{cccccc} {\rm CON3} & {\rm N1}^{\rm B}{\rm H}-{\rm O2}^{\rm A} & 0.01823 & 0.06548 & -0.01200 & 0.01419 & 0.00218 \\ {\rm C6}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & 0.00910 & 0.03058 & -0.00550 & 0.00657 & 0.00107 \\ {\rm CON4} & {\rm N1}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & 0.01308 & 0.07895 & -0.01408 & 0.01691 & 0.00238 \\ {\rm CON5} & {\rm N3}^{\rm B}{\rm H}-{\rm O1}^{\rm A} & 0.02421 & 0.09154 & -0.01779 & 0.2034 & 0.00255 \\ {\rm S4}^{\rm A}{\rm H}-{\rm O4}^{\rm B} & 0.01651 & 0.05926 & -0.00980 & 0.01231 & 0.00251 \\ {\rm CON6} & {\rm N3}^{\rm B}{\rm H}-{\rm O1}^{\rm A} & 0.02371 & 0.08999 & -0.01731 & 0.01990 & 0.00260 \\ {\rm S4}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & 0.01660 & 0.06558 & -0.00951 & 0.01195 & 0.00244 \\ {\rm CON7} & {\rm N1}^{\rm B}{\rm H}-{\rm O2}^{\rm A} & 0.01690 & 0.06558 & -0.01118 & 0.01379 & 0.00261 \\ {\rm CS}^{\rm B}{\rm H}-{\rm O1}^{\rm A} & 0.00764 & 0.02350 & -0.00433 & 0.00510 & 0.00077 \\ {\rm CON8} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & 0.01802 & 0.06761 & -0.01208 & 0.01449 & 0.00244 \\ {\rm N1}^{\rm B}{\rm H}-{\rm S4}^{\rm A} & 0.01504 & 0.03789 & -0.00701 & 0.00824 & 0.00123 \\ {\rm CON9} & {\rm O2}^{\rm A}{\rm H}-{\rm O4}^{\rm B} & 0.03808 & 0.12466 & -0.0334 & 0.03225 & -0.00109 \\ {\rm N3}^{\rm B}{\rm H}-{\rm N3}^{\rm A} & 0.03299 & 0.08347 & -0.02239 & 0.02213 & -0.00126 \\ {\rm CON10} & {\rm O2}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & 0.01669 & 0.03397 & -0.00620 & 0.07735 & -0.00126 \\ {\rm CON11} & {\rm C7}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & 0.01669 & 0.03397 & -0.00620 & 0.07735 & -0.00126 \\ {\rm CON12} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm A} & 0.01447 & 0.03711 & -0.00672 & 0.07799 & 0.00126 \\ {\rm CON14} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm A} & 0.01642 & 0.06161 & -0.01060 & 0.01300 & 0.00240 \\ {\rm CON14} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & 0.01669 & 0.05392 & -0.00845 & 0.01735 & 0.00015 \\ {\rm CON15} & {\rm N3}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & 0.01642 & 0.06161 & -0.01060 & 0.01300 & 0.00240 \\ {\rm O2}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & 0.01642 & 0.06161 & -0.01060 & 0.01300 & 0.00240 \\ {\rm CON14} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm A} & 0.01541 & 0.06313 & -0.001142 & 0.01137 \\ {\rm CON15} & {\rm N3}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & 0.01777 & 0.05414 & -0.01037 & 0.01274 & 0.00237 \\ {\rm CON16} & {\rm N3}^{$		C6 ^A H…O2 ^B	0.01211	0.03998	-0.00720	0.00860	0.00140
$\begin{array}{c} {\rm CoN4} & {\rm N1}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & 0.09910 & 0.03058 & -0.00505 & 0.00657 & 0.00107 \\ {\rm CON4} & {\rm N1}^{\rm B}{\rm H}-{\rm O2}^{\rm A} & 0.01988 & 0.07895 & -0.01408 & 0.01691 & 0.00283 \\ {\rm O2}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & 0.01305 & 0.00139 & 0.00295 \\ {\rm S4}^{\rm A}{\rm H}-{\rm O4}^{\rm B} & 0.01651 & 0.05926 & -0.00980 & 0.01231 & 0.00251 \\ {\rm CON5} & {\rm N3}^{\rm B}{\rm H}-{\rm O1}^{\rm A} & 0.02371 & 0.08999 & -0.01731 & 0.01990 & 0.00242 \\ {\rm CON7} & {\rm N1}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & 0.01607 & 0.05753 & -0.00951 & 0.01195 & 0.00244 \\ {\rm CON7} & {\rm N1}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & 0.01667 & 0.02350 & -0.00433 & 0.00510 & 0.00077 \\ {\rm CS}^{\rm B}{\rm H}-{\rm O1}^{\rm A} & 0.00764 & 0.02350 & -0.00433 & 0.00510 & 0.00241 \\ {\rm N1}^{\rm B}{\rm H}-{\rm S4}^{\rm A} & 0.01504 & 0.03788 & -0.00701 & 0.08224 & 0.00123 \\ {\rm CON9} & {\rm O2}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & 0.03615 & 0.12200 & -0.03134 & 0.03225 & -0.00199 \\ {\rm N3}^{\rm B}{\rm H}-{\rm N3}^{\rm A} & 0.03205 & 0.08237 & -0.02339 & 0.02213 & -0.00126 \\ {\rm CON10} & {\rm O2}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & 0.01696 & 0.08377 & -0.00620 & 0.0735 & -0.000126 \\ {\rm CON11} & {\rm C7}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & 0.01696 & 0.03977 & -0.00620 & 0.0735 & -0.00126 \\ {\rm CON12} & {\rm N3}^{\rm B}{\rm H}-{\rm N3}^{\rm A} & 0.03205 & 0.08237 & -0.02246 & 0.02133 & -0.00126 \\ {\rm CON11} & {\rm C7}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & 0.01698 & 0.06769 & -0.01142 & 0.01417 & 0.00275 \\ {\rm CON12} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & 0.01698 & 0.06769 & -0.01142 & 0.01417 & 0.00275 \\ {\rm CON13} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & 0.01617 & 0.06534 & -0.01084 & 0.01339 & 0.02213 \\ {\rm CON14} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & 0.01617 & 0.06534 & -0.01084 & 0.01359 & 0.00275 \\ {\rm CON14} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & 0.016198 & 0.06769 & -0.01142 & 0.01417 & 0.00237 \\ {\rm CON14} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & 0.01617 & 0.06534 & -0.01084 & 0.01359 & 0.00275 \\ {\rm CON14} & {\rm N3}^{\rm B}{\rm H}-{\rm O2}^{\rm B} & 0.01642 & 0.05161 & -0.01073 & 0.01224 & 0.00135 \\ {\rm CON14} & {\rm N3}^{\rm A}{\rm H}-{\rm O2}^{\rm B} & 0.01426 & 0.05208 & -0.00845 & 0.01073 & 0.00229 \\ {\rm CON14}$	CON3	N1 ^B H…O2 ^A	0.01823	0.06548	-0.01200	0.01419	0.00218
$ \begin{array}{ccccc} {\rm CON4} & {\rm N1}^{\rm B}{\rm H}{\rm \dots}{\rm O2}^{\rm A} & 0.01988 & 0.07895 & -0.01408 & 0.01691 & 0.00283 \\ {\rm O2}^{\rm A}{\rm H}{\rm \dots}{\rm O4}^{\rm B} & 0.01308 & 0.04696 & -0.00897 & 0.01035 & 0.00139 \\ {\rm S4}^{\rm A}{\rm H}{\rm \dots}{\rm O4}^{\rm B} & 0.01651 & 0.05926 & -0.00980 & 0.01231 & 0.00255 \\ {\rm CON6} & {\rm N3}^{\rm B}{\rm H}{\rm \dots}{\rm O1}^{\rm A} & 0.02371 & 0.08999 & -0.01731 & 0.01990 & 0.00260 \\ {\rm S4}^{\rm A}{\rm H}{\rm \dots}{\rm O2}^{\rm B} & 0.01607 & 0.05753 & -0.00951 & 0.01139 & 0.00244 \\ {\rm CON7} & {\rm N1}^{\rm B}{\rm H}{\rm \dots}{\rm O2}^{\rm A} & 0.01620 & 0.06761 & -0.01208 & 0.01449 & 0.00241 \\ {\rm CON8} & {\rm N3}^{\rm B}{\rm H}{\rm \dots}{\rm O2}^{\rm B} & 0.01504 & 0.02350 & -0.00433 & 0.00510 & 0.00077 \\ {\rm CON8} & {\rm N3}^{\rm B}{\rm H}{\rm \dots}{\rm O2}^{\rm B} & 0.01820 & 0.06761 & -0.01208 & 0.01449 & 0.00241 \\ {\rm N1}^{\rm B}{\rm H}{\rm \dots}{\rm S4}^{\rm A} & 0.01504 & 0.03789 & -0.00711 & 0.08824 & -0.00128 \\ {\rm CON9} & {\rm O2}^{\rm A}{\rm H}{\rm \dots}{\rm O2}^{\rm B} & 0.03625 & 0.08347 & -0.02339 & 0.02213 & -0.00126 \\ {\rm CON10} & {\rm O2}^{\rm A}{\rm H}{\rm \dots}{\rm O2}^{\rm B} & 0.01669 & 0.03397 & -0.02246 & 0.02153 & -0.00093 \\ {\rm CON11} & {\rm C7}^{\rm A}{\rm H}{\rm \dots}{\rm O2}^{\rm B} & 0.01649 & 0.03397 & -0.00620 & 0.00735 & 0.00115 \\ {\rm N1}^{\rm B}{\rm H}{\rm \dots}{\rm S4}^{\rm A} & 0.01447 & 0.03701 & -0.00622 & 0.00799 & 0.00224 \\ {\rm CON12} & {\rm N3}^{\rm B}{\rm H}{\rm \dots}{\rm O2}^{\rm A} & 0.01442 & 0.06161 & -0.01060 & 0.01300 & 0.00240 \\ {\rm S4}^{\rm A}{\rm H}{\rm \dots}{\rm O4}^{\rm B} & 0.01649 & 0.05392 & -0.00872 & 0.01142 & 0.00155 \\ {\rm CON13} & {\rm N3}^{\rm B}{\rm H}{\rm \dots}{\rm C4}^{\rm A} & 0.01447 & 0.03701 & -0.006670 & 0.0735 & 0.00115 \\ {\rm CON14} & {\rm N3}^{\rm B}{\rm H}{\rm \dots}{\rm C4}^{\rm A} & 0.01442 & 0.06161 & -0.01060 & 0.01300 & 0.00240 \\ {\rm S4}^{\rm A}{\rm H}{\rm \dots}{\rm O4}^{\rm B} & 0.01642 & 0.06161 & -0.01060 & 0.01300 & 0.00240 \\ {\rm CON14} & {\rm N3}^{\rm B}{\rm H}{\rm \dots}{\rm C4}^{\rm B} & 0.01442 & 0.06161 & -0.01067 & 0.00742 & 0.00235 \\ {\rm CON15} & {\rm N3}^{\rm B}{\rm H}{\rm \dots}{\rm C4}^{\rm B} & 0.01441 & 0.05313 & -0.01117 & 0.01347 & 0.00237 \\ {\rm CON16} & {\rm N3}^{\rm B}{\rm H}{\rm \dots}{\rm C4}^{\rm B} & 0.01464 & 0.05996 & -0.01020 & 0.01259 & 0.00276 \\ {\rm CON17} & {\rm N3}^{\rm$		C6 ^A H…O2 ^B	0.00910	0.03058	-0.00550	0.00657	0.00107
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	CON4	N1 ^B H…O2 ^A	0.01988	0.07895	-0.01408	0.01691	0.00283
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		O2 ^A H…O2 ^B	0.01308	0.04696	-0.00897	0.01035	0.00139
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	CON5	N3 ^B H…O1 ^A	0.02421	0.09154	-0.01779	0.02034	0.00255
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		S4 ^A H…O4 ^B	0.01651	0.05926	-0.00980	0.01231	0.00251
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	CON6	N3 ^B H…O1 ^A	0.02371	0.08999	-0.01731	0.01990	0.00260
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		S4 ^A H…O2 ^B	0.01607	0.05753	-0.00951	0.01195	0.00244
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	CON7	N1 ^B H…O2 ^A	0.01690	0.06558	-0.01118	0.01379	0.00261
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		C5 ^B H…O1 ^A	0.00764	0.02350	-0.00433	0.00510	0.00077
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	CON8	N3 ^A H1…O2 ^B	0.01820	0.06761	-0.01208	0.01449	0.00241
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		N1 ^B H…S4 ^A	0.01504	0.03789	-0.00701	0.00824	0.00123
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	CON9	O2 ^A H…O4 ^B	0.03808	0.12466	-0.03334	0.03225	-0.00109
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		N3 ^B H…N3 ^A	0.03299	0.08347	-0.02339	0.02213	-0.00126
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	CON10	$O2^{A}HO2^{B}$	0.03615	0.12200	-0.03119	0.03084	-0.00034
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		N3 ^B H…N3 ^A	0.03205	0.08237	-0.02246	0.02153	-0.00093
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	CON11	$C7^{A}HO2^{B}$	0.01069	0.03397	-0.00620	0.00735	0.00115
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		N1 ^B H…S4 ^A	0.01447	0.03701	-0.00672	0.00799	0.00126
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	CON12	N3 ^A H2…O4 ^B	0.01698	0.06769	-0.01142	0.01417	0.00275
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	CON13	N3 ^B H…O2 ^A	0.01642	0.06161	-0.01060	0.01300	0.00240
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		S4 ^A H…O4 ^B	0.01469	0.05392	-0.00872	0.01110	0.00238
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	CON14	N3 ^A H2…O4 ^B	0.01617	0.06534	-0.01084	0.01359	0.00275
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	CON15	N3 ^A H1…O4 ^B	0.01714	0.06313	-0.01117	0.01347	0.00231
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		N3 ^B HS4 ^A	0.01349	0.03510	-0.00607	0 00742	0.00135
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	CON16	N3 ^B H…O2 ^A	0.01612	0.06041	-0.01037	0.01274	0.00237
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	001110	S4 ^A H…O2 ^B	0.01426	0.05208	-0.00845	0.01073	0.00229
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	CON17	N3 ^B H…O2 ^A	0.01544	0.05996	-0.01020	0.01259	0 00240
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	001111	$\Omega^{A}H.\Omega^{B}$	0.01477	0.05414	-0.01024	0.01189	0.00165
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	CON18	N3 ^A H2…O4 ^B	0.01484	0.06118	-0.00990	0.01260	0.00270
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	CON19	N3 ^A H1O2 ^B	0.01662	0.06146	-0.01079	0.01308	0.00229
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	001110	N3 ^B HS4 ^A	0.01301	0.03409	-0.00581	0.00717	0.00136
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	CON20	C7 ^A H…O4 ^B	0 01049	0.03363	-0.00611	0.00726	0.00115
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	001120	N3 ^B HS4 ^A	0.01197	0.03243	-0.00531	0.00671	0.00140
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	CON21	S4 ^A H…O4 ^B	0.01702	0.05899	-0.01002	0.01238	0.00116
CON22 N3 ^A H1···O4 ^B 0.01411 0.05366 -0.00909 0.01125 0.00216 C6 ^B H1···S4 ^A 0.00359 0.00949 -0.00137 0.00187 0.00050 CON23 O2 ^A H···O4 ^B 0.02722 0.10306 -0.02160 0.02368 0.00208 N3 ^A H2···O4 ^B 0.01369 0.05376 -0.00913 0.01128 0.00216	CONLI	C6 ^B H1O2 ^A	0.00448	0.01455	-0.00258	0.00311	0.00053
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	CON22	N3 ^A H1O4 ^B	0.01411	0.05366	_0.00200	0.01125	0.00000
CON23 O2 ^A H···O4 ^B 0.02722 0.10306 -0.02160 0.02368 0.00208 N3 ^A H2···O4 ^B 0.01369 0.05376 -0.00913 0.01128 0.00216	CONLL	C6 ^B H1S4 ^A	0.00359	0.00949	-0.00137	0.00187	0 00050
N3 ^A H2···O4 ^B 0.01369 0.05376 -0.00913 0.01128 0.00216	CON23	$\Omega^{A}H\Omega^{B}$	0.00000	0 10306	-0.02160	0.02368	0.00000
	CONLO	N3 ^A H2O4 ^B	0.01369	0.05376	_0.00913	0.01128	0.00216
C6 ^B H2O2 ^A 0.00512 0.01863 -0.00316 0.00391 0.00075		C6 ^B H2…O2 ^A	0.00512	0.01863	-0.00316	0.00391	0.00075

Electron Energy Density

The Laplacian of the electron density $(\nabla^2 \rho_b)$ is another important topological property which can be used to estimate H-bonds. According to QTAIM, the closed shell interactions (e.g., ionic bonds, H-bonds, and van der Waals interactions) correspond to a positive $\nabla^2 \rho_b$ value at BCP, whereas for covalent bonds, the $\nabla^2 \rho_b$ has a



FIGURE 3. Correlation between the electron density ρ_b at the BCPs in the logarithmic value (ln ρ_b) and the H-bond parameter δR .

negative value [19, 20]. There is a well-known relationship resulting from the virial theorem between $\nabla^2 \rho_b$ and energetic properties of BCP:

$$\frac{1}{4}\nabla^2 \rho_b = 2G_b + V_b \tag{4}$$

$$H_b = G_b + V_b \tag{5}$$

where G_b (always positive) and V_b (always negative) are the kinetic and potential energy densities, respectively, and H_b is the total energy density. The sign of H_b will depend on which contribution, potential or kinetic, will locally prevail on the BCP. $H_b < 0$ reflects a prevalence of the potential energy, which is a consequence of the stabilization of the accumulated electron charge, a typical feature of covalent interactions [39, 40]. In this way, a partial covalent character is attributed to the H-bonds exhibiting $H_b < 0$. Moreover, the $\nabla^2 \rho_b$ at BCP is low and positive, which is typical of closed shell interactions. Therefore, $\nabla^2 \rho_b$ and H_b at H…Y BCP can be used as criteria to characterize H-bonds. Koch and Popelier [22] proposed for weak and medium Hbonds that both $\nabla^2 \rho_b$ and $H_b > 0$; for strong Hbonds it is: $\nabla^2 \rho_b > 0$ and $H_b < 0$, whereas for very strong ones both $\nabla^2 \rho_b$ and $H_b < 0$. The latter are usually classified as covalent in nature. 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.

According to the criteria of H-bonds proposed by Koch and Popelier [20], all H-bonds have positive $\nabla^2 \rho_b$ values and fall within the 0.024–0.139 a.u. range. As shown in Table II, the values of $\nabla^2 \rho_b$ (0.125 and 0.122) of $O2^A H \cdots O4^B$ H-bonds in **CON9** and **CON10** are the biggest ones among complexes, and the two smallest of H_b (-0.00126 of $O2^A H \cdots O4^B$ and -0.00109 of $N3^B H \cdots N3^A$ Hbonds) are also found in **CON9**, which indicates the strengths of the two H-bonds in **CON9** are strongest, and a partial covalent character is attributed to them. The two H-bonds with negative H_b values in **CON10** are stronger as well. The H_b values of other intermolecular H-bonds in complexes are all positive and are weak H-bonds according to above criteria.

Because both the bond distance and electron energy density are relate to the strength of Hbond, the relationship between $\nabla^2 \rho_b$ and $R_{\text{H}...\text{Y}}$ was also investigated. Because of different atoms as H-acceptor in different H-bonds, δR defined in Eq. (2) was used to replace $R_{\text{H}...\text{Y}}$ for regression analysis, a linear relationship between the logarithmic $\nabla^2 \rho_b$ and δR can be expressed as follows:

$$\ln \nabla^2 \rho_b = -4.0306 + 2.0160 \delta R \quad r = 0.9864 \quad (6)$$

The fitted curve was shown in Figure 4. Therefore, the estimate results of the strength of Hbonds by QTAIM are consistent with those by bond lengths analysis.

NBO ANALYSIS AND ENERGY

The NBO analysis was also performed here to deepen the nature of H-bonds. The results of NBO analysis were shown in Table III. As shown



FIGURE 4. Correlation between the logarithmic Laplacian of the electron density at the BCPs of H-bonds (In $\nabla^2 \rho_b$) and the H-bond parameter δR .

Complexes	H-bonds	E(2) ^a (kcal⋅mol ⁻¹)
CON1	N1 ^B H…O1 ^A	5.73(3.96)
	S4 ^A H…O2 ^B	2.97(2.53)
CON2	N1 ^B H…O1 ^A	5.77(3.71)
	C6 ^A H…O2 ^B	1.05(0.90)
CON3	N1 ^B H…O2 ^A	2.22(3.33)
	C6 ^A H…O2 ^B	0.58(0.15)
CON4	N1 ^B H…O2 ^A	5.22
	O2 ^A H…O2 ^B	0.82(1.84)
CON5	N3 ^B H…O1 ^A	5.21(3.86)
	S4 ^A H…O4 ^B	3.20(1.68)
CON6	N3 ^B H…O1 ^A	5 09(3 73)
00110	S4 ^A H…O2 ^B	2 95(1 79)
CON7	N1 ^B H…O2 ^A	4 44
00111	C5 ^B HO1 ^A	0 43(0 53)
CON8	N3 ^A H1O2 ^B	1 97(3 11)
00110	N1 ^B HS4 ^A	1 70(6 18)
	02 ^A H04 ^B	6 18(12 3/1)
00113	N3 ^B HN3 ^A	10 16
CON10	$\Omega 2^{A}H\Omega 2^{B}$	5 80/11 13)
CONTO		18 18
		0.10
CONT	N1 ^B HS/ ^A	0.31(0.00)
		2 50(1 61)
CON12		2.59(1.01)
CONTS	NJ 1102 S/ ^A HO/ ^B	2 03(0 51)
		2.33(0.31)
CON14		2.47(1.02)
CONTS		1.70(2.00)
CONIIG		2.50(1.24)
CONTO		3.30(1.24)
00117		2.06(0.57)
CONT		3.37 1 15/0 17)
00110		1.15(2.17)
		2.16(0.47)
CONT9		1.02(2.55)
00100		1.77(4.64)
CON20		0.93(0.68)
00104	$N3^{\circ}H\cdots S4^{\circ}$	0.99(4.48)
CON21	S4 [°] H···O4 [°]	2.65(0.76)
00100		0.18(0.15)
CON22	N3 [°] H1···O4 ^B	1.39(1.20)
00100		0.07(0.33)
CON23	02 H···O4 ^B	5.34(5.59)
	N3 ⁻ H2···O4 ^D	1.54(0.26)
	C6°H2…O2 ^A	0.1

^aThe values are O (or S) sp hybrid branch to form the Hbond; those in the parentheses are O (or S) p hybrid branch. The lone pair of N atom is mainly of p character. See discussion in the text.

in Table III, the O (and S) atom involved in Hbond has two branches: one has sp hybrid characteristics, and the other one has more p hybrid

characteristics; they correspond to two E(2) values, respectively. In contrast to the O (S) atoms, the N atom shows p characteristics in H-bonds. Thereby, the O (S) atoms exhibit more flexibility (less anisotropic) than the N atom in H-bond. The two largest E(2) value of 19.16 and 18.18 kcal·mol⁻¹ are found for the N3^BH…N3^A H-bond in CON9 and CON10, respectively, which indicates the strongest charge-transfer effect happened to them. The sum of E(2) values of both O(sp) and O(p) branch for N1^BH…O1^A intermolecular H-bond in CON1 and CON2 are 9.69 and 9.48 kcal·mol⁻¹, respectively, which are bigger than other H-bonds. Therefore the intermolecular N1^BH…O1^A H-bond in CON1 and CON2 are stronger, and the strength of other H-bonds is comparatively weaker. In addition, the relationship between E [2] and ρ_b was also investigated because E(2) is responsible for the strength of Hbond, and the $E(2) \sim \rho_b$ correlation was plotted in Figure 5. As shown in Figure 5, E(2) linearly



FIGURE 5. Correlation between the sum of second perturbation energies E(2) (the sum of sp and p branch, in kcal·mol⁻¹) and the electron density ρ_b at BCPs of H-bonds. (a) O atom as H-acceptor and (b) S atom as H-acceptor.

depend on ρ_b as well, and the regression equations for the H-bonds involving S and O atom as H-acceptor, respectively, are expressed as

$$E(2) = -1.9502 + 641.8651\rho_b \quad r = 0.9973 \tag{7}$$

$$E(2) = -4.5122 + 553.0078\rho_b \quad r = 0.9748 \tag{8}$$

where the E(2) is the sum of sp and p branch for the O or S atoms.

Based on the NBO analysis, the binding energies (ΔE) of Cys-Thy complexes were decomposed into several terms and were summarized in Table IV. ΔE can be decomposed as follows:

$$\Delta E = \Delta E_{\rm prep} + \Delta E_{\rm int} \tag{9}$$

where the preparation energy ΔE_{prep} is the amount of energy required to deform the separate bases from their free monomer structure to the geometry that they acquire in the pair complex; the interaction energy ΔE_{int} represents the actual energy change when the prepared bases are combined to form the pair complex. In general, ΔE_{prep} is positive because the structural deformation brings the molecular energy to a higher energy level, whereas ΔE_{int} is a negative value unless the complex is unstable. According to NBO theory [23], ΔE_{int} is decomposed into the charge-transfer (CT) and noncharge-transfer (NCT) parts

$$\Delta E_{\rm int} = \Delta E_{\rm NCT} + \Delta E_{\rm CT} \tag{10}$$

where ΔE_{CT} account for the orbital interaction and polarization interactions, $\Delta E_{\rm NCT}$ consists of the classical electrostatic interaction and the Pauli steric repulsion interaction. The $\Delta E_{\rm CT}$ term can be closely tracked by E(2) in Eq. (1), as proposed by Reed et al. [41]. To estimate the total CT effects between cysteine and thymine moiety in complexes, the $\Delta E_{\rm CT}$ terms were obtained by summarizing E(2) for intermolecular H-bonds listed in Table III. In the NBO scheme, $\Delta E_{\rm CT}$ is negative because it is evaluated as the variational energy lowering because of expanding the variational space on each monomer to include unfilled orbitals on the other monomer. Thereby, $\Delta E_{\rm NCT}$ can be further calculated with Eq. (10) and is positive as shown in Table IV.

As shown in Table IV, the absolute values of $\Delta E_{\rm CT}$ in **CON9** (-37.68 kcal·mol⁻¹) and **CON10** (-35.20 kcal·mol⁻¹) are the two biggest ones, but ΔE (2.94 and 3.20 kcal·mol⁻¹) is not the largest ones, because of the higher $\Delta E_{\rm prep}$ (8.09 and

TABLE IV_

Preparation energies (ΔE_{prep}), charge-transfer energies (ΔE_{CT}), noncharge-transfer energies (ΔE_{NCT}), interaction energies (ΔE_{int}), and binding energies (ΔE) of the Cys-Thy complexes, in kcal·mol⁻¹, calculated at B3LYP/6-311++G(d,p) level.

Complex	$\Delta E_{\rm prep}$	$\Delta E_{\rm int}$	ΔE	$\Delta E_{\rm CT}$	$\Delta E_{\rm NCT}$
CON1	0.83	-9.22	-8.39	-15.19	5.97
CON2	0.83	-9.06	-8.23	-11.43	2.37
CON3	0.56	-6.49	-5.93	-6.28	-0.21
CON4	0.38	-6.42	-6.04	-7.88	1.46
CON5	0.56	-6.30	-5.74	-13.95	7.65
CON6	0.53	-6.11	-5.58	-13.56	7.45
CON7	0.27	-6.08	-5.81	-5.40	-0.68
CON8	1.49	-5.34	-3.85	-12.96	7.62
CON9	8.09	-5.15	2.94	-37.68	32.53
CON10	7.90	-4.70	3.20	-35.20	30.50
CON11	0.30	-4.60	-4.30	-8.92	4.32
CON12	0.28	-4.31	-4.03	-4.20	-0.11
CON13	0.81	-4.30	-3.49	-8.41	4.11
CON14	0.30	-4.29	-3.99	-3.49	-0.80
CON15	0.94	-4.22	-3.28	-11.32	7.10
CON16	0.74	-4.20	-3.46	-7.99	3.79
CON17	0.35	-4.17	-3.82	-6.69	2.52
CON18	0.29	-4.15	-3.86	-2.63	-1.52
CON19	0.89	-3.99	-3.10	-10.58	6.59
CON20	0.25	-3.34	-3.09	-7.08	3.74
CON21	0.48	-3.08	-2.60	-3.74	0.66
CON22	0.49	-3.05	-2.56	-2.99	-0.06
CON23	8.37	-1.08	7.29	-12.73	11.65

7.90 kcal·mol⁻¹) indicating the serious structural deformation to form the complexes. On the other hand, although the CT effects ($-15.19 \text{ kcal·mol}^{-1}$) in **CON1** is weaker than those in **CON9** and **CON10**, the smaller ΔE_{prep} result in a comparatively higher binding energy. Therefore, the ΔE_{prep} is also an important factor for the stability of complexes except for H-bonds. Additionally, the binding energy of **CON23** is much smaller than other complexes, which means the weakest hydrogen bonding interactions exist in **CON23**.

VIBRATIONAL FREQUENCIES

The harmonic vibration frequencies of all intermolecular H-bonds in complexes and monomers calculated at the B3LYP/6-311++G (d, p) level were given in Table V. Because of the concurrence of several inter- and intramolecular H-bonds in one complex, the mixture of vibrational modes is unavoidable, so more than one X-H vibrational modes can be found for some H-bonds. For

TΛ	DI	V
IA	DL	 v

The X-H stretching frequency (intensity in parentheses) of intermolecular H-bonds in complexes and monomers (frequency in cm^{-1} and intensity in $km \cdot mol^{-1}$).

Complex	H-bond	V _{H-X} ^a	Δv	Complex	H-bond	V _{H-X} ^a	Δv
CON1	N1 ^B H…O1 ^A	3410.9(833)	-228.5	CON18	N3 ^A H2…O4 ^B	3566.3(200) a	-19.9
	S4 ^A H…O2 ^B	2596.4(247)	-69.9			3479.1(18) s	-4.8
CON2	N1 ^B H…O1 ^A	3408.9(882)	-230.5				11.4
	C6 ^A H…O2 ^B	3048.9(17)	22.4	CON19	N3 ^A H1…O2 ^B	3588.8(45) a	2.6
CON3	N1 ^B H…O2 ^A	3520.9(494)	-118.5			3466.1(488) ^d s	-17.8
	C6 ^A H…O2 ^B	3048.0(4)	21.5				-1.6
CON4	N1 ^B H…O2 ^A	3526.4(627)	-113.0		N3 ^B H…S4 ^A	3460.2(185) ^d	-135.9
	O2 ^A H…O2 ^B	3411.9(219)	-72.0	CON20	C7 ^A H…O4 ^B	3145.0(8) a	6.9
		(),	-55.8			3084.9(6) s	8.8
CON5	N3 ^B H…O1 ^A	3380.9(869)	-215.2		N3 ^B H…S4 ^A	3469.4(523)	-126.7
	S4 ^A H…O4 ^B	2602.3(242)	-64.0	CON21	S4 ^A H…O4 ^B	2601.2(195)	-65.1
CON6	N3 ^B H…O1 ^A	3387.0(864)	-209.1		C6 ^B H…O2 ^A	3107.4(14) a	-0.9
	S4 ^A H…O2 ^B	2606.4(208)	-59.9			3091.6(6) a	5.5
CON7	N1 ^B H…O2 ^A	3557.2(469)	-82.2			3033.8(23) s	0.4
	C5 ^B H…O1 ^A	3194.5(10)	1.9	CON22	N3 ^A H1…O4 ^B	3588.1(36) a	1.9
CON8	N3 ^A H1…O2 ^B	3454.6(75) ^c	-29.3			3477.0(111) s	-6.9
			-13.1				9.3
	N1 ^B H…S4 ^A	3472.6(906)	-166.8		C6 ^B H…S4 ^A	3110.0(12) a	1.7
CON9	O2 ^A H…O4 ^B	3379.4(1695)	-104.5			3087.5(5) a	1.4
		. ,	-88.3			3032.8(15) s	-0.6
	N3 ^B H…N3 ^A	3137.4(1216)	-458.7	CON23	O2 ^A H…O4 ^B	3612.7(422) ^e	128.8
CON10	O2 ^A H…O2 ^B	3422.1(1481)	-61.8			3594.7(472) ^e	127.0
			-45.6		N3 ^A H2…O4 ^B	3612.7(422) ^e	26.5
	N3 ^B H…N3 ^A	3163.6(1230)	-432.5			3594.7(472) ^e	8.5
CON11	C7 ^A H…O2 ^B	3145.1(10) a	7.0			3516.8(11) s	32.9
		3084.5(10) s	8.4				49.1
	N1 ^B H…S4 ^A	3481.9(689)	-157.5		C6 ^B H2…O2 ^A	3115.4(12) a	7.1
CON12	N3 ^A H2…O4 ^B	3548.5(251) a	-37.7			3094.8(7) a	8.7
		3470.2(47) s	-13.7			3039.0(11) s	5.6
			2.5	А	N3H	3586.2(18) a	
CON13	N3 ^B H…O2 ^A	3492.9(307)	-103.2		O2H+N3H ^b	3483.9(121)	
	S4 ^A H…O4 ^B	2624.4(161)	-41.9			3467.7(157)	
CON14	N3 ^A H2…O4 ^B	3555.7(233) a	-30.5		C7H2	3138.1(1) a	
		3474.4(33) s	-9.5			3076.1(14) s	
			6.7		C6H	3026.5(10)	
CON15	N3 ^A H1…O4 ^B	3458.7(426) ^c a	-25.2		S4H	2666.3(0)	
	N3 ^B H…S4 ^A	3451.0(294) ^c	-9.0	В	N1H	3639.4(104.1)	
			-145.1		N3H	3596.1(67)	
CON16	N3 ^B H…O2 ^A	3494.9(296)	-101.2		C5H	3192.6(5)	
	S4 ^A H…O2 ^B	2626.5(139)	-39.8		C6H	3108.3(14) a	
CON17	N3 ^B H…O2 ^A	3507.5(395)	-88.6			3086.1(10) a	
	O2 ^A H…O2 ^B	3449.9(177)	-34.0			3033.4(22) s	
			-17.8				

^a "a" Denote as asymmetric stretching mode, "s" denote as symmetric stretching mode.

^b Combined OH stretching with symmetric NH₂ stretching vibration mode.

^c Mix slightly with other vibration modes.

^d Stronger mixture between symmetric N3^AH₂ stretching and N3^BH stretching vibration mode. ^e Stronger mixture between asymmetric N3^AH₂ stretching and O2^AH stretching vibration mode.

example, the O2—H stretching vibrational mode mix with the N3-H stretching vibrational mode in free cysteine molecule because of the existence of the intramolecuar O2^AH···N3^A H-bond, so Table V list two Δv values for the change of O2-H stretching vibrational mode. As to NH₂ and CH₃ group, symmetric and asymmetric stretching vibration were found and listed in Table V, respectively.

The change of the stretching frequency is usually used to estimate the strength of H-bond. Compared with free monomer, most of stretching frequencies associated with H-bond in complexes shift to lower frequencies. The N3^BH stretching frequency of N3^BH…N3^A H-bond in CON9 and CON10 have the largest red shift values with 458.7 and 432.5 cm⁻¹, respectively, which indicate that the N3^BH…N3^A H-bond in CON9 and CON10 should be the strongest Hbonds among these complexes. The red shift values of $N1^{B}H...O1^{A}$ (CON1 and CON2) and $N3^BH{\cdots}O1^A$ H-bonds (CON5 and CON6) are beyond 200 cm⁻¹, respectively, and they can be considered as the stronger H-bonds, which is consistent with the analysis of the geometry. The H-accept ability of hydroxyl O2 atom in cysteine is weaker than carbonyl O1, so the H-bonds involving O2 as H-acceptor have smaller red shift than above involving O1 as H-acceptor. The red shift values of N1BH...S4A (CON8 and CON11) and N3^BH…S4^A (CON15, CON19 and CON20) H-bonds fall in about 126–166 cm^{-1} , which shows that these H-bonds are weaker than above ones involving NH as H-donor and O (or N) atom as H-acceptor. The shift of H-bonds involving C atom are small, and blue shifts have also found in these H-bonds. For example, the blue shift of the H-bond $C6^{A}H...O2^{B}$ in **CON2** and CON3 is 22.4 and 21.5 cm⁻¹, respectively. Although the mixture of vibrational modes occurred in the bifurcation H-bonds consisting of O2^AH···O4^B and N3^AH2···O4^B in CON23 is too serious to assign them, it is clear that the blue shift happened for O2^AH and N3^AH2 stretching modes.

Because the change of both H-bond length (ΔR_{X-H}) and vibrational frequency shifts (Δv) can be used to estimate the strength of H-bond, the correlation should exist between them. To study the relationship between of Δv and ΔR_{X-H} , a linear correlation analysis was carried out, a linear correlation was shown in Figure 6, and the fitted equation is



FIGURE 6. Correlation between the frequency shifts Δv and the bond elongation ΔR_{X-H} .

$$\Delta v = -14.9098 - 18293.6\Delta R_{\rm X-H} \quad r = 0.9743 \quad (11)$$

On the basis of harmonic vibrational approximation, it is easy to understand this linear correlation if these frequencies represent the localized X-H stretching and almost do not depend on the proton acceptors.

Conclusions

In this work, the Cys-Thy complexes have been studied at B3LYP/6-311++G(d, p) level. The nature of H-bonds was analyzed through structures, energies, frequencies, and electron density topological analysis. More than 10 kinds of H-bonds including intra- and intermolecular H-bonds have been found in complexes. Most of intermolecular H-bonds involve O (or N) atom as H-acceptor. Although CON9 and CON10 involve the strongest H-bond $(N3^{B}H \cdots N3^{A})$, respectively, they are not the most stable complexes because of the serious deformation. CON1 is the most stable complex that attribute to the smaller deformation and stronger H-bonds. Therefore, both H-bonds and structural deformation are important factors for the stability of complexes. Some important relationships between structural parameters (ΔR_{X-H} and δR), frequency shift (Δv), and electron density topological parameters (ρ_b and $\nabla^2 \rho_b$) have been found. This work can have some medical implication, because cysteine is a precursor to the formation of certain antioxidants. Stabilized and highly interacting systems of Cys-Thy complexes could interfere with the biological role of cysteine by limiting its availability in these processes.

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