

Modeling of Hydrogen Bonds in Monohydrated 2,4-Dithiothymine: An Ab Initio and AIM Study

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Received: June 21, 2005; In Final Form: September 24, 2005

Twelve tautomers of 2,4-dithiothymine are calculated at the MP2/6-31+G(d) level, and the most stable one is referred to the di-keto form (P12). Then four H-bonded complexes between P12 and water are optimized at the MP2/6-31+G(d) level of theory. The calculation of vibrational frequencies and natural bond orbital analysis are also carried out at the same level to investigate the hydrogen bonds involved in all the systems. Within all the four complexes, three types of hydrogen bonds are formed, in which the O–H···S and N–H···O bonds are the normal bonds with the X–H bond elongation and red shift of the corresponding stretch frequencies, while the C–H···O interaction is an improper, blue-shifting hydrogen bond accompanied with the contraction of the C–H bond and a blue shift of the C–H stretch frequency. The topological properties are investigated with the atoms-in-molecules (AIM) theory. The NMR chemical shielding for the isolated and the four monohydrated 2,4-dithiothymine are calculated using the “gauge-including atomic orbital” (GIAO) method. The ¹H chemical shifts are influenced by the formation of hydrogen bonds.

1. Introduction

Nowadays, there has been continuous interest in the structural and functional properties of modified nucleic acid bases, since most of them are widely implicated for a variety of biological activities.¹ For example, incorporation of heavier atoms into DNA bases leads to therapeutically important classes of nucleic acid components.^{2–5} One important class of such derivatives originates from the substitution of the thio group in place of the exocyclic oxo group in both purines and pyrimidines. Numerous sulfur-substituted pyrimidines and purines have been found to be clinically useful drugs. More specifically, 2-thiouracil (2TU) and 4-thiouracil (4TU), identified as minor components of t-RNA,^{6,7} can be used as mutagenic, anticancer, and antithyroid drugs.^{8–13} Owing to their large biochemical interest, it is not surprising that they have been the subject of both extensive experimental^{14–26} and theoretical studies.^{27–41}

Previous theoretical calculations mainly focused on the tautomerism and proton transfer of the thiobases. In 1986, Leś et al.²⁷ reported the tautomerism of uracil, cytosine, isocytosine, and some of their thio derivatives studied with the MNDO method. In 1990, they²⁸ investigated the tautomerism of 2- and 4-thiouracil at the HF/3-21G* level. Kryachko et al.^{29,30} studied the protonated and deprotonated thiouracils and their complexes with water using the B3LYP/6-31+G(d,p) method. Civcir³¹ reported the thermodynamics data of 2-thiocytosine, 2,4-dithiouracil, and 2,4-dithiocytosine and their 1-methyl analogues studied by using semiempirical AM1 and PM3 quantum chemical calculations both in the gas phase and in aqueous

solution. A series of studies about thiobases^{32–39} were carried by Leszczyński's research group. They studied the IR spectra of 2-thiouracil, 4-thiouracil, and 2,4-dithiouracil both theoretically and experimentally,³⁵ and investigated 2,4-dithiouracil tautomers at the HF/3-21G* level.³³ Then they reported the tautomeric equilibria and proton transfer in isolated and monohydrated cytosine, isocytosine, and their thio analogues at the MP2/6-31G(d) level.^{38,39} Eriksson et al. studied the hydrogenation of thiouracils and their base pairs with adenine theoretically.⁴⁰ In 2004, theoretical study on tautomerism and proton transfer of 2,4-dithiothymine was reported by Zhang et al. using the B3LYP/6-31+G(d) level,⁴¹ and the most stable one was referred as P12 (see Figure 1). In this paper, twelve tautomers of isolated 2,4-dithiothymine and its four hydrogen-bonded complexes with water are studied. In our research, all the 12 tautomers are optimized under the MP2/6-31+G(d) computational level and the same conclusion is drawn that P12 is the most stable. Therefore, we chose P12 as our target and tried to search all the possible structures as it interacts with water. The results show that the water molecule tries to stay close with the S atom(s) on the 2,4-dithiothymine molecule and only four stable configurations are obtained. Then the four complexes are studied carefully.

2. Computational Details

Calculations are carried out using the GAUSSIAN 98 program package.⁴² The basis sets implemented in the program are employed without modification. The electron correlation energies are calculated by applying the second-order Møller-Plessett perturbation theory (MP2).^{43–47} This theory has been successfully used to describe intermolecular interactions, especially weak interactions such as C–H···O contacts.^{48–50} The

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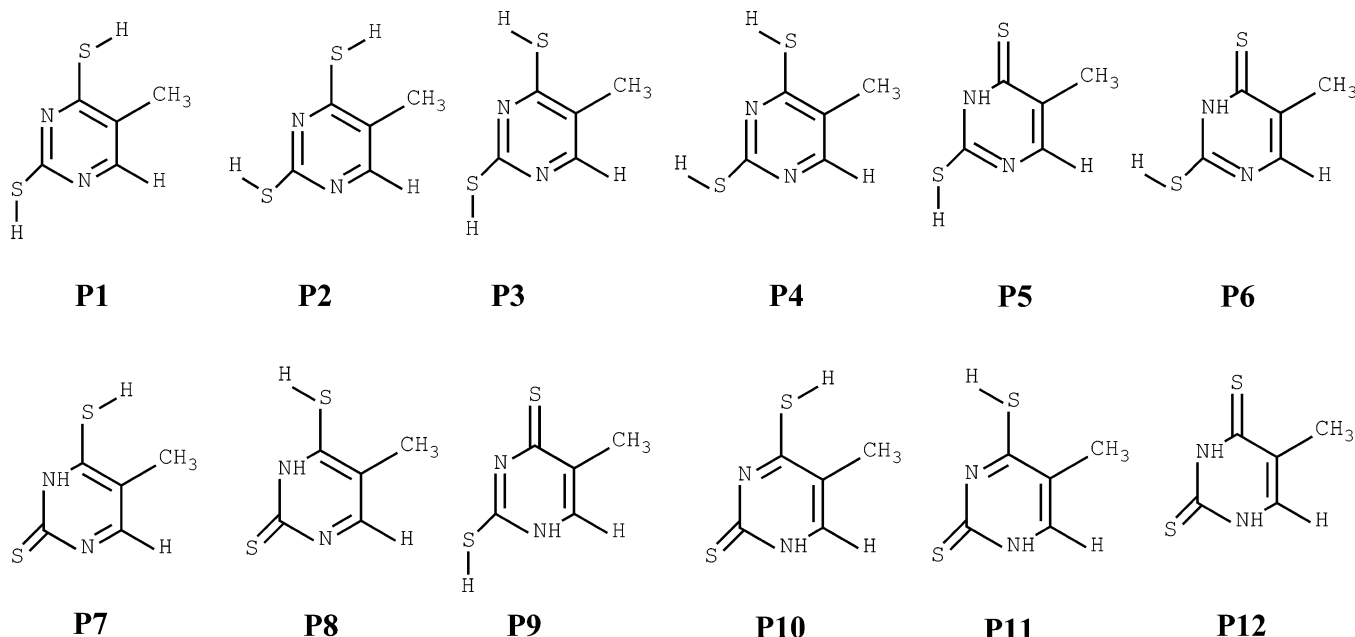


Figure 1. Schematic drawing of the 2,4-dithiothymine tautomers.

standard Pople's 6-31+G(d) basis set^{51–55} is used in conjunction with the MP2 method. Each geometry of the complexes is optimized at the MP2/6-31+G(d) level, and the four complexes are confirmed as true minima on the potential energy surface by the presence of only real frequencies after the corresponding vibrational analysis. The analysis goes further with those obtained by means of the natural bond orbital (NBO) theory of Weinhold and co-workers.⁵⁶

The corrected interaction energy (ΔE) excluding the inherent basis set superposition error (BSSE) is evaluated, and the BSSE is calculated using the Boys–Bernardi counterpoise technique.⁵⁷

The topological properties of the electronic charge density are characterized using the “atoms in molecules” (AIM) theory of Bader.⁵⁸ The AIM analysis is applied to studies of properties of a variety of hydrogen-bonded systems exhibiting both conventional and nonconventional hydrogen bonds.^{59–64} This theory offers a rigorous way of partitioning any system into its atomic fragments, considering the gradient vector field of its electron density. By means of a topological analysis of the electron density, features such as bond critical points and paths of maximum electron density can be utilized to draw a molecular graph (i.e., the network of bond paths that connects linked atoms). In particular, a hydrogen bond is evidenced in the charge density by a bond path linking the proton and the acceptor atom. Popelier^{65,66} suggested the criteria for the existence of hydrogen bonding based on the topological properties of the electronic density and a set of integrated properties related to the hydrogen atom involved. The bond critical points (BCPs), $\rho(r_c)$, and the eigenvalues of the Hessian of the charge density at the critical point, $\lambda_1 < \lambda_2 < \lambda_3$, are obtained using the AIM2000 (Version 1.0) program⁶⁷ at the MP2/6-31+G(d) level. The derived measures are the Laplacian of the charge density at the point, $\nabla^2\rho(r_c) = \sum_{i=1}^3\lambda_i$, and ratio, $|\lambda_1|/\lambda_3$. These measures are used in the following for the description of hydrogen bonding.

The NMR chemical shifts for 2,4-dithiothymine and its four monohydrated complexes are calculated using “gauge-including atomic orbital” (GIAO) method,^{68,69} implemented into the GAUSSIAN 98 program package.⁴² The chemical shifts are a difference of the chemical shielding (^1H and ^{13}C) of the studied systems and the chemical shielding of the reference compound tetramethylsilane, $\text{Si}(\text{CH}_3)_4$. The structure of $\text{Si}(\text{CH}_3)_4$, as a

TABLE 1: Gas Phase Total (E_0 in a.u.) and Relative Energies (ΔE in kJ/mol) at 0 K, for the Twelve Tautomers of 2,4-Dithiothymine, Obtained at the MP2/6-31+G(d) Level and from Reference

isomer	E_0	ΔE	ΔE^a
	MP2/6-31+G(d)	MP2/6-31+G(d)	B3LYP/6-31+G(d)
P1	−1097.97	54.4	68.9
P2	−1097.97	54.3	69.2
P3	−1097.98	42.4	59.2
P4	−1097.98	43.7	60.5
P5	−1097.98	40.6	47.1
P6	−1097.98	49.7	55.7
P7	−1097.96	88.3	94.7
P8	−1097.96	89.4	94.4
P9	−1097.96	84.5	90.1
P10	−1097.96	79.0	78.5
P11	−1097.97	62.9	65.3
P12	−1097.99	0.0	0.0

^a From ref 41.

standard, is optimized at the MP2/6-31+G(d) level. To be comparable, the calculation of the nuclear shielding of the reference compound and the isolated and monohydrated 2,4-dithiothymine are carried out both at the MP2/6-31+G(d) level of theory.

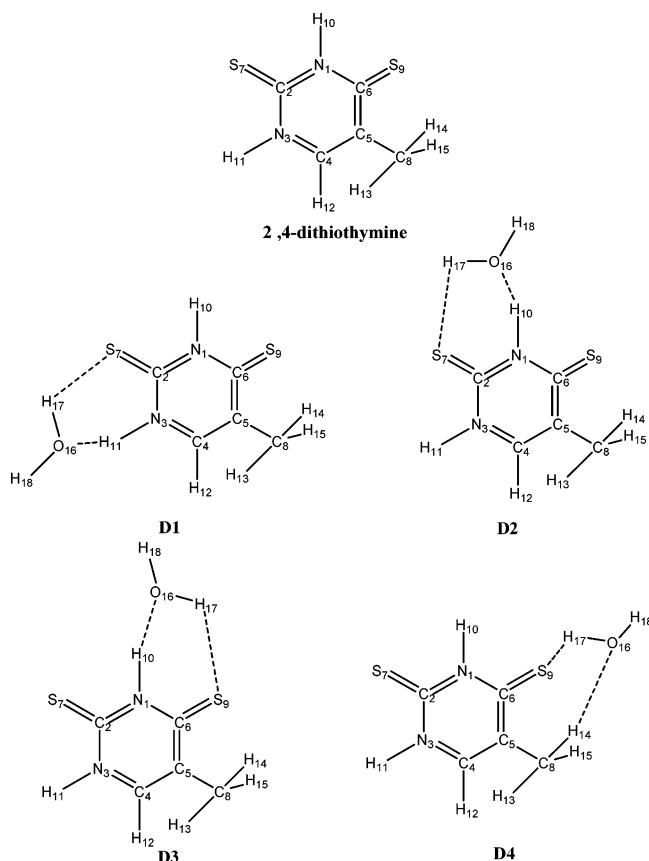
3. Results and Discussion

3.1 Structures and Stabilities of the Twelve Tautomers of Isolated 2,4-Dithiothymine. The structures of the twelve tautomers of 2,4-dithiothymine are shown in Figure 1. In Zhang's study,⁴¹ they were theoretically studied at the B3LYP/6-31+G(d) level, and the most stable one was referred as P12. In this paper, all the twelve tautomers of 2,4-dithiothymine are optimized at the MP2/6-31+G(d) computational level. Their gas-phase total and relative energies are listed in Table 1. From the data it is shown that despite some changes in the order of stability, P12 has the lowest total energy and its total energy is 40.6 kJ/mol lower than that of the second lower one (P5), whereas this energy difference is 47.1 kJ/mol calculated at B3LYP/6-31+G(d) level in ref 41. Thus, from the data it is suggested that the di-keto form of 2,4-dithiothymine, P12, is referred as the most stable one, which is same as the conclusion of ref 41.

TABLE 2: Optimized Geometry of the Most Stable Tautomer (P12) of 2,4-Dithiothymine at MP2/6-31+G(d), Compared with Those of 2,4-Dithiouracil

bond	2,4-dithiothymine	2,4-dithiouracil ^a	angle	2,4-dithiothymine	2,4-dithiouracil ^a
N1–C2	1.377	1.360(1.348)	N1–C2N3	112.3	114.1(118.4)
C2–N3	1.374	1.363(1.406)	C2–N3–C4	124.0	127.5(125.5)
N3–C4	1.376	1.382(1.358)	N3–C4–C5	122.1	114.2(117.4)
C4–C5	1.363	1.445(1.414)	C4–C5–C6	118.1	119.6(118.9)
C5–C6	1.451	1.331(1.365)	C5–C6–N1	114.3	121.5(119.8)
C6–N1	1.395	1.377(1.360)	C6–N1–C2	128.9	123.2(128.6)
C2–S8	1.650	1.657(1.645)	N1–C2–S8	124.0	122.8(125.9)
C4–S9	1.649	1.641(1.684)	N3–C4–S9	125.4	121.2(119.3)

^a From ref 33, only the most stable structure (the di-keto form) is listed here. The structural parameters are computed at HF/3-21G* level, and the crystallographic bond length and angles are given in parentheses.

**Figure 2.** Structures of 2,4-dithiothymine and the four hydrogen bonded complexes of 2,4-dithiothymine and water.

Lacking any experimental data about 2,4-dithiothymine, we tried to compare our computed results with some analogical system. The calculated data are listed in Table 2, along with the structural data of 2,4-dithiouracil (both calculated and experimental data) obtained from ref 33. It is shown from the data that the stable gas-phase geometry of 2,4-dithiothymine is very similar to that of 2,4-dithiouracil and agrees well with experiment. So our computation is reliable and accurate, and the data is used for our further discussion.

3.2 Geometries, Energies, and Vibrational Analysis. The geometries of four different complexes of 2,4-dithiothymine with water are optimized at MP2/6-31+G(d) level, and then the interaction energies excluding the inherent basis set superposition error (BSSE) are evaluated using the Boys–Bernardi counterpoise technique. Structures and atomic numbering of 2,4-dithiothymine and its four hydrated complexes are shown in Figure 2, and the respective geometrical, vibrational, and energetical characteristics are presented in Table 3.

From Figure 2, two hydrogen bonds are formed between 2,4-dithiothymine and water in each complex. In complexes D1, D2, and D3, the two interactions are of the same types as O–H···S and N–H···O interactions, whereas in complex D4, the two interactions show some characteristics different from O–H···S and C–H···O interactions. We wanted to find some other configurations without the O–H···S interaction, but tried in vain. Analyzing the intermolecular distances of the complexes, we found that the C–H···O distance in complex D4 (2.4812 Å) is considerably longer than the N–H···O intermolecular distances in the other three complexes (about 1.85 Å); whereas all the O–H···S distances are about 2.5–2.6 Å. This suggests that the interactions in complex D4 are weaker than those in the other three complexes. Furthermore, we look over the interaction energies and find that the interaction energy of complex D1 is most stable, its interaction energy is –9.10 kcal/mol; whereas complex D4 has the highest interaction energy (–3.22 kcal/mol) and the interactions in it should be the weakest.

From data in Table 3, the formation of the O–H···S hydrogen bond is accomplished by a nonnegligible prolongation of the O–H covalent bond. For example, the equilibrium O16–H17 distance of water increases by 0.0105 Å in O–H···S bond of D1 complex (from ca. 0.9710 Å to ca. 0.9815 Å), while the shortest elongation of the O16–H17 distance (0.0013 Å) comes from the D2 complex (from ca. 0.9710 Å to ca. 0.9723 Å). The same analysis is carried out on the N–H···O interactions in complexes D1, D2, and D3. The results show that N–H bonds involved in the N–H···O H-bonds are weakened upon the formation of the H-bonds. For instance, the equilibrium N3–H11 distance of complex D1 increases by 0.0138 Å and the N1–H10 distances of complexes D2 and D3 both increase by 0.0147 Å. The calculated shifts in X–H stretching vibration frequencies upon the formation of complexes agree with geometrical results. The largest red shift was found for the N1–H10 stretching frequency of complex D3 (258 cm^{–1}). Also, both the O16–H17 (in water) symmetrical and antisymmetrical stretch frequencies of water show some large, though considerably smaller, red shift upon the formation of the complexes; the largest red shift of O16–H17 stretching frequency was found for the asymmetrical stretching frequency (126 cm^{–1}). All these data are consistent with the existence of N–H···O and O–H···S H-bonds in complexes D1, D2, and D3.

As to complex D4, the situation is different. The geometrical and vibrational data are consistent with the existence of the two H-bonds of the O–H···S type and one of the C–H···O type. As for complexes D1, D2, and D3, the O–H distance is again 0.005 Å longer upon the formation of the O–H···S H-bond (from 0.9710 to 0.9760 Å) and the red shifts of symmetrical and antisymmetrical O16–H17 stretching frequencies are 41 and 60 cm^{–1}, respectively. Whereas, the change in the C8–

TABLE 3: Selected Intermolecular Distances($r_{\text{H}\cdots\text{Y}}$), Bond Lengths($R_{\text{X}-\text{H}}$), Vibrational Stretching Frequencies ($\nu_{\text{X}-\text{H}}$), Vibrational Intensities ($I_{\text{X}-\text{H}}$) in the Isolated Monomer and in the Complexes, and the Interaction Energies (ΔE) of the Complexes Determined at the MP2/6-31+G(d) Level

system	X-H \cdots Y	$R_{\text{X}-\text{H}}$ (Å)	$r_{\text{H}\cdots\text{Y}}$ (Å)	$\nu_{\text{X}-\text{H}}$ (cm $^{-1}$) ^a	$I_{\text{X}-\text{H}}$	ΔE (kcal/mol)
monomer	N3-H11	1.0166		3613	138.7	
	N1-H10	1.0211		3554	46.0	
	C8-H14	1.0945		3190	12.1	
H ₂ O	O16-H17	0.9710		3893(3747)	70.6(11.6)	
D1	N3-H11 \cdots O16	1.0304	1.8478	3366	789.1	-9.10
	O16-H17 \cdots S7	0.9815	2.5188	3830(3621)	115.4(223.3)	
D2	N1-H10 \cdots O16	1.0358	1.8516	3300	449.0	-6.56
	O16-H17 \cdots S7	0.9723	2.5954	3845(3673)	113.2(56.3)	
D3	N1-H10 \cdots O16	1.0358	1.8419	3297	450.7	-6.47
	O16-H17 \cdots S9	0.9779	2.6125	3845(3671)	117.7(60.7)	
D4	C8-H14 \cdots O16	1.0939	2.4812	3193	3.1	-3.22
	O16-H17 \cdots S9	0.9760	2.5530	3852(3687)	139.4(84.2)	

^a Note: for the O-H stretch frequencies, we present the symmetrical stretch frequencies, while the asymmetrical stretching frequencies are listed in brackets.

H14 distance is so slight, about 0.0006 Å longer (from ca. 1.0945 to 1.0939 Å), so as to be neglected, the corresponding C8-H14 stretching frequency is blue shifted by 3 cm $^{-1}$ (from 3190 to 3193 cm $^{-1}$) accompanied by a very small decrease of the vibrational intensity.

So the O-H \cdots S and N-H \cdots O H-bonds studied here are preferred as the classical, red-shift ones; and the C-H \cdots O H-bond is considered as the improper, blue-shift H-bond which was systematically studied by Hobza.^{70,71} In the description of Hobza's, upon the formation of an improper, blue-shift H-bond, the X-H bond is not elongated but shortened, accompanied with an increase of the X-H stretch vibration frequency compared to the noninteracting species. This type of interaction is quite different from the traditional H-bond. Of course much more data is needed to support our geometrical data. Therefore the natural bond orbital (NBO) and electron density topological analysis based on the atoms in molecules (AIM) theory are carried out for all of the four H-bonded complexes.

3.3 Electron Density Topological Analysis. The theory of "atoms in molecules" is first an extension of quantum mechanics to subdomains properly defining an atom as an open system. It has also proven to be a useful and successful tool in the interpretation of the charge density toward a wide variety of chemical concepts. Popelier^{65,66} suggested a set of criteria for the existence of H-bonding based on topological properties of the electron density and a set of integrated atomic properties related to the hydrogen atom involved. The criteria are as follows: (i) correct topological pattern (i.e., the existence of a bond critical point (bcp) and a bond path); (ii) proper value of electron density and Laplacian of electron density at this bcp; (iii) penetration of H and Y atoms; (iv) increase of a hydrogen net charge; (v) energetic destabilization of hydrogen; (vi) decrease of dipolar polarization; (vii) decrease of hydrogen atomic volume. In this paper we calculated the electron density topological properties of our systems using the AIM2000 program.

Complexes D1, D2, and D3. The formation of the hydrogen bonds in each complex gives rise to the appearance of three critical points (see Figure 3). Two are (3, -1) critical points linking the atoms S7 \cdots H17 and O16 \cdots H11 in D1, S7 \cdots H17 and O16 \cdots H10 in D2, and S9 \cdots H17 and O16 \cdots H10 in D3, and the other one is a (3, +1) critical point appearing between the two bond critical points. Table 4 gives the topological properties of the (3, -1) critical points formed upon dimerization. The topological properties of the electron density at the (3, -1) critical points in S7 \cdots H17 (D1 and D2) and S9 \cdots H17 (D3), as well as in O16 \cdots H11 (D1) and O16 \cdots H10 (D2 and D3), are

very similar, despite the different stabilization energy of the corresponding complexes (see Table 3). The electron density at the critical points varies from 0.0128 to 0.0315 au. Typically they are about an order of magnitude smaller than those found for a covalent bond. The value for the S \cdots H interactions (0.0128 to 0.0151 au) are sensibly lower than those for the O \cdots H interactions (0.0309 to 0.0315 au), in agreement with the differences in geometrical distances for the intermolecular contacts (see above and Table 3). As expected for closed-shell interactions, the Laplacian of the electron density from the interatomic surface toward the interacting nuclei, as noted in the positive value of λ_3 , which is much larger than the other two eigenvalues.

An additional criterion for hydrogen bonding is based on the mutual penetration of the hydrogen (H) and the acceptor atom (Y) upon hydrogen bond formation. To estimate this penetration, the nonbonded atomic radii of those atoms have to be compared to the corresponding bonded radii. In the bonded complex the atomic radius is determined as the distance to the intermolecular bond critical point from the atom, and the nonbonded atomic radius is determined as the distance from the atom to an isodensity contour (a value of 0.001 au has been adopted here) in the direction of the hydrogen bond. The results in Table 4 indicate a mutual penetration of the interacting H-bond acceptor and hydrogen atoms varying about 1.1 and 1.9 Å for the N-H \cdots O and O-H \cdots S contacts, respectively.

According to Popelier's criteria for hydrogen bonding, the hydrogen atoms involved in hydrogen bonding exhibit similar changes in selected integrated atomic properties, which are (i) an increase in the net charge, (ii) a lowering in the absolute value of the atomic energy, (iii) a reduction in the first moment, and finally (iv) a decrease in the atomic volume. All these trends are found for the hydrogen atoms in the X-H bonds that participate in intermolecular interactions, as can be seen from inspection of Table 5. For the N-H bonds, the net charge is increased by about 0.07 units of electron, the atomic energy decreases in absolute value of about 0.038 au, the first moment is reduced by about 0.04 au, and the atomic volume is diminished by around 9.5 au; whereas for the O-H bonds, all these changes are found to be smaller than those for the N-H bonds. It has been found that the net charge is increased by about 0.04 units of electron, the atomic energy decreases in absolute value of about 0.03 au, the first moment is reduced by about 0.01 au, and the atomic volume is diminished by around 2 au for the O-H bonds.

Complex D4. The formation of complex D4 also gives rise to the appearance of three critical points (see Figure 3). Two

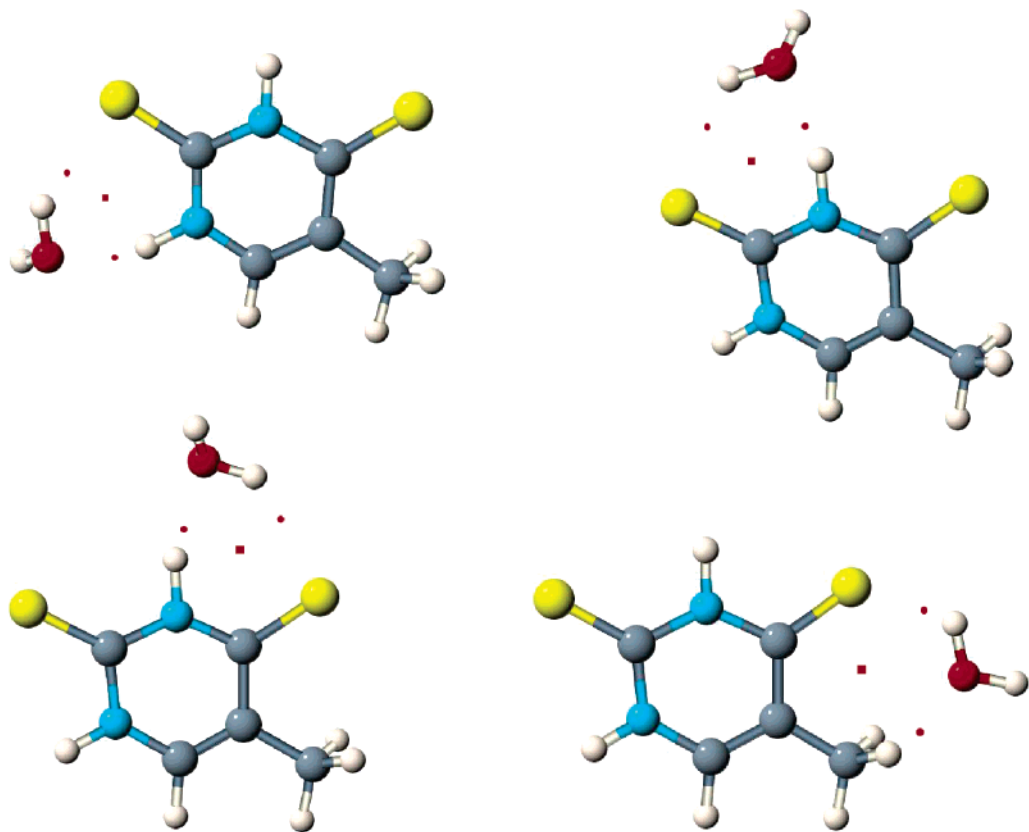


Figure 3. Representation of the bond (circle) and ring (square) critical points formed in the four complexes.

TABLE 4: Electron Density Topological Properties at the (3, −1) Critical Points for the X–H···Y Contacts Formed upon Complexation between 2,4-Dithiopyrimidine and Water

system	interaction	ρ	$\nabla^2\rho$	λ_1	λ_2	λ_3	Δr_H	Δr_Y	$\Delta r_Y + \Delta r_H$
D1	N3–H11···O16	0.0310	0.1123	−0.0464	−0.0448	0.2035	0.98	0.93	1.91
	O16–H17···S7	0.0151	0.0489	−0.0148	−0.0140	0.0778	0.57	0.58	1.15
D2	N1–H10···O16	0.0309	0.1105	−0.0468	−0.0448	0.2020	0.97	0.93	1.90
	O16–H17···S7	0.0130	0.0458	−0.0121	−0.0109	0.0687	0.62	0.49	1.11
D3	N1–H10···O16	0.0315	0.1128	−0.0482	−0.0460	0.2069	0.98	0.94	1.92
	O16–H17···S9	0.0128	0.0449	−0.0119	−0.0107	0.0675	0.65	0.48	1.13
D4	C8–H14···O16	0.0085	0.0335	−0.0079	−0.0071	0.0495	0.51	0.56	1.07
	O16–H17···S9	0.0127	0.0429	−0.0121	−0.010	0.0659	0.58	0.53	1.11

TABLE 5: Integrated Atomic Properties^a for the Hydrogen Atoms in the X–H Involved in the Hydrogen Bonding in the Four Complexes and in the Respective Isolated Monomers with the Change for a Given Property in the Complexes Relative to the Isolated Monomer

system	interaction	q^0	q	Δq	E^0	E	ΔE	$ M ^0$	$ M $	$\Delta M $	ν^0	ν	$\Delta\nu$
D1	N3–H11···O16	0.501	0.431	−0.070	−0.394	−0.356	0.038	0.159	0.120	−0.039	24.30	14.98	−9.32
	O16–H17···S7	0.418	0.378	−0.040	−0.350	−0.316	0.034	0.162	0.151	−0.011	20.41	17.87	−2.54
D2	N1–H10···O16	0.490	0.423	−0.067	−0.387	−0.349	0.037	0.159	0.119	−0.040	24.20	14.70	−9.50
	O16–H17···S7	0.418	0.382	−0.038	−0.350	−0.320	0.030	0.162	0.153	−0.009	20.41	18.45	−1.96
D3	N1–H10···O16	0.490	0.421	−0.069	−0.387	−0.348	0.039	0.159	0.118	−0.041	24.20	14.51	−9.69
	O16–H17···S9	0.418	0.381	−0.037	−0.350	−0.320	0.030	0.162	0.154	−0.008	20.41	18.62	−1.79
D4	C8–H14···O16	0.959	0.929	−0.030	−0.593	−0.585	0.008	0.152	0.131	−0.021	46.46	41.93	−4.53
	O16–H17···S9	0.418	0.399	−0.019	−0.350	−0.332	0.018	0.162	0.157	−0.005	20.41	18.61	−1.80

^a All values in atomic units: q , net charge; E , energy; $|M|$, first moment; ν , volume.

are (3, −1) critical points between atoms O16···H14 and S9···H17, and the other is a ring critical point located between the two intermolecular (3, −1) critical points. For the S9···H17 bond, the electron density at the (3, −1) critical point is 0.0127 au, same as the values for S7···H17 (D1 and D2) and S9···H17 (D3) contacts. However, the electron density at the (3, −1) critical point for O16···H14 contact (0.0085 au) in complex D4 is much smaller than those for H···O bonds in the other three complexes. Indeed, the mutual penetration of the hydrogen-bond acceptor and hydrogen atom is about 0.8 Å smaller for complex

D4 than for the corresponding contacts in the other three complexes.

Table 5 also shows the changes in the integrated atomic properties for the hydrogen atoms involved in hydrogen bonding for complex D4. Again, all the changes follow the expected trends pointed out by Popelier. Importantly, the changes experienced by the hydrogen atom in the C7–H12 bond are sensibly smaller than those found for the hydrogen atom in the O–H bonds in the complexes D1, D2, and D3.

3.3. Natural Bond Orbital Analysis. *Complexes D1, D2, and D3.* Analyzing the NBO densities, we found an electron density transfer (EDT) of 7 me from water to 2,4-dithiothymine (D1), an EDT of 15 me from water to 2,4-dithiothymine (D2, D3). Investigating individual densities in the N3–H11...O16 contacts of complex D1, we found electron density decreases by 27 me at the O16 lone electron pairs and a large electron density increase in the 2,4-dithiothymine N3–H11 σ^* antibonding orbital (24 me). In the case of O16–H17...S7 contact, we found that the electron densities of all the π bonding orbital and lone electron pairs involved in the 2,4-dithiothymine hyperconjugation system decrease and the electron density of the water O16–H17 σ^* antibonding orbital increases by 18 me. From the second-order perturbation theory analysis in NBO basis, two largest intermolecular interactions are found from the S7 lone electron pairs to the water O16–H17 σ^* antibonding orbital ($E_2 = 8.10$ kcal/mol) and from the O16 lone electron pairs to the N3–H11 σ^* antibonding orbital ($E_2 = 22.10$ kcal/mol). Electron density increase in N3–H11 and O16–H17 σ^* antibonding orbitals leads to weakening of both bonds, their elongation, and a concomitant red shift of the respective stretch vibration frequencies. This gives clear evidence about formation of the standard H-bond of both the O–H...S and N–H...O type. The situation in complexes D2 and D3 is similar.

Complex D4. From the NBO densities of complex D4 it is found that an electron density of 10 me is transferred from 2,4-dithiothymine to water instead of from water to 2,4-dithiothymine found in complexes D1, D2, and D3. As to the O16–H17...S9 contact, the situation is same as that for the other three complexes, while the electron densities of all the π bonding orbital and lone electron pairs involved in the 2,4-dithiothymine hyperconjugation system decrease and the electron density of the water O16–H17 σ^* antibonding orbital increases by 13 me. In the case of the C8–H14...O16 contact, the situation is very complicated. The electron densities both in the C8–H14 σ^* antibonding orbital and the O16 lone electron pairs decrease slightly (both about -1 me) upon formation of the complex, while some greater changes are found that the electron density in the C5–C8 σ^* antibonding orbital is increased by 46 me and the electron density in the N1–C6 σ^* antibonding orbital decreases by 48 me. From the second-order perturbation theory analysis in the NBO basis, the interactions from the 2,4-dithiothymine S9 lone electron pairs to the water O16–H17 σ^* antibonding orbital ($E_2 = 0.84$ kcal/mol) and from the water O16 lone electron pairs to the C8–H14 σ^* antibonding orbital ($E_2 = 1.07$ kcal/mol) are very faint, while a stronger interaction is found from the C6–S9 π bonding orbital to the C8–H14 ($E_2 = 4.41$ kcal/mol). This reflects a different target of EDT in this complex: X–H bond in the proton donor in the H-bonded complexes and remote (nonparticipating) part of the proton donor in the improper H-bonded complexes. The changes of electron densities upon formation of complex D4 suggests the O16–H17...S9 contact a H-bond and the C8–H14...O16 contact an improper, blue-shifting H-bond instead of a H-bond.

3.4. NMR Chemical Shielding. The NMR chemical shieldings of isolated 2,4-dithiothymine and its four monohydrated complexes are calculated using gauge-including atomic orbital (GIAO) method at MP2/6-31+G(d) level of theory. The ^1H and ^{13}C chemical shieldings are listed in Table 6 and Table 7, respectively.

It is found from data in Table 6 that the nuclear shift of H10 atom in complex D2 or D3 is 3.5 ppm higher than in the isolated 2,4-dithiothymine; whereas the nuclear shifts of H10 atoms in complexes D1 and D4 are almost same as that in the isolated

TABLE 6: GIAO MP2/6-31+G(d) Calculated ^1H Chemical Shieldings (δ/Ppm) for Isolated and Monohydrated 2,4-Dithiothymine

H atom	monomer	D1	D2	D3	D4
10	9.2	9.3	12.7	12.7	9.3
11	6.9	10.5	6.9	7.0	7.1
12	6.4	6.6	6.4	6.5	6.6
13	0.9	0.9	0.9	0.9	0.9
14	1.7	1.7	1.7	1.7	2.2
15	1.7	1.6	1.6	1.7	1.6
17	1.2	3.8	3.4	3.3	1.9
18	1.2	1.6	1.7	1.8	0.5

TABLE 7: GIAO MP2/6-31+G(d) Calculated ^{13}C Chemical Shieldings (δ/ppm) for Isolated and Monohydrated 2,4-Dithiothymine

C atom	monomer	D1	D2	D3	D4
2	197.0	198.0	197.8	197.1	196.6
4	142.8	144.0	141.7	143.8	145.1
5	123.5	124.1	125.1	123.3	125.8
6	216.1	215.6	216.6	217.8	218.9
8	24.3	24.2	24.4	24.3	23.7

2,4-dithiothymine. From the analysis above it is shown that the H10 atoms in complexes D2 and D3 are involved in a N–H...O hydrogen bond, thus the electron density around the D10 atoms of D2 and D3 is lower than the others (isolated 2,4-dithiothymine, D1 and D4). The same situation is found for the H11 atom of complex D3, which is also involved in a hydrogen bond: the chemical shift of the H11 atom is 10.5 ppm (about 3.5 ppm higher than it in the isolated 2,4-dithiothymine and the other three complexes). The situation for the H14 atom of complex D4 is similar in that as a contributor to a H-bond, the chemical shift of the H14 atom in D4 is 0.5 ppm higher than in others. This difference is very small as compared with above data (i.e., the chemical shieldings of H10 atoms in complexes D2 and D3, H11 atom in complex D1). From above analysis it is known that the C–H...O interaction (in D4) is weaker than the N–H...O interactions in the other three complexes. Thus it is suggested that the chemical shift of the hydrogen atom will be higher upon the formation of a hydrogen bond.

We also give the calculated ^{13}C chemical shieldings for the isolated and monohydrated 2,4-dithiothymine in Table 7 to give some useful information for experimentalists in the future studies of the hydrated thio analogues of thymine.

4. Conclusion

Twelve tautomers of 2,4-dithiothymine are studied theoretically, and analysis of the relative energies shows that the di-keto form of 2,4-dithiothymine, P12, is the most stable one. The computed structural data is close to the structural data of 2,4-dithiouracil both experimentally and theoretically. Four H-bonded complexes between 2,4-dithiothymine and water are optimized at the MP2/6-31+G(d) level of theory. Analysis on the structural data shows that three types of H-bonds are formed upon the complexation of 2,4-dithiothymine and water. Harmonic vibrational analysis formed at the correlated MP2 level reveals that the O–H...S and N–H...O bonds are standard H-bonds, while the C–H...O bond found in complex D4 is an improper, blue-shift H-bond of type. Vibrational analysis results agreed with atom-in-molecule Bader analysis of electron density and with natural bond orbital analysis. The ^1H and ^{13}C NMR chemical shieldings of isolated and monohydrated 2,4-dithiothymine are studied, and the formation of hydrogen bonds gives contribution to the rise of ^1H chemical shifts.

Acknowledgment. This project was supported by national natural science foundation of china (No. 20373045) and the Special Research Foundation of Doctoral Education of Chinese University (20020610024). N.-B.W. acknowledges the support of a CERG grant from the Research Grants Council of Hong Kong (Account No.: 9040742 (CityU 1114/02P)).

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