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DFT AND MP2 INVESTIGATIONS ON THE HYDROGEN BONDING INTERACTION BETWEEN 5,6-DIHYDROTHYMINE AND DNA BASES: A, C, G, T

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5,6-Dihydrothymine (DHT) is a nucleobase lesion induced by the action of ionizing radiation on thymine residue in DNA. In this work, we present the hydrogen bonding base pairs involving 5,6-dihydrothymine bound to four bases in DNA: adenine (A), cytosine (C), guanine (G), and thymine (T). Full geometry optimizations are performed for the studied complexes by the B3LYP method. Interaction energies are corrected for the basis set superposition error, using the full Boys-Bernardi counterpoise correction scheme. Hydrogen bonding patterns of these base pairs are characterized using NBO and AIM analysis. According to the calculated binding energies and structural parameters, the stability of the base pairs decrease in the following order: DHT:G ~ DHT:A > DHT:C > DHT:T.

K e y w o r d s: DNA bases, hydrogen bond, 5,6-dihydrothymine.

INTRODUCTION

Hydrogen bonding interaction plays a unique role in chemical and biochemical systems, especially between nucleic acid bases [1]. These interactions contribute to the stability and conformational variability of nucleic acids. A proper description of these H-bonded interactions helps to understand the basic principles governing the formation of 3D nucleic acid architectures [2, 3]. Due to the importance, there have been numerous studies (experimental [4] and computational [5—7]) concerned with the association of nucleotide base pairs.

The computational studies range from Watson—Crick base pairs [8, 9] to unusual base pairs [10, 11]. J. Šponer and coworkers discussed the key electronic properties of standard and modified nucleobases and the energetics of standard base pairs, mismatched base pairs, thio-base pairs, and others [12]. The hydrogen-bonded complexes of nucleobases are primarily stabilized by the electrostatic interaction, while the dispersion attraction is also important [13]. The reliability of *ab initio* calculations depends on two factors: the quality (size) of the basis set of atomic orbitals and the inclusion of electron correlation effects.

DNA is a major target of ionizing radiation and UV-light irradiation that induce many genetoxic effects such as mutagenicity, carcinogenicity, and lethality. 5,6-Dihydrothymine is a significant lesion in cells exposed to ionizing radiation in an anaerobic environment [14]. In the present work, we study the hydrogen bond characters and binding energies of the base pairs between 5,6-dihydrothymine and DNA bases, which may be useful to study the structure of DNA and the pairing property of the damaged base 5,6-dihydrothymine.

COMPUTATIONAL DETAILS

The complexes were fully optimized and characterized as minima by frequency analysis using GAUSSIAN 03 [15] at the B3LYP/6-31+G** level. Energy calculations were subsequently performed at the B3LYP/6-31+G** and MP2/6-31+G** levels. Generally, the energy of a system will decrease during the course of new complex formation. The decreased energy is the binding energy, which is generally related to the stability of the corresponding complex. Interaction energies were obtained as the difference between the energy of the complex and the energies of the molecules in isolation, using the supermolecule method [16]. This procedure is known to be subject to a major error: the basis set superposition error (BSSE) [17]. This error is a purely mathematical artifact due to that different basis sets are used for energy evaluations of the supersystem and the subsystems. To avoid it, the counterpoise (CP) correction was used to correct for BSSE.

According to Møller—Plesset perturbation theory, the MP2 stabilization energy of the base pair describing the interaction between monomers is given by

$$\Delta E^{\mathrm{MP2}} = \Delta E^{\mathrm{HF}} + \Delta E^{\mathrm{COR}}, \tag{1}$$

where

$$\Delta E^{\mathrm{HF}} = E^{\mathrm{HF}}_{\mathrm{AB—AB}} - E^{\mathrm{HF}}_{\mathrm{A—AB}} - E^{\mathrm{HF}}_{\mathrm{B—AB}} \tag{2}$$

is the HF interaction energy between the bases. And the ΔE^{COR} is the correlation interaction energy within the framework of second-order Møller—Plesset perturbation theory.

At the same time, the MP2 stabilization energy is given by

$$\Delta E^{\mathrm{MP2}} = E^{\mathrm{MP2}}_{\mathrm{AB—AB}} - E^{\mathrm{MP2}}_{\mathrm{A—AB}} - E^{\mathrm{MP2}}_{\mathrm{B—AB}}. \tag{3}$$

In the above-mentioned expression, $E^{\mathrm{Y}}_{\mathrm{X—Z}}$ is the energy of a system X computed by the Y method with the basis set Z.

The Natural Bond Orbital (NBO) [18] analysis was performed at the B3LYP/6-31+G** level. This was carried out by examining all possible interactions between filled (donor) Lewis-type NBOs and empty (acceptor) non-Lewis NBOs and estimating their energetic importance by second-order perturbation theory. For each donor NBO(i) and acceptor NBO(j) the stabilization energy $E^{(2)}$ associated with delocalization (2e-stabilization) i/j is estimated as

$$E^{(2)} = \Delta E_{ij} = q_i[\mathrm{F}^2_{(i,j)} / \ (\varepsilon_i - \varepsilon_j)], \tag{4}$$

where q_i is the donor orbital occupancy; ε_i and ε_j are the diagonal elements (orbital energies), and $\mathrm{F}_{(i,j)}$ is the off-diagonal NBO Fock matrix element.

Atoms in Molecules (AIM) theory is a very useful tool in analyzing hydrogen bonds [19]. The most interesting aspect of Bader′s AIM theory is that it redefines the concept of the chemical bond in terms of the topological properties of ρ_c, namely its gradient field $\nabla\rho_c$ and its curvature or Laplacian $\nabla^2\rho_c$. So, the bond critical point (BCP) is a point along the trajectory of the gradient path (bond path, BP) connecting two local electron density maxima with $\nabla\rho_c = 0$ (nuclei) and lying at the borderline of the two atomic basins involved. With a large electronic density at the hydrogen BCP and a positive value of $\nabla^2\rho_c$ indicating a strong hydrogen bond (HB), the electron densities ρ_c and Laplacians $\nabla^2\rho_c$ of various nonclassical HB base pairs at BCPs have been calculated at the B3LYP/6-31+G** level. The topological analysis was performed using the AIM2000 program.

RESULTS AND DISCUSSION

Calculations at the B3LYP/6-31+G** level led to DHT:A(A1—A3), DHT:C(C1—C4), DHT:G(G1—G5), DHT:T(T1) structures for the damaged base pairs (Fig. 1). These complexes are stabilized with near-linear hydrogen bonds. Table 1 lists the interaction energies, and Table 2 collects the selected structural properties for the hydrogen-bonded complexes studied in this work.

1. Interaction energy. Interaction energies with the BSSE correction for each of the damaged base pairs are reported in Table 1 under the convention that negative ΔE corresponds to a favorable

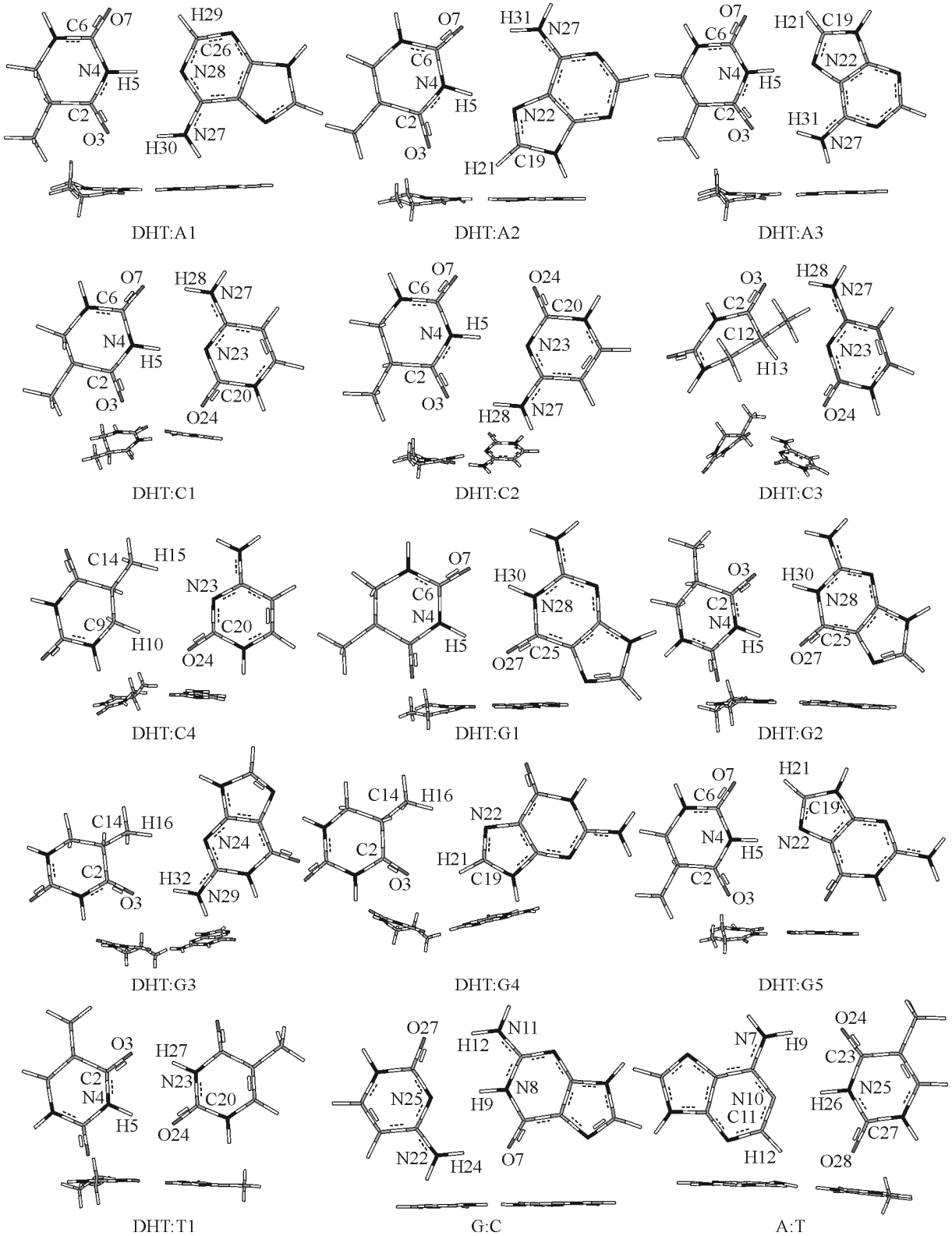


Fig. 1. Optimized structures of the hydrogen-bonding complexes

Table 1

Interaction energies of DHT:A, DHT:C, DHT:G, *and* DHT:T *conformers* (kcal/mol) *obtained by the* B3LYP *and* MP2 *methods*

Pair	B3LYP/6-31+G**		MP2/6-31+G**			
	ΔE	ΔE_{CP}	ΔE_{HF}	ΔE_{CORR}	ΔE_{MP2}	ΔE_{CP}
G:C	–28.4	–27.5	–22.7	–8.1	–30.8	–26.5
A:T	–14.6	–13.9	–9.6	–7.1	–16.7	–13.4
DHT:A1	–11.4	–11.0	–7.4	–7.2	–14.5	–10.8
DHT:A2	–12.8	–12.0	–8.7	–7.5	–16.2	–12.2
DHT:A3	–12.4	–11.7	–8.3	–7.7	–16.0	–11.9
DHT:C1	–10.8	–10.0	–7.4	–7.6	–15.0	–10.7
DHT:C2	–9.7	–9.0	–6.0	–7.9	–13.9	–9.7
DHT:C3	–9.0	–8.3	–8.6	–5.5	–14.1	–10.0
DHT:C4	–5.6	–5.3	–5.6	–2.7	–8.3	–6.3
DHT:G1	–15.3	–14.7	–13.0	–5.2	–18.2	–14.5
DHT:G2	–13.8	–13.2	–11.0	–5.7	–16.7	–13.1
DHT:G3	–5.9	–5.5	–4.9	–3.4	–8.3	–5.9
DHT:G4	–4.1	–3.8	–3.9	–3.0	–6.9	–4.8
DHT:G5	–6.9	–6.4	–5.0	–5.7	–10.7	–7.7
DHT:T1	–9.6	–8.9	–7.4	–4.9	–12.3	–8.9

ΔE_{HF} is the HF interaction energy; ΔE_{CORR} is the correlation interaction energy; ΔE_{MP2} is the MP2 stabilization energy; ΔE_{CP} is the BSSE-corrected binding energy.

binding energy. The results show that B3LYP/6-31+G** and MP2/6-31+G** give similar results. Table 1 shows that the binding energies of the base pairs range from –3.8 kcal/mol to –14.7 kcal/mol, and the binding energies of normal base pairs G:C and A:T are –27.5 kcal/mol and –13.9 kcal/mol (B3LYP/6-31+G**) respectively. Moreover, the results of the MP2 method show that the stabilization of the H-bonded base pair is primarily due to electrostatic interactions. However, for weakly hydrogen-bonded base pairs, the correlation interaction energy amounts to ~40 % of the stabilization energy.

The comparison of the formation energies of the systems shows that the DHT:G1 complex is the most negative among all the studied complexes. The B3LYP calculation shows that the formation energy is –14.7 kcal/mol. The interaction energy of the DHT:G1 structure is lower than the pairing energy of the canonical G:C base pair by ~12.8 kcal/mol [20, 21]. It can be deduced that the binding ability of DHT is much lower than that with C when bound in the DHT:G1 structure. The binding energy shows that DHT:G1 is the most stable among the complexes formed by DHT. But whether it is an inveterate rogue? We need to investigate the geometry character of the base pair and the difference between DHT:G1 and normal base pairs. Among the complexes, DHT:G2 is found to have the interaction energy of –13.2 kcal/mol. In the case of the DHT:C complex, Table 1 shows that the stabilization energy of the DHT:C1 complex is –10.0 kcal/mol.

The DHT:A1, DHT:A2, and DHT:A3 base pairs are marked by lower pairing energies. The BSSE-corrected pairing energy values are respectively: –11.0 kcal/mol, –12.0 kcal/mol, and –11.7 kcal/mol. These are near to the pairing energy of the normal A:T base pair (HB = –13.9 kcal/mol) [22—24]. In the case of DHT:T, the interaction energy for DHT:T1 is found to be less negative (–8.9 kcal/mol).

2. Hydrogen bond (HB) analysis. The energy difference method can only be used to evaluate the overall hydrogen bonding energy of the base pair. It is impossible to identify the strength of each individual HB by this procedure. The strength of a localized HB may be found from the HB length, second-order perturbation energy $E^{(2)}$, and electron density ρ_c. All these parameters are easily calculated

Table 2

Optimized geometry parameters, *electron density* ρ_c, e/Bohr^3, *Laplacian of the electron density* $\nabla^2\rho_c$, e/Bohr^5, *selected* NBO *charge*, *and hydrogen bond stabilization energy* $E^{(2)}$, kcal/mol *calculated for the base pairs at the* B3LYP/6-31+G** *level*

H-bond	*d*, Å	θ, deg.	NBO charge	$E^{(2)}$, kcal/mol	ρ_c, e/Bohr^3	$\nabla^2\rho_c$, e/Bohr^5
1	2	3	4	5	6	7
			G:C			
$O_{27}…H_{12}N_{11}$	1.912	178.3	–0.694, 0.464, –0.859	19.58	0.0273	0.0772
$N_{25}…H_9N_8$	1.914	177.2	–0.649, 0.467, –0.663	25.87	0.0326	0.0786
$N_{22}H_{24}…O_7$	1.761	179.2	–0.805, 0.475, –0.690	33.03	0.0383	0.1119
			A:T			
$N_7H_9…O_{24}$	1.922	173.8	–0.827, 0.463, –0.665	18.33	0.0266	0.0759
$N_{10}…H_{26}N_{25}$	1.828	179.1	–0.604, 0.477, –0.680	39.87	0.0399	0.0895
$C_{11}H_{12}…O_{28}$	2.865	132.4	0.257, 0.250, –0.650	1.03	0.0043	0.0164
			DHT:A1			
$C_{26}H_{29}…O_7$	2.656	133.8	0.256, 0.252, –0.651	1.16	0.0067	0.0237
$N_{28}…H_5N_4$	1.735	179.2	–0.603, 0.475, –0.705	37.61	0.0497	0.1054
$O_3…H_{30}N_{27}$	1.909	173.0	–0.652, 0.461, –0.829	16.23	0.0276	0.0784
			DHT:A2			
$O_7…H_{31}N_{27}$	1.901	172.1	–0.692, 0.466, –0.827	15.95	0.0268	0.0810
$N_{22}…H_5N_4$	1.714	174.3	–0.535, 0.478, –0.708	38.82	0.0507	0.1128
$C_{19}H_{21}…O_3$	2.659	122.7	0.220, 0.262, –0.623	0.97	0.0066	0.0248
			DHT:A3			
$C_{19}H_{21}…O_7$	2.600	123.5	0.222, 0.266, –0.666	1.20	0.0074	0.0274
$N_{22}…H_5N_4$	1.707	174.9	–0.536, 0.477, –0.705	39.60	0.0516	0.1139
$O_3…H_{31}N_{27}$	1.941	172.2	–0.650, 0.462, –0.829	14.19	0.0250	0.0728
			DHT:C1			
$O_7…H_{28}N_{27}$	1.790	174.8	–0.700, 0.469, –0.826	23.69	0.0358	0.1069
$N_{23}…H_5N_4$	1.841	171.6	–0.649, 0.481, –0.710	25.40	0.0379	0.0883
			DHT:C2			
$O_3…H_{28}N_{27}$	1.816	174.9	–0.663, 0.466, –0.827	13.74	0.0371	0.0886
$N_{23}…H_5N_4$	1.851	171.4	–0.647, 0.481, –0.700	24.63	0.0339	0.0998
			DHT:C3			
$O_3…H_{28}N_{27}$	1.876	166.5	–0.659, 0.468, –0.827	8.64	0.0274	0.0872
$N_{23}…H_{13}C_{12}$	2.492	125.3	–0.620, 0.326, –0.394	1.69	0.0111	0.0360
$O_{24}…H_{13}C_{12}$	2.632	164.7	–0.663, 0.326, –0.394	1.46	0.0072	0.0246
			DHT:C4			
$O_{24}…H_{10}C_9$	2.206	180.0	–0.661, 0.299, –0.287	6.48	0.0159	0.0466
$N_{23}…H_{15}C_{14}$	2.705	163.6	–0.604, 0.256, –0.699	1.75	0.0074	0.0216
			DHT:G1			
$O_7…H_{30}N_{28}$	1.721	178.2	–0.719, 0.471, –0.664	31.81	0.0426	0.1286
$O_{27}…H_5N_4$	1.785	173.9	–0.663, 0.491, –0.708	27.31	0.0363	0.1038
			DHT:G2			
$O_3…H_{30}N_{28}$	1.747	179.7	–0.676, 0.468, –0.665	29.46	0.0403	0.1200
$O_{27}…H_5N_4$	1.789	172.3	–0.661, 0.492, –0.696	26.73	0.0358	0.1028

Continued Table 2

1	2	3	4	5	6	7
			DHT:G3			
$N_{24}…H_{16}C_{14}$	2.512	172.5	–0.606, 0.287, –0.706	3.29	0.0105	0.0295
$O_3…H_{32}N_{29}$	1.871	166.3	–0.645, 0.472, –0.859	15.13	0.0270	0.0909
			DHT:G4			
$N_{22}…H_{16}C_{14}$	2.404	174.7	–0.467, 0.294, –0.703	3.58	0.0120	0.0351
$O_3…H_{21}C_{19}$	2.161	151.3	–0.629, 0.267, 0.179	5.07	0.0160	0.0521
			DHT:G5			
$O_7…H_{21}C_{19}$	2.156	134.5	–0.688, 0.274, 0.196	5.27	0.0179	0.0572
$N_{22}…H_5N_4$	1.908	164.1	–0.499, 0.486, –0.709	20.36	0.0318	0.0796
			DHT:T1			
$O_3…H_{27}N_{23}$	1.814	167.8	–0.648, 0.490, –0.677	22.38	0.0329	0.1002
$O_{24}…H_5N_4$	1.819	168.0	–0.683, 0.490, –0.699	21.91	0.0324	0.0995

from the optimized structures. Table 2 lists the equilibrium distance between the proton and the proton acceptor atom. This quality is generally correlated with ΔE, with a stronger HB associated with a shorter length. For each HB, the second-order perturbation energy $E^{(2)}$ and the electron density ρ_c are listed in Table 2.

As the stable complex, DHT:G1 shows a configuration with a HB between O_7 and $H_{30}N_{28}$ with a distance of 1.721 Å, and a HB between O_{27} and H_5N_4 with a distance of 1.785 Å. In DHT:G1, HBs ($O_7…H_{30}N_{28}$ and $N_4H_5…O_{27}$ bond angles are 178.2° and 173.9° respectively) are essentially linear. The $O_7…H_{30}N_{28}$ HB has a $E^{(2)}$ energy of 31.81 kcal/mol, an electron density ρ_c of 0.0426 e/Bohr^3, and a Laplacian of the electron density $\nabla^2\rho_c$ of 0.1286 e/Bohr^5. And the $N_4H_5…O_{27}$ HB has a $E^{(2)}$ energy of 27.31 kcal/mol, an electron density ρ_c of 0.0363 e/Bohr^3, and a Laplacian of the electron density $\nabla^2\rho_c$ of 0.1038 e/Bohr^5. It is clear that short strong NH…O HBs contribute to the stability of the DHT:G1 complex.

Since the hydrogen bond properties are sometimes evaluated by charge distributions, for the better understanding of the problem, we considered the atomic charges for the included atoms. As presented in Fig. 1, HBs are the main factors of the base pairs. Strong HBs are formed between DHT and DNA bases, and the HB lengths are found to be within 2.8 Å. For the more strongly H-bonded conformers (DHT:G1, DHT:A1, DHT:T1, and DHT:C1) the corresponding NH…O and NH…N contacts have preferable H…O/N separations and near-linear HB arrangements.

3. Hydrogen bonding energy as a function of geometry parameter. Apart from the characterization of DNA base pairs, an important task is the evaluation of interaction energies of DNA base pairs in ″away from equilibrium″ geometries present in the actual structural contexts, and a comparison of these geometries and interaction energies with the fully-optimized geometries of these base pairs. The HB potential is the function that relates its energy to the geometrical parameters of the hydrogen bridge: its length R(O…O) and angles between the O…O direction and the OH group and/or lone pair of the proton accepting the oxygen atom [25]. The hydrogen-bonding configurations found in DNA exhibit great variability and usually do not correspond to the most favorable arrangements of isolated monomers in hydrogen bonding conformations. Consequently, the essential base—base interactions are significantly affected by DNA polymorphism. Thus, it seems to be interesting to see how the polymorphism affects the structural and energy properties of the base pairs.

The buckle angle was set according to the definition as described in Fig. 2, *a*. We have investigated the dependence of the interaction energy on the angle between DHT and the DNA base. Fig. 2, *b* gives the torsional potential energy curve for four conformers from –90 to 90° at the B3LYP/6-31+G** level. Four minima are shown in the potential energy curves. The relative energy of DHT:G1 compared to DHT:T1 (~6 kcal/mol) is in good agreement with the results from Table 1. It is clear from

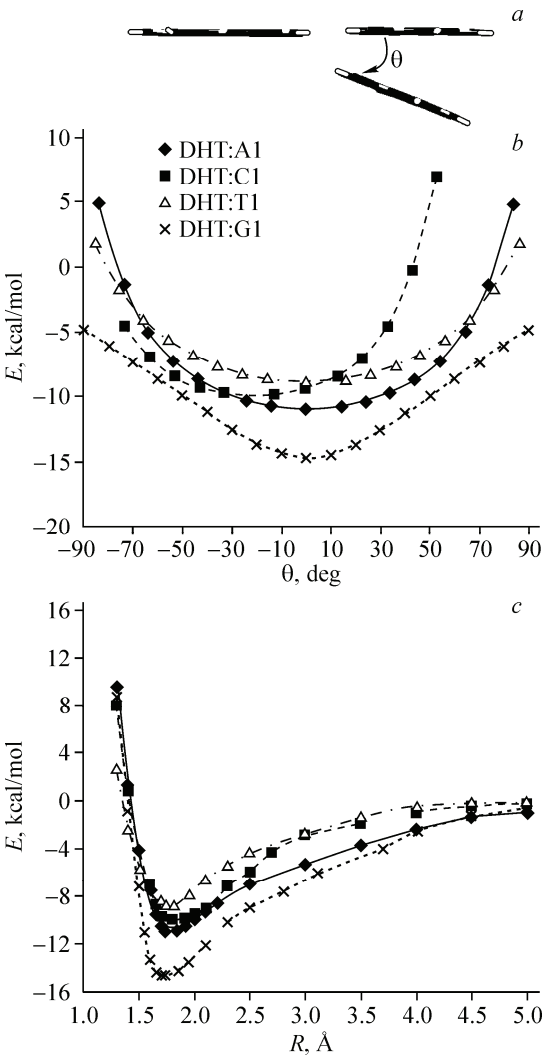
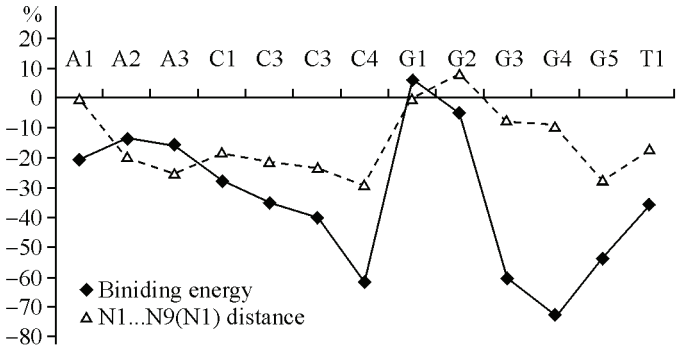


Fig. 2. Molecular diagram showing the definition of the buckle angle θ (*a*); interaction energy (in kcal/mol) as a function of the buckle angle (in deg.) for DHT:A1, DHT:C1, DHT:G1, and DHT:T1 base pairs. Variation of the HB energy as θ is between –90° and 90° (*b*); The interaction energy (in kcal/mol) as a function of the separation (in Å) between the donor and the acceptor for the base pairs (*c*)

the figure that the interaction energy considerably depends on the buckle angle. More importantly, the Δ*E* curve shows how sensitive the interaction energy is to this rising angle, rapidly losing its attractive character (negative Δ*E*) and becoming progressively more repulsive as the angle is brought larger.

Fig. 2, *c* shows the interaction energy of four hydrogen-bonded complexes as a function of the separation. By definition, a larger negative energy indicates a stronger hydrogen-bonding interaction. Results presented in Fig. 2, *c* show that for each complex, there is a sharp energy minimum at a separation of ~1.8 Å. At a larger separation, the interaction energy for each complex decays slowly, with a rate proportional to the distance, resembling the behavior of electrostatic interactions. There is a marked difference in the interaction energies: ranging from –14.7 kcal/mol for DHT:G1 to –8.9 kcal/mol for DHT:T1. The minimum interaction energies for DHT:A1 and DHT:C1 are –11.0 kcal/mol and –10.0 kcal/mol respectively.

4. Differences between damaged pairs and the normal pair. Here, a detailed structural study on the base-mispairing specificities and underlying pairing energies of the modified base would throw light on the pairing property of DHT. The calculated N1…N9(N1) distances and binding energies of the damaged base pairs were compared to the Watson-Crick A:T pair as shown in Fig. 3. The N1…N9(N1) distances presented are in consonance with available experimental reports. For example, the N1…N9 dis-



Base pair	A1	A2	A3	C1	C2	C3	C4	G1	G2	G3	G4	G5	T1	GC	AT
N1...N9(N1) distance(Å)	8.86	7.13	6.63	7.24	6.97	6.81	6.28	8.85	9.57	8.20	8.01	6.41	7.34	9.02	8.87

Fig. 3. The percent difference between the damaged base pairs and the normal A:T pair. In all cases, the binding energy and the N1…N9 distance of the standard A:T pair was set as the reference point

tance of the classical G:C base pair is 9.06 Å [26], derived from its X-ray crystal structure, and the calculated value is 9.02 Å, which corresponds to a ~0.44 % deviation.

The percent difference of the binding energy is defined as $(E_{complex} - E_{A:T})/E_{A:T}$. As shown in Fig. 3, the binding energies of DHT:C1, DHT:C2, and DHT:C3 pairs are less negative than that of the normal A:T pair. It can be deduced that DHT may not easily pair with cytosine. As for the DHT:T1 base pair, the binding energy of DHT:T1 is less negative than that of A:T, and the N1…N1 distance (7.34 Å) indicates that DHT cannot accommodate into a DNA double helix in the optimized structure. The binding energy of DHT:A2 is more negative than that of the DHT:A1 pair, while the N1…N9 distance indicates that DHT:A1 can more easily accommodate into a DNA double helix in the optimized structure. This means that DHT preferentially forms a base pair with adenine in the conformer of DHT:A1. Moreover, there are five possibilities for DHT in either *syn* or *anti* conformation pairs with guanine. In the five possible structures, DHT:G1 and DHT:G2 are energetically more favourable than the normal A:T pair, and the N1—N9 distances of G1 and G2 are similar to those in normal A:T and G:C base pairs. This configurational feature suggests that it may be accommodated into a DNA double helix in the optimized structure. Although only of theoretical interest, the calculated results show that DHT may form a base pair with guanine or adenine in DHT:A1, DHT:A2, DHT:G1, and DHT:G2 conformers.

CONCLUSIONS

We have investigated the base pairs between 5,6-dihydrothymine(DHT) and DNA bases using B3LYP and MP2 methods. It is observed that DHT binds less strongly with DNA bases compared to normal thymine and cytosine bases. The interaction energies calculated for the complexes vary from –3.8 kcal/mol to –14.7 kcal/mol. A significant measurement of ρ_c and $\nabla^2\rho_c$ for all the observed HBs is positive within the following ranges: 0.0043—0.0516 e/Bohr^3 for the electron density and 0.0164—0.1286 e/Bohr^5 for its Laplacian. Among the interacting complexes, DHT:G2 and DHT:G1 are found to have the higher negative interaction energy. The bond lengths, collinear angles, NBO analysis, and AIM analysis also support the result obtained from the binding energy values. While compared with the normal G:C pair, the interaction energy of DHT:G1 shows that the binding of DHT to guanine is of less possibility.

Finally, according to the calculated binding energies and structural parameters, the stability of the base pairs decrease in the following order: DHT:G ~ DHT:A > DHT:C > DHT:T. It is clear that the noncomplementary base-pairing (DHT:G2, DHT:G1, DHT:A1 and DHT:A2) are stabilizing enough to play a significant role in DNA structures. It is expected that the inclusion of the appropriate consideration for many of these non-canonical base pairs would improve the accuracy of DNA replication and structure prediction.

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