J Comput Aided Mol Des (2010) 24:409–416
DOI 10.1007/s10822-010-9348-2

The effect of CH_3, F and NO_2 substituents on the individual hydrogen bond energies in the adenine–thymine and guanine–cytosine base pairs

A. Ebrahimi · S. M. Habibi Khorassani · H. Delarami · H. Esmaeeli

Received: 12 December 2009 / Accepted: 18 March 2010 / Published online: 30 March 2010

Abstract The substituent effects on the geometrical parameters and the individual hydrogen bond (HB) energies of base pairs such as X–adenine–thymine (X–**A**–**T**), X–thymine–adenine (X–**T**–**A**), X–guanine–cytosine (X–**G**–**C**), and X–cytosine–guanine (X–**C**–**G**) have been studied by the quantum mechanical calculations at the B3LYP and MP2 levels with the 6–311++G(d,p) basis set. The electron withdrawing (EW) substituents (F and NO_2) increase the total binding energy (ΔE) of X–**G**–**C** derivatives and the electron donating (ED) substituent (CH_3) decreases it when they are introduced in the 8 and 9 positions of **G**. The effects of substituents are reversed when they are located in the 1, 5, and 6 positions of **C**, with exception of CH_3 in the 1 position and F in the 5 position, which in both cases the ΔE value decreases negligibly small. With minor exceptions (X=8–CH_3, 8–F, and 9–NO_2), both ED and EW substituents increase slightly the ΔE values of X–**A**–**T** derivatives. The individual HB energies (ΔE_{HB}s) have been estimated using electron densities that calculated at the hydrogen bond critical points (HBCPs) by the atoms in molecules (AIM) method. Most of changes of individual HBs are in consistent with the ED/EW nature of substituents and the role of atoms entered H-bonding. The remarkable change is observed for NO_2 substituted derivative in each case.

A. Ebrahimi (✉) · S. M. Habibi Khorassani · H. Delarami
Department of Chemistry, University of Sistan & Baluchestan, P.O. Box 98135-674, Zahedan, Iran
e-mail: Ebrahimi@hamoon.usb.ac.ir

H. Esmaeeli
Department of Eletrical and Computer Engeenering, University of Sistan & Baluchestan, P.O. Box 98135-674, Zahedan, Iran

Keywords Individual hydrogen bond · Electron density · Base pair · Adenine–thymine · Guanine–cytosine

Introduction

The hydrogen bond formation in Watson–Crick type base pairs is fundamental for molecular recognition in the duplex formation of nucleic acids [1, 2]. It is also essential for the transmission of genetic information [1, 3]. Many studies have been performed on the natural nucleic acid base pairs [1, 4–6].

The difference in flexibility between adenine–thymine (**A**–**T**) and guanine–cytosine (**G**–**C**) base pairs may be an additional factor for molecular recognition during the binding of other molecules to DNA, especially in the case of intercalation processes [7, 8]. Several ab initio molecular orbital studies on the substitution effect on hydrogen-bond formation energy of adenine–uracile–X (**A**–**U**–X), X–adenine–uracile (X–**A**–**U**), guanine–cytosine–X (**G**–**C**–X), and X–guanine–cytosine (X–**G**–**C**) base pairs have already been reported by Kawahara et al. [9–13]. Recently, a density functional study of the influence of C5 cytosine substitution in base pairs with guanine has been performed by Moser et al. [14]. On the other hand, many studies have analyzed the interaction of different metal cations to **G** and their influence on base pairing [15–24]. The variation of dissociation energy and H-bond character of the **G**–C^+ and Li–**G**–C^+ cations have been investigated by Sun and Bu [24].

Although many theoretical studies performed on the total hydrogen bond energy of the Watson–Crick type base pairs, especially the **A**–**T** and **G**–**C** base pairs [5, 10, 16, 25–31], a few studies performed on the individual hydrogen bond energies [32–35]. Asensio et al. [32] evaluated

the cooperative hydrogen bonding in the **A–T** and **G–C** base pairs. They rotated one of the bases with respect to the other about the axis of each HB to estimate the energies of the individual H-bonds in each pair. Dong et al. [34] estimated the individual contribution of each intermolecular HB in multiple H-bonded systems, especially in **A–T** and **G–C**, using a simple atom-replacement approach. Grunenberg estimated the relative strength of each HB in **A–T** and **G–C** using the compliance constants [33]. In previous work [35], we evaluated the strength of individual HBs for several complexes with multiple HBs, including **A–T** and **G–C**, using the electron densities ρ calculated by atoms in molecules (AIM) method at the bond critical points (BCPs). The electron-donating (ED) and electron-withdrawing (EW) groups change the binding energies of the **A–T** and **G–C** base pairs. Usually, the cytosine derivatives possessing an ED group form a more stable pair with guanine (in comparison with **G–C**) and the guanine derivatives possessing an EW group form a more stable pair with cytosine (in comparison with **G–C**). In addition, the adenine derivatives possessing an EW group and the thymine derivatives possessing an ED group form more stable pairs with the thymine and adenine bases, respectively (in comparison with **A–T**) [8]. Although many studies were performed on the effects of substituents on the total binding energies and the geometries of the **G–C** and **A–T** base pairs [8, 36], but no studies were done on the effects of substituents on the individual H-bond energies. In this work, we have investigated the substituent effects on the individual hydrogen bond energies in the **A–T** and **G–C** base pairs (see Fig. 1) using the values of ρ calculated by AIM analysis at the hydrogen bond critical points (HBCPs) [37]. Also, we have compared the geometry parameters and the energy data in the **A–T** and **G–C** derivatives.

Computational details and methodology

Two well-known **A–T** and **G–C** base pairs have been selected to calculate the effect of CH_3, F, and NO_2 substituents on the estimated individual H-bond energy ΔE_{HB} by the ρ values calculated at HBCPs. In the previous work [35], we used linear, quadratic and exponential relations to estimate the individual ΔE_{HB}s by fitting several parameters, such that the $\Delta E - \sum \Delta E_{HB}$ value converged to zero (where ΔE are the total binding energy and ΔE_{HB}s are the individual binding energies). The procedure has also been employed in the present study.

The geometry optimization for all the X–**A**–**T**, **A**–**T**–X, X–**G**–**C**, and **G**–**C**–X base pairs and their monomers have been performed at the B3LYP/6–311++G** [38] level of theory with the Gaussian03 program package [39]. Single point calculations have been performed at MP2/6–311++G** level of theory. Moreover, the basis set superposition error (BSSE) has been estimated by counterpoise (CP) technique [40]. Topological analysis of electron charge density has been done using AIM2000 software [41] on the wave functions obtained at the mentioned level.

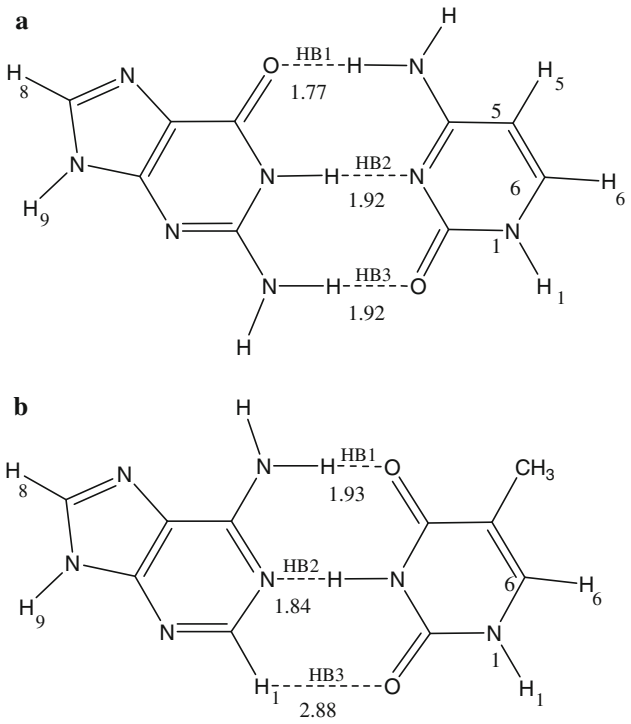

Fig. 1 **a** The **G–C** and **b** **A–T** base pairs. The HB lengths are in Å

Results and discussion

Each of the CH_3, F and NO_2 substituents were located in the 8 or 9 position of purine and 1, 5, or 6 position of pyrimidine (with the exception of 5 position of **A–T**). The **G–C** and **A–T** base pairs are labeled in Fig. 1. The calculated total binding energies and the changes of HB lengths and individual HB energies are shown in Table 1. The ρ values calculated by the AIM analysis at X–H···Y BCPs are also given in that table. The values of ΔE_{HB} estimated by quadratic relation are identical to the values estimated by linear relation (the values in the parentheses in Table 1). The differences between the values estimated by the exponential and linear relations (ΔE_{HB}(exponential) − ΔE_{HB}(linear)) are in the range of −0.75 to 1.21 kcal/mol. During the subsequent discussions, we use the values estimated by the exponential relation.

The HB1, HB2, and HB3 lengths respectively are equal to 1.77, 1.92 and 1.92 Å in **G–C** and 1.93, 1.84 and 2.88 Å in the **A–T** base pair (HB lengths are presented in Fig. 1). The substituents change the H-bond lengths when they are

Table 1 The total binding energies (in kcal/mol), the changes in the H-bond lengths (in pm) and the estimated individual $\Delta\Delta E_{HB}$s (in kcal/mol), and the ρ values (in au) calculated at the HBCPs by the AIM analysis

	ΔE_{tot}	[a]$\Delta\Delta E_{HB1}$	$\Delta\Delta E_{HB2}$	$\Delta\Delta E_{HB3}$	[a]Δr_1	Δr_2	Δr_3	ρ_1	ρ_2	ρ_3
X–G–C										
8–CH3	−22.41	−0.15(−0.22)	0.15(0.18)	0.21(0.25)	−0.83	0.06	0.65	0.038	0.033	0.026
8–F	−23.30	0.00(0.07)	−0.35(−0.39)	−0.32(−0.35)	0.35	−0.77	−1.16	0.037	0.033	0.027
8–NO_2	−24.68	0.84(1.25)	−1.31(−1.49)	−1.58(−1.82)	4.23	−1.90	−4.80	0.034	0.034	0.030
9–CH_3	−22.22	0.02(−0.02)	0.20(0.22)	0.18(0.21)	−0.52	0.09	0.40	0.038	0.033	0.026
9–F	−23.33	0.34(0.50)	−0.51(−0.59)	−0.53(−0.62)	1.70	−0.79	−1.75	0.036	0.033	0.027
9–NO_2	−24.24	0.56(0.87)	−1.23(−1.43)	−0.94(−1.06)	2.79	−2.48	−3.04	0.035	0.035	0.028
X–C–G										
1–CH_3	−22.56	0.26(0.31)	0.11(0.12)	−0.30(−0.37)	0.68	0.48	−1.48	0.037	0.032	0.027
1–F	−21.58	−0.51(−0.75)	0.86(1.01)	0.69(0.77)	−1.33	3.16	3.36	0.039	0.030	0.024
1–NO_2	−21.53	−1.34(−1.81)	1.21(1.49)	1.22(1.42)	−4.04	3.65	5.59	0.041	0.030	0.023
5–CH_3	−23.05	−0.10(−0.09)	−0.03(−0.01)	−0.29(−0.33)	−0.16	0.03	−1.36	0.038	0.033	0.027
5–F	−22.63	−0.59(−0.74)	0.14(0.19)	0.45(0.54)	−1.81	0.09	2.17	0.039	0.032	0.025
5–NO_2	−20.72	−0.54(−0.91)	1.34(1.57)	1.10(1.24)	−2.40	4.09	5.22	0.040	0.029	0.023
6–CH_3	−22.82	0.25(0.34)	−0.29(−0.36)	−0.15(−0.17)	0.87	−0.82	−0.46	0.037	0.033	0.027
6–F–	−22.17	−0.36(−0.49)	0.28(0.33)	0.54(0.62)	−1.12	0.66	2.61	0.039	0.032	0.025
6–NO_2	−21.84	−1.06(−1.44)	0.77(0.95)	1.08(1.27)	−3.81	1.53	4.94	0.041	0.031	0.023
[b]**G–C**	−22.62	−9.53(−10.05)	−7.62(−7.60)	−5.47(−4.97)	1.77	1.92	1.92	0.038	0.033	0.026
X–A–T										
8–CH_3	−12.33	0.12(0.16)	−0.10(−0.15)	0.00(0.00)	0.68	−0.47	−1.14	0.025	0.040	0.004
8–F	−12.30	−0.11(−0.16)	0.15(0.21)	0.02(0.01)	−0.51	1.00	0.99	0.026	0.039	0.004
8–NO_2	−12.51	−0.78(−1.02)	0.55(0.84)	0.08(0.03)	−4.20	3.20	7.30	0.028	0.037	0.004
9–CH_3	−12.37	0.04(0.05)	−0.06(−0.08)	0.01(0.00)	0.22	−0.10	−0.19	0.026	0.040	0.004
9–F	−12.41	−0.34(−0.45)	0.24(0.37)	0.04(0.01)	−1.90	1.56	3.48	0.027	0.038	0.004
9–NO_2	−12.32	−0.66(−0.88)	0.59(0.88)	0.09(0.03)	−3.10	3.80	9.20	0.028	0.036	0.003
X–T–A										
1–CH_3	−12.45	−0.20(−0.25)	0.09(0.15)	0.01(0.00)	−1.21	0.69	−0.42	0.026	0.039	0.004
1–F	−12.93	0.27(0.44)	−0.79(−1.00)	−0.06(−0.02)	0.82	−3.83	−7.32	0.025	0.044	0.005
1–NO_2	−13.07	0.51(0.74)	−1.09(−1.41)	−0.13(−0.05)	2.90	−4.60	−13.80	0.024	0.044	0.005
6–CH_3	−12.39	−0.22(−0.28)	0.14(0.22)	0.05(0.02)	−1.56	0.63	4.37	0.027	0.039	0.004
6–F	−12.72	0.10(0.19)	−0.47(−0.56)	0.00(0.00)	0.36	−1.80	−1.38	0.025	0.041	0.004
6–NO_2	−15.88	0.01(0.25)	−3.42(−3.72)	−0.12(−0.06)	4.20	−4.40	−9.70	0.023	0.044	0.005
[b]**A–T**	−12.35	−4.15(−3.64)	−7.73(−8.62)	−0.47(−0.10)	1.93	1.84	2.88	0.026	0.040	0.004

The data in the parentheses correspond to the second order polynomial and linear relations

[a] $\Delta\Delta E_{HBi} = \Delta E_{HBi}$ (substituted base pair)—ΔE_{HBi} (canonical base pair), $\Delta r = r_{HBi}$ (substituted base pair)—r_{HBi} (canonical bas pair)

[b] the data correspond to **G–C** and **A–T** base pairs that obtained without imposing C_S symmetry upon geometry optimization of dimers and monomers. In these rows, the energy data correspond to individual H-bond energies (in kcal/mol) not their changes. Instead of changes, bond lengths themselves are given in Å in these rows

introduced in different positions of the **G–C** and **A–T** base pairs. In each category, the most distinct change in the HB lengths corresponds to NO_2-substituted complexes; the longest and shortest HB1 among the **G–C** derivatives correspond to 8–NO_2–**G–C** and 1–NO_2–**C–G**, which respectively are 4.23 pm longer and 4.04 pm shorter than those of **G–C**. Also, the highest and the lowest HB1 lengths among the **A–T** derivatives correspond to 6–NO_2–**T–A** and 8–NO_2–**A–T**, which respectively are 4.20 pm longer and 4.20 pm shorter than those of **A–T**. The changes of HB2 and HB3 lengths in the **G–C** derivatives are also comparable with those in the **A–T** derivatives. As can be seen in Table 1, the 5–NO_2–**C–G** complex has the longest HB2, and 9–NO_2–**G–C** complexes has the shortest HB2, which respectively are 4.09 and 2.48 pm longer and shorter than those in the **G–C** base pair. In the **A–T** derivatives, the longest and the shortest HB2 correspond to 9–NO_2–**A–T** and 1–NO_2–**T–A**, which changed by 3.80 and −4.40 pm

relative to **A–T**. Finally, the longest HB3 among the **G–C** derivatives corresponds to 1–NO_2–**C–G,** which is 5.59 pm longer than that in **G–C** and the shortest HB3 corresponds to 8–NO_2–**G–C,** which is 4.80 pm shorter than that in **G–C**. The highest and lowest HB3 lengths among the **A–T** derivatives correspond to 9–NO_2–**A–T** and 1–NO_2–**T–A**, respectively, which the former increased by 9.20 pm and the latter decreased by 13.80 relative to unmodified base pair. Thus, it can be inferred that the most obvious effect on the HB length corresponds to the NO_2 substituted case in each category and this result is in a good agreement with previous results [8]. With the exception of 5–CH_3–**C–G** (the HB1 length decreased by 0.16 pm and HB2 increased by 0.03 pm) and 1–CH_3–**C–G** (the HB2 length increased by 0.48 pm), the changes of HB lengths are in accord with the ED/EW nature of substituents in **G–C** derivatives. In the **A–T** derivatives, the changes of HB1 and HB2 lengths are totally in agreement with the nature of substituents and the role of atoms entered H-bonding, but the changes of improper HB3 (C–H···O) lengths are not. These behaviors could be attributed to the effects of HBs on each other. In addition, when CH_3 is introduced in the 1 position in the vicinity of NH_2 group, the spatial interaction between them can affect the HB1 in 1–CH_3–C–G. Also, according to the atoms entered H-bonding in the **A–T** derivatives, it is expected that the effect of a substituent on HB3 (that is expected to be similar to HB1) and HB2 be in opposite directions. But, the weak improper HB (HB3, C–H···O) could be affected by the nearest HB (HB2); with some exceptions the changes of HB3 bonds are similar to HB2 ones.

The HB3 length experiences a large variation in all the **A–T** NO_2-derivatives. The Δr_3 and Δr_2 values have similar signs; given the poor character of HB3 interaction, the distance variations are likely to be driven by the behavior of HB2. Thus, a high change in HB2 is accompanied with a higher change in HB3 for **A–T** NO_2-derivatives.

Binding energies in the **A–T** and **G–C** derivatives have been calculated by single point calculation at MP2/6–311++G** level on the structures optimized at B3LYP/6–311++G** level using BSSE correction. From comparison between the stabilization energies of the **G–C** derivatives possessing an EW group and the stabilization energy of **G–C** is deduced that the binding energies in the **G–C** derivatives possessing an EW group in the 1, 5 or 6 position are lower than those in **G–C** derivatives possessing an ED group in the same position. Cytosine acts as an HB donor in HB1 and as HB acceptor in HB2 and HB3. Thus, the ED groups make cytosine a more powerful HB acceptor in HB2 and HB3, which enhance those HBs and increase total binding energy with the exception of HB2 in 1–CH_3–**C–G**. Interaction between the CH_3 group introduced in the 1 position of cytosine and the O_2 atom can affect the basicity of N3 atom, weakens HB2, and decreases the total binding energy.

The stabilization energies of the **G–C** derivatives possessing an EW group in the 8 or 9 position are higher while the stabilization energies of the **G–C** derivatives possessing an ED group are lower than those of **G–C**. The EW groups make **G** a stronger HB donor in HB2 and HB3 interactions, enhance those HBs, and increase the total binding energies. The trends in the total stabilization energies of the **G–C** derivatives depend on the position of substituents; $CH_3 > F > NO_2$ in the 1, 5, and 6 positions and $NO_2 > F > CH_3$ in the 8 and 9 positions.

The trends reported by Meng et al. [8] are in agreement with the above mentioned results with the exception of 5- and 6-position substituted **G–C**, in which the trends in the stabilization energies were $CH_3 > NO_2 > F$ and $F > CH_3 > NO_2$, respectively. In the 5- and 6-position substituted **G–C**, the order of stabilization energies obtained in the present work is expected to be more reliable with respect to the electronic characteristics of the substituents and the types of the atoms entered the hydrogen bonding. With two HB acceptors and one HB donor on the cytosine base, it is expected that the EW groups decrease the total HB energies of 1-, 5- and 6-position substituted **G–C**.

The stabilization energies have slightly been affected by mentioned substituents in the **A–T** derivatives. The trends in the total binding energies of the **A–T** derivatives are not identical when substituents locate in different positions; $NO_2 > F > CH_3$ for 1 and 6 positions, $F > CH_3 > NO_2$ for 9 and $NO_2 > CH_3 > F$ for 8 position. With the exception of F and NO_2 substituents in the 1 and 6 positions, the orders are in accord with the results of Meng et al. [8]. As can be seen, the effects of substituents on the stabilization energies of **A–T** derivatives are not in accord with the ED/EW nature of substituents. For example, the impact of F, NO_2 and CH_3 groups on binding energies are identical in the 1 and 6 positions (they increased slightly). The effects of F (and CH_3) and NO_2 groups on the stabilization energy in the 8 (and 9) position are in opposite directions. The effects of substituents in the 8 and 9 positions are also in opposite directions; the total binding energy decreases when the CH_3 or the F group is introduced in the 8 position and increases when each of substituents is introduced in the 9 position.

Herein, the main purpose is the investigation of the effect of ED and EW substituents on the individual HBs and the comparison of individual HB energies in the **A–T** and **G–C** derivatives with those in the **A–T** and **G–C** base pairs and also with each other. The estimated HB1, HB2 and HB3 energies are equal to −9.53, −7.62 and −5.47 kcal/mol, and −4.15, −7.73 and −0.47 kcal/mol in **G–C** and **A–T**, respectively, without imposing C_S symmetry upon geometry optimization. The individual ΔE_{HB}s in **G–C** and **A–T**, and

the difference between those values and the corresponding values in the **G**–**C** and **A**–**T** derivatives are given in Table 1. Comparison between different **G**–**C** derivatives indicates that the trend in the HB1 energy in the 9-position substituted **G**–**C** derivatives is $CH_3 > F > NO_2$ while the trend in HB2 and HB3 energies is $NO_2 > F > CH_3$. Such orders are also observed for the individual ΔE_{HB}s in the 8-position substituted **G**–**C** derivative. Thus, the EW groups strengthen HB2 and HB3 and weaken HB1; the reverse is true for ED substituents in the mentioned positions. Herein, the ΔE_{HB1} values estimated by linear fitting are in better agreement with Δr_1 values; the negative $\Delta\Delta E_{HB1}$ value comes with the negative Δr_1 in 9–CH_3–**G**–**C** and the positive $\Delta\Delta E_{HB1}$ value comes with the positive Δr_1 in 8–F–**G**–**C**. In so many words, the O atom becomes a more powerful HB acceptor, while other two centers become less powerful HB donors by the ED substituents. The observation is reversed by EW groups.

The results indicate that the NO_2 substituent is a more powerful EW group relative to F in both positions, such that the weakening of HB1 and the strengthening of HB2 (and HB3) with NO_2 are more than those with F substituent (see Table 1). In the 1-, 5- and 6-position substituted **G**–**C** derivatives, the HB1 energies follow the order $NO_2 > F > CH_3$ and the order of the HB2 and HB3 energies is $CH_3 > F > NO_2$. Thus, as mentioned for X–**G**–**C** derivatives, the HB1 becomes more powerful by the EW groups while HB2 and HB3 become more powerful by the ED groups in the X–**C**–**G** derivatives. With some exceptions, the reverse is true for the effect of ED substituents on ΔE_{HB1} and the effects of EW substituents on ΔE_{HB2} and ΔE_{HB3}. It should be mentioned that the value of ΔE_{HB1} increases when CH_3 is introduced in the 5 position and the values of ΔE_{HB2} decreases when this substituent is introduced in the 1 position, which are not in accord with the ED/EW nature of substituents. These behaviors have been discussed in relation to the changes in geometrical properties.

In the 9-position substituted **A**–**T**, the HB1 and HB2 energies follow the orders $NO_2 > F > CH_3$ and $CH_3 > F > NO_2$, respectively. Moreover, the changes for HB1 and HB2 are in opposite directions. Such orders are also observed for the individual ΔE_{HB}s in the 8-position substituted derivatives. Thus, the EW substituents in the 8 and 9 positions increase ΔE_{HB1} and decrease ΔE_{HB2}. The reverse is true for ED substituents.

The effect of substitutions on individual HBs in the 1 and 6 positions and 8 and 9 positions are in opposite directions. As can be seen from data in Table 1, ΔE_{HB1} decreases and ΔE_{HB2} increases when the EW substituents are introduced in the 1 and 6 positions. The reverse is true for ED groups.

Also, the change in the HB3 energy by substituent in **A**–**T** is less than in **G**–**C**. In the 1- and 6-position substituted complexes, the trends in $|\Delta\Delta E_{HB}|$ of HB1, HB2 and HB3 are $CH_3 > F > NO_2$, $NO_2 > F > CH_3$ and $NO_2 > F > CH_3$, respectively. Among these results, the orders of changes for the HB1 and HB2 energies are in agreement with the ED/EW nature of the substituents and the types of atoms entered the H-bonding. The changes of HB3 energies are not consistent with that nature of substituents. Maybe this is caused by the effect of each HB on others. The individual ΔE_{HB}s obtained by the second order polynomial and linear relations are slightly different from those obtained by exponential relation, and similar orders have been observed for the changes of ΔE_{HB}s estimated by three relations.

The highest change in the HB2 energy corresponds to the 6–NO_2–**T**–**A** derivative. In the 6 position, the resonance effect pulls the electron density from the vicinity of the O atoms and N–H bond toward this group and makes thymine a weaker proton acceptor in HB1 and HB3 positions and a more powerful proton donor in HB2. This effect is more obvious for HB2 such that its energy increases by 3.5 kcal/mol, which is the highest change in an individual HB among all cases. Although a decrease in the ΔE_{HB3} is expected, but this weak improper HB is affected by HB2 such that its energy increases by 0.12 kcal/mol. The NO_2 substituent in the 1 position of thymine impact on the atoms entered H-bonding only by inductive effect.

As seen in Table 1, the highest ΔE_{HB1}, ΔE_{HB2} and ΔE_{HB3} values in the **G**–**C** derivatives correspond to 1–NO_2–**C**–**G**, 8–NO_2–**G**–**C** and 8–NO_2–**G**–**C** base pairs, respectively. The lowest ΔE_{HB1}, ΔE_{HB2} and ΔE_{HB3} values correspond to 8–NO_2–**G**–**C**, 5–NO_2–**C**–**G** and 1–NO_2–**C**–**G** base pairs, respectively. Thus, the most obvious changes in ΔE_{HB}s are observed for NO_2 substituted complexes. In the **A**–**T** derivatives, the highest ΔE_{HB1}, ΔE_{HB2} and ΔE_{HB3} values correspond to 8–NO_2–**A**–**T**, 6–NO_2–**T**–**A** and 1–NO_2–**T**–**A** base pairs, respectively. The changes of estimated ΔE_{HB}s in **A**–**T** are less than those in **G**–**C** derivatives. Herein, the lowest ΔE_{HB1}, ΔE_{HB2} and ΔE_{HB3} values correspond to 1–NO_2–**T**–**A**, 9–NO_2–**A**–**T** and 9–NO_2–**A**–**T**, respectively.

Very good relationships were observed between the H-bond lengths and the estimated individual ΔE_{HB}s in the previous work [35]. The N–H···O, C–H···O and N–H···N hydrogen bond lengths versus the estimated individual ΔE_{HB}s are plotted in Fig. 2, in which good correlations are observed between the N–H···O (and all C–H···O bond) lengths and estimated individual ΔE_{HB}s, but, no meaningful relationship is observed between all N–H···N H–bond lengths and the estimated ΔE_{HB}s. Very good relationships are observed between them when the N–H···N bond lengths are plotted versus their ΔE_{HB}s for the **A**–**T** and **G**–**C** derivatives, separately. Thus, different chemical environments around the central N–H···N hydrogen bonds in the **A**–**T** and **G**–**C** derivatives change the substituent effect.

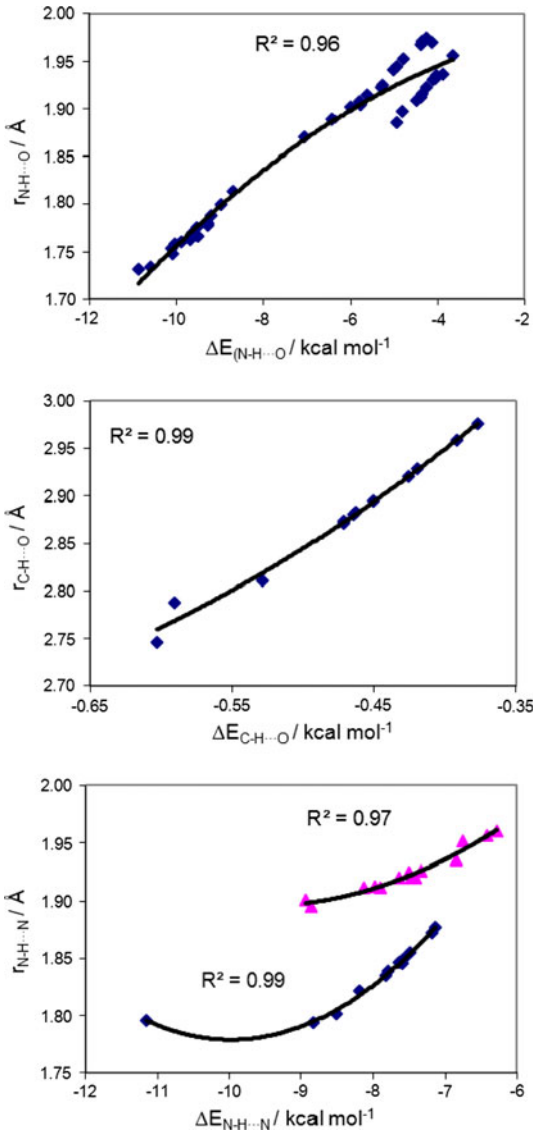

Fig. 2 Correlation between the hydrogen bond lengths and the individual ΔE_{HB}s for **a** all N–H···O bonds, **b** C–H···O bonds in **A–T** derivatives, and **c** N–H···N bonds in **G–C** (*filled triangle*) and **A–T** (*filled diamond*) derivatives

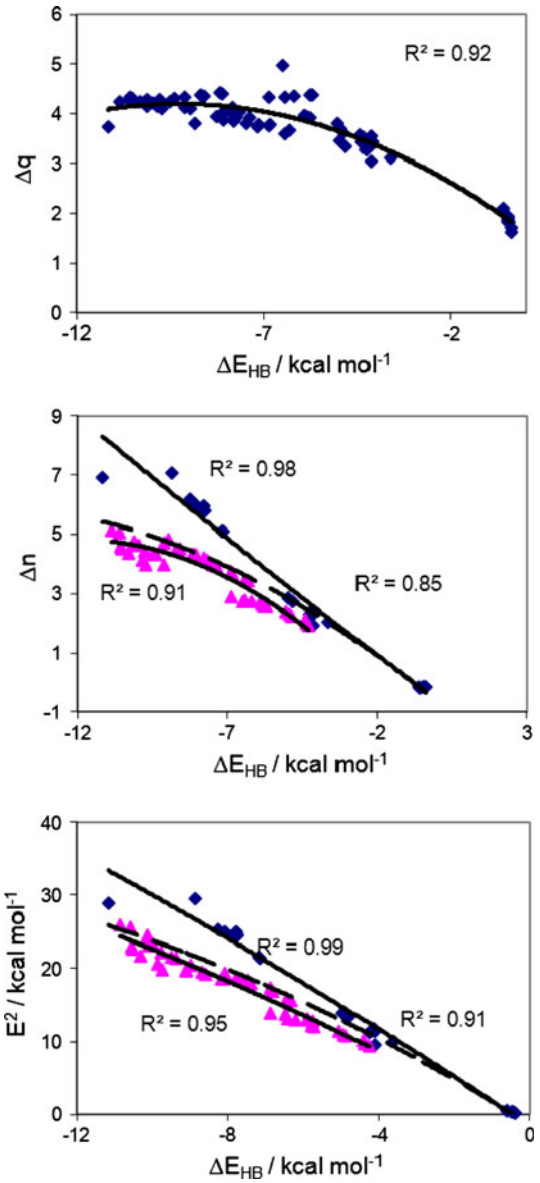

Fig. 3 Correlation between individual ΔE_{HB}s and **a** the change in natural charge on the H atoms **b** the change in occupation number of σ^*_{H-Y} and **c** $E^{(2)}$ value of $n_X \rightarrow \sigma^*_{H-Y}$ interaction in the **A–T** (*filled diamond*) and **G–C** (*filled triangle*) derivatives (the *dashed lines* present correlation between NBO data and ΔE_{HB}s for both the **A–T** and **G–C** derivatives)

The population analysis [42] has also been performed on the optimized structures of the **A–T** and **G–C** derivatives and their monomers at the B3LYP/6–311++G** level of theory using the NBO 3.1 program [43] under Gaussian03 program package. The natural charge on the H atom, the donor-acceptor interaction energy of $n_{(N,\ O)} \rightarrow \sigma^*_{(N-H,\ O-H\ and\ C-H)}$ and the occupation numbers of σ^*_{H-Y} orbitals have also been considered for individual H-bonds. The correlation between individual ΔE_{HB}s and the change of natural charge on the H atom is shown in Fig. 3. As seen, higher changes in the natural charges are accompanied by higher ΔE_{HB}s with a very good relationship between them for all base pairs, including the **A–T** and **G–C** derivatives, $R^2 = 0.92$. The change of the occupancy of σ^*_{H-Y} orbitals and the donor acceptor interaction energy $E^{(2)}$ versus ΔE_{HB}s are shown in Fig. 3. Increasing the occupancy of σ^*_{H-Y} and the $E^{(2)}$ value of $n_X \rightarrow \sigma^*_{H-Y}$ in the **A–T** and **G–C** derivatives is accompanied with the increasing individual ΔE_{HB}s with very good relationships. The R^2 values for $\Delta n \sim \Delta E_{HB}$ and $E^{(2)} \sim \Delta E_{HB}$ pairs are equal to 0.98 (0.91) and 0.99 (0.95) in the **A–T** (**G–C**) derivatives. Thus, there are very good relationships between the results of natural population analysis and the individual ΔE_{HB}s estimated in this work.

Conclusions

Most of estimated individual ΔE_{HB}s in the **G–C** and **A–T** derivatives using calculated ρ_{BCP}s at HBCPs are in agreement with the ED/EW nature of substituents and the role of atoms entered in H-bonding. Substitution increases the total binding energy of a **G–C** derivative when an EW group is introduced in the 8 or 9 position of the guanine or an ED group is introduced in the 1, 5 or 6 position of cytosine. The change of total binding energy in **G–C** derivatives is higher than that in the **A–T** derivatives.

The estimated ΔE_{HB1} value decreases and the ΔE_{HB2} and ΔE_{HB3} values increase when the EW groups are introduced in the 8 or 9 position of **G**. An opposite effect is observed for the ED substituents in these two positions. Moreover, the effects of substituents in the 1, 5, and 6 positions of cytosine and 8 and 9 positions of guanine are approximately in opposite directions.

The ΔE_{HB1} value increases and the ΔE_{HB2} value decreases when the EW substituents are introduced in the 8 and 9 positions of adenine in **A–T** derivatives. The reverse is true for ED groups. The effects of substitutions on individual HBs in the 1 and 6 positions of thymine and in the 8 and 9 positions of adenine are also in opposite directions. The change of ΔE_{HB3} by substituents in the **A–T** derivatives is less than that in the **G–C** derivatives, such that the change in that ΔE_{HB} value is influenced by the changes in other two ΔE_{HB}s, especially HB2, and the orders of estimated ΔE_{HB3} are not in agreement with the predictions.

There are good relationships between the results of natural population analysis and estimated individual hydrogen bond energies.

References

1. Xue C, Popelier PLA (2008) Computational study of substituent effects on the interaction energies of hydrogen–bonded Watson–Crick cytosine–guanine base pairs. J Phys Chem B 112:5257–5264
2. Watson JD, Crick FHC (1953) A structure for deoxyribose nucleic acid. Nature 171:737–738
3. Brenner S, Jacob F, Meselson M (1961) An unstable intermediate carrying information from genes to ribosomes for protein synthesis. Nature 190:576–581
4. Guerra CF, Bickelhaupt FM, Snijders JG, Baerends EJ (1999) The nature of the hydrogen bond in DNA base pairs: the role of charge transfer and resonance assistance. Chem A Eur J 5:3581–3594
5. Hobza P, Sponer J (1999) Structure, energetics, and dynamics of the nucleic acid base pairs: nonempirical ab initio calculations. Chem Rev 99:3247–3276
6. Hobza P, Zahradnik R, Mueller–Dethlefs K (2006) The world of non–covalent interactions. Chem Commun 71:443–531
7. Shishkin OV, Sponer J, Hobza P (1999) Intramolecular flexibility of DNA bases in adenine–thymine and guanine–cytosine Watson–Crick base pairs. J Mol Struct 477:15–21
8. Meng F, Liu C, Xu W (2003) Substituent effects of R (R=CH_3, CH_3O, F and NO_2) on the **A–T** and **G–C** base pairs: a theoretical study. Chem Phys Lett 373:72–78
9. Kawahara SI, Uchimaru T, Taira K, Sekine M (2002) An ab initio study of the hydrogen bond energy of base pairs formed between substituted 9–methylguanine derivatives and 1–methylcytosine. J Phys Chem A 106:3207–3212
10. Kawahara SI, Kobori A, Sekine M, Uchimaru T (2001) Theoretical study of the hydrogen bond energy of base pairs formed between substituted 1–methylcytosine derivatives and 9–methylguanine. J Phys Chem A 105:10596–10601
11. Kawahara SI, Wada T, Kawauchi S, Uchimaru T, Sekine M (1999) Ab initio and density functional studies of substituent effects of an A–U base pair on the stability of hydrogen bonding. J Phys Chem A 103:8516–8523
12. Kawahara SI, Uchimaru T, Taira K, Sekine M (2001) Ab initio evaluation of the substitution effect of the hydrogen bond energy of the Watson–Crick type base pair between 1–methyluracil and substituted 9–methyladenine derivatives. J Phys Chem A 105:3894–3898
13. Xue CX, Popelier PLA (2009) Prediction of interaction energies of substituted hydrogen–bonded Watson–Crick cytosine–guanine (8X) base pairs. J Phys Chem B 113:3245–3250
14. Moser A, Guza R, Tretyakova N (2009) Density functional study of the influence of C5 cytosine substitution in base pairs with guanine. Theor Chem Account 122:179–188
15. Burda JV, Sponer J, Hobza P (1996) Ab initio study of the interaction of guanine and adenine with various mono–and bivalent metal cations (Li+, Na+, K+, Cs+; Cu+, Ag+, Au+; Mg2+, Ca2+, Sr2+, Ba2+; Zn2+, Cd2+, and Hg2+). J Phys Chem 100:7250–7255
16. Fonseca Guerra C, Bickelhaupt FM, Snijders JG, Baerends EJ (2000) Hydrogen bonding in DNA base pairs: reconciliation of theory and experiment. J Am Chem Soc 122:4117–4128
17. Russo N, Toscano M, Grand A (2001) Bond energies and attachments sites of sodium and potassium cations to DNA and RNA nucleic acid bases in the gas phase. J Am Chem Soc 123:10272–10279
18. Petrov AS, Lamm G, Pack GR (2002) Water–mediated magnesium–guanine interactions. J Phys Chem B 106:3294–3300
19. Cerda BA, Wesdemiotis C (1996) Li^+, Na^+, and K^+ binding to the DNA and RNA nucleobases bond energies and attachment sites from the dissociation of metal ion–bound heterodimers. J Am Chem Soc 118:11884–11892
20. Munoz J, Sponer J, Hobza P, Orozco M, Luque FJ (2001) Interactions of hydrated Mg^{2+} cation with bases, base pairs, and nucleotides electron topology, natural bond orbital, electrostatic, and vibrational study. J Phys Chem B 105:6051–6060
21. Gresh N (1999) Complexes of pentahydrated Zn^{2+} with guanine, adenine, and the guanine–cytosine and adenine–thymine base pairs structures and energies characterized by polarizable molecular mechanics and ab initio calculations. J Phys Chem B 103:11415–11427
22. Sponer J, Sabat M, Gorb L, Leszczynski J, Lippert B, Hobza P (2000) The effect of metal binding to the N7 Site of purine nucleotides on their structure, energy, and involvement in base pairing. J Phys Chem B 104:7535–7544
23. Gadre SR, Pundlik SS, Limaye AC, Rendell AP (1998) Electrostatic investigation of metal cation binding to DNA bases and base pairs. Chem Commun 5:573–574
24. Sun L, Bu Y (2005) Marked variations of dissociation energy and H–bond character of the guanine–cytosine base pair induced by one–electron oxidation and Li^+ cation coupling. J Phys Chem B 109:593–600
25. Destexhe A, Smets J, Adamowicz L, Maes G (1994) Matrix isolation FT–IR studies and ab initio calculations of hydrogen–

bonded complexes of molecules modeling cytosine or isocytosine tautomers. 1. pyridine and pyrimidine complexes with water in argon matrixes. J Phys Chem 98:1506–1514
26. Gould IR, Kollman PA (1994) Theoretical investigation of the hydrogen bond strengths in guanine–cytosine and adenine–thymine base pairs. J Am Chem Soc 116:2493–2499
27. Hobza P, Sponer J, Polasek M (1995) H–bonded and stacked DNA base pairs: cytosine dimer An ab initio second–order moller–plesset study. J Am Chem Soc 117:792–798
28. Sponer J, Hobza P (1996) Nonempirical ab initio calculations on DNA base pairs. Chem Phys 204:365–372
29. Sponer J, Hobza P (1996) Thermodynamic characteristics for the formation of H–bonded DNA base pairs. Chem Phys Lett 261:379–384
30. Sponer J, Leszczynski J, Hobza P (1996) Nature of nucleic acid–base stacking: nonempirical ab initio and empirical potential characterization of 10 stacked base dimers comparison of stacked and H–bonded base pairs. J Phys Chem 100:5590–5596
31. Sponer J, Hobza P (2000) Interaction energies of hydrogen–bonded formamide dimer, formamidine dimer, and selected DNA base pairs obtained with large basis sets of atomic orbitals. J Phys Chem A 104:4592–4597
32. Asensio A, Kobko N, Dannenberg JJ (2003) Cooperative hydrogen–bonding in adenine–thymine and guanine–cytosine base pairs density functional theory and moller–plesset molecular orbital study. J Phys Chem A 107:6441–6443
33. Grunenberg J (2004) Direct assessment of interresidue forces in Watson–Crick base pairs using theoretical compliance constants. J Am Chem Soc 126:16310–16311
34. Dong H, Hua W, Li S (2007) Estimation on the individual hydrogen–bond strength in molecules with multiple hydrogen bonds. J Phys Chem A 111:2941–2945
35. Ebrahimi A, Habibi khorasani SM, Delarami H (2009) Estimation of individual binding energies in some dimers involving multiple hydrogen bonds using topological properties of electron charge density. Chem Phys 365:18–23
36. Meng F, Wang H, Xu W, Liu C, Wang H, Xu W, Liu C (2005) Theoretical study of GC^{+}/GC base pair derivatives. Chem Phys 308:117–123
37. Bader RFW (1990) Atoms in molecules: a quantum theory. Oxford University Press, Oxford
38. Backe AD (1993) Density–functional thermochemistry. III. The role of exact exchange. J Chem Phys 98:5648–5652
39. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JA Jr, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA (2003) Gaussian03 (Revision B03). Gaussian, Inc, Pitts burgh, PA
40. Boys SB, Bernardi F (1970) The calculations of small molecular interaction by the difference of separate total energies some procedures with reduce error. Mol Phys 19:553–566
41. Biegler Konig FW, Schonbohm J, Bayles D (2001) Software news and updates AIM2000. J Comput Chem 22:545–559
42. Reed AE, Curtiss LA, Weinhold F (1988) Intramolecular interactions from a natural bond orbital, donor–acceptor viewpoint. Chem Rev 88:899–936
43. Glendening D, Reed AE, Carpenter JE, Weinhold F, NBO version 3.1