Investigation of Substituent Effects on the Strength of Hydrogen Bond in the Guanine: Cytosine Base Pairs: A Theoretical Study

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In the present work, the substituent effect on the strength of H-bonds in the guanine-cytosine base pair was studied when the substituents are connected to the guanine base through a phenyl ring. In this study, guanine was substituted in the H8 and H9 positions by electron donating (ED) and electron withdrawing (EW) groups mediated by a phenyl ring in the gas phase. The calculations were performed at B3LYP/6-311++G(d,p) level. The results show that the values of stabilization energies (ΔE^{HB}) of EW groups are more negative than those of ED groups. These results indicate that the complexes containing EW groups are more stable than ED ones. Also, the energies of the intermolecular hydrogen bond have been estimated by the EML and MAEM's formulas. Most of the changes in intermolecular hydrogen bond are in agreement with the nature of substituents. The influence of substituent on the stability of complexes is investigated by atoms in molecules and natural bond orbital analyses. The atoms in molecules theory was also used to get further understanding of the nature of H-bond interactions. There is excellent relationship between the charge distribution and the stabilization energy.

Keywords: Guanine-cytosine, Substituent effect, Intermolecular hydrogen bond, AIM and NBO

INTRODUCTION

The formation of hydrogen bond in the Watson-Crick base pairs is a key factor for molecular identification within the duplex formation of DNA and RNA [1]. Also, these bonds are important for the transmission of genetic data [2]. Owing to their biological activity, most substituted or unsubstituted nucleic bases have been often studied experimentally [3]. For instance, synthetic pyrimidines derivatives have been used as anticancer, medicinal drug and antivirial agent [4].

Various theoretical studies have been performed on the interaction energies between the natural nucleic acid in the base pairs. Hobza *et al.* have been investigated the interaction energies of natural nucleic acid base pairs by theoretical studies [5,6]. Sponer *et al.*, in 2004, show that H-bonded base pairs are primarily stabilized by electrostatic interactions [7]. Considering the role of charge transfer and resonance assistance, the nature of H-bonds in DNA base pairs has been also studied by Guerra et al. . Based on the BP86/TZ2P calculations, they realized that the hydrogen bonding in DNA base pairs is not especially electrostatic character. In contrast, a fundamental charge transfer in this H-bond occurred between O and N lone pairs and N-H $\sigma*$ acceptor orbitals [8]. Recently, Guerra *et al.* have shown that the most interaction in WC base pair complexes corresponds to the donor-acceptor σ-orbital interactions between N or O lone pairs on one base pairs and N-H $\sigma*$ orbitals on the other base. This interaction participates in strength to the electrostatic interaction phrase [9,10]. Grunenberg investigated the commonplace potential constants based on quantum chemistry for the Watson-Crick base pairs adenine-thymine (AT) and guanine-cytosine (GC), permitting a unique quantification of individual hydrogen bond strengths. They found that the central hydrogen bond N-H⋯N between G and C is actually the strongest hydrogen bond in both Watson-Crick base pairs [11].

For many years, substituent effects are commonplace in

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systems containing covalent bond that they find various applications in material chemistry, medicinal chemistry, organic chemistry and biochemistry [12]. Studies of substituent effects have boosted our understanding of chemical mechanisms and established chemical models and notions [13]. The substituent effects on hydrogen bond energy have already been reported by Kawahara et al. using ab initio molecular orbital study in base pairs A:U^X, A^X:U, C^X:G and C:G^X [14-17]. Also, Meng *et al.* considered the substituent effects (CH$_3$, CH$_3$O, F and NO$_2$) on the AT and GC base pairs [18], and in an independent study that massive substitutes such as 2-nitronaphthalene, 1-nitro-4-vinylbenzene, 1-hydroxy-4-vinylbenzene and 2-hydroxynaphthalene [19]. Recently, Guerra *et al.* considered the effect of fluorine, chlorine, and bromine substituents by replacing the hydrogen atom H8 in a purine (A, G) and/or H6 in a pyrimidine (T, C) on hydrogen bond lengths, strength, and bonding mechanism [20]. They also analyzed the substituent effect (X = NH$^-$, NH$_2$, NH$_3^+$, O$^-$, OH, or OH$_2^+$) in Watson-Crick G:C base pairs; these substitutes were introduced in purine-C8 and/or pyrimidine-C6 positions by the same level of theory [21]. Moser *et al.* have reported the influence of C5 cytosine substitution in base pairs with guanine using density functional theory [22]. The changes of dissociation energy and H-bond character of the G-C$^+$ and Li-G-C$^+$ cations have been studied by Sun and Bu [23].

It is well established that phenyl rings easily transfer the electronic character of ED and EW groups connected to the centers or on other positions of the ring. The effect of this electron charge transfer on different chemical phenomena or reactions has been widely studied especially when the reactive centers and the substituents are in meta or pare positions. The present work deals with the substituent effects on the interaction energy of the G:C base pair in which the EW and ED groups mediated by a phenyl ring are introduced at the H8 and H9 positions of guanine. Also, we analyzed how the hydrogen bond length and strength are affected by replacing hydrogen atoms H8 and H9 in G by EW and ED groups through a phenyl ring. Furthermore, we have investigated the substituent effects on the strength of hydrogen bond in G:C (see Scheme 1) using the values of ρ calculated by AIM analysis at the hydrogen bond critical points (HBCPs).

COMPUTATIONAL METHODS

Since DFT method includes electron correlation effect and describes the electronic properties of molecules and solids enough accurately, we used this method in the present study. The geometries of each isolated monomer and super molecule (G^X:C Watson-Crick) were optimized using the Becke 3-parameter hybrid exchange functional and Lee-Yang-Parr correlation functional (B3LYP) [24,25] of density functional theory as implemented in GAUSSIAN 09 [26] suite at 6-311++G(d,p) level. Recently, B3LYP/6-311++G(d,p) has been successfully applied on similar systems [27] and have been verified to give accurate normal mode frequencies, characteristics of intra and intermolecular hydrogen bonds and geometries. The interaction energies of the complexes were corrected for basis set superposition error (BSSE) by the counterpoise method [28]. The frequency analysis was carried out on the optimized geometries of various substituted complexes at the same level to confirm that the optimized structures are in their minima.

Six substituents have been selected for the X-ph-G-C base pairs (X = NO$_2$, NH$_2$, OH, O$^-$, Cl, F) that two of them are electron-withdrawing, two of them are electron-donating, and others are halogens.

The difference between the total energy of a base pair and the corresponding monomers is defined as ΔE^{HB} (Eq. (1)). The more stable base pair complex has a more negative ΔE^{HB}. The quantity of $\Delta\Delta E$ is described as the substituent effect on ΔE^{HB} (Eq. (2)). A more negative $\Delta\Delta E$ value means that the substituted base pair is more stable than the unsubstituted one

$$\Delta E^{HB} = E(G^X{:}C) - \{E(G^X) + E(C)\} \qquad (1)$$

$$\Delta\Delta E = \Delta E^{HB}(G^X{:}C) - \Delta E^{HB}(G{:}C) \qquad (2)$$

Analysis of the electronic charge density (ρ) and its Laplacian ($\nabla^2\rho$) was performed using the theory of molecular structure suggested by Bader [29]. The calculated electron density, ρ, and its second derivative, $\nabla^2\rho$ were used for describing the nature of the intermolecular N-H···N and N-H···O hydrogen bonds. The AIM 2000 program [30] was used to analyze the BCPs.
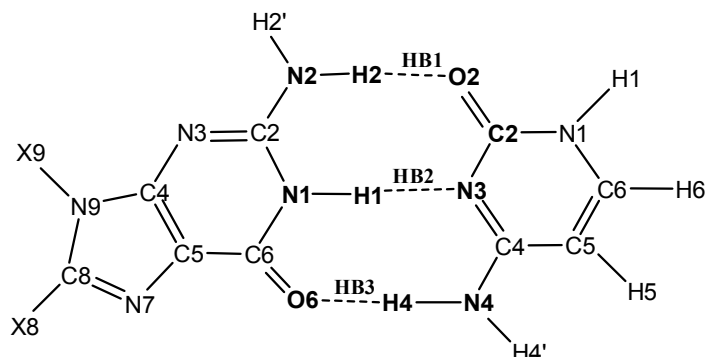
Scheme 1

The population analysis was carried out by the natural bond orbital (NBO) method [31] at the B3LYP/ 6-311++G(d,p) level on the optimized structures using NBO program for a better understanding of the intermolecular interactions[31].

RESULTS AND DISCUSSIONS

Geometrical Descriptors

The six substituents (NO_2, NH_2, OH, O⁻, Cl and F) are located at para and meta positions of phenyl ring. The substituted positions are the H8 and H9 positions of purine. Table 1 indicates the stabilization energies ΔE^{HB} and the substitution effect values ($\Delta\Delta E$) of the substituted pairs of the corresponding G:C. The interaction energy of the G^{ph}:C base pair in 8 and 9 positions was -103.65 and -103.45 kJ mol⁻¹, respectively. For EW/ED groups, the values of $\Delta\Delta E$ for all complexes are negative/positive, indicating that these modified base pairs are more/less stable than unmodified G:C. The most stable and unstable complexes for $G^{8(9X)}$:C where the substituents are located in para position correspond to O⁻ and NH_2, with the interaction energies of -109.60 (-108.20) and -101.99 (-102.01) kJ mol⁻¹, respectively. Also, The most stable and unstable complexes in meta position correspond to NO_2 and NH_2, with the interaction energies of -105.73 (-107.48) and -103.14 (-102.27) kJ mol⁻¹, respectively.

There are three hydrogen bonds in guanine-cytosine base pair. As shown in Scheme 1, they are marked by HB1, HB2, and HB3. The hydrogen bond lengths of $G^{8,9X}$:C were also listed in Table 1. In our calculations, the lengths of

HB1, HB2 and HB3 in the G:C base pair are 1.916, 1.918, and 1.773 Å, respectively. Table 1 shows that the HB1 and HB2 lengths were elongated by EDGs for $G^{8,9X}$:C derivatives and HB3 lengths were contracted. On the contrary, the HB1 and HB2 lengths were contracted and HB3 lengths were elongated for $G^{8,9X}$:C derivatives by EWGs. These results can be illustrated by the atomic charges of O, N and H atoms involving hydrogen bond. The natural charges on the H, N and O atoms (q_H, q_N and q_O) obtained using NBO calculations at the B3LYP/ 6-311++G(d,p) level of theory are reported in Table 2. As one would expect, simply from the hydrogen pattern shown in Scheme 1, guanine derivatives act as electron donors in the hydrogen bonds HB1 and HB2, and as electron acceptors in HB3. Thus, the charge transfers have been occurred from G to C through HB1 and HB2, and the reverse transfer occurred through HB3. The O(2) and H(2) atoms contribute to HB1 and N(3) and H(1) involved in HB2. The O(2) and N(3) atoms have negative charge and the natural charge on H(1) and H(2) atoms are positive. The introduction of an EWG on $G^{8,9X}$ is expected to aid the transfer through HB1 and HB2, and thereby strengthen these hydrogen bonds. Similarly, this EWG would weaken HB3. This contribution is reversed for EDGs.

Topological Descriptors

The topological analysis of electron densities established by Bader *et al.* [29,33-35] can be used to study the nature of bond formed in the G:C base pair and its derivatives. H-bonding can be specified by the change of electron density for the bonded moiety. With formation of

Table 1. Selected   Geometrical Parameters,   Counterpoise Corrected Interaction Energies (ΔE^{HB}) and Substitution Effect ($\Delta\Delta E$)[a]

	ΔE^{HB} (kJ mol^{-1})	$\Delta\Delta E$ (kJ mol^{-1})	d_{HB1} (Å)	d_{HB2} (Å)	d_{HB3} (Å)
8-Cl	-104.74	-1.09	1.913	1.916	1.777
	-104.63	-0.98	1.912	1.915	1.777
8-F	-104.39	-0.74	1.914	1.917	1.775
	-104.68	-1.03	1.913	1.915	1.777
8-NH$_2$	-101.99	1.65	1.926	1.921	1.763
	-103.14	0.51	1.921	1.919	1.769
8-NO$_2$	-107.78	-4.13	1.893	1.910	1.795
	-105.73	-2.08	1.901	1.912	1.788
8-O$^-$	-109.60	-5.95	1.879	1.904	1.806
	-105.71	-2.06	1.902	1.912	1.787
8-OH	-102.88	0.77	1.918	1.919	1.772
	-104.21	-0.57	1.914	1.917	1.774
8-H	-103.65	0.00	1.916	1.918	1.773
9-Cl	-104.94	-1.50	1.912	1.913	1.777
	-105.04	-1.59	1.912	1.912	1.778
9-F	-104.53	-1.08	1.913	1.914	1.777
	-104.91	-1.46	1.913	1.913	1.778
9-NH2	-102.01	1.44	1.928	1.919	1.767
	-102.27	1.18	1.926	1.917	1.770
9-NO2	-107.99	-4.54	1.896	1.906	1.788
	-107.48	-4.03	1.900	1.908	1.785
9-O$^-$	-108.20	-4.75	1.893	1.904	1.790
	-106.84	-3.39	1.901	1.909	1.785
9-OH	-103.26	0.19	1.920	1.917	1.771
	-103.44	0.01	1.920	1.915	1.773
9-H	-103.45	0.00	1.919	1.916	1.774

[a]The normal and italic data correspond to para and meta positions, respectively.

Table 2. The Natural Atomic Charges Obtained Using NBO Calculations[a]

|	HB1		HB2		HB3	
	$q_{(H2)}$	$q_{(O2)}$	$q_{(H1)}$	$q_{(N3)}$	$q_{(H4)}$	$q_{(O6)}$
8-Cl	0.4367	-0.6861	0.4474	-0.6543	0.4493	-0.6799
	0.4367	-0.6860	0.4475	-0.6544	0.4491	-0.6799
8-F	0.4366	-0.6861	0.4473	-0.6542	0.4494	-0.6812
	0.4366	-0.6861	0.4473	-0.6542	0.4494	-0.6812
8-NH$_2$	0.4356	-0.6857	0.4462	-0.6535	0.4502	-0.6872
	0.4360	-0.6860	0.4467	-0.6538	0.4498	-0.6828
8-NO$_2$	0.4382	-0.6870	0.4488	-0.6550	0.4484	-0.6711
	0.4374	-0.6860	0.4481	-0.6547	0.4487	-0.6770
8-O$^-$	0.4392	-0.6876	0.4498	-0.6557	0.4475	-0.6627
	0.4374	-0.6860	0.4481	-0.6546	0.4487	-0.6768
8-OH	0.4360	-0.6857	0.4466	-0.6536	0.4499	-0.6850
	0.4365	-0.6862	0.4471	-0.6541	0.4495	-0.6813
8-H	0.4363	-0.6860	0.4469	-0.6539	0.4496	-0.6820
9-Cl	0.4357	-0.6851	0.4474	-0.6570	0.4541	-0.6748
	0.4356	-0.6852	0.4474	-0.6570	0.4541	-0.6743
9-F	0.4355	-0.6851	0.44720.	-0.6568	0.45420.4541	-0.6756
	0.4356	-0.6853	4474	-0.6570		-0.6746
9-NH$_2$	0.4339	-0.6844	0.44610.	-0.6561	0.4549	-0.6803
	0.4343	-0.6843	4464	-0.6563	0.4547	-0.6792
9-NO$_2$	0.4373	-0.6858	0.4487	-0.6578	0.4533	-0.6693
	0.4369	-0.6861	0.4483	-0.6576	0.4536	-0.6702
9-O$^-$	0.4375	-0.6858	0.4489	-0.6580	0.4531	-0.6683
	0.4367	-0.6859	0.4482	-0.6575	0.4537	-0.6709
9-OH	0.4347	-0.6850	0.4466	-0.6564	0.4546	-0.6780
	0.4348	-0.6849	0.4468	-0.6565	0.4545	-0.6773
9-H	0.4349	-0.6849	0.4468	-0.6565	0.4545	-0.6773

[a]The normal and italic data correspond to NBO calculations in para and meta positions, respectively.

Table 3. Topological Properties of Electron Density (in a.u.) at Bond Critical Point of H-bonds[a,b]

	$\rho_{HB} \times 10^2$	$\nabla^2\rho_{HB} \times 10^2$	$H_{HB} \times 10^2$
8-Cl	2.677(3.295)3.700	9.447(8.864)11.993	0.185(-0.088)-0.073
	2.678(3.303)3.696	9.450(8.875)11.989	0.185(-0.091)-0.070
8-F	2.668(3.288)3.714	9.422(8.860)12.014	0.186(-0.085)-0.078
	2.677(3.298)3.698	9.447(8.869)11.992	0.185(-0.089)-0.072
8-NH2	2.595(3.254)3.830	9.195(8.838)12.212	0.196(-0.072)-0.122
	2.626(3.271)3.777	9.289(8.851)12.128	0.192(-0.079)-0.101
8-NO2	2.802(3.340)3.528	9.834(8.897)11.671	0.167(-0.106)-0.013
	2.750(3.326)3.594	9.680(8.893)11.788	0.175(-0.100)-0.035
8-O⁻	2.895(3.387)3.427	10.100(8.936)11.470	0.150(-0.126)0.020
	2.745(3.324)3.607	9.665(8.893)11.813	0.176(-0.099)-0.040
8-OH	2.643(3.268)3.752	9.352(8.849)12.064	0.190(-0.077)-0.093
	2.666(3.288)3.722	9.416(8.863)12.028	0.187(-0.085)-0.081
8-H	2.654(3.277)3.735	9.379(8.854)12.045	0.189(-0.081)-0.086
9-Cl	2.681(3.318)3.697	9.459(8.898)11.985	0.185(-0.096)-0.071
	2.680(3.322)3.689	9.455(8.904)11.969	0.185(-0.098)-0.069
9-F	2.677(3.307)3.697	9.453(8.889)11.978	0.186(-0.092)-0.072
	2.677(3.319)3.688	9.450(8.901)11.964	0.186(-0.097)-0.068
9-NH₂	2.583(3.265)3.797	9.157(8.852)12.149	0.198(-0.076)-0.109
	2.598(3.282)3.766	9.206(8.870)12.093	0.196(-0.082)-0.098
9-NO₂	2.782(3.375)3.592	9.763(8.945)11.800	0.169(-0.119)-0.034
	2.760(3.358)3.621	9.698(8.932)11.852	0.173(-0.113)-0.044
9-O⁻	2.800(3.391)3.569	9.818(8.962)11.756	0.167(-0.126)-0.026
	2.753(3.351)3.624	9.681(8.926)11.854	0.174(-0.110)-0.045
9-OH	2.630(3.284)3.752	9.306(8.870)12.073	0.192(-0.083)-0.092
	2.630(3.296)3.738	9.306(8.883)12.048	0.192(-0.088)-0.087
9-H	2.636(3.292)3.730	9.327(8.877)12.032	0.191(-0.086)-0.084

[a]The normal data, data in the parentheses and italic data correspond to HB1, HB2 and HB3, respectively. [b]The first and second rows correspond to AIM calculations in para and meta positions, respectively.
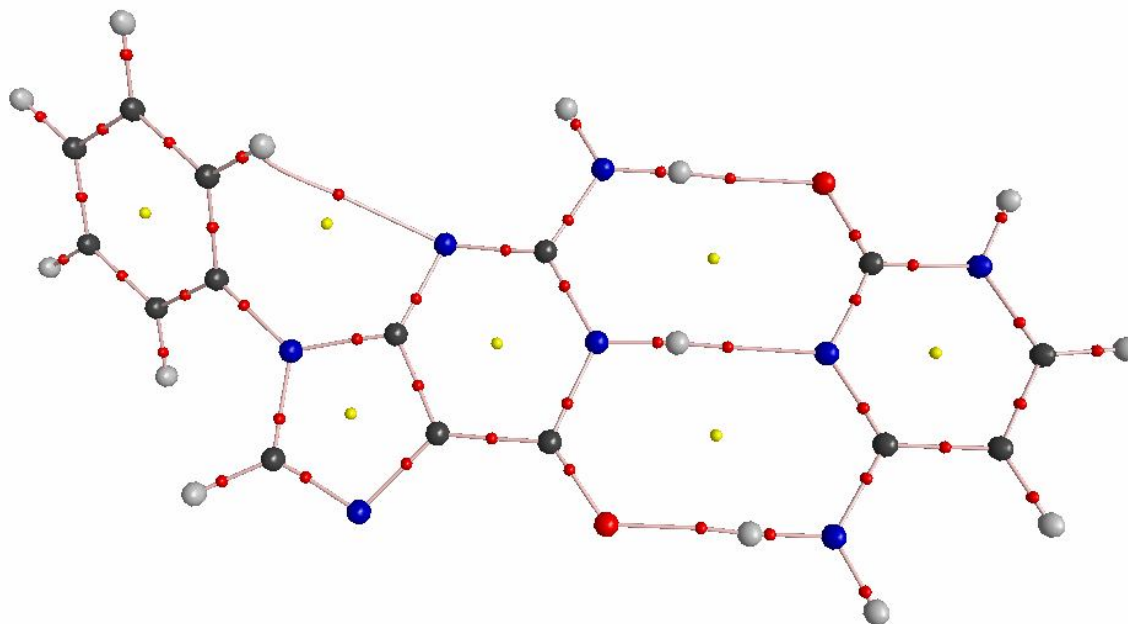
Fig. 1.

the H-bond, the electron density decreases around the proton and proton acceptor, while it increases between the proton and its acceptor. Bader *et al.* mentioned that the shared interactions (as covalent and polar bonds) have negative $\nabla^2\rho(r)$ at the BCP commonly corresponds to a local accumulation of electron density into the line of interaction linking the nuclei. In contrast, the closed shell interactions (as ionic bonds or any other interaction between molecules such as van der Waals, medium-weak hydrogen bonding, *etc.*) have a positive Laplacian and the electron density is decreases in the interatomic surface [36].

The total energy density is the sum of potential electronic and the local kinetic energies, $V(r)$ and $G(r)$, respectively, at the BCP [37]

$$H\ (r_{BCP}) = V\ (r_{BCP}) + G\ (r_{BCP})$$

where the potential energy corresponds to Laplacian of the electron density by the local form of the virial theorem [28]

$$V\ (r_{BCP}) = 1/4\nabla^2\rho\ (r_{BCP}) - 2G\ (r_{BCP})$$

and the kinetic energy is obtained by partitioning of the electron density [38]

$$G\ (r_{BCP}) = 3/10\ (3\pi^2)^{2/3}\rho\ (r_{BCP})^{5/3} + 1/6\ \nabla^2\rho\ (r_{BCP})$$

Cremer and Kraka found that the local kinetic energy density $G(r_{BCP})$ in closed-shell interactions is more than local potential energy density $V(r_{BCP})$, because $G(r_{BCP})$ and $V(r_{BCP})$ are everywhere positive and negative, respectively, thus $H(r_{BCP}) > 0$. Moreover, the greater of $|V(r_{BCP})|$ causes the greater of the shared character of the interaction and the stability of the structure. It is also viewed that the value of kinetic energy per electron is large ($G(r_{BCP})/\rho(r_{BCP}) > 1$ in atomic units) in closed-shell interactions [39].

The values of ρ_{HB}, $\nabla^2\rho_{HB}$, and H_{HB} at the BCPs were determined by the AIM method at the B3LYP/6-311++G(d,p) level of theory (Table 3). A typical of molecular graph is drawn in Fig. 1. The order of ρ_{HB1} and ρ_{HB2} values are identical for EW groups, while this order is reversed for HB3. An opposite behavior is observed for EDGs.

The total electron energy density at BCP (H_{BCP}) and Laplacian ($\nabla^2\rho(r_{BCP})$) are two topological parameters often applied to classify and characterize hydrogen bonds. Rozas

Table 4. The Values of H-bond Energy (kJ mol^{-1}) Estimated by EML and MAEM's Formulas[a,b]

	E_{HB1}	E_{HB2}	E_{HB3}
8-Cl	-26.14, -26.16	-31.41, -31.52	-41.26, -41.20
	24.52, 24.53	25.95, 26.02	34.59, 34.55
8-F	-26.03, -26.14	-31.32, -31.46	-41.47, -41.24
	24.43, 24.52	25.91, 25.98	34.71, 34.57
8-NH$_2$	-25.03, -25.45	-30.89, -31.11	-43.27, -42.45
	23.69, 24.00	25.69, 25.81	35.75, 35.29
8-NO$_2$	-27.89, -27.16	-31.99, -31.82	-38.64, -39.61
	25.81, 25.28	26.25, 26.17	33.01, 33.59
8-O$^-$	-29.20, -27.10	-32.62, -31.79	-37.11, -39.82
	26.75, 25.23	26.58, 26.16	32.07, 33.71
8-OH	-25.69, -26.00	-31.07, -31.32	-42.04, -41.59
	24.19, 24.41	25.79, 25.92	35.02, 34.78
8-H	-25.83	-31.19	-41.78
	24.28	25.85	34.88
9-Cl	-26.19, -26.17	-31.73, -31.80	-41.20, -41.08
	24.55, 24.54	26.14, 26.18	34.55, 34.47
9-F	-26.15, -26.14	-31.59, -31.75	-41.19, -41.06
	24.53, 24.52	26.07, 26.15	34.54, 34.46
9-NH$_2$	-24.86, -25.07	-31.04, -31.27	-42.73, -42.25
	23.56, 23.72	25.78, 25.90	35.44, 35.15
9-NO$_2$	-27.59, -27.29	-32.49, -32.27	-39.62, -40.05
	25.58, 25.36	26.53, 26.42	33.61, 33.87
9-O$^-$	-27.85, -27.20	-32.71, -32.17	-39.27, -40.09
	25.77, 25.30	26.65, 26.37	33.40, 33.89
9-OH	-25.50, -25.50	-31.30, -31.46	-42.04, -41.83
	24.04, 24.04	25.92, 26.00	35.03, 34.91
9-H	-25.59	-31.40	-41.70
	24.11	25.97	34.83

[a]The normal and italic data correspond to calculations in para and meta positions, respectively. [b]The results in first and second rows were obtained using EML and MAEM's formulas, respectively.

Table 5. The Energy Value of most Donor-acceptor Interaction (kJ mol^{-1}) in HB1, HB2 and HB3[a]

	$E^{(2)}$ HB1	$E^{(2)}$ HB2	$E^{(2)}$ HB3
8-Cl	12.46, 12.46	18.83, 18.83	21.45, 21.45
8-F	12.39, 12.39	18.76, 18.76	21.59, 21.59
8-NH$_2$	11.82, 12.05	18.40, 18.58	22.73, 22.19
8-NO$_2$	13.42, 13.01	19.29, 19.13	19.86, 20.47
8-O$^-$	14.18, 12.97	19.75, 19.10	18.91, 20.59
8-OH	12.17, 12.37	18.54, 18.75	22.00, 21.67
8-H	12.27	18.64	21.80
9-Cl	12.62, 12.61	19.24, 19.29	21.08, 21.01
9-F	12.54, 12.55	19.14, 19.26	18.80, 20.96
9-NH$_2$	11.75, 11.95	16.61, 18.62	22.06, 21.78
9-NO$_2$	13.43, 13.25	19.81, 19.65	20.08, 20.35
9-O$^-$	13.53, 13.19	19.96, 19.56	19.84, 20.37
9-OH	12.17, 11.6	18.88, 18.98	21.62, 21.51
9-H	12.27	18.97	21.28

[a]The normal and italic data correspond to NBO calculations in *para* and *meta* positions, respectively.

et al. [40] suggested that weak H-bonds have $\nabla^2\rho$ (r_{BCP}) > 0 and H_{BCP} > 0, medium H-bonds are characterized by $\nabla^2\rho$ (r_{BCP}) > 0 and H_{BCP} < 0, strong H-bonds reveal $\nabla^2\rho$ (r_{BCP}) < 0 and H_{BCP} < 0.

According to the results, $\nabla^2\rho_{HB1}$ and H_{BCP1} values are positive for all derivatives G:C, indicating that HB1 has been considered as weak H- bonds. One can classify HB2 and HB3 in all derivatives G:C in this work as medium ones

(except for the 8-O⁻ substituent in *para* position showing that HB3 can be characterized as weak hydrogen bond).

Espinosa *et al.* in 1998 [41] suggested that the hydrogen-bond energy, E_{HB}, could be extracted from the potential energy density

$$E_{HB} = 0.5 \, V \, (r_{BCP})$$

In 2011, Mata *et al.* [42] proposed that a more accurate value could be found from the kinetic energy density

$$E_{HB} = 0.429 \, G \, (r_{BCP})$$

The values of $E_{EML,HB}$ and $E_{MAEM,HB}$ are reported in Table 4. The data in Table 4 show that for all complexes, the order in $E_{EML,HB}$ values is $E_{EML,HB3} > E_{EML,HB2} > E_{EML,HB1}$ for both meta and *para* position. Furthermore, the values of $E_{EML,HB1}$ and $E_{EML,HB2}$, for EWGs are greater than those for EDGs, while the $E_{EML,HB3}$ value for EDGs is greater than that for EWGs. Also, the trend of $E_{MAEM,HB}$ values is similar to $E_{EML,HB}$. Regarding to the natural atomic charges, the introduction of an EWG on guanine increases/decreases the tendency of H/N atoms to form H-bond in HB1 and HB2. The opposite behavior is observed in HB3. In systems with multiple H-bonds, the strength of one H-bond is affected by an adjacent H-bond. Here, the reinforcement/weakening of HB2/HB3 with introduction of EWGs in all complexes lead to increasing/decreasing $E_{EML,HB3}$ value.

Molecular Orbital Descriptors

The NBO analysis has been performed on the studied complexes to gain more insight into the influence of EW and ED groups on hydrogen bond. The NBO analysis is a useful tool for describing charge transfer in the interacting orbitals; *i.e.*, changes of charge density in antibonding and lone pair orbitals and also the factors that are responsible for the changes in the internal geometry of the molecule. The NBO calculations show that the most important dono-acceptor interaction in HB1 and HB3 is LpO → σ*N-H, while it is LpN → σ*N-H in HB2. The energy values of these interactions ($E^{(2)}$ HB) are gathered in Table 5. The values of $E^{(2)}_{HB1}$ for EWGs are greater than those for EDGs. The order of $E^{(2)}_{HB1}$ values in *para* position is similar to that

in meta position. Similar to $E^{(2)}_{HB1}$, the value of $E^{(2)}_{HB2}$ for EWGs is greater than that for EDGs for both meta and para positions, while the value of $E^{(2)}_{HB3}$ for EWGs is lower than that for EDGs for both meta and para positions. This difference arises from the fact that HB1 and HB2 act as the electron donor, while HB3 acts as an electron acceptor. Thus, introduction of an EWG would strengthen/weaken HB1 and HB2/HB3. It is worthwhile to note that there is a correlation between bond length and stabilization energy $E^{(2)}$; *i.e.*, smaller bond lengths (strong hydrogen bonds) have larger stabilization energy.

CONCLUSIONS

We performed quantum chemical calculations on six substituents of Watson- Crick type base pairs formed between unmodified guanine and modified cytosine monomers, in which substituents were placed at positions 8 and 9 of guanine. The values of stabilization energies (ΔE^{HB}) of EW groups are more negative than those of ED groups. These results indicate that the complexes containing EW groups are more stable than ED ones. The energies of the intermolecular H-bonds were evaluated by the EML and MAEM's formulas. The estimated E_{HB1} and E_{HB2} values by these two methods increase and the E_{HB3} values decrease when the EW groups are introduced at positions 8 or 9 of guanine. This behavior is reversed for the ED substituents in these two positions. This difference arises from this fact that HB1 and HB2 act as the electron donor, while HB3 acts as an electron acceptor. Thus, the charge transfers occurred from guanine to cytosine through HB1 and HB2, and the reverse transfer have been occurred through HB3.

The nature and strength of H-bonds were determined by AIM analysis. Also, the most important donor-acceptor interactions were investigated by NBO analysis. The excellent correlations were found between the stabilization energy and the results of AIM and NBO analyses.

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