

## The Effect of Some Mono and Bivalent Metal Cations on the Individual Hydrogen Bond Energies in A-T and G-C Base Pairs

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The effect of interactions of various Ia and IIa cations with two positions of the adenine-thymine (A-T) and guanine-cytosine (G-C) base pairs on the geometries and individual hydrogen bond (HB) energies have been investigated by using the atoms in molecules (AIM) method at the B3LYP/6-311++G(d,p) level of theory. The cations that possess higher charge/radius ( $q/r_{\text{rad}}$ ) ratio make higher changes on the individual HB energies and the total binding energies of G-C base pair, while no meaningful changes are observed for the A-T base pair. The effect of coordination with cations on the H-bond energies of A-T type complexes, especially in the X'-A-T derivatives, is slight and different from the G-C complexes. The changes of total binding energies are most important in the presence of bivalent cations. The estimated individual  $E_{\text{HBs}}$  are in good agreement with the results of natural bond orbital (NBO) analysis and also with the structural parameters of HBs.

**Keywords:** Individual hydrogen bond, Electron density, Base pair, Adenine-thymine, Guanine-cytosine

### INTRODUCTION

Interactions between metal cations and nucleic acids are very important in biological systems and play a key role in determining the structure and function of many fundamental blocks of living organisms [1-4]. Quantum mechanical calculations have been used for a long time to investigate the nucleic acid base pairs and their complexes with the metal ions [5-6]. The conformational behavior and function of DNA are often influenced in the presence of metal ions [7-9]. Preliminary calculations on the interactions between bases (or base pairs and model complexes) and metal cations were carried out in the 1980s [6,10-15]. Metal cations are known to play an important role in both the stabilization and destabilization of DNA [1,2,16-18]. These ions can also interact with phosphate groups and the sugar moieties of DNA. The cations influence on the formation of uncommon forms of DNA, such as triplexes, quadruplexes, bulges, junctions, *etc.* [19-22]. Moreover the alkali metal ions have inhibiting influence on the chain initiation process by RNA polymerases which may in turn change the extent and accuracy of the RNA synthesis [23,24].

Various experimental and theoretical studies were dedicated to the gas-phase interaction of metal cations with the

nucleic acid bases [25-29]. Many studies were performed to analyze the interactions of various metal cations with the guanine, adenine, and also the A-T and G-C base pairs [13,30-35], such that the metal ion binding to the Watson-Crick base pairs has been characterized relatively well [36]. Interactions between bivalent metal cations and nucleic acids have been the subject of intense research because of their significance for DNA replication and transcription [37,38]. For example, interaction of hydrated metal cations of group IIa ( $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Sr}^{2+}$ ,  $\text{Ba}^{2+}$ ) and group IIb ( $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Hg}^{2+}$ ) with the A-T and A-A reverse-hoogsteen (AA rH) DNA base pairs have been investigated by Sponer *et al.* [39]. The main sites for cation coordination are the N7, N9 and O6 atoms of guanine and adenine, the O4 atom of uracil and thymine, and the N3 and O2 atoms of cytosine [40]. Although the influences of various cations on the DNA base pairs were previously examined in many studies [11-14] a few works have been performed on the dependence of individual hydrogen bonds to those interactions [41]. In this work, we have investigated the effect of some mono- and bivalent cations on the individual hydrogen bond energies in the A-T and G-C base pairs using electron charge density  $\rho$  and electronic potential energy calculated by the atoms in molecules (AIM) analysis [42] at the X-H...Y BCPs. Also, we have compared geometry parameters and energy data in the A-T and G-C base pairs in the presence of various cations.

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## COMPUTATIONAL DETAILS AND METHODOLOGY

The geometry optimizations have been performed at the B3LYP/6-311++G\*\* [43] level of theory with the Gaussian03 program package [44]. The single point calculations have been carried out at the MP2/6-311++G\*\* level of theory, where the basis set superposition error (BSSE) [45] has been estimated using counterpoise (CP) technique. Vibrational frequency analyses were also performed at the same level to ensure that the structures are in local minima. The  $\Delta E$  values have been corrected for zero point energy at the B3LYP/6-311++G\*\* level. The topological analysis of electron charge density  $\rho$  has been performed by AIM2000 software [46] on the wave functions obtained at the mentioned level in order to calculate the  $\rho$  values at the hydrogen bond critical points (HBCPs). In addition, we have used the following equations to estimate the individual  $E_{\text{HBs}}$  by fitting the  $a$  to  $f$  parameters [47,48]:

$$E_{\text{HB},i} = 100a(1 - e^{\rho_i}) \quad (1)$$

$$E_{\text{HB},i} = b\rho_i^2 + c\rho_i \quad (2)$$

$$E_{\text{HB},i} = d\rho_i + f \quad (3)$$

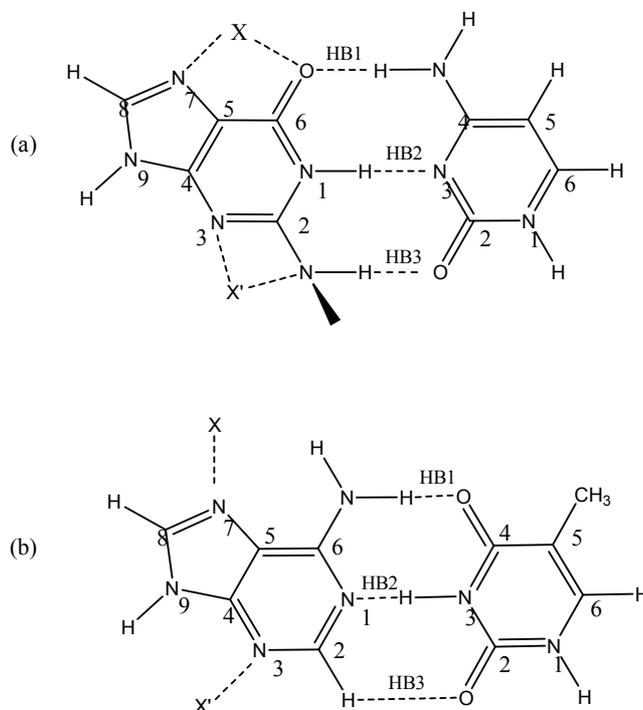
The following equation

$$E_{\text{HB},i} = 0.5V_{\text{HB},i} \quad (4)$$

has previously been used in the estimation of the intramolecular HB energies [49,50]. In the present work, that equation has also been used in the estimation of the individual  $E_{\text{HBs}}$ .

## RESULTS AND DISCUSSION

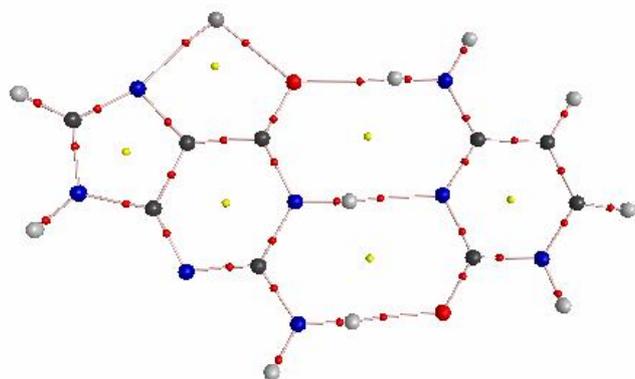
Some Ia ( $\text{Li}^+$ ,  $\text{Na}^+$  and  $\text{K}^+$ ) and IIa ( $\text{Mg}^{2+}$  and  $\text{Ca}^{2+}$ ) metal cations have been chosen for interaction *via* two positions with the A-T and G-C base pairs. All the complexes are kept planar during the optimization and correspond to the minimum of stationary points with respect to the results of frequency calculations with the expectation of Li-A-T, Na-A-T and K-A-T cases that correspond to the first order saddle point. Cations



**Fig. 1.** (a) The G-C and (b) A-T base pair. The coordination positions (X and X') indicated on the figure.

are permitted to interact with the N7 atom of adenine in the A-T (X) pair and with the N7 and O6 atoms of guanine in the G-C (X) base pair. Those positions are known to be the most active sites in DNA. The interaction of cations with the N3 atom of adenine in A-T (X') and with the N2 and N3 atoms of guanine in the G-C (X') pairs have also been considered; few studies have been performed in the latter positions in both the A-T and G-C base pairs. Structures and numbering of atoms are shown in the Fig. 1. A typical molecular graph obtained from AIM analysis on the wave functions at the B3LYP/6-311++G\*\* level of theory is shown in Fig. 2. As can be seen, a common feature of the dimers is the formation of BCPs and ring critical points (RCPs) between two units.

The  $\rho_{\text{HBCP}}$  and  $V_{\text{HBCP}}$  values calculated by AIM analysis and the H-bond lengths are reported in Table 1. The BSSE and ZPVE corrections to the total binding energies, in addition to the individual estimation of  $E_{\text{HBs}}$  from the  $\rho_{\text{HBCP}}$  and  $V_{\text{HBCP}}$  values are given in Table 2. The  $E_{\text{HB}}$  values estimated by the quadratic and linear relations are identical (the values given in



**Fig. 2.** The molecular graph obtained from AIM analysis on the wavefunction obtained at the B3LYP/6-311++G\*\* level of theory for Li-G-C. Small red spheres, small yellow spheres, and lines correspond to BCPs, RCPs and bond paths, respectively.

parentheses). The values estimated by the exponential relation will be considered during the following discussion.

The HB1-HB3 bond lengths (see Fig. 1 for numbering of H-bonds) are equal to 1.771, 1.919 and 1.919 Å in G-C and 1.930, 1.838 and 2.879 Å in A-T base pairs, respectively [40]. All H-bond lengths have been changed after coordination with Ia and IIa cations. As reported in Table 1, the HB1 bond length (which is the closest HB to cation) increases in all coordinated G-C base pairs, whereas the HB2 and HB3 bond lengths decrease upon the coordination of cations. The changes in the HB bond lengths in the presence of bivalent ions are larger than those in the presence of monovalent cations. These results are in good agreement with the previous results [13]. The longest HB1 bond in the X-G-C derivatives corresponds to the Ca-G-C and the shortest one corresponds to the K-G-C. Those are 0.454 and 0.128 Å longer in comparison with G-C, respectively. The highest contraction in the HB2

**Table 1.** The Hydrogen Bond Lengths in Å,  $\rho_{\text{HBCP}} \times 10^2$  Values in a.u. and  $V_{\text{HBCP}}$  Values in kcal mol<sup>-1</sup>

	$r_1$	$r_2$	$r_3$	$X_1$	$X_2$	$X_3$
Li-G:C	1.999	1.845	1.770	2.203, <b>-9.708</b>	3.914, <b>-18.867</b>	3.740, <b>-20.212</b>
Li'-G:C	1.897	1.801	1.736	2.713, <b>-12.862</b>	4.357, <b>-22.085</b>	4.193, <b>-23.364</b>
Na-G:C	1.965	1.875	1.782	2.391, <b>-10.838</b>	3.654, <b>-17.096</b>	3.641, <b>-19.422</b>
Na'-G:C	1.868	1.835	1.756	2.901, <b>-14.173</b>	4.013, <b>-19.637</b>	3.993, <b>-21.813</b>
K-G:C	1.953	1.893	1.792	2.460, <b>-11.207</b>	3.501, <b>-16.103</b>	3.555, <b>-18.775</b>
Mg-G:C	2.220	1.791	1.618	1.328, <b>-5.158</b>	4.515, <b>-22.330</b>	5.480, <b>-34.604</b>
Ca-G:C	2.225	1.842	1.639	1.342, <b>-5.184</b>	3.994, <b>-18.765</b>	5.195, <b>-32.103</b>
Li-A:T	1.760	1.948	3.086	3.876, <b>-20.928</b>	3.034, <b>-13.402</b>	0.271, <b>-0.907</b>
Na-A:T	1.770	1.938	3.073	3.781, <b>-20.233</b>	3.111, <b>-13.860</b>	0.279, <b>-0.940</b>
K-A:T	1.794	1.926	3.042	3.568, <b>-18.644</b>	3.207, <b>-14.470</b>	0.298, <b>-1.015</b>
Li'-A:T	1.870	1.868	2.823	2.948, <b>-14.119</b>	3.621, <b>-17.733</b>	0.476, <b>-1.644</b>
Na'-A:T	1.929	1.835	2.710	2.562, <b>-11.599</b>	3.922, <b>-19.905</b>	0.607, <b>-2.116</b>
Ca'-A:T	1.711	1.901	2.888	4.388, <b>-24.336</b>	3.292, <b>-15.879</b>	0.418, <b>-1.377</b>
Mg'-A:T	1.877	1.959	3.033	2.857, <b>-13.556</b>	2.901, <b>-12.666</b>	0.296, <b>-0.991</b>
G-C <sup>a</sup>	1.771	1.919	1.919	3.995, <b>-20.095</b>	3.784, <b>-14.842</b>	2.39, <b>-12.263</b>
A-T <sup>b</sup>	1.930	1.838	2.879	2.561, <b>-11.805</b>	3.981, <b>-19.581</b>	0.424, <b>-1.504</b>

$r_i$  values correspond to HB<sub>i</sub> lengths.  $X_i$  values correspond to  $\rho \times 10^2$  and V (bold) data, respectively, at the *i*th critical point. See Fig. 1 for numbering the individual H-bonds. <sup>a</sup> and <sup>b</sup> correspond to the H-bond lengths and the  $\rho$  values reported in Ref. [47].

**Table 2.** The Total Binding Energies and the Individual HB Energies in kcal mol<sup>-1</sup>

	$\Delta E^a$	$\Delta E^b$	$E_{HB1}$	$E_{HB2}$	$E_{HB3}$
Li-G:C	28.66	26.12	-4.84(-4.06), <b>-4.85</b>	-12.37(-12.86), <b>-9.43</b>	-11.45(-11.74), <b>-10.11</b>
Li'-G:C	39.25	36.98	-7.34(-6.56), <b>-6.43</b>	-16.49(-16.97), <b>-11.04</b>	-15.41(-15.71), <b>-11.68</b>
Na-G:C	27.08	24.43	-5.44(-4.78), <b>-5.42</b>	-10.86(-11.19), <b>-8.55</b>	-10.79(-11.11), <b>-9.71</b>
Na'-G:C	37.65	35.34	-8.42(-7.82), <b>-7.09</b>	-14.68(-14.99), <b>-9.82</b>	-14.55(-14.84), <b>-10.91</b>
K-G:C	25.76	23.56	-5.61(-5.03), <b>-5.60</b>	-9.94(-10.21), <b>-8.05</b>	-10.20(-10.52), <b>-9.39</b>
Mg-G:C	39.81	38.35	-2.26(-1.33), <b>-2.58</b>	-15.60(-15.55), <b>-11.16</b>	-21.96(-22.93), <b>-17.30</b>
Ca-G:C	35.58	34.01	-2.32(-1.42), <b>-2.59</b>	-12.87(-12.67), <b>-9.38</b>	-20.39(-21.48), <b>-16.05</b>
Li-A:T	14.54	13.58	-8.44(-9.00), <b>-10.46</b>	-5.81(-5.50), <b>-6.70</b>	-0.29(-0.04), <b>-0.45</b>
Na-A:T	14.63	13.60	-8.23(-8.70), <b>-10.12</b>	-6.10(-5.88), <b>-6.93</b>	-0.30(-0.04), <b>-0.47</b>
K-A:T	14.32	13.32	-7.57(-7.89), <b>-9.32</b>	-6.43(-6.37), <b>-7.23</b>	-0.33(-0.05), <b>-0.51</b>
Li'-A:T	15.28	14.08	-6.19(-6.03), <b>-7.06</b>	-8.54(-9.10), <b>-8.87</b>	-0.56(-0.15), <b>-0.82</b>
Na'-A:T	15.78	14.58	-5.09(-4.63), <b>-5.80</b>	-9.94(-10.89), <b>-9.95</b>	-0.75(-0.26), <b>-1.06</b>
Ca'-A:T	8.97	8.08	-4.94(-5.71), <b>-12.17</b>	-3.60(-3.21), <b>-7.94</b>	-0.42(-0.05), <b>-0.69</b>
Mg'-A:T	20.02	19.32	-9.70(-9.81), <b>-6.78</b>	-9.95(-10.11), <b>-6.33</b>	-0.37(-0.10), <b>-0.50</b>
<b>G-C<sup>c</sup></b>	24.51	22.69	-10.68, <b>-10.05</b>	-6.37, <b>-7.42</b>	-7.47, <b>-6.13</b>
<b>A-T<sup>d</sup></b>	12.36	11.11	-4.11, <b>-5.90</b>	-7.78, <b>-9.79</b>	-0.47, <b>-0.75</b>

The first number in these columns corresponds to the exponential equation. The data in the parentheses correspond to the second order polynomial and the linear equations. The bold data correspond to electronic potential energies. <sup>a</sup> $\Delta E = E_{M-G-C}$  (or M-A-T) -  $E_{M-G}$  (or M-A) -  $E_C$  (or T). <sup>b</sup>The  $\Delta E$  values calculated at the B3LYP/6-311++G\*\* level and corrected by zero point energy. <sup>c</sup> and <sup>d</sup> correspond to  $\Delta E$  and  $E_{HB}$  values reported in Ref. [47].

bond length corresponds to Mg-G-C and the lowest contraction corresponds to K-G-C. The changes are equal to 0.128 and 0.026 Å, respectively, in comparison with the G-C. The longest and shortest HB3 in the X-G-C complexes correspond to Mg-G-C and K-G-C, which are decreased by 0.301 and 0.127 Å, respectively, in the presence of cation.

As can be seen in Table 1, the most important changes in the HB lengths correspond to Mg-G-C and the lowest changes correspond to K-G-C with the exception of HB1 length in which the most important change corresponds to Ca-G-C. The elongation of HB1 on the coordination of G base with cations can be attributed to the reduction of electron charge on the O atom, which is accompanied by a decrease in the positive charge on the cation. The reduction of electron charge on the O atom decreases its tendency in the HB formation and lengthens the bond. Also, the decrease in the HB2 and HB3 lengths could be attributed to enhancement of proton donation

of N-H group. The electron density of N-H groups is inclined toward the N atom by induction, which increases the tendency of N-H in the HB formation. Thus, the HB2 and HB3 bond lengths decrease.

The optimization of structures coordinated in X' position of G-C were only successfully terminated for the Li<sup>+</sup> and Na<sup>+</sup> cations. Among the X'-G-C complexes, the longest HB1 bond corresponds to Li'-G-C and the shortest one corresponds to Na'-G-C, which are increased by 0.126 and 0.097 Å, respectively, in comparison with the G-C base pair. The most important reductions of HB2 and HB3 lengths correspond to Li'-G-C, which are equal to 0.118 and 0.183 Å. The least reductions of those HB lengths correspond to Na'-G-C that are equal to 0.084 and 0.163 Å. Thus, interaction between G and cation, which increases its effect on the HB lengths, is increased by increasing in the q/rad ratio of cations. The q/rad values can be found in the Supporting Information.

The effects of cation on the HB lengths at the X' position could be interpreted similar to that at the X position. Coordination with cation at the X' position makes the base pair out of plan.

In the X-A-T derivatives, the geometry optimization has been completed for the Li<sup>+</sup>, Na<sup>+</sup> and K<sup>+</sup> cations. It is expected that the induction effects increase the tendency of N-H group and decrease the propensity of N atom for the HB formation. These changes strengthen HB1 and weaken HB2. It can be inferred that the interaction between the cation and the N7 atom in the X position decreases the negative charge on N6, increases the positive charge on H6, and decreases the negative charge on N1. On the contrary to predictions, HB3 that is very far from cation is enlarged upon coordination. The interaction between cation and base rotates the center of pyrimidine ring toward the metal cation in the A-T base pair, and away from it in the G-C; this phenomenon has also been discussed in the previous work [19]. Thus, the strengthening of HB1 and weakening of HB2 increase the length of terminal HB (HB3). The most important reduction of HB1 length corresponds to Li-A-T by 0.170 Å and the least reduction of this HB corresponds to K-A-T by 0.136 Å. Also, the highest HB2 length corresponds to Li-A-T and the lowest HB2 length corresponds to K-A-T, which are increased by 0.11 and 0.088 Å, respectively. Induction effects decrease the electron density on the N-H group in HB1 and on the N atom in HB2, which increase the tendency of N-H and decrease the tendency of N in the formation of HB1 and HB2, respectively. Thus, the changes of HB lengths are in good agreement with the q/rad ratio of cations (Li<sup>+</sup> > Na<sup>+</sup>). The highest and lowest changes in the HB3 lengths correspond to Li-A-T and K-A-T, respectively, which are increased by 0.207 and 0.163 Å, respectively.

The X'-A-T complexes have been optimized in the presence of Li<sup>+</sup>, Na<sup>+</sup>, Mg<sup>2+</sup> and Ca<sup>2+</sup> cations. At the X' position, the interaction between cation and the A-T base pair decreases the HB1 length, increases the HB2 length (in all complexes with the exception of Na'-A-T), increases HB3 length in Mg'-A-T and Ca'-A-T, and decreases this HB length in the Li'-A-T and Na'-A-T complexes. The most important contraction of HB1 bond corresponds to Ca'-A-T and the least contraction of that corresponds to Na'-A-T. The longest and shortest HB2 correspond to Mg'-A-T and Na'-A-T,

respectively. Finally, the highest and lowest contractions of HB3 bond correspond to Na'-A-T and Mg'-A-T, respectively. Although, the changes of HB1 lengths are in agreement with the q/rad ratio of cations (the effect of cations on these HB lengths is increased by increasing the ratio q/rad), the short distance between cations and HBs perturbs the correlation between HB lengths and q/rad ratios.

A comparison between binding energies of X(or X')-G-C complexes and G-C base pair shows that the coordination with cations significantly increases the binding energies. As can be seen from Table 2, the binding energies of G-C derivatives are higher than those of A-T derivatives. This is due to the high dipole moment of G (6.7 D) compared to A (2.6 D), and to the more favorable orientation of the cations and G dipole moment [29,34,51]. Guanine acts as a HB acceptor in HB1 and HB donor in HB2 and HB3. Thus, coordination of guanine with more positive cations at the X position makes it a better HB donor in HB2 and HB3, which strengthens the HBs and increases total binding energies. The q/rad ratio of IIa metal cations is more than Ia cations. Thus, the binding energy of X(or X')-G-C complexes with bivalent cations is more than monovalent cations. The highest binding energy (39.81 kcal mol<sup>-1</sup>) corresponds to Mg-G-C and the lowest binding energy (25.76 kcal mol<sup>-1</sup>) corresponds to K-G-C, which increased by 15.3 and 1.25 kcal mol<sup>-1</sup>, respectively, relative to G-C base pair. These results are in agreement with the q/rad ratio of cations. As expected, the results indicate a clear inverse correlation between the radius of the cation and the binding energy [52].

In the X-A-T complexes, the changes of binding energies are not completely in agreement with the q/rad of cations. As can be seen in Table 2, the binding energy of Na-A-T is higher than Li-A-T (by 0.09 kcal mol<sup>-1</sup>). Also, Ca'-A-T has the least binding energy among the A-T derivatives. On the other hand, the highest interaction energy corresponds to Mg'-A-T, which is increased by 7.66 kcal mol<sup>-1</sup> in comparison with A-T.

The main aim of the present work is the evaluation and comparison of the cation effects on the individual E<sub>HBs</sub> in the X-A-T and X-G-C complexes. The E<sub>HB1</sub>, E<sub>HB2</sub> and E<sub>HB3</sub> values were estimated equal to -10.68, -6.37 and -7.47 kcal mol<sup>-1</sup> and -4.11, -7.78 and -0.47 kcal mol<sup>-1</sup> in G-C and A-T, respectively [40]. The individual E<sub>HBs</sub> in the X-G-C and X-A-T complexes are gathered in Table 2. As can be seen, the E<sub>HB1</sub> decreases

and two other  $E_{\text{HBs}}$  increase upon coordination in the X-G-C base pairs. The changes are in accord with the behavior of centers of the G unit that participate in the HB interactions. The trend in the  $E_{\text{HB1}}$  value in the X-G-C complexes is K-G-C (-5.61) > Na-G-C (-5.44) > Li-G-C (-4.84) > Ca-G-C (-2.32) > Mg-G-C (-2.26 kcal mol<sup>-1</sup>). Thus, more positive cations significantly decrease the  $E_{\text{HB1}}$  value. The proton transfer ability decreases and the HB length increases by the increase in the atomic number and ionic radius of cations. On the other hand, the increase in the q/rad ratio decreases the charge density on the O atom and weakens the O...H-N interaction. Among X'-G-C complexes, the  $E_{\text{HB1}}$  value in Na'-G-C (-8.42 kcal mol<sup>-1</sup>) is higher than Li'-G-C (-7.34 kcal mol<sup>-1</sup>). Although the coordinated cation in X' position is very far from HB1, its effect is also in agreement with the reactivity of cation. The order of HB2 and HB3 energies in the X-G-C complexes is Mg-G-C > Ca-G-C > Li-G-C > Na-G-C > K-G-C. Thus, it can be inferred that a higher q/rad ratio makes the N-H groups better proton donors, enhance HB2 and HB3 energies, and increases the total binding energy. The q/rad ratio for divalent cations is higher than that in monovalent cations, which is in agreement with the effect of coordination on binding energies. Also, the  $E_{\text{HB2}}$  and  $E_{\text{HB3}}$  values in Li'-G-C are higher than those in Na'-G-C, which is in agreement with the q/rad ratio and the reactivity of cations. As can be seen HB3 is greater influenced by cation interaction. As expected from the fact that this H-bond is the closest to the metal site, thus being more influenced by cations.

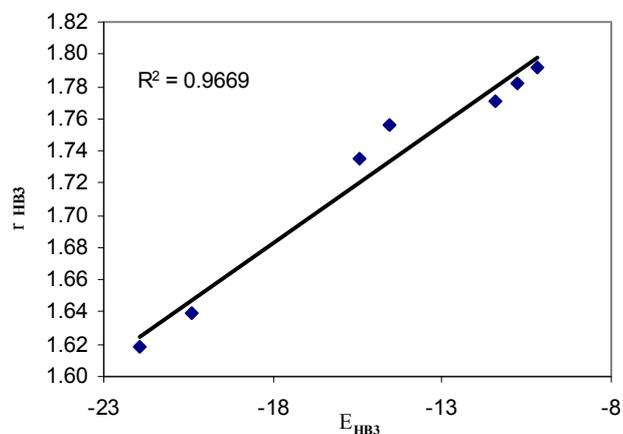
The  $E_{\text{HB1}}$  value in the X-A-T and X'-A-T complexes is higher in comparison with the A-T base pair. The  $E_{\text{HB2}}$  value in the X-A-T complexes is lower in comparison with the A-T base pair, but a reverse trend is observed for the X'-A-T complexes with the exception of Ca'-A-T. As can be seen in Table 2, HB3 is weakened upon coordination in the X-A-T complexes. In the X'-A-T complexes, HB3 is strengthened upon coordination with the Li<sup>+</sup> and Na<sup>+</sup> cations, while the reverse tendency is observed for Ca<sup>2+</sup> and Mg<sup>2+</sup>. The order of  $E_{\text{HB1}}$  in the X-A-T complexes is Li-A-T > Na-A-T > K-A-T. With respect to the type of atoms of A that participate in HBs, it is expected that the  $E_{\text{HB1}}$  and  $E_{\text{HB3}}$  individual interaction energies are increased and  $E_{\text{HB2}}$  is decreased upon coordination. The energy information in this table also confirms that the  $E_{\text{HB1}}$  and  $E_{\text{HB2}}$  values are completely in

agreement with the mentioned discussion in X-A-T complexes, while the  $E_{\text{HB3}}$  values are not. The order of  $E_{\text{HB2}}$  in X-A-T derivatives is K-A-T > Na-A-T > Li-A-T. The trends in  $E_{\text{HB1}}$  and  $E_{\text{HB2}}$  are in agreement with the q/rad ratios of cations. The trend in  $E_{\text{HB3}}$  is similar to  $E_{\text{HB2}}$  for X-A-T complexes, which is not in agreement with the chemistry of atoms participating in HB2. As discussed in the case of geometrical changes, rotation around the center of pyrimidine ring lengthens the terminal HB3 and weakens it. The order obtained for  $E_{\text{HB3}}$  is in agreement with the change of HB3 length.

In the X'-A-T complexes, the trend of decreasing of  $E_{\text{HB1}}$  is Mg'-A-T > Li'-A-T > Na'-A-T > Ca'-A-T. Herein, with the exception of the lowest value of  $E_{\text{HB1}}$  for Ca'-A-T other energy values are in agreement with the q/rad ratio of cations. It should be mentioned that the Ca'-A-T derivative has been optimized with a symmetry constraint (Cs) because of the convergence difficulties upon optimization process. The value of  $E_{\text{HB2}}$  is in order Mg'-A-T > Na'-A-T > Li'-A-T > Ca'-A-T, which (with the exception of Mg'-A-T) is in agreement with the q/rad ratio of cations; *i.e.*, the HB2 interaction is more weakened by more positive cations. Finally,  $E_{\text{HB3}}$  decreases in order Na'-A-T > Li'-A-T > Ca'-A-T > Mg'-A-T with increasing the q/rad ratio of cations.

Herein, meaningful relationships are also observed between HB lengths and the estimated individual  $E_{\text{HBs}}$ . The N-H...O bond length in X(G-C) base pairs *vs.* estimated individual  $E_{\text{HB3}}$  is plotted in Fig. 3. Also, there are good linear correlations for other H-bond lengths *vs.* estimated  $E_{\text{HBs}}$  (see Supporting Information). The difference between the sum of individual HB energies calculated by Eq. (4) and the total binding energies is in the range of -0.91 to 11.83 kcal mol<sup>-1</sup>. Thus, this equation is not reliable for the estimation of individual  $E_{\text{HBs}}$ .

The population analysis has been performed on the optimized structures of A-T and G-C derivatives and their monomers by the natural bond orbital (NBO) method [53] at the B3LYP/6-311++G\*\* level of theory using NBO program [54] under Gaussian03 program package. The natural charge on the H atom, the donor-acceptor interaction energy of  $n_{(\text{N}, \text{O})} \rightarrow \sigma^*_{(\text{N-H}, \text{O-H} \text{ and } \text{C-H})}$  and the occupation numbers of  $\sigma^*_{\text{H-Y}}$  orbitals have been considered for individual HBs. Meaningful relationships with the good correlation coefficients are

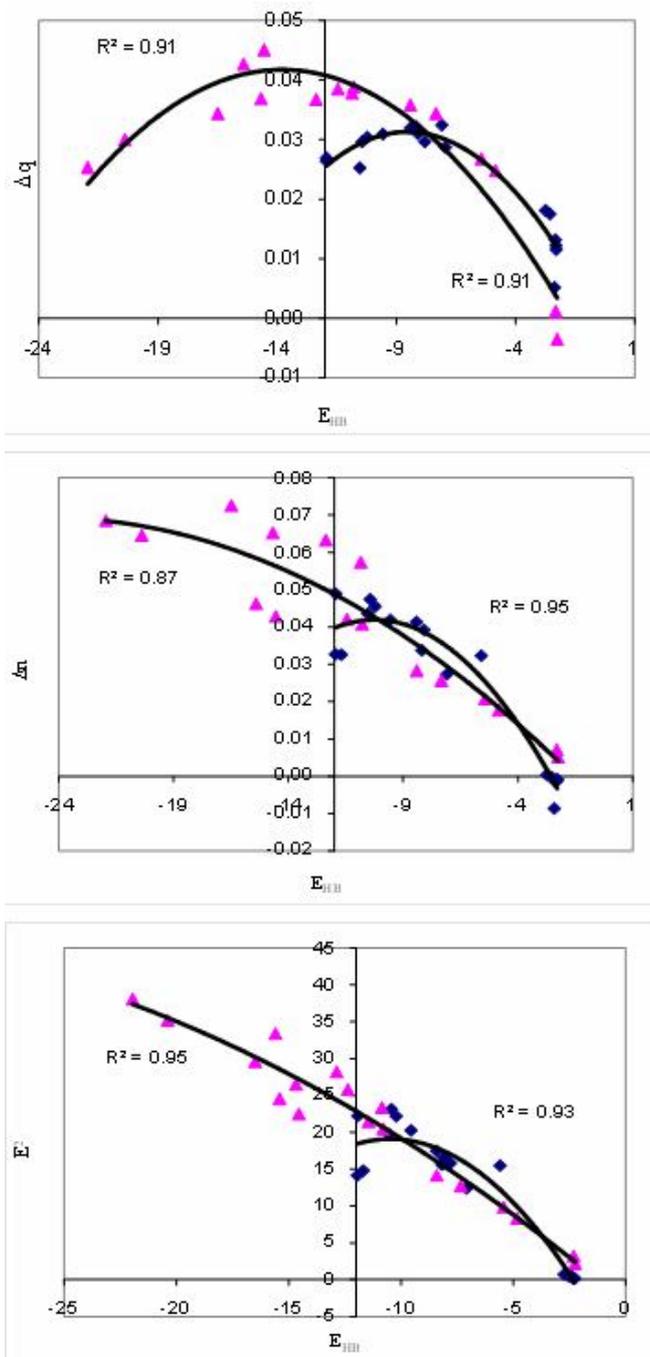


**Fig. 3.** Relationship between the hydrogen bond length ( $r_{\text{H}\cdots\text{X}}$  in Å) and the individual  $E_{\text{HB}}$  (in  $\text{kcal mol}^{-1}$ ).

observed between the NBO parameters and individual  $E_{\text{HB}}$ s estimated in this work. The correlations between individual  $E_{\text{HB}}$ s and the change of NBO parameters are shown in Fig. 4. As shown, higher changes in the natural charges are generally accompanied by higher  $E_{\text{HB}}$ s with meaningful relationships. The change of the occupancy of  $\sigma^*_{\text{H-Y}}$  orbitals and the donor acceptor interaction energy  $E(2)$  vs.  $E_{\text{HB}}$ s are also shown in Fig. 4. Increasing the occupancy of  $\sigma^*_{\text{H-Y}}$  and the  $E(2)$  value of  $n_{\text{X}} \rightarrow \sigma^*_{\text{H-Y}}$  in the A-T and G-C derivatives is generally accompanied by the increase in the individual  $E_{\text{HB}}$ s. Relationships between the individual  $E_{\text{HB}}$ s and NBO parameters for  $\text{M}^+$  and  $\text{M}^{2+}$  complexes can be found in the Supporting Information.

## CONCLUSIONS

The individual  $E_{\text{HB}}$ s estimated using the  $\rho_{\text{HBCP}}$  values in X-G-C and X'-G-C derivatives are in agreement with the  $q/\text{rad}$  ratio of cations. The values of  $E_{\text{HB1}}$  and  $E_{\text{HB2}}$  estimated in the X-A-T derivatives are also in agreement with the  $q/\text{rad}$  ratio of cations and atoms participating in H-bonding, but the values of  $E_{\text{HB3}}$  are not. Thus, HB3 is affected by the changes of two other HBs. In the X'-A-T derivatives, the estimated  $E_{\text{HB1}}$  and  $E_{\text{HB2}}$  values are in agreement with the  $q/\text{rad}$  ratio of cation with the exception of Ca'-A-T (for HB1) and Mg'-A-T (for HB2) complexes. Herein, HB1 and HB2 affect HB3, such that



**Fig. 4.** Correlation between individual  $E_{\text{HB}}$ s and a) the changes of natural charges on the H atoms b) the changes of occupation number of  $\sigma^*_{\text{H-Y}}$  or c) the changes of  $E(2)$  values of  $n_{\text{X}} \rightarrow \sigma^*_{\text{H-Y}}$  interactions in the A-T (filled diamond) and G-C (filled triangle) derivatives.

the estimated  $E_{\text{HB3}}$  value cannot be in agreement with the  $q/\text{rad}$  ratio. The effect of coordination with cations on the H-bond energies of **A-T** type complexes, especially in the  $X^{\text{L}}\text{-A-T}$  derivatives, is slight and different from the **G-C** complex. Also, the total binding energies in **G-C** derivatives significantly are increased in the presence of more positive cations, while the changes of binding energies in the **A-T** derivatives are not in agreement with the charges of cations. There are good relationships between the individual  $E_{\text{HBS}}$  and NBO parameters and also HB lengths.

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