The effect of metal alkali cations (Li+, Na+, K+) on the properties of hydrogen bonds in $A_{anti}G_{anti}$ and $A_{syn}G_{anti}$ mispairs

Sotoodeh Bagheri[1] and MOJDEH RAFIZADEH[2]

[1]Vali-e-Asr University of Rafsanjan
[2]Department of Chemistry, Faculty of Science, Vali-e-Asr University of Rafsanjan, P.O.Box77176, Rafsanjan, Iran

May 8, 2020

Posted on Authorea 8 May 2020 — CC BY 4.0 — https://doi.org/10.22541/au.158896305.53917028 — This a preprint and has not been peer reviewed. Data may be preliminary.

Abstract

The effect of interactions of Li+, Na+ and K+ cations with two configuration of the A–G mispairs, AantiGanti and AsynGanti, on the geometries and hydrogen bond energies have been studied at the MP2/6-311++G(d,p) level of theory. For each ion type, the most stable complex in AantiGanti and AsynGanti configurations are related to binding cation to N3 atom of guanine and N1 atom of adenine, respectively. The AantiGanti configuration is higher in the absolute values of binding energy than the AsynGanti configuration, indicating that AantiGanti configuration is more stable than AsynGanti ones. The results indicate that the strength of hydrogen bonds depends on the type and position of cations in considered systems. The values of hydrogen bonding energies estimated by the EML formula in AantiGanti mismatch are higher than AsynGanti case. The influences of cations binding in hydrogen bond strength are confirmed by the results of natural bond orbital (NBO) and atoms in molecules (AIM) analyses

Introduction

The genetic information of the cell is stored in nucleic acids. The two main classes of nucleic acids are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Nucleic acids play a main role in vary biological events concerned with the utilization of genetic information. Each nucleic acid contains four of five possible nitrogen-containing bases: adenine (A), guanine (G), cytosine (C), thymine (T), and uracil (U). All nucleic acids contain the bases A, C, and G; T, however, is found only in DNA, while U is found in RNA. Adenine and guanine have a fused-ring skeletal structure derived of purine, hence they are called purine bases. Similarly, the simple-ring structure of cytosine, uracil, and thymine is derived of pyrimidine, so those three bases are called the pyrimidine bases. Watson and Crick in 1953 proposed that the DNA is made up of two strands that are twisted around each other to form a right-handed helix, called a double helix [11. Watson, J. D., Crick, F. H. C. *Nature (London)* .**1953** ,171, 737-738.]. Base-pairing takes place between a purine and pyrimidine. This allows an 'A' to pair with a 'T' through two hydrogen bonds and a 'G' with a 'C' through three hydrogen bonds. In other words, adenine and thymine are complementary base pairs, and cytosine and guanine are also complementary base pairs.

The incorporation of non-Watson-Crick base pairs in duplex DNA is one of the errors affecting DNA replication [22. Kornberg, A., Baker, T. A. DNA replication. Freeman, New York. **1992** .-33. Drake, J. H. The molecular basis of mutation. Holden-Day, San Francisco.**1970** .44. Tamm, C., Stazewski, P.*Angew Chem Int Ed Engl,* **1990** , 29, 36–57.]. Such pairings are referred to as mismatches or mispairs, such as guanine pairing with adenine. Mismatch base pairing occurs in both prokaryote and eukaryote cells during genetic recombination and/or replication and as a consequence of biosynthetic errors during nucleic acid synthesis. Mispairs have been encountered in several biological processes [55. Brown, T., Hunter, W. N. *Biopolymers*

,**1997** , 44, 91–103.]. The effect of mismatches on DNA structure and stability studied in several papers [66. Roongta, V. A., Jones, C. R., Gorenstein, D. G. *Biochemistry* ,**1990** , 29, 5245-5258.-77. Urakawa, H., Noble, P. A., El Fantroussi, S., Kelly, J. J., Stahl, D. A. *Appl. Environ. Microbiol* . **2002** , 68, 235-244.88. Yang, M., McGovem, M. E., Thompson, M. *Anal. Chim. Acta* , **1997** , 346, 259-275.]. The conformation and stability of base-pair mismatches in DNA duplexes are investigated by physical methods such as nuclear magnetic resonance spectroscopy [99. Patel, D. J., Shapiro, L., Hare, D., In Nucleic Acids and Molecular Biology (Eckstein, F., Lilley. D. M., eds). Springer-Verlap. Berlin, Heidelberg, New York,**1987** , vol. 1, pp. 70-84.], X-ray crystallography [1010. Kennard, In Nucleic Acids and Molecular biology (Eckstein, F., Lilley, D. M., eds). Springer-Verlag. Berlin, Heidelberg, New York. **1987** , vol. 1. pp. 25-52.] and ultraviolet light melting studies [1111. Martin, F. H., Castro, M. M., Aboul-Ela, F., Tinoko, I. Jr., *Nucl. Acids Res* .**1985,** 13, 8927-8938.].

Adenine – Guanine mismatches are possible in DNA [1212. Hunter, W.N., Brown, T. In: Neidle S (ed) Oxford handbook of nucleic acid structure. Oxford University Press, Oxford, **1999** , pp 313–330.] and RNA structures [1313. Leontis, N. B., Stombaugh, J., Westhof, E. *Nucleic Acids Res* , **2002** , 30, 3497–3531.]. It is known that the A-G mismatch is conformationally variable. A-G mismatch can come in different forms, involving the dominant or a rare adenine tautomer of A or a protonated adenine [1414. Lippert, B., Gupta, D. *Dalton Trans.***2009** , 4619–4634.]. The two most common DNA mispairs containing neutral bases are A_{anti}-G_{anti}[1515. Privé, G. G., Heinemann, U., Chandrasegaran, S., Kan, L-S., Kopka, M. L., Dickerson, R. E. *Science* . **1987** , 238, 498–504.] and A_{syn}-G_{anti}[1616. Brown, T., Hunter, W. N., Kneale, G., Kennard, O.*Proc Natl Acad Sci USA* , **1986** , 83, 2402–8406.]. Ultraviolet light melting studies [1717. Brown, T., Leonard. G. A., Booth, E. D., Chambers, J. *J. Mol. Biol.* **1989** , 207, 455-467.] and nuclear magnetic resonance spectroscopy [1818. Gao, X., Patel, D. J. *J. Amer. Chem. Soc.***1988** , 110, 5178-5182.] have been applied to probe the variability in the stability and conformation of the A-G mismatch as a function of pH. Both the A_{anti}-G_{anti} and A_{syn}-G_{anti} mismatches exist at neutral pH depending on the base stacking environment.

Interactions between nucleic acids and metal cations has attracted considerable attention duo to the biological role that these ions play in determining the structure and function of fundamental blocks of living organisms [1919. Egli, M. *Chem. Biol.***2002** , 9, 277–286.-2020. Anastassopoulou, J. *J. Mol. Struct.* **2003** , 651–653, 19–26.2121. Dugid, J., Bloomfield, V. A., Benevides, J., Thomas, G. J., *Biophys. J.***1993** , *65* , 1916–1928.2222. Krasovska, M. V., Sefcikova, J., Reblova, K., Schneider, B., Walter, N. G., Sponer, J.*Biophys J* . **2006** , 91, 626-638.]. To better understand mechanisms of metal–nucleic acid interactions occurring in vivo, numerous in vitro studies of model reactions and structures of metal–nucleic acid complexes have been carried out [2323. Hud, N. V., Polak, M. *Curr. Opin. Struct. Biol.* , **2001** , 11, 293-301.-2424. Sigel, H., Song, B. *Met. Ions Biol. Syst.* , **1996** , 32, 135-205.2525. Martin, R. B.*Acc. Chem. Res.* **1985** , 18, 32-38.].

Also, interactions between bases or base pairs and metal cations are investigated by Quantum Mechanical Calculations [2626. Colson, A.O., Besler, B., Close, D. M., Sevilla, M. D. *J. Phys. Chem.***1992** , 96, 661-668.-2727. Valdespino-Saenz, J., Martinez, A. *J. Mol. Struct. (THEOCHEM)* , **2010** , 939, 34-43.2828. Burda, J. V., Sÿponer, J., Hobza, P. *J. Phys. Chem.* **1996** , 100, 7250-7255.]. The most important conclusion from initial calculations, were carried out in the 1980s, show that the polarization effects of base pairing increases due to the metal coordination [2929. Basch, H., Krauss, M., Stevens, W. J. *J. Am. Chem. Soc* . **1985** ,107, 7267-7271.-3030. Lipinski, J. *J. Mol. Struct. (THEOCHEM)* , **1989** , 201, 87-98.3131. Del Bene, J. *J. Mol. Struct (THEOCHEM)* , **1985** , 124, 201-212.]. In several study, Syponer et al., investigated the interactions between mono- and divalent metal cations and nucleobases, as well as the Watson-Crick and reverse Hoogsteen base pairs [3232. Sÿponer, J., Burda, J. V., Mejzlik, P., Leszczynski, J., Hobza, P. J. *Biomol. Struct. Dyn.* **1997** , 14, 613-628.,3333. Burda, J. V., Sÿponer, J., Leszczynski, J., Hobza, P. *J. Phys. Chem. B.* **1997** , 101, 9670-9677.,28]. The results demonstrated that every cation has a rather unique interaction with the DNA bases and base pairs. The binding energies and geometries are determined by the charges, atomic radii, electronic structure of the cation and relativistic effects. Also, the effect of interactions of mono and bivalent metal cations with A-T and G-C base pairs have been studied by Ebrahimi et al., [3434. Delarami, H., Ebrahimi, A., Habibi Khorassani, S. M., Abedini S., Mostafavi, N.*Phys. Chem. Res.,* **2013** ,

Posted on Authorea 8 May 2020 — CC BY 4.0 — https://doi.org/10.22541/au.158896305.53917028 — This a preprint and has not been peer reviewed. Data may be preliminary.

1, 81-89.]. They are shown that 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. In another study, interaction between the G-C base pair and hydrated Mg^{2+},Ca^{2+}, Sr^{2+}, Ba^{2+}, Zn^{2+}, Cd^{2+}, and Hg^{2+} metal cations investigated [3535. Sÿponer, J., Burda, J. V., Sabat, M., Leszczynski, J., Hobza, P. *J. Phys. Chem. A.* **1998** , 102, 5951-5957.]. The results indicate that the strength of the G-C base pair is enhanced due to the coordination of the hydrated cation.

In pervious our work, we theoretically demonstrate the influence of binding of Cu^{+} ion to N3- and N7-positions of hypoxanthine on the energetic, geometrical and topological properties of hypoxanthine–guanine, hypoxanthine–adenine, hypoxanthine–cytosine, hypoxanthine–thymine and hypoxanthine–hypoxanthine mismatches [3636. Masoodi, H. R., Bagheri, S., Ghaderi, Z., *Journal of Biomolecular Structure and Dynamics* , **2018** , 37,1923-1934.]. In this work, we have investigated the effect of Li^{+}, Na^{+} and K^{+} cations on the properties of hydrogen bonds in the preferred tautomeric forms A_{anti}-G_{anti} and A_{syn}-G_{anti} mismatches. Also, we have compared geometry parameters and energy data in the A_{anti}-G_{anti} and A_{syn}-G_{anti} mispairs in the presence of various cations.

Computational methods

The structures of all complexes were optimized by the second-order Møller–Plesset perturbation theory (MP2) with the 6-311++G(d,p) basis set using Gaussian 09 suite of programs [11. Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G. A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H. P., Izmaylov, A. F., Bloino, J., Zheng, G., Sonnenberg, J. L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery, J. A., Jr., Peralta, J. E., Ogliaro, F., Bearpark, M., Heyd, J. J., Brothers, E., Kudin, K. N., Staroverov, V. N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J. C., Iyengar, S. S., Tomasi, J., Cossi, M., Rega, N., Millam, J. M., Klene, M., Knox, J. E., Cross, J. B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W., Martin, R. L., Morokuma, K., Zakrzewski, V. G., Voth, G. A., Salvador, P., Dannenberg, J. J., Dapprich, S., Daniels, A. D., Farkas, Ö., Foresman, J. B., Ortiz, J. V., Cioslowski, J., Fox, D. J. Gaussian, Inc., Wallingford CT, **2009** .]. All studied complexes have a nearly linear arrangement (Cs symmetric). It has previously been indicated that very little energy is required to make the nucleobases co-planar [22. Fonseca Guerra, C., Bickelhaupt, F. M., Snijders, J. G., Baerends, E. J. *Journal of the American Chemical Society,* **2000** , 122, 4117–4128.,33. Moroni, F., Famulari, A., Raimondi, M., Sabat, M. *J Phys Chem* ,**2003** , 107, 4196–4202.].

The basis set superposition error (BSSE) has been considered by the Boys-Berrnardi counterpoise method [44. Boys, S. F., Bernardi, F. *Mol. Phys* . **1970** , 19, 553-566.] in the geometry optimization.

The topological electron charge density has been analyzed by the quantum theory of atoms in molecules (QTAIM) approach [55. Bader, R. F. W. Atoms in molecules: a quantum theory, Oxford University Press, Oxford, **1990** .] using AIM 2000 program [66. Biegler Konig, F., Schonbohm, J. *J. Comput. Chem* .**2002** , 23, 1489–1494.] on the obtained wave functions at MP2/6-311++G(d,p) level of theory. The features of bond critical points (BCPs) of the hydrogen bond were analyzed. It is well-known that characteristics of BCPs, such as the electron density (ρ(r)), their Laplacians ([?]$^2\rho$(r)), and that energy densities of BCPs (H(r)) allow us to categorize interactions and these topological parameters are also treated as measure of hydrogen bonding strength.

Moreover, the population analysis was performed by the natural bond orbital (NBO) method [77. Reed, A. E., Curtiss, L. A., Weinhold, F. *Chem. Rev* . **1988** , 88, 899–926.] at the HF/6-311++G(d,p) level on the optimized structures using NBO program under Gaussian 09 program package [88. Glendening, E. D., Reed, A. E., Carpenter, J. E., Weinhold, F. NBO Version 3.1. Department of chemistry, university of california-irvine, Irvine, **1995** .]. The NBO analysis is carried out by considering all possible interactions between filled donor and empty acceptor natural bond orbitals and estimating their energetic importance by second-order perturbation theory. Donor–acceptor interaction energy ($E^{(2)}$) is above threshold (0.5 kcal) in

Posted on Authorea 8 May 2020 — CC BY 4.0 — https://doi.org/10.22541/au.158896305.53917028 — This a preprint and has not been peer reviewed. Data may be preliminary.

all complexes.

Electrostatic Potential (ESP) generated by a chemical species is widely used as a tool for exploring its properties and locating potential sites for interaction with other moieties. To get a deeper insight into the nature of the interaction, the electrostatic potentials (ESP) have also been calculated using Multiwfn software [99. Lu, T., Chen, F.*J. Comput. Chem* . **2012** , 33, 580-592.] and visualized by VMD [1010. Humphrey, W., Dalke, A., Schulten, K. *J. Mol. Graphics,* **1996** , 14, 33–38.] software.

Results and discussion

Molecular electrostatic potential maps (MEPs) are very helpful in identifying the electron deficient and electron rich areas in molecules and have been employed extensively in several studies [11. Mottishaw, J. D., Erck, A. R., Kramer, J. H., Sun, H., Koppang, M.*J. Chem. Educ* . **2015** , 92, 1846–1852.,22. Khan, I., Panini, P., Ud-Din Khan, S., Rana, U. A., Andleeb, H., Chopra, D., Hameed, S., Simpson, J. *Cryst. Growth Des* .**2016** , 16, 1371–1386.]. The molecular electrostatic potentials have been calculated to investigate the influence of cation binding on the properties of hydrogen bonds in considered systems. Figure 1 show electrostatic potential map for isolated adenine and guanine. One can see that the basins of negative potential are located around N3 and N7, and O6 atoms of guanine and N3 and N7, and N1 atoms of adenine.

The influence of metal alkali binding on the properties of hydrogen bonds in $\mathbf{A_{anti}G_{anti}}$ mispair

The O6 of guanine and N1 of adenine in the $A_{anti}G_{anti}$ mispair are blocked by the hydrogen bonding. One can expect that N3 and N7 of guanine and adenine to be principal acceptors of cations. The G(3), G(7), A(3) and A(7) symbols are used to display these positions, respectively. The schematic representation of optimized structure of $A_{anti}G_{anti}$ mispair in the presence of cations are presented in Figure 2. In agreement with previous studies [11. Sÿponer, J., Burda, J.V., Sabat, M., Leszczynski, J., Hobza, P. *J. Phys. Chem. A,***1998** , *102,* 5951-5957.,34], calculations indicate that there is simultaneous coordination of the cation to both the N7 and O6 sites of guanine.

The binding energy has been evaluated using the following equation

$[?]E = E_{mispair}$ - [?] E_{mon}

Where $E_{mispair}$ and E_{mon} are the energies of $A_{anti}G_{anti}$ mispair and monomers in their optimized geometries (DNA bases, metal-adenine or metal-guanine), respectively (see Table 1). Unlike A(3) position, the cations binding to A(7), G(7) and G(3)-positions amplified the absolute values of binding energy (?[?]E ?). For each ion type, the G(3) tautomer is the most stable among all. Contrary to A(7) position, the ?[?]E?values in A(3), G(7) and G(3)-positions are in agreement with the charge/radius (q/rad) ratio of cations.

Also, the interaction (ΔE_{int}) and deformation (ΔE_{def}) energies of the considered systems were calculated. The interaction energies were evaluated as the difference between the energy of the mispair and the sum of the energies of the separated monomers, by the same geometries as they have in the complex. The difference between the binding energy and the interaction energy is the deformation energy of the monomers (see Table 1). Unlike ΔE_{def}, the value of ΔE_{int} is negative and makes a positive contribution to the ΔE. As evident from Table 1, the interaction energy is the most dominant contribution to the binding energy in all studied systems. The good relationship is found between $[?]E_{int}$ and [?]E values with coefficient of determination $R^2 = 0.9929$ in studied systems.

The NH...O and NH...N hydrogen bonding (HB1 and HB2, respectively) intermolecular energies were calculated based on the Espinosa–Molins–Lecomte (EML) empirical criteria based on the obtained electron density distribution at the BCPs of the hydrogen bonds

$E_{EML,HB} = 0.5V(r)$

Where V(r) is the value of a local potential energy at the BCPs (see Table 1). Contrary to G(7) and G(3)-positions, the absolute value of $E_{EML,HB1}$ (?$E_{EML,HB1}$?) in A(7) and A(3)-positions upon interactions with alkali ions increases. An opposite behavior is found for $E_{EML,HB2}$. The results indicate that unlike G(7) and

Posted on Authorea 8 May 2020 — CC BY 4.0 — https://doi.org/10.22541/au.158896305.53917028 — This a preprint and has not been peer reviewed. Data may be preliminary.

G(3)-positions, increase in ion charge density in A(7) and A(3)-positions is accompanied by increasing in ?$E_{EML,HB1}$?and decreasing in the ?$E_{EML,HB2}$?values. For each ion, the ?$E_{EML,HB1}$? and ?$E_{EML,HB2}$? orders in $A_{anti}G_{anti}$ mismatch are respectively as following:

A(7) > A(3) > G(3) > G(7)

G(7) > G(3) > A(7) > A(3)

The NH...O and NH...N hydrogen bond lengths (d_{HB1} and d_{HB2}, respectively) in $A_{anti}G_{anti}$ mismatch have been changed after interaction with cations. These distances are often treated as a rough measure of the strength of hydrogen bonds. As reported in Table 2, d_{HB1} in A(7) and A(3)-positions decreases, whereas d_{HB2} increases upon interactions with alkali ions. A reverse behavior is found for G(7) and G(3)-positions. The highest contraction in the HB1 and HB2 bond lengths correspond to Li^+ cation in A(7) and G(7)-positions, respectively. Also, the highest expansion in the HB1 and HB2 bond lengths correspond to Li^+ cation in G(7) and A(3)- positions, respectively. Contrary to A(3) and A(7) positions, the d_{HB1} values in G(7) and G(3)-positions are in agreement with the charge/radius (q/rad) ratio of cations. An opposite behavior is found for d_{HB2} values. Also, the results indicate that the shortest hydrogen bond length is related to highest absolute value of corresponding $E_{EML,HB}$ and vice versa.

For each individual NH...X (X=O, N) hydrogen bond, the combinations of d_{N-H} and $d_{X\cdots H}$ have been shown to be very useful for studying hydrogen bonding phenomenon [22. Golubev, N. S., Shenderovich, I. G., Smirnov, S. N., Denisov, G. S., Limbach, H. H. *Chem Eur J* , **1999** , 5, 492–497.].

$q_1 = 0.5\ (d_{N-H} - d_{X\cdots H})$

$q_2 = d_{N-H} + d_{X\cdots H}$

Whereas the proton in NH...X (X=O, N) hydrogen bond is located on average closer to N, the q_1 values is negative. On the other hand, q_2 value goes through a minimum that leads to the strongly $N^{\delta+}\cdots H\cdots X^{\delta-}$hydrogen bond. The values of q_1 and $q_2$in studied systems are also gathered in Table 2. Contrary to A(7) and A(3)-positions, the absolute values of q_1(?q_1?) and q_2 associated with HB1 increase in G(7) and G(3)-positions. This behavior is reversed for HB_2. The results indicate that unlike A(7) and A(3)- positions, increase in ion charge density in G(7) and G(3)-positions is accompanied by increasing in ?q_1?and $q_2$values corresponding HB1. A reverse order are found for ?q_1?and q_2 values corresponding HB2.

For two type of considered hydrogen bond, there are good relationships between $|q_1|$, q_2 and corresponding bond length values. As evident from Figure 3, second order polynomial relationships are found between the absolute values of q_1 and q_2 and corresponding E_{EML} for each hydrogen bond in considered systems.

Natural bond orbital (NBO) analysis stresses the role of intermolecular orbital interaction in the complex. In NBO theory, atomic charge assignments are based on natural population analysis, where each natural atomic charge is simply determined from the summed natural atomic orbitals populations on the atom [33. Reed, A. E., Weinstock, R. B., Weinhold, F. *J. Chem. Phys* . **1985** , 83, 735-746.]. The atomic charge on atoms involved in hydrogen bond formation in isolated adenine and guanine in the presence of cations have been calculated by NBO approach. One can see from Table 3 that the cation binding to N7 and N3 atoms of isolated adenine increases positive charge of H atom participating in HB_1 and decreases negative charge of N atom participating in HB_2. One can expected that the strength of HB_1 increases due to interaction cations with adenine in these positions. This behavior is reversed for HB_2. The interaction of cations with N3 atom of isolated guanine leads to increases positive charge of H atom participating in HB_2 and decreases negative charge of O atom participating in HB_1. Thus, the strength of HB_1 and HB2 are expected to decrease and increase, respectively.

The negative and positive atomic charge on O and H atoms participating respectively in HB_1 and HB_2 increases due to interaction of cations with N7 atom of isolated guanine. One can expected that the strength of HB_2 increases due to interaction cations with guanine in N7 site. Although, the negative atomic charge

Posted on Authorea 8 May 2020 — CC BY 4.0 — https://doi.org/10.22541/au.158896305.53917028 — This a preprint and has not been peer reviewed. Data may be preliminary.

on O atom increased in this position, the strength of HB_1 decreases. This can be explained by the fact that a second attractive side in guanine, i.e. not only nitrogen N7 but also oxygen O6.

For each acceptor NBO (j) and donor NBO (i), the stabilization energy $E^{(2)}$ associated with electron delocalization between donor and acceptor is estimated as:

$$E^2 = q_i \frac{(F_{i,j})^2}{\varepsilon_j - \varepsilon_i}$$

Where q_i is the orbital occupancy, $\varepsilon_i$and ε_j are diagonal elements, and $F_{i,j}$is the off-diagonal NBO Fock matrix element [45]. In Table 3, we analyze the main contributions to donor-acceptor second-order energies (E^2). The most important donor–acceptor interactions connected to HB_1 and HB_2 are Lp_O - $\sigma^*_{N–H}$ and Lp_N - $\sigma^*_{N–H}$, respectively. The results indicated that interaction of cations with N3 and N7 sites of adenine increase the $E^{(2)}$ values of HB_1. A reverse behavior is found for N3 and N7 sites of guanine. The $E^{(2)}$ values of HB_2amplified/diminished in the presence of cations in N3 and N7 positions of guanine /adenine. Contrary to G(7) and G(3)-positions, increase in ion charge density in A(7) and A(3)- positions is accompanied by increasing in $E^{(2)}$ values corresponding HB1. An opposite behavior are found for HB2. For HB_1 and HB_2 interactions, there is a good linear relationship between E_{EML} values and corresponding $E^{(2)}$ values of these interaction (see Figure 4(a)). Also, the results indicate that second order polynomial correlation exists between the $E^{(2)}$ values and corresponding hydrogen bond lengths with coefficient of determination R^2=0.9985 and in R^2=0.9980 respectively for HB_1 and HB_2 in studied systems.

The QTAIM is useful to analyze various intra and intermolecular interactions. The results indicate that the bond critical points of the hydrogen bonds was found. The electron density at the BCP of the hydrogen bond may be treated as a measure of the hydrogen bond strength [44. Galvez, O., Gomez, P. C., Pacio, L. F. *J. Chem. Phys* . **2003** , 118, 4878-4895.,55. Domagala, M., Grabowski, S. J. *J. Phys. Chem. A.* **2005** , 109, 5683-5688.]. Rozas et al. have introduced a classification of hydrogen bonds according to their strength [66. Rozas, I., Alkorta, I., Elguero, J. *J. Am. Chem. Soc* . **2000** , 122, 11154-11161. Figure1. Electrostatic potentials mapped on the molecular surfaces of isolated (a) guanine, (b) adenine bases with VMD software. Figure 2. The Schematic representation of optimized structure of $A_{anti}G_{anti}$ mispair in the presence of cations (M= Li^+, Na^+ and K^+) in (a) N3 (b) N7 sites of adenine and (c) N3 (d) N7 sites of guanine, respectively. Figure 3. Relationships between E_{EML} values and (a) ?q_1? and (b) q_2 for each hydrogen bond in $A_{anti}G_{anti}$ systems involving cations. The (*) and ()$symbols correspond to HB_1 and HB_2, respectively. Figure 4. Relationships between E_{EML} and corresponding (a) E^{(2)} and (b) r(r)$
$Li^+, Na^+ and K^+) in (a) N1 (b) N3 sites of adenine and (c) N3 (d) N7 sites of guanine, respectively. Figure 6. Relationships between$
$bonds show both [?]^2 r(r) and H(r) values positive; for medium H-bonds [?]^2 r(r) > 0 and H(r) < 0 and also for strong H-$
$bonds the [?]^2 r(r) as well as H(r) are negative. The results of AIM analysis are gathered in Table 4. Unlike G(3) and G(7)-$
$positions, the r(r) values at the BCP of the HB1 (r_{HB1}) in the presence of cations in N7 and N3 -$
$positions of adenine increase. The r(r) values at the BCP of HB_2 (r_{HB2}) amplified/diminished in the presence of cations in N3 and$
$positions, the r_{HB1} values in A(3) and A(7) positions are in agreement with the charge/radius (q/rad) ratio of cations. An opposite be$

The influence of metal alkali binding on the properties of hydrogen bonds in $A_{syn}G_{anti}$ mispair

The O6 of guanine and N7 atom of adenine in the $A_{syn}G_{anti}$ mispair directly contributes in the formation of hydrogen bonds. Thus, N3 and N7 of guanine and N1 and N3 adenine to be principal acceptors of cations. The G(3), G(7), A(1) and A(3) symbols are used to display these sites, respectively. The schematic representation of optimized structures are shown in Figure 5. In agreement with previous investigations [49,34], a simultaneous coordination of the cation to both the N7 and O6 sites of guanine is observed.

The values of [?]E, $[?]E_{int}$ and $[?]E_{def}$ are reported in Table 5. The results indicate the cations binding to A(1), A(3) and G(3)-positions amplified the absolute values of binding energy. Unlike Li^+ cation, the ?[?]E ?values diminished in the presence of Na^+ and K^+ cations in N7 site of guanine. For each ion type, the A(1) tautomer is the most stable among all. Contrary to ΔE_{def} values, ΔE_{int} makes a positive contribution to the ΔE. The contribution of ΔE_{int} is dominant in all considered systems. The results in Table 5 indicate

Posted on Authorea 8 May 2020 — CC BY 4.0 — https://doi.org/10.22541/au.158896305.53917028 — This a preprint and has not been peer reviewed. Data may be preliminary.

that a direct correlation exists between [?]E_{int} and [?]E values with coefficient of determination R^2= 0.9967 in $A_{syn}G_{anti}$ systems involving cations. It is observed that the reduction in ion charge density is associated with decreasing the absolute values of [?]E_{int} and [?]E values.

Also, hydrogen bonding energies are calculated by the EML formula (see Table 5). Unlike G(7) and G(3)-sites, the ?$E_{EML,HB1}$? in A(1) and A(3)-sites upon interactions with alkali ions increases. A reverse behavior is observed for $E_{EML,HB2}$. Contrary to G(7) and G(3)-positions, the ?$E_{EML,HB1}$?values in A(1) and A(3)-positions are in agreement with the charge/radius (q/rad) ratio of cations. This opposite order is reversed for $E_{EML,HB2}$values. For each ion, the ?$E_{EML,HB1}$? and ?$E_{EML,HB2}$? values in $A_{syn}G_{anti}$ mismatch increase respectively as following:

A(1) > A(3) > G(3) > G(7)

G(7) > G(3) > A(1) > A(3)

As evident from Tables 1 and 5, the $A_{anti}G_{anti}$ configuration is higher in the absolute values of binding energy than the $A_{syn}G_{anti}$ configuration, indicating that $A_{anti}G_{anti}$ configuration is more stable than $A_{syn}G_{anti}$ one. Also, the absolute values of hydrogen bonding intermolecular energies ($E_{EML,HB}$) in $A_{anti}G_{anti}$mismatch are higher than $A_{syn}G_{anti}$ ones.

The most geometrical parameters of the considered systems are given in Table 6. The results indicat that the length of HB1 and HB2 in $A_{syn}G_{anti}$ are greater than corresponding in $A_{anti}G_{anti}$ mispair. One can see that d_{HB1} in A(1) and A(3)-sites decreases, whereas d_{HB2} increases upon interactions with alkali ions. An opposite behavior is observed in G(7) and G(3)-sites. The highest contraction in the HB1 and HB2 bond lengths correspond to Li^+ cation in A(1) and G(7)- positions, respectively. Also, the highest expansion in the HB1 and HB2 bond lengths correspond to Li^+ cation in G(7) and A(3)- positions, respectively. The results indicate that unlike A(1) and A(3)- positions, increase in ion charge density in G(7) and G(3)-positions is accompanied by increasing in HB1 bond lengths. A reverse order are found for HB2 bond lengths. The results indicate that the increasing in d_{HB} is accompanied by decreasing of corresponding ?$E_{EML,HB}$? values and vice versa.

Unlike A(1) and A(3)-sites, the interaction of cations with G(7) and G(3)-sites leads to increases ?q1?and q2 values corresponding HB1. A reverse order are found for ?q1?and q2 values corresponding HB2. Contrary to A(1) and A(3)- positions, the ?q1?and q2 values corresponding HB1 in G(7) and G(3)-positions are in agreement with the charge/radius (q/rad) ratio of cations. This behavior is reversed for HB_2. There are good relationships between $|q_1|$, q_2 and corresponding bond length values. The maximum value of d_{HB} is accompanied by the highest $|q_1|$ and q_2 values for any type of hydrogen bond and vice versa. Figure 6 shows that there are second order polynomial relationships between the absolute values of q_1 and q_2 and corresponding E_{EML} for each hydrogen bond in considered systems.

The results of NBO analysis are gathered in Table 7. The results indicate that the cation binding to N3 and N1 atoms of isolated adenine increases positive charge of H atom participating in $HB_1$and decreases negative charge of N atom participating in HB_2. One can expected that the strength of HB_1 increases due to interaction cations with adenine in these positions. An opposite behavior is expected for HB2. The changes in atomic charge on N3 and N7 atoms in isolated guanine in the presence of cations are discussed in previous section. The most important donor–acceptor interactions connected to HB_1 and HB_2 are Lp_O -σ $*_{N–H}$ and Lp_N -σ $*_{N–H}$, respectively. The results indicate that the $E^{(2)}$ values of HB1 and HB2 in $A_{anti}G_{anti}$ are greater than corresponding in $A_{syn}G_{anti}$ mispair. Unlike G(3) and G(7)-sites, interaction of cations with A(1) and A(3)-sites increase the $E^{(2)}$ values of HB_1. This behavior is reversed for $E^{(2)}$ values of HB2. Contrary to G(7) and G(3)-positions, increase in ion charge density in A(1) and A(3)- positions is accompanied by increasing in $E^{(2)}$ values corresponding HB1. An opposite behavior are found for HB2. The results indicate that second order polynomial relationship exists between the $E^{(2)}$ values and corresponding d_{HB} with coefficient of determination R^2=0.9992 and R^2=0.9982 respectively for HB_1 and HB_2 in studied systems. For each hydrogen bonds, there is a good linear relationship between E_{EML} values and corresponding $E^{(2)}$ values of these interaction. These correlations are shown in Figure 7(a).

Posted on Authorea 8 May 2020 — CC BY 4.0 — https://doi.org/10.22541/au.158896305.53917028 — This a preprint and has not been peer reviewed. Data may be preliminary.

As given in Table 8, the ρ_{HB1} and ρ_{HB2}values obtained using AIM analysis show that cations binding to N3 and N1 atoms of adenine strengthens HB_1 and weakens HB_2 in $A_{syn}G_{anti}$mispair. Contrary to HB_2, the strength of HB_1 decreases in the presence of cations in G(7) and G(3)- sites. Unlike G(7) and G(3)-positions, the ρ_{HB1}values in A(1) and A(3)-positions are in agreement with the charge/radius (q/rad) ratio of cations. This behavior is reversed for ρ_{HB2} values. The results indicate that the ρ_{HB1} and ρ_{HB2} values in $A_{anti}G_{anti}$ are greater than corresponding in $A_{syn}G_{anti}$ mispair.

The nature of hydrogen bonds in $A_{syn}G_{anti}$ mispair involving cation is dependent on position of ions. In the presence of cations in N1 and N3 atoms of adenine, HB1 has medium strength while HB2 of weak strength is observed. Also, $A_{syn}G_{anti}$ mispair involving cations in G(7) and G(3)- positions are characterized by the positive values of $[?]^2\rho(r)$ and H(r) in the BCP of the HB1 showing that this interaction may be classified as weak bonds. Although $[?]^2\rho(r)$ at the BCP of the HB2 in systems involving cations in N3 and N7 atoms of guanine is positive, H(r) is negative, indicating that HB2 has medium strength. There are good linear relationships between $E^{(2)}$ values and corresponding $\rho_{(r)}$ at the BCP of hydrogen bonds of considered systems. The linear coefficients of determination between ρ_{HB1}, ρ_{HB2} and $E^{(2)}$ values are equal to 0.9994 and 0.9981, respectively. Also, there are good linear correlations between $\rho_{(r)}$ and corresponding E_{EML} values in studied systems. This correlation is displayed in Figure 7(b).

Conclusion

For A–G mispairs, two preferred tautomeric forms are considered, that is, $A_{anti}G_{anti}$ and $A_{syn}G_{anti}$ mispairs. The interaction of Li^+, Na^+ and K^+cations with A_{anti}-G_{anti} and A_{syn}-G_{anti} mispairs are investigated at the MP2/6-311++G(d,p) level of theory. The natural bond orbital (NBO) method as well as the quantum theory of atoms in molecules (AIM) is applied to characterize hydrogen bond interactions in the considered systems. For each ion type, , the most stable complex in $A_{anti}G_{anti}$ and $A_{syn}G_{anti}$ configurations is related to binding cation to N3 atom of guanine and N1 atom of adenine, respectively.

In general, the $A_{anti}G_{anti}$ configuration is more stable than $A_{syn}G_{anti}$ one. The strength of the hydrogen bonds generally correlate well with the type and position of cations. Also, the absolute values of hydrogen bonding intermolecular energies, was calculated using EML formula, in $A_{anti}G_{anti}$ mismatch are higher than $A_{syn}G_{anti}$ ones. In general, the length of HB1 and HB2 in $A_{syn}G_{anti}$ are greater than corresponding in $A_{anti}G_{anti}$mispair. The results indicate that the values of $E^{(2)}$and $\rho(r)$ at the BCP of the hydrogen bond in $A_{anti}G_{anti}$ are greater than corresponding in $A_{syn}G_{anti}$ mispair. Also, that the maximum value of the $\rho_{(r)}$ is related to highest absolute value of corresponding E_{EML} for each hydrogen bond and vice versa.

Acknowledgments

The authors thank the Vali-e-Asr University of Rafsanjan for financial supports and Computational Quantum Chemistry Laboratory for computational facilities.

Reference

Hosted file

`Figure 1.docx` available at https://authorea.com/users/319725/articles/449443-the-effect-of-metal-alkali-cations-li-na-k-on-the-properties-of-hydrogen-bonds-in-aantiganti-and-asynganti-mispairs

Hosted file

`Figure 2.docx` available at https://authorea.com/users/319725/articles/449443-the-effect-of-metal-alkali-cations-li-na-k-on-the-properties-of-hydrogen-bonds-in-aantiganti-and-asynganti-mispairs

Hosted file

`Figure 3.docx` available at https://authorea.com/users/319725/articles/449443-the-effect-of-metal-alkali-cations-li-na-k-on-the-properties-of-hydrogen-bonds-in-aantiganti-and-

Posted on Authorea 8 May 2020 — CC BY 4.0 — https://doi.org/10.22541/au.158896305.53917028 — This a preprint and has not been peer reviewed. Data may be preliminary.

asynganti-mispairs

Hosted file

Figure 4.docx available at https://authorea.com/users/319725/articles/449443-the-effect-of-metal-alkali-cations-li-na-k-on-the-properties-of-hydrogen-bonds-in-aantiganti-and-asynganti-mispairs

Hosted file

Figure 5.docx available at https://authorea.com/users/319725/articles/449443-the-effect-of-metal-alkali-cations-li-na-k-on-the-properties-of-hydrogen-bonds-in-aantiganti-and-asynganti-mispairs

Hosted file

Figure 6.docx available at https://authorea.com/users/319725/articles/449443-the-effect-of-metal-alkali-cations-li-na-k-on-the-properties-of-hydrogen-bonds-in-aantiganti-and-asynganti-mispairs

Hosted file

Figure 7.docx available at https://authorea.com/users/319725/articles/449443-the-effect-of-metal-alkali-cations-li-na-k-on-the-properties-of-hydrogen-bonds-in-aantiganti-and-asynganti-mispairs

Posted on Authorea 8 May 2020 — CC BY 4.0 — https://doi.org/10.22541/au.158896305.53917028 — This a preprint and has not been peer reviewed. Data may be preliminary.