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## **Theoretical Study of G4–M<sup>+</sup>–G4 (M = Li, Na and K) Complexes: Structure, Stability and Electrostatic Potential**

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## Theoretical Study of G4–M<sup>+</sup>–G4 (M = Li, Na and K) Complexes: Structure, Stability and Electrostatic Potential #

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### Abstract

**Motivation.** Guanine-rich DNA can form a G-quadruplex structure in the presence of Na<sup>+</sup> or K<sup>+</sup> ions. These structures are important in the design of DNA-interactive antitumour drugs, and the investigation of structure and properties of G-quadruplex is currently an area of major interest. Single guanine tetrad with metal ions has been extensively studied previously, while *in vivo* the guanine tetrads are mostly stacked, and thus the sandwiched structures of G4–M<sup>+</sup>–G4 need to be investigated.

**Method.** In this paper the “sandwich” models of the metal ion (Li<sup>+</sup>, Na<sup>+</sup> and K<sup>+</sup>) G-tetrads complexes have been studied using *ab initio* and density functional theory methods.

**Results.** The results show that with the increasing of the cation radius, the structure of the G4–M<sup>+</sup>–G4 becomes looser and looser. Binding energies indicate that the Li<sup>+</sup> complex is the most stable one without hydration effect correction, while the stability sequence changes to K<sup>+</sup> > Na<sup>+</sup> > Li<sup>+</sup> after considering the hydration effect, which coincides with the experimental situation. The electrostatic potential maps show that the optimal position of potassium in the guanine quadruplex is intercalated between two guanine tetrads, while the sandwich complexes of lithium and sodium are not the optimal structure.

**Conclusions.** Together with ion size and hydration, the electrostatic potential of the sandwich guanine tetrads influence the structural and energetic properties of the cation binding stacked guanine tetrads.

**Keywords.** Guanine tetrad; sandwich model; density functional theory; DFT; cation.

### Abbreviations and notations

BSSE, basis set superposition error	HF, Hartree-Fock
DFT, density functional theory	NBO, natural bond orbital
G4, guanine tetrad	

# Dedicated on the occasion of the 65<sup>th</sup> birthday to Danail Bonchev.

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## 1 INTRODUCTION

Guanine-rich oligonucleotides are inhibitors for fibrinogen action in thrombin and HIV viral mediated cell fusion [1]. Guanine-rich sequences, which exist in telomeres [2] at the ends of linear chromosomes, can form G tetrads where multiple guanines are organized around a central cation in a four-stranded structure [3]. As telomere maintenance mechanisms and the transcriptional regulation of oncongen expression are of potential importance for drug design, G-quadruplexes have been proved to be potentially important targets in drug development, and G-quadruplex-based inhibitors of telomerase may be relevant to cancer therapy [4,5]. In the presence of specific monovalent (Na<sup>+</sup>, K<sup>+</sup>, and Rb<sup>+</sup>) or divalent metal cations (Mg<sup>2+</sup>, Ca<sup>2+</sup>, Ba<sup>2+</sup> and Sr<sup>2+</sup>), guanine-rich sequences can form stable G-quadruplex DNA structures [6,7], presumably by coordination with eight carbonyl oxygen atoms present between stacked tetrads. However, it is also known that Na<sup>+</sup> and K<sup>+</sup> stabilize different G-tetrad structures in telomere sequences [8–10]. The experimental studies have shown that the metal cations were very close to the axis, ions with large radii like K<sup>+</sup> are located in the cavity between two tetrads, whereas ions with smaller radii like Na<sup>+</sup> may be located either in the central cavity of a single tetrad or each guanine O6 atom in the DNA structure is shared by two Na<sup>+</sup> ions above and below the G-tetrad plane [9]. On the other hand, the solvation energies of cations have to be taken into account for the cation selectivity of tetrads by many researchers [10–12].

G-tetrads are structure subsets of G-quadruplex and have attracted considerable interests in both theoretical [11–17] and experimental [18,19] chemistry. The increasing availability of three-dimensional structures [20–22] has greatly improved our understanding of the G-tetraplex function, and molecular dynamics simulation [23,24] has also been a complementary tool to experimental methods. However, most of the theoretical work is focused on the single guanine and cation while the sandwiched structure G<sub>4</sub>-M<sup>+</sup>-G<sub>4</sub> has been infrequently studied [25,26]. In our previous work [27], the interactions between one guanine tetrad and metal cations (Na<sup>+</sup>, K<sup>+</sup>) have been studied and one of the reasons leading to the difference between theoretical and experimental outcomes may be that in vivo the cation may also be positioned intercalated between two stacked guanine tetrad and this is different from calculation. Therefore, in this paper, we want to supplement previous theoretical studies of the interaction between G-tetrad and alkali metal cations.

## 2 MATERIALS AND METHODS

Meyer and coworkers [26] have studied G-tetrad sandwich complexes with Na<sup>+</sup> and K<sup>+</sup> ions at four symmetries and they found out that such complexes are most stable at S<sub>8</sub> symmetry. Therefore, in this paper, the initial structure of G<sub>4</sub>-M<sup>+</sup>-G<sub>4</sub> has been arranged to have S<sub>8</sub> symmetry. The metal ions intercalate between the two stacked guanine tetrads, thus make “sandwich” models.

Conventional *ab initio* and DFT methods have been used to predicate the interactions between nucleic acid bases [28–31] and they can get data that are not available by experiments, such as information about the interaction energies and cooperative effects. Even base tetrad is relatively large systems for *ab initio* calculations with inclusion of electron correlation. Therefore, such calculations are limited to small fragments without considering environment. DFT method has proved to be successful in the close agreement between calculated and experimental geometrical parameters and less time-consuming than *ab initio* methods. Thus we use DFT method in most of our calculation.

The sandwich models G4–M<sup>+</sup>–G4 have been fully optimized using HF method and DFT method at 6–31G(d) level. The three DFT methods used are B3LYP, B3P86 and B3PW91, as implemented in Gaussian 03 package, which is a linear combination of Hartree–Fock exchange, Slater exchange and B88 gradient-corrected exchange with the correlation functionals of Lee, Yang and Parr (LYP), Perdew (P86), Perdew and Wang (PW91), respectively. To test the reliability of 6–31G(d) basis set, optimization has been performed on G4–Na<sup>+</sup>–G4 with larger basis set, 6–31G(d, p). The total binding energy has been defined as the energy difference between the sandwich complex and the sum of the monomers,

$$\Delta E = E [\text{G4–M}^+\text{–G4}] - 2E [\text{G4}] - E [\text{M}^+]$$

Basis set superposition error (BSSE) have been evaluated using the counterpoise method of Boys and Bernadi [32].

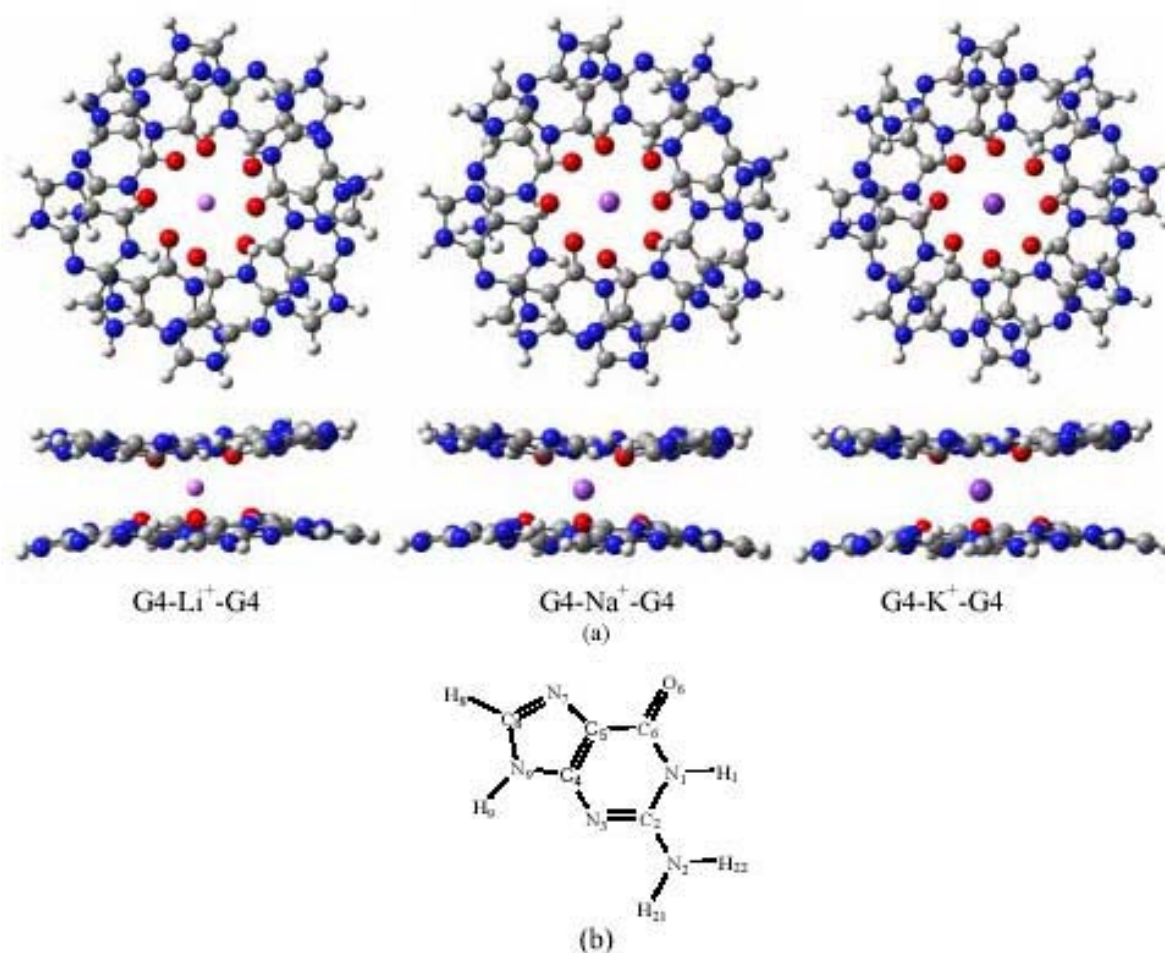
### 3 RESULTS AND DISCUSSION

The structures of G4–M<sup>+</sup>–G4 are depicted in Figure 1. The selected geometrical parameters at different levels are listed in Table 1 and the energy properties are in Table 2. The electrostatic potential maps are shown in Figure 2. Previous theoretical studies of the structure of the ‘sandwich’ model have been performed using HF/6–31G(d,p) method and the outcomes are also listed in Table 1. The crystal diffraction data with 1.2 Å resolution have been used to be compared with. Due to the fact that the experiments could only detect the positions of heavy atoms, the selected bond distances of the two types hydrogen bonds is that of O6...(H1)–N1 and N2–(H22)...N7.

#### 3.1 Geometries

The structure of guanine tetrad in the complex is similar with that in the co-plane model [27], while slightly twisted from the side view. DFT method with small basis set such as 3–21G(d) did not give accurate geometrical parameter, and the hydrogen bond distances are too short compared with those obtained using HF method and DFT method with larger basis set and those from experiment. At HF level with 6–31G(d) basis set, the distances between cations and O6 atoms of

guanine are 2.763 Å for lithium, 2.803 Å for sodium and 2.934 Å for potassium, while the corresponding parameters calculated by B3LYP method at 6–31G(d) level are 2.684 Å for lithium, 2.729 Å for sodium and 2.851 Å for potassium, respectively. The results of other two DFT methods are slightly different from B3LYP method. The X-ray crystallography results [33] of the Na<sup>+</sup>-O6 distance is 2.78 Å for the G4(2) plane and the two hydrogen bond distances of O6...(H1)-N1 and N2-(H22)...N7 for the G4(2) plane are 2.86 Å and 2.85 Å respectively. HF method doesn't include electron correlation and might underestimate the H-bonding interaction, thus lead to long hydrogen bond. The three DFT methods obtained similar bond distances as that from X-ray crystallography, which suggests that DFT methods are suitable for calculations of this type of complexes.



**Figure 1.** (a) The optimized geometries of G4-M<sup>+</sup>-G4 complex at B3LYP/6–31G(d) level (from top view and side view). (b) The atom labels of guanine.

From Table 1 it could be seen that with the increasing of the atom number, the M...O6 distance and the two hydrogen bond distances in guanine tetrads have all elongated. That is to say, as the atom number increases, the cation radius increases, which makes the sandwich structure less compact.

**Table 1.** Selected geometrical parameters of G4–M<sup>+</sup>–G4 complexes at different level

parameters	HF	HF	B3LYP	B3P86	B3PW91	B3LYP	B3LYP	B3P86	B3PW91	Exp <sup>b</sup>	
	B1	B2 <sup>a</sup>	B3	B3	B3	B1	B2	B1	B2		
Li	M...O6	2.763		2.553	2.530	2.570	2.684		2.641	2.686	
	O6...(H1)–N1	2.961		2.714	2.672	2.694	2.863		2.821	2.853	
	O6...H1	1.966		1.683	1.632	1.656	1.849		1.805	1.838	
	N2–(H22)...N7	2.994		2.764	2.726	2.737	2.888		2.843	2.864	
	N7...H22	2.001		1.717	1.673	1.686	1.862		1.815	1.838	
Na	M...O6	2.803	2.791	2.621	2.602	2.648	2.729	2.719	2.688	2.750	2.78
	O6...(H1)–N1	2.972		2.720	2.678	2.703	2.868	2.852	2.828	2.865	2.86
	O6...H1	1.974	1.971	1.684	1.635	1.661	1.851	1.834	1.809	1.847	
	N2–(H22)...N7	3.006		2.790	2.752	2.759	2.905	2.885	2.862	2.883	2.85
	N7...H22	2.015	2.005	1.745	1.702	1.712	1.882	1.862	1.836	1.859	
K	M...O6	2.934	2.927	2.750	2.726	2.807	2.851		2.806	2.905	
	O6...(H1)–N1	2.987		2.735	2.689	2.723	2.881		2.839	2.877	
	O6...H1	1.983	1.979	1.696	1.644	1.679	1.859		1.814	1.855	
	N2–(H22)...N7	3.083		2.836	2.792	2.788	2.950		2.905	2.914	
	N7...H22	2.071	2.066	1.796	1.746	1.745	1.932		1.885	1.895	

<sup>a</sup> From Ref [11].

<sup>b</sup> Taken from the Protein Data Bank with the code 244D and the parameters are those of the fourth guanine tetrad[33]. The data were obtained using X-ray diffraction method with the resolution 1.2 Å.

<sup>c</sup> All bond lengths and bond distances are in angstrom. B1 is the abbreviation of 6–31G(d) basis set and B2 is 6–31G(d,p) while B3 is 3–21G(d) basis set.

Considering that the hydrogen polarization may have important effect on the H–bonding system, the G4–Na<sup>+</sup>–G4 system have been also calculated at B3LYP level with 6–31G(d,p) basis set and the obtained geometrical parameters are also shown in Table 1. From the results we could see that adding polarization functional affects the geometry of the ‘sandwich’ model slightly and the differences of bond distances are no more than 0.02 Å, which implies that DFT method with 6–31(d) basis set is enough to predict reliable geometrical results.

Among the three DFT method, B3P86 obtain the shortest M...O6(G) distance while B3PW91 obtain the longest one. As to the two hydrogen bond distances of O6...(H1)–N1 and N2–(H22)...N7, it turns to be that B3LYP method predicts the longest bond distance while B3P86 method predicts the shortest bond distance.

### 3.2 Stabilization Energies

The interaction energies calculated using HF/6–31G(d) method are –123.70 kcal/mol, –119.80 kcal/mol and –106.32 kcal/mol for Li, Na, and K, respectively, which are much higher than the corresponding value of the DFT method and suggest that electron correlation is important in determining the energetic properties of intermolecular interaction systems.

Table 2 listed the BSSE corrected energies of Gu *et al.* [11], the difference between their results at HF/6–311G(d) level and ours at HF/6–31G(d) level are minor and no more than 10 kcal/mol, which also suggests that 6–31G(d) basis set are enough to obtain reliable results for such system. B3LYP method with 6–31G(d) and 6–31G(d,p) basis sets obtained similar interaction energies for G4–Na<sup>+</sup>–G4 complex and the difference is only 0.25 kcal/mol, which further confirms that adding

polarization functional to hydrogen affects the interaction energy of this system slightly and B3LYP/6–31G(d) method is suitable for such system.

The G4-M<sup>+</sup>-G4 interaction energies (with and without BSSE corrected) at different levels are summarized in Table 2. The G4-M<sup>+</sup>-G4 interaction energy with BSSE amounts to –124.51 kcal/mol for the lithium complex, –118.83 kcal/mol for the sodium complex and –103.67 kcal/mol for potassium complex at BLYP/6–31G(d) level, while those without BSSE are –147.32 kcal/mol, –141.73 kcal/mol and –124.69 kcal/mol for Li, Na and K, respectively. Thus we can see that BSSE is large in such system and cannot be left uncorrected. The other two DFT methods calculated at 6–31G(d) level showed a little higher stabilization energies as compared with the B3LYP method.

**Table 2.** Energy properties of G4-M<sup>+</sup>-G4 complexes at different level

		HF	HF	B3LYP	B3LYP	B3P86	B3PW91
		6–31G(d)	6–311G(d,p) <sup>a</sup>	6–31G(d)	6–31G(d,p)	6–31G(d)	6–31G(d)
Li	$E_{\text{total}}$	–4322.8153908		–4348.1719218		–4359.4334557	–4346.5279170
	$\Delta E$	–123.70		–147.32		–141.98	–135.04
	$\Delta E_{\text{BSSE}}$	–108.57		–124.51		–123.37	–117.80
				(–28.04) <sup>b</sup>			
Na	$E_{\text{total}}$	–4477.2329178	–4478.2787488	–4502.9597031	–4503.0836871	–4514.3636152	–4501.2792684
	$\Delta E$	–119.80		–141.73	–141.98	–134.92	–128.25
	$\Delta E_{\text{BSSE}}$	–104.63	–110.71	–118.83		–116.27	–112.26
				(–34.44)			
K	$E_{\text{total}}$	–4914.5241186	–4915.6006445	–4940.5763030		–4952.1545338	–4938.8848696
	$\Delta E$	–106.32		–124.69		–117.94	–112.91
	$\Delta E_{\text{BSSE}}$	–92.84	–97.48	–103.67		–100.32	–99.69
				(–62.13)			

<sup>a</sup> Single point energy calculated at HF/6–311G(d,p) level on the HF/6–31G(d,p) optimized geometry from Ref [11].

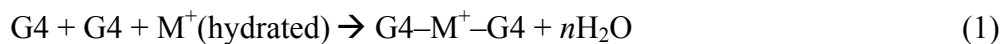
<sup>b</sup> The values in parentheses are hydration corrected stabilization energies.

<sup>c</sup> Total energies are in a.u. and binding energies in kcal/mol.

The binding preference between the cations and the guanine tetrads in the tetraplexes follows the Li<sup>+</sup> > Na<sup>+</sup> > K<sup>+</sup> order, *i.e.*, small alkali ions attract the base O6 atoms in an extraordinarily strong manner and smaller ions are more tightly bonded to guanine tetrads, which indicates the domination of electrostatic interaction in the G4-M<sup>+</sup>-G4 systems.

However, the stabilization sequence from experiments is K<sup>+</sup> > Na<sup>+</sup> > Li<sup>+</sup> [34]. The calculated energy results are not in accord with that of experiment, which may be because the environment around the ‘sandwich’ model is more complex than we could consider in calculation. The experiments are carried out in aqueous solutions, while what we calculated are in gas phase. In aqueous solutions, the smaller ions also have a larger affinity for water molecules except for guanine tetrad and the balance between these two opposing trends decides the binding sequence [10].

The hydration effect of the cations must be considered and we carried out hydration energy correction on G4-M<sup>+</sup>-G4 system according to the following equation:



$$\Delta E(1) = \Delta E(2) - \Delta E(3)$$

At room temperature the hydration free energies of  $Li^+$ ,  $Na^+$  and  $K^+$  calculated using PCM method at B3LYP/6–31G(d) level are  $-96.47$ ,  $-84.39$  and  $-41.54$  kcal/mol, respectively. After the hydration correction, the stabilization energies of the sandwich cation–G–tetrad complexes are  $-28.04$ ,  $-34.44$  and  $-62.13$  kcal/mol for  $Li^+$ ,  $Na^+$  and  $K^+$  respectively. Consequently, the stability sequence changed to  $K^+ > Na^+ > Li^+$ , which reproduces the experimental ion selectivity.

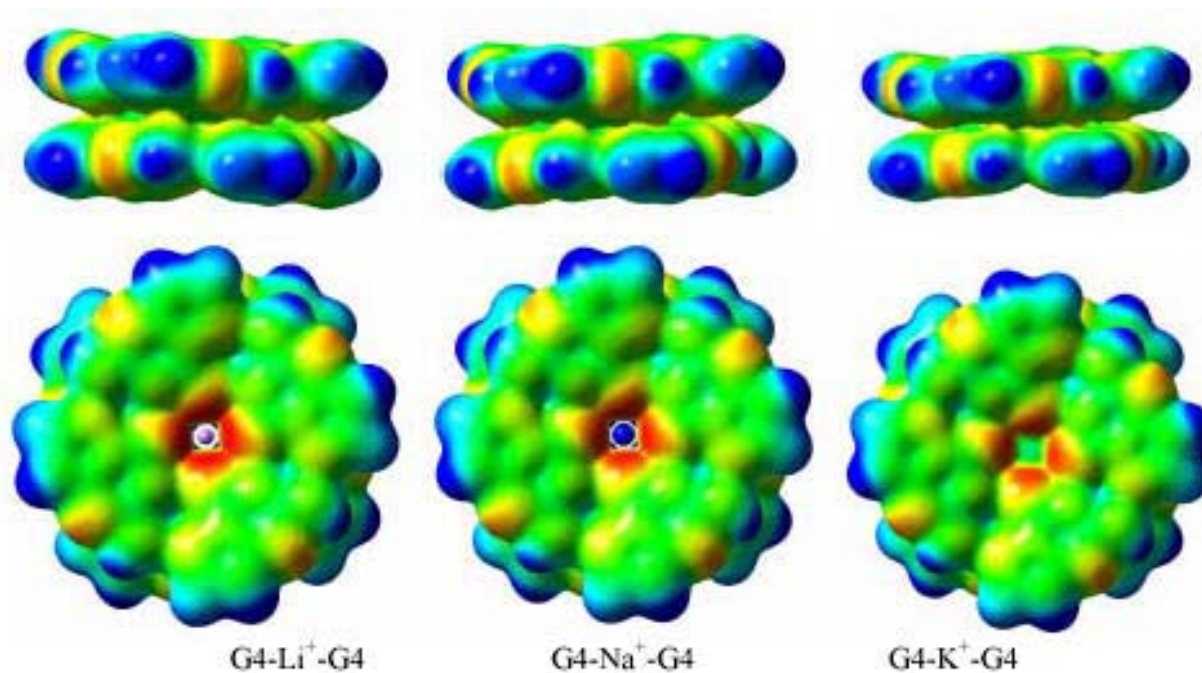
In addition, the model we proposed only includes the guanine base groups and the ribose and phosphate groups are excluded due to the calculation limits, which is quite different from *in vivo*. Although stacking interactions between guanine bases and ion–dipole interaction between ions and carbonyl groups may be important in stabilizing the sandwich structure, chelation of cations with phosphate groups is also essential [35]. Last, the calculated system only includes two stacked guanine tetrads, while usually several G–tetrads are stacked together, with the tetrads over and under the G–tetrad also influence the system.

### 3.3 Electronic structures, charge distributions and electrostatic potential maps

Natural Bond Orbital (NBO) analysis shows that instead of the formal charge of +1 for the alkali ions, there is a much lower positive charge on the cations in the complex and the bases lose negative charge, *i.e.*, it is 0.856, 0.850 and 0.870 e for Li, Na, and K, respectively. Charge transfer from the cations to the base monomers in the three alkali and guanine tetrads complexes is slightly different from each other, therefore charge transfer is not the major reason controlling the stability of the sandwich complexes.

The components of HOMO and LUMO orbitals of the three complexes are alike. The HOMO orbital consists of  $p_z$  orbitals of C2, N3, C4, C5, N7 and C8 atoms, and  $s$  orbitals of N2 and O6 atoms, while the LUMO orbital is mainly made up of the  $s$  orbitals of C4, C5, C6, O6, N7 and C8 atoms.

The ESP maps of the three complexes (Figure 2) from side view are alike, the electron density of the two stacked guanine tetrads overlap and this indicates that the base stacking plays a certain role in stabilizing the sandwich complexes. The overlap of the two guanine tetrads from the side view also explains why the stacked tetrads are not perturbed. The electrostatic potential maps of the  $G4-M^+-G4$  complexes reveal a significant electron density distribution difference of Li, Na and K ions complexes.



**Figure 2.** Electrostatic potential of G4-M<sup>+</sup>-G4 (M = Li, Na and K) complexes mapped onto the surface of the electron density of 0.002 unit (side view and top view). The blue line represents the positive part of the electrostatic potential, and the red line is the negative part. The contour spacing is 0.12 au for the positive part and 0.01 au for the negative part. Electrostatic potential of the G4-M<sup>+</sup>-G4 (M = Li, Na and K) complexes are mapped onto the surface of the electron density of 0.002 unit.

As the ESP is mapped onto the electron density isosurface, the empty space around the Li<sup>+</sup> and Na<sup>+</sup> in the cavity of the complexes suggests no electron density and thus no orbital interaction between these two cations and the surrounding O atoms of guanines. On the other hand, the filled space on the central cavity of the G4-K<sup>+</sup>-G4 complex clearly illustrates the non-negligible distribution of the electron density on the outer orbitals of K<sup>+</sup>. Thus, the interaction between K<sup>+</sup> and the G-tetrads is further intensified by this orbital interaction. The difference between the Li and Na complexes is that there exists positive electron density around the Na atom while not for Li atom. The situation of Na<sup>+</sup> is between those of Li<sup>+</sup> and K<sup>+</sup>, thus Na<sup>+</sup> may be situated either in the center of one G-tetrad or in the sandwich position of two G-tetrads, which is in accord with that of Louit [36]. It has been shown that ions with small radii like Li<sup>+</sup> inhibit the self-association guanosine gels [34].

## 4 CONCLUSIONS

Sandwich complexes G4-M<sup>+</sup>-G4 (Li<sup>+</sup>, Na<sup>+</sup> and K<sup>+</sup>) have been studied using three DFT methods at 6-31G(d) level in this paper and the geometries, energies and electronic structures have been discussed in detail. The results show that the three structures have alike properties. The complex becomes more and more stable as from Li to K, while after considering hydration effect the stability sequence changes to a quite reverse sequence. The ESP map shows that the electron density

between the ion and the O atoms of guanines increases as from Li to K, which may be the explanation that the K complexes is the most stable complex of the three. From the discussion we could conclude that together with ion size and hydration, electrostatic potential of the sandwich guanine tetrads also affect the structural and energetic properties of cation binding stacked guanine tetrads.

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