6308 J. Phys. Chem. A 2000, 104, 6308−6313

A Remarkable Alteration in the Bonding Pattern: An HF and DFT Study of the Interactions between the Metal Cations and the Hoogsteen Hydrogen-Bonded G-Tetrad

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Received: February 14, 2000; In Final Form: April 25, 2000

The HF and DFT levels of theory were applied to study the interaction between monovalent cations and guanine tetrads. The calculations reveal that cation−guanine-tetrad complexes adopt the normal four-stranded Hoogsteen-bonded G-tetrad structure, and no bifurcated hydrogen bonds which stabilize the noninteracting G-tetrads were found. The gas-phase binding sequence between the monovalent cations and the G-tetrad complexes follows the order $Li^+ > Na^+ > K^+$. After the hydration correction, the stability sequence of the monovalent cation−guanine-tetrad complexes in aqueous solutions follows the trend $K^+ > Na^+ > Li^+$. The preferential binding of potassium over sodium and sodium over lithium in water solutions reproduces the experimental ion selectivity of the guanine tetraplex. In addition, the weak stabilization energy of the K^+−G-tetrad in the coplanar form is consistent with the fact that the potassium cation tends to locate between two successive tetrads. The results of this study justify the conclusion of Hud et al. that the ion selectivity exhibited by the guanine tetraplexes in water solutions is dominated by the relative free energies of hydration. While the experimental measurement of the cation−oxygen distances in the sodium ion complex that is coplanar with the guanine tetrad in the crystal of a parallel-stranded guanine tetraplex (2.34 ± 0.02 Å) has been successfully reproduced at the HF level (2.331 Å), the slightly shorter Na^+−O6 distance and the significant decrease in the hydrogen bond lengths predicted by the DFT approach suggests an overestimation of the hydrogen bonding in the guanine tetrad by this method.

Introduction

Guanine-rich oligonucleotides are known to be inhibitors for fibrinogen action in thrombin and HIV viral mediated cell fusion.[1−5] The formation of the Hoogsteen-bonded guanine tetrads leads to novel four-stranded structures[6−10] in guanine-rich oligonucleotides such as d(T2G4) found in *Tetrahymena* telomeric DNA, d(T4G4) in *Oxytricha*, d(T2G3) in human, and d(T3AG3) in *Arabidopsis*.[11−14] A number of proteins have been identified to process specific binding to the G-tetraplex structures.[15,16] G-tetraplexes have been postulated to be crucial for dimerization of HIV RNA.[17]

It has been found that the existence of interactions with a metal ion is essential in the formation of the G-tetrad complexes.[18−24] Recent studies have also demonstrated the function of the ammonium ion in stabilizing the G-tetraplex.[25] Physicochemical studies of the G-tetraplex structures have revealed that the stability and conformation of the tetraplexes depend on the type of cation presented. Monovalent cations stabilize the tetraplexes in the order $K^+ > Na^+ > Li^+$.[20,21,26] On the basis of experimental observations, the preferential binding of K^+ versus Na^+ or Li^+ in guanine tetraplexes has been proposed to be governed by an optimal fit of this cation between the two guanine tetrads.[9,27] However, this optimal fit hypothesis has been challenged. Using the free energy perturbation calculation method, Ross and Hardin investigated the origin of the ion selectivity of the G-tetrads. They concluded that the "optimal fit" does not explain the Na^+/K^+ selectivity.[18] Later, the thermodynamic analysis by Hud et al. suggests that the preferred coordination of K^+ over Na^+ in d(G3T4G3) is actually dominated by the relative free energy of hydration.[28]

Our recent ab initio study of the molecular structure of the G-tetrad without the presence of cations has shown that instead of the normal four-stranded Hoogsteen-bonded G-tetrad structure, the G-tetrad is stabilized by bifurcated hydrogen bonds.[29] To understand how the different types of cation influence the structure of the G-tetraplex, it is necessary to investigate their interactions with the G-tetrad. One way to determine whether an ion provides the best fit for a host is to examine the change in the host structure caused by the interaction of the ion. This kind of change in the G-tetrad can only be directly predicted through reliable theoretical calculations. In addition, a solvent can influence the properties of the G-tetrad. Recent studies indicate the crucial role of water in stabilizing the proton transfer in guanine[30] and in changing the molecular geometries of guanine−cytosine complexes.[31]

Previous theoretical studies of the structure of the G-tetrads and metal cations complexes have been performed using the molecular mechanics (MM) and the molecular dynamics methods (MD)[32−35] in which the classical empirical potentials depend on the atom−atom pairwise additivity and cover only electrostatic, dispension, and repulsion contributions. The ab initio studies of trimers of DNA bases have demonstrated the importance of the noadditivity of the interaction in the H-bonded triads of nucleobases.[36] Besides, the drastic and different approximations for varied potential models are introduced in the MM calculations, and the calculated properties of nucleobases are known to be force-field dependent.[37,38]

In this study quantum chemistry ab initio calculations were applied to investigate the interactions between the monovalent

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10.1021/jp000591f CCC: $19.00

cations and the G-tetrads. Our attention is focused on the following aspects: (1) How do different cations change the structure of the G-tetrad? (2) What is the stabilizing sequence of the monovalent cations of Li, Na, and K of the cation−G-tetrad complexes? and (3) What is the origin of the ion selectivity of the guanine-tetrad? The details of these phenomena could only be revealed by accurate quantum chemistry computational studies. Because of the relatively large size of such a system, no reliable ab initio theoretical studies of the energy minimum structure of the metal ion and G-tetrad complex have been reported so far.

Calculation Methods

The Hartree−Fock self-consistent-field (HF−SCF) method and the density functional theory (the B3LYP approach)[39−41] in conjunction with the valence triple-ζ basis set augmented with d and p-like polarization functions[42] (6-311G(d,p)) was used to ensure a correct description of the H-bonded system. The basis sets used for the cations are the double-ζ basis plus one set of d-functions and was derived by Ahlrichs et al.[43] The number of basis functions in the studied systems varies from 927 (G4-Li) to 1850 (G4-K-G4). Our previous studies of hydrogen-bonded systems involving DNA bases have shown that the B3LYP approach, which covers the electronic correlation effects, predicts reliable interaction energies and is compatible with the MP2/6−31(d,p) method.[44,45] The HF method was used because in a comparison study of mixed DNA base tetrads, we have found that the DFT approach might overestimate the H-bonding interaction between DNA bases, resulting in an H-bond length that is too short.[46] The Gaussian-94 software[47] was used in the calculations.

The energy minimum structures of the cation−G-tetrad complexes were located both at the HF and the B3LYP levels by the analytic gradient techniques. Their calculated interaction energies were corrected for the basis set superposition error (BSSE).[48]

Although the nonplanar initial structures and the NOSYMMETRY key word were used in the calculations, D_4 symmetry was revealed during the optimization for all of the three cation−G-tetrad coplanar structure complexes.

Results and Discussion

Geometry. The optimized structures of the cation−guanine-tetrad coplanar complexes are depicted in Figures 1−3. The guanine tetrad without the presence of cations has also been optimized at the B3LYP/6-311G(d,p) level of theory. The DFT and HF level structural parameters of the G-tetrad are given in Figure 4 for comparison.

At the HF level, the distances between the cations and the O6 atoms of the guanines are calculated to be 2.173 Å for lithium, 2.331 Å for sodium, and 2.600 Å for potassium. The corresponding values are 2.150, 2.301, and 2.557 Å at the DFT level, respectively. The HF level result for the Na^+−G-tetrad complex is in excellent agreement with the experimental measurement of the molecular structure of the sodium ion coplanar with the guanine tetrad in the crystal of a parallel-stranded guanine tetraplex (2.34 ± 0.02 Å).[23] DFT predictions of the molecular parameters are close to the HF values. Our discussion will focus on the HF results and will leave the comparison between the DFT and HF results for later sections.

The striking change compared to the bifurcated hydrogen bond structure of the G-tetrad without the presence of a cation is that in the presence of a cation the guanine-tetrad adopts the normal four-stranded Hoogsteen-bonded G-tetrad structure. The hydrogens of the amino group in guanine form strong H-bonds with the N7 atoms of the other guanine monomers ($R_{N\cdots H}$ = 1.928 Å for the Li^+−G-tetrad, 2.021 Å for the Na^+−G-tetrad, and 2.236 Å for the K^+−G-tetrad complex). No bifurcated hydrogen bonds are formed. In addition, the hydrogen bond between the O6 and the H at N1 is not affected by the presence of Li^+ or Na^+. These hydrogen bond lengths are 2.040 Å for Li^+ and 2.042 Å for the Na^+−G-tetrad, which is very close to that of the G-tetrad (2.039 Å). It is slightly elongated in the K^+−G-tetrad complex (2.116 Å), approximately an 0.08 Å increase predicted at the HF level. As found in the previous study, to balance the interactions among the oxygen atoms in the central part of the G-tetrad, which repel each other due to the electrostatic interactions, the tetrad adopts the bifurcate H-bond form.[29] The effect of the cations in alterating the

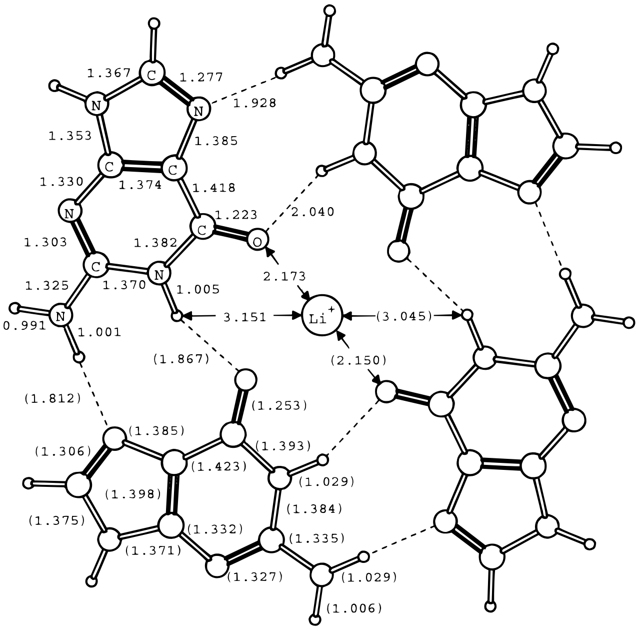

Figure 1. Optimized structure of the Li^+−G-tetrad complex. Values without parentheses are optimized at the HF level. Values in parentheses are optimized at the B3LYP level. Atomic distances in Å.

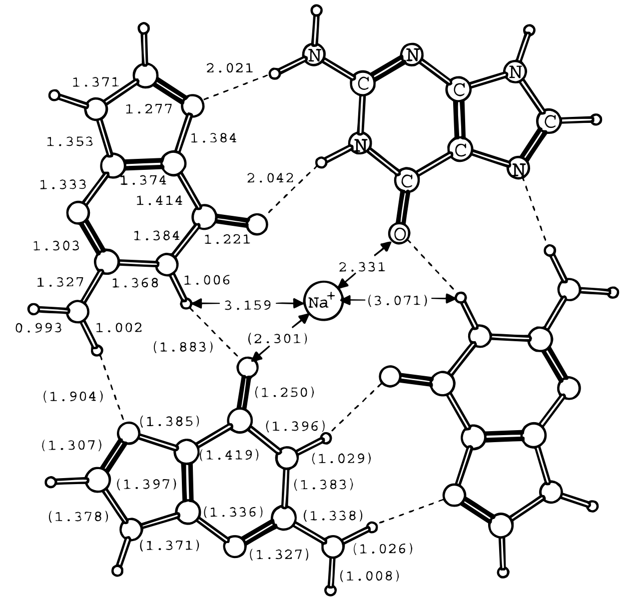

Figure 2. Optimized structure of the Na^+−G-tetrad complex. Values without parentheses are optimized at the HF level. Values in parentheses are optimized at the B3LYP level. Atomic distances in Å.

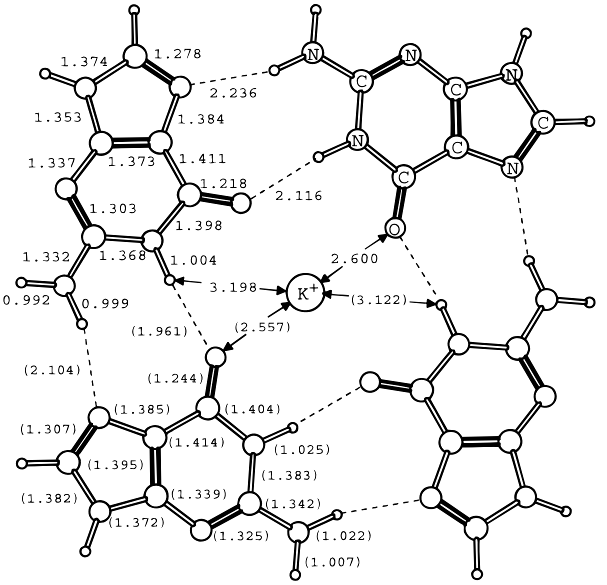

Figure 3. Optimized structure of the K$^+$−G-tetrad complex. Values without parentheses are optimized at the HF level. Values in parentheses are optimized at the B3LYP level. Atomic distances in Å.

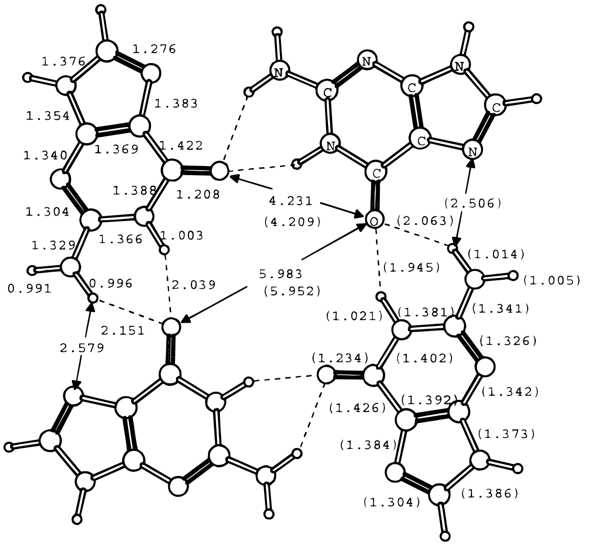

Figure 4. Optimized structure of the G-tetrad. Values without parentheses are optimized at the HF level. Values in parentheses are optimized at the B3LYP level. Atomic distances in Å.

TABLE 1: Energy Properties of the Coplanar Cation−Guanine-Tetrad Complexes Evaluated at the HF/6-311G(d,p) and B3LYP/6-311G(d,p) Levels[a]

	Li$^+$−G-tetrad	Na$^+$−G-tetrad	K$^+$−G-tetrad
	In Hartree		
E^{I}	−2165.64362	−2320.03958	−2757.33111
	−2178.40009	**−2333.16660**	**−2770.78930**
E^{II}	−2158.17705	−2158.19384	−2158.20502
	−2170.89188	**−2170.90506**	**−2170.90981**
E^{III}	−7.23612	−161.65892	−599.001653
	−7.28576	**−162.08160**	**−599.761002**
E^{IV}	−2158.22090	−2158.22170	−2158.22182
	−2170.91489	**−2170.91593**	**−2170.91605**
	In kcal/mol		
$E^{\mathrm{I}} - E^{\mathrm{III}} - E^{\mathrm{IV}}$	−117.1	−99.8	−67.5
	−125.2	**−106.1**	**−70.4**
$E^{\mathrm{IV}} - E^{\mathrm{II}}$	−27.5	−17.4	−10.6
	−14.4	**−6.8**	**−4.0**

[a] Basis sets for metals are DZP of Ahlrichs et al.[43] The bold numbers are B3LYP results. E^{I}: Total energy of the optimized cation−guanine-tetrad complexes. E^{II}: Energy of the guanine tetrad with the geometry of the optimized cation−guanine-tetrad complex while the cation basis set is kept in the calculation. E^{III}: Energy of the cation within all guanine-tetrad basis sets kept in the calculation. E^{IV}: Energy of the optimized guanine tetrad with the cation basis set added in the center.

G-tetrad structure is clearly through a neutralization of the significant concentration of the negative charges in the central area of the G-tetrad.

The size of the cations influence the structural parameters of the cation−G-tetrad complexes. The diagonal O6 distances increase from 4.356 Å for lithium to 4.662 Å for sodium and 5.200 Å for potassium. Also, the hydrogen bonds are weakened following the increase in the size of the cations. The O6−H and the N7−H bond lengths are 2.040 and 1.982 Å in the Li$^+$−G-tetrad and 2.042 and 2.021 Å in the Na$^+$−G-tetrad complex. More pronounced changes are predicted for the K$^+$−G-tetrad complex where these two bond lengths increase to 2.116 and 2.236 Å, respectively. It seems that a smaller cation leads to better H-bonding which is especially obvious in the case of the N7−H bond. This effect can be interpreted as the domination of electrostatic interaction between the cation and the O6 atom of guanine. The high charge density in the small Li$^+$ cation results in a stronger electrostatic attraction. Also, a smaller cation leads to a larger structural change in the G-tetrad, as can be seen in the figures. Even the lengths of the O6−C6 bond of the guanine molecules increases as the radius of the cation decreases. At the HF level, $R_{\mathrm{O6-C6}}$ is 1.218 Å for the K$^+$−G-tetrad complexes, 1.221 Å for Na$^+$, and 1.223 Å for Li$^+$. This larger structural distortion is also followed by a larger change in energy (see below).

In general, the B3LYP approach predicts a longer bond length than the HF method for DNA bases. Following this trend, the bond lengths inside the guanine molecules are about 0.02 Å longer at the B3LYP level. However, the intermolecular bond lengths obtained at the DFT level are much shorter than those predicted by the HF method. In the absence of cations, two O6−H distances amount to 1.945 Å and 2.063 Å at the DFT level, about 0.1 Å shorter than those obtained from the HF prediction. The lengths of the DFT level hydrogen bonds of O6−H amount to 1.961 Å in the K$^+$−G-tetrad, 1.883 Å in the Na$^+$−G-tetrad, and 1.867 Å in the Li$^+$−G-tetrad. The corresponding bond lengths predicted by the HF method are equal to 2.116, 2.042, and 2.040 Å, respectively, and are greater by approximately 0.15 Å. The DFT method also predicts the N7−H bonds to be approximately 0.12 Å shorter in the cation−guanine-tetrad complexes. It is reasonable to believe that the slightly shorter cation−O6 distances predicted at the DFT level are due to the stronger hydrogen bonding. Because the HF method reproduces the sodium−oxygen distance accurately, the short Na$^+$−O6 distance predicted by the DFT method might be interpreted as an overestimation of the strengths of the hydrogen bonding in the guanine tetrad.

To explain the preference for K$^+$ over Na$^+$ and Li$^+$ in the tetraplexes, it has been suggested that the potassium cation may increase the electron delocalization in the guanine aromatic system and enhance the inner hydrogen bonding.[18] The changes in the O6−H bond length suggest that the presence of a cation does enhance the hydrogen bonding. However, this enhancement does not support the ion selectivity of the guanine tetraplexes. The small Li$^+$ cation induces the shortest inner hydrogen bonds.

Energetic Properties. The calculated energies of the studied systems are summarized in Table 1. The interaction energies of the cations with the G-tetrad are calculated as the energy difference between the energy of the cation−G-tetrad complex and that of the cation and the optimized G-tetrad ($\Delta E = E^{\mathrm{I}} - E^{\mathrm{III}} - E^{\mathrm{IV}}$). To account for the basis set superposition errors, the BSSE corrections were included in the energies of both cations (E^{III}) and the optimized guanine tetrad (E^{IV}). The interaction energies of the systems are quite sizable, as shown in the table. The lithium cation, which has the smallest size, has the biggest ΔE (−125.2 kcal/mol at the DFT and −170.6 kcal/mol at HF levels). The Na^+−G-tetrad is about 19.1 kcal/mol (17.3 kcal/mol at the HF level) less stable than the Li^+−G-tetrad. The stabilization energy of the coplanar K^+−G-tetrad complex is 35.7 kcal/mol lower than the Na^+−G-tetrad and 54.8 kcal/mol lower than Li^+−G-tetrad at the DFT level. Similar results are predicted by the HF method. The corresponding stabilization energy differences are 32.3 and 49.6 kcal/mol. It is clear that these kinds of trends are consistent with the changes in the hydrogen bonding, as discussed above. Therefore, the gas-phase binding order between the monovalent cations and the G-tetrad in the coplanar complexes is $\mathrm{Li}^+ > \mathrm{Na}^+ > \mathrm{K}^+$.

Interestingly, in a water solution, a dramatic change of binding preferences is observed in the experiments.[20,21,26] The stabilization sequence follows the order $\mathrm{K}^+ > \mathrm{Na}^+ > \mathrm{Li}^+$.

The observed changes can be explained by taking into consideration all factors responsible for establishing water−solute equilibria. First, it should be noted that although the smaller ions are tightly bonded to the guanine-tetrad in the gas phase, they also have a larger affinity for water molecules. In a water solution, the smaller cations such as Li^+ are much better solvated by the solvent. The transfer of the smaller cations from water into the guanine strands requires overcoming the higher energy barrier. The tradeoff between these two opposing processes may change the binding sequence. At room temperature the hydration free energies of K^+, Na^+, and Li^+ are −80.6, −98.2, and −122.1 kcal/mol, respectively. The corresponding enthalpies are −76.7, −96.9, and −123.0 kcal/mol.[49] After the hydration correction, the stabilization energies of the coplanar cation G-tetrad complexes at the HF level amount to 5.9 kcal/mol for Li^+, −2.9 kcal/mol for Na^+, and 11.2 kcal/mol for K^+. At the DFT level, these values are −2.2 kcal/mol, −9.2 kcal/mol, and 6.3 kcal/mol, respectively. Consequently, the stability order of the coplanar monovalent cation−guanine-tetrad complexes in aqueous solution should be $\mathrm{Na}^+ > \mathrm{Li}^+ > \mathrm{K}^+$.

The ion selectivity of the guanine tetrad in the coplanar form can be evaluated according to the free energies of the following process:

$$\mathrm{K}^+\text{−G-tetrad} + \mathrm{Na}^+\,(\text{hydrated}) \rightarrow \mathrm{Na}^+\text{−G-tetrad} + \mathrm{K}^+\,(\text{hydrated})$$

$$\Delta G = -18.1\ \text{kcal/mol (DFT) or } -14.7\ \text{kcal/mol (HF)}$$

and

$$\mathrm{Na}^+\text{−G-tetrad} + \mathrm{Li}^+\,(\text{hydrated}) \rightarrow \mathrm{Li}^+\text{−G-tetrad} + \mathrm{Na}^+\,(\text{hydrated})$$

$$\Delta G = 4.8\ \text{kcal/mol (DFT) or } 6.6\ \text{kcal/mol (HF)}$$

The ion selectivity sequence is then $\mathrm{Na}^+ > \mathrm{Li}^+ > \mathrm{K}^+$.

The preferential binding of sodium over lithium in water solutions reproduces the experimental ion selectivity of the guanine tetraplex. Meanwhile, the positive stabilization energy of the K^+−G-tetrad does not conflict with the experimental observations. It reflects the fact that the potassium cation tends to locate between two successive tetrads and indicates that the results of the calculations should be augmented by a study of the K^+−(G-tetrad)$_2$ species.[21,26,50]

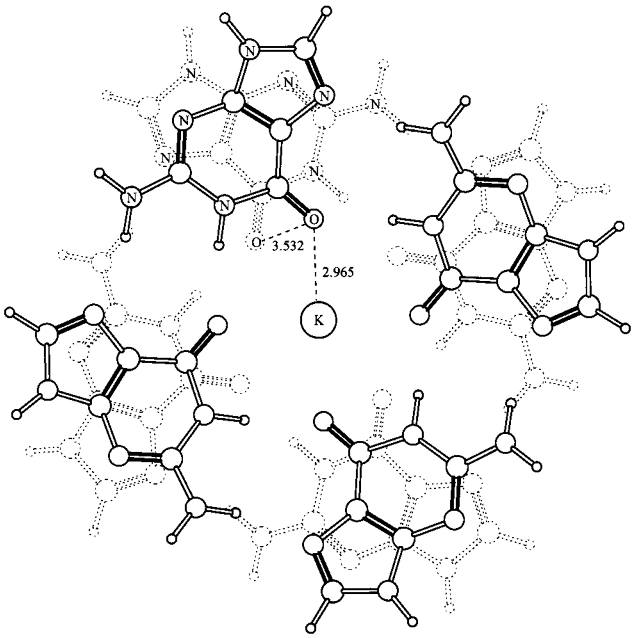

Figure 5. Optimized structure of the K^+-2G-tetrads in the "sandwiched" form. The dotted-line structure depicts the G4 beneath the full-line upper G-tetrad. Optimization has been made at the HF/6-31G(d,p) level, with the double-ζ plus d-functions of Ahlrichs for the potasium. In this structure, the G-tetrads are not in the planary form. Atomic distances in Å.

The relaxation energy of the G-tetrad corresponds to the energy variations governed by the geometric change in the tetrad necessary to host a cation. This component of energy can be readily calculated as the energy difference between the G-tetrad in the cation−guanine-tetrad complex geometry and in the optimized tetrad geometry. The relaxation energy is a good measurement of the "optimal fit" of cations: the smaller the relaxation energy, the better the fit. The relaxation energy of the K^+−G-tetrad complex is the least (4.0 kcal/mol at the DFT and 10.6 kcal/mol at the HF levels) among the complexes studied. Combined with the geometric changes in the cation−G-tetrad complexes, it allows us to conclude that the potassium ion is best coordinated by the guanine tetrad. Thus, the "optimal fit" theory cannot explain the ion selectivity exhibited in the coplanar cation−guanine-tetrad complexes.

To estimate the interaction energy between the G-tetrads and the potassium cation that is "sandwiched" between the two G-tetrads, the model system consisting of one potassium cation intercalated between two G-tetrads has been fully optimized at the HF level of theory (C_4 symmetry was applied). The basis sets used are 6-31G(d,p) for the guanines and the double-ζ plus d-functions of Ahlrichs for the potassium. The optimized structure shown in Figure 5 resembles the structures of G_2−Na−G_{-2} reported in the crystal measurements.[23,24] A single point energy calculation has been performed using the larger 6-311G(d,p) basis set for the optimized structure. The total energy for this "sandwiched" K^+−2G-tetrad complex is calculated to be $E(\mathrm{K}^+\text{−2G-tetrads}) = -4915.59884$ hartree at the HF/6-311G(d,p)//HF/6-31G(d,p) level. The interaction energy between the G-tetrads and the potassium cation ($\Delta E'$) is then evaluated as

$$\begin{aligned}\Delta E' &= E(\mathrm{K}^+\text{−2G-tetrads}) - E^{\mathrm{III}} - 2E^{\mathrm{IV}}\\ &= -96.35\ \text{kcal/mol}\end{aligned}$$

which is about 26 kcal/mol more than that of the coplanar structure at the HF level. The crystal structures of the Na^+−G-tetraplexes reveal that the sodium cations can be either between two successive tetrads or inside the plane of one G-tetrad.[23,24] This strongly suggests that the interaction energies between the sodium cation and the G-tetrads are of no substantial difference for the coplanar structure and the "sandwich" structure. Consequently, the Na^+−G-tetrad interaction energy of the coplanar structure could be used to approximate the average interaction energy between the sodium cations and the guanine tetrads. On the other hand, the fact that the potassium cation tends to locate between two successive tetrads[21,26,50] indicates that the "sandwich" structure represents the mode of the interaction between the potassium cation and the guanine tetrads.

The stabilization energy of the "sandwich" K^+−G-tetrads complex is 6.3 kcal/mol lower than that of the Na^+−G-tetrad at the HF level. Therefore, the gas-phase binding sequence between the monovalent cations and the G-tetrads still follows the trend $Li^+ > Na^+ > K^+$.

In a water solution after the hydration correction, the stabilization energy of the "sandwich" potassium cation−G-tetrads complex, obtained by adding to the calculated ΔE the ion hydration enthalpies derived experimentally,[49] amounts to −14.8 kcal/mol at the HF level. Consequently, the stability sequence of the monovalent cation−guanine-tetrad complexes in a water solution becomes $K^+ > Na^+ > Li^+$.

The ion selectivity of the guanine tetrads in a water solution can be evaluated according to the free energies of the following process:

$$K^+\text{−2G-tetrads} + Na^+ \text{(hydrated)} \rightarrow Na^+\text{−G-tetrad} + \text{G-tetrad} + K^+ \text{(hydrated)}$$
$$\Delta G = 11.3 \text{ kcal/mol (HF)}$$

We have used here the calculated energy differences and the experimental ΔG for the ions. Since there is no phase change involved in this process, the changes of entrophy should be small and the applied procedure is justified.

The ion selectivity sequence is then $K^+ > Na^+ > Li^+$, which reproduces the experimental ion selectivity of the guanine tetraplex.

The predicted change in the stability trends of the monovalent cation−guanine-tetrad complexes from the gas phase to a water solution confirms the conclusion of Hud et al.[28] that the ion selectivity exhibited by the guanine tetraplexes in water solutions is dominated by relative free energies of hydration.

Conclusions

The comprehensive study of the intraction between metal ions and G-tetrads enables us to address the following issues.

(1) The optimized cation−guanine-tetrad complex structures show a significant change in the bond pattern compared to the bifurcated hydrogen bond structure of the G-tetrad in the absence of a cation. The cation−guanine-tetrad complexes adopt the normal four-stranded Hoogsteen-bonded G-tetrad structure, and no bifurcated hydrogen bonds were found. The effect of the cations in changing the G-tetrad structure is clearly through the neutralization of the significant concentration of the negative charge in the central area of the G-tetrad.

(2) The gas-phase binding sequence between the monovalent cations and the G-tetrads follows the order $Li^+ > Na^+ > K^+$. This stability sequence changes after inclusion of the hydration corrections, and the ion selectivity of the guanine tetrads in aqueous solutions is of the order $K^+ > Na^+ > Li^+$.

(3) The changes of the tetrad inner hydrogen bond lengths suggest that the presence of cation does enhance the hydrogen bonding. However, this enhancement does not govern the ion selectivity of the guanine tetraplexes. The small Li^+ cation induces the shortest inner hydrogen bonds.

Both geometric parameters and stabilization energies of the coplanar form of the cation−guanine-tetrad complexes indicate that potassium is the best coordinated inside the guanine tetrad. Accordingly, we conclude that the "optimal fit" theory does not explain the ion selectivity exhibited in the cation−guanine-tetrad complexes. Our results confirm the conclusion of Hud et al.[28] that the ion selectivity exhibited by the guanine tetraplexes in water solutions is dominated by relative free energies of hydration.

(4) The lowest relaxation energy and the smallest geometric distortion of the K^+−G-tetrad in the coplanar form combined with the 26.0 kcal/mol increase in the K^+−G-tetrads interaction energy in the "sandwich" form enables us to conclude that the potassium cation should be located in the cavity formed by two successive guanine tetrads. The experimental results suggest that there is no such preference for the sodium cation G-tetraplex. Since both the "optimal fit" theory and the "enhanced inner hydrogen bonding" assumption fail to explain the ion selectivity exhibited in the coplanar cation−guanine-tetrad complexes, the origin of the preferred coordination of K^+ over Na^+ between two successive guanine tetrads is the ability of K^+ to strengthen the octacoordination−oxygen interactions as suggested by Ross and Hardin.[18]

(5) This study also reveals the accuracy of the HF and DFT methods in studying the geometrical parameters of large DNA fragments. The experimental measurement of the sodium ion coplanar with the guanine tetrad in the crystal of a parallel-stranded guanine tetraplex (2.34 ± 0.02 Å)[23] has been well reproduced at the HF level. The too short Na^+−O6 distance and the significant decrease of the hydrogen bond lengths predicted by the DFT approach suggest an overestimation of the hydrogen bonding by this method.

Acknowledgment. This work was facilitated by NSF grant Nos. 9805465 and 9706268 and the NIH grant GM08047.

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