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Origin of Na^+/K^+ Selectivity of the Guanine Tetraplexes in Water: The Theoretical Rationale

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Theoretical study of the "sandwich" models of the metal ion (Na^+ and K^+) G-tetrad complexes has been performed at the HF/6-311G(d,p)//HF6-31G(d,p) level. The distances between cations and the O6 atoms of guanines have been predicted to be 2.826 Å for sodium and 2.951 Å for potassium in the G4−M−G4(inter) model and 2.791 Å for sodium and 2.927 Å for potassium in the G4-M−G4(intra) model. These results are consistent with the Na^+−O6 distance of 2.75 ± 0.02 Å in the corresponding crystal structures. The binding energy between the cations and the G tetrad in the tetraplexes is greater for Na^+ than for K^+. This suggests the domination of the electrostatic interaction in the cation-tetraplexes systems. After the hydration energy correction, the stability sequence of monovalence cations in the guanine tetraplexes is found to be $K^+ > Na^+$. This finding gives the first direct theoretical evidence to support the hypothesis of Hud et al. that the preferred coordination of K^+ over Na^+ in G tetraplexes is actually dominated by relative energies of hydration.

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 Hoogsteen bonded guanine tetrads leads to four-stranded structures[6−10] in guanine-rich oligonucleotides.[11−14] It has been found that the existence of interactions with a metal ion or an ammonium ion are essential in the formation of the G-tetrad complexes.[15−22] Physicochemical studies of G-tetraplex structures have revealed that the stability and conformation of tetraplexes depend on the type of cation presented. Monovalence cations stabilize tetraplexes in the order of $K^+ > Na^+$.[17,18,23] On the basis of the experimental observations, the preferential binding of K^+ versus Na^+ in guanine tetraplexes has been proposed to be governed by an optimal fit of this cation between two guanine tetrads.[9,24] However, this optimal fit hypothesis has been challenged by Ross and Hardin. Using the free energy perturbation calculation method, they investigated the origin of the ion selectivity of G tetrads. They concluded that the "optimal fit" does not explain Na^+/K^+ selectivity.[15] The results of the thermodynamic analysis performed later by Hud et al. suggested that the preferred coordination of K^+ over Na^+ in $d(G_3T_4G_3)$ is actually dominated by relative free energies of hydration.[25]

On the basis of detailed analysis of the cation−G-tetrad interactions, our recent quantum chemistry study[26] concludes that the "optimal fit" proposal does not explain the ion selectivity exhibited in the cation−G-tetrads complexes. Assuming that the interaction energies between the sodium cation and the G tetrads are of no substantial differences for the coplanar and the "sandwich" structures, the results of the calculations[26] support the suggestion of Hud et al. However, this assumption has not been checked directly. Experimentally, cations are found to be located either between two tetraplexes (intertetraplexs) or within one tetraplex (intratetraplex).[20] The model used in the previous study only mimics the intertetraplex structures of G4−M−G4(inter) reported in crystal measurements (see Figure 1). The relevant model of the intratetraplex structures of G4−M−G4(intra) has never been studied (Figure 2). A direct theoretical evidence of the hydration dominating the Na^+/K^+ selectivity in the G tetraplexes should include the important G4−M−G4(intra) model. Also the assumption that the interaction energies between the sodium cation and the G tetrads are of no substantial differences for the coplanar structure and the "sandwich" structure should be further examined by the direct comparison with the reliable theoretical calculations for both structures.

In this paper, we report the ab initio theoretical study of the "sandwich" model of the metal ion (Na^+ and K^+) G-tetrad complexes. The result gives the first direct theoretical evidence to support the proposition that the preferred coordination of K^+ over Na^+ in G tetraplexes is actually dominated by relative energies of hydration. The models studied were two stacked guanine tetrads with a K^+ or Na^+ cation intercalating in between. Two conformations which resemble the within tetraplex (G4−M−G4(intra)) and the between tetraplexes (G4−M−G4(inter)) structures were fully optimized as the local minima on the potential energy surface by the Hartree−Fock self-consistent-field (HF−SCF) method in conjunction with the valence double-ζ basis set augmented with d- and p-like polarization functions[27] (HF/6-31G(d,p)). The basis sets used for the cations were the double-ζ basis plus one set of d functions of Ahlrichs et al.[28] To ensure reliable interaction energy predictions of the complexes, single-point energy calculations have been performed using the larger valence triple-ζ basis set augmented with d- and p-like polarization functions[27] 6-311G(d,p), over the optimized structures (HF/6-311G(d,p)//HF/6-31G(d,p)). Gaussian 94 software[29] was used in the calculations.

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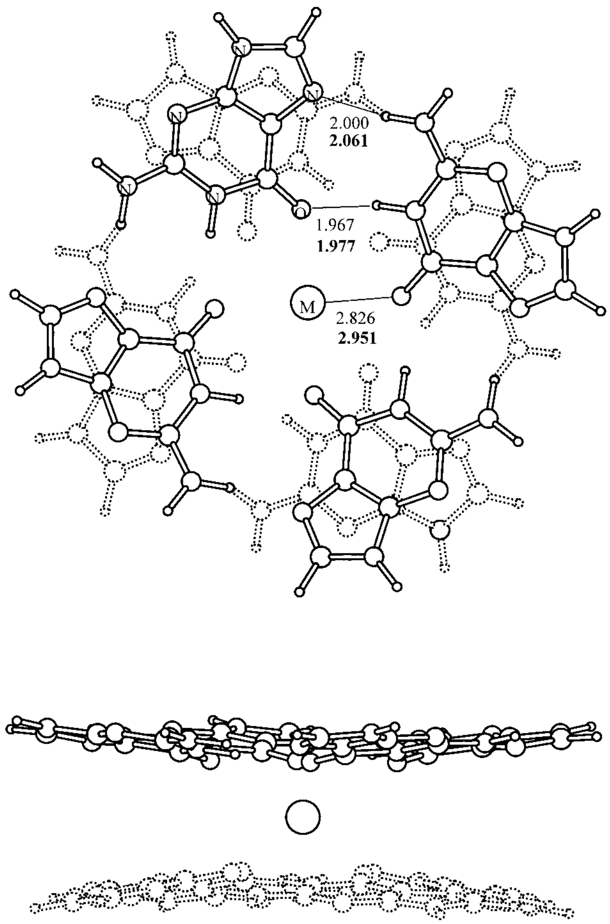

Figure 1. Optimized structure of the G4$-$M$-$G4(inter) complex. Lightface is for Na$^+$, and bold is for K$^+$. Distances are in angstroms. The G tetrads are twisted a little as shown in the side view.

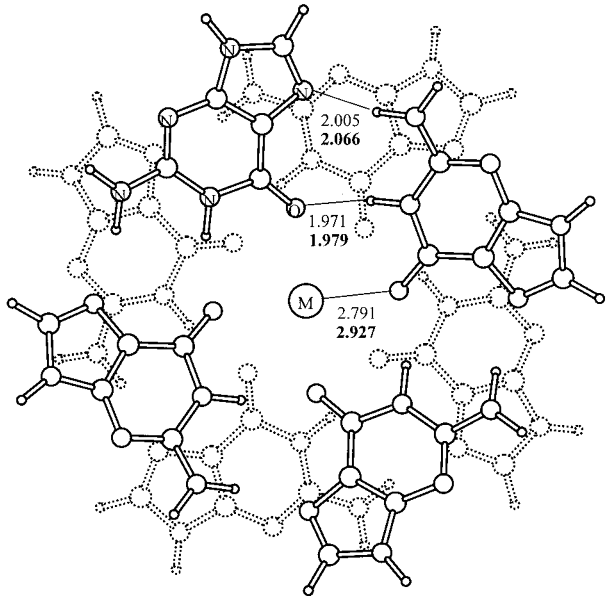

Figure 2. Optimized structure of the G4$-$M$-$G4(intra) complex. Lightface is for Na$^+$, and bold is for K$^+$. Distances are in angstroms.

Results and Discussion

The initial structure of G4 was taken from our previous computational study on the G tetrad. The cations were placed in the center between two successive G4 with a plane$-$plane distance of 3.4 Å, as suggested by the crystal structure.[20] The complexes were then fully optimized using the analytical gradients method. The optimized structures of cation$-$G-tetrads complexes along with selected important geometric parameters are depicted in Figures 1 and 2. The structure of the G tetrad is close to that in the co-plane model. However, the G tetrads are slightly twisted as shown in the side view. At the HF level, the distances between cations and the O6 atoms of guanines are predicted to be 2.826 Å for sodium and 2.951 Å for potassium in the G4$-$M$-$G4(inter) model. For a comparison, the Na$^+-$O6 distance in the corresponding crystal structures amounts to 2.75 ± 0.02 Å.[20] For the G4$-$M$-$G4(intra) model, the theoretical predictions of the M$-$O6 distance are 2.791 Å for Na$^+$ and 2.927 Å for K$^+$, respectively. Because the ions (Na$^+$) coordinated between tetrad planes G4(2) and G4(3) shift toward the G4(3) plane in the crystal structure, there is no direct comparison available. However, the X-ray crystallography results[20] of the average Na$^+-$O6 distance of 2.89 ± 0.07 Å for the G4(2) plane and of 2.60 ± 0.07 Å for the G4(3) plane justify the G4$-$M$-$G4(intra) model. The distance between K$^+$ and the averaged G4 plane (with plane RMS of 0.28 Å) amounts to 1.95 and 1.98 Å for the intra and inter models, respectively. The shorter cation$-$G4 distance of 1.67 Å predicted based on the K$^+-$G4 model at the DFT level[33] is clearly due to the stronger electrostatic interaction between the cation and the O6 atoms. This is consistent with the even shorter K$^+-$O6 distance of 2.59 Å (as compared to 2.951 and 2.927 Å in this study) in the cation-guanine study.[34] The distance between Na$^+$ and the G4 plane (with plane RMS of 0.29 Å) amounts to 1.77 and 1.79 Å for the intra and inter models, respectively, which is about half of the crystal data distance (3.4 Å) between two G4$-$G4 planes.[20] The slightly larger G4$-$G4 plane distances predicted in this study are most likely due to the dispersion interaction which is not included in the HF method. The H(N1)···O6 and H(N2)···N7 hydrogen bonds, which held the guanines together to form the tetrad, are basically unchanged as compared to the coplanar models considered in the previous study.[26] The H(N1)···O6 and H(N2)···N7 bond lengths amount to approximately 1.97 and 2.00 Å for the G4$-$Na$^+-$G4 complexes and 1.98 and 2.06 Å for the G4$-$K$^+-$G4 complexes, respectively, in both the within and between tetraplexes models.

The cation-tetrad interaction energies (BSSE corrected) are summarized in Table 1. The cation-tetrad interactions in the intratetraplex model are larger (about 1$\sim$2 kcal/mol) than those in the intertetraplex model for both Na$^+$ and K$^+$ complexes. The K$^+-$tetrad interaction energy amounts to $-$97.48 kcal/mol for the G4$-$M$-$G4(intra) model and $-$96.36 kcal/mol for the G4$-$M$-$G4(inter) model. The interaction energy for the corresponding Na$^+$ complexes is evaluated to be $-$110.71 kcal/mol and $-$108.05 kcal/mol, about 13.2 and 11.5 kcal/mol more than that of the K$^+$ complexes, respectively. On the other hand, the cation$-$tetrad interaction energy in the coplanar Na$^+-$tetrad model has been reported to be $-$99.8 kcal/mol, about 2.4$\sim$3.4 kcal/mol larger than that of the G4$-$K$^+-$G4 complexes. Therefore, the binding preference between the cations and the G tetrad in the tetraplexes follows the Na$^+$ > K$^+$ order. The conclusion that smaller ions are more tightly bonded to guanine tetrads suggests the domination of the electrostatic interaction in the cation$-$tetraplexes systems. However, it should be noted that although the smaller ions are more tightly bonded to the guanine tetrad, they also have a larger affinity for water molecules. In aqueous solutions, the smaller cation Na$^+$ is much better solvated by water than K$^+$. The transfer of smaller cations from water into the guanine strands is associated with the higher energy barrier. The balance between these two opposing trends may change the binding sequence. At room temperature, the

TABLE 1: Energy Properties of the G4−M−G4 Complexes Calculated at the HF/6-311G(d,p)//HF/6-31G(d,p) Level[a]

	E(complex)	*E*(cation)	*E*(G4−G4)	*E*(G4)	Δ*E*$^{\text{relaxation}}$, kcal/mol	Δ*E*, kcal/mol
G4−K−G4(intra)	−4915.600 644 5	−599.001 720 5	−4316.397 830 6	−2158.222 022 6	14.4	−97.48
G4−K−G4(inter)	−4915.598 838 2	−599.001 706 3	−4316.397 085 6		14.7	−96.35
G4−Na−G4(intra)	−4478.278 748 8	−161.659 084 2	−4316.380 466 6		20.0	−110.71
G4−Na−G4(inter)	−4478.274 500 5	−161.659 070 4	−4316.381 356 6		19.6	−108.05

[a] *E* is in hartree except Δ*E*. *E*(cation) was calculated for the cation with the basis sets of G4−M−G4. *E*(G4−G4) was calculated for G4−G4 complex with the basis sets of G4−M−G4. E(G4) was calculated for the optimized G4 with the basis sets of G4−M−G4. Δ*E* = *E*(complex) − *E*(cation) − 2*E*(G4). Δ*E*$^{\text{relaxation}}$ = [*E*(G4−G4) − 2*E*(G4)]/2.

hydration free energies of K$^+$ and Na$^+$ amount to −80.6 and −98.2 kcal/mol, respectively.[30] The corresponding enthalpies are −76.7 and −96.9 kcal/mol, respectively.[30] The stabilization energy of the complexes G4−K$^+$−G4 amounts to −20.8 to −19.7 kcal/mol after the hydration correction. On the other hand, this hydration corrected stabilization energy amounts to −13.8 to −11.9 kcal/mol for the G4−Na$^+$−G4 models and −2.9 kcal/mol for the coplanar Na$^+$−G4 model,[26] respectively. Consequently, the stability sequence of monovalence cations in the guanine tetraplexes in aqueous solution should be K$^+$ > Na$^+$. The ion selectivity of guanine tetrads in an aqueous solution can be evaluated according to the free energies of the following process:

$$\text{G4}-\text{Na}^+-\text{G4} + \text{K}^+\,(\text{hydrated}) \rightarrow \text{G4}-\text{K}^+-\text{G4} + \text{Na}^+\,(\text{hydrated})$$

Because the geometries of G4−Na$^+$−G4 and G4−K$^+$−G4 species are similar, at the first approximation, the change in the entropy due to the cation exchange in this process can be ignored. The difference between the binding energies of the cation and the tetrads predicted for different cations is a reasonable approximation for this free energy change. The Δ*G* for this process is calculated to be −4.5 kcal/mol (within the tetraplex) and −5.9 kcal/mol (between tetraplexes). For a comparison, the NMR and the kinetics experimental estimations are about −0.8 kcal/mol for each coordinated ion.[25,32] The ion selectivity sequence is then K$^+$ > Na$^+$, which reproduces the experimental ion selectivity of guanine tetraplex. On the other hand, the Δ*G* obtained without considering the entropy change due to the cation exchange in G4−M−G4 is about 4 kcal/mol larger than the experimental estimation. This agreement might be improved if the entropy is taken into account.

The change in the stability sequence of the monovalence cation−guanine-tetrad complexes after including the ion hydration effects confirms the conclusion of Hud et al.[25] that the ion selectivity exhibited by the guanine tetraplexes in water solutions is dominated by relative free energies of hydration.

The difference between the interaction energy of the Na$^+$ tetrad in the present models and the previously considered coplaner model[26] is significant. The cation−tetrad interaction energy for the G4−M−G4 model is about 9∼11 kcal/mol larger than for the coplaner model. However, this difference does not change the conclusions derived in the previous study. Because the presence of the successive cations in the adjacent position of the tetraplex reduces the out of plane changes in the G tetrads, inside the tetraplexes, the cation−tetrad interaction energy is expected to be smaller than that predicted from the G4−M−G4 model. In fact, about 10 kcal/mol of interaction energy difference for the two extreme models (G4−Na$^+$−G4 and coplaner Na$^+$−G4) could be taken as the maximum variation for the values of the interaction energy between cation sodium and G tetraplexes. Under the influence of the neighboring sodium ions, one Na$^+$ could be easily driven away from its equilibrium position toward a G tetrad as shown in the crystal structures. On the other hand, about 30 kcal/mol energy difference for the K$^+$−G4 interaction between the two models (G4−K$^+$−G4 and coplaner K$^+$−G4) agrees with the results of the previous computational studies[26,33] and the well-documented fact that potassium cations tend to locate between two successive tetrads.[18,23,31]

Present study enable us to reexamine the "optimal fit" rationale for stabilization of the G-tetrad complexes by comparing the relaxation energies that correspond to the energy variation owing to the geometric changes in the tetrad to host a cation. This part of energy can be readily calculated as the energy difference between the G tetrad in the cation tetrads complex geometry and the optimized tetrad geometry. Relaxation energy is a good measurement for the optimal fit of cations. A better host should have the smaller relaxation energy. The relaxation energy of the G4−K$^+$−G4 complex has been evaluated to be 14.4 kcal/mol in the G4−M−G4(intra) model and 14.7 kcal/mol in the G4−M−G4(inter) model. In the G4−Na$^+$−G4 complex, the corresponding relaxation energies amount to 20.0 and 19.6 kcal/mol, respectively. It is clear that the cage formed by the G4−G4 complex is a better host for K$^+$. Without considering the hydration energy, the binding energy of the best fitting cation K$^+$ is still lower than that of Na$^+$ as shown in the discussion above. Thus, the optimal fit proposal fails in explaining the ion selectivity exhibited in the guanine tetraplexes. The only explanation for the ion selectivity is that the preferred coordination of K$^+$ over Na$^+$ in the G tetraplexes is dominated by relative energies of hydration.

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