Isoguanine Complexes: Quintet versus Tetrad

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Isoguanine (2-oxo-6-aminoguanine, isoG) quintet and its cation (Na^+ and K^+) complexes have been investigated by density functional theory (DFT) in order to understand the formation and stability of the high-order self-pairing of isoG systems. The comparison of the relative stability of the quintet with that of the tetrad indicates preferential formation of the isoG tetrad in the absence of metal ions. This preference is governed by the entropy of the system as revealed in this study. The large interaction energy evaluated for complexes of cations with the isoG quintet suggests that metal ions are crucial for regulating the strand association. This study also provides direct evidence for the orbital interaction between K^+ and the surrounding oxygen atoms in the tetrad and quintet complexes.

Introduction

Isoguanine (2-oxo-6-aminoguanine, isoG, Figure 1) occurs naturally and may have contributed to early biopolymer evolution.[1,2] Similarly to guanine, the higher-order self-pairing of isoguanine has also been established by regulating the presence of metal ions.[1,3−7] The higher-order self-pairing of isoG has been found to have strong metal ion dependence. Monovalent cations can regulate the degree of strand association in nonstandard DNA.[1] Beyond the tetraplexes, isoG-contained DNA pentaplexes have been designed and characterized.[1,3] DNA pentaplexes are expected to be able to form ion channels due to their morphological similarity to the pentameric α-helical peptides, which have been implicated as ion channels.[8]

To better understand these highly ordered self-pairing systems, it is necessary to identify their energy properties and the geometric characteristics. As the core of DNA pentaplexes, the isoG quintet has been proposed to possess a cyclic structure with hydrogen bonds H(N6)···N3′ and H1···O2′ between the neighboring isoG bases (Figure 2).[1,3] Accordingly, each base acts as double donor and double acceptor for protons in H-bonds. The isoG quintet is then expected to be remarkably stable even without the presence of metal ions due to the cooperative effect of H-bonding.[9,10] However, the stability differences between the isoG tetrad and quintet have not been investigated. Although the bonding sector angle of 67° for isoG, defined by the intersection of vectors along the van der Waals donor−donor and acceptor−acceptor atom surfaces,[1] does not favor the planar tetrad structure in the Hoogsteen style, our recent study has demonstrated that, by adopting the bifurcated H-bonding pattern, the isoG tetrads adopt planar or near-planar cyclic forms of extraordinary stability.[9] On the other hand, the entropy loss is expected to be more significant for the formation of a quintet than for a tetrad. The interaction energy between monovalent cations and the isoG polymer (tetrad and quintet) is of vital
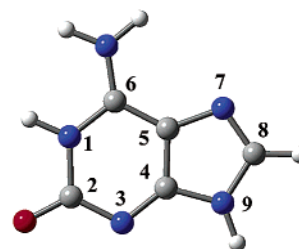
Figure 1. 2-Oxo-6-aminoguanine (isoG). Color representations for atoms are red for O, blue for N, gray for C, and white for H.

importance to understand the regulation mechanism of the metal ions in strand association. Accurate quantum chemistry investigations might be the only way to reveal these details at present.

Here we report a density functional theory- (DFT-) based quantum chemical study of the stability, structure, H-bonding pattern, and electrostatic potential properties of the isoguanine quintet and its K^+ and Na^+ complexes. The relative stability of the quintet is compared to that of the tetrad. It could be used to justify preferential formation for the isoG tetrad in the absence of metal ions. The large interaction energy evaluated for cations with the isoG quintet suggests that the metal ions may dominate in regulating the strand association.

Calculation Methods

The local minima of the quintet complexes have been fully optimized by analytic gradient techniques. The method used was the density functional theory (DFT) with Becke's three-parameter (B3)[11] exchange functional along with the Lee−Yang−Parr (LYP) nonlocal correlation functional (B3LYP).[12,13] The standard valence triple-ζ basis set augmented with d- and p-type polarization functions, 6-311G(d,p),[14] was used for all elements. In most cases the geometries and frequencies of the molecules calculated at the B3LYP/6-311G level agree well with experiments.[15,16] However, for some hydrogen-bonding systems, the DFT methods fails, especially for geometries. Since the DFT level represents the best computationally efficient approach

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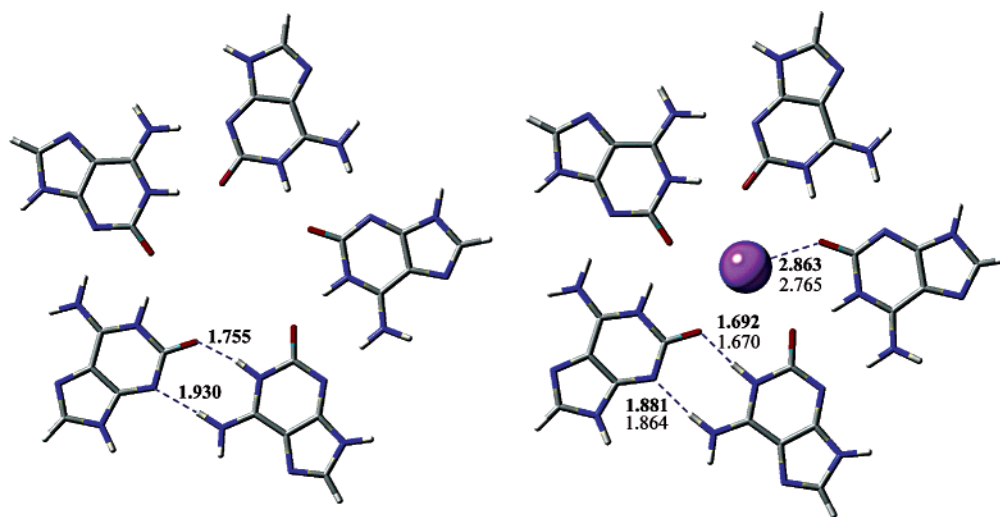
Figure 2. Geometry of the optimized isoG quintet and the optimized K$^+$ (boldface type) and Na$^+$ (lightface type) isoG quintet complexes. Hydrogen bond lengths are given in angstroms. Color representations for atoms are purple for K$^+$ or Na$^+$, red for O, blue for N, gray for C, and white for H.

TABLE 1: Energy Properties of IsoG Quintet Evaluated at the B3LYP/6-311G(d,p) Level[a]

	isoG5	isoG4[b]	isoG4[b]	isoG
symmetry	C_{5h}	C_{2h}	S_4	
E (hartrees)	−2713.628 169	−2170.902 859	−2170.898 653	−542.690 716
E^0 (hartrees)	−2713.038 867	−2170.431 022	−2170.426 373	−542.574 618
G_{298} (hartrees)	−2713.131 430	−2170.507 124	−2170.503 681	−542.607 780
ΔE (kcal mol^{-1})	−109.55	−87.85	−85.21	
ΔE^0 (kcal mol^{-1})	−104.30	−83.18	−80.26	
ΔE^0(BSSE) (kcal mol^{-1})	−90.85	−74.22	−71.86	2.77,[c] 2.10[d]
ΔG_{298}(BSSE) (kcal mol^{-1})	−44.21 (−8.84)	−39.28 (−9.82)	−37.12 (−9.28)	

[a] E is the total energy, G_{298} is the Gibbs free energy at 298 K, E^0 and ΔE^0 are vibrational zero point energy corrected, $\Delta E = E(\text{isoGn}) - nE(\text{isoG})$, $\Delta E^0 = E^0(\text{isoGn}) - nE^0(\text{isoG})$, and $\Delta E^0(\text{BSSE}) = E^0(\text{isoGn}) - nE^0(\text{isoG}) + n\text{BSSE}(\text{isoG})$, where n is the 5 for quintet and 4 for tetrad. $\Delta G_{298}(\text{BSSE}) = G_{298}(\text{isoGn}) - nG_{298}(\text{isoG}) + n\text{BSSE}(\text{isoG})$ is the BSSE-corrected ΔG_{298}. Number in parentheses is $\Delta G_{298}/n$, i.e., ΔG_{298} for each basis. [b] Data for tetrad are taken from ref 9. [c] BSSE of monomer in quintet. [d] BSSE of monomer in tetrad.
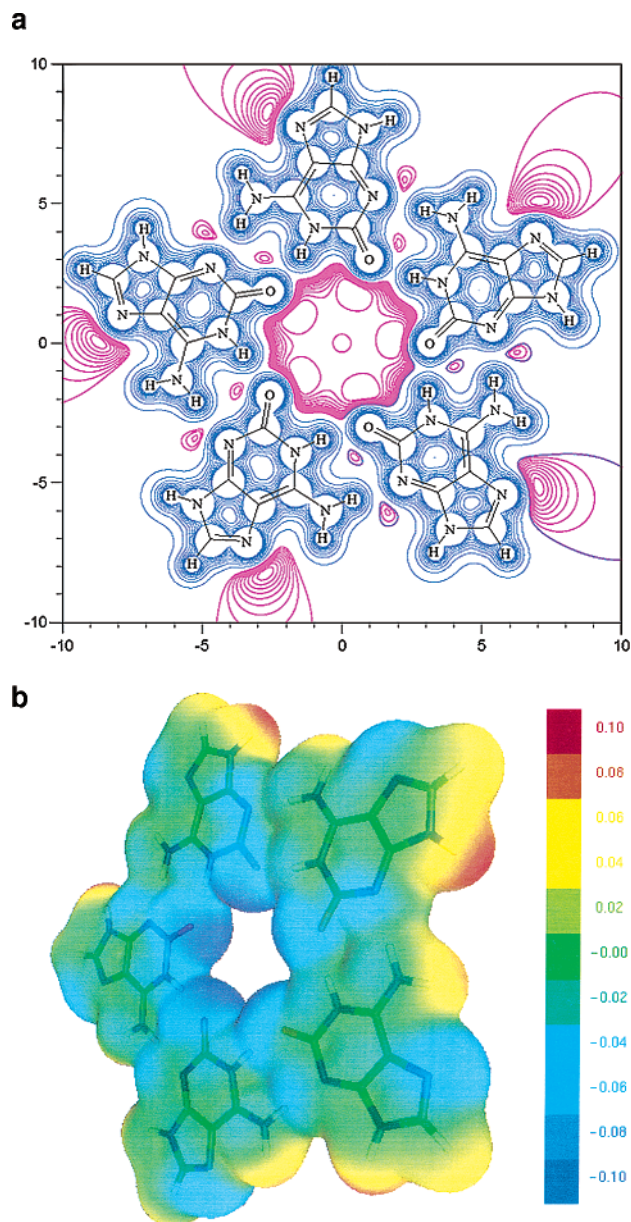
available for such large systems as considered in our study and since recent investigations of the H-bonded guanine tetrads suggest that the B3LYP/6-311G(d,p) approach is a reliable method for comparison studies,[10] this approach has been applied in our present work. In the vibrational frequencies calculations, the force constants were determined analytically. The Gaussian-98 package of programs[17] was used in the calculations. The basis set superposition error (BSSE) was corrected according to Boys' approach.[18]

Results and Discussions

IsoG Quintet. The fully optimized structure of the isoG quintet adopts a planar form characterized by C_{5h} symmetry as displayed in Figure 2. The subsequently performed analytical vibrational frequency computation confirms that this structure is the local minimum on the potential energy surface. The isoG quintet is the first one that adopts the planar structure among the other high-order cyclic guanine-like base-pairing systems with the highest symmetry (S_4 for both the G and isoG tetrads). The H-bond length of H(N6)···N3′ and H1···O2′ amounts to 1.930 and 1.755 Å, respectively. The corresponding values for the isoG base pairs amount to 2.137 and 1.961 Å. In the C_{2h} symmetry conformer of the isoG tetrad, which is the most stable one among the isoG tetrads, these two H-bonds possess lengths of 1.920 and 1.740 Å, about 0.010 and 0.015 Å shorter than in the quintet, respectively. Meanwhile, the corresponding bond distances in the G tetrad (S_4 symmetry) amount to 2.040 and 1.772 Å [ref 19, also in this study]. As a consequence, stronger H-bonding is expected for the isoG quintet.

The small value of the lowest vibrational frequency (about 4 cm^{-1}) suggests a flat potential energy surface. The corresponding vibrational mode exhibits the out-of-plane motion of the bases. The lowest IR-active modes are observed at 314 cm^{-1} with the intensity of 0.01 unit, which relate to the in-plane wagging motion of the HN6H amino group in isoG. This motion has been predicted at 265 cm^{-1} for the isolated isoG in our previous investigation. Out-of-plane motions for the same group have been located at 485 and 488 cm^{-1} with intensities of 0.02 and 0.01, respectively. This corresponds to the mode at 290 cm^{-1} in free isoG. The H(N1) out-of-plane vibrations in the quintet have been found at 939 and 945 cm^{-1}, with intensities of 0.01 and 0.04. In the isoG monomer, this motion appears at 612 cm^{-1}. The big blue-shifts revealed in the vibrational mode analysis support the existence of strong H-bonding between the bases in the quintet.

The total binding energy $-\Delta E$ of this quintet has been evaluated to be 109.55 kcal/mol, or 21.91 kcal/mol per each isoG base (Table 1). A similar binding energy has been predicted for the tetrads, 21.96 kcal/mol per base for the C_{2h} structure and 21.30 kcal/mol for the S_4 symmetrical structure of the isoG tetrad.[9] It should be noted that four pairs of bifurcated H-bonds hold the S_4 symmetrical isoG tetrad. As a comparison, the binding energy for the isoG base pairs amounts to only 15.34 kcal/mol.[9] Cooperative effects in H-bonding[9,10] for this cyclic system are substantial. Inclusion of entropy adjusts the relative binding ability. The BSSE-corrected free energy change ΔG_{298} has been found to be −8.84 kcal/mol per base in the quintet, −9.82 kcal/mol for the C_{2h} isoG tetrad, and −9.28 kcal/mol

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a

b

Figure 3. (a, top panel) Contour plot of the electrostatic potential of the isoG quintet on the complex plane. The blue line represents the positive part of the electrostatic potential, and the pink line is the negative part. The contour spacing is 0.1 au for the positive part and 0.01 au for the negative part. (b, bottom panel) Electrostatic potential of the isoG quintet is mapped onto the surface of the electron density of 0.002 unit. The projection of the electrostatic potential on the 0.002 electron density surface clearly clarifies that the central area is the only location to host a cation for the isoG quintet.

for the S_4 tetrad. Without the presence of cations, the slight energetic preference for the isoG tetrad is governed by the entropy of the system.

An electrostatic potential map (Figure 3) demonstrates that the best hosting position for cations exists in the central cavity of the isoG quintet. The electrostatic potential remains almost constant inside the cavity as illustrated in the contour plot. The projection of the electrostatic potential on the 0.002 electron density surface clearly clarifies that the central area should be the only position to host a cation for the isoG quintet.

Metal Ion–IsoG Quintet Complexes. Figure 2 also displays the optimized K$^+$– and Na$^+$–isoG quintet structures along with the main geometric parameters. The optimizations were performed with the planar symmetry constraints for the complexes.

TABLE 2: Energy Properties of the Coplanar Cation–IsoG Quintet Complexes Evaluated at the B3LYP/6-311G(d,p) Levels[a]

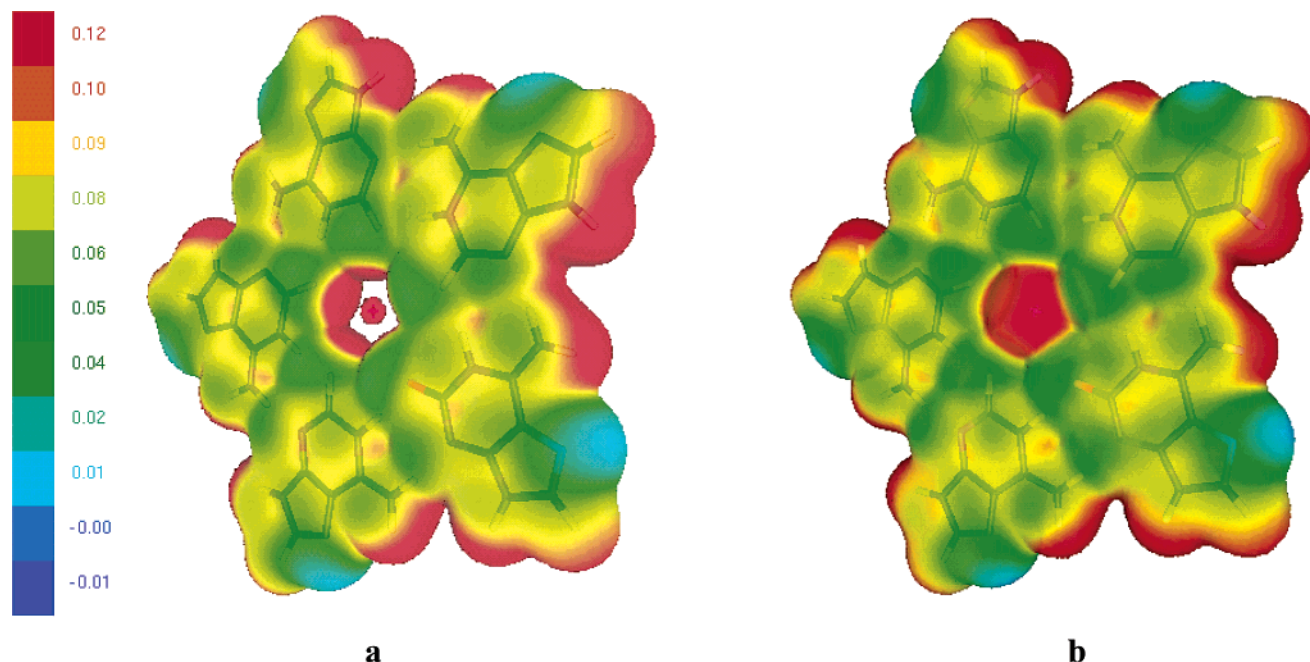|	Na$^+$–isoG quintet	K$^+$–isoG quintet
E^I (hartrees)	−2875.879 924	−3313.537 967
E^{II} (hartrees)	−2713.633 452	−2713.633 370
E^{III} (hartrees)	−162.087 887	−599.761 191
ΔE (kcal mol^{-1})	−99.56	−89.99

[a] E^I is the total energy of the optimized cation–isoG quintet complex. E^{II} is the energy of the optimized isoG quintet with cation basis set added in the center. E^{III} is the energy of cation with isoG quintet basis sets kept in the calculation. $\Delta E = E^I - E^{II} - E^{III}$.

The atomic distance between the cation and O2 amounts to 2.863 Å for K$^+$ and 2.765 Å for Na$^+$. The corresponding distances in the planar form of the guanine tetrads have been reported to be 2.658 and 2.316 Å, respectively.[20] Due to the influence of cations, the H-bond lengths of H(N6)···N3′ and H1···O2′ are reduced to 1.881 and 1.692 Å for K$^+$ complexes and to 1.864 and 1.670 Å for Na$^+$ complexes, respectively. The presence of a cation in the central cavity of the quintet seems to strengthen the H-bonding between the bases. A similar phenomenon is also observed in cations interacting with guanine tetrad systems.[20]

Although the planar constrained complexes are neither local minima nor the transition-state structures, vibrational frequency analyses suggest that the real local minimum energy structures should be near planar. K$^+$ and Na$^+$ are unlikely to be located outside of the quintet plane, contrary to K$^+$ in the G tetrad.[21,22] Two vibrational modes with imaginary frequencies of $i6$ and $i7$ cm^{-1} in the K$^+$ quintet complexes correspond to the small flapping motion of the bases against the quintet plane. Another two flapping motions of the bases appear at 12 and 14 cm^{-1}. The out-of-plane motion of K$^+$ has been predicted as the fifth vibrational mode with a frequency of 18 cm^{-1}. Similar vibrational characteristics have been observed for the Na$^+$ complex in which the out-of-plane motion of Na$^+$ has been located as the seventh mode at 22 cm^{-1}. Since the vibrational modes characterized by imaginary frequencies are very small, the energy and geometry of the local minimum of the metal–quintet complex is expected to be close to that of the complex optimized with the planarity constraint.

The calculated energies of the considered systems are summarized in Table 2. The interaction energies of the cations with the isoG quintet are calculated as the energy difference between the energy of the cation–isoG quintet complex and that of the cation and the optimized isoG quintet ($\Delta E = E^I - E^{II} - E^{III}$). To avoid the basis set superposition error, the BSSE corrections were included in the energies of both the cations (E^{III}) and the optimized isoG quintets (E^{II}). The binding energy between the cation and the isoG quintet has been evaluated to be −99.56 kcal/mol for Na$^+$ and −89.99 kcal/mol for K$^+$, respectively. Since the cation–isoG tetrad complexes do not possess near-planar structures as revealed by Davis et al.,[5] there is no direct comparison that can be made with the cation–isoG tetrad system. However, the coplanar structures of the cation–guanine complexes provide an indirect reference. Considering that the interaction energy in the coplanar cation–guanine tetrad complexes has been evaluated to be −106.1 kcal/mol for Na$^+$,[20] about 5.5 kcal/mol stronger than that in the isoG quintet, and −70.4 kcal/mol for K$^+$,[20] about 19.6 kcal/mol weaker than in the isoG quintet, larger metal ions seems to favor the quintet structure. It is clear that when hydration enthalpies of the cations are taken into consideration, the K$^+$ cation is preferred over the Na$^+$ ion by the isoG quintet.

Figure 4. Electrostatic potential of cation isoG quintet complexes mapped onto the surface of the electron density of 0.002 unit: (a) Na^+ and (b) K^+. The cap on the central cavity of the K^+ isoG quintet complex illustrates the partial occupation of the electrons on the outer orbitals of K^+.

A comparison of the electrostatic potential maps of the Na^+– and K^+–isoG quintet complexes (Figure 4) with that of the isoG quintet (Figure 3) enables one to understand the importance of the presence of cations in the pentaplexes. A cation-bound isoG quintet is well suited for stacking between the two successive isoG quintets as is revealed by the details of their electrostatic potential maps. The electrostatic interaction between the cation-bound and nonbound isoG quintet benefits the stabilization of the pentaplexes.

The electrostatic potential maps of the Na^+– and K^+–isoG quintet complexes also demonstrate a significant electron density distribution difference between the Na^+ and K^+ ions complexes. Since the ESP is mapped onto the electron density isosurface with the value of 0.002 unit, the empty space around Na^+ in the cavity of the isoG quintet suggests no electron density and therefore no orbital interaction between Na^+ and the surrounding O atoms. On the other hand, the cap on the central cavity of the K^+–isoG quintet complex clearly illustrates the nonnegligible distribution of the electron density on the outer orbitals of K^+. This might be the first direct evidence of the orbital interaction between K^+ and the surrounding oxygen atoms in the tetrad and quintet complexes. Consequently, the interaction between K^+ and the quintet is further intensified by this orbital interaction.

Conclusions

The geometric and energy characteristics of the isoG quintet and its Na^+ and K^+ complexes investigated in this study enable us to conclude the following:

(1) Cooperative effects in H-bonding[9,10] for the cyclic quintet of isoG systems are substantial.

(2) In the absence of metal ions, the isoG tetrad is relatively more energetically favored than the quintet. The preferential formation for the isoG tetrad is mainly governed by the entropy of the system.

(3) Larger metal ions stabilize the quintet structure through orbital interactions between the metal ions and the oxygen forming the cavity of isoG quintet.

This study also provides direct evidence for the orbital interaction between K^+ and the surrounding oxygen atoms in tetrad and quintet complexes.

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