Structures and Properties of the Planar G·C·G·C Tetrads: Ab Initio HF and DFT Studies

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To reveal the details of molecular geometries and properties of the GCGC tetrad, reliable quantum chemical methods (HF and DFT) in conjunction with a large basis set (6-311G(d,p)) were used to locate the local minima of the GCGC tetrad structures and to predict their energies and electrostatic potential maps. The study reveals that both A type forms of the GCGC tetrad form stable structures. The stabilization energies relative to the isolated bases amount to approximately 72 kcal/mol more than was predicted for the isolated G tetrad. The inter GC pair interaction contributes about 17−19 kcal/mol to the total stabilization energy. The large stabilization energies confirm that the stabilization of the tetrads plays a key role in the four-stranded helices. The **GCGC-a1** conformer formed through the inter base pair H(N4)−O6 hydrogen bonding is about 2 kcal/mol more stable than the **GCGC-a2** form. However, the relative stability of both forms could be affected by the presence of cations that might balance the electrostatic repulsion of the O6−O6′ atomic pair in the tetrad. The study also reveals the importance of the cooperative effect of hydrogen bonding in the formation of GCGC tetrads. The presence of the inter base pair hydrogen bond intensifies the intra GC base pair hydrogen bonding by approximately 2 kcal/mol for each GC pair in the tetrads.

Introduction

The structure of DNA tetraplexes, formed by the H-bonding interactions between two DNA duplexes, has been considered to provide possible models for DNA strand exchange processes.[1,2] The guanine−cytosine−guanine−cytosine (GCGC) tetrad is one of the important tetrads discovered in the different DNA tetraplexes. It was first proposed theoretically by Löwdin in 1964 for association of two Watson−Crick double helices in the models of DNA replication.[3] Later experimental studies have shown that the GCGC tetrads do actually exist.[4−11]

There are two main types of GCGC tetrads (Scheme 1, types A and B). Both are formed by the association of two GC base pairs in the opposite direction. In type A which is roughly planar,[8,9,11] two GC base pairs are linked through the hydrogen bonding between the O6 atoms of the guanine residues and the H atoms of the amino group of the cytosine residues. In type B, the two pairs are held together through the hydrogen bonding of the O2 of the cytosine in one base pair and the H atom of the amino group of the guanine in the other. The GCGC tetrad of type B has been found to possess a nonplanar structure. The GC pairs are tilted at about 30° relative to one another along the axis going through the CG bonds.[7,11]

An unresolved issue is the stability of the GCGC tetrad of type A. Using NMR techniques two GCGC tetrads of type A are found to be sandwiched between two G4 tetrads in the tetraplex formed by the G-rich strand of d(CGG)·d(CCG), which repeats with the oligonucleotide $dGCGGT_3GCGG$ in the presence of a sodium cation.[8] On the other hand, the G4 tetrads are shown to be flanked by the GCGC tetrads of type A in the d(GGGCT4GGGC) tetraplexes.[9] These experimental evidence implies that this GCGC tetrad itself could be stable in its optimum conformation. However, the experiments with the presence of potassium cations suggest that the GCGC tetrad might be unstable.[10−12] The interstrand hydrogen-bonding alignments are not seen in the K cation-coordinated d(GGGCT4GGGC) tetraplex.[10] Moreover, different arrangements have been proposed for the GCGC tetrad of type A. One of them was developed theoretically[3] and was derived from a computer-modeling study[6] (A1 in Scheme 1). In this conformation two GC base pairs are bonded to each other via the H atom at N4 of the cytosine residues and the O6 atom of the guanine residues. The N7 atoms of the guanines are not involved in the formation of the tetrad. In another conformation (A2 in Scheme 1), the H atom at N4 of cytosine has been suggested to be hydrogen-bonded to the N7 atom in the guanine of the opposite GC pair.[4,5] In the third A type conformation of the GCGC tetrad, there are bifurcated hydrogen bonds that hold the two GC pairs together (A3 in Scheme 1) as claimed by Ketani et al.[8,9]

Recent quantum chemical studies of the Hoogsteen-type guanine, Watson−Crick-type thymine−adenine−thymine−adenine, Hoogsteen-type thymine−adenine−thymine−adenine, and adenine−guanine−adenine−guanine tetrads suggest that the stabilization of the tetrads plays a key role in the four-stranded helices.[13−15] Therefore, it is important to determine if the isolated GCGC tetrad is stable. Although the structure and stability of

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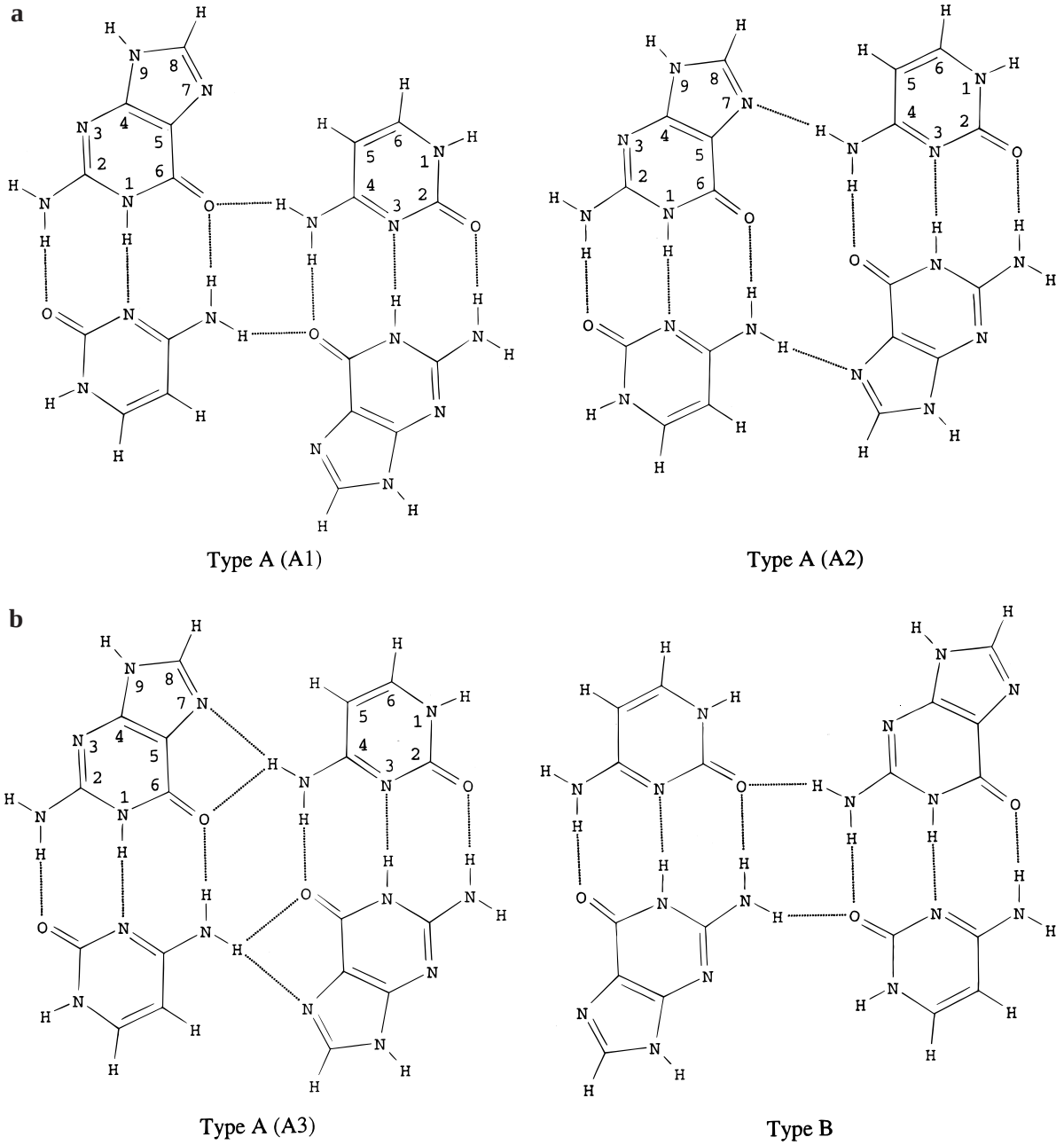
SCHEME 1: Two Main Types of GCGC Tetrad[a] A and B



[a] Both are formed by the association of two GC base pairs in the opposite direction. There are three conformations for type A. Depending on the different inter base pair H-bonding that held the GC pairs together, they are labeled as A1, A2, and A3.

tetraplexes do not solely depend on the interactions of the isolated tetrads of the bases, the base pairing might be the crucial factor in the formation of tetraplexes. The details of the interactions and the base pairing could only be explored by accurate computational studies. Such an approach could be considered as the first step in understanding interactions that stabilize DNA tetraplexes. However, an additional investigations are necessary in order to address environmental effects coming from the solvent and other nucleic acid tetrads.

In this paper we report the first quantum chemistry study of the stability and structure of the A type GCGC tetrad. The aim of our study is to reveal the details of molecular geometries, the energy properties, and the electrostatic potential characteristics involved in the formation of the GCGC tetrad. Specifically, we will address the following questions: (1) is the isolated GCGC tetrad stable? and (2) which is the most stable form among the three possible conformers?

Method of Calculation

The local minima of the GCGC tetrad structures have been fully optimized by analytic gradient techniques using both Hartree−Fock theory (HF) and density functional theory with Becke's three-parameter (B3)[16] exchange functional along with the Lee−Yang−Parr (LYP) nonlocal correlation functional (B3LYP).[17,18] The standard valence triple-ζ basis set augmented with six d-type and three p-type polarization functions, 6-311G(d,p),[19] was used in the calculations. Mebel, Morokuma, and Lin[20] demonstrated that the geometries and frequencies of the molecules calculated at the B3LYP/6-311G(d,p) level agree well with experiment. The absolute deviations

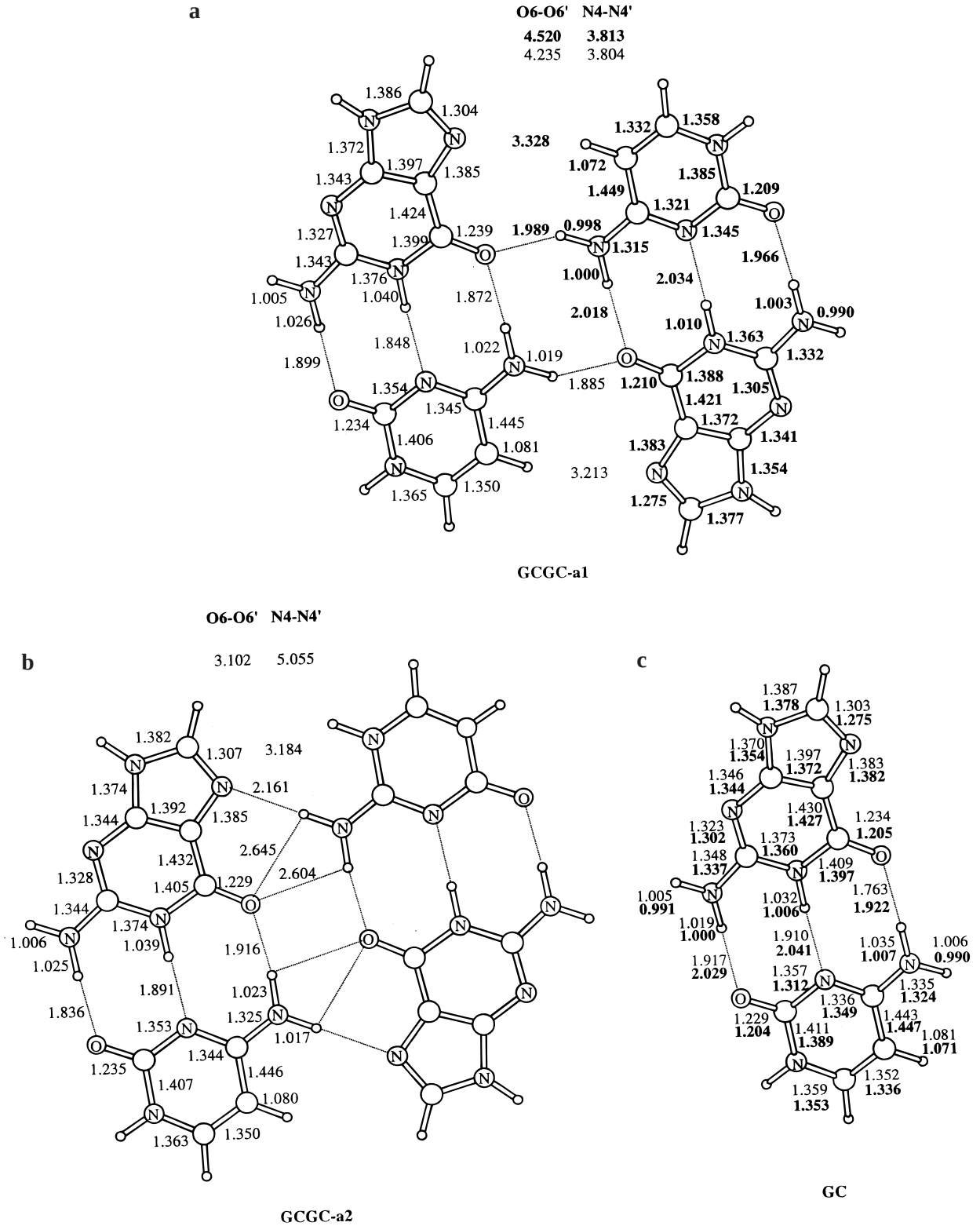


Figure 1. Fully optimized GCGC tetrads of type A. Two different conformations are labeled as **GCGC-a1** and **GCGC-a2**. The **GCGC-a1 form resembles A1 in Scheme 1 in which the two base pairs are bonded to each other via the H atom at N4 of the cytosine residues and the O6 atom of the guanine residues. However, GCGC-a2** could be either A2 or A3 in Scheme 1, depending on the definition of H-bonding. Optimized GC base pair parameters are also listed for comparison. Atomic distances in Å. Calculations are performed at the B3LYP/6-311G(d,p) and the HF/ 6-311G(d,p) levels. The HF results are in bold.

for the bond lengths and angles at the B3LYP/6-311G(d,p) level are smaller than those obtained at the ab initio MP2/6-31G(d) and QCISD/6-31G(d) levels of theory.[21] Our previous studies on hydrogen-bonded systems involving DNA bases have shown that the B3LYP approach predicts reliable interaction energies and is compatible with the MP2/6−31(d,p) method.[22,23] The performance of the HF approximation was also examined in this study because it yields longer hydrogen bonds than the B3LYP method while it predicts a similar stabilization energy for the G tetrad, the TATA tetrads, and the AGAG tetrad as

TABLE 1: Energy Properties of the Bases, Base Pairs, and Base Tetrads Calculated at the B3LYP/6-311G(d,p) and HF/6-311G(d,p) Levels (Bold)

	E (hartree)	BSSE (kcal/mol)	ΔE^a (kcal/mol)	$\Delta E^{BSSE\ b}$ (kcal/mol)	$\Delta E(I)^{BSSE\ c}$ (kcal/mol)
base					
guanine	−542.697 912 7	−2.63			
	−539.527 512 6	**−1.80**			
cytosine	−395.037 895 7	−2.46			
	−392.713 191 7	−1.63			
base pair					
GC	−937.784 315 3	−1.97	−30.44[d]	−25.35	
	−932.282 249 7	**−1.23**	**−26.07[d]**	**−22.64**	
tetrad					
GCGC-a1	−1875.605 315 1		−83.90	−73.72	−19.08
	−1864.596 707 1		**−72.35**	**−65.49**	**−17.13**
GCGC-a2	−1875.602 317 8		−82.02	−71.84	−17.20

[a] $\Delta E = E$(tetrad) − 2E(base1) − 2E(base2). [b] $\Delta E^{BSSE} = \Delta E$ − 2BSSE(base1) − 2BSSE(base2) for the tetrad and ΔE − BSSE(base1) − BSSE(base2) for the base pair. [c] $\Delta E(I)^{BSSE} = E$(tetrad) − 2E(base pair) − 2BSSE(base pair). [d] $\Delta E = E$(base pair) − E(base1) − E(base2).

shown in our previous calculations.[13,14] The Gaussian-94 package of programs[24] was used in the calculations. Boys' routine has been used to correct the BSSE.[25]

Results and Discussion

Geometry. Two different conformers of the GCGC tetrad have been located as the local minima of the potential energy surface at the B3LYP/6-311G(d,p) level. The optimized structures and the geometric parameters are depicted in Figure 1. The geometric parameters of the GC base pair optimized at the same theoretical level are also listed in the figure for comparison. Although there was no planarity restriction applied during the optimization, the final optimized structures are almost planar. The deviations from the tetrad plane are less than 0.02 Å in both structures. One of the local minima clearly corresponds to A1 (**GCGC-a1** in Figure 1) in which the two base pairs are bonded to each other via the H atom at N4 of the cytosine residues and the O6 atom of the guanine residues. This structure has also been located through the optimization at the HF/6-311G(d,p) level. The inter GC base pair H(N4)−O6 hydrogen bond length is evaluated to be 1.885 Å at the B3LYP/6-311G-(d,p) level (1.989 Å at the HF level). As revealed by the calculations, the N7 atoms of the guanines are not involved in the formation of the tetrad. The closest H atom of the cytosine is about 3.2 Å away from the N7 atom of the guanine. The formation of the GCGC tetrad in the **GCGC-a1** form depends solely on the H-bonding interaction between the H(N4) of the cytosines and the O6 of the guanines. No substantial change has been observed in the geometric parameters of the cytosines and the guanines compared to those of the GC base pair. However, the formation of the tetrad influences the intra base pair H-bonding. The presence of the inter base pair H(N4)−O6 hydrogen bonding weakens the intra base pair H(N4)−O6 hydrogen bonds. The intra bases-pair H(N4)−O6 hydrogen bond length increases from 1.763 Å in the GC bases pair to 1.872 Å in the **GCGC-a1** tetrad; the elongation is about 0.11 Å. However, the formation of the **GCGC-a1** tetrad seems to strengthen the other two pairs of the intra base pair hydrogen bonds. The N3−H(N1) bond length is 1.848 Å in the tetrad, about 0.06 Å shorter than in the GC pair (1.910 Å). The less affected intra base pair O2−H(N2) bond length is reduced by approximately 0.02 Å in the tetrad compared to the isolated GC pair. A similar change can also be seen in the HF level result in which the increase in the intra base pair H(N4)-O6 bond distance is about 0.10 Å while the decreases of the N3−H(N1) and the O2−H(N2) bond lengths are 0.01 and 0.06 Å, respectively.

The geometric parameters of the **GCGC-a2** structure in Figure 1 suggest that this form resembles the A2 conformer characterized by the hydrogen bonding between the H atom at N4 of the cytosine and the N7 atom of the guanine residues in the tetrad. This local minimum energy structure can only be located at the DFT level of theory. The inter GC base pair H(N4)−N7 bond distance is predicted to be 2.161 Å at the B3LYP/6-311G(d,p) level, indicating that the inter base pair interaction in **GCGC-a2** is weaker than that in **GCGC-a1**. This form is different from the **GCGC-a1** conformer in which there is only one pair of H-bond holding the two GC pairs together. The **GCGC-a2** is stabilized by another two pairs of weaker H(N4)−O6 interactions. These two H(N4)−O6 atomic distances are 2.645 and 2.604 Å, respectively. Similar to the **GCGC-a1** conformation, the weaker inter base pair interactions between the two H atoms at N4 of cytosine and the O6 atom of guanine reduce the intra GC pair H(N4)−O6 hydrogen bonding while slightly extending the N3−H(N1) and O2−H(N2) intra base pair hydrogen bonds. The intra base pair H(N4)−O6 bond length is evaluated to be 1.916 Å, about 0.15 Å longer than that in the isolated GC pair. The shortening of the N3−H(N1) bond by 0.02 Å and of the O2−H(N2) bond by 0.08 Å in the **GCGC-a2** form is close to those in the **GCGC-a1** conformer. It should be noted that the O6−O6′ atomic distance in **GCGC-a2** amounts to 3.102 Å, approximately 1.1 Å closer than in **GCGC-a1**. The electrostatic repulsion should be stronger in the **GCGC-a2** form. This extra electrostatic repulsion contribution could be balanced by the two pairs of the H(N4)−O6 interactions between the two opposite GC pairs. It is well-known that hydrogen bonding described by the HF approach is much weaker than by the DFT method. The fact that the **GCGC-a2** conformer is not stable at the HF/6-311G(d,p) level indicates that the even weaker H(N4)-O6 interactions described by the HF/6-311G-(d,p) method are not sufficient to balance the O6−O6′ repulsion in the short atomic distance.

Stability. The energy characteristics of the GCGC tetrads are listed in Table 1. At the B3LYP/6-311G(d,p) level, the total energy of the **GCGC-a1** conformation is about 1.9 kcal/mol lower than the energy of the **GCGC-a2** form. The stabilization energy, relative to the isolated bases of the tetrad, is 73.7 kcal/mol for the former and 71.8 kcal/mol for the latter. This amounts to approximately 5−7 kcal/mol higher than the stabilization energy predicted for the guanine tetrad[13,14] (66.5 kcal/mol after the BSSE[25] correction) at the same theoretical level. There are eight strong H-bonds in both of the planar G tetrad and the GCGC tetrads. This 5−7 kcal/mol of stabilization energy improvement in the GCGC tetrad could be attributed to existence

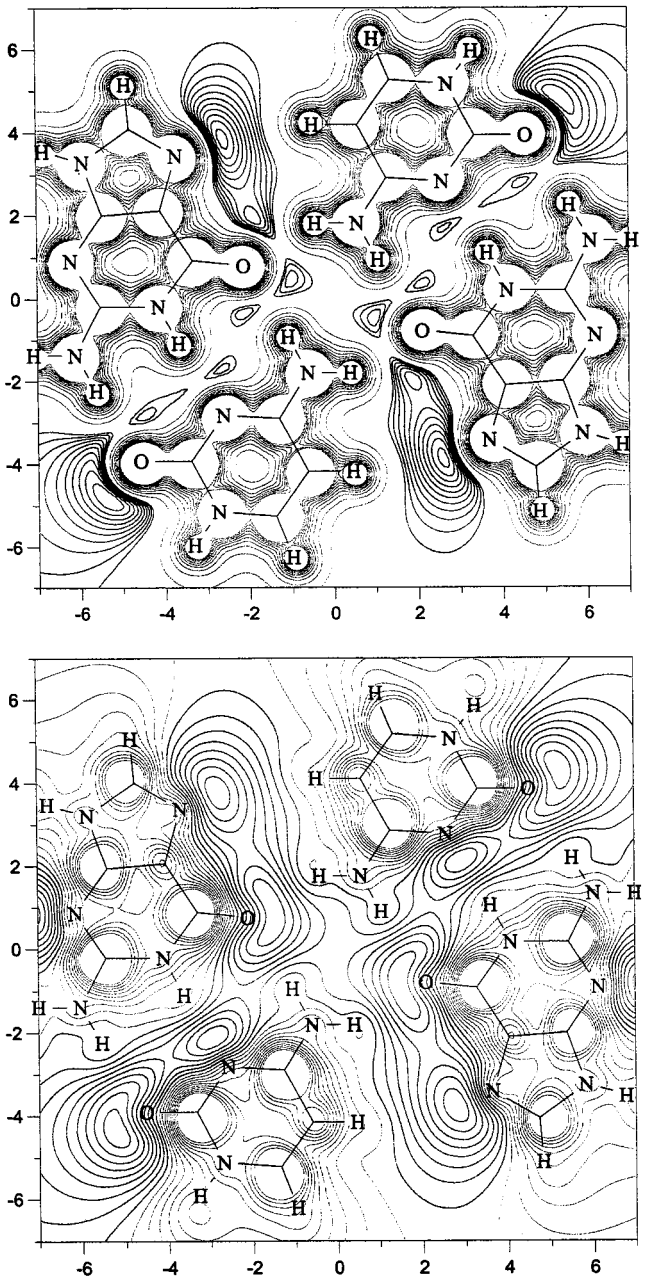


Figure 2. Electrostatic potential map of **GCGC-a1**. The top panel is the ESP on the plane of the tetrad. The bottom panel is the ESP map 2 Å above the plane. The thin line represents the positive part of the electrostatic potential, and the thick line is the negative part. The contour spacing in the top panel is 0.1 au for the positive part and 0.01 au for the negative part. The contour spacing in the bottom panel is 0.01 au for both the positive and the negative parts. The unit of the axes is in Å.

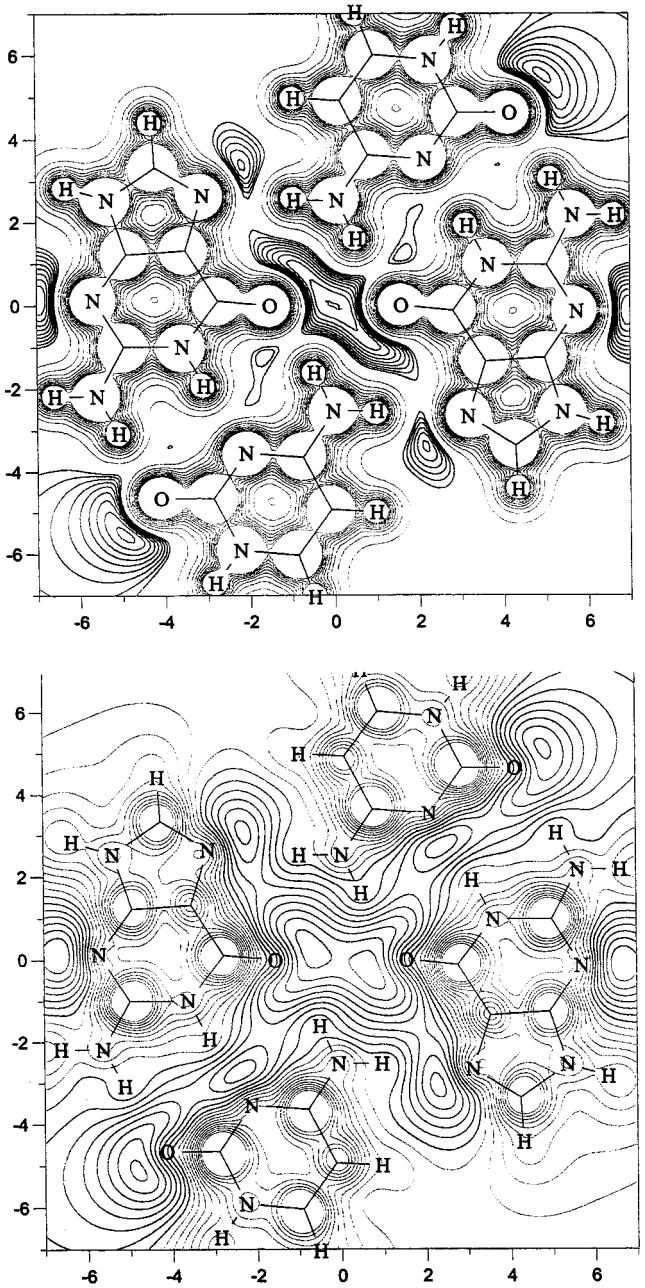


Figure 3. Electrostatic potential map of **GCGC-a2**. The top panel is the ESP on the plane of the tetrad. The bottom panel is the ESP map 2 Å above the plane. The thin line represents the positive part of electrostatic potential, and the thick line is the negative part. The contour spacing in the top panel is 0.1 au for the positive part and 0.01 au for the negative part. The contour spacing in the bottom panel is 0.01 au for both the positive and the negative parts. The unit of the axes is in Å.

of the six strong intra base pair H-bonds in the GC pairs. However, the inter base pair H-bonds in the two conformers of the GCGC tetrad also play a significant role. The energy difference between the GCGC tetrads and the two GC base pairs is 19.1 kcal/mol for the **GCGC-a1** form and 17.2 kcal/mol for the **GCGC-a2** conformation. Subtracting these from the stabilization energy relative to the isolated bases, one may account for the 54.64 kcal/mol stabilization energy of two GC base pairs. Compared to the isolated GC pair in which the stabilization energy amounts to 25.35 kcal/mol after BSSE, there is an extra stabilization energy of about 2 kcal/mol for each GC pair in the tetrad. This can also be seen from the HF result. The extra stabilization energy is about 1.5 kcal/mol for each GC pair in the tetrad as predicted by the HF/6-311G(d,p) approach. The fact that the presence of the inter base pair H-bonds further stabilizes the GC base pair in the tetrads suggests the importance of the cooperative effect in the GCGC tetrad.

In **GCGC-a1** the stabilization energy $\Delta E(I)^{\mathrm{BSSE}}$ could be considered as the only contribution from the inter base pair H(N4)−O6 H-bonding because there is no interaction involving the N7 atom of guanine. The bonding energy is then estimated to be 9.5 kcal/mol for each of the H(N4)−O6 hydrogen bonds in the tetrad at the B3LYP/6-311G(d,p) level (8.6 kcal/mol at the HF/6-311G(d,p) level). However, the H(N4)-N7 stabilization energy $\Delta E(I)^{\mathrm{BSSE}}$ of 17.2 kcal/mol in **GCGC-a2** should not be simply assigned to the formation of hydrogen bonding between

the opposite GC pairs. There are two additional contributions involving interactions between the two H atoms at N4 of cytosine and the one O6 atom of guanine that also stabilize this conformation. As discussed above, a fraction of the H(N4)−O6 interactions in **GCGC-a2** is compensated by the extra electrostatic repulsion due to the short O6−O6′ atomic distance. Accordingly, if there is a cation around the central area of the GCGC that could compensate for the O6−O6′ repulsion, one might expect that the **GCGC-a2** form of the tetrad will be more stable.

Electrostatic Potential. An easy way to predict how different geometries could alter reactivity in intact DNA is to analyze the electrostatic potential (ESP) map. ESP can also be used to predict the possible metal interaction sites. The electrostatic potentials of the two conformations of the GCGC tetrad are depicted in Figures 2 and 3. The contour plot of ESP of the **GCGC-a1** form shows that the electrostatic potential in the center of the GCGC tetrad is slightly positive, suggesting that the O6−O6′ electrostatic repulsion has been screened by the H atoms of the amino group of the cytosine residues. Cations could not be hosted in the center of this form. In the plane 2 Å above the tetrad, the ESP of the central area is slightly negative as seen from the bottom panel of Figure 2. However, the most negative electrostatic potential area is located close to O6 and N7 of the guanines. Introducing a cation around the central area of the **GCGC-a1** form will not further stabilize this tetrad. We expect that the **GCGC-a1** conformer is more stable in the absence of any cation around its central area. The most negative part of the ESP of the **GCGC-a2** form is in the center of the tetrad (Figure 3), indicating the strong electrostatic repulsion between the O6−O6′ atomic pair. Cations hosted in this center are expected to further stabilize this form. Considering that the O6−O6′ atomic distance is about 3.2 Å in **GCGC-a2**, hosting a cation in the center of the tetrad seems to be impractical. However, the small O6−O6′ atomic distance does not prevent cations from resting in the central area above the tetrad. The contour map of ESP drawn at the plane 2 Å above the tetrad shows that the most negative area is close to the center. Unlike the **GCGC-a1** form, a small size cation hosting in the central area above the tetrad is expected to further stabilize the **GCGC-a2** conformer through a balancing of the O6−O6′ repulsion.

To further understand the roles of the GCGC tetrad in the tetraplexes, it is important to reveal how the cations such as Na^+ and K^+ interact with the GCGC tetrads. Also it will be interesting to see whether the cooperative effect exists in the B type of the GCGC tetrad in which two GC pairs are held together through the hydrogen bonding of the O2 of the cytosine in one base pair and the H atom of the amino group of the guanine in the other. Theses studies are in progress in our laboratories.

Conclusions

The reliable data obtained using quantum chemical methods enable us to address the following.

Both A type conformations of the GCGC tetrad form stable structures. The stabilization energies amount to about 72 kcal/mol relative to the isolated bases. The inter GC pair interactions contribute about 17−19 kcal/mol to the total stabilization energy, and such a stabilization energy confirms that the stabilization of the tetrads plays a key role in the four-stranded helices. These tetrads are even more stable than the G tetrad in the absence of cations.

The **GCGC-a1** conformer formed through the inter base pair H(N4)−O6 hydrogen bonding is about 2 kcal/mol more stable than the **GCGC-a2** form. However, the relative stability of the conformers could be affected by the presence of cations that are able to balance the electrostatic repulsion of the O6−O6′ atomic pair in the tetrad.

The cooperative effect of the hydrogen bonding has been found to be important for the formation of the GCGC tetrads. The presence of the inter base pair hydrogen bond enhances the intra GC base pair hydrogen bonding about 2 kcal/mol for each GC pair in the tetrads.

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