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A Theoretical Study of Thymine and Uracil Tetrads: Structures, Properties, and Interactions with the Monovalent K^+ Cation

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The molecular geometries, energy properties, H-bonding patterns, and electrostatic potential characters of the thymine (T) and uracil (U) tetrads and the role of the potassium cation in the formation of the T tetrad and U tetrad have been studied at the B3LYP/6-311G(d,p) and the HF/6-311G(d,p) levels of theory. Both the T and the U tetrads are found to be stable in the isolated form. The stabilization energy of the U tetrad is about 6.8 kcal/mol more than that of the T tetrad. The lower stabilization energy of the T tetrad suggests the repulsion between the methyl group of the bases and the O2 atoms of their neighbors. While the nonplanar U tetrad has a bowl-like shape, the nonplanar T tetrad exhibits a propeller structure. The presence of a cation is critical for the formation of T or U tetrads in the G tetrad-containing tetraplexes. The cation−tetrad interaction energy has been evaluated to be about 65 kcal/mol for both tetrads. The similarity between both the cation−tetrad interaction energies and the K^+−O4 distances predicted for the both tetrads suggests that the electrostatic interaction between the K^+ ion and the O4 atoms dominates the cation−tetrad interactions. It has been found that the K^+−T tetrad and the K^+−U tetrad complexes alone could not be stable in aqueous solutions because of the high hydration energy of K^+. However, the stacking of the T tetrad or the U tetrad on the adjacent G tetrad will be greatly enhanced in the presence of potassium cations in the tetraplexes.

Introduction

Telomeres are found at the ends of linear eukaryotic chromosomes and have been reported to be crucial for various biological functions.[1−3] The length of the telomeric DNA has been reported to be related to aging and cancers.[4−7] Different DNA-base tetrad structures, such as the guanine tetrad,[8−10] the adenine tetrad,[11] and the guanine−cytosine−guanine−cytosine tetrad,[12−16] have been detected in telomeric DNA. A uracil tetrad has been found in RNA.[17] Recently, a thymine-formed tetrad (T tetrad) has been reported to exist in the parallel-stranded DNA formed by *Saccharomyces cerevisiae* telomere repeats.[18] Like other tetrads, a stable thymine tetrad is expected to have the potential to generate a variety of structures. In the NMR experiment, the T tetrad has been found to be formed only via O4···H(N3) H bonds in one plane. The NMR experimental results also suggest that the T tetrad can be stacked on the adjacent G tetrad in different ways.[18]

The stability of the T tetrad in the tetraplexes depends on the stability of the tetrad itself and the stacking interactions with the adjacent guanine tetrads. On the other hand, the U tetrad, which is structurally and chemically similar to the T tetrad, has been found to stack on a G tetraplex as a "finishing structure".[17] Recent quantum chemical studies of A tetrads,[19] G tetrads,[20,21] GCGC tetrads,[22] TATA tetrads,[23] and AGAG tetrads[23] suggest that the bonding energy of a single hydrogen bond in the tetrads amounts to 4−9 kcal/mol. It should be interesting to verify whether the hydrogen-bonding pattern in the T tetrad and U tetrad falls within this range. The presence of a monovalent cation such as a potassium cation is important for the formation of the T tetrad or U tetrad in the G tetrad-containing tetraplexes.[17,18] The structures and stability of tetraplexes do not solely depend on the interactions in isolated tetrads. The base-pairing interactions and the cation−tetrad interactions might be crucial factors in the stabilization of tetraplexes. The details of such interactions and the base pairing could only be explored by accurate computational studies.

As an extension to our previous studies of DNA-base tetrads, the molecular structures and the stabilities of the thymine (T) tetrad and the uracil (U) tetrad have been investigated using the ab initio Hartree−Fock (HF) method and the density functional theory (DFT). We report here the first quantum chemical study of the T and U tetrads and their complexes with a cation. The purpose of our study is to reveal the details of the molecular geometries, energy properties, H-bonding patterns, and electrostatic potential characteristics and the influence of the potassium cation involved in the formation of the T and U tetrads. Although the properties of such species could be affected by their surroundings, previous studies of the various tetrads have shown that the stability of the tetrads in the isolated form is the main contribution to the formation of the tetrads in the tetraplexes.[19−23]

Method of Calculation

The local minima of the T tetrad and U tetrad have been fully optimized by analytic gradient techniques. Because of the sizes of the studied systems, the optimizations were not followed by frequency calculations. The methods used were the ab initio HF and the DFT with Becke's three parameter (B3)[24] exchange functional along with the Lee−Yang−Parr (LYP) nonlocal correlation functional (B3LYP).[25,26] The standard valence

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triple-ζ basis set augmented with six d-type and three p-type polarization functions, 6-311G(d,p),[27] was used in conjunction with both methods. It is well-known that the geometries and frequencies of the molecules calculated at the B3LYP/6-311G-(d,p) level agree well with experiment.[28] The absolute deviations for the bond lengths and angles at the B3LYP/6-311G(d,p) level are smaller than those at the MP2/6-31G(d) and QCISD/6-31G-(d) levels of theory.[29] Although previous studies have suggested that the B3LYP/6-31G(d,p) method might be not suitable for a consistent study of the whole range of DNA-base interactions because of the insufficiency in describing the dispersion interactions,[30,31] the density functional method predicts reliable interaction energies of the hydrogen-bonded systems.[30−32] Because hydrogen bonding dominates the stability of the tetrads, the B3LYP/6-311G(d,p) level is a cost efficient approach to the study of such large systems. For a comparison, the HF approximation was also used because it predicts similar stabilization energies for the other tetrads as shown in our previous studies.[19−23] The interaction between the monovalent cation K^+ and the tetrads has been studied at the ab initio HF level. The basis set used in the calculation for potassium was the double-ζ basis plus one set of d functions as derived by Ahlrichs et al.[33] To estimate the stability of the planar form of the tetrads, plane constraint was added during the optimization procedure for these structures. The Gaussian 94 package of programs[34] was used in the calculations. The Boys' routine has been applied to correct the basis-set superposition error (BSSE).[35]

Results and Discussion

Both planar and nonplanar forms of the thymine and the uracil tetrads have been located as the local minima on the potential energy surface at both the HF/6-311G(d,p) and B3LYP/6-311G-(d,p) levels. The optimized structures and the geometric parameters are depicted in Figures 1 and 2. All of the structures show C_4 symmetry.

Overall, the optimized structures resemble the structure of the T tetrad and U tetrad reported in the experimental studies.[17,18] Thymines are held together through the hydrogen bonds between the H(N3) atom of one thymine and the O4 atom of the other base. The same bonding pattern is also observed in the U tetrad. An examination of the obtained results enables us to reveal the details concerning the formation of the tetrads.

T Tetrad. At the B3LYP/6-311G(d,p) level, the nonplanar form of the T tetrad has been predicted to have a stabilization energy of 18.10 kcal/mol, relative to the four separated thymines (see Table 1), which is about 3.8 kcal/mol more than that of the planar form. This energy difference at the HF level amounts to approximately 2.5 kcal/mol. The origin of this energy difference can be understood on the basis of the geometric differences of the two forms.

In the planar form, the hydrogen-bond length of O4···H(N3) has been evaluated to be 2.093 Å and the bond angle of O4···H−N3 to be 170° at the B3LYP/6-311G(d,p) level of theory. This value for the bond length suggests that the H bonds that hold the tetrad are not very strong. An ab initio HF method yields weaker H bonds with a bond length of 2.255 Å and a bond angle of 169° as can be seen from Figure 1. In addition to the O4···H(N3) H bond, there is weak interaction between the two methyl hydrogen atoms and the O2 atom. The H(C)···O2 distances amount to 2.542 Å and the C−H···O2 angle to 107° in the planar form. It is important to notice that the O4−O4′ and the O4−O2′ distances in the planar form are quite different. The former amounts to 4.05 Å, while the latter amounts to only 3.65 Å. This uneven structure will be adjusted in the nonplanar conformation.

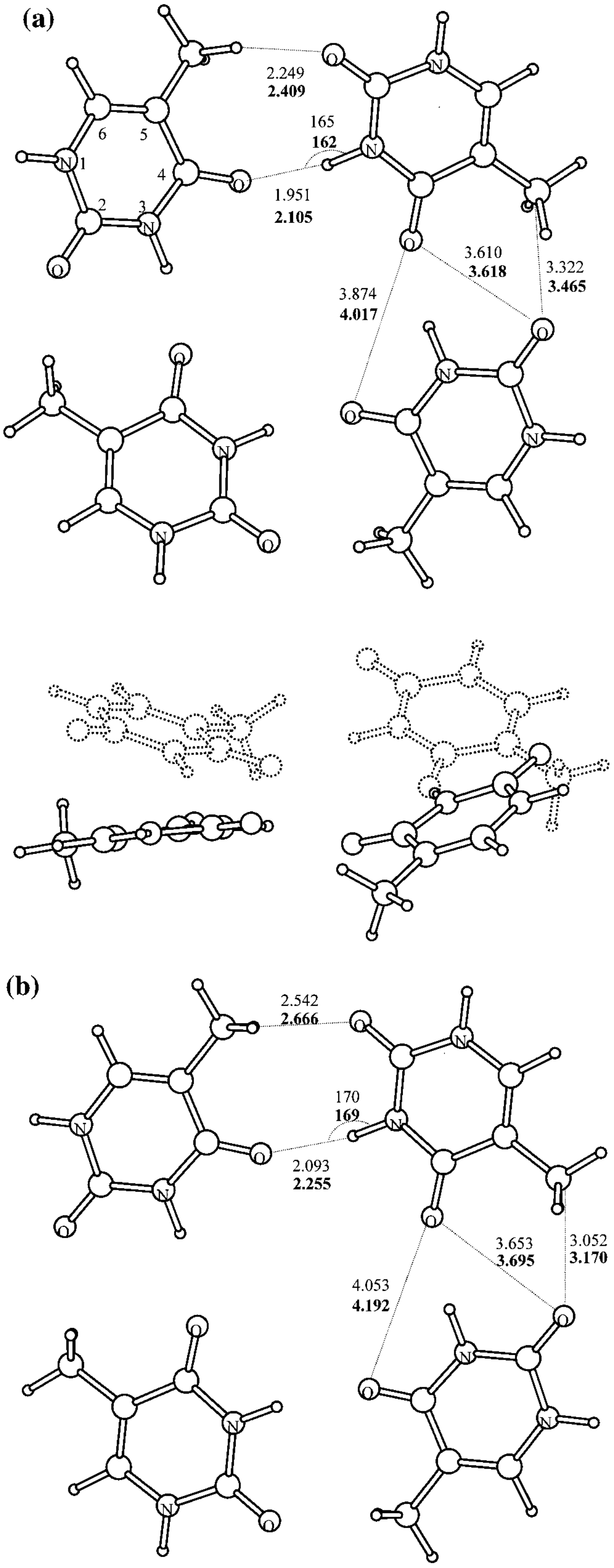

Figure 1. The optimized structures and the parameters of the nonplanar form (a) and the planar form (b) of the thymine tetrad. Side view of the nonplanar structure is also given in part a. Atomic distances are given in Å, and angles are given in deg. The basis set used in all calculations is 6-311G(d,p). DFT is denoted by plain text, and HF is denoted by a bold font.

In the nonplanar form, the bonding between O4 and H(N3) is a little stronger than in the planar form. The bond length of O4···H(N3) has been calculated to be 1.952 Å, about 0.06 Å

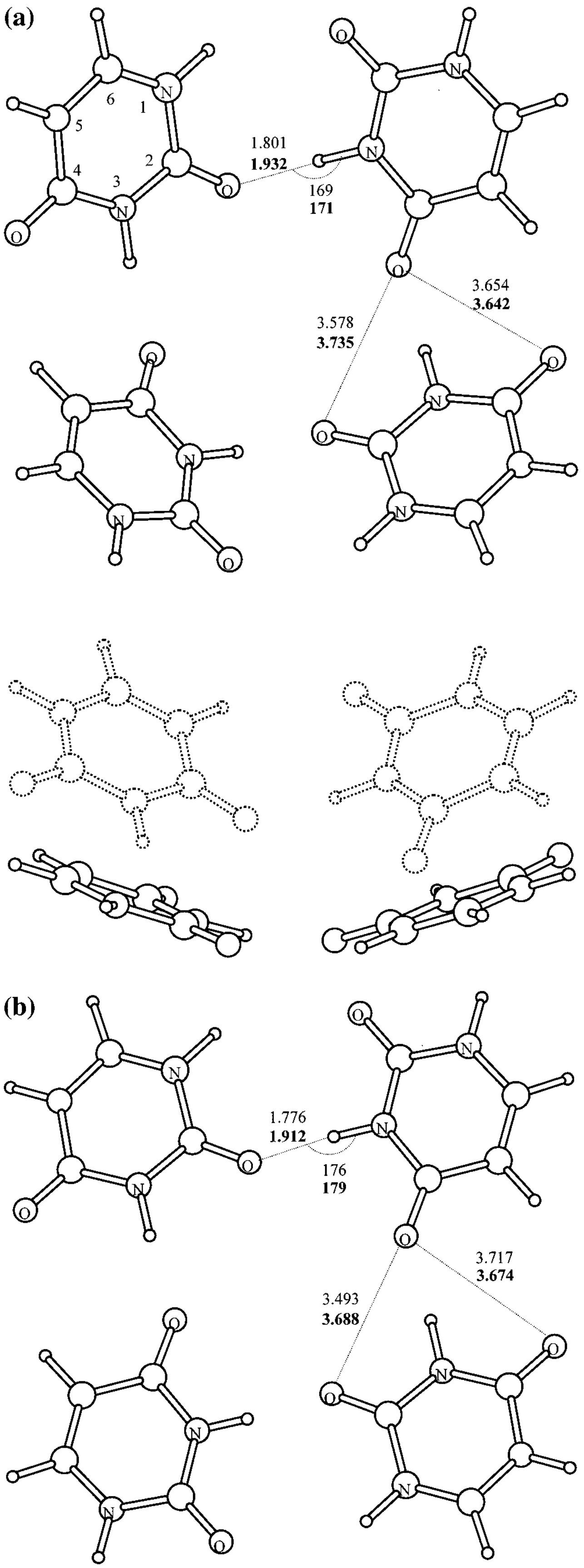

Figure 2. The optimized structures and the parameters of the nonplanar form (a) and the planar form (b) of the uracil tetrad. Side view of the nonplanar structure is also given in part a. Atomic distances are given in Å, and angles are given in deg. The basis set used in all calculations is 6-311G(d,p). DFT is denoted by plain text, and HF is denoted by a bold font.

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

base/tetrad	*E* (hartree)	BSSE (kcal/mol)	ΔE^a (kcal/mol)	$\Delta E^{\mathrm{BSSE}\ b}$ (kcal/mol)
thymine	−454.264 69	−2.15		
	−451.623 53	**−1.24**		
uracil	−414.934 61	−2.20		
	−412.575 16	**−1.31**		
		Planar		
T4	−1817.095 26		−22.91	−14.31
	−1806.521 91		**−17.64**	**−12.68**
U4	−1659.790 08		−30.06	−24.26
	−1650.341 31		**−25.66**	**−20.42**
		Nonplanar		
T4	−1817.101 31		−26.70	−18.10
	−1806.526 26		**−20.17**	**−15.21**
U4	−1659.791 15		−30.73	−24.93
	−1650.341 54		**−25.80**	**−20.56**

[a] $\Delta E = E(\text{tetrad}) - 4E(\text{base})$. [b] $\Delta E^{\mathrm{BSSE}} = \Delta E - 4\mathrm{BSSE}(\text{base})$.

shorter than that of the planar form, and the bond angle of O4···H−N3 amounts to 165° at the B3LYP/6-311G(d,p) level. The O4−O4′ distance is now reduced to 3.87 Å, while the O4−O2′ distance remains almost unchanged. On the other hand, the interaction between the methyl hydrogen and the O2 atom seems to be stronger than in the planar form. The H(C)···O2 distance amounts to 2.249 Å (about 0.30 Å shorter), and the C−H···O2 angle is equal to 167° in the nonplanar form. Because the nonplanar form is 3.8 kcal/mol more stable, the stronger repulsion caused by the short H(C)···O2 atomic pair should be no stronger than the repulsion from the two longer H(C)···O2 atomic pairs in the planar form. In fact, this repulsion should be viewed as the repulsion between the methyl group at the C5 position and the O2 atom of its neighbor base. In the planar form, the distance between C_{methyl} and O2′ amounts to 3.05 Å at the B3LYP/6-311G(d,p) level. However, this distance increases to 3.32 Å in the nonplanar form. This methyl−O2′ repulsion is very significant, and its role will be further addressed by a comparison with the U tetrad (see below). The stronger O4···H(N3) H bonding, similar O4−O4′ and O4−O2′ distances, and less methyl−O2′ repulsion account for the increase in the stabilization energy of 3.8 kcal/mol in the nonplanar form of the T tetrad. Each O4···H(N3) bond contributes at least 4.5 kcal/mol to the stabilization of this tetrad.

It is interesting to notice that unlike the other tetrads such as the A tetrads and the TATA tetrads, which adopt a bowl shape in their nonplanar form, the nonplanar form of the thymine tetrad presents a propeller-like structure. Obviously, the existence of this unique propeller structure is due to the repulsion between the methyl group in one thymine and the O2′ atom of its neighbor.

U Tetrad. Similar to the thymine tetrad, the optimized conformers of the U tetrad also resemble the experimental structure.[17] To form the U tetrad, uracils are held together through the hydrogen bonds between the H(N3) and the O4 atoms of the neighboring uracils.

The stabilization energy of the nonplanar U tetrad has been estimated to be 24.9 kcal/mol at the DFT level which is about 6.8 kcal/mol more than that of the T tetrad (18.1 kcal/mol). Without the methyl groups at their C5 positions, uracils could easily adjust their orientations to form better H bonds in the U tetrad. Each O4···H(N3) bond contributes at least 6.25 kcal/mol to the total stabilization energy. On the other hand, the planar U tetrad shows the similar O4···H(N3) H bond length as compared to its nonplanar structure. The energy difference

TABLE 2: The Energy Properties of the K$^+$−Tetrad Complexes Calculated at the HF/6-311G(d,p) Levels[a]

	E(complex) (hartree)	E(tetrad+basis) (hartree)	E(K$^+$+basis) (hartree)	ΔE[b] (kcal/mol)	ΔE^{BSSE} [c] (kcal/mol)
K$^+$−T tetrad					
planar	−2405.629 06	−1806.524 78	−599.001 67	−66.30	−64.39
nonplanar	−2405.634 06	−1806.529 11	−599.001 67	−66.70	−64.81
K$^+$−U tetrad[d]					
planar	−2249.446 47	−1650.344 34	−599.001 65	−65.05	−63.06
K$^+$			−599.001 51		

[a] E(tetrad+basis) is calculated as the energy of optimized tetrad structure with basis functions of K in the center. E(K$^+$+basis) is calculated as the energy of K$^+$ with basis functions of the tetrad located according to the optimized complex structure. [b] ΔE = E(complex) − E(tetrad) − E(K$^+$). [c] ΔE^{BSSE} = E(complex) − E(tetrad+basis) − E(K$^+$+basis). [d] No optimized form of the nonplanar K$^+$−U tetrad was found.

between the planar and the nonplanar U tetrad amounts to only 0.6 kcal/mol at the B3LYP/6-311G(d,p) level. Similar results are also revealed at the HF/6-311G(d,p) level.

In the planar form, the hydrogen bond length of O4···H(N3) has been predicted to be 1.776 Å and the O4···H−N3 bond angle to be 176° at the B3LYP/6-311G(d,p) level of theory. The H bonds that hold the tetrad are much stronger than those of the T tetrad. A similar result is also obtained at the HF/6-311G(d,p) level. The O4···H(N3) bond length of 1.913 Å and the bond angle of 179° are predicted by the HF method. The bonding between the O4 and H(N3) atoms has been slightly decreased in the nonplanar form. The bond length of O4···H(N3) in the nonplanar form has been calculated to be 1.801 Å, 0.03 Å longer than that of the planar form, and the bond angle of O4···H−N3 to be 169° at the B3LYP/6-311G(d,p) level. The corresponding HF predictions are 1.932 Å and 171°, respectively. The bowl shape has been predicted for the nonplanar form of the U tetrad as shown in Figure 2. Because the nonplanar form of the U tetrad is a little more stable than the planar form (0.6 kcal/mol), the weakening of the O4···H(N3) H bond in the bowl-shaped U tetrad must be compensated by other interactions. This compensation for the nonplanar form includes the increasing of the O4−O4′ atomic distance in the tetrad so as to reduce the O4−O4′ repulsion. In the nonplanar form the O4−O4′ atomic distance is 3.58 Å, 0.10 Å longer than that in the planar form.

Although T and U tetrads share a similar bonding pattern, they have different nonplanar structures. This is due to the fact that in the T tetrad the nonplanarity arises from the repulsion between the methyl group and the O2 atom in the neighboring pairs while in the U tetrad the nonplanarity results from the O4−O4′ repulsion. Because the methyl group on the C5 of thymine is the only structural difference compared with uracil, the lower stabilization energy of the T tetrad suggests that the repulsion between the methyl group and the O2 atom of the neighboring thymine is the main factor in destabilizing the T tetrad.

Electrostatic Potentials. The electrostatic potentials (ESPs) reveal important information on properties of the studied systems. By analyzing the ESP maps, it is easy to predict the stacking interactions between the tetrads. ESP can also be used to predict the possible metal interaction sites. In general, the contour plots of the ESP of the T tetrad and U tetrad are similar. These ESPs are also very much similar to the ESP predicted for the G tetrad.[20] In the plane of the tetrads, the most negative part of the electrostatic potential is located in the central area of the tetrads. The presence of a monocation in the center of the tetrads would further stabilize the tetrads. However, there is an important difference observed for the ESP maps of the T and U tetrads. The ESP in the center of the T tetrad is less negative than that of the U tetrad. Because previous studies have shown that cations such as Na$^+$ and K$^+$ could be hosted between the G tetrads or in the plane of the G tetrad, the more negative ESP in the central area of the U tetrad suggests that K$^+$ should be hosted better in the center of the U tetrad than in the T tetrad. On the other hand, the more negative ESP located 1.5 Å above the central area of the T tetrad plane implies a better cation hosting position for the T tetrad.

The presence of a cation is critical for the formation of the T tetrad or the U tetrad in the G tetrad-containing tetraplexes. The ESPs located 1.5 Å above the tetrad plane are negative in the central area for both tetrads. Because the negative electrostatic potential appears around the central area 1.6 Å above of the guanine−tetrad plane,[20] these negative centers of the T and U tetrads are expected to be balanced by the presence of a cation in the central area when stacked to or between the G tetrad in the tetraplexes.

K$^+$−Tetrad Interactions. The cation−tetrad complexes have been optimized as the local energy minima at the HF level. The plane constraint was applied for the considered planar form of the K$^+$−T tetrad complex. No restrictions were used in the optimization for the other cation−tetrad complexes. The interaction energies between the tetrads and monovalent potassium cation, K$^+$, are listed in Table 2, and the main geometric properties are depicted in Figures 3 and 4.

The presence of a K$^+$ in the center of the T tetrad further weakens the O4···H(N3) hydrogen bonding in the planar form of the tetrad. The bond length of O4···H(N3) in the T tetrad amounts to 2.549 Å, about a 0.25 Å increase due to the presence of the K$^+$. This effect also has been found in the nonplanar K$^+$−T tetrad system in which the bond distance of O4···H(N3) is estimated to be 2.238 Å, about 0.13 Å longer than in the isolated nonplanar T tetrad (2.105 Å at the HF/6-311G(d,p) level). Both planar and nonplanar forms have almost the same K$^+$−O4 distance (2.740 Å for the former and 2.735 Å for the latter). The propeller structure of the nonplanar T tetrad has been preserved in the nonplanar K$^+$−T tetrad complex, implying that the propeller conformation is fairly stable. The cation has been found to be about 1.3 Å above the center of the tetrad. As expected from an analysis of the ESP maps above, the K$^+$−T tetrad complex is slightly less stable when the cation is hosted in the center of the T tetrad plane. The interaction energy calculated as the difference between the energy of the cation−tetrad complex and the energy of the individual tetrad and cation amounts to −64.39 kcal/mol, about 0.4 kcal/mol less than that of the nonplanar form.

Optimization of the K$^+$−U tetrad complex leads only to the planar form. Similar changes as revealed for the T tetrads have also been observed in the geometry of the U tetrad. Typically, the bond length of O4···H(N3) amounts to 2.192 Å in the K$^+$−U tetrad complex, 0.18 Å longer than in the planar form of the U tetrad. The cation−O4 distance amounts to 2.640 Å at the HF/

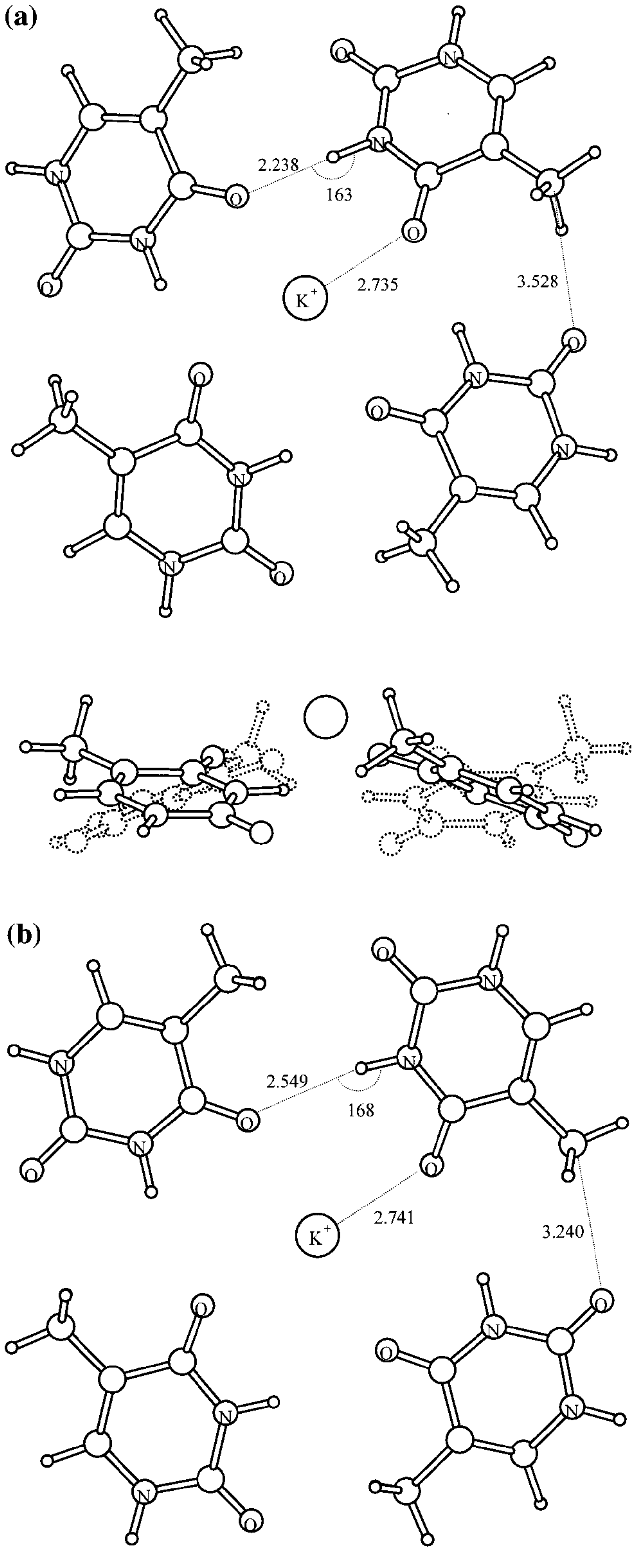

Figure 3. The optimized structures and the parameters of the nonplanar form (a) and the planar form (b) of the K$^+$−T tetrad complex. A side view of the nonplanar structure is also given in part a. Atomic distances are given in Å, and angles are given in deg. The basis set used in the calculations is 6-311G(d,p) for the tetrad and the double-ζ basis plus one set of d functions derived by Ahlrichs et al. for potassium.

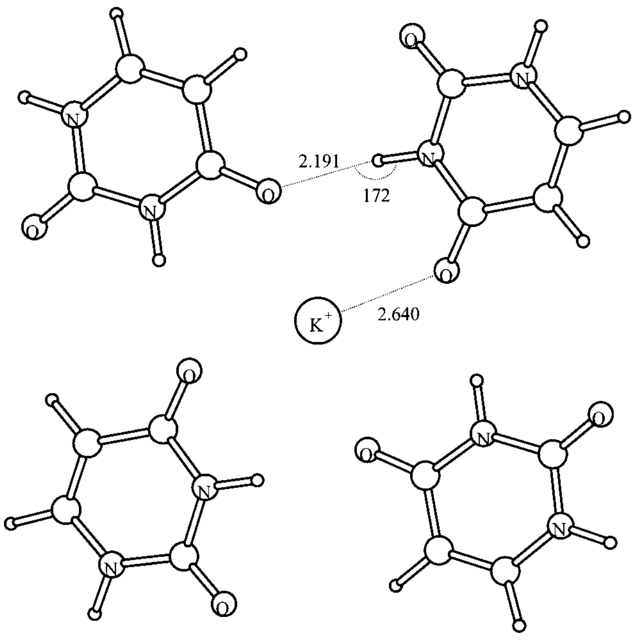

Figure 4. The optimized structures and the parameters of the planar form of the K$^+$−U tetrad complex. Atomic distances are given in Å, and angles are given in deg. The basis set used in the calculations is 6-311G(d,p) for the tetrad and the double-ζ basis plus one set of d functions derived by Ahlrichs et al. for potassium.

6-311G(d,p) level, about 0.10 Å shorter than that in the T tetrads. The cation−tetrad interaction energy has been evaluated to be −65.05 kcal/mol, also close to that of the T tetrads. The similar cation−tetrad interaction energies suggest that the electrostatic interaction between the K$^+$ ion and the O4 atoms dominates the cation−tetrad interactions for both complexes.

Considering that the hydration free energy and the corresponding enthalpy of K$^+$ at room temperature are −80.6 and −76.7 kcal/mol,[36] respectively, it is clear that the K$^+$−T tetrad and the K$^+$−U tetrad complexes should not be stable in aqueous solutions. The formation of the T tetrad and U tetrad in the tetraplexes depends on the stability of the tetrads themselves and on their stacking interactions with the adjacent G tetrads. On the other hand, because the K$^+$−G tetrad complex is quite stable in water solutions, the stacking of the T tetrad or U tetrad on the adjacent G tetrad will be greatly enhanced in the presence of potassium cations in the tetraplexes. A potassium cation sandwiched between the T tetrad or U tetrad and the adjacent G tetrad is expected to further stabilize the T tetrad or U tetrad in the tetraplexes.

Conclusion

The theoretical study of T and U tetrads enables us to derive the following conclusions.

(1) Both T and U tetrads are stable in the isolated form. The U tetrad is about 6.8 kcal/mol more stable than the T tetrad. The O4···H(N3) H bond in the tetrads is the main factor in the formation of the tetrad. The contribution of the bonding energy of each O4···H(N3) bond amounts to at least 4.5 kcal/mol in the T tetrad and 6.3 kcal/mol in the U tetrad. The lower stabilization energy of the T tetrad suggests the repulsion between the methyl group of a base and the O2 atom of its neighbor.

(2) Although the T and U tetrads share similar bonding patterns, they have different nonplanar structures. The propeller structure in the T tetrad arises from the repulsion between the methyl group and the O2 atom, while with the bowl-like structure in the U tetrad suggests that the nonplanarity results from the O4−O4′ repulsion.

(3) The presence of a cation is critical for the formation of the T tetrad or U tetrad in the G tetrad-containing tetraplexes. The negative ESP centers of the T and U tetrads have to be balanced by the presence of a cation when stacked on or between the G tetrad in the tetraplexes.

(4) The cation−tetrad interaction energy has been evaluated to be around −64 kcal/mol for both tetrads. The similar cation−tetrad interaction energies and the similar K^+−O4 distances observed for the T tetrad and the U tetrad suggest that the electrostatic interaction between the K^+ ion and the O4 atoms dominates the cation−tetrad interactions.

(5) Because the hydration free energy and the corresponding enthalpy of K^+ at room temperature are −80.6 and −76.7 kcal/mol,[36] respectively, it is clear that the K^+−T tetrad and the K^+−U tetrad complexes should not be stable in aqueous solutions. The formation of the T tetrad and U tetrad in the tetraplexes depends on the stability of the tetrads themselves and on their stacking interaction with the adjacent G tetrads.

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