Density Functional Study of Adenine Tetrads with N6−H6···N3 Hydrogen Bonds

Michael Meyer*,† and Jürgen Sühnel‡

Revotar Biopharmaceuticals AG, Neuendorfstrasse 24a, D-16761 Hennigsdorf, Germany, and Biocomputing Group, Leibniz Institute for Age Research − Fritz Lipmann Institute, Jena Centre for Bioinformatics, D-07745 Jena, Germany

Received: October 23, 2007; In Final Form: February 1, 2008

The structure and energy of A-tetrads with N6−H6···N3 H-bonds was studied using B3LYP and BH&H density functional theory. The planar A-tetrad with C_{4h} symmetry is more stable than the nonplanar structures at C_4 and S_4 symmetry. This structure corresponds to a local energy minimum. The energies of the structures with N6−H6···N1 and N6−H6···N7 H-bonds studied previously are of similar magnitude. Structures of A-tetrad complexes with sodium and potassium were most stable at S_4 symmetry, and similarly, sandwich complexes consisting of two tetrads and a single cation were most stable at S_8 symmetry. Relative energies of sandwich complexes with different symmetries obtained with the B3LYP and BH&H methods were quite different. BH&H overestimates the interaction energies between hydrogen-bonded neighbor bases relative to B3LYP.

Introduction

DNA tetraplexes have been selected frequently to study the processes of cation recognition and self assembly.[1,2] Further, tetraplexes are relevant for nanowires in bio-nanotechnology and for the design of anti-cancer drugs targeting telomerase in an indirect manner.[3−6]Another potential application is the treatment of radioactive waste since they show a high degree of selectivity for Ra^{2+}.[7] Therefore, tetraplexes and tetrads, the tetraplex building blocks, have been studied by a broad range of experimental and theoretical methods.[1,8]

Quantum-chemical studies on guanine (G)-tetrads, the most frequently occurring building block of tetraplexes, provided valuable information in addition to experimental data.[9−13] Studies on unusual tetrads may reveal differences between the standard building blocks of tetraplexes and the less common tetrads, thereby providing clues for the preference of classical G-tetrads. Thus far, quantum-chemical studies on unusual polyads include the AGAG-,[14] ATAT-,[14] GCGC-,[15] U-,[12] iG-[16] tetrads and two different A-tetrad structures.[17,18] More recently, sandwich complexes consisting of two polyads and a cation in between, have been studied by density functional calculations.[19−22] Further, QM/MM calculations[23] and molecular dynamics studies on tetraplexes have been performed.[24,25]

The environment of the nucleic acids may enforce a variety of different structural arrangements of the bases in general. This is also a consequence of the abundance of pairing formations of A and other bases arising from stacking or H-bonding. Some of the structures in a crystal may not even be in a local minimum in the gas phase. Various structures adopted by A-pairs have been studied by molecular dynamics and by DFT.[26,27] Here, we report on a quantum-chemical study of the properties of an A-tetrad with a cyclic N6−H6···N3 H-bond topology resembling the H-bond patterns occurring in the crystal structure of rU(BrdG)r(AGGU).[28] In this hexameric crystal structure, the A-tetrad interacts with four U bases to form an octad. In other tetraplexes, A-tetrads with a N6−H6···N1 or N6−H6···N7 hydrogen bond patterns have been found.[29,30] First, we present structural features and interaction energies and perform a comparison with A-tetrads previously reported.[17] Second, we describe complexes formed by a single tetrad and sodium or potassium cations. Third, we present the features of sandwich complexes consisting of two tetrads and an intercalating cation.

Methods

Initial tetrad structures have been generated adopting geometries from the tetraplex crystal structure containing an A-tetrad with N6−H6···N3 H-bonds (NDB ID: UR0024, PDB ID: 1MDG).[28] To save computation time, geometry optimizations have been performed imposing symmetry constraints taking into account planar (C_{4h}) and nonplanar (S_4, C_4) structures (Figure 1). Tetrad cation complexes have been generated subsequently by adding sodium or potassium ions to the optimized tetrad structures leading to complexes of C_4, C_{4h}, and S_4 symmetry (Figure 2). Finally, sandwich complexes consisting of two stacked tetrads and a sodium or potassium cation located in between have been generated from optimized fragments (C_{4h}, D_4, and S_8 symmetry, Figure 3).

Tetrads have been studied using the B3LYP hybrid density functional method[31,32] with the DGauss DZVP basis sets optimized for DFT calculations.[33,34] The optimized structures have been checked by subsequent frequency calculations and interaction energies have been corrected for the basis set superposition error (BSSE).[35] Structures and interaction energies have also been analyzed using the BH&H functional proposed recently to yield reasonable stacking energies at moderate computational effort.[36,21] All DFT calculations were carried out with Gaussian98 and Gaussian03[37] at the Fritz Lipmann Institute.

Relative energies with respect to the most stable structure are denoted by ΔE_r. The interaction energies were calculated according to a previously described scheme.[12] The total tetrad interaction energy was calculated according to eq 1, where

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* Corresponding author. Fax: +49 33022025030. E-mail: m.meyer@revotar-ag.de.

† Revotar Biopharmaceuticals.

‡ Jena Centre for Bioinformatics.

10.1021/jp710242k CCC: $40.75

E(A4) denotes the energy of the adenine tetrad and E(A) is the energy of a single base in the full tetrad-centered basis.

$$\Delta E = E(\mathrm{A4}) - 4E(\mathrm{A}) \tag{1}$$

For the tetrads with four symmetry-equivalent bases, the total interaction energy can also be expressed according to eq 2.

$$\Delta E = 4\,\Delta E^{\mathrm{n}} + 2\,\Delta E^{\mathrm{d}} + \Delta E^{\mathrm{c}} \tag{2}$$

ΔE^{n} is the interaction energy between H-bonded neighbor base pairs. The interaction energy between opposite base pairs is given by ΔE^{d}. The cooperative contribution ΔE^{c} is adjusted so that the sum of eq 2 equals ΔE.

In the complex, each base is distorted from its ideal monomer geometry, and the corresponding deformation energy ΔE^{def} is the energy difference between the structure adopted by a single base in the complex and the optimized structure of this base alone.

$$\Delta E^{\mathrm{T}} = \Delta E + 4\Delta E^{\mathrm{def}} \tag{3}$$

Furthermore, the zero point vibration energy difference ΔZPE between the tetrad and four individual bases contributes to ΔE_0 according to

$$\Delta E_0 = \Delta E^{T} + \Delta \mathrm{ZPE} \tag{4}$$

We discuss the interaction between all bases of structures corresponding to local minima at the ΔE_0 level, whereas interaction energies of other structures are discussed in terms of ΔE^{T}.

For the metal ion tetrad complex ($n = 1$) and the sandwich complex ($n = 2$), we also calculate the interaction energy ΔE^{ML} between the metal ion and the ligand

$$\Delta E^{\mathrm{ML}} = E(\mathrm{M(A4)}_n) - nE(\mathrm{A4}) - E(\mathrm{M}) \qquad n = 1, 2 \tag{5}$$

Results

In the following section, we present the results determined at the B3LYP/DZVP level, as this corresponds to the method used in a number of our previous studies. Other studies have been carried out at the same hybrid density functional level but with different basis sets. At the end of each section, we describe the most important difference between the results determined at the B3LYP/DZVP level and those determined at the BH&H/DZVP level.

A-Tetrad A4. The A-tetrad has been analyzed for different relative base−base orientations adopting a planar C_{4h} symmetry or nonplanar C_4 and S_4 symmetries (Figure 1). The bases may interact for all symmetries via N6−H6···N3 H-bonds to form cyclic H-bonded tetrads. Frequency calculations indicate that only the C_{4h}-symmetric structure with N6−H6···N3 H-bonds corresponds to a local minimum.

The nonplanar S_4- and C_4-symmetric conformations are 8.58 and 0.65 kcal/mol less stable than the C_{4h}-symmetric conformation. The interaction energy between neighbor bases ΔE^{n} is −4.9 kcal/mol for the planar C_{4h}-symmetric structure, and the total interaction energy ΔE^{T} is −18.9 kcal/mol. The non-additive contribution for the planar A-tetrad conformation is about 5% of ΔE (Table 1a).

The geometrical analysis reveals that the A-tetrad is characterized by an N6−H6···N3 angle of 172.7° in the C_{4h} structures. The length of the H6−H6···N3 H-bond is 2.11 Å. Further, there is a relatively short C2−H2···N3 distance of 2.40 Å with a C2−H···N3 angle of 150.7°. The slightly less stable C_4-symmetric structure shows similar geometric features (Table 1a).

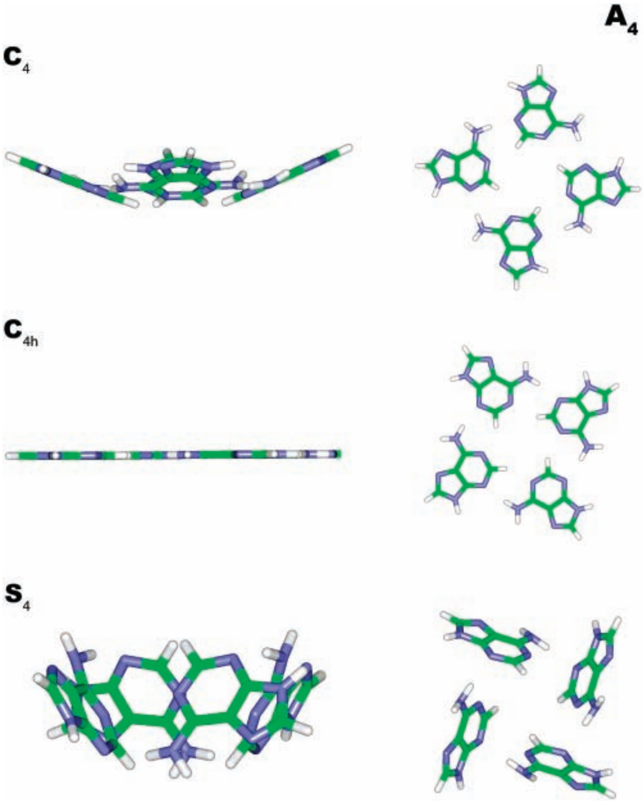

Figure 1. Structures of the A-tetrad with N6−H···N3 H-bonds.

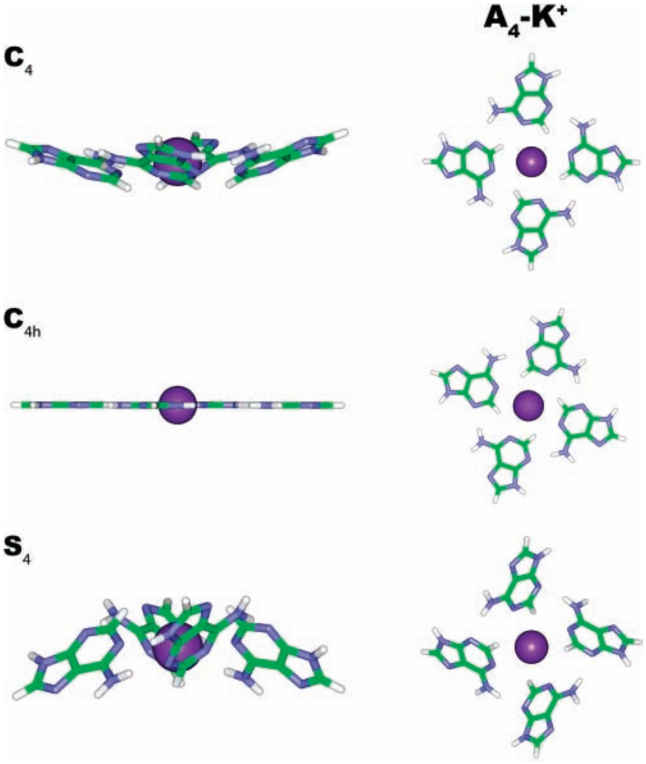

Figure 2. Structures of the potassium complex with a single A-tetrad with N6−H···N3 H-bonds.

BH&H/DZVP predicts shorter hydrogen bonds and C−H···O contacts in the A-tetrad (Table 1b). These geometrical features correspond approximately to a doubling of the neighbor interaction energy ΔE^{n}. This leads to much higher values of

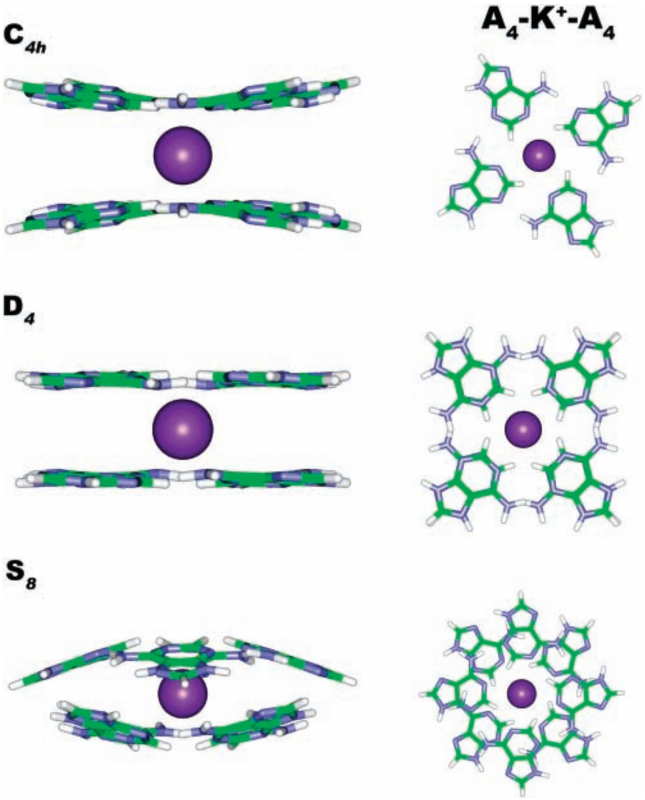

Figure 3. Structures of the potassium complex with two A-tetrads with N6−H•••N3 H-bonds.

−39.7 and −35.3 kcal/mol for ΔE^{T} and ΔE_0, respectively. An optimization of the bowl-type C_4-symmetric structure obtained with B3LYP/DZVP with BH&H/DZVP leads to a completely planar C_{4h}-symmetric geometry. The energy difference between the C_{4h}- and the S_4-symmetric structure is much smaller at BH&H level than at B3LYP level.

A-Tetrad Cation Complex A4M. In the presence of sodium or potassium cations, nonplanar S_4-symmetric complex structures are more stable than planar structures with the cation located at the center (Figure 2). The complexes of the A-tetrad with sodium and potassium are quite different at C_4 symmetry. In the potassium complex, the H-bond pattern N6−H•••N3 is preserved. In contrast, sodium cations have a more drastic influence on the structure. Instead of a N6−H•••N3 H-bond pattern, we found only structures with a N6−H•••N1 H-bond pattern. This type of structure is not in the focus of this investigation as it was described previously.[17] Table 2a shows that the interaction between the sodium cation and the tetrad ΔE^{ML} is stronger than the interaction of the potassium ion and the tetrad. This cation ligand interaction energy is the major contribution to the total interaction energy ΔE.

The most striking difference between the results obtained with both density functional methods are the contributions to the interaction energy. According to BH&H/DZVP, the fractional contribution of ΔE^{ML} to ΔE is much smaller than for B3LYP/DZVP. This is in line with the much higher BH&H/DZVP next neighbor interaction energy of a single tetrad described in the section above. Optimizations of the C_4-symmetric sodium complexes with both DFT methods converge to structures with the N6−H•••N1 H-bonds, whereas the N6−H•••N3 H-bonds are preserved in potassium complexes.

Sandwich Complex A4MA4. For the sandwich complexes, the structures with S_8 symmetry are more stable than the structures with C_{4h} or D_4 symmetry (Figure 3). In these structures, the hydrogen bond distance r(N6−H•••N3) is slightly shorter than that in a single tetrad (Table 1a and Table 3a). Again, there is a stronger interaction between sodium and the ligands than between potassium and the ligands.

TABLE 1: Energies and Geometries of Adenine Tetrads[a]

(a) B3LYP/DZVP method

		C_{4h}	C_4	S_4
E	(H)	−1869.56052	−1869.55948	−1869.54684
ΔE_r	(kcal/mol)		0.65	8.58
ΔE^n	(kcal/mol)	−4.9		
ΔE^d	(kcal/mol)	0.1		
ΔE^c	(kcal/mol)	−1.1		
ΔE	(kcal/mol)	−20.5		
ΔE^{def}	(kcal/mol)	0.4		
ΔE^T	(kcal/mol)	−18.9		
ΔE^{ZPE}	(kcal/mol)	2.3		
ΔE_0	(kcal/mol)	−16.6		
r(N6-H•••N3)	(Å)	2.11	2.08	2.12
r(C2-H•••N3)	(Å)	2.40	2.53	
α (N6-H•••N3)	(°)	172.7	172.7	164.8
α (C2-H•••N3)	(°)	150.7	150.7	

(b) BH&H/DZVP method

		C_{4h}	C_4	S_4
E	(H)	−1856.56817	−1856.56816	−1856.56619
ΔE_r	(kcal/mol)		0.0	1.24
ΔE^n	(kcal/mol)	−10.2		
ΔE^d	(kcal/mol)	0.1		
ΔE^c	(kcal/mol)	−1.1		
ΔE	(kcal/mol)	−41.7		
ΔE^{def}	(kcal/mol)	0.5		
ΔE^T	(kcal/mol)	−39.7		
ΔE^{ZPE}	(kcal/mol)	4.4		
ΔE_0	(kcal/mol)	−35.3		
r(N6-H•••N3)	(Å)	1.94	1.94	1.99
r(C2-H•••3)	(Å)	2.21	2.21	
α (N6-H•••N3)	(°)	171.1	171.0	158.6
α (C2-H•••N3)	(°)	151.1	151.0	

[a] Abbreviations: E total energy; ΔE_r relative energy with respect to the most stable structure; ΔE^n pair interaction energy between hydrogen-bonded neighbor bases; ΔE^d pair interaction energy between non-neighbor bases; ΔE^c cooperative interaction energy; ΔE interaction energy; ΔE^{def} deformation energy of each base; ΔE^T total interaction energy corrected for deformation; ΔE^{ZPE} change of zero point energy due to tetrad formation; ΔE_0 total interaction energy corrected for deformation and zero point energy change; r distance; and α angle of H-bond. Interaction energies are listed for the most stable structure.

Both density functional methods predict that the S_8-symmetric structure is the most stable sandwich complex. However, the relative energies are dramatically different. In contrast to B3LYP/DZVP, there is hardly a difference of the interaction energy ΔE^{ML} for the different cations sodium and potassium complexes at the BH&H/DZVP level.

Discussion

Relative Energies of A4 Base Tetrad Structures. Single nucleic acid tetrads with an H-bond pattern corresponding to the tetraplex crystal structures may adopt either planar C_{4h}-symmetric or nonplanar S_4-symmetric structures. For the A-tetrad with N6−H•••N3 hydrogen bonds, the C_{4h}-symmetric structure corresponds to a local energy minimum. In contrast, for A-tetrads with N6−H•••N7 and N6−H•••N1 H-bonds, the nonplanar S_4 structures are more stable than the C_{4h}-symmetric ones.[17] However, neither the planar C_{4h} nor the nonplanar S_4 structure with the before-mentioned H-bond patterns correspond to local minima. When comparing the most stable structures at different H-bond topologies, the A-tetrad with N6−H•••N7 H-bonds is 0.70 kcal/mol more stable than the one with N6−

TABLE 2: Energies and Geometries of A4-M Tetrad Cation Complexes[a]

(a) B3LYP/DZVP method

M		Na		K		
		C_{4h}	S_4	C_{4h}	C_4	S_4
E	(H)	−2031.71441	−2031.73378	−2469.31829	−2469.32081	−2469.32215
ΔE_r	(kcal/mol)	12.15		2.42	0.84	
ΔE^{ML}	(kcal/mol)		−81.8			−59.8
ΔE	(kcal/mol)		−84.4			−67.5
ΔE^{def}	(kcal/mol)		0.6			0.7
ΔE^{T}	(kcal/mol)		−82.0			−64.7
ΔE^{ZPE}	(kcal/mol)		3.9			3.7
ΔE_0	(kcal/mol)		−78.1			−61.0
r(N6−H···N3)	(Å)	2.01	2.29	2.11	2.09	2.11
r(C2−H···N3)	(Å)	2.52		2.44	2.61	
α (N6−H···N3)	(°)	174.6	167.9	177.4	172.3	167.7
α (C2−H···N3)	(°)	164.3		165.3	138.2	
r(M···N1)	(Å)	3.06	2.53	3.14	3.14	3.02

(b) BH&H/DZVP method

M		Na		K		
		C_{4h}	S_4	C_{4h}	C_4	S_4
E	(H)	−2018.0950	−2018.12001	−2455.11789	−2455.11884	−2455.12007
ΔE_r	(kcal/mol)	15.69		1.37	0.77	
ΔE^{ML}	(kcal/mol)		−84.7			−66.2
ΔE	(kcal/mol)		−112.8			−98.2
ΔE^{def}	(kcal/mol)		0.6			1.1
ΔE^{T}	(kcal/mol)		−110.4			−93.8
ΔE^{ZPE}	(kcal/mol)		5.8			6.0
ΔE_0	(kcal/mol)		−104.6			−87.8
r(N6−H···N3)	(Å)	1.86	2.08	1.92	1.90	1.90
r(C2−H···N3)	(Å)	2.15		2.23	2.30	
α (N6−H···N3)	(°)	172.5	155.9	174.4	172.9	165.1
α (C2−H···N3)	(°)	166.6		167.0	149.3	
r(M···N1)	(Å)	2.92	3.01	2.98	2.99	2.87

[a] Sodium complexes of C_4 symmetry show a different H-bond pattern. For abbreviations, see Table 1 and text.

TABLE 3: Energies and Geometries of the A4-M-A4 Sandwich Complex[a]

(a) B3LYP/DZVP method

M		Na			K		
		C_{4h}	D_4	S_8	C_{4h}	D_4	S_8
E	(H)	−3901.27952	−3901.28948	−3901.29715	−4338.89357	−4338.90295	−4338.91188
ΔE_r	(kcal/mol)	11.06	4.81		11.50	5.6	
ΔE^{ML}	(kcal/mol)			−59.1			−55.2
r(N6−H···N3)	(Å)	2.05	2.07	2.02	2.07	2.09	2.03
r(C2−H···N3)	(Å)	2.36	2.35	2.41	2.37	2.37	2.43
α (N6−H···N3)	(°)	173.0	173.2	169.8	173.0	173.5	169.6
α (C2−H···N3)	(°)	155.9	155.1	145.1	156.2	154.0	144.1
r(M···N1)	(Å)	3.67	3.60	3.76	3.72	3.65	3.80

(b) BH&H/DZVP method

M		Na			K		
		C_{4h}	D_4	S_8	C_{4h}	D_4	S_8
E	(H)	−3874.70102	−3874.73661	−3874.76559	−4311.73546	−4311.77029	−4311.80001
ΔE_r	(kcal/mol)	40.52	18.18		40.51	18.65	
ΔE^{ML}	(kcal/mol)			−67.4			−67.7
r(N6−H···N3)	(Å)	1.89	1.92	1.85	1.90	1.92	1.85
r(C2−H···N3)	(Å)	2.17	2.16	2.19	2.18	2.17	2.20
α (N6−H···N3)	(°)	171.8	170.8	167.1	171.9	171.1	167.1
α (C2−H···N3)	(°)	158.7	156.1	147.9	158.6	156.0	147.8
r(M···N1)	(Å)	3.39	3.33	3.49	3.40	3.34	3.50

[a] For abbreviations, see Table 1 and text.

H···N3 H-bonds (C_{4h} symmetry), whereas the tetrad with N6−H···N1 H-bonds is 1.88 kcal/mol less stable (B3L/DZVP level). This indicates that A-tetrads may adopt a variety of structures with different H-bond patterns that can easily be modulated by cations, the nucleic acid backbone, or solvent. One source for nonplanar arrangements of G-tetrads is the pyramidal nitrogen of amino groups.[12] The energy difference between the pyramidal and the planar structure of the amino group in G is 0.74 kcal/mol.[38] On the other hand, for A, the energy difference between the planar and the pyramidal nitrogen atom is only 0.02 kcal/mol,[38] and therefore, the amino groups cannot enforce a nonplanar complex structure. Similarly, the energy difference between both amino group structures is very small in C (0.03 kcal/mol) and the planar structure of C-tetrads corresponds to a local energy minimum in the absence of cations. In contrast, the S_4-symmetric T-tetrad structure corresponds to a local energy minimum and is more stable than the planar structure. As T does not have amino groups, it is clear that the planarity of the amino groups is only one of many parameters governing the planarity of tetrads.

Base−Base Interaction Energies. For the A-tetrad with N6−H···N3 H-bonds, the interaction energy ΔE^{T} is 18.9 kcal/mol. This value is somewhat weaker than for the N6−H···N7 H-bond structure and somewhat stronger than for the N6−H···N3 H-bond structure. In general, as expected for all of these A-tetrad structures, the interaction energy is much smaller than those for the iG- and G-tetrads having two base−base H-bonds instead of one.[12,16] The main contribution to ΔE^{T} arises from the next-neighbor interaction energy ΔE^{n} of 4.9 kcal/mol for each pair of bases. This is somewhat smaller than the corresponding pair interaction energy in the T-tetrad at S_4 symmetry having also only a single H-bond between neighbor bases. The interaction energies listed in Table 1 support the general finding that the deformation energies and the cooperative energies are small if ΔE^{T} is small like in tetrads with a single H-bond between neighbor bases.

It should be noted that the A-tetrad structures contain an A-pair substructure that has been studied previously by Kelly and co-workers.[26] For this A-pair designated $A_2A_4(12)$, the PBE and B3LYP interaction energies are weaker than the BH&H and are stronger than the B3LYP interaction energies between hydrogen-bonded neighbor bases (Table 1.) In the A-pair, H-bond distances are longer than those in the planar tetrad, whereas the corresponding angles are almost unchanged.

Ligand Alkali Metal Ion Interaction Energies. The tetrad sodium interaction energies of A4M are smaller in magnitude than the ones of the sodium complexes with C4, G4, U4, T4, and GCGC studied previously.[39] This holds also for all potassium complexes except for the complex with T4. Similarly, the interaction energy between the cation and both tetrads in the sandwich complexes is much smaller in A4-M-A4 compared with the corresponding complexes G4-M-G4, C4-M-C4, T4-M-T4, and U4-M-U4.[20]

Performance of Density Functional Methods. The B3LYP density functional method was previously used for study of a series of tetrads and tetrads cation complexes since the widely accepted standard tool offers a better efficiency compared with MP2 calculations and it provided results of reasonable accuracy for H-bonded systems and cation−base interactions. On the other hand the application of this method has been criticized for studies of stacked systems.[40] Density fitted local second-order Møller−Plesset perturbation theory (DF-LMP2)[41] and specifically designed density functional methods have been proposed as an alternative.[42,43] Additionally, the BH&H functional has been proposed as an alternative for stacked systems because it provided promising results in comparison with MP2 and CCSD(T) calculations.[21,36]

Our calculations indicate a moderate agreement between the BH&H and the B3LYP methods for single tetrads or tetrad cation complexes. The interaction energies between the H-bonded neighbor bases in the A-tetrad are quite different. For sandwich complexes, both methods predict the S_4-symmetric structures to be most stable. However, the relative energies are much more different, at least with the basis set of medium size used in this study. Recently, BH&H has been subjected to comparative computational studies with different performance results. On the one hand, it has been shown that BH&H underestimates the distance of weakly bound charge-transfer complexes,[44] and more recently it has been concluded that BH&H yields reasonable geometries for nucleic acid bases but it overestimates interaction energies other than stacking energies.[43,45] This finding agrees with the overestimate of the interaction energy between the hydrogen-bonded neighbor bases ΔE^{n} in this study (Table 2a,b). It also explains that the hydrogen bonds are somewhat shorter than the ones obtained with B3LYP. On the other hand, it has also been noted for nucleic acid bases that BH&H yields an excellent agreement with MP2 potential surfaces, and therefore the geometry is well-reproduced, whereas B3LYP failed for stacking, even though it is satisfactory for H- bonds.[46,47]

The discussion about the suitability of novel DFT methods suitable for nucleic acid bases is ongoing. Most recently, the PWB6K, MO5-2X, and KT1 functionals and the TPSS functional with an empirical dispersion calculation have been proposed as promising methods for this purpose.[43,45,47]

Conclusion

The interaction between the nucleic acid bases in A-tetrads is weak in comparison to G-tetrads. This enables the formation of a variety of different structures for this particular tetrad. The comparative density functional calculations with the B3LYP and BH&H methods lead to substantially different relative energies for stacked systems. The choice of the DFT method for molecular systems including stacking interactions has to be checked carefully.

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