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Structure and the energy of base pairing in non-natural bases of nucleic acids: the azaguanine–cytosine and azaadenine–thymine base pairs

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Abstract

Watson–Crick optimized geometries and the energies of base pairing for the natural pairs of nucleic bases: adenine–thymine (AT) and guanine–cytosine (GC) have been recalculated by ab initio methods in order to compare results to those found for the non-natural azaadenine–thymine (AAT) and azaguanine–cytosine (AGC) pairs. Geometry optimizations carried out at the HF/6-31G** level and energies obtained at MP2/6-31G**, show that AAT and AGC have hydrogen bonding patterns similar to the natural AT and GC and that the interaction energies (ΔH^0_{int}) for the former are ca. 7 kcal/mol more stable than the latter. Accordingly, the pairs based on azapurines would be favored with respect to the natural pairs. Some possible explanations why nature does not use extensively the azabases in base pairing are given.

Keywords: Ab initio; Azapurines; Interaction energies; Non-natural pairs

1. Introduction

Hydrogen bonding formation between complementary bases of DNA and RNA is one of the most important and specific cases of molecular recognition in biological

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systems [1]. In fact, the interaction between complementary bases allows the preservation of the genetic code. According to Watson and Crick [1] adenine–thymine (AT) pair is stabilized by two hydrogen bonds, whereas guanine–cytosine (GC) recognizes each other by three hydrogen bonds. Field-ionization mass spectrometry experiments in the gas phase [2] indicate that the interaction energies (ΔH^0_{int}) for GC and AT are ca. −21.0 and −12.9 kcal/mol, respectively. In chloroform [3,4] and dimethylsulfoxide [5] solutions the GC interaction energy decreases to ca. −11 and −6 kcal/mol, respectively. Molecular dynamics simulations of AT and GC in aqueous solution show that free energy changes associated with base pairing are ca. −4.3 and −5.8 kcal/mol, respectively [6]. These results are consistent with the experimental value of ca. −2.0 kcal/mol increment in ΔG^0 for each hydrogen bond formed [7–9]. Application of continuum solvation models coupled to molecular mechanics also agrees with the values reported by Lavery [6]. Gould and Kollman [10] have reported theoretical calculations on the Watson–Crick (WC) pairs 9-methylguanine-1-methylcytosine and 9-methyladenine-1-methylthymine and the Hoogsteen (H) pair 9-methyladenine-1-methylthymine. Full geometry optimization on the isolated bases and the corresponding pairs were carried out at the HF/6-31G* level. Harmonic frequency calculations at this level reveal that the GC(WC) is a true minima, whereas AT(WC) and AT(H) showed at least one imaginary frequency associated with adenine-methyl group rotation. These geometries were not reoptimized as the methyl group is far away enough from the A and T interface and hence the orientation of this group would not exert a significant effect on the ΔH^0_{int}. In energy calculations at the HF and MP2 levels to account for electron correlation, the 6-31G* and Dunning double-ξ plus polarization function (DZP) basis sets were used. Their calculations led to the conclusion that $\Delta H^0_{\text{int.}}$ for AT is ca. −11.9 kcal/mol, which is in good agreement with the value of −12.9 found in field mass spectrometry experiments [2]. The AT(H) pair was found to be ca. 1 kcal/mol more stable than the WC structure. For the GC(WC) pair a value of −25.3 kcal/mol was found. This value does not compare well with the experimental value of −21.0 kcal/mol. A remarkable theoretical value of −11.32 kcal/mol [11] has been derived for the AT(WC) pair using the minimal MINI-1 Huzinaga basis set [12].

Interaction energies for AT and GC pairs have also been calculated using all-electron local spin density functional (LSD) theory. To include non-local effects (NLSD), the Becke–Perdew corrections [13–15] were introduced as an extra term in the SCF procedure. The results show that neither LSD nor NLSD approximations reproduce the experimental data [16]. In 1990, Piccirilli et al. [17] showed that a set of novel bases could be incorporated by DNA and RNA polymerases into both nucleic acids duplexes. The work shows the feasibility of expanding the genetic code beyond the two particular base-pairing schemes AT and GC. Leach and Kollman [18] carried out molecular mechanics and semiempirical calculations on several duplexes containing the Π and K novel bases proposed by Piccirili et al. They arrived at the conclusion that not only did the Π–K pair possess a ΔH^0_{int} comparable to the natural counterpart but the duplexes containing this non-natural pair are slightly less stable than the natural analogs. The development of new nucleosides or nucleotides containing non-natural bases that might work as antibiotic, antiviral, or anticancer

agents is an active area of research. These nucleoside analogs would interact with the AT and GC natural pairs replacing either A or G bases and thereby modifying the transcription process [19–21] or, as is found in some flagellated protozoan parasites (as trichomonads foetus and vaginalis) [22], acting as an alternative substrate for hypoxanthine phosphoribosyl transferarese.

In previous papers [23,24], we reported the prototropic tautomerism, both in the gas phase and in aqueous solution, of two new non-natural bases that are closely related to the natural purines. In fact, azaadenine (AA) and azaguanine (AG) differ from the natural bases in that the C8–H group has been replaced by a nitrogen atom. The presence of this atom provides an additional basic center affecting the basicities of the other nitrogens in the molecule, induces structural changes in the purine ring as well as different biological activity as a result of a distinct glycosyl conformation as compared with the natural purines. At the biological level AA has been studied for its antileukemic [25] and antibiotic [26] activities, whereas AG has been found to be incorporated into several RNA fractions of *Bacillus cereus* [25], replacing guanine (G) residues,. The replacement of G by AG does not occur randomly. It has been found that the AG/G ratio is higher in terminal purines nucleosides and in short nucleic acids chains. In the present work, we have theoretically studied the structure (HF/6-31G**) and energetics (MP2/6-31G**) of AAT and AGC Watson–Crick pairs. In order to properly compare the interaction energies calculated for these non-natural pairs, we have also derived the ΔH^0_{int} for the natural AT and GC pairs. The inclusion of ZPE and basis set superposition error (BSSE) [27] corrections for AT(WC) and GC(WC) leads to theoretical values of ca. −12.0 and −21.3 kcal/mol which are in good agreement with the experimental values of ca. −12.9 and −21.0 kcal/mol, respectively. Although, no experimental values have been reported for the ΔH^0_{int} for AAT and AGC pairs, the above results lend credence to the calculated values for these non-natural pairs. Some possible explanations for the low incorporation of aza analogs of purine RNA bases are also given.

2. Computational methods

Ab initio geometry optimizations for the molecules studied here were carried out at the HF/6-31G** level. The initial geometries for the base pairs were those reported for the isolated nucleic acids bases [23,24,28,29]. Frequency calculations and IR intensities were carried out at the equilibrium geometries yielding all real frequencies and hence all calculated structures are local minima. Energy calculations were performed at the MP2/6-31G** level to include electron correlation in the frozen core approximation. The energies were corrected for zero point vibrational energies (unscaled). In fact, scaling ZPE by 0.9, as usual, to account for the overestimation of Hartree–Fock vibrational frequencies is quite constant along the series of molecules studied here and does not make difference in the general conclusions of this study. For each natural and non-natural pairs, the enthalpies were derived by adding ZPE and the thermal correction $(H - H_0)$ to the energies calculated at MP2/6-31G**. In the calculation of the interaction energies the following procedure was

used: the ΔE values were obtained by subtracting the energies of the isolated purine and pyrimidine bases to the energy of the corresponding pair. The same procedure was applied to obtain ΔZPE and $\Delta(H - H_0)$ values, whereas the BSSE (Basis set superposition error) were calculated using the counterpoise method (CPM) formulated by Boys and Bernardi [27]. Accordingly, we have $\mathrm{BSSE}(XY) = E(X)_X + E(Y)_Y - E(X)_{XY} - E(Y)_{XY}$, where $E(X)_{XY}$ stands for the energy of X calculated at the supermolecule (pair) basis set, whereas $E(X)_X$ is the energy of X derived using its own basis set. The CPM must be taken as an upper estimate to the BSSE and it is kown to work well for the HF level. Conflicting views as to whether BSSE should be applied or not to correlated methods have been reported [30,31]. To estimate the effect of water on the tautomerism of the isolated bases, the solute–solvent interactions were taken into account by incorporating the electric field of the bulk dielectric into the electronic structure of the solute to produce the self consistent reaction field (SCRF). The PCM (polarized continuum method) [32,33], which is able to reproduce well the solvation energies of a number of molecules for which experimental data is available, was used to estimate the free energies of solvation in aqueous solution. The standard free energy of the solute in a solvent ($G^0_{\mathrm{soln.}}$) is given by $G^0_{\mathrm{soln.}} = \Delta G^0_{\mathrm{gas}} + \Delta G^0_{\mathrm{s}}$, where $\Delta G^0_{\mathrm{gas}}$ is the gas free energy change and ΔG^0_{s} corresponds to the free energy of solvation. Accordingly, our calculations account for the polarization contributions and non-electrostatic terms such as cavitation, dispersion, and repulsion energies. All calculations were carried out with Gaussian 98 series of programs [34].

3. Results and discussions

Azapurines (azaadenine and azaguanine) are purine derivatives in which the imidazole C8–H group has been replaced by a nitrogen atom. Accordingly, they can be considered as being formed by a pyrimidine ring fused to a triazole ring. These non-natural bases like the natural adenine and guanine are capable of existing in several tautomeric forms as a result of proton migration from one basic ring center to another. When exocyclic atoms or groups are considered, additional tautomeric forms can be generated. In fact, the hydroxo $\Longleftrightarrow$ oxo and amino $\Longleftrightarrow$ imino equilibria results in 15 tautomeric forms in azaguanine. To focus our study on those species that exist in appreciable concentration, we carried out a stepwise elimination procedure. Thus, the optimized geometries for all possible forms were obtained at AM1 level and all species having energies greater than 10 kcal/mol with respect to the most stable one were eliminated. The remaining species were further optimized by ab initio methods at the HF/6-31G** level. To be consistent with the experimental data for natural purines, just those species with relative energies $\Delta E < 2.5$ kcal/mol remained. In fact, it has been observed that a single species is present in the gas phase if ΔE is ca. 4.5–12 kcal/mol, whereas values of ca. 0–0.5 kcal/mol indicate that tautomeric forms are in similar concentrations. When ΔE values are between 1.0 and 2.5 kcal/mol, one tautomer predominates while the other is in a rather low concentration but still experimentally measurable [35]. According to the above criterion, only

one tautomeric form for each azapurine was considered for pairing with thymine and cytosine. In other words, we have considered in the pairing scheme just the azaadenine [9] and azaguanine [9] (hereafter called azaadenine and azaguanine, respectively). The same tautomeric forms were considered for adenine and guanine. For comparative purposes, the relevant optimized structural parameters for free (unpaired) guanine (G), azaguanine (AG), adenine (A), azaadenine (AA), cytosine (C), and thymine (T) are given in Table 1. The atom numbering used in this and other tables is shown in Fig. 1. The calculated gas phase values compare well with the available experimental data [36–40]. Thus, for AG the largest deviation in bond distances and angles are ca. 0.26 Å and 3°, respectively. For AA a better correlation is observed as the largest bond distance and angle deviations are ca. 0.04° and 1.5°, respectively. Generally speaking, azapurines are quite planar, the pyrimidine and triazole ring make an angle of ca. 1° only. An interesting feature of AG base is the non-planarity of the amino group, which turns out to be a local minima for these structures. A planar $-NH_2$ group produces one imaginary frequency indicating that

Table 1
Bond distances (Å) and angles (degrees) for the isolated bases

	AG	AD	G	A	C	T
Bond distances[a]						
N1–C2(N3–C2)	1.361	1.334	1.359	1.326	1.362	1.370
C2–N3(C2–N1)	1.293	1.310	1.289	1.312	1.402	1.367
N3–C4(N1–C6)	1.352	1.332	1.355	1.329	1.348	1.378
C4–C5(C5–C6)	1.371	1.373	1.368	1.376	1.340	1.330
C5–C6(C5–C4)	1.438	1.408	1.436	1.401	1.445	1.471
H9–N9(H1–N1)	0.993	0.993	0.993	0.993	0.994	0.994
N2–C2(N4–C4)	1.350	1.334	1.359	1.340	1.343	
H21–N2	0.994	0.992	0.994	0.992	0.990	
H22–N2	0.993	0.992	0.994	0.991	0.990	
C8(N8)–N9	1.350	1.344	1.374	1.370		
H1–N1	0.997		0.996			0.997
H8–C8			1.071	1.071	1.071	
O6–C6(O2–C2)	1.190		1.194		1.197	1.195
H6–C6					1.074	1.074
Bond angles[a]						
N1C2N3	124.2	129.2	123.9	128.7	116.5	113.4
C2N3C4(C2N1C6)	112.4	111.2	112.7	111.6	123.2	123.4
N3C4C5(N1C6C5)	128.7	126.3	128.9	126.5	120.4	123.0
C4C5C6	119.3	116.8	118.6	116.1	115.6	117.6
N2C2N1(N4C4N1)	119.4	122.8	119.8	122.4	117.6	
H21N2C2(H41N4C	115.5	118.9	114.3	119.1	118.0	
H22N2C2(H42N4C	120.2	120.8	118.7	120.4	121.9	
H9N9N8(C8)	120.6	120.1	127.7	127.4		
H1N1C6	113.9		113.9			116.6
H8C8N7			125.7	125.1		
O6C6(C2)–N1	119.6		119.1		125.1	123.4
H6C6C5					123.0	122.3

[a] Bond distances and angles in parentheses correspond to C and T.

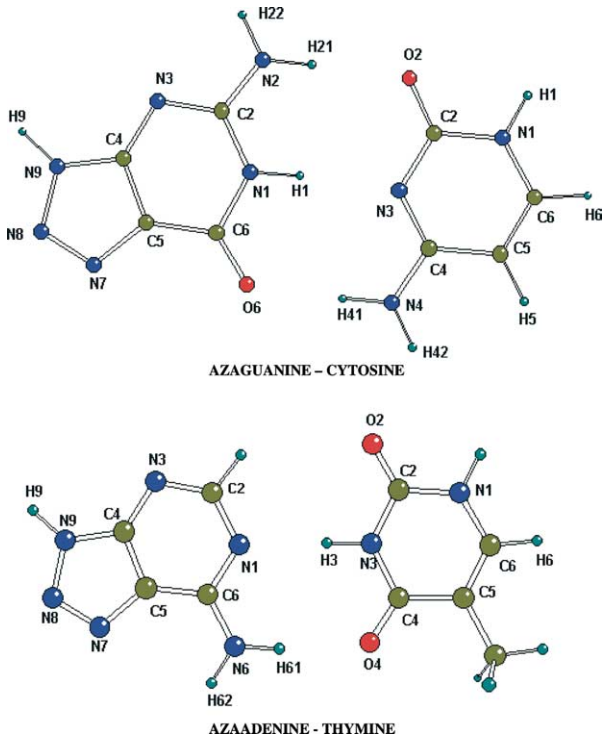

Fig. 1. Optimized structures and atom numbering for the azapurine base pairs.

the structure might correspond to a transition state. In fact, the $-NH_2$ group is pyramidal in AG and G, but planar in AA and A. Frequency calculations at HF/6-31G**, for these species, yielded all real vibrations. Cytosine and thymine in their more stable tautomeric form were also optimized at the HF/6-31G** level. In both cases, structural parameters are consistent with experimental data for 1-methyl-thymine and 1-methyl-cytosine. The prototropic tautomerism in these pyrimidine bases was also studied here, but the most stable oxo and oxo-amino were used for T and C, respectively (see Table 2).

AG and G were paired with C in the Watson–Crick fashion, i.e., as to produce three hydrogen bonds, whereas AA and A form just two hydrogen bonds with thymine. The AGC, GC, AAT, and AT pairs were all optimized at the HF/6-31G** level. Fig. 1 shows the optimized geometries for AGC and AAT pairs. A comparison of bond lengths and angles in these pairs with the corresponding isolated bases, shows that the largest deviations are ca. 0.06 Å and 1.2°. In general, the isolated bases geometries are altered very little by the pairing process. In Table 3, the calculated structural parameters for all atoms involved in hydrogen bonding, are given. From this table, one can infer that non-natural bases (AG and AA) interact with C and T in a similar way that the natural pairs do. In fact, the bond distances and angles for the non-natural pairs are just about the same as those found for the natural ones.

Table 2
Bond distances (Å) and angles (degree) for the bases in the pairs

	AG	AD	G	A	C	T
Bond distances[a]						
N1–C2(N3–C3)	1.364	1.337	1.361	1.333	1.350	1.367
C2–N3(C2–N1)	1.306	1.308	1.303	1.310	1.388	1.370
N3–C4(N1–C6)	1.342	1.334	1.345	1.331	1.353	1.374
C4–C5(C5–C6)	1.375	1.373	1.373	1.375	1.336	1.331
C5–C6(C5–C4)	1.431	1.411	1.427	1.404	1.446	1.469
H9–N9(H1–N1)	0.992	0.993	0.993	0.993	0.994	0.994
N2–C2(N4–C4)	1.331	1.326	1.336	1.332	1.323	
H21–N2(H41–N4)	0.992	1.001	0.991	0.999	1.007	
H22–N2(H42–N4)	1.002	0.992	1.001	0.992	0.991	
N8(C8)–N9	1.353	1.345	1.377	1.371		
H1–N1	1.009		1.008			1.013
H8–C8			1.071	1.071	1.071	
O6–C6(O2–C2)	1.206		1.210		1.209	1.205
H6–C6					1.074	1.074
Bond angles[a]						
N1C2N3	123.9	128.8	123.5	128.3	117.5	113.9
C2N3C4(C2N1C6)	112.3	111.1	112.6	111.6	122.5	123.3
N3C4C5(N1C6C5)	128.8	126.6	129.0	126.7	120.6	122.8
C4C5C6	118.7	117.1	118.0	116.4	116.3	117.3
N2C2N1(N6C6N3)	116.2	120.0	116.3	119.5	118.3	
H21N2C2(H41N4C)	122.9	120.3	122.9	120.5	120.2	
H22N2C2(H42N4C)	117.0	119.7	117.1	119.3	120.7	
H9N9N8(C8)	120.2	120.2	127.7	127.4		
H1N1C6	115.2		115.3			117.1
H8C8N7			125.7	125.2		
O6C6N1(O2C2N3)	120.3		119.6		124.1	120.8
H6C6C5					122.9	122.3

[a] Bond distances and angles in parentheses correspond to C and T.

The non-bonded distances between the electronegative centers (O···N and N···N) are also similar and agree well with the values reported by Santamaria and Vazquez [29]. All bond distances are ca. 3.0 Å, whereas the bond angles are in the range 175–178°. The optimized geometries of the natural and non-natural pairs (see Fig. 1) reveal that the amino group becomes planar upon hydrogen bonding formation [41] and hence all four pairs studied here posses planar structures. This finding agree well with the results previously reported [10,42]. The geometry of the $-NH_2$ group seems to be very flexible. In fact, Sponer and Hobza [43] have shown that the amino group could participate in bifurcated hydrogen bonding as a result of its deformability. The amino group would also be important in stacking interactions and conformational variability of DNA. The ab initio calculations also indicate that the $-NH_2$ group become non-planar when hydrogen bonding takes place between bases of the same and different turn of the helix structure of DNA.

The calculated dipole moment (μ) of each pair in the gas phase shows that μ_{AT} (2.1 Da) is smaller than μ_{GC} (6.5 Da), which is in good agreement with the calulated

Table 3
Bond distances (Å) and angles (degrees) for the atoms involved in hydrogen bonding in A–T, AA–T, G–C, and AG–C pairs

	AG–C	G–C	AD–T	A–T
Bond distances[a]				
H21(P)···O2(PY)	1.989	2.021	2.059	2.093
H1(P)···N3(PY)	2.024	2.033		
N1(P)···H3(PY)			1.987	1.976
O6(P)···H41(PY)	1.945	1.916		
Bond angles[a]				
N2(P)–H2(P)–O2(PY)	177.8	178.6	173.3	175.1
N1(P)–H1(P)–N3(PY)	175.6	176.1		
O6(P)–H41(PY)–N4(PY)	175.8	176.9		
N1(P)–H3(PY)–N3(PY)			178.0	178.8
Non-bonded distances				
N2(P)···N2(PY)	2.990	3.021	3.055	3.086
N1(P)···N3(PY)	3.031	3.039	3.000	2.990
N6(P)···N4(PY)	2.948	2.022		

[a] P, purine bases; PY, pyrimidine bases.

values previously reported [29]. This behaviour is also observed in the corresponding azapurines pairs, though μ are substantially larger (5.4 and 10.6 Da for AAT and AGC, respectively). Despite the rather large differences between the dipole moments,the PCM–SCRF method [32,33] predicts similar free energies of solvation for the AG and G-based pairs ($\Delta\Delta G_S^0 < 1$ kcal/mol). This situation is also observed for the AA and A base pairs. The charge distribution in the rings might play an important role in non-natural bases insertion into the DNA and RNA chains [44]. In fact, from a comparison of the charge distributions of the isolated and paired bases one can infer that, for the pairs studied here, a negative partial charge is transferred from a pyrimidine base to a purine one.

In fact, many of the atoms of the paired purine bases show a charge sligthly more negative than in the isolated bases. The most negative charges are centered at N7 and N3 in the purine bases whereas in the pyrimidines they are centered on the O16 and N1 atoms. Thus, for N7 the atomic partial charges are −0.52 in the GC and AGC pairs whereas in AT and AAT a value of ca. −0.57 has been estimated. These atoms are potentially interaction sites for metal ions and polar small molecules. The above results are consistent with the finding that the platinum atom in dichlorodiamin platinum (II), generally used as a drug, binds to N7 of purines in the nucleotides [45]. On the other hand, the interaction of some metal ions with other basic centers in the rings that do not participate in hydrogen bonding could lead to mutagenesis. In fact, metal ions bonded to N7 can produce the protonation of N1 and the corresponding deprotonation of N3, leading to an ionized pair. Sponer et al. [46] have suggested that the protonated bases pairs are more stable (by ca. 40 kcal/mol) than the neutral natural complexes as a consequence of the larger electrostatic attractions. This finding is considered also to be an important phenomenon in the mutation of nucleic acids.

In Table 4, the interaction energies (ΔH^0_{int}) are given. These energies include ZPE, $H - H_0$, and BSSE corrections for the pairs studied at the HF/6-31G** and MP2/6-31G** levels, respectively. We already mentioned that BSSE corrections might not be appropriate when correlated levels are used. In fact, from Table 4 it can be inferred that for AT and GC the BSSE calculated at MP2/6-31G** is approximately twice the value observed at the HF level. Our BSSE, both at the HF and MP2 levels, agree well with the values reported previously [10]. The study of the relative stabilities of the non-natural pairs is important since a rough idea about insertion capabilities of these bases can be inferred. At MP2/6-31G** the GC pair is ca. 7.9 kcal/mol more stable than AT pair. This fact cannot be due to the extra hydrogen bond formation only in GC, but it is likely that the larger polarities of guanine and cytosine, as compared with adenine and thymine, contribute to stabilize this pair this relative to the AT one. The corrected HF ΔH^0_{int} are −21.3 and −13.3 kcal/mol for the GC and AT pairs, respectively, whereas at the correlated MP2 level the corresponding values are −22.9 and −14.9 kcal/mol consistent with field-ionization mass spectrometry experiments that yielded −21.0 and −13.0 kcal/mol for the 1-methylcytosine-9-methylguanine and 1-methyl thymine-9-methyladenine, respectively. The values of −25.5 and −13.7 at HF/6-31G** and −24.3 and −16.6 kcal/mol at MP2/6-31G** interaction energies for the non-natural pairs AGC and AAT are also consistent with the experimental values. The rather small differences in ΔH^0_{int} favoring the non-natural and natural pairs would indicate that azapurines could, in principle, extensively be inserted into the nucleic acids. The fact that non-natural azapurine bases do not insert to a large extent points to factors other than a pure energetic one in controlling their insertion into RNA. It is likely that in the natural AT and GC pairs, the hydrogen bonded to C8 in the imidazole ring, lies next to the glycosidic bond so that the number of rotamers between the bases pairs and the deoxyribosyl moiety are limited and biologically acceptable. In azapurine based pairs, since the hydrogen on the N8 in the triazole ring, is lacking, the number of rotamers is theoretically unlimited. It has been suggested that significant changes in the conformation of the glycosidic bond (N9–C1′) could be responsible for the behavior of the azapurines. Thus, the X-ray diffraction study of the 8-azaadenosine monohydrate nucleoside [45] shows a syn and anti conformations (torsion angle ca. 104° for the anti conformer) around the glycosidic bond, which are apparently stabilized by electrostatic interactions between N8 and C2′. The enzyme adenosine deaminase has little effect on the

Table 4
Interaction energies ($\Delta H_{int.}$) for the natural and non-natural nucleic acids pairs calculated at HF/6-31G** and MP2/6-31G** levels[a]

Pair	E	BSSE	$\Delta(H - H_0)$	ΔZPE	$\Delta H_{int.}$
AG–C	−30.69 (−26.82)	5.45 (2.35)	−4.33	5.27	−24.31 (−25.53)
G–C	−30.67 (−25.71)	6.01 (2.59)	−4.35	6.15	−22.86 (−21.32)
AA–T	−17.86 (−12.16)	4.86 (2.02)	−4.18	0.58	−16.60 (−13.74)
A–T	−17.42 (−11.81)	4.91 (2.21)	−3.87	1.48	−14.90 (−11.98)

[a] The energetics calculated at the HF/6-31G** level are given below the MP2 values in parenthesis. All energies in hartrees.

nucleoside as no deamination takes place when a syn conformation is present [45]. However, many other more important processes such as primer extension, proof-reading activity, and low DNA or RNA polymerase affinity for azapurines might take place.

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