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REGULAR ARTICLE

Adenine versus guanine quartets in aqueous solution: dispersion-corrected DFT study on the differences in π-stacking and hydrogen-bonding behavior

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Abstract We have investigated the performance of the dispersion-corrected density functionals (BLYP-D, BP86-D and PBE-D) and the widely used B3LYP functional for describing the hydrogen bonds and the stacking interactions in DNA base dimers. For the gas-phase situation, the bonding energies have been compared to the best ab initio results available in the literature. All dispersion-corrected functionals reproduce well the ab initio results, whereas B3LYP fails completely for the stacked systems. The use of the proper functional leads us to find minima for the adenine quartets, which are energetically and structurally very different from the C_{4h} structures, and might explain why adenine has to be sandwiched between guanine quartets to form planar adenine quartets.

Keywords Density functional calculations · Dispersion · DNA quartets · Hydrogen bonding · π-Stacking

Dedicated to Professor Sandor Suhai on the occasion of his 65th birthday and published as part of the Suhai Festschrift Issue.

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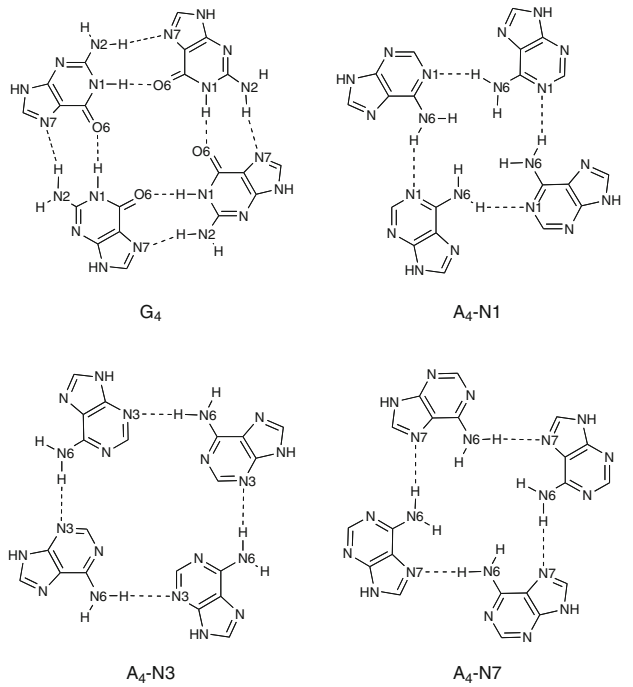
1 Introduction

Besides the well-known Watson–Crick pairing of nucleic acid bases in the helical DNA molecule, these bases are known in telomeres to form cyclic hydrogen-bonded quartets [1–11] (see Scheme 1), which, in turn, are able to stack together through π-stacking interactions. These quartet structures of DNA bases are increasingly recognized for their biological importance [1–11].

By far the longest-known is the guanine quartet (G_4), which has an exceptional stability due to its capacity to form two hydrogen bonds between neighboring guanines, i.e., the N1–H···O6 and N2–H···N7 hydrogen bonds (see Scheme 1). Furthermore, the stabilization of guanine quartets can be enhanced by cations [2]. This high stability of G_4 facilitates through stacking the formation of other quartets, for instance of A_4 [4–7]. However, the experimental evidence for the existence of adenine quartets is rare. To our knowledge, adenine quartets have only been observed experimentally sandwiched between two guanine quartets in [4–7]. The adenine quartets are formed with one hydrogen bond between adjacent bases (see Scheme 1). The three quartets have as proton-donor the N6–H bond of the amino-group and as proton-acceptor the N1 atom (A_4-N1) [4, 5], the N3 atom (A_4-N3) [6], and the N7 atom (A_4-N7) [7], respectively. The guanine quartet, as well as

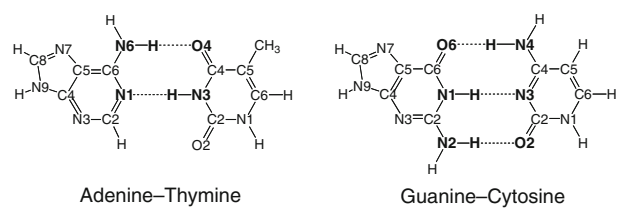


Scheme 1 Guanine and adenine quartets

the three adenine quartets, has been the subject of computational studies [12–19].

In this work, we analyze the stability of these four quartets in the gas phase and in aqueous solution using dispersion-corrected density functional theory (DFT-D). First, we explore the performance of different DFT-D variants for the hydrogen-bonded (see Scheme 2) and stacked DNA base pairs (see Fig. 1, later on) by comparing them with high-level ab initio results [20–22]. In our previous work, we showed that the hydrogen bonds between adjacent bases from opposite strands in DNA are described adequately by a number of GGA, meta-GGA and hybrid DFT approaches (for instance BP86) [23, 24]. However, most of the current DFT approaches, ranging from GGA via meta-GGA to hybrid DFT, fail in describing π-stacking interactions between two bases within each of the two DNA strands [25, 26].

After having established the proper dispersion-corrected functional, we investigate for the four quartets three different configurations which are of C_{4h}, C_4 and S_4 point group symmetry and which all have the cyclic hydrogen bonds as



Scheme 2 Watson–Crick base pairs

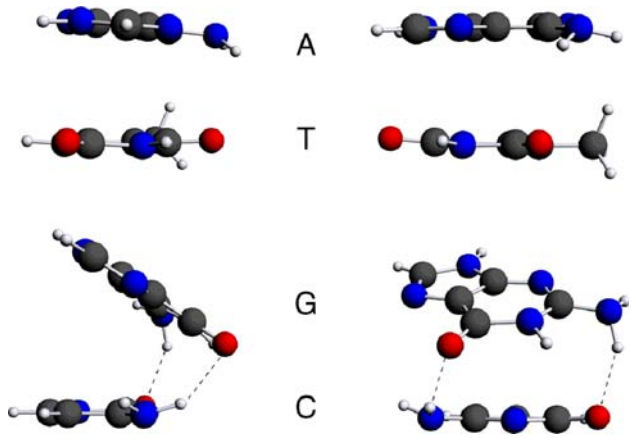


Fig. 1 Stacked AT and GC dimers in the gas phase shown from two side views (BLYP-D/TZ2P)

shown in Scheme 1. The adenine quartets have been observed experimentally in a planar configuration [4–7], and we examine whether these quartets remain in a planar configuration when the stabilization by the guanine quartets is not present. Finally, we test the applicability of the widely used B3LYP functional for these quartets in the different symmetries and we show that the neglect of the dispersion correction will even lead to erroneous conclusions.

2 Computational methods

All calculations were performed using the Amsterdam density functional (ADF) program developed by Baerends et al. [27–38], and the QUantum-regions Interconnected by Local Descriptions (QUILD) program by Swart and Bickelhaupt [39, 40]. The QUILD program is a wrapper around ADF (and other programs) and is used for its superior geometry optimizer which is based on adapted delocalized coordinates [39]. The numerical integration was performed using the procedure developed by te Velde et al. [34, 35].

The MOs were expanded in a large uncontracted set of Slater type orbitals (STOs) containing diffuse functions: TZ2P (no Gaussian functions are involved) [36]. The basis set is of triple-ζ quality for all atoms and has been augmented with two sets of polarization functions, i.e., 3*d* and 4*f* on C, N, O and 2*p*, 3*d* on H. The 1*s* core shells of carbon, nitrogen and oxygen were treated by the frozen-core approximation [30]. An auxiliary set of *s*, *p*, *d*, *f* and *g* STOs was used to fit the molecular density and to represent the Coulomb and exchange potentials accurately in each self-consistent field cycle [37].

Calculations were done using dispersion-corrected DFT-D as developed by Grimme [41–47] for a correct treatment of the stacking interactions between the DNA bases. The

density functionals are augmented with an empirical correction for long-range dispersion effects, described by a sum of damped interatomic potentials of the form C_6R^{-6} added to the usual DFT energy [41–47]. Equilibrium structures were optimized using analytical gradient techniques [38]. Geometries and energies were calculated with the generalized gradient approximation (GGA) at BLYP [48, 49], BP86 [48, 50] and PBE [51] as well as with the dispersion-corrected variants BLYP-D, BP86-D and PBE-D. Furthermore, the hybrid functional M06-2X [52] has been used for the computation of geometries and energies of AT and GC (both hydrogen-bonded and stacked dimers) and for the systems with stacking interactions involved. For the quartets the B3LYP [49, 53, 54] has been used to compute energies in a single-point fashion using the BLYP-D geometries.

At the BLYP-D level of theory, all energy minima of hydrogen-bonded AT and GC pairs, stacked AT and GC dimers, and the global energy minima of DNA-base quartets have been verified in the gas phase and in water to be equilibrium structures through vibrational analysis [55–57]. The lowest energy minima were found to have zero imaginary frequencies (see also Electronic Supplementary Material). For the dispersion-corrected functionals the basis set superposition error (BSSE) on the bond energy was not calculated because the dispersion correction [42] has been developed such that the small BSSE effects are absorbed into the empirical potential. For the bond energy calculated with the uncorrected functionals the BSSE has been computed and corrected through the counterpoise method [58], using the individual DNA bases as fragments.

Solvent effects in water have been estimated using the conductor-like screening model (COSMO) [59, 60], as implemented in the ADF program [61]. For settings see [62]. The continuum solvent model performs adequately for the determination of geometries as has been done in this work. However, for the calculation of spectra of molecules in a solvent, it is essential to take into account the first shell of solvent molecules explicitly [63–69]. For instance, Nicu et al. [63] showed that the VCD spectrum of 2-benzoic acid is influenced by the hydrogen bonding with the solvent due to the donor–acceptor interaction (which of course is not taken into account by continuum solvent models). According to the work by Riley et al. [70] the dispersion correction does not need to be modified for the solvated systems.

3 Results and discussion

3.1 AT and GC pairs

The hydrogen-bond distances and energies of the Watson–Crick base pairs AT and GC in the gas-phase and in aqueous solution are given in Tables 1 and 2, respectively, together with the best ab initio estimate by Sponer et al. [20]. The base pairs have been optimized in C_s symmetry and the bases in C_1 in accordance with our previous work [23, 24]. The hydrogen bond energy for AT and GC is defined as the difference in energy between the optimized pair and the fully optimized bases. From Tables 1 and 2, we see that the hydrogen bond energies for AT and GC obtained with the dispersion-uncorrected density functionals, including the M06-2X functional, are all a few kilocalorie per mole more weakly bound than the CCSD(T) reference value with a clear underestimation of the hydrogen-bond energies by the B3LYP functional. The hydrogen-bond energies acquired with the dispersion-corrected density functionals are all slightly more strongly bound than the CCSD(T) reference value. Although the BP86-D and the PBE-D results already agree well with the ab initio results, the best agreement with CCSD(T) is obtained with BLYP-D. At BLYP-D/TZ2P, the hydrogen-bond energy for the Watson–Crick AT and GC pairs amounts to −16.7 and −30.1 kcal/mol, which has to be compared with −15.4 and −28.8 kcal/mol, respectively, at CCSD(T)/aug-cc-pVQZ//RI-MP2/cc-pVTZ [20–22]. This close agreement between dispersion-corrected functionals

Table 1 Hydrogen bond distances (Å) and bond energies (kcal/mol) for AT computed at various levels of theory

Method	N6–O4	N1–N3	ΔE^a
Best ab initio			
RI-MP2/aug-cc-pVQZ// RI-MP2/cc-pVTZ[b]			–15.1
"CCSD(T)/aug-cc-pVQZ"// RI-MP2/cc-pVTZ[b]	2.86	2.83	–15.4
DFT			
BLYP	2.92	2.88	–11.0
BP86	2.85	2.81	–12.3
PBE	2.87	2.80	–13.9
B3LYP/cc-pVTZ[c]	2.93	2.88	–11.6
M06-2X	2.91	2.79	–13.5
BLYP-D	2.89	2.78	–16.7
BP86-D	2.83	2.74	–17.9
PBE-D	2.84	2.75	–18.0
Inclusion of water			
BLYP-D	2.91	2.82	–9.8
BP86-D	2.85	2.78	–10.8
PBE-D	2.86	2.80	–11.1

Calculations were done in C_s symmetry with a TZ2P basis set

[a] Bond energy with inclusion of BSSE correction

[b] Data from Refs. [20–22]. The coupled-cluster energy has been obtained by adding a correction to the MP2 energies. This correction is calculated as a difference between the coupled-cluster energy and the MP2 energy obtained with smaller basis sets as explained in Refs. [20–22]

[c] Data taken from Ref. [23]

Table 2 Hydrogen bond distances (Å) and bond energies (kcal/mol) for GC computed at various levels of theory

Method	O6–N4	N1–N3	N2–O2	ΔE^a
Best ab initio				
RI-MP2/aug-cc-p VQZ//RI-MP2/cc-pVTZ[b]	2.75	2.90	2.89	–27.7
"CCSD(T)/aug-cc-p VQZ"//RI-MP2/cc-pVTZ[b]	2.75	2.90	2.89	–28.8
DFT				
BLYP	2.79	2.94	2.93	–23.2
BP86	2.73	2.88	2.87	–25.2
PBE	2.73	2.89	2.87	–26.9
B3LYP/cc-pVTZ[c]	2.79	2.94	2.93	–24.4
M06-2X	2.74	2.89	2.88	–26.5
BLYP-D	2.74	2.89	2.88	–30.1
BP86-D	2.70	2.84	2.83	–31.9
PBE-D	2.70	2.86	2.85	–31.9
Inclusion of water				
BLYP-D[d]	2.85	2.90	2.84	–13.6
BP86-D	2.80	2.85	2.79	–14.9
PBE-D	2.82	2.87	2.80	–15.0

Calculations were done in C_s symmetry with a TZ2P basis set

[a] Bond energy with inclusion of BSSE correction

[b] Data from Refs. [20–22]. The coupled-cluster energy has been obtained by adding a correction to the MP2 energies. This correction is calculated as a difference between the coupled-cluster energy and the MP2 energy obtained with smaller basis sets as explained in Refs. [20–22]

[c] Data taken from Ref. [23]

[d] Structure optimized in C_1 symmetry. Vibrational analysis yields one small imaginary frequency (i15.4 cm^{-1}) which disappears either in an explicit scan of the PES along the corresponding normal mode or in an reoptimization after displacement along that normal mode

Table 3 Stacking energies (kcal/mol) and distances between the bases (Å) for AT and GC computed at various levels of theory

Method	AT		GC	
	R(C4–N1)[a]	ΔE^b	R(N1–C2)[a]	ΔE^b
Best ab initio				
"CCSD(T)/aug-cc-p VQZ"//RI-MP2/cc-pVTZ[c]	3.31	–11.6	3.34	–16.9
DFT				
M06-2X	3.29	–9.6	3.17	–14.9
BLYP-D	3.39	–11.7	3.36	–16.9
BP86-D	3.26	–12.3	3.30	–17.4
PBE-D	3.40	–11.2	3.37	–17.0
B3LYP//BLYP-D	3.39	2.3	3.36	–7.5
PBE//BLYP-D	3.39	–1.4	3.36	–10.1
Inclusion of water				
BLYP-D	3.35	–8.0	3.32	–5.0
BP86-D	3.25	–8.5	3.27	–5.8
PBE-D	3.36	–7.7	3.33	–5.0
B3LYP//BLYP-D		4.2		6.0

Calculations were done in C_1 symmetry with a TZ2P basis set

[a] For the definition of the distances see Ref. [41]

[b] Bond energy with inclusion of BSSE correction

[c] Data from Refs. [20–22]. The coupled-cluster energy has been obtained by adding a correction to the MP2 energies. This correction is calculated as a difference between the coupled-cluster energy and the MP2 energy obtained with smaller basis sets as explained in Refs. [20–22]. Distances were obtained from Refs. [20–22]

and ab intio results for the hydrogen-bonded and stacked AT and GC pair was also found by Grimme and co-workers [43] with Gaussian-type triple and quadruple-zeta basis sets. Furthermore, the inclusion of water as a solvent has been investigated. The hydrogen bonds between the AT and GC in water are half as strong as the same hydrogen bonds in the gas phase.

The π-stacking interaction in the AT and GC dimers in the gas phase and in aqueous solution are given in Table 3, together with the best ab initio estimate by Sponer et al. [20]. For the *stacked* AT and GC pairs, the dispersion corrected functionals are in close agreement with the ab initio results. The M06-2X energies are about 2 kcal/mol too weakly bound, which has also been found by Kabelac et al. [71, 72] for the M05-2X functional. The BLYP-D energies of −11.7 and −16.9 kcal/mol, respectively, are in excellent agreement with the CCSD(T)/aug-cc-pVQZ//RI-MP2/TZVPP ones of −11.6 and −16.9 kcal/mol, respectively [20–22].

The B3LYP functional appears to be completely inadequate for describing stacked DNA bases, similar to what we have found previously for regular GGA functionals such as BP86 [25]. This follows from numerical experiments in which we evaluate the stacking energies in the gas phase and in water with B3LYP/TZ2P at the BLYP-D/TZ2P equilibrium structures, i.e., B3LYP/TZ2P//BLYP-D/TZ2P. In the gas phase, this yields for the stacked AT a slightly repulsive result of 2.1 kcal/mol. For GC the stacking energy in the gas phase amounts to −7.5 kcal/mol. The same numerical experiment has been done for PBE, which gives the AT pair bonded by only 1.4 kcal/mol and the GC pair by 10.1 kcal/mol at the PBE/TZ2P//BLYP-D/TZ2P level. Note that the reason for the attractive B3LYP and PBE energies of stacked GC is the presence of two hydrogen-bonding like interactions in the stacked GC system in which G and C are, in fact, not exactly parallel but under a slight angle. This is because of the aforementioned "partial" hydrogen bonds which B3LYP or PBE are able to describe. Stacked GC differs in this respect from stacked AT which is bound by a more pure π-stacking interaction which B3LYP or PBE is *not* able to describe properly (see Fig. 1). The stacked GC pair is therefore not

Table 4 Hydrogen bond energies (kcal/mol) for DNA quartets in the gas phase and in water

	BLYP-D				B3LYP//BLYP-D			
	C_{4h}	C_4	S_4	S_4 local	C_{4h}	C_4	S_4	S_4 local
Gas phase								
G_4	−79.2	[a]	−79.8		−66.4		−66.3	
A_4-N1	–25.5	–30.2	–46.0	–31.2	–9.5	–12.1	–9.7	–14.4
A_4-N3	–33.1	–32.7	–32.8	–25.1	–19.9	–19.1	–10.0	–9.0
A_4-N7	–31.9	–33.1	–45.5		–19.4	–19.1	–7.4	
Water								
G_4	−33.6	[a]	−33.8		−20.0		−20.3	
A_4-N1	–10.9	–17.0	–33.2	–15.3	3.0	–1.3	1.3	–0.4
A_4-N3	–16.8	–16.3	–17.0	–15.3	–6.3	–6.2	–5.7	6.7
A_4-N7	–16.2	–16.3	–27.2		–6.9	–6.5	6.0	

Calculations were done with a TZ2P basis set

[a] C_4 starting geometry collapses spontaneously to C_{4h} structure

a good benchmark to evaluate the adequacy of functionals for stacking interactions. However, starting from a stacked AT or GC pair the optimization with the B3LYP or PBE functional leads eventually to a hydrogen bonded base pair because of the erroneous description of the stacking interactions by these functionals. In water, both the AT and GC stacks would, according to B3LYP, not exist, which is evidently incorrect.

3.2 Adenine and guanine quartets

The results of our BLYP-D/TZ2P study on the formation of the G_4, A_4-N1, A_4-N3 and A_4-N7 quartets in the point group symmetries C_{4h}, C_4 and S_4 in the gas phase and in water are summarized in Table 4 (energies), Figs 2, 3, 4, 5 and Tables S1–S4 of the ESM (geometries). The geometries are in both phases almost similar, except for the A_4-N3 minima in the S_4 symmetry. For the C_{4h} symmetry the hydrogen bond lengths are given for the gas phase and the condensed phase in Fig. 2. In the C_4 symmetry we find for all quartets bowl-shaped structures (see Fig. 3). The S_4 structures in water are presented in Fig. 4. For G_4 and A_4-N3 quartets the systems are slightly distorted from planarity and for A_4-N1 and A_4-N7 we find stacked dimers with cyclic hydrogen bonds in between (for A_4-N1 with four N6(H)···N1 and for A_4-N7 with four N6(H)···N7 hydrogen bonds as presented in Scheme 1). The number of imaginary frequencies from the vibrational analysis of the structures in different symmetries can be found in Table S6 of the ESM. The hydrogen bond energies for B3LYP have been calculated with the BLYP-D geometries to give a qualitative impression of how B3LYP is unable to reproduce energies for stacked complexes (see Table 4).

In accordance with previous work of Meyer et al. [18] at the B3LYP level, we find in the gas phase for the G_4 quartet that the difference between the C_{4h} and the S_4 structures is small, only 0.6 kcal/mol (see Table 4; Fig. 4). Also for the A_4-N3 quartet, we find geometrically equivalent structures as in previous work [17] at the B3LYP level. However, we find that all structures are energetically very similar (within 0.4 kcal/mol equal), whereas Meyer et al. [17] found that at the B3LYP level the S_4 structure is 8.6 kcal/mol higher in energy than the C_{4h} structure.

For the A_4-N1 and the A_4-N7 quartets, we find that the S_4 structure is more than 16 and 12 kcal/mol, respectively, lower in energy than the other symmetric structures. This is in sharp contrast with previous work [18] at the B3LYP level, where the S_4 structure of A_4-N1 is only a few

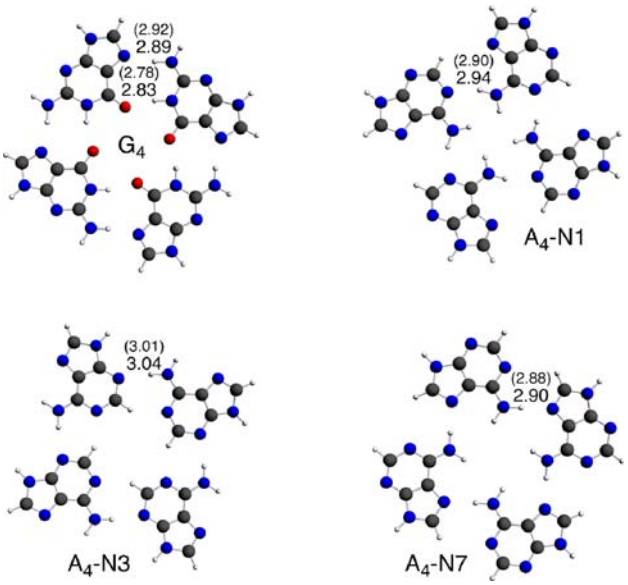


Fig. 2 The C_{4h} structures in water of G_4, A_4-N1, A_4-N3 and A_4-N7 at the BLYP-D/TZ2P level of theory. Hydrogen-bond distances (Å) are given for aqueous solution (gas-phase values in *parentheses*)

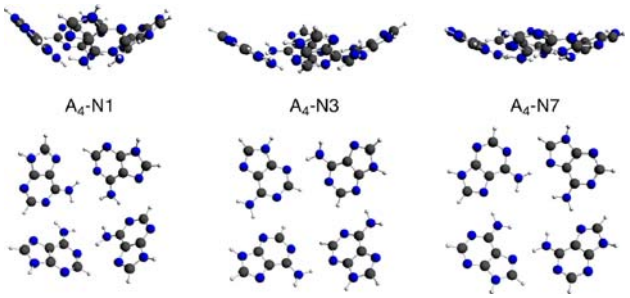


Fig. 3 *Side view* and *top view* of the C_4 structures in water of A_4-N1, A_4-N3 and A_4-N7 at the BLYP-D/TZ2P level of theory

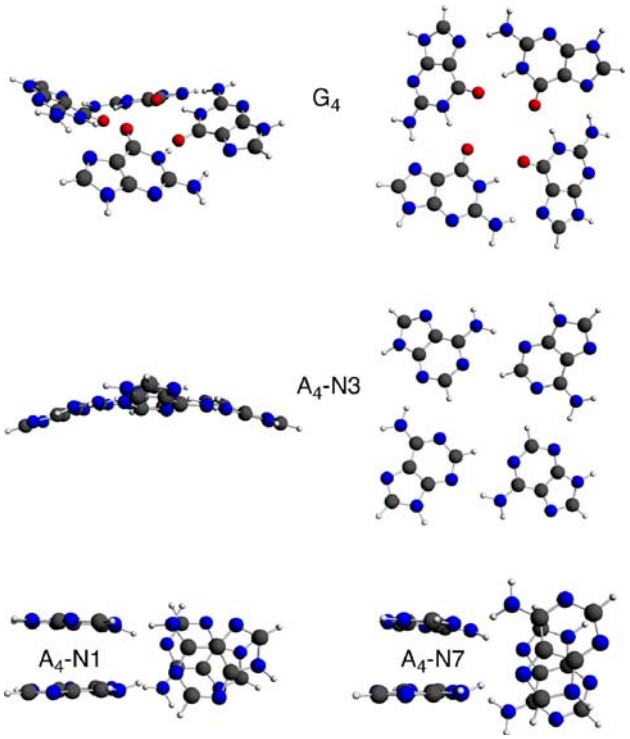


Fig. 4 Structures of the S_4 global minima in water of G_4, A_4-N1, A_4-N3 and A_4-N7 at the BLYP-D/TZ2P level of theory (for G_4 and A_4-N3 a *side* and a *top view* are shown)

kilocalorie per mole lower in energy than the C_4 and C_{4h} structures, and for the A_4-N7 quartet all symmetric structures are within 0.5 kcal/mol energetically equal. The difference can be ascribed to the difference in the geometries. Our S_4 minima are stacked dimers with hydrogen bonds in between, whereas the B3LYP minima [18] look more like a distorted C_{4h} structure. For the A_4-N1 quartet we were able to find a local minimum in the S_4 symmetry at the BLYP-D/TZ2P level (see Fig. 5), which is very similar to the B3LYP structure. The bond energy of the local S_4 minimum amounts only to −31.2 kcal/mol, while the bond energy of the global S_4 minimum is −46.0 kcal/mol. To analyze if the B3LYP functional could reproduce this result, we calculated the B3LYP/TZ2P bonding energies

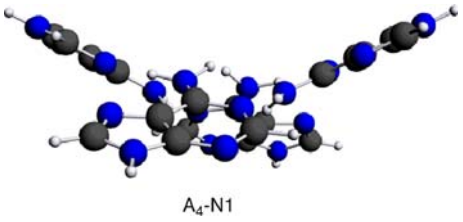


Fig. 5 *Side view* of the local S_4 minimum in the gas phase of A_4-N1 at the BLYP-D/TZ2P level of theory

with our BLYP-D/TZ2P structures: the bond energy of the stacked dimers with hydrogen bonds in between (Fig. 4) amounts then to −9.7 kcal/mol and of the "distorted C_{4h}" structure (Fig. 5) to −14.4 kcal/mol. Thus, in addition to a general underestimation of the stability of our stacked model systems, the B3LYP functional also yields the wrong energetic ordering of the minima (see also Table 4). This demonstrates once more how the B3LYP functional leads to qualitatively wrong chemical conclusions.

3.3 To stack or not to stack

In aqueous solution, our results show again that for the G_4 and the A_4-N3 all three symmetries are very close in energy and that it costs only 0.2 kcal/mol in both cases to go from the S_4 geometry (as presented in Fig. 4) to the flat C_{4h} symmetric geometry. Such planarization is necessary in order to form stacked systems.

The bonding energy (−33.6 kcal/mol) of the G_4 quartet in the C_{4h} symmetry is twice as large as the bonding energy (−16.8 kcal/mol) of the A_4-N3 quartet and therefore G_4 is, as expected, more stable. The A_4-N1 and the A_4-N7 quartets bind in the S_4 geometry with −33.2 and −27.2 kcal/mol, respectively, which is of the same magnitude as the bonding energy of G_4. To go from the nonplanar stacked system in the S_4 geometry (see Fig. 4) to the planar C_{4h} geometry, which is needed to form stacks of quartets, it costs 22.3 kcal/mol for the A_4-N1 quartet and 11.0 kcal/mol for the A_4-N7 in aqueous solution.

The relatively low stability of planar A_4-N1 and A_4-N7 quartets and their strong tendency to form S_4-symmetric nonplanar arrangements might be the decisive factor behind the fact that these A_4 quartets are not so often observed experimentally. This also explains why these quartets are found sandwiched between two G_4 quartets, which supplies the required stabilization of the planar configuration through stacking interactions.

4 Conclusions

We have shown that the dispersion-corrected density functionals, especially BLYP-D, are very well suited for

describing both hydrogen bonded AT and GC pairs and stacked AT and GC dimers, with bond energies and distances that are in excellent agreement with the best ab initio CCSD(T) benchmark data in the literature.

The B3LYP functional fails completely to describe the stacked AT and GC dimers. Furthermore, B3LYP fails to reproduce the strong tendency of A_4 quartets to adopt nonplanar structures. Our findings imply that B3LYP should not be used for DNA systems that involve π-stacking interactions.

Our BLYP-D results show that in water G_4 is the most strongly bound quartet and easily adopts a planar geometry. The planar geometries of all A_4 quartets studied are two to three times less stable than planar G_4. In addition, by far the most stable A_4 structure is nonplanar. In other words, A_4 has, unlike G_4, a strong tendency to adopt a geometry that is unsuitable for stacking. This explains the fact that A_4 quartets have been experimentally observed in stacks only in between G_4 quartets: they are less stable and nonplanar and therefore need the stabilization of planar G_4 in order to form larger stacks.

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