Hydrogen-Bonded Nucleic Acid Base Pairs Containing Unusual Base Tautomers: Complete Basis Set Calculations at the MP2 and CCSD(T) Levels

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The total interaction energies of altogether 15 hydrogen-bonded nucleic acid base pairs containing unusual base tautomers were calculated. The geometry properties of all selected adenine−thymine and guanine−cytosine hydrogen-bonded base pairs enable their incorporation into DNA. Unusual base pairing patterns were compared with Watson−Crick H-bonded structures of the adenine−thymine and guanine−cytosine pairs. The complete basis set (CBS) limit of the MP2 interaction energy and the CCSD(T) correction term, determined as the difference between the CCSD(T) and MP2 interaction energies, was evaluated. Extrapolation to the MP2 CBS limit was done using the aug-cc-pVDZ and aug-cc-pVTZ results, and the CCSD(T) correction term was determined with the 6-31G*(0.25) basis set. Final interaction energies were corrected while taking into account both tautomeric penalization determined at the CBS level and solvation/desolvation free energies. The situation for the adenine−thymine pairs is straightforward, and tautomeric pairs are significantly less stable than the Watson−Crick pair consisting of the canonical forms. In the case of the guanine−cytosine pair, the Watson−Crick structure made by canonical forms is again the most stable. The other two structures are, however, energetically rather similar (by 5 and 6 kcal/mol), which provides a very small but non-negligible chance of detecting these structures in the DNA double helix (1:5000). Due to the fact that DNA bases and base pairs incorporated into DNA are solvated less favorably than in isolated systems, this probability represents the very upper limit. The results clearly show how precisely the canonical building blocks of DNA molecules were chosen and how well their stability is maintained.

Introduction

The structure of DNA and molecular interactions maintaining the structure and the stability of DNA are among the most topical questions in chemistry since the structure was discovered by Watson and Crick.[1] The reason is simple: DNA stores and transfers genetic information. A crucial prerequisite for these actions is the complementarity of adenine−thymine and guanine−cytosine. In DNA, all of these bases exist in the so-called canonical form. According to Crick, H-bonding could not provide the exact specificity necessary, for he believed that hydrogens of bases did not have fixed locations but they were rather instantly hopping between possible tautomeric positions.[2]

Many calculations on isolated nucleic acid bases were performed in the gas phase, microhydrated environment and bulk water environment with the aim of comparing the stability of various tautomers with their canonical form.[3−16] Some of these studies revealed that it was possible that unusual base pairs were present in nucleic acids. A thorough and accurate study of the stability and geometry properties of base pairs with unusual base tautomers in vacuo and in a more biologically relevant environment is, however, still missing.

A key question remains: why nature has selected the canonical rather than the tautomeric forms of nucleic acid bases. To answer this question, highly accurate calculations on the stability of nucleic acid bases and their complexes should be performed. Such calculations for isolated bases are now feasible, but when we move to base pairs, the calculations become much more time-consuming. The first papers on DNA base pairs have appeared only recently where stabilization energies were determined with chemical accuracy, that is, with an accuracy of ±1 kcal/mol.[17] The respective energies were determined at the complete basis set (CBS) limit of highly correlated CCSD(T) calculations. The CBS limit was reached by the extrapolation from total energies determined with aug-cc-pVDZ and aug-cc-pVTZ as well as aug-cc-pVTZ and aug-cc-pVQZ basis sets.[17]

The aim of the presented paper is to evaluate the stabilization energies of adenine−thymine and guanine−cytosine base pairs containing various tautomeric forms. Other than the bare stabilization energy in vacuo, the role of environment will also be considered.

Accurate interaction energies between unusual base pair tautomers compared with canonical base pairs could be, on the one hand, another clue providing information about the possible existence of rare tautomeric forms in nucleic acids. On the other hand, the confirmation of the exceptional position of the so-called canonical base pairs would be another manifestation of selection in nature.

Methods

1. Selection of Geometries. Pairs of tautomeric nucleic acid bases were created using our chemical intuition with respect to geometry restriction (see below). The monomers of the nucleic acid tautomers (with their structures determined by MP2/cc-pVTZ gradient optimizations) were taken from our previous papers.[13−16] The geometries of the base pairs were determined using the gradient optimization with the resolution of identity

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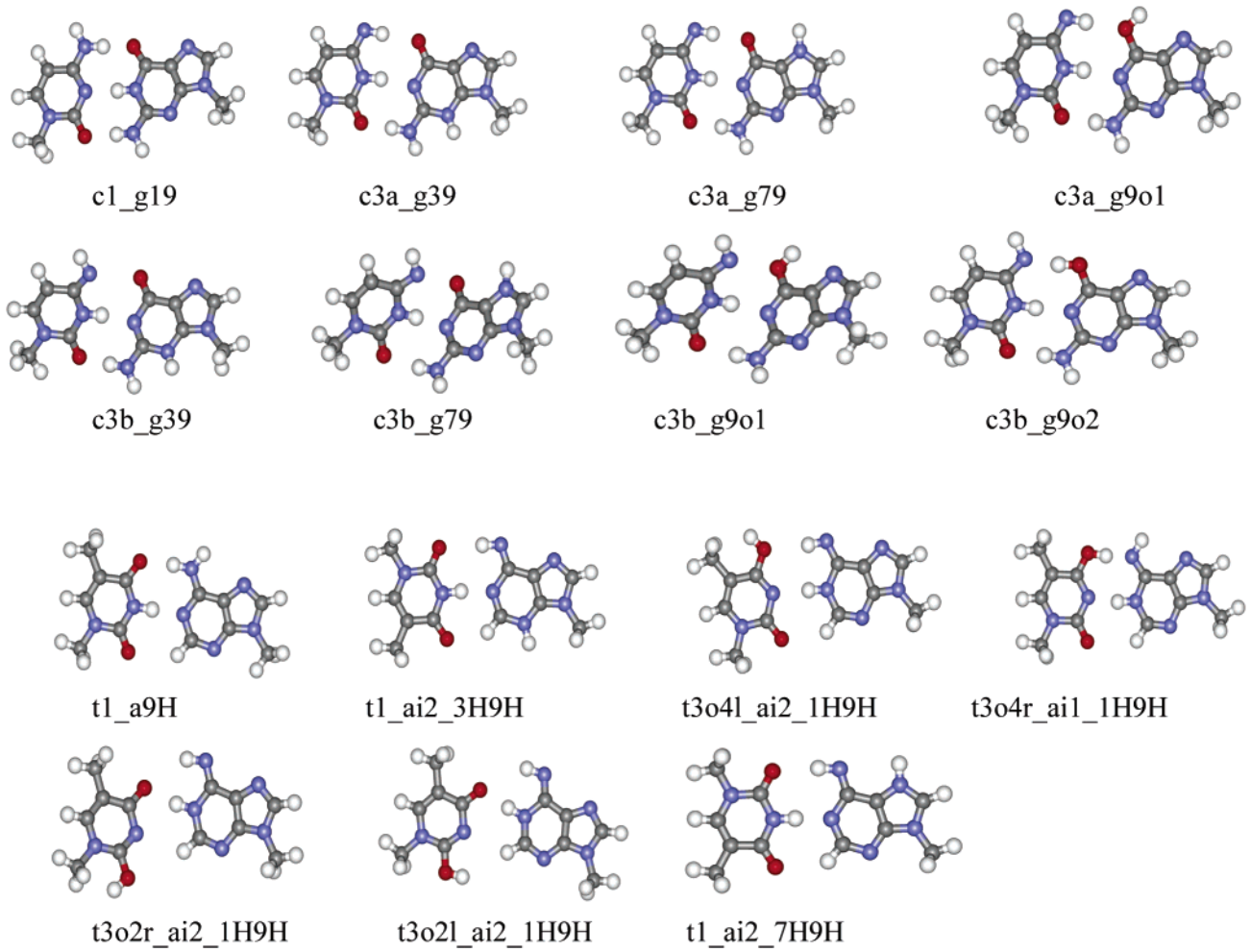

Figure 1. Nucleic acid base pairs containing tautomeric forms of nucleic acid bases.

MP2 (RI-MP2) procedure using the cc-pVTZ basis set. This procedure yielded altogether 15 base pairs: 7 adenine−thymine and 8 guanine−cytosine base pairs (cf. Figure 1). It must be emphasized that all of these structures could be incorporated into a DNA molecule, because the position that binds to sugar remains free. For all RI-MP2 calculations, the TurboMole 5.8 program was used.[18]

2. Complete Basis Set Limit of the MP2 Stabilization Energies. The Hartree−Fock (HF) interaction energy converges with respect to the one-electron basis set already for relatively small basis sets, but the correlation part of the interaction energy converges to its complete basis set limit much more slowly. For this reason, the HF and correlation energies are extrapolated separately. Several extrapolation schemes have been suggested in the literature to correct the computed results for basis set incompleteness error.[19,20] In the presented paper, we used the schemes of Helgaker et al.:[20,21]

$$E_X^{HF} = E_{CBS}^{HF} + Ae^{-\alpha X}, \quad E_X^{corr} = E_{CBS}^{corr} + BX^{-3} \quad (1)$$

where E_X and E_{CBS} are energies for the basis set with the largest angular momentum, X ($X = 2$ for DZ and 3 for TZ), and for the complete basis set, respectively, and α is the coefficient from the original work.[20] Further details about the scheme and results for some other DNA base pairs can be found in our previous papers.[22−25]

In the present work, the RI-MP2 calculations used for extrapolation to the CBS limit were performed with the standard aug-cc-pVDZ and aug-cc-pVTZ basis sets of atomic orbitals. We utilized the augmented Dunning correlation-consistent basis sets[26,27] rather than the nonaugmented ones to reduce the extrapolation error.

In our previous paper on canonical DNA base pairs, we performed extrapolation not only from the presently used basis sets but also from more extended basis sets (aug-cc-pVTZ, aug-cc-pVQZ).[22] In the latter, considerably more expensive calculations, the differences yielded in the extrapolated interaction energies were only small.

3. Correction for Higher-Order Correlation Effects. The MP2/CBS interaction energies suffer from the lack of higher correlation energy contributions, and this problem is eliminated by adding the CCSD(T) correction term, covering the difference between the MP2 and CCSD(T) interaction energies. Contrary to single interaction energies, their difference exhibits only a small basis set dependence.[28] Therefore, we utilized the 6-31G*-(0.25) basis set for this purpose.

We approximated the CBS CCSD(T) interaction energy as follows:

$$\Delta E_{CBS}^{CCSD(T)} = \Delta E_{CBS}^{MP2} + (\Delta E^{CCSD(T)} - \Delta E^{MP2})|_{6-31G^*(0.25)} \quad (2)$$

The last term in this equation was computed using the Molpro 2002.6[29] program package.

4. Free Energies of Solvation. Bulk water was modeled with a continuum model based on the C-PCM (COSMO)[30,31,32] methodology implemented in Gaussian 03.[33,34] The cavity was

TABLE 1: Total Interaction Energies of Nucleic Acid Base Pairs with Different Contributions[a]

	1	2	3	4	5	6	7	8
	G···C	E_{int}^{CBS}	$\Delta E^{CCSD(T)} - \Delta E^{MP2}$	tautomeric penalization	total gas-phase interaction energy	ΔG_{solv}	total absolute interaction energy	total relative interaction energy
1	c1_g19	−30.8	−0.47	0.0	−31.2	30.33	−0.90	0.00
2	c3a_g39	−21.6	−0.18	21.9	0.1	28.24	28.34	29.25
3	c3a_g79	−21.1	−0.17	20.1	−1.1	25.51	24.41	25.31
4	c3a_g9o1	−15.9	−0.09	2.6	−13.4	17.49	4.10	5.01
5	c3b_g39	−13.9	0.23	20.8	7.1	24.02	31.08	31.98
6	c3b_g79	−13.3	0.58	19.0	6.3	29.84	36.14	37.04
7	c3b_g9o1	−11.7	0.3	1.6	−9.8	15.08	5.28	6.19
8	c3b_g9o2	−23.2	0.28	44.8	21.8	19.44	41.26	42.17
	A···T	E_{int}^{CBS}	$\Delta E^{CCSD(T)} - \Delta E^{MP2}$	tautomeric penalization	total gas-phase interaction energy	ΔG_{solv}	total absolute interaction energy	total relative interaction energy
1	t1_a9H	−16.8	0.04	0.00	−16.8	17.68	0.91	0.00
2	t1_ai2_3H9H	−13.9	0.12	31.75	18.0	16.64	34.59	33.68
3	t1_ai2_7H9H	−13.7	0.21	32.84	19.4	26.25	45.63	44.71
4	t3o4l_ai2_1H9H	−13.8	−0.21	34.66	20.6	24.99	45.63	44.72
5	t3o4r_ai1_1H9H	−32.9	0.66	27.84	−4.4	25.7	21.29	20.38
6	t3o2r_ai2_1H9H	−14.3	0.01	44.89	30.6	28.57	59.18	58.27
7	t3o2l_ai2_1H9H	−13.4	0.06	35.04	21.7	25.11	46.82	45.91

[a] Figures of the presented structures are depicted in Figure 1. All energies are in kilocalories per mole. E_{int}^{CBS}: MP2 interaction energies evaluated at the complete basis set limit. $\Delta E^{CCSD(T)} - \Delta E^{MP2}$: the difference between MP2 and CCSD(T) interaction energies. Tautomeric penalization: the energy difference of base pair formation from tautomers. ΔG_{solv}: solvation free energy.

described by UAHF radii (united atoms radii optimized for the HF/6-31G* level of theory). Single point (SP) calculations considering gas-phase optimized geometries were carried out at the HF/6-31G*/UAHF level using the Gaussian 03[33,34] standard parameters (UAHF, scaling 1.2, the solvent-excluded surface (SES)) as recommended.

5. Penalization Energies. In order to compare different base pairs containing different tautomeric forms (not only canonical tautomers) of nucleic acid bases, we calculated the penalization energies of tautomers in a pair. The penalization energy is then defined as a difference between energies of the optimized canonical and tautomeric forms. We used the CBS enegies to calculate penalization energies. Similar strategies have been used for calculating the relative stabilities of hydrated complexes.[35,36]

Results and Discussion

The interaction energies of adenine···thymine and guanine···cytosine base pairs containing various tautomers (cf. Figure 1) are shown in Table 1. The first line in each part contains the results for the canonical bases and Watson−Crick (WC) arrangement of bases.

The GC base pair will be discussed first. The second column of Table 1 shows MP2 interaction energies evaluated at the complete basis set limit. The stabilization energies differ considerably, and this is due to the fact that the dipole moments of single tautomers also differ considerably. This explains for example the lower stability of the GC pair **4** but also the considerably higher stabilization of the AT structure **4** (see later). Evidently, the WC structure is by far the most stable, and the stabilization energy difference when compared with the second structure (c3a_g39) is ∼9 kcal/mol. The remaining structures in Table 1 are even less stable. The H-bonding pattern of structures **2**−**4** is the same as that of the GC WC structure, but the respective stabilization energies differ considerably. Obviously, the combination of canonical amino-keto/amino-keto tautomers is energetically the most favorable. The transition to imino-keto/amino-keto tautomer pairs reduces the stabilization, and this reduction is the largest when imino-keto/amino-enol tautomers are considered. Structure **1**, as well as structures **2**−**4**, contains three H-bonds, whereas in the case of structures **5**−**7** one (attractive) H-bond is replaced by a repulsive electrostatic interaction between the N and O atoms. Consequently, the stabilization energy of these three base pairs is the lowest. All of the structures considered are H-bonded, and for these structures, we found only a small difference between the MP2 and CCSD(T) interaction energies.

The third column of the table confirms this; all of the values showing the difference between the MP2 and CCSD(T) interaction energies are smaller than 0.7 kcal/mol, which is less than 3% of the MP2 stabilization energy (the same is true for the AT base pairs). It is evident that the very expensive CCSD(T) calculations can be omitted and that the much less expensive MP2/CBS calculations yield sufficiently accurate stabilization energies. It should be noted that the same conclusion was reached for approximately 100 H-bonded DNA base pairs when canonical tautomers were considered.[17] The present data extend this important finding to H-bonded pairs containing any tautomeric form.

The fourth column shows the sum of the penalization energies of the tautomers (defined as the energy difference between the optimized canonical and tautomeric forms) in a pair. Pairs **4** and **7** clearly have this term close to zero; all of the other structures are characterized by a high penalization energy. By putting the energies for columns 2, 3, and 4 together, we obtain the total interaction energies for various GC pairs in vacuo. Column 5, which summarizes these numbers, clearly shows that the WC structure of canonical tautomers is considerably more stabilized than any other structure. Structures **4** and **7** are less stable, namely, by as much as 18 and 21 kcal/mol.

The gas-phase interaction energies and interaction energies of bases in DNA differ, and one of the main reasons is inclusion of the solvent. To improve the model, we included the solvent. We are, however, aware of the fact that the base pairs in DNA are not fully hydrated, since the sugar−phosphate backbone prevents it. Hence, the real situation in DNA is somewhere between the gas-phase model and the fully hydrated model.

The sixth column shows the changes of solvation free energies of various GC pairs. This value is defined as a difference between the solvation free energy of the isolated (optimized) monomers and the free energy of an optimized pair. All of these

numbers are positive, which indicates that the isolated bases are solvated better than a pair. The differences between these changes are substantial, and pairs **4** and **7** are penalized by solvation considerably less than the remaining pairs. By adding the values from the fifth and sixth columns together, we obtain the final interaction energies of the tautomeric bases corrected not only by the tautomeric penalization but also for solvation/desolvation effects. By analyzing these values, we ascertain that it is only structure **1** (the WC structure) that possesses a negative interaction energy while all of the other structures are characterized by positive interaction energies. Two structures, **4** and **7**, are relatively close to the WC structure (by 5 and 6 kcal/mol), whereas all of the other structures differ by more than 25 kcal/mol. This means that structure **1** will be populated dominantly, and nonzero populations will be found only for structures **4** and **7**. On the basis of the Boltzmann equation, only structure c3a_g9o1 will exist together with the c1_g19 base pair, although only two structures from 10 000 will be present. The very great difference between structures **1**, **4**, and **7** and the other structures clearly excludes any possibility of finding these structures in a water environment.

The small negative value of the total interaction energy for the WC structure is understandable in light of the known fact that planar H-bonded structures hydrate worse than stacked structures, as a result of which only stacked structures exist in a liquid phase.

The situation with the AT pairs is almost the same. The second column of Table 1 seems to be more promising for the existence of tautomeric base pairs, as the stabilization energy of the t3o4r_ai2_1H9H is more than twice higher than the stabilization energy of the canonical base pair. The tautomeric penalization of structure **5** is, however, high and completely compensates for the surprisingly large stabilization energy of the pair. The total gas-phase interaction energy (column 5) is negative only for structures **1** and **5**, thus indicating that only these structures will coexist in the gas phase. Since the energy difference is more than 12 kcal/mol, the population of the second structure will be negligible (at room temperature about 10^{-9}).

The sixth column shows changes in solvation free energies. Here, like in the case of the GC pairs, all of the values are large and positive, which indicates that isolated bases hydrate better than base pairs. By putting values from the fifth and sixth columns together, we obtain the total interaction energies of the AT base pairs corrected for both the tautomer penalization and solvation. Investigating the values of this column, we find that only structure **1** (the Watson−Crick structure) possesses this energy close to zero, whereas all of the other pairs are characterized by very high (positive) values. This indicates that, in the case of AT pairs, only the Watson−Crick structure will be populated.

Finally, allow us to mention that the above-discussed calculations concern the isolated base pairs in vacuo and in a water environment. Our aim was to discuss the situation in DNA, where solvation will be restricted. Nevertheless, we believe that the present conclusions are valid also for DNA, because the restriction in solvation will be similar for all pairs.

Conclusions

(i) For the optimized H-bonded tautomeric base pairs, the CCSD(T) correction term is negligible, and the interaction energies of these pairs can be with sufficient accuracy approximated by the MP2/CBS values.

(ii) The interaction energies of the canonical and tautomeric pairs for the GC pairs differ considerably, while in the case of the AT pairs one tautomeric pair possesses a stabilization energy which is twice larger than that of the canonical pair.

(iii) The tautomeric penalization of all AT pairs is very high, while in the case of the GC pairs two other structures possess small penalization.

(iv) The gas-phase total interaction energies of the canonical and tautomeric pairs of AT differ considerably, and the Watson−Crick canonical pair is by 12 kcal/mol more stable than the second pair, which still possesses an attractive interaction energy. The situation in the case of the GC pairs is different, with four pairs characterized by an attractive interaction energy. The energy difference between the most stable canonical pair and the first tautomeric pairs is, however, even greater than in the case of the AT pair.

(v) When considering the role of the water environment, we obtain two differing pictures. In the case of the AT pairs, only the canonical Watson−Crick pair will be populated; the population of all the other pairs will be negligible. In the case of the GC pairs, the canonical GC (Watson Crick) structure will be populated dominantly, but structures c3a_g9o1 and c3b_g9o1 will be populated non-negligibly as well.

(vi) Our results confirmed that the only populated base pairs that could be incorporated into DNA are those consisting of both canonical tautomers. This is the case with the AT pairs. For the GC pair, the existing probability (2:10000) is not negligible. It should be, however, added that this is the limiting case and the real situation in the DNA is different. The reason is that DNA bases as well as pairs inside DNA are solvated much less than in the considered free systems. Consequently, the probability found represents the very upper limit and the real numbers will be somewhere between isolated systems and fully hydrated ones. The results clearly indicate how precisely the canonical building blocks of the DNA molecules were selected and how well their stability is maintained.

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