Systematic Quantum Chemical Study of DNA-Base Tautomers

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Received 2 June 2003; Accepted 21 July 2003

Abstract: The relative energies of the energetically low-lying tautomers of pyridone, cytosine, uracil, thymine, guanine, and iso-cytosine are studied by a variety of different quantum chemical methods. In particular, we employ density functional theory (DFT) using the six functionals HCTH407, PBE, BP86, B-LYP, B3-LYP, and BH-LYP, and the *ab initio* methods Hartree-Fock (HF), standard second-order Møller-Plesset perturbation theory (MP2), an improved version of it (SCS-MP2), and quadratic configuration interaction including single and double excitations (QCISD) and perturbative triple corrections [QCISD(T)]. A detailed basis set study is performed for the formamide/formamidic acid tautomeric pair. In general, large AO basis sets of at least valence triple-ζ quality including f-functions (TZV) are employed, which are found to be necessary for an accurate energetic description of the various structures. The performance of the more approximate methods is evaluated with QCISD(T)/TZV(2df,2dp) data taken as reference. In general it is found that DFT is not an appropriate method for the problem. For the tautomers of pyridone and cytosine, most density functionals, including the popular B3-LYP hybrid, predict a wrong energetic order, and only for guanine, the correct sequence of tautomers is obtained with all functionals. Out of the density functionals tested, BH-LYP, which includes a rather large fraction of HF exchange, performs best. A consistent description of the nonaromatic versus aromatic tautomers seems to be a general problem especially for pure, nonhybrid functionals. Tentatively, this could be assigned to the exchange potentials used while the functional itself, including the correlation part, seems to be appropriate. Out of the *ab initio* methods tested, the new SCS-MP2 approach seems to perform best because it effectively reduces some outliers obtained with standard MP2. It outperforms the much more costly QCISD method and seems to be a very good compromise between computational effort and accuracy.

 J Comput Chem 25: 83–98, 2004

Key words: DNA base tautomers; DFT; MP2; QCISD(T)

Introduction

DNA bases have been the subject of numerous experimental and computational studies in recent years. In their famous 1953 publication,[1] Watson and Crick stated the importance of tautomeric forms of pyrimidine and purine nucleic acid bases with respect to the three-dimensional stacking in DNA. The 2-pyridone/2-hydroxypyridine system shown in Figure 1 represents the smallest model system related to this problem. Similar to α, β-unsaturated carbonyl compounds an equilibrium of an oxo (keto) and hydroxy (enol) tautomer is established. Previous studies (see, e.g., refs. 2–4) were able to show that the tautomeric equilibrium strongly depends on the chemical environment and might differ from crystalline state, aqueous or other solution and gas phase.

For the larger DNA bases with, for example, two CO or NH groups there exist more possible tautomers, which are sometimes very close in energy. Accurate relative energetic data for these are an important issue especially when spectroscopic data are interpreted. In this respect, modern quantum chemical methods that could provide an accuracy of about 0.1 kcal/mol for this property would be very helpful in complementing many experimental studies.

When choosing the computational level of theory to describe such medium-sized organic molecules (e.g., guanine contains 78 electrons), the balance between accuracy of the theoretical model and the required computational effort is a challenging and very often problematic task. The computational cost strongly depends on the choice of appropriate basis sets and the formal scaling behavior of the computation time with system size for the chosen

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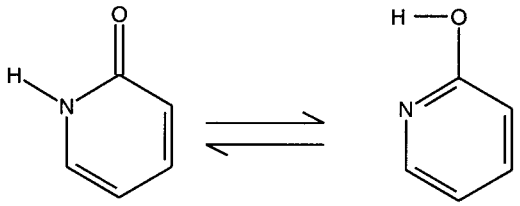

Figure 1. The tautomeric system 2-pyridone/2-hydroxypyridine.

theoretical method. Density functional theory (DFT)[5,6] usually provides fast and sufficiently accurate results for chemical problems of this type, although there are indications[7] that the tautomerism of the DNA bases is not described very well. High level *ab initio* methods, like coupled-cluster (CCSD)[8] or the very similar quadratic configuration interaction (QCISD)[9] method are in principle applicable, and if the triples excitations (T) are included, should yield the desired accuracy. However, these methods inherently have a steep scaling behavior with system size [$\mathcal{O}(N_{el}^7)$], and thus, very soon the limits of present day hardware resources are exceeded. Prior to the advent of DFT, second-order Møller-Plesset perturbation theory (MP2)[10,11] was the simplest and least expensive way of incorporating electron correlation effects in *ab initio* electronic structure calculations. It still has certain advantages over DFT, for example when dispersion forces are important. There are also indications that MP2 or improved versions of it (SCS-MP2)[12] describe "aromatization" reactions (which are an important issue in the compounds considered here) much better than common density functionals such as the popular B3-LYP.[13,14]

In a recent article Fogarasi[7] reported significant deviations for the relative energies of the three lowest cytosine tautomers when using DFT, MP2, and coupled-cluster methods. This, and the general importance of DNA bases and their tautomers, has prompted us to perform a systematic and comprehensive computational study of the energetically low-lying tautomers of pyridone (**2**), cytosine (**3**), uracil (**4**), thymine (**5**), guanine (**6**), and isocytosine (**7**) (see Fig. 2). The formamide/formamidic acid (**1**) tautomeric pair is used as a much smaller model to study AO basis set incompleteness effects.

Our basic motivation here is not to compare directly with experiment, which would require the inclusion of vibronic (entropic) and environmental effects. Rather, a methodological study of the relative energies (ΔE) of several DNA-base tautomers and related molecules in the gas phase is performed. We provide conclusive answers to the question of which of the above mentioned computational models are applicable to the problem. In particular we employ DFT, Hartree-Fock (HF), MP2, QCISD, and QCISD(T) methods. The DFT calculations are performed with various pure and hybrid type functionals, including also more recent ones such as HCTH407 or PBE. In general, we employ large one-particle expansions to avoid contamination of the results with basis set effects. In our opinion, this point has not been considered carefully enough in most previous theoretical studies. Although in some cases experimental gas phase energetic data are available, we decided to compare and evaluate the more approximate approaches against QCISD(T) results as reference data.

Computational Details

All calculations were performed on a parallel LINUX-PC-cluster using the TURBOMOLE 5.5[15] program suite. In the DFT calcu-

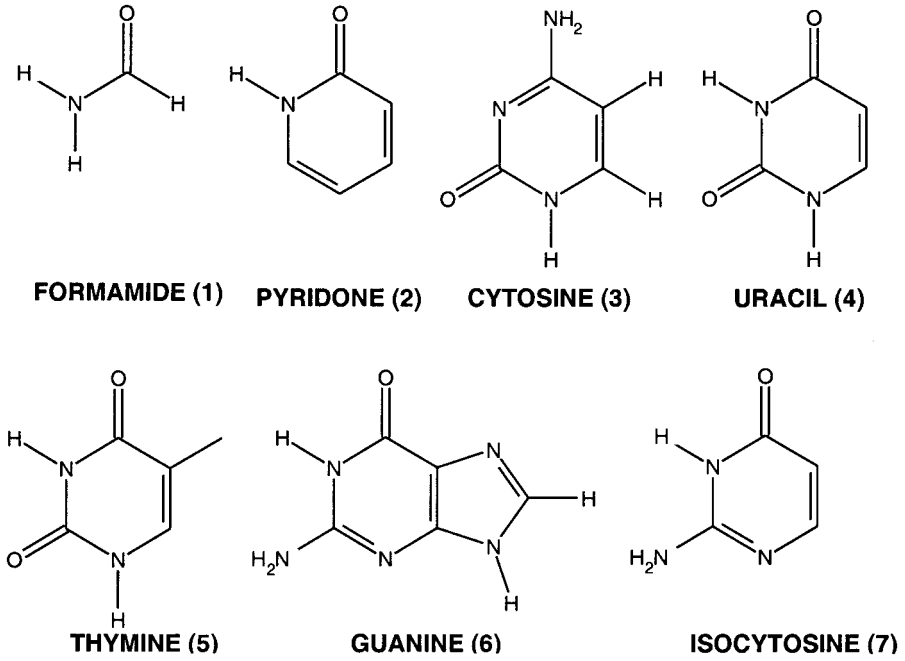

Figure 2. Oxo-tautomers of the investigated molecules.

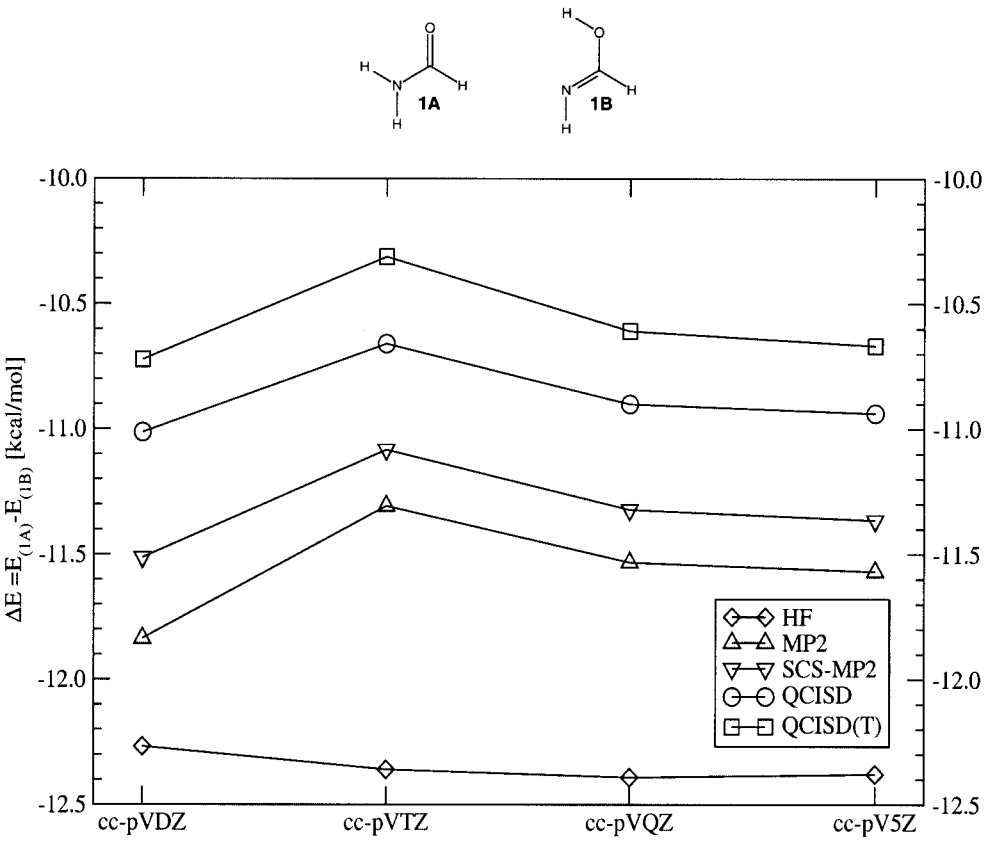

Figure 3. Basis set dependence of the relative energy of formamide (**1A**) with respect to formamidic acid (**1B**) for several *ab initio* methods.

lations various pure and hybrid functionals have been employed, namely HCTH407,[16] PBE,[17,18] B-P86[19,20] (further denoted as B-P), B-LYP,[19,21] B3-LYP,[21,22] and BH-LYP.[23] The default *m*3 numerical quadrature grid was applied in all DFT calculations. The resolution of identity (RI) approximation[24,25] was used for the nonhybrid functionals and in the MP2 and QCI calculations. The QCI treatments were performed with the RICC program developed in our group.[26] The basis sets were taken from the TURBOMOLE basis set library.[27] If not mentioned otherwise, a basis set of valence-triple-ζ quality with polarization functions TZV(2df,2pd)[28] was used. In order to reduce the computational cost, the triples correction in the QCI calculations was obtained using a smaller TZV(d,p) basis set and subsequently added to the QCISD/TZV(2df,2pd) result. In accordance with conclusions of Klopper et al.,[29] the errors due to this approximation are very small [i.e., less than 0.1 kcal/mol compared to QCISD(T) calculations, where the triples were also obtained using a TZV(2df,2pd) basis set]. In order to check the basis set dependence of our results, additional calculations for the 2-pyridone/2-hydroxypyridine system using a SV(d),[30] a TZV(d), and a very large QZV(3d2fg,2pd) basis set were performed for all methods. Complete geometry optimizations were carried out for all considered density functionals, HF, and MP2 methods. A full list of the B3-LYP/TZV(2df,2pd) optimized structural parameters is given in the supplementary material.

The SCS-MP2 model represents a recently introduced[12] improved version of standard MP2 in which the correlation energy is partitioned into parallel- and antiparallel-spin components that are separately scaled. It provides significantly improved energetics compared to standard MP2 for a wide variety of chemical systems often reaching QCISD(T) accuracy. The topic investigated here seems to be a good test of how this new quantum chemical method performs in practice on a relatively difficult electron correlation problem.

Results

Formamide/Formamidic Acid

The formamide (**1A**)/formamidic acid (**1B**) tautomeric pair (see Fig. 3) represents the smallest model system that includes structural features relevant for the problem of this study, namely an amino group in direct neighborhood of a carbonyl group. Following the reaction from **1A** to **1B,** an imino and a hydroxy group are formed. In contrast to pyridone and the DNA bases, no aromatic system is involved so that the basic tautomeric effect can be monitored exclusively. Furthermore, this system is so small that a very detailed basis set study can be performed that should provide

Table 1. Selected Optimized Bond Distances for 2-Pyridone and 2-Hydroxypyridine, Using Different Quantum Chemical Methods.

Variable	HCTH407	PBE	B-P	B-LYP	B3-LYP	BH-LYP	HF	MP2
				2A				
N_1—C_2	1.412	1.422	1.421	1.429	1.407	1.387	1.378	1.401
N_1—H	1.009	1.019	1.018	1.017	1.010	1.000	0.993	1.010
C_2—O	1.222	1.232	1.232	1.234	1.222	1.208	1.198	1.228
				2B				
N_1—C_2	1.324	1.334	1.333	1.336	1.323	1.310	1.303	1.326
C_2—O	1.349	1.359	1.359	1.367	1.352	1.338	1.331	1.355

Bond distances are in Å.
The TZV(2df,2pd) basis set was used.

reliable error estimates also for the DNA base tautomers. Previous theoretical investigations[31–33] assigned formamide to be 11–13 kcal/mol more stable than formamidic acid, which is the reason that unsubstituted formamidic acid has not been experimentally observed so far. According to spectroscopical investigations[34–36] that revealed almost planar geometries, the formamide structures were optimized in C_s-symmetry. A detailed investigation of the structure of formamide can be found in ref. 37, where high level electron correlation calculations in combination with sufficiently large basis sets yield a planar geometry. The B3-LYP/TZV(2df,2dp) structures were used for the MP2 and QCI calculations. A second isomer of **1B,** which corresponds to a 180° rotation of the hydroxy group, is found about 5.0 kcal/mol higher in energy and will not be considered in this study. Dunning's correlation consistent AO sets[38] up to valence pentuple-ζ quality (cc-pV5Z) were used. Note that the results obtained with the corresponding Karlsruhe basis sets (i.e., TZV and QZV) are very similar but due to a missing V5Z basis set could not be employed here. The results are graphically displayed in Figure 3. Increasing the level of correlation decreases the energetic difference between the two tautomers, whereas the application of a larger basis set increases the energetic gap, even though to a lesser extent. The approximate error of the correlated calculations, when using a triple-ζ instead of a pentuple-ζ basis set, is 0.3 kcal/mol. The difference between the quadruple-ζ and pentuple-ζ results is below 0.1 kcal/mol. The HF results are more or less constant for the three largest basis sets. Note also that the good error compensation at work for the small cc-pVDZ basis set is not transferable to the aromatic systems where such basis sets provide unreliable results.

2-Pyridone/2-Hydroxypyridine

The 2-pyridone (**2A**)/2-hydroxypyridine (**2B**) tautomeric pair expands the formamide model by the aspect of aromatization. Following the reaction from **2A** to **2B,** the oxo group is converted to a hydroxy group and a cyclic conjugated system with aromatic character is established. This equilibrium has been studied extensively in the past, both experimentally[39–41] and by quantum chemical calculations.[42–46] Experimental gas phase studies[47,48] yielded an enthalpy difference of 0.77 kcal/mol in favor of 2-hydroxypyridine (**2B**). If corrected for zero-point vibrational effects [B3LYP/TZV(d,p)], this corresponds to an energy difference (ΔE) of 0.95 kcal/mol. Theoretical investigations that used high-level correlation methods such as QCI and coupled-cluster[44–46] predicted a ΔE of 0.76–0.88 kcal/mol. Note, however, that this almost perfect agreement with experiment is somewhat fortunate because too small AO basis sets without f-functions (see below) were used.

The geometry optimizations of both tautomers resulted in C_s-symmetrical structures, even when started from nonplanar geometries. Important geometric parameters are listed in Table I.

The HF and BH-LYP optimizations yield the shortest bond lengths, whereas those from B-LYP, B-P, and HCTH407 are slightly longer. However, the overall deviations are small (0.03–0.05 Å) and the computational method does not seem to have a large influence on the molecular geometries. Disregarding the HF geometries and taking only the correlated methods into account, the deviations are even reduced to 0.03–0.04 Å. In the following, the optimized B3-LYP structures, which are also very similar to those from MP2, were used for the higher correlated methods [SCS-MP2, QCISD, QCISD(T)] for which no analytical gradient is currently available.

Figure 4 presents the relative energies of 2-pyridone (**2A**) with respect to 2-hydroxypyridine (**2B**). The errors for ΔE with respect to the QCISD(T) results for the applied methods are summarized in Table II.

A closer inspection of the data reveals a rather strong dependence of the results on the chosen density functional. With the exception of BH-LYP all functionals predict a wrong energetic order for the tautomers. The B-LYP and the relatively new HCTH407 functionals are worst, yielding a ΔE value of -1.9 kcal/mol, followed by PBE and B-P with values of -1.5 and -1.4 kcal/mol in favor of 2-pyridone. B3-LYP gives a smaller deviation, but still a wrong sign for ΔE. The good performance of BH-LYP (error of -0.3 kcal/mol, correct order) seems to indicate that a larger fraction of "exact" HF-exchange (50% in this case) is necessary. This view is also corroborated by the excellent result from HF theory. Although the MP2 method predicts the correct order of the isomers, the energy difference is overestimated by 1.7 kcal/mol. The new SCS-MP2 approach significantly improves the result and ΔE is found only 0.1 kcal/mol above the corresponding

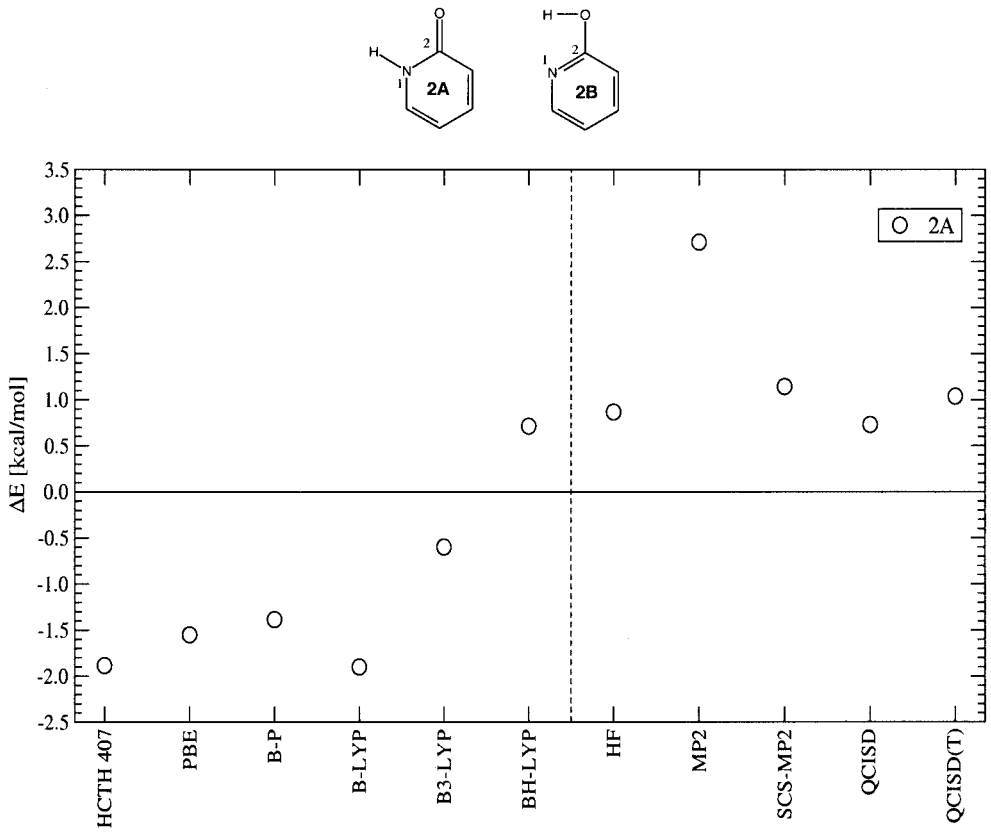

Figure 4. Relative energies of 2-pyridone (**2A**) with respect to 2-hydroxypyridine (**2B**) obtained by various quantum chemical methods [TZV(2df,2dp) basis set].

QCISD(T) value. The result from QCISD is 0.3 kcal/mol below that of the reference, indicating that the inclusion of triples is of moderate importance.

Table 2. Error of the Relative Energy[a] of 2-Pyridone (**2A**) with Respect to 2-Hydroxypyridine (**2B**) Obtained by Various Quantum Chemical Methods.

Method	Error [kcal/mol][a] **2A**
HCTH407	−2.9
PBE	−2.5
B-P	−2.4
B-LYP	−2.9
B3-LYP	−1.6
BH-LYP	−0.3
HF	−0.1
MP2	1.7
SCS-MP2[b]	0.1
QCISD[b]	−0.3

[a]The total energy of **2B** at the QCISD(T) level is −322.9739 E_h, the corresponding relative energy is 1.0 kcal/mol.
[b]B3-LYP/TZV(2df,2pd) geometry.
The TZV(2df,2dp) basis set was used.

The medium size of **2** allows a limited basis set study, which should provide reliable error estimates also for the other systems studied. The results obtained with our standard TZV(2df,2dp) basis set, the smaller SV(d), TZV(d,p) basis sets, and the large QZV(3d2fg,2dp) basis set are shown graphically in Figure 5. Out of the density functionals we include only BH-LYP and B3LYP because the latter is representative also for the nonhybrids HCTH407, PBE, B-P, and B-LYP.

For convenience, the SV(d) results, which would increase the scale too much, have not been included. This basis set yields completely unreliable results, that is, the ΔE values with all methods are incorrectly predicted to be negative ranging from −2.7 (HF) to −5.6 kcal/mol (HCTH407). The variations of the ΔE values with the other basis sets are much smaller, reaching 0.6 (B3-LYP) and 0.4 kcal/mol [MP2 and QCISD(T)] at most. Furthermore, test calculations with Dunning's correlation consistent cc-pVTZ and cc-pVQZ basis sets gave very similar results. Considering the data given in Figure 5 it should be clear that conclusive answers require the inclusion of the 2df set of polarization/correlation functions, which, however, significantly increases the computational effort for the larger systems studied. This indicates that many of the previously performed studies employing smaller AO basis sets are not decisive. If we compare only the TZV(2df,2dp) and QZV(3d2fg,2dp) results, the various methods behave differently. While the DFT results seem to be almost

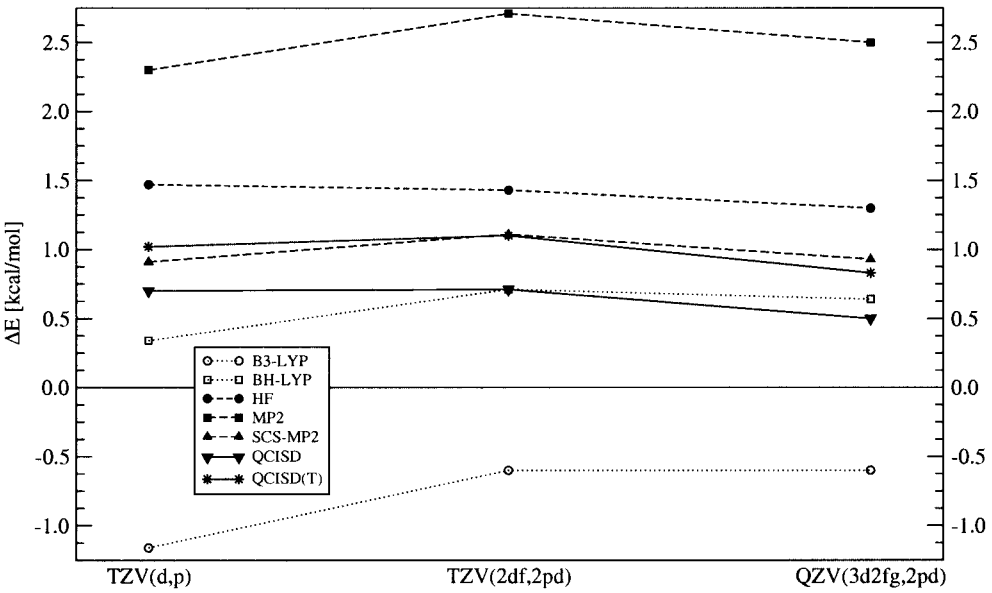

Figure 5. Basis set dependence of the relative energy of **2A** with respect to **2B** using various quantum chemical methods and B3-LYP/TZV(2df,2dp) geometries.

converged at the TZV(2df,2dp) level, the ΔE values from the correlated *ab initio* calculations slightly decrease. Because it can be expected that the QCISD(T)/QZV(3d2f1g,2d1p) results deviate by about 0.1 kcal/mol from the basis set limit (see the section Formamide/Formamidic Acid), we can conclude that our error bars with the TZV(2df,2dp) basis set may be on the order of 0.2–0.3 kcal/mol. This estimate seems to be very conservative considering the almost perfect agreement between theoretical and experimental ΔE values (1.1 and 0.95 kcal/mol) for **2.** Furthermore, it should be noted that the error bars do not significantly affect our general conclusions regarding the performance of the more approximate treatments compared to the QCISD(T) reference data.

Comparison of the results for formamide and pyridone allows a separation of the energetic effects into two different components.

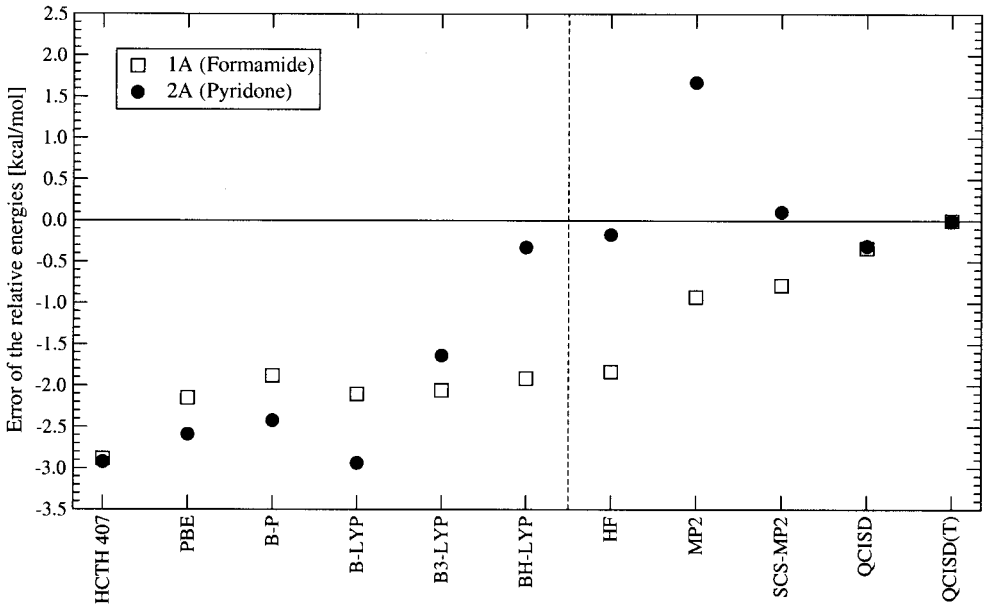

Figure 6. Deviation of the relative energies of the formamide and pyridone tautomeric pairs with respect to QCISD(T) results [TZV (2df, 2pd) basis set].

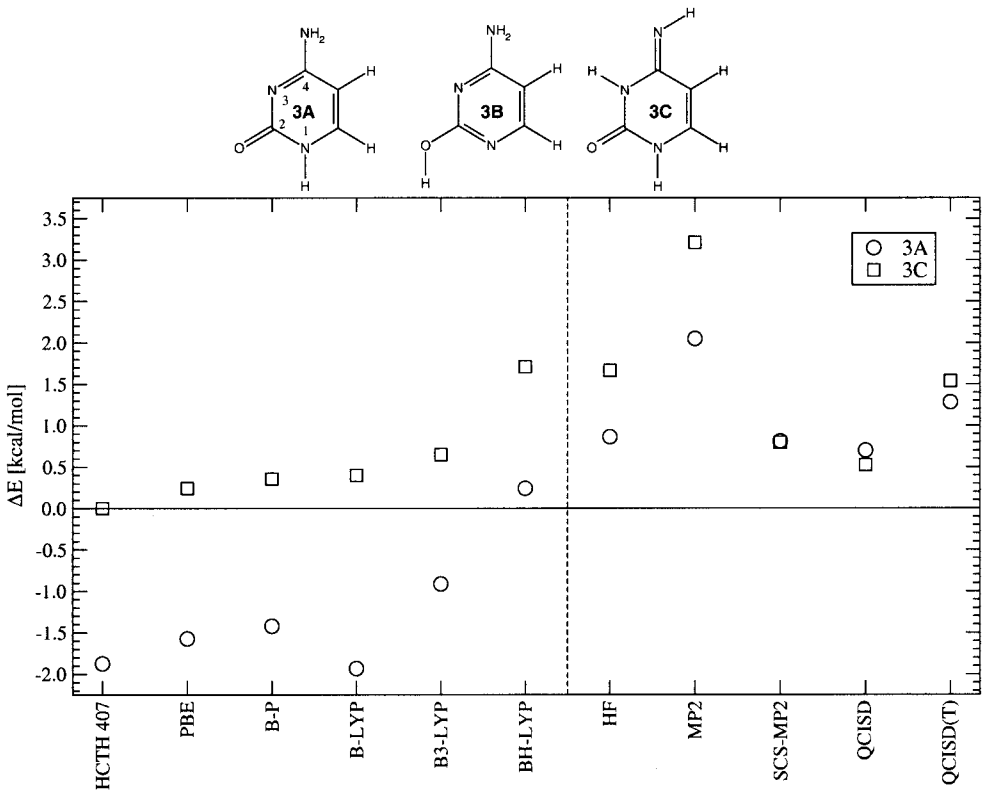

Figure 7. Relative energies of cytosine tautomers with respect to **3B** obtained by various quantum chemical methods [TZV(2df,2dp) basis set].

Figure 6 shows the deviations of the relative energies of the formamide and pyridone tautomeric pairs with respect to the QCISD(T)/TZV(2df,2pd) results. Note that the QCISD(T) ΔE values have been calculated to -10.4 kcal/mol for formamide and $+1.1$ kcal/mol for pyridone. This means that for formamide the oxo-form is more stable, whereas for pyridone the aromatic hydroxo-tautomer is energetically preferred. The energetic gain obtained by aromatization counteracts the basic tautomeric effect and is approximately of the same magnitude (for pyridone it is even slightly larger, so that the order is reversed).

Figure 6 illustrates in how far the different quantum chemical methods perform with respect to this compensation (aromatization vs. tautomeric effects). MP2 and SCS-MP2 show quite small errors for formamide, but behave differently for pyridone where MP2 overshoots. HF and BH-LYP show deviations of about 2.0 kcal/mol for formamide but the overestimation of the aromatization component counteracts and thus, the errors for pyridone are small. B3-LYP cannot compensate the error, and for the nonhybrid functionals, the effect changes sign, leading to overall larger deviations for the pyridone system.

Before continuing with the other systems, a closer look at the origin of the DFT problems seems necessary. While performing the various DFT calculations we observed that the energetic order of the two tautomers changes in the course of the SCF iterations. This has been studied systematically by using the converged HF density as an input for the various density functionals and *not* evaluating them self-consistently. Surprisingly, in these treatments the DFT problems completely disappear and all functionals now yield the correct energetic order with ΔE values between 1.6 (B3LYP and BLYP) and 2.0 kcal/mol (PBE). Because, for example, the LYP correlation functional alone also yields a small but correct contribution to ΔE when evaluated with the HF density (0.4 kcal/mol in favor of **2B**), we can conclude that the exchange potentials (and *not* the total density functional from which it is derived) are responsible for the error.

Cytosine

Previous investigations[49–56] have shown that there are six possible tautomers of cytosine, three low-lying ones and three forms, that are found in a range of 8.0–10.0 kcal/mol higher in energy. Our study is restricted to the three most stable tautomers (see Fig. 7): the nonaromatic 2-oxo form (**3A**), the aromatic 2-hydroxy form (**3B**), and a 4-imino form (**3C**). In a recent study, Fogarasi[7] reported significant deviations between the relative energies of these three tautomers obtained by DFT and coupled cluster calculations. All *ab initio* treatments predicted the aromatic 2-hydroxy tautomer (**3B**), which corresponds to **2B,** to be the lowest in energy, whereas DFT gave lower energies for the nonaromatic 2-keto-4-amino-tautomer (**3A**). A recent high level *ab initio* study[56] predicted ΔE values of 1.6 kcal/mol (**3A**) and 1.9 kcal/mol (**3C**) at the CCSD(T)/cc-pVTZ level of theory. The authors addi-

Table 3. Selected Optimized Bond Distances of the Investigated Cytosine Tautomers Using Different Quantum Chemical Methods.

Variable	HCTH407	PBE	B-P	B-LYP	B3LYP	BH-LYP	HF	MP2
				3A[a]				
N_1—C_2	1.426	1.436	1.431	1.443	1.423	1.404	1.398	1.413
C_2—N_3	1.362	1.372	1.373	1.377	1.366	1.356	1.358	1.373
N_3—C_4	1.316	1.326	1.324	1.329	1.315	1.300	1.293	1.313
N_1—H	1.007	1.017	1.018	1.015	1.008	0.998	0.991	1.007
C_2—O	1.216	1.225	1.226	1.226	1.215	1.201	1.192	1.218
C_4—N	1.353	1.362	1.370	1.366	1.354	1.342	1.340	1.362
				3B				
N_1—C_2	1.332	1.342	1.342	1.345	1.331	1.317	1.312	1.330
C_2—N_3	1.323	1.333	1.332	1.335	1.324	1.313	1.312	1.328
N_3—C_4	1.335	1.346	1.346	1.349	1.336	1.322	1.317	1.334
C_2—O	1.343	1.353	1.352	1.360	1.344	1.328	1.320	1.346
C_4—N	1.358	1.366	1.367	1.372	1.361	1.349	1.348	1.367
				3C				
N_1—C_2	1.391	1.401	1.400	1.406	1.391	1.375	1.371	1.386
C_2—N_3	1.371	1.381	1.380	1.386	1.373	1.361	1.359	1.373
N_3—C_4	1.401	1.410	1.410	1.418	1.404	1.390	1.389	1.397
N_1—H	1.005	1.015	1.014	1.013	1.006	0.996	0.990	1.006
N_3—H	1.008	1.019	1.018	1.017	1.010	1.000	0.994	1.010
C_2—O	1.214	1.223	1.223	1.225	1.212	1.199	1.190	1.216
C_4—N	1.281	1.290	1.289	1.291	1.277	1.262	1.254	1.283

[a]Planar geometries with HCTH407, PBE, B3LYP, and HF. A pyramidal NH_2-group was obtained with MP2 and B-P, respectively.
Bond distances are in Å.
The TZV(2df,2pd) basis set was used.

tionally applied different extrapolation techniques to correct for basis set incompleteness. These effects are about 0.2–0.3 kcal/mol, which is in perfect agreement with our error estimate (see previous section).

If (as before) the HF structure is excluded, the geometry optimizations with the different methods show only insignificant deviations for the bond lengths (see Table III). Except for MP2 and B-P, which predict a nonplanar structure for **3A** caused by a pyramidal NH_2-group, all other methods yield planar geometries. A detailed discussion of the effect of nonplanarity can be found in ref 7. These corrections are below 0.3 kcal/mol (e.g., 0.14 kcal/mol for **3A** with MP2) and do not influence the overall energetic orders obtained by the various methods. For this reason all single point calculations were performed using the planar B3-LYP geometry.

The calculated relative energies for the three cytosine tautomers are presented in Figure 7 and the corresponding errors are given in Table IV. Similar to **1,** the results from most of the DFT calculations contradict those from *ab initio* theory. Opposed to all other methods, HCTH407, PBE, B-P, B-LYP, and B3-LYP predict the nonaromatic 2-oxo cytosine (**3A**) to be more stable than the aromatic 2-hydroxy tautomer (**3B**). All DFT methods yield 4-imino cytosine (**3C**) as the energetically most unfavorable structure. HCTH407 gives a difference of only 0.1 kcal/mol between **3B** and **3C.** Out of all density functionals, only BH-LYP reproduces the energetic order of the QCISD(T) calculations (**3B** > **3A** > **3C**), which has also been found in refs. 7 and 56, although the relative energy of **3A** is underestimated by 1.1 kcal/mol.

As for the pyridone system, the correlation energy contribution to the ΔE value is small, as indicated by the surprisingly good HF result. MP2 significantly overestimates the relative energies of **3A** (by 0.8 kcal/mol) and **3C** (by 1.7 kcal/mol). The errors from the

Table 4. Errors of the Relative Energies of Cytosine Tautomers with Respect to **3B** Obtained by Various Quantum Chemical Methods.

	Error [kcal/mol][a]	
Method	**3A**	**3C**
HCTH407	−3.2	−1.6
PBE	−2.9	−1.4
B-P	−1.4	−1.2
B-LYP	−3.2	−1.2
B3-LYP	−2.2	−0.9
BH-LYP	−1.1	0.1
HF	−0.4	0.1
MP2	0.8	1.7
SCS-MP2[b]	−0.5	−0.8
QCISD[b]	−0.6	−1.1

[a]The total energy of **3B** at the QCISD(T) level is −394.2988 E_h, the relative energies of **3A** and **3C** are 1.3 and 1.6 kcal/mol, respectively.
[b]B3-LYP/TZV(2df,2pd) geometry.
The TZV(2df,2dp) basis set was used.

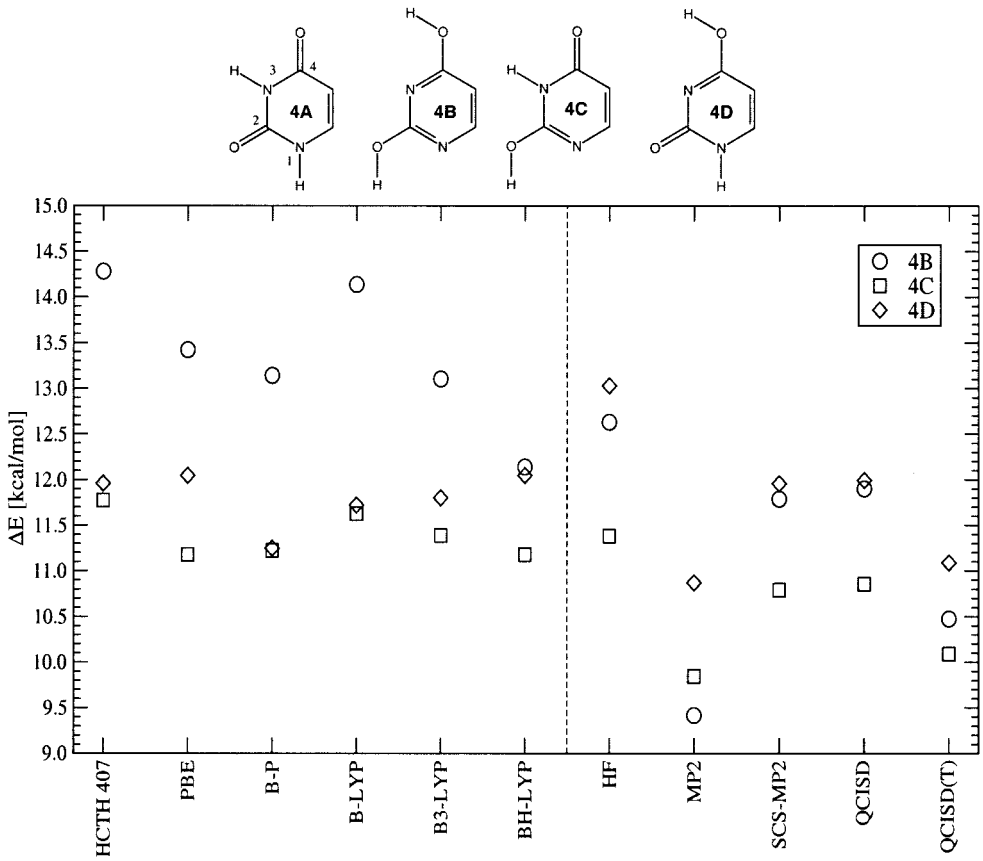

Figure 8. Relative energies of uracil tautomers with respect to **4A** obtained by various quantum chemical methods [TZV(2df,2dp) basis set].

SCS-MP2 approach are about 50% smaller than those from standard MP2. **3A** and **3C** are now correctly predicted to be very close in energy, similar to what is found with both QCI methods. The inclusion of the perturbative triples correction mainly increases the gap between the aromatic and the keto/imino tautomers, which is also similar to **1.** It should be noted that our QCISD(T) reference values are in very good agreement with those obtained from CCSD(T) with a comparable basis set [ΔE(**3A**) = 1.4 kcal/mol, ΔE(**3C**) = 1.6 kcal/mol[7]].

Uracil

Previous DFT and MP2-studies examined up to 12 different tautomers.[57,58] The four energetically lowest-lying structures are shown in Figure 8: **4A** is the 2,4-dioxo tautomer, **4B** the 2,4-dihydroxy tautomer, with both hydroxyl groups pointing to the neighboring nitrogen atoms, **4C** refers to the 2-hydroxy-4-oxo, and **4D** to the 2-oxo-4-hydroxy tautomer. In the latter structures the hydroxyl hydrogens are directed towards the unsaturated nitrogen atoms. Other theoretical[49–51,57–61] and experimental investigations[57–59,61] have shown that the 2,4-dioxo-form (**4A**) is the most stable tautomer ($\Delta E \approx 10$ kcal/mol). The previous DFT and MP2 studies revealed contradicting stability sequences, that is **4A** > **4C** > **4D** ≈ **4B** with B3-LYP and **4A** > **4C** ≈ **4B** > **4D** with MP2.

The geometry optimizations for these four C_s-symmetric isomers resulted in very similar structures with all applied methods. As in the preceding examples, HF tends to give the shortest bond lengths and B-P the longest. Regarding the correlated methods exclusively, the maximum deviation in the bond lengths is found to be 0.03 Å.

As in the previous studies, the 2,4-dioxo tautomer (**4A**) is predicted to be most stable by all applied methods (see Figure 8 and Table V). The other tautomers are found in a range of 9–15 kcal/mol above this isomer, but depending on the method their order is different. All DFT calculations predict that the aromatic 2,4-dihydroxy tautomer (**4B**) is the most unstable one, lying 12–14 kcal/mol higher in energy compared to **4A,** whereas the *ab initio* methods place the 2-oxo,4-hydroxy-form (**4D**) highest. The overdestabilization of the aromatic form with DFT is similar to what has been observed for **1** and **2.** HCTH407 and B-LYP give errors of 3.8 and 3.6 kcal/mol. The deviations for PBE, B-P, and B3-LYP are somewhat smaller (2.6–2.9 kcal/mol), but still very large, and only BH-LYP yields an acceptable error (0.6 kcal/mol). The remaining tautomers **4C** and **4D** are very close in energy with most functionals. The energy difference between them is below 0.2

Table 5. Errors of the Relative Energy of Uracil Tautomers with Respect to **4A,** Obtained by Various Quantum Chemical Methods.

	Error [kcal/mol][a]		
Method	**4B**	**4C**	**4D**
HCTH407	3.8	1.7	0.9
PBE	2.9	1.3	0.3
B-P	2.6	1.1	0.2
B-LYP	3.6	1.5	0.6
B3-LYP	2.6	1.3	0.7
BH-LYP	1.6	1.1	0.9
HF	2.1	1.3	1.9
MP2	−1.1	−0.2	−0.3
SCS-MP2[b]	1.3	0.7	0.9
QCISD[b]	1.4	0.8	0.9

[a]The total energy of **4A** at the QCISD(T) level is: −414.1890 E_h, the relative energies of **4B, 4C,** and **4D** are 10.5, 10.1, and 11.1 kcal/mol.
[b]B3-LYP/TZV(2df,2pd) geometry.
The TZV(2df,2dp) basis set was used.

kcal/mol for HCTH407, PBE, B-P, and B-LYP and 0.4 kcal/mol with B3-LYP. The corresponding values from BH-LYP and the *ab initio* methods are in the range of 0.8–1.2 kcal/mol. Compared to the QCISD(T) reference values, the DFT errors are much larger for the 2-hydroxy,4-oxo (**4C**) form than for the 2-oxo,4-hydroxy system (**4D**). The HF calculations result in the stability sequence **4C** > **4B** > **4D,** with **4B** being slightly below **4D** and rather strong overestimations [2.1 (**4B**), 1.3 (**4C**), and 1.9 kcal/mol (**4D**)] of the relative energies. Standard MP2 stabilizes the aromatic 2,4-dihydroxy form (**4B**) more than all other methods, yielding a wrong energetic order. The deviation from the reference value is more than 1.0 kcal/mol for this tautomer, whereas for the other two structures it is only 0.2–0.3 kcal/mol. The SCS-MP2 and QCISD results are more or less identical and correctly reproduce the order of the QCISD(T) calculations, but overestimate the ΔE values systematically by 0.7–1.4 kcal/mol.

Thymine

Replacing the hydrogen atom at the 5-position of uracil by a methyl group gives thymine. This structural similarity is also reflected in the energetics, as will be seen in this section. Previous HF and MP2 calculations[62,63] predicted the 2,4-dioxo tautomer (**5A**) to be most stable, followed by the 2-hydroxy, 4-oxo tautomer (**5C**) and the aromatic 2,4-dihydroxy tautomer (**5B**). The 4-hydroxy, 2-oxo form (**5D**) is found to be highest in energy.

All four structures were calculated in C_s-symmetry, and as noted before, the optimizations revealed no substantial deviations

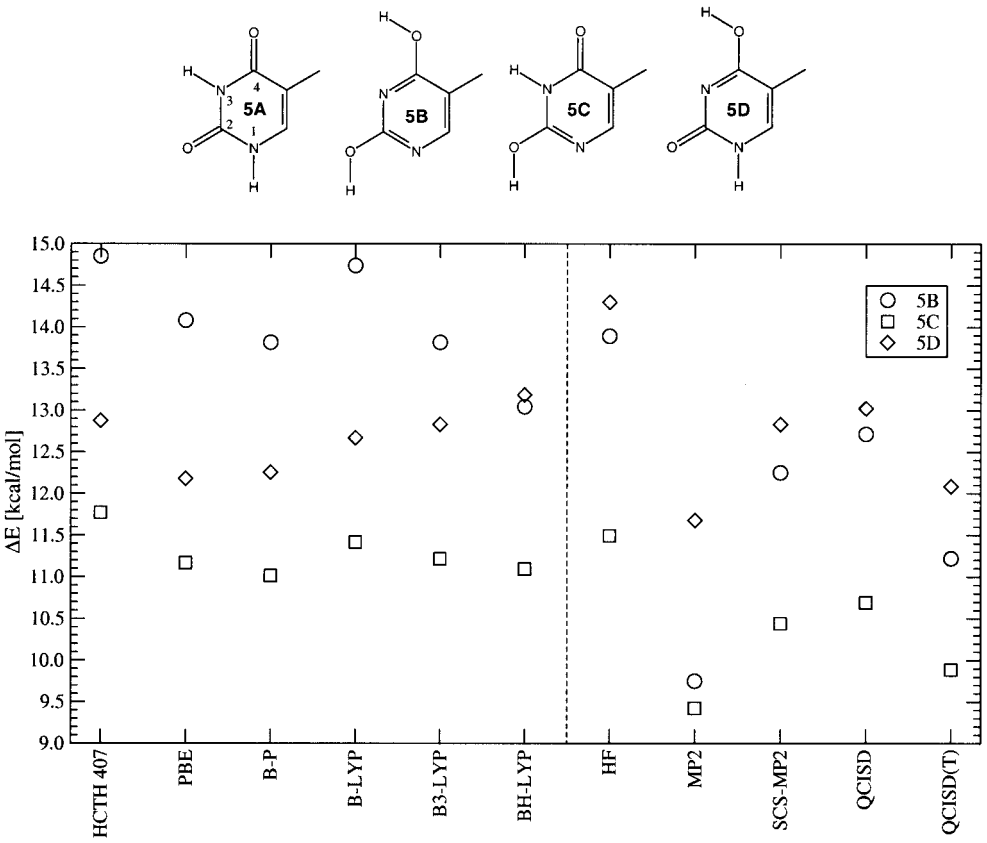

Figure 9. Relative energies of thymine tautomers with respect to **5A** obtained by various quantum chemical methods [TZV(2df,2dp) basis set].

Table 6. Errors of the Relative Energy of Thymine Tautomers with Respect to **5A** Obtained by Various Quantum Chemical Methods.

	Error [kcal/mol][a]		
Method	**5B**	**5C**	**5D**
HCTH407	3.6	1.9	0.8
PBE	2.8	1.3	0.1
B-P	2.5	1.1	0.2
B-LYP	3.4	1.5	0.6
B3-LYP	2.5	1.3	0.7
BH-LYP	1.7	1.2	0.9
HF	2.6	1.6	0.7
MP2	−1.5	−0.5	−0.4
SCS-MP2[b]	1.0	0.5	0.7
QCISD[b]	1.4	0.8	0.9

[a]The total energy of **5A** at the QCISD(T) level is −453.4184 E_h, the relative energies of **5B, 5C,** and **5D** are 11.3, 9.9, and 12.1 kcal/mol.
[b]B3-LYP/TZV(2df,2pd) geometry.
The TZV(2df,2dp) basis set was used.

between the molecular geometries as obtained from the different methods. The calculated relative energies for the four thymine tautomers are given in Figure 9 and the errors with respect to the QCISD(T) data are presented in Table VI. In agreement with previous studies,[62,63] the 2,4-dioxo tautomer (**5A**) is by far the most stable one. The other three tautomers (**5B–5D**) are found in a range of ≈10–15 kcal/mol higher in energy. Furthermore, with all applied methods, the nonaromatic 2-hydroxy, 4-oxo structure (**5C**) is the next most stable form of thymine. Regarding **5B** and **5D,** a disagreement between most DFT and the *ab initio* methods is found. Although the energetic difference is rather small in many cases, most density functionals favor **5D** over **5B.** The largest deviations from the QCISD(T) result are found for the 2,4-dihydroxy tautomer **5B.** HCTH407 and B-LYP show the largest errors with 3.6 and 3.4 kcal/mol. The deviations from PBE, B-P, and B3-LYP are somewhat smaller (2.8, 2.5, and 2.5 kcal/mol), and for BH-LYP it drops to 1.7 kcal/mol. Similar to the corresponding uracil structures, the deviations become significantly smaller for the 2-hydroxy, 4-oxo (**5C**) and the 4-hydroxy, 2-oxo tautomer (**5D**). None of the DFT errors are larger than 2.0 kcal/mol for **5C** and larger than 1.0 kcal/mol for **5D.** As noted before, only BH-LYP reproduces the same energetic order as the *ab initio* methods. As for uracil, HF strongly overestimates the relative energies and pure MP2 underestimates these values, but here both methods correctly reproduce the energetic order of the QCISD(T) results. Both the SCS-MP2 and QCISD results are better than MP2, that is, the ΔE values of **5B–5D** are just systematically shifted by 0.5–1.4 kcal/mol.

Guanine

A recent experimental infrared and UV study[64] reported the coexistence of four guanine tautomers (see Fig. 10) in the gas phase. Additionally to the previously found 9H-oxo and 9H-hydroxy (**6A, 6B**) forms and the 7H-oxo form (**6C**), a new absorption band was detected that was assigned to the 7NH hydroxy form (**6E**). Previous theoretical studies[51,53,65–69] of the relative energies of the tautomers in question are only partly consistent. Independent from the computational level it seems clear that the 7H-enol form (**6E**) is the most unstable tautomer (4–5 kcal/mol above the lowest lying structure **6C**). The energetic order of the other structures (**6A–6C**) strongly depends on the chosen level of theory. In a detailed HF, DFT(B3LYP), MP2, and MP4 study[66] including a large number of basis sets, it was demonstrated that the energetic difference between the 9H- and 7H-oxo tautomers is very small and the calculated numbers can change sign, depending on the chosen level of correlation and the quality of the basis set.

Our present study covers the 9H-oxo (**6A**), two rotamers of the 9H hydroxy (**6B** and **6D**), the 7H-oxo (**6C**), 7H-hydroxy (**6E**), and a 9H-imino (**6F**) forms of guanine. The amino tautomers (**6A–6E**) are all nonplanar due to the pyramidalization of the NH_2 group. The imino form (**6F**) is planar even when optimized without any symmetry restrictions.

The relative energies of the investigated tautomers are shown in Figure 10 and the corresponding errors are given in Table VII. The imino tautomer (**6F**) is found to be 13–15 kcal/mol higher in energy than the 7H-oxo form (**6C**) with all methods (for reasons of scaling it is not included in Fig. 10). Furthermore, it is obvious that the 7H-hydroxy form (**6E**) is the second-highest lying isomer with relative energies of 4–5 kcal/mol above **6C,** which agrees with previous theoretical investigations. The other four tautomers (**6A–6D**) are much closer in energy. Their DFT energies are found in a range of 3 kcal/mol, and for the *ab initio* methods, this range even drops below 1 kcal/mol. With our reference method QCISD(T) the ΔE values are 0.5 (**6A**) and 0.6 kcal/mol (**6B**) with respect to **6C.** A definite answer to the question of order in this case would require larger AO basis sets, which is currently not feasible.

In comparison with the *ab initio* methods, DFT overestimates the relative energies of the two 9H-hydroxy forms (**6B** and **6D**). The largest deviations are found with the HCTH407 and B-LYP functionals (2.0 kcal/mol) closely followed by PBE (1.7 and 1.6 kcal/mol). The deviations for the 9H-oxo tautomer (**6A**) are below 0.5 kcal/mol. For BH-LYP the deviations with respect to the QCISD(T) values are again rather small (**6A** and **6B:** 0.1 kcal/mol, **6D:** 0.2 kcal/mol). The HF method underestimates the relative energies by 0.3–0.8 kcal/mol. The 7H-6-hydroxy tautomer (**6E**), which is found 0.5 kcal/mol above the QCISD(T) value, is clearly an exception. HF is the only method that yields a negative relative energy for the 9H-6-oxo tautomer (**6A**), although the difference (0.2 kcal/mol) is rather small. Opposed to all other systems studied, the MP2 values almost perfectly match the QCISD(T) results.

The SCS-MP2 and QCISD deviations are very similar and below 1.0 kcal/mol. It should be noted that all methods yield the correct energetic order.

Iso-Cytosine

According to a previous HF/MP2 study[70] in which 14 isomers of iso-cytosine were investigated, the two energetically lowest-lying tautomers are the 6-oxo (**7A**) and the 6-hydroxy form (**7B**). At the HF/6-31G(d,p) level of theory, **7B** was predicted to be 2.4 kcal/mol more stable than **7A** and MP2 calculations increased this difference to 2.7 kcal/mol. The lowest 6-oxo imino tautomer (**7C**)

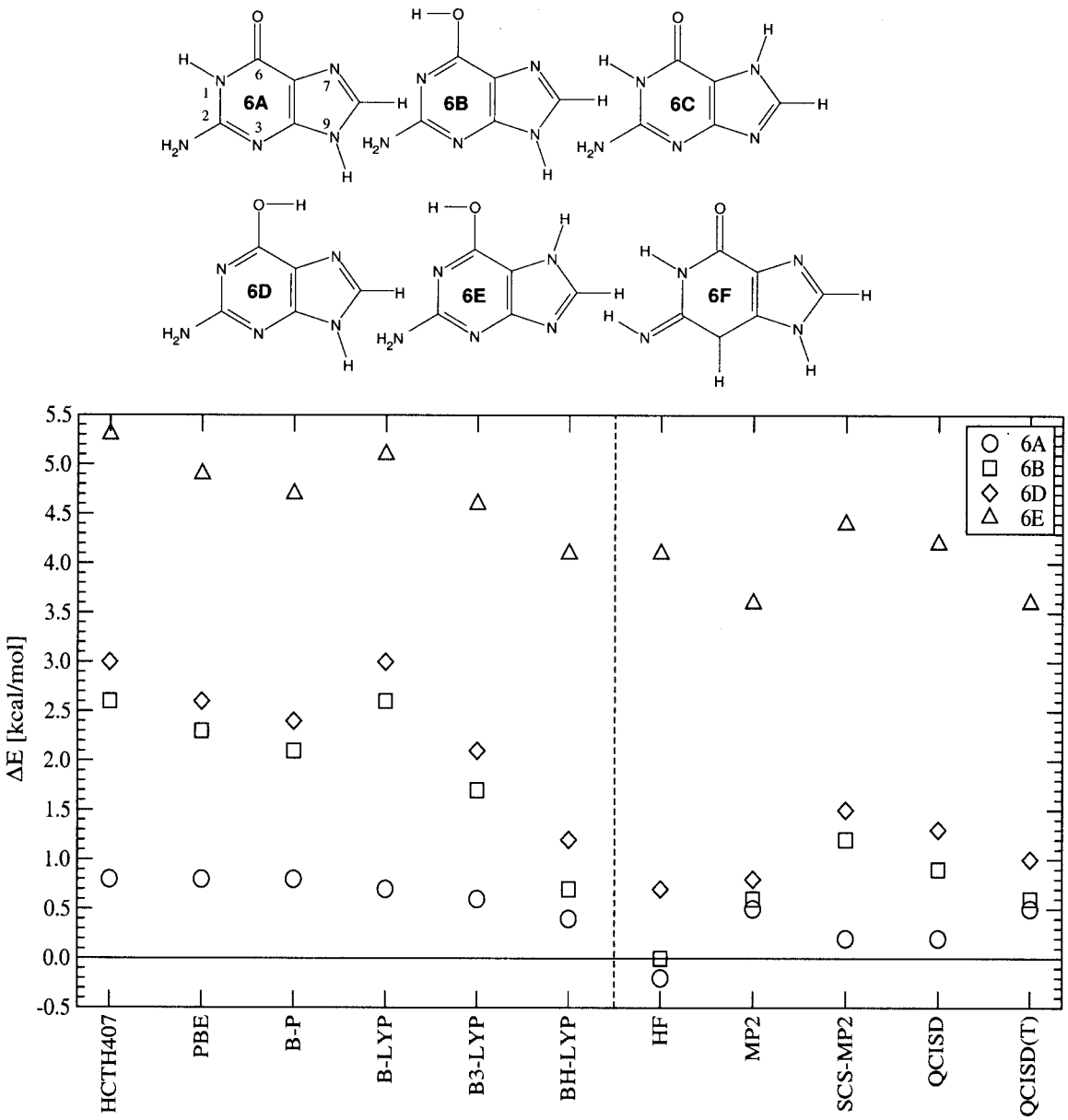

Figure 10. Relative energies of guanine tautomers with respect to **6C** obtained by various quantum chemical methods [TZV(2df,2dp) basis set]. Because of its high relative energy (13–15 kcal/mol), the data for **6F** are not included.

was found about 9 kcal/mol above **7B.** All other isomers were found in a range of 10–40 kcal/mol above the previously mentioned molecules. The structures of **7A** and **7B** are nonplanar due to the pyramidal arrangement of the NH_2-group.

The relative energies of the 6-oxo tautomer are shown in Figure 11 while Table VIII presents the errors of the methods including **7C.** With the exception of the B-LYP and HCTH407 functionals, all applied methods predict an identical energetic order, which is in agreement with the previous investigation.[70] The B-LYP and HCTH407 relative energies of **7A** and **7B** are close to zero and do not allow clues about a distinct order of stability, and furthermore deviate by more than 2 kcal/mol from the QCISD(T) results. B-P, PBE, and B3-LYP underestimate the energetic gap between the two lowest tautomers by 1.3–1.7 kcal/mol, whereas for BH-LYP and HF this underestimation is reduced to 0.3 and 0.5 kcal/mol. MP2 overestimates the relative energy of **7A** by 0.8 kcal/mol and QCISD underestimates it by 0.5 kcal/mol. Of all the methods applied, SCS-MP2 is closest to the QCISD(T) reference value.

The deviations increase for the imino tautomer (**7C**). HCTH407, PBE, B-P, and B-LYP underestimate the relative energy by more than 2.0 kcal/mol. The BH-LYP result almost

Table 7. Errors of the Relative Energy of Guanine Tautomers with Respect to **6C** Obtained by Various Quantum Chemical Methods.

	Error [kcal/mol][a]				
Method	**6A**	**6B**	**6D**	**6E**	**6F**
HCTH407	0.3	2.0	2.0	1.7	−0.1
PBE	0.3	1.7	1.6	1.3	−0.5
B-P	0.3	1.5	1.4	1.1	−0.6
B-LYP	0.2	2.0	2.0	1.5	−0.9
B3-LYP	0.1	1.1	1.1	1.0	−0.6
BH-LYP	−0.1	0.1	0.2	0.5	−0.4
HF	−0.7	−0.6	−0.3	0.5	−0.8
MP2	0.0	0.0	−0.2	0.0	0.7
SCS-MP2[b]	−0.3	0.6	0.5	0.8	−0.7
QCISD[b]	−0.3	0.3	0.3	0.6	−1.0

[a]The total energy of **6C** at the QCISD(T) level is −541.686315 E_h, the corresponding relative energies are 0.5 (**6A**), 0.6 (**6B**), 1.0 (**6D**), 3.6 (**6E**), and 14.6 kcal/mol (**6F**).
[b]B3-LYP/TZV(2df,2pd) geometry.
The TZV(2df,2dp) basis set was used.

matches the QCISD(T) value, outperforming all other density functionals. Again, the error from HF is rather small (0.2 kcal/mol). Standard MP2 overestimates the energetic difference by 1.5 kcal/mol while SCS-MP2 significantly improves the description. The inclusion of the triples correction in the QCI calculations seems to be mandatory here, as indicated by the relatively large QCISD error of 1.1 kcal/mol.

Discussion

In order to get some insight into the overall performance of the applied methods, a statistical analysis including the mean deviation (MEAN), mean absolute deviation (MAD), root mean square error (RMS), and maximum error (MAX) was carried out. These values were derived from the deviations of the relative energies from the corresponding QCISD(T) values for all calculated tautomers. The results are shown in Table IX and Figure 12.

With the exception of BH-LYP all DFT methods show MAD and RMS values larger than 1.0 kcal/mol. HCTH407 and B-LYP perform worst, with MAD values of 1.9 and 1.8 kcal/mol and RMS errors of 2.2 and 2.1 kcal/mol, respectively. Especially the RMS and MAX which are very reliable indicators for the quality of the results, are extremely high for those two functionals. The RMS errors with PBE and B-P are smaller (1.8 and 1.6 kcal/mol), but only BH-LYP yields an acceptable overall description of the problem. The data clearly show that increasing the fraction of HF exchange significantly improves the results, as can be seen by a

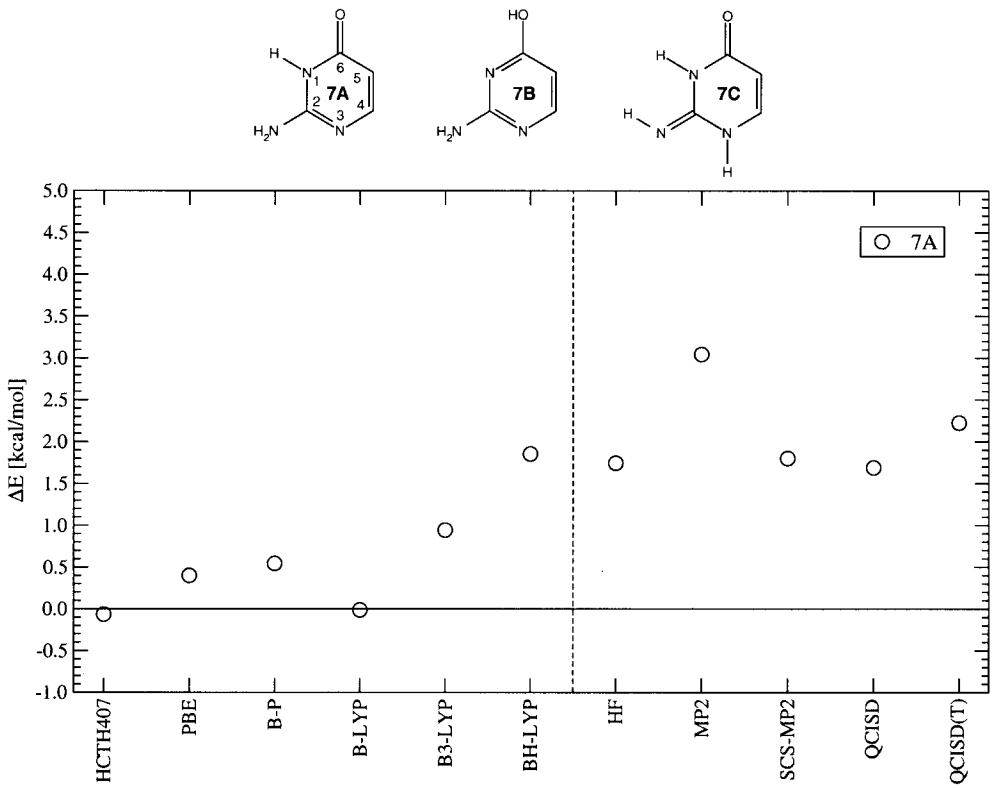

Figure 11. Relative energy of the iso-cytosine tautomer **7A** with respect to **7B** obtained by various quantum chemical methods [TZV(2df,2dp) basis set].

comparison of B-LYP (0% HF-exchange), B3-LYP (20% HF-exchange), and BH-LYP (50% HF-exchange) errors. The RMS and MAD values drop by approximately 30% when applying the B3-LYP and by approximately 60% when applying the BH-LYP density functional. The MAX decreases by 1.1 kcal/mol when going from B-LYP to B3-LYP and by 0.9 kcal/mol from B3-LYP to BH-LYP.

The performance of the HF model is better than that of B-P and B3-LYP but not as good as that with the BH-LYP functional. For MP2, the MAD, RMS, and MAX errors are 0.8, 0.7, and 1.7 kcal/mol, respectively, that is, similar to those from the best density functional. The new SCS-MP2 approach, which causes no additional computational cost compared to standard MP2, reduces the RMS error by 0.1 kcal/mol and slightly reduces the MAD. The MAX is decreased by 0.4 kcal/mol, which can be considered as a significant improvement over standard MP2. A more detailed analysis furthermore shows that the actual performance of SCS-MP2 is even better than suggested by the statistical data. The errors are more uniform, meaning that the description of the higher-lying isomers relative to each other is significantly improved and only the energy difference with respect to the lowest one is still improvable. The outliers obtained by conventional MP2 originate from static correlation effects, which are relatively important in these unsaturated (aromatic) systems. SCS-MP2 damps these contributions by scaling down the spin parallel correlation energy, as outlined in ref. 12, and thus reaches a better performance than the conventional method. Note that although computationally cheaper by two orders of magnitude, SCS-MP2 is almost always better than QCISD, which provides RMS, MAD, and MAX of 0.9, 0.8, and 1.4 kcal/mol. These numbers indicate the moderate importance of the perturbative triples correction.

The large errors for the relative energies as obtained by most density functionals originate from the bad description of the aromatic structures. In cases where a nonaromatic tautomer is the most stable form, like in uracil, thymine, and guanine, the relative energies of the aromatic tautomers are severely overestimated. For uracil and thymine these errors are between 2.5 and 3.8 kcal/mol. For pyridone, cytosine, and iso-cytosine, where the aromatic tautomer is most stable, this results in large underestimations for the other tautomers.

The results for the particular molecules can be summarized as follows:

1. Pyridone and cytosine: all DFT methods except BH-LYP give the wrong energetic order. MP2 overestimates the relative energies of the oxo(imino) forms and SCS-MP2 represents a significant improvement.
2. Uracil and thymine: the relative energies of the two lowest-lying tautomers are correctly reproduced by all applied methods. DFT and *ab initio* methods yield contradicting results for the two energetically high-lying structures.
3. Guanine: almost all methods predict an identical energetic order for the examined tautomers.
4. Iso-cytosine: all methods except HCTH407 and B-LYP yield a correct order. The DFT methods tend to underestimate the relative energies.

Table 8. Errors of the Relative Energy of Iso-Cytosine Tautomers with Respect to **7B** Obtained by Various Quantum Chemical Methods.

	Error [kcal/mol][a]	
Method	**7A**	**7C**
HCTH407	−2.3	−2.4
PBE	−1.8	−2.2
B-P	−1.7	−2.1
B-LYP	−2.2	−2.8
B3-LYP	−1.3	−1.4
BH-LYP	−0.3	−0.1
HF	−0.5	0.2
MP2	0.8	1.5
SCS-MP2[b]	−0.4	−0.8
QCISD[b]	−0.5	−1.1

[a]The total energy of **7B** at the QCISD(T) level is −394.300789 E_h, the relative energies of **7A** and **7C** are 2.2 and 7.7 kcal/mol, respectively.
[b]B3-LYP/TZV(2df,2pd) geometry.
The TZV(2df,2dp) basis set was used.

Table 9. Mean Deviation, Root Mean Square (RMS), Mean Absolute Deviation (MAD), and Maximum Errors (MAX) with Respect to QCISD(T)/TZV(2df,2dp) Relative Energies (in kcal/mol).

Method	MEAN	RMS	MAD	MAX
HCTH407	−0.4	2.2	1.9	3.8
PBE	0.1	1.8	1.5	2.9
B-P	0.1	1.6	1.4	2.7
B-LYP	0.2	2.1	1.8	3.6
B3-LYP	0.3	1.4	1.2	2.6
BH-LYP	0.4	0.9	0.7	1.7
HF	0.5	1.2	0.9	2.6
MP2	0.1	0.8	0.7	1.7
SCS-MP2	0.2	0.7	0.6	1.3
QCISD	0.2	0.9	0.8	1.4

Conclusions

This study of the relative energies of the tautomers of six DNA bases and related molecules has shown that an accurate energetic description within 0.1–0.2 kcal/mol is a quite challenging task. By using relatively large AO basis sets and the highly correlated QCISD(T) model we could provide the most accurate results obtained so far theoretically. There are indications, however, that in order to achieve the desired target accuracy, even larger basis sets are needed in the explicitly correlated calculations. Although DFT has proven to be a reliable and fast tool for optimizing the different molecular structures, it fails to correctly predict the energetics of several systems. In particular, a consistent description of nonaromatic versus aromatic tautomers seems to be a problem especially for pure, nonhybrid functionals. Tentatively, this could be assigned to the exchange potentials used. The best agreement with respect to the QCISD(T) reference data is obtained

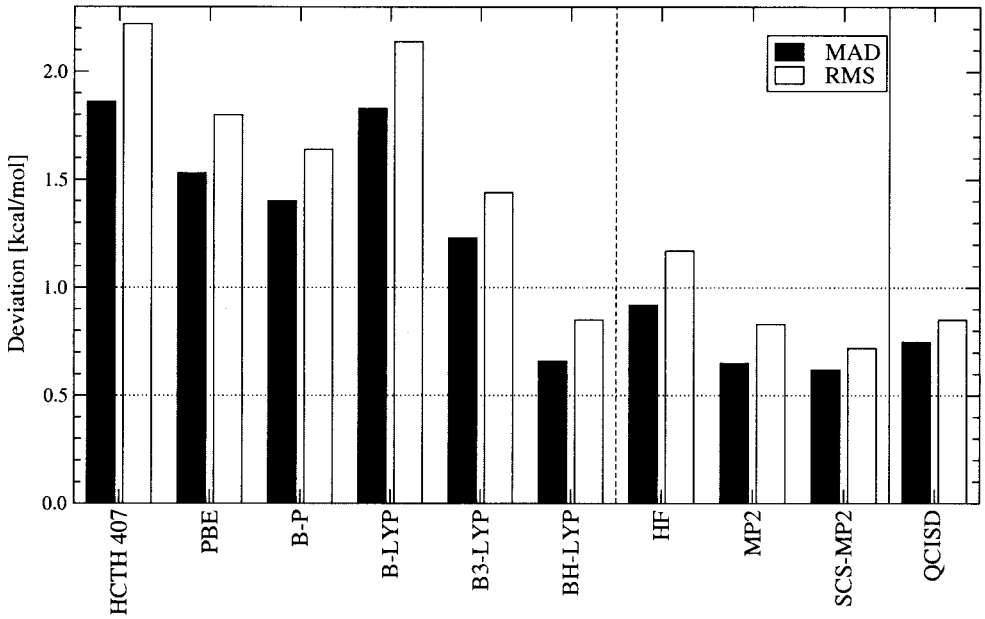

Figure 12. Mean absolute deviation (MAD) and root mean square errors (RMS) with respect to QCISD(T)/TZV(2df,2dp) relative energies.

with the BH-LYP functional, which clearly outperforms the commonly used B3-LYP model. The simple HF approach is surprisingly accurate. This has its origin in the roughly constant correlation energy for the tautomers of a particular system. Out of the *ab initio* methods tested, the recently introduced improved second-order perturbation theory (SCS-MP2) seems to perform best. It outperforms the much more costly QCISD method and seems to be a very good compromise between computational effort and accuracy. When using the RI approximation, MP2 and SCS-MP2 require similar computation time as the DFT(BH-LYP) calculations up to 1500–2000 basis functions. This suggests the SCS-MP2 method as the most valuable tool for studies on nucleic acid base tautomers or even larger systems as e.g. nucleic acid base pairs.

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