Toward the Exact Solution of the Electronic Schrödinger Equation for Noncovalent Molecular Interactions: Worldwide Distributed Quantum Monte Carlo Calculations†

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Quantum Monte Carlo (QMC) calculations on the stacked (st) and Watson/Crick (wc) bound adenine/thymine (A/T) and cytosine/guanine (C/G) DNA base pair complexes were made possible with the first large scale distributed computing project in *ab initio* quantum chemistry, Quantum Monte Carlo at Home (QMC@HOME). The results for the interaction energies (wc-A/T = 15.7 kcal/mol, wc-C/G = 30.2 kcal/mol, st-A/T = 13.1 kcal/mol, st-C/G = 19.6 kcal/mol) are in very good agreement with the best known coupled-cluster based estimates. The accuracy of these values is further supported by calculations on the S22 benchmark set of noncovalently bound systems, for which we obtain a small mean absolute deviation of 0.68 kcal/mol. Our results support previous claims that the stacking energies are of comparable magnitude to the interactions of the commonly discussed hydrogen-bonded motif. Furthermore, we show that QMC can serve as an advantageous alternative to conventional wave function methods for large noncovalently bound systems. We also investigated in detail all technical parameters of the QMC simulations and recommend a careful optimization procedure of the Jastrow correlation factors in order to obtain numerically stable and reliable results.

Introduction

Noncovalent interactions among basic building blocks of biomacromolecules like DNA, RNA and proteins are imposing major challenges for today's science.[1,2] Besides hydrogen bonding and electrostatic interactions—which can both be accounted for in a reasonably accurate manner even within the framework of current density functional theory (DFT)—the dispersion interactions, especially involved in the stacking of the basic building blocks, remain a challenging task for quantum chemistry.[3,4] For a realistic description of these systems, dispersion effects are essential as counteracting part for the Pauli exchange repulsion, and need very advanced quantum chemical methods to be described accurately.[5] However, methods capable of correctly describing dispersion cannot routinely be applied to larger systems due to the so-called computational "scaling wall".[6] Current DFT can give an acceptable good description of hydrogen-bonded systems, but fail to do so for stacked complexes,[3,4] and although interesting developments to overcome these shortcomings are on the way,[7,8] the results cannot be considered as being *ab initio*, which makes error estimates for new and untested systems difficult. Precisely for the future development of all approximate methods (including classical force fields), quantum chemistry needs more rigorous approaches, that can provide high accuracy reference data for calibration.

A promising method for the highly accurate description of noncovalent interactions in medium to large systems is fixed node diffusion Monte Carlo (FNDMC).[9] This quantum Monte Carlo (QMC) method is capable of solving the fully correlated electronic Schrödinger equation exactly within the boundary conditions of a given many particle fermion nodal hypersurface.[10] The remaining "fixed node error" (FNE) cancels out (within typically necessary and attainable statistical accuracy) for noncovalently bound systems,[11] as the approximate nodal hypersurface of the complex is to a large extent similar to the product of the approximate nodal hypersurfaces of the monomers, and therefore errors related to the approximation of nodal hypersurfaces should cancel out for binding energies. Calculations on smaller noncovalently bound complexes confirmed this assumption.[12,13] Within the statistical error bars given, FNDMC can therefore be considered as being able to solve the electronic Schrödinger equation for noncovalent interactions. Overviews on quantum Monte Carlo methods have been published,[10,14] and the same holds for details of the FNDMC algorithm used by our workgroups.[15] An approach with an improved optimization algorithm and more complex trial wave functions was proposed for noncovalently bound systems.[16] Interaction energies were merely presented for the parallel displaced benzene dimer (2.2-(3) kcal/mol) and are within the statistical error bars identical to what we obtain with our simpler approach, and hence this proceeding does not seem reasonable to us. General advantages of the FNDMC method are a negligible basis set dependence and a favorable scaling behavior of N^{3-4} with system size (improved scaling algorithms are possible and currently under development).[17,18]

Due to a large prefactor, however, QMC calculations are very CPU-time intensive (in spite of the favorable scaling, that makes FNDMC more and more economic with increasing system size). A solution to this problem can be found in the ideal parallelizability of FNDMC (thanks to the Monte Carlo nature of the algorithm), that allows for massive parallel calculations on thousands of processors, and therefore the effective exploitation

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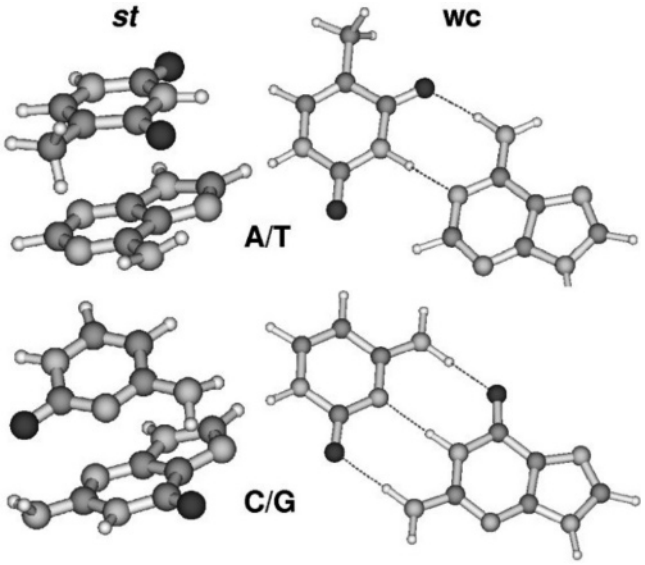

Figure 1. Structures of the A/T(st), A/T(wc), C/G(st) and C/G(wc) DNA base pairs.

of modern developments in high-performance-computing. This feature of the QMC algorithm will likely become more and more important in the future, as further gains in computing power are considered to be possible only within "high density computing" concepts (e.g., multicore processors). Furthermore, FNDMC offers the possibility to open up unused computing resources, institution-wide and even in the general public, because FNDMC is not explicitly wave-function based, so that only small data amounts have to be transferred to and from the computer-nodes. Based on the insight that the world's computing power is no longer concentrated in supercomputers centers, but distributed in hundreds of millions of personal computers belonging to the general public, "public resource computing" (PRC) or "volunteer computing" (VC) is a way to open up new resources for scientific research. On the basis of the BOINC (Berkeley Open Infrastructure for Network Computing) software system,[19] our Quantum Monte Carlo at Home (QMC@HOME) project[20] allows PC owners all over the world to participate in our research through the donation of spare computing time. At the time of writing, the project supplies around 15 TFlop/s sustained computing power for our research into QMC for medium to large systems. Thanks to hundreds of thousands of volunteers worldwide, PRC thus provides the opportunity to acquire computing power in the range of a top500 supercomputer for the price of a mid-size server-system. Centered on standard web-server components, the BOINC software system provides mechanisms for the necessary work-scheduling, data-handling and accounting as well as several user community features, and thus allows for a relatively easy setup of a secure and reliable scientific computing project. This way the FNDMC calculations were done by a specially adapted version of the program Amolqc.[21]

Although our project is still in a beta test stage (considering technical aspects of software engineering and project administration), we were able to obtain conclusive results for the DNA base pair interaction energies of the adenine/thymine (A/T) and cytosine/guanine (C/G) stacked (st) and Watson−Crick (wc) bound complexes (see Figure 1). Theoretical research of nucleic acid base pair interaction focuses on these systems, because the understanding of their fundamental interactions forms the basis for many scientific aspects of DNA biomacromolecules. While on the one hand experimental data on these and similar complexes are missing,[3] systems of this size are on the other hand out of range for standard CCSD(T) calculations with a sufficiently large AO basis set, the current "gold standard" of quantum chemistry[6] (an interesting alternative is the approximate local CCSD(T) treatment).[22,23] Additionally, extensive checks for all simulation parameters and calculations on the S22 benchmark set[3] of noncovalently bound systems were made, to ensure the accuracy of our results.

TABLE 1: Interaction Energies of DNA Base Pairs (kcal/mol)

	FNDMC,[a] present work	CCSD(T) estimates[b]
A/T, st	−13.1(8)	−11.6
A/T, wc	−15.7(9)	−15.4
C/G, st	−19.6(9)	−16.9
C/G, wc	−30.2(9)	−28.8

[a] Statistical errors in parentheses. [b] Values are taken from ref 33, estimated errors due to the basis set extrapolation and remaining correlation errors are about 1−2 kcal/mol.

Computational Details

For our FNDMC calculations we use guidance functions of the Slater−Jastrow type, with Hartree−Fock (HF) determinants and Schmidt−Moskowitz type correlation functions.[24] Gaussian quadruple-ζ valence basis sets were fully optimized[25] for soft-ECPs by Ovcharenko et al.[26] Correlation parameters were optimized by variance minimization. HF, MP2 and SCS-MP2[27] single point calculations were done with a slightly modified version of the TURBOMOLE 5.6 suite of programs.[28] Complete basis set (CBS) values were extrapolated according to Halkier et al.,[29] using TZ and QZ basis sets. Geometries for the S22 set were taken from Jurecka et al.,[3] and all other geometries were optimized at the DFT-D(BLYP)/TZV(2d,2p) level of theory.[30]

Results and Discussion

DNA Base Pairs. Our results are presented in Table 1. The FNDMC interaction energies are based on calculations within the QMC@HOME project, where each energy value is evaluated from around 1500−2000 work-units, each of 4000 steps with an equilibrated and statistically independent ensemble of 100 walkers. This way, the calculation of a ground state energy for one of the DNA base pairs lasts on about 2000 of the more than 38000 participating hosts approximately 2 days, with a first sensible estimate available after 1 day. QMC@HOME allowed us to carefully check all technical simulation parameters (including finite sample size effects, equilibration length and time step dependence) by separate, independent calculations. These absolutely necessary checks would have been impossible to perform on nonprofit computing resources without QMC@HOME. Not to our surprise, the optimization of the used correlation function parameters turned out to be a crucial step and since for PRC-distributed calculations no reference energy exchange is possible, a thorough investigation of finite sample size errors was mandatory, which is described in the following.

In FNDMC, the wave function is evolved in imaginary time toward the ground state with a diffusion process which relies on the mathematical equivalence of the imaginary time-dependent Schrödinger equation and a generalized diffusion equation:

$$\Psi_{(R,\tau+\delta\tau)} = \int G_{(R,R',\delta\tau)} \Psi_{(R',\tau)} \, \mathrm{d}R'$$

This process is governed by the unknown Green's function

$$G_{(R,R',t)} = \langle R|\mathrm{e}^{-(H-E_{\mathrm{ref}})\tau}|R'\rangle$$

of the system that is approximated by the short-time approximation

$$\mathrm{e}^{-(H-E_{\mathrm{ref}})\tau} \approx \mathrm{e}^{-\mathrm{T}\tau}\cdot\mathrm{e}^{-(V-E_{\mathrm{ref}})\tau}$$

where $\mathrm{e}^{-T\tau}$ results in a diffusion step and $\mathrm{e}^{-(V-E_{\mathrm{ref}})\tau}$ in a weight or branching step. Importance sampling with a guide or trial function[31]

$$\Psi_G = \Phi\cdot\mathrm{e}^{U}$$

results in the weight step $\mathrm{e}^{-(E_{\mathrm{l}}-E_{\mathrm{ref}})\tau}$ with the local energy

$$E_{\mathrm{l}} = \frac{H\Psi_G}{\Psi_G}$$

Since the kinetic energy operator T does not commute with the potential or local energy, this ansatz is exact only for a time step τ of zero and might lead to time step errors even for small time steps, depending on the overall trial wave function quality. Time step errors can normally be circumvented by extrapolation to $\tau = 0$. For systems as large as the DNA base pairs, special care has to be taken for the convergence of the correlation function parameter optimization, as the nonlinear optimization process may result in Jastrow factors of different quality for systems of considerably different size (e.g. monomers and complexes). Such Jastrow factors would yield trial wave functions of different quality that could lead to different time step errors for monomers and complexes. In our case, the quality of a Jastrow factor can be measured by the FNDMC variance, because the variance is a measure for the overall quality of the trial wave function, which is in our case the product of a (constant) HF determinant Φ and the (optimized) Jastrow factor e^{U}.

$$\Psi_G = \Phi\cdot\mathrm{e}^{U}$$

The function U consists of two-body and three-body terms

$$U_{aij} = \sum_{k}^{N_a} c_{ka}(\bar{r}_{ai}^{\,l_{ka}}\bar{r}_{aj}^{\,m_{ka}} + \bar{r}_{aj}^{\,l_{ka}}\bar{r}_{ai}^{\,m_{ka}})\bar{r}_{ij}^{\,n_{ka}}$$

with

$$\bar{r} = \frac{r}{1 + b\cdot r}$$

where a and i,j refer to nuclei and electrons, respectively, with interparticle distances r. The Jastrow factor parameters are optimized by variance minimization (see Computational Details section for more details and references).

To check for the convergence of the Jastrow optimization, we have investigated the time step dependence of absolute and relative energies of adenine, thymine and their hydrogen-bonded and stacked complexes for Jastrow factors of different quality. The results are shown in Figures 2 to 4: Figures 2 to 4 each show the time step behavior of the absolute energy for different Jastrow factors, first for the adenine/thymine stacked (Figure 2) dimer, then for the involved monomer adenine (Figure 3), and finally for the binding energies of the stacked (Figure 4) complexes. Corresponding curves for the Watson−Crick bound dimer and the thymine monomer were also calculated, and they show the same trends with a less problematic behavior for the relative energies.

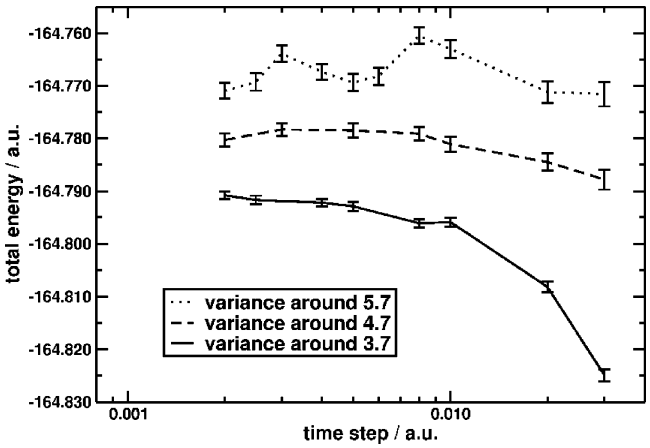

Figure 2. Time step dependence of the absolute energy of the adenine/thymine stacked base pair for three Jastrow factors of different quality (dotted, dashed and solid curves).

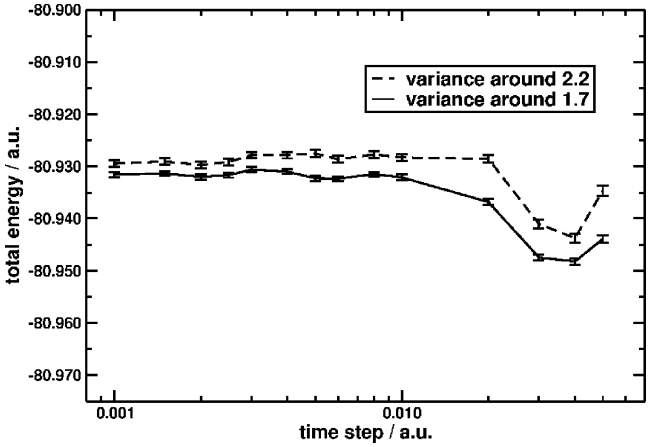

Figure 3. Time step dependence of the absolute energy of adenine for two Jastrow factors of different quality (dashed and solid curves). Energy axis spacing is the same as in the corresponding curves for the complexes.

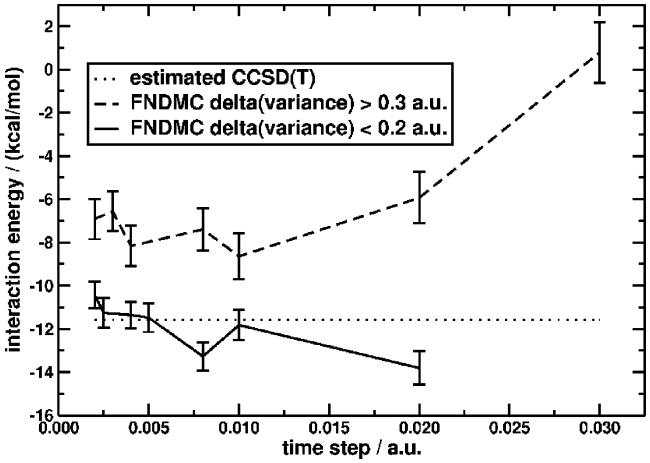

Figure 4. Time step dependence of the interaction energy of the adenine/thymine stacked base pair for two sets of Jastrow factors of different quality (dashed and solid curves) and estimated CCSD(T) values (dotted curve); delta(variance) is the complex variance minus the sum of the monomer variances.

As can be seen from Figure 2, we encounter a strong dependence of the energy on the Jastrow factor quality for the stacked adenine/thymine base pair. Figure 3 shows that this

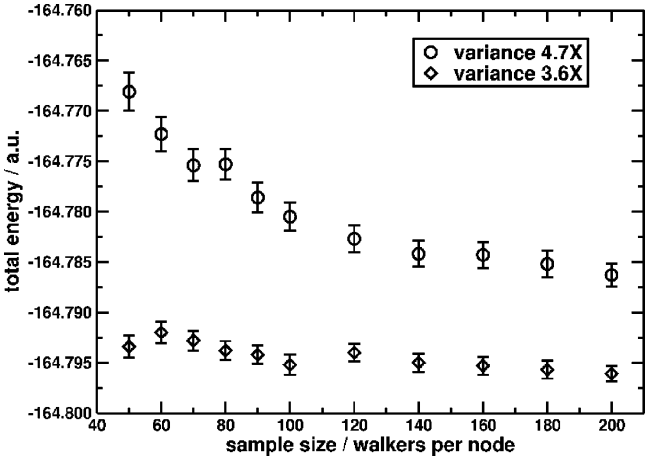

Figure 5. Sample size dependence of the absolute energy of the adenine/thymine stacked base pair for two Jastrow factors of different quality (circles and diamonds).

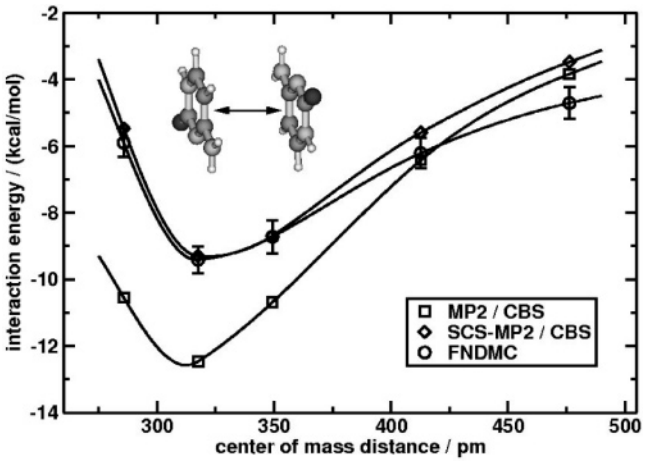

Figure 6. Cytosine/cytosine potential curve. The sum of the fragment energies is taken as zero of energy.

behavior is greatly alleviated for the smaller monomer systems. The different characteristics of the curves can be assigned to different finite time step errors related to monomer and complex trial wave functions of different overall quality. The finite time step error should vanish for an extrapolation to a time step of zero (i.e., the curves for the different Jastrow factors should converge for $\tau = 0$), but for trial wave functions with a quality below a certain threshold we encounter finite sample size errors, that prevent the dotted curve in Figure 2 from converging to the correct value when reaching a time step of zero (see below for more information on our investigation of finite sample size effects). Even considering the more regular time step behavior of the dashed and solid curves in Figure 2, an extrapolation to a zero time step turns out to be problematic. For reliable calculations on larger molecules we thus need equally good Jastrow factors for monomers and complexes, to make sure that time step errors cancel out. As a measure of equality we can use the FNDMC variance. If we have Jastrow factors of the same quality, the variance (that rises linearly with system size) of the monomers should sum up to the complex variance. Figure 4 shows that our consideration about the Jastrow factor optimization holds for the DNA base pairs: If the variance difference (complex variance minus sum of monomer variances, termed delta(variance)) is below a certain threshold, we get reliable results for the interaction energies with reasonable small time steps (see the solid curve in Figure 4, we observe the same trend also for the omitted Watson−Crick bound complex, that shows a less problematic behavior). If the variance difference is greater than about 0.2 atomic unit, the results get significantly influenced by the different time step behavior (see the dashed curve in Figure 4).

Errors related to the finite sample size of an individual FNDMC simulation run are commonly referred to as "population control error" (PCE).[32] For weakly coupled simulations like our PRC calculations (where no reference energy exchange is possible), one ends up with many independent data points each based on a relative small sample. To exclude finite sample size effects on our results, we have investigated the sample size dependence of the absolute energy for the stacked adenine/thymine complex with two Jastrow factors of different quality (see Figure 5). As mentioned above, a Jastrow factor of higher quality can be identified by a lower variance. Because a lower variance leads to decreased fluctuations of the weights, which lead to decreased branching, which in turn leads to decreased fluctuations of the reference energy, Jastrow factors of higher quality should encounter less pronounced finite sample size effects. This is confirmed by the different development of the curves in Figure 5. With the afterward chosen sample size of 100 walkers no PCE can be observed for the Jastrow factor of higher quality. For the Jastrow factor of lower quality a sample size of 100 walkers is not sufficient to exclude finite sample size effects (this is the reason for the above-named problems with the dotted curve in Figure 2). Alternative ways to limit the population control error have been suggested by Umrigar et al.[32]

We also performed checks for the numerical stability of our approach by considering the geometry dependence of the interaction energies. This is of some importance because the estimated CCSD(T) values,[3] which we take for comparison, have been calculated with geometries optimized at the RI-MP2/TZVPP level[33] while we use DFT-D(BLYP)/TZV(2d,2p) geometries.[30] The DFT-D method has been proven to provide excellent geometries for noncovalently bound systems.[34] In any case, comparative FNDMC calculations on the DNA base pair model geometries of the S22 benchmark set[3] (see below) showed that geometry effects on the relative energies are smaller than the statistical error of our FNDMC calculations and the basis set extrapolation scheme used to obtain the estimated CCSD-(T) values. Considering geometry dependence in more detail, we chose the cytosine/cytosine dimer (C/C), a commonly used model system for geometry dependence in stacking[4] for further tests. The C/C potential curve (see Figure 6) shows the overall good performance of FNDMC compared to complete basis set (CBS) extrapolated SCS-MP2[27] values, the most accurate method for large $\pi-\pi$-stacked systems available.[35,36] For larger distances the FNDMC values begin to deviate from the SCS-MP2 values, presumably because numerical problems with the used Schmidt−Moskowitz Jastrow correlation factors come into play, as indicated by the impossibility to optimize reasonable Jastrow factors for much larger intermolecular distances. This however is not relevant for the calculation of the interaction energies of the DNA bases, because these were taken as the difference between complex and fragment energies. An important conclusion for future work is that additional efforts to obtain better trial wave functions should be invested. Interaction energies from MP2, the most popular quantum chemical method in the field, are also shown for comparison, approving that dispersion effects are strongly overestimated at this level.

In comparison to our FNDMC interaction energies, Table 1 shows estimated CCSD(T)/CBS data, the best known reference values until now. We want to mention that results of presumably

TABLE 2: Results for the S22 Benchmark Set (kcal/mol)[a]

		FNDMC,[a] present work	CCSD(T) estimates[b]	deviation kcal/mol	deviation %
1	$(NH_3)_2$	−3.19(9)	−3.17	−0.02	−1
2	$(H_2O)_2$	−5.34(9)	−5.02	−0.32	−6
3	formic acid dimer	−20.19(23)	−18.61	−1.58	−8
4	formamide dimer	−17.05(23)	−15.96	−1.09	−7
5	uracil dimer	−21.60(55)	−20.65	−0.95	−5
6	2-pyridoxine·2-aminopyridine	−17.63(49)	−16.71	−0.92	−6
7	adenine·thymine WC	−15.88(79)	−16.37	0.49	3
8	$(CH_4)_2$	−0.48(8)	−0.53	0.05	10
9	$(C_2H_4)_2$	−1.38(13)	−1.51	0.13	9
10	benzene·CH_4	−0.63(21)	−1.50	0.87	58
11	benzene dimer PD	−1.65(42)	−2.73	1.08	40
12	pyrazine dimer	−3.70(42)	−4.42	0.72	16
13	uracil dimer	−10.72(60)	−10.12	−0.60	−6
14	indole·benzene	−4.11(55)	−5.22	1.11	21
15	adenine·thymine stack	−10.89(69)	−12.23	1.34	11
16	ethene·ethane	−1.22(12)	−1.53	0.31	20
17	benzene·H_2O	−3.69(24)	−3.28	−0.41	−12
18	benzene·NH_3	−2.49(22)	−2.35	−0.14	−6
19	benzene·HCN	−3.40(43)	−4.46	1.06	24
20	benzene dimer T	−3.77(39)	−2.74	−1.03	−37
21	indole·benzene T-shape	−6.52(50)	−5.73	−0.79	−14
22	phenole dimer	−7.10(46)	−7.05	−0.05	−1
	MD	−0.03			
	MAD	0.68			
	rms	0.82			
	$\Delta_{min-max}$	2.92			

[a] Statistical errors in parentheses. [b] Values are taken from ref 3, estimated errors due to the basis set extrapolation and remaining correlation errors are about 1−2 kcal/mol.

the same good quality as the CCSD(T) values were obtained recently with symmetry adapted perturbation theory (SAPT).[37] While the accuracy of these results is harder to judge (as only perturbation up to second order is included, while for polar systems one would also expect the third order to become important),[38] they are in good agreement with the coupled-cluster data, deviating by a uniform upward shift in the relative energies of 1.2−1.6 kcal/mol.

Our FNDMC interaction energies are, within the given error bars, in very good agreement with the estimated CCSD(T)/CBS values. The largest deviation is found for the G/C stacked complex, where the DFT-D geometry used is quite strongly tilted and on the way to a hydrogen-bonded structure (see Figure 1), which is reflected in the lower binding energy.

The S22 Benchmark Set. This well-established test set covers two important noncovalent interaction types, as the binding situation of the first seven complexes is dominated by H-bonds, while entries eight to fifteen provide more or less purely dispersion-bonded systems, and the last seven are mixed cases. Our results presented in Table 2 are based on QMC@HOME calculations, with each energy value evaluated from 250 to 2000 work-units, each of n·4000 steps with an equilibrated and statistically independent ensemble of 100 walkers. (n is chosen so that each work-unit is not shorter than around 5−10 h, which has turned out to be a convenient value.) All results for this set are obtained as "black box" results (i.e., without manual selection of trial wave functions) by FNDMC calculations based on three consecutive Jastrow factor optimizations, so that the FNDMC variance differences between dimer and monomers are as small as possible (as described above in more detail for the DNA base pairs).

In comparison to our FNDMC interaction energies, Table 2 also shows estimated CCSD(T)/CBS data, which is the best known reference for this benchmark set.[3] Again, all FNDMC interaction energies are in very good agreement with the reference values, resulting in a mean absolute deviation (MAD) from the reference of 0.68 kcal/mol. Whereas 13 out of 22 entries show a deviation larger than 0.5 kcal/mol, and 7 larger than 1.0 kcal/mol, only the formic acid dimer (deviation of −1.58 kcal/mol) and the adenine/thymine stacked complex (deviation of 1.34 kcal/mol) deviate by more than 1.2 kcal/mol. Errors of FNDMC larger than the statistical error are found for 15 out of 22 entries, but while 8 of these are larger than 0.5 kcal/mol, only one entry (the formic acid dimer) deviates by more than 1.0 kcal/mol (−1.35 kcal/mol) from the reference value, when taking the statistical error into account. Within our approach of choosing trial wave functions according to the variance difference, we do not expect to be able to go beyond this accuracy of 0.5 to 1.0 kcal/mol. The uniform distribution of deviations around zero (see Figure 7) suggests that the remaining error is not of systematic nature (in contrast to the systematic errors of MP2 shown for comparison), which is also supported by the fact that the largest percentage deviations are found for smaller interaction energies (entries 10, 11, 20). The overall good performance of FNDMC for the S22 benchmark set provides strong support for the statement that FNDMC can be considered as being able to solve the electronic Schrödinger equation for noncovalent interactions.

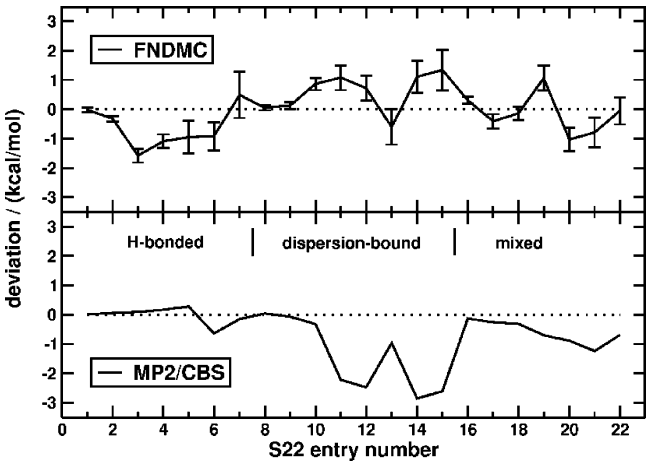

Figure 7. Deviation of S22 interaction energies from the reference data[3] for FNDMC and MP2/CBS (with counterpoise correction). MP2 data taken from ref 36.

Conclusions

Our FNDMC interaction energies are, within the given error bars, both for the DNA base pairs and for the entire S22 benchmark set, in very good agreement with the estimated CCSD(T)/CBS values. From a theoretical point of view, our results for the DNA base pairs have to be considered as the most accurate nucleic acid base pair interaction energies reported up to now. They confirm that noncovalent interactions in stacked geometries are of comparable magnitude to those in hydrogen-bonded (Watson−Crick) mode. While our work supports previous estimates[3]—which is of particular importance, because stacked interactions are expected to be problematic within the extrapolation-scheme-based calculations (as dispersion effects are overestimated by MP2, see above)—we want to emphasize that our approach is not limited to systems of medium size, as CCSD(T) based estimates are. With FNDMC, quantum chemistry has the opportunity to develop a reference method for larger noncovalently bound systems (e.g., larger DNA fragments or protein folding), that allows for the efficient utilization of modern developments in computer technology.

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