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Spin-Component Scaling Methods for Weak and Stacking Interactions

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Abstract: New scaling parameters are presented for use in the spin-component scaled (SCS) variant of density fitted local second-order Møller−Plesset perturbation theory (DF-LMP2) that have been optimized for use in evaluating the interaction energy between nucleic acid base pairs. The optimal set of parameters completely neglects the contribution from antiparallel-spin electron pairs to the MP2 energy while scaling the parallel contribution by 1.76. These spin-component scaled for nucleobases (SCSN) parameters are obtained by minimizing, with respect to SCS parameters, the rms interaction energy error relative to the best available literature values, over a set of ten stacked nucleic acid base pairs. The applicability of this scaling to a wide variety of noncovalent interactions is verified through evaluation of a larger set of model complexes, including those dominated by dispersion and electrostatics.

1. Introduction

Intermolecular interactions between nucleic acid base pairs play a crucial role in the structure of nucleic acids such as DNA and RNA. In particular, stacking interactions between base pairs is a major driving force in processes such as molecular recognition and the folding of nucleic acids, among many others.[1−21] Computational modeling of such interactions is an attractive prospect, both for an increased understanding of structure and folding processes themselves and for possible design of new drugs with nucleic acids as their target. However, carrying out such calculations is far from trivial: the size of biologically relevant sections of DNA rules out the use of ab initio methods for entire systems and limits such approaches to smaller model systems such as base pairs of specific interest. Hybrid QM/MM approaches are therefore attractive, in which only part of the overall system is treated with quantum chemical methods.

A further problem arises from the computational methods required to describe London dispersion forces that dominate stacking interactions. The prototypical model for π-stacking interactions is the benzene dimer, and as such it has been investigated exhaustively within the limits of currently available methodology and computer hardware (see refs 22−26 and references therein). This work makes it clear that correlated calculations with basis sets of at least triple-ζ quality are required to attain even a qualitatively accurate picture. Calculation of accurate interaction energies for stacked nucleic acid bases requires a similar theoretical treatment. Second-order Møller−Plesset perturbation theory (MP2) is the most commonly used and computationally tractable method of describing dynamic electron correlation, which is ultimately the source of dispersion forces. Unfortunately, this method is known to consistently overestimate binding energies in both the benzene dimer and stacked nucleic acid base pairs. Coupled cluster theory, particularly CCSD(T), is accepted as the standard for evaluating noncovalent interaction energies, providing highly accurate binding energies when used with basis sets of at least aug-cc-pVTZ quality. Such calculations rapidly become prohibitively computationally demanding, especially when the additional time necessary to compute a counterpoise correction[27] (CP) for basis set superposition error (BSSE) is included. Therefore, the current method of choice for stacking interactions extrapolates to the complete basis set limit from a series of MP2 interaction energies and then adds a CCSD(T) correction using a smaller basis set,[20] an approach termed "CBS(T)" by some authors.

Recently, Grimme[28] proposed the spin-component scaling (SCS) MP2 method, which scales the correlation energy due

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to parallel- and antiparallel-spin electron pairs, in order to overcome some of the known problems with canonical MP2. Previous work with SCS-MP2 shows impressive performance in calculating energies and geometries of small model systems[28−31] as well as larger host−guest systems, heats of formations, and reaction barriers.[32−36] We recently tested this approach, coupled with density-fitted, local MP2 (DF-LMP2)[37] for the benzene dimer, obtaining highly accurate binding energies and optimized geometries.[26] Local correlation methods[38−40] are virtually free of BSSE by construction, meaning they do not require CP correction. They also offer the potential for linear scaling with system size, enabling the study of much larger systems than with canonical MP2. Density fitting approximations (also known as resolution of the identity, RI) of the electron repulsion integrals yield a further order of magnitude reduction in computation time. Our DF-SCS-LMP2 calculations reproduced the CCSD(T) potential energy curves[23] for three orientations of the benzene dimer to within 0.1−0.2 kcal mol^{-1}, in a small fraction of the time required for CCSD(T) calculation.

In an effort to simplify and further accelerate the SCS-MP2 method, Head-Gordon has proposed a scaled opposite-spin (SOS) method, in which the parallel-spin contribution to the MP2 energy is neglected and the antiparallel contribution is scaled by a factor of 1.3.[41] While this allows use of a faster SOS-MP2 algorithm, it has yet to be tested on all but the smallest of systems. The same group has also developed an operator to adjust scaling depending on the distance between electrons, termed modified opposite-spin (MOS), to improve upon the SOS-MP2 description of long-range interactions.[42]

In this paper, we calculate DF-LMP2, DF-SCS-LMP2, and DF-SOS-LMP2 interaction energies for a set of stacked nucleic acid base pairs and compare these energies with the best available estimates from the literature.[20] With a view to obtaining accurate binding energies for larger and larger models of DNA, we propose a new a set of SCS scaling parameters, which we term spin-component scaled for nucleobases (SCSN), that accurately reproduce literature values for the stacked nucleic acid base pairs investigated. As a test of this DF-SCSN-LMP2 method, we compare the results to those for standard DF-LMP2 as well as the original SCS and SOS methods for a larger set of molecules, namely that denoted "S22" by Hobza et al.[21] This set includes complexes bound solely by dispersion forces, by electrostatic forces alone, and by combinations of these. As such, it provides a stringent test of the SCSN parameters proposed.

2. Computational Procedure

All ab initio calculations were carried out with the MOLPRO package of programs,[43] locally modified to separately output parallel- and antiparallel-spin electron pair energy contributions. Geometries of ten stacked nucleic acid base pairs and the S22 set were taken from refs 20 and 21, respectively. These geometries were obtained using the rigid monomer approximation. DF-SCS-LMP2 results employed the default scaling factors of 6/5 for antiparallel spins and 1/3 for parallel spins, while for DF-SOS-LMP2 data the parallel-spin scaling factor is set to zero and that of the antiparallel spins to 1.3.

Table 1. Interaction Energies (kcal mol^{-1}) of Stacked Nucleic Acid Base Pairs[a]

complex	DF-LMP2	SCS	SOS	SCSN	best estimate[b]
A···A	−10.87	−7.69	−6.10	−8.83	−8.5
A···C	−11.63	−8.79	−7.38	−10.29	−10.2
A···U	−11.05	−8.23	−6.82	−9.71	−9.8
C···C	−10.47	−8.16	−7.00	−9.78	−10.0
C···U	−10.54	−8.25	−7.10	−10.12	−10.4
G···A	−13.44	−10.17	−8.53	−11.78	−11.4
G···C	−11.42	−8.87	−7.59	−10.23	−10.6
G···G	−14.12	−10.86	−9.23	−12.64	−12.7
G···U	−12.76	−9.97	−8.57	−11.92	−12.1
U···U	−8.07	−5.97	−4.92	−7.47	−7.5
RMSE	1.31	1.67	3.02	0.24	
MD	1.12	−1.62	−3.00	−0.04	
MAD	1.12	1.62	3.00	0.20	

[a] SCS, SOS, and SCSN empirical scalings were all applied to the DF-LMP2 energy contributions from parallel- and antiparallel-spin pairs of electrons. [b] CBS(T) values from ref 20.

Initial Hartree Fock calculations utilized the DF−HF method[44] (also referred to as RI−HF[45] by some authors), but neither this nor subsequent DF-LMP2 calculations used local fitting domains.[37,44] All calculations employed the aug-cc-pVTZ augmented correlation consistent basis set of Dunning et al.[46] as the AO basis, with the aug-cc-pVTZ MP2-fitting[47] and cc-pVTZ JK-fitting[45] auxiliary basis sets of Weigend et al. applied in the DF-LMP2 and DF−HF calculations, respectively.

Orbital localization was performed with the Pipek−Mezey method.[48] The two most diffuse basis functions of each angular momentum type were the cause of poor localization in some cases. Their contribution was therefore removed from the localization criterion by setting the corresponding rows and columns of the overlap matrix to zero, and localized orbitals were obtained using a Newton−Raphson algorithm.

LMP2 localizes the occupied orbitals and projects out the occupied space from the virtual orbitals to create a set of projected atomic orbitals (PAOs).[38−40] Excitations from the dominant part of the occupied orbitals are then restricted to subspaces (domains) of the spatially close PAOs. Domain selection was carried out using a completeness criterion of 0.985, with the procedure described by Boughton and Pulay.[49] To ensure that only domains resembling bonding interactions were generated the Löwdin charge for a hydrogen atom to be included in the domain was increased to 0.15. Invariance to unitary transformations of the π-orbitals was achieved through merging the domains of those orbitals. Domains were all determined at large intermolecular separation and kept fixed in the calculation of the interaction energy.

3. Results and Discussion

Interaction energies for stacked nucleic acid base pairs are shown in Table 1 as evaluated by DF-LMP2, DF-SCS-LMP2, and DF-SOS-LMP2 approaches, along with CBS(T) literature values. It is clear that DF-LMP2 itself consistently overestimates the interaction energy, leading to a root-mean-square error (RMSE) of 1.3 kcal mol^{-1}. This shortcoming of MP2 and related methods has been documented before

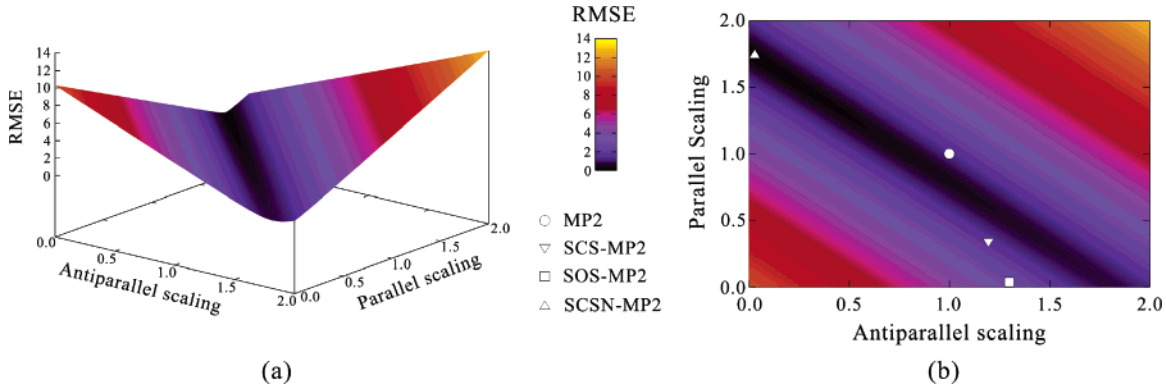

Figure 1. Plots of the root-mean-square error (RMSE) of the interaction energies of ten stacked nucleic acid base pairs compared to literature best estimates generated by separately scaling the parallel- and antiparallel-spin electron pairs contribution to the MP2 energy: (a) shows a three-dimensional surface of the RMSE values, while (b) is a two-dimensional projection of the same surface, with symbols indicating the position of different variants of MP2.

and therefore comes as no surprise. However, there is substantial variability in the discrepancy of DF-LMP2 from literature values, the largest being 2.4 kcal mol^{-1}, for A...A but the smallest just 0.1 kcal mol^{-1}, for C...U.

The default SCS parameters reduce binding energy in all cases and in doing so overcompensate for the deficiencies of DF-LMP2. This is most evident in those systems for which DF-LMP2 performs well, such as C...C and C...U, whereas DF-SCS-LMP2 yields reasonable interaction energies for A...A and G...A, for which DF-LMP2 performs poorly. Thus it seems that the default parameters reported by Grimme are not ideal for this set. Still worse are the results from SOS, which performs poorly compared with both DF-LMP2 and its SCS variant. The RMSE of this method is almost twice that of those approaches, and just as with SCS it overcompensates to produce interaction energies that are smaller (in absolute terms) than literature data. Since overcompensation occurs in both cases when the antiparallel contribution is increased and the parallel decreased, this may suggest that reducing the singlet scaling and increasing the triplet may be beneficial in this case. In any case, it is clear that neither SCS nor SOS scaling factors give an overall benefit over standard DF-LMP2 for these complexes.

To assess the effect of SCS parameters on the binding energy of stacked nucleic acid base pairs, the binding energy of the ten base pairs was calculated using a range of parallel and antiparallel scaling factors, and the RMSE was compared with the best available literature values evaluated. Figure 1 displays the RMSE for both parameters in the range of 0.00−2.00. This displays a valley of points with RMSE values of less than 1.0, such that any of the scalings corresponding to those points would be a reasonable choice for nucleic acid base pairs. However, the valley is rather flat, making it difficult to visually distinguish any local minima.

To obtain a more rigorous set of parameters, code was written to locate the optimum values of scaling parameters, using the analytical gradient of the RMSE expression and the BFGS algorithm, as described in ref. 50. This resulted in optimal values of −0.53 for antiparallel spins and 2.28 for parallel, which give a very low RMSE value of 0.17 kcal mol^{-1}. While this represents impressive accuracy, it is in effect a subtraction of correlation energy due to antiparallel spins from the binding energy. This does not seem to be physically realistic and hence may not be transferable to other systems outside this training set. We therefore constrained both parameters to be ≥0.0: this yielded a new set of 1.76 for parallel-spin electron pairs and 0.0 (i.e., no contribution) of the antiparallel component. The RMSE value for this pair of parameters was 0.24 kcal mol^{-1}, i.e. only marginally higher than the global optimum values and much lower than any of the methods tested above. Interaction energies of the ten base pairs are reported in Table 1 as DF-SCSN-LMP2. Encouragingly, unlike SCS or SOS parameters these new SCSN values reproduce accurate interaction energies for all ten base pairs, regardless of how close the original DF-LMP2 values were to the literature value.

To test the SCSN parameters, we have applied the same methodology to a larger and more varied set of complexes. To do this, we employ the set of 22 complexes denoted "S22" by Hobza et al.,[21] which includes stacked, hydrogen-bonded, and "mixed" complexes. Table 2 reports interaction energies for the S22 set obtained with DF-LMP2, DF-SCS-LMP2, DF-SOS-LMP2 and DF-SCSN-LMP2, along with CBS(T) literature values from ref 21. The first seven complexes (from the ammonia dimer to the Watson−Crick (WC) structure of the adenine·thymine complex) are all primarily bound by hydrogen bonding. The next eight systems (the methane dimer to the adenine·thymine stack) are all examples of London dispersion interaction, and finally the remaining seven systems have a mixture of both hydrogen bonding and dispersion binding them together.

The RMSE values again illustrate that on average DF-LMP2 produces binding energies that are on average 1 kcal mol^{-1} from literature values. Thus, it performs rather better than the default SCS or SOS scaling. In all cases SCS reduces binding energy, yet DF-LMP2 already underestimates binding energy in several complexes. Only in cases where canonical MP2 or DF-LMP2 substantially overestimates binding, such as the benzene and pyrazine dimers and the indole·benzene stacked complex, does SCS scaling produce more accurate results. In common with Table 1, SOS scaling produces binding energies that are even less negative than SCS and hence are even further from the best estimates. Although the SCSN parameters were optimized only for the

Table 2. Comparison of Interaction Energies (kcal mol^{-1}) for the S22 Set of Model Complexes[a]

complex	DF-LMP2	SCS	SOS	SCSN	best estimate[b]
ammonia dimer	−2.81	−2.40	−2.19	−2.84	−3.17
water dimer	−4.62	−4.16	−3.94	−5.01	−5.02
formic acid dimer	−17.30	−15.67	−14.86	−19.53	−18.61
formamide dimer	−14.81	−13.45	−12.77	−16.08	−15.96
uracil dimer (HBond)	−19.22	−17.40	−16.49	−21.33	−20.65
2-pyridoxine·2-aminopyridine	−15.72	−13.74	−12.75	−16.75	−16.71
adenine·thymine (HBond)	−15.35	−13.55	−12.65	−16.04	−16.37
methane dimer	−0.45	−0.27	−0.19	−0.32	−0.53
ethene dimer	−1.33	−0.81	−0.54	−1.14	−1.51
benzene·methane	−1.71	−1.08	−0.76	−1.35	−1.50
benzene dimer (PD)	−4.54	−2.51	−1.50	−2.91	−2.73
pyrazine dimer	−6.32	−4.15	−3.06	−4.64	−4.42
uracil dimer (stacked)	−10.26	−7.67	−6.38	−9.66	−10.12
indole·benzene (stacked)	−7.58	−4.52	−3.00	−5.30	−5.22
adenine·thymine (stacked)	−13.71	−9.78	−7.81	−11.90	−12.23
ethene·ethyne	−1.26	−0.88	−0.69	−1.60	−1.53
benzene·water	−3.33	−2.71	−2.41	−3.23	−3.28
benzene·ammonia	−2.48	−1.85	−1.54	−2.23	−2.35
benzene·hydrogen cyanide	−5.00	−4.11	−3.66	−5.16	−4.46
benzene dimer (T-shape)	−3.45	−2.33	−1.77	−2.89	−2.74
indole·benzene (T-shape)	−6.70	−5.08	−4.27	−6.01	−5.73
phenol dimer	−7.27	−5.94	−5.28	−6.90	−7.05
RMSE	1.05	1.65	2.39	0.36	
MD	0.15	−1.26	−1.97	0.04	
MAD	0.81	1.26	1.97	0.27	

[a] SCS, SOS, and SCSN empirical scalings were all applied to the DF-LMP2 energy contributions from parallel- and antiparallel-spin pairs of electrons. [b] CBS(T) values from ref 21.

stacked nucleic acid base pairs of Table 1, they also produce excellent results for the entire S22 set. Once again, SCSN performs well both in situations where standard DF-LMP2 overestimates the dispersion energy, such as the benzene dimer, as well as in cases where the unscaled approach produces reasonable values or even underestimates the binding energy. There are few cases where SCSN produces less accurate interaction energies than DF-LMP2: these include the methane dimer, the stacked uracil dimer, and the benzene·hydrogen cyanide complex. Even in these cases, SCSN results are still within 0.7 kcal mol^{-1} of CBS(T) data. As expected, the mean deviation (MD) indicates that both SCS and SOS consistently underestimate the binding energies in the S22 set, while the canonical and SCSN results are much more evenly spread on either side of the literature values. The mean absolute deviation (MAD) correlates with the trend seen in the RMSE values, and SCSN energies typically deviate little from the best available.

Further support for our choice of scaling factors comes from the observation that an RMSE of 0.802 kcal mol^{-1} results from the values obtained from gradient-based optimization (i.e., −0.53 for antiparallel and 2.28 for parallel: individual interaction energies are reported in the Supporting Information). While this is still an improvement over canonical DF-LMP2, it indicates that these parameters are indeed not transferable to the larger S22 set and therefore are not as applicable to a wide variety of systems as SCSN.

In our previous investigation of three isomers of the benzene dimer, DF-SCS-LMP2/aug-cc-pVTZ performed exceedingly well when compared with CCSD(T)/aug-cc-pVQZ results, with errors within 0.2 kcal mol^{-1} along entire potential energy scans of intermonomer separation. Applying SCSN scaling parameters to these potential energy curves (see the Supporting Information for plots of parallel-displaced and T-shaped benzene dimers) results in a slight reduction of accuracy when compared to the default SCS values. However, performance is still acceptable, with values within 0.3−0.4 kcal mol^{-1} of those from CCSD(T).

Default SCS scaling values only appear to work well when MP2 strongly overestimates the dispersion contribution to the interaction energy: this is difficult to predict a priori. Their usefulness for binding energies of truncated sections of DNA is therefore questionable, and this approach should be employed with caution, despite the encouraging results for some model systems.[26,28,31] SOS amplifies this problem, and, in light of the poor performance for both sets of data, it is hard to recommend its use in the evaluation of nucleic acid binding energies. However, Figure 1 suggests that increasing the antiparallel scaling to approximately 1.7 would considerably improve binding energies of stacked base pairs. DF-SCSN-LMP2 provides excellent interaction energies for systems bound by hydrogen bonds, dispersion interaction, and a mixture of the two. The combination of its performance for the benzene dimer and a wider range of noncovalent interactions displayed in Table 2 for the S22 set of model complexes suggests that DF-SCSN-LMP2 should be capable of providing high quality interaction energies in a wide range of systems. This is therefore a promising method for investigating the structure of and interactions involved in small sections of nucleic acids and proteins and their interactions with small molecules and drugs.

As shown in Figure 1, very many combinations of parallel and antiparallel contributions give rise to low errors for the ten stacked nucleobases and hence to a valley of acceptable solutions. As such, the specific scaling parameters we recommend should probably not be overinterpreted for physical meaning. However, it does seem evident that in all acceptable combinations the sum of parallel and antiparallel contributions is less than 2.0, i.e., one must reduce the binding energy due to electron correlation from that given by canonical MP2 to obtain RMSE < 1.0. As these SCSN scaling parameters have been specifically optimized for obtaining accurate binding energies for noncovalent interactions, and more specifically such interactions between nucleic acid base pairs, they have not been tested for general quantum chemical applicability. This is in contrast to both SCS- and SOS-MP2 which were designed to be more general methods. As such, we cannot currently recommend that SCSN scaling is utilized in applications other than the evaluation of noncovalent interactions.

The SCSN parameters were optimized based on parallel and antiparallel contributions evaluated with the aug-cc-pVTZ basis set. While the use of larger basis sets has not been extensively tested, it may be possible that doing so will produce binding energies further from the literature best estimates. Smaller basis sets should be employed with caution when the reference energy is obtained with DF−HF as the SCF BSSE is unlikely to be minimized in such situations. Existing basis set extrapolation schemes such as that of Helgaker et al.[51,52] can be generally expected to increase the binding energy of noncovalently bound systems, and hence at the CBS limit the SCS- and SOS-MP2 interaction energies should be improved while the typically overbinding canonical MP2 will be worse. As SCSN produces values very close to the literature values with the aug-cc-pVTZ basis set, an extrapolation will either improve or worsen a result depending on which side of the literature value the original value lies. It should also be noted that as SCSN completely neglects the contribution to the correlation energy from antiparallel-spin electron pairs the existing extrapolation schemes will be less optimal than in the case of canonical MP2.

As in the case of SOS-MP2, it may be possible to derive a more efficient algorithm for SCSN-MP2, since the contributions from antiparallel-spin electron pairs are neglected. However, as the SCSN scaling is readily applied to the already highly efficient DF-LMP2 results at no additional computational cost, this seems unnecessary at present. Additionally, DF-LMP2 provides qualitatively correct descriptions of noncovalent interactions, such that comparison of DF-SCSN-LMP2 with canonical DF-LMP2 binding energies may act as a form of "sanity check" highlighting potentially problematic systems.

4. Conclusions

The combination of the DF-LMP2 approach with empirical SCS scaling that appeared so promising for the benzene dimer has been shown to provide, on average, worse quality interaction energies for stacked nucleic acid base pairs and the S22 set of noncovalent interactions than canonical DF-LMP2. SOS scaling, which neglects the parallel-spin electron pair contribution, provides binding energies that are further still from the best estimate literature values. We hence propose a set of alternative SCS scaling parameters where the antiparallel contribution to the energy is eliminated and the parallel scaling is set to 1.76. These values were obtained by calculating the rms error from literature values for 10 stacked base pairs over a wide range of parameters. Gradient-based optimization indicated a physically unrealistic set of parameters, which despite giving a very small RMSE are not transferable to a more varied set of complexes. We term these new parameters "spin-component scaled for nucleobases" (SCSN) MP2 or DF-SCSN-LMP2.

Validation of this approach used Hobza's S22 set of model complexes as well as potential energy scans of the benzene dimer. This confirms that the SCSN method provides excellent quality results for a range of noncovalent interactions including hydrogen bonding and dispersion interactions. SCSN again outperforms the other scaling parameters on test, in addition to canonical DF-LMP2. These interactions are typical of those present between DNA bases, such that the SCSN scaling parameters are promising for study of such systems. The SCSN variant of DF-LMP2 seems especially promising, as the local nature of the electron correlation ensures that BSSE is minimized and potentially expensive counterpoise corrections can be avoided. The relatively low cost of the DF-LMP2 approach also means that reasonably large basis sets can be employed. When SCSN scaling is applied, the current evidence indicates that the result can be expected to be within 0.5 kcal mol^{-1} of that from much more expensive extrapolation and correction schemes.

Supporting Information Available: Potential energy curves for both the parallel-displaced and T-shaped configurations of the benzene dimer, along with interaction energies for stacked nucleic acid base pairs obtained with SCS parameters of −0.53 and 2.28. This material is available free of charge via the Internet at http://pubs.acs.org.

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