

Assessment of the Performance of the M05–2X and M06–2X Exchange-Correlation Functionals for Noncovalent Interactions in Biomolecules

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Abstract: The highly parametrized, empirical exchange-correlation functionals, M05–2X and M06–2X, developed by Zhao and Truhlar have been shown to describe noncovalent interactions better than density functionals which are currently in common use. However, these methods have yet to be fully benchmarked for the types of interactions important in biomolecules. M05–2X and M06–2X are claimed to capture “medium-range” electron correlation; however, the “long-range” electron correlation neglected by these functionals can also be important in the binding of noncovalent complexes. Here we test M05–2X and M06–2X for the nucleic acid base pairs in the JSCH-2005 database. Using the CCSD(T) binding energies as a benchmark, the performance of these functionals is compared to that of a nonempirical density functional, PBE, and also to that of PBE plus Grimme’s empirical dispersion correction, PBE-D. Due to the importance of “long-range” electron correlation in hydrogen-bonded and interstrand base pairs, PBE-D provides more accurate interaction energies on average for the JSCH-2005 database when compared to M05–2X or M06–2X. M06–2X does, however, perform somewhat better than PBE-D for interactions between stacked base pairs.

1. Introduction

Noncovalent interactions between biomolecules are important for the structure of DNA, RNA, and proteins.^{1–5} The ability to describe these interactions computationally is essential for the

in silico design of drug molecules.⁶ In accurate quantum mechanical computations, a high degree of electron correlation must be included to reliably account for dispersion interactions. The current standard for accurately computing the interaction energy within a small, noncovalently bound complex is coupled-cluster with singles and doubles including perturbative triples [CCSD(T)].⁷ Unfortunately, the applicability of CCSD(T) is hindered by the formal $\mathcal{O}(N^7)$ complexity of the method (more specifically, $\mathcal{O}(o^3v^4)$, where o and v are the number of occupied and virtual orbitals, respectively); to describe noncovalent interactions in large systems, less computationally expensive methods must be employed. The recently developed⁸ spin-component scaled CCSD has been shown to produce results which closely match CCSD(T); however, the formal scaling of this approach remains high at $\mathcal{O}(N^6)$. Second-order Møller–Plesset perturbation theory (MP2) offers another approach for describing noncovalent interactions; with formal $\mathcal{O}(N^5)$ complexity, MP2 can be extended to much larger systems than are accessible with coupled-cluster methods. However, MP2 is substantially less accurate than the more rigorous coupled-cluster approaches.⁹ While spin-component scaling^{10–12} significantly improves the accuracy of MP2 on average, there are nevertheless cases where the accuracy is not as good as desired, or the system is too large for the computation to be feasible. More efficient methods that can effectively treat noncovalent interactions are necessary if complexes with 100 atoms or more are to be studied routinely. One approach is to reduce the computational scaling of coupled-cluster methods, and this is being actively pursued by several research groups.^{13–16} Another approach is to attempt to improve the reliability of methods which are already applicable to larger systems.

Approximate density functional theory (DFT) is widely used today for examining a variety of chemical systems with dozens of atoms or more.¹⁷ The application of DFT to noncovalently bound complexes has been limited due to the failure of most density functional approximations to describe dispersion interactions, which can be critical for noncovalent complexes. Dispersion interactions are inherently long-range electron correlation effects, which are not captured by the popular local or semilocal density functionals.^{18–24} Several approaches exist for improving existing density functionals to handle dispersion effects. Among the more physically motivated approaches, Röthlisberger and co-workers have added effective atom-centered nonlocal potentials which have been fit to benchmark *ab initio* data;^{25,26} Langreth, Lundqvist, and co-workers have introduced a van der Waals density functional (vdW-DF) which adds nonlocal terms to the correlation energy functional;²⁷ and Becke has proposed a novel approach that formulates the dispersion interaction in

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terms of the dipole moment that would be created when considering an electron and its exchange hole.^{28–30}

A more pragmatic and simple approach is to add empirical terms that model dispersion interactions.^{31–35} These DFT-D approaches require only computation of interactions between atoms pairs; therefore, the additional computational expense is negligible. Alternatively, the highly parametrized empirical M05–2X and M06–2X functionals developed by Zhao and Truhlar have also shown promise for noncovalent interactions.^{36–39} According to Zhao and Truhlar, the M05 and M06 series of functionals implicitly account for “medium-range” electron correlation because of the way they are parametrized, and this is sufficient to describe the dispersion interactions within many complexes.³⁹ These authors define “medium-range” correlation to be that found in complexes separated by about 5 Å or less.⁴⁰ While initial tests of these functionals have been very promising,⁴¹ they have yet to be fully benchmarked for biologically relevant noncovalent interactions.

In this letter, we analyze the performance of M05–2X and M06–2X for the nucleic acid base pairs from the JSCH-2005 database.⁴² This database contains stacked, hydrogen-bonded, and interstrand base pairs, totaling 124 in all. Using the CCSD(T) interaction energies as a benchmark, M05–2X and M06–2X are compared to a density functional that fails to describe dispersion interactions, the generalized gradient approximation (GGA) of Perdew, Burke, and Wang (PBE).⁴³ In contrast to M05–2X and M06–2X, which are parametrized to fit a large number of experimental and higher-level theoretical data, all parameters in PBE (other than those in the underlying local spin density approximation) are physical constants. Grimme’s empirical dispersion correction^{34,35} is then applied to the PBE binding energies to assess the performance of the increasingly popular DFT-D approach. The JSCH-2005 database provides a rigorous test of M05–2X and M06–2X for the description of some of the types of noncovalent interactions that are important in biomolecules.

2. Theoretical Methods

The DFT-D approach of Grimme is a widely applicable method for correcting the performance of standard density functionals.^{34,35,44} This method utilizes a damped R^{-6} term to model the dispersion interactions (eqs 1, 2, and 3).

$$E_{\text{DFT-D}} = E_{\text{DFT}} - s_6 \sum_{i=1}^{N-1} \sum_{j>i}^N \frac{C_6^{ij}}{R_{ij}^6} f_{\text{dmp}}(R_{ij}) \quad (1)$$

$$C_6^{ij} = \sqrt{C_6^i C_6^j} \quad (2)$$

$$f_{\text{dmp}}(R_{ij}, R_r, d) = \frac{1}{1 + e^{-d(R_{ij}/R_r - 1)}} \quad (3)$$

The geometries of the base pairs in the JSCH-2005 set were taken from Jurečka et al.⁴² All density functional computations were performed using Q-Chem 3.1.⁴⁵ The empirical dispersion correction was computed using a locally modified version of PSI 3.3⁴⁶ (although these terms have since been added directly to Q-Chem by one of the authors, CDS). For use with the PBE functional, Grimme recommends a global scaling factor, s_6 , of 0.7 for his dispersion correction term.³⁵ All energy computations were performed using Dunning’s aug-cc-pVDZ basis set, which

Table 1. Performance of Various Methods for 124 Nucleic Acid Dimers from the JSCH-2005 Set^a

| method | MSE ^b | MUE ^c | STD ^d | MAX ^e |
|---------------------------------------|------------------|------------------|------------------|------------------|
| 38 H-Bonded Complexes ^g | | | | |
| PBE/aug-cc-pVDZ | 2.59 | 2.59 | 0.81 | 4.85 |
| PBE-D/aug-cc-pVDZ ^f | −0.53 | 0.70 | 0.79 | 3.17 |
| M05–2X/aug-cc-pVDZ | 1.98 | 1.98 | 0.62 | 3.22 |
| M06–2X/aug-cc-pVDZ | 1.62 | 1.62 | 0.58 | 2.76 |
| 32 Interstrand Complexes ^h | | | | |
| PBE/aug-cc-pVDZ | 1.83 | 1.84 | 2.06 | 9.27 |
| PBE-D/aug-cc-pVDZ ^f | 0.16 | 0.58 | 1.36 | 5.03 |
| M05–2X/aug-cc-pVDZ | 1.02 | 1.23 | 1.41 | 5.66 |
| M06–2X/aug-cc-pVDZ | 0.74 | 1.08 | 1.41 | 5.53 |
| 54 Stacked Complexes ⁱ | | | | |
| PBE/aug-cc-pVDZ | 7.48 | 7.57 | 2.46 | 14.28 |
| PBE-D/aug-cc-pVDZ ^f | 1.41 | 1.53 | 0.79 | 3.05 |
| M05–2X/aug-cc-pVDZ | 2.48 | 2.59 | 0.96 | 4.56 |
| M06–2X/aug-cc-pVDZ | 0.95 | 1.08 | 0.80 | 2.78 |
| JSCH-2005 Nucleic Acids | | | | |
| PBE/aug-cc-pVDZ | 4.52 | 4.56 | 3.28 | 14.28 |
| PBE-D/aug-cc-pVDZ ^f | 0.49 | 1.03 | 1.28 | 5.03 |
| M05–2X/aug-cc-pVDZ | 1.95 | 2.05 | 1.17 | 5.66 |
| M06–2X/aug-cc-pVDZ | 1.10 | 1.25 | 1.00 | 5.53 |

^a Empirical terms added to counterpoise corrected PBE/aug-cc-pVDZ interaction energies. All energies are in kcal mol^{−1}. Errors are computed relative to the benchmark interaction energies of Hobza and co-workers.⁴² ^b Mean signed error. ^c Mean unsigned error. ^d Standard deviation. ^e Maximum absolute deviation. ^f PBE/aug-cc-pVDZ with Grimme’s dispersion correction.³⁴ ^g Average benchmark interaction energy of −20.79 kcal mol^{−1}. ^h Average benchmark interaction energy of −1.00 kcal mol^{−1}. ⁱ Average benchmark interaction energy of −7.84 kcal mol^{−1}.

would be the most tractable of Dunning’s augmented basis sets in studies of large systems.⁴⁷ It is possible that larger basis sets would improve the performance of M05–2X and M06–2X; however, in order for these methods to be applicable to larger systems, they must be reliable with modest basis sets. We comment on the performance of PBE and PBE-D with larger basis sets below. All binding energies were counterpoise corrected using the scheme of Boys and Bernardi.⁴⁸ All density functional computations were performed using a Lebedev grid with 302 angular points for each of the 100 radial points included. This grid is larger than those used by default by most electronic structure program packages, but it appears necessary to avoid artifacts due to numerical integration for noncovalent interactions, particularly when using meta-GGA functionals.²⁴

3. Results and Discussion

The JSCH-2005 set of nucleobase dimers has been used previously as a benchmark for dispersion corrected DFT methods,^{49–51} including the DFT-D method of Grimme.^{34,35} Counterpoise corrected PBE/aug-cc-pVDZ interaction energies are reported here to allow comparison to a standard DFT approximation. Results for the methods tested are summarized in Table 1. Examples of complexes included in the JSCH-2005 database are shown in Figure 1. For the entire set of molecules, PBE/aug-cc-pVDZ underestimates the binding energy (overestimates the interaction energy) between the base pairs by 4.52 kcal mol^{−1} on average. PBE only overestimates the binding energy for two complexes out of the 124 base pairs in the set. This is due to the failure of PBE to capture the dispersion interactions within the complexes. Only the electrostatic,

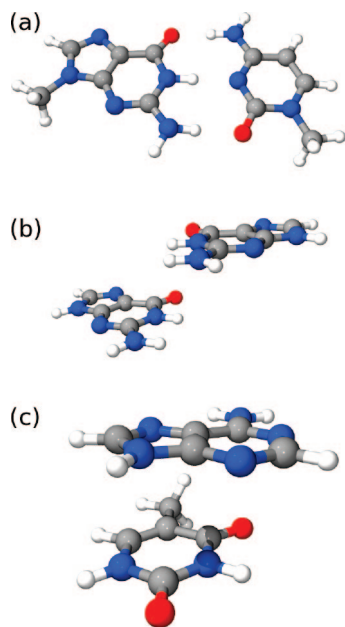


Figure 1. Representative geometries for (a) hydrogen-bonded base pairs (mG...mC WC), (b) interstrand base pairs (G...G IS), and (c) stacked base pairs (TA08/3.16 A/Ts), using the nomenclature of ref 42.

exchange, and induction interactions are captured by this functional. Since this functional almost always underestimates the binding energy, the addition of empirical dispersion terms substantially improves the performance. The mean signed error in interaction energies is reduced to 0.49 kcal mol⁻¹, and the mean unsigned error is reduced from 4.56 to 1.03 kcal mol⁻¹. This simple correction greatly increases the accuracy of PBE/aug-cc-pVDZ without increasing the computational cost in any significant way. In another study of this test set, Antony and Grimme⁵¹ found that PBE-D with a polarized triple- ζ basis set yields a mean unsigned error of 0.82 kcal mol⁻¹, demonstrating that only minor improvements are obtained for DFT-D by increasing the basis set size. On the other hand, larger basis sets reduce the size of the basis set superposition error, and Antony and Grimme argue that polarized triple- ζ basis sets are large enough that one can dispense with the counterpoise correction.

M05-2X/aug-cc-pVDZ describes the interactions between the complexes in the JSCH-2005 database more accurately than PBE/aug-cc-pVDZ. M05-2X tends to underestimate the binding energies by about 2 kcal mol⁻¹ relative to the CCSD(T) benchmark values. M06-2X also tends to underbind these complexes, but it reduces the mean unsigned error to 1.25 kcal mol⁻¹. While this represents a tremendous improvement over traditional density functionals for noncovalent interactions, nevertheless, the M05-2X and M06-2X functionals do not perform better than Grimme's simple DFT-D approach. The PBE-D/aug-cc-pVDZ approximation has a lower mean signed error, mean unsigned error, and maximum error. The M05-2X and M06-2X functionals are only improved with respect to the standard deviation. M05-2X performs markedly worse than PBE-D with respect to the mean signed error and mean unsigned error. M06-2X is comparable to, although slightly worse than, PBE-D.

Dispersion interactions are especially important in the description of stacked base pairs. The failure of PBE to describe dispersion interactions is especially evident for the stacked subset of the JSCH-2005 set. For these complexes, PBE/aug-cc-pVDZ grossly underestimates the attractive interactions. The maximum error of PBE for the stacked base pairs is 14.28 kcal mol⁻¹ for a complex which CCSD(T) predicts to be bound by 14.57 kcal mol⁻¹. Obviously, PBE cannot be used to treat systems that include stacking interactions. The inclusion of empirical dispersion terms improves the PBE binding energies immensely; the mean unsigned error is reduced from 7.57 to 1.53 kcal mol⁻¹. The "medium-range" electron correlation apparently captured by M05-2X is sufficient to reduce the unsigned error for stacked complexes to 2.59 kcal mol⁻¹. While this improves greatly over PBE, it does not improve over PBE-D. Of the four methods tested, M06-2X is the best able to describe stacking interactions between base pairs. The mean unsigned error for M06-2X/aug-cc-pVDZ is 1.08 kcal mol⁻¹. This suggests that for stacked base pairs, when the electron clouds of each monomer are in relatively close proximity to one another, the electron correlation included in the M06-2X functional is sufficient to describe the relevant dispersion interactions, as also indicated by previous work.⁴¹

Hydrogen bonded complexes are dominated by electrostatic interactions, and thus traditional density functionals are capable of computing acceptable binding energies. PBE/aug-cc-pVDZ has a mean unsigned error of 2.95 kcal mol⁻¹ for the hydrogen-bonded base pairs, and one should note that the average binding energy of the hydrogen-bonded complexes is much larger than the binding energies of stacked complexes. The inclusion of an empirical dispersion term to the PBE/aug-cc-pVDZ energies further improves the binding energies. PBE-D/aug-cc-pVDZ has a mean unsigned error of 0.70 kcal mol⁻¹. Neither M05-2X or M06-2X match the quality of the PBE-D energies for the hydrogen-bonded systems. A notable result is that PBE, M05-2X, and M06-2X all uniformly underestimate the attraction between hydrogen-bonded base pairs. While dominated by electrostatic interactions, dispersion interactions also play an important role in the binding of these complexes. The performance of PBE-D versus M05-2X and M06-2X for hydrogen-bonded complexes shows that it is not sufficient to include only the "medium-range" electron correlation which M05-2X and M06-2X are said to capture.

The third subset of complexes in the JSCH-2005 database is comprised of interstrand base pairs. These complexes are bound primarily by a combination of electrostatic interactions and dispersion interactions. The intermonomer separation in these complexes is larger than it is between the stacked and hydrogen-bonded bases; as a consequence, these complexes are not bound as strongly. PBE/aug-cc-pVDZ has a mean unsigned error for this set of molecules of 1.84 kcal mol⁻¹; however, the strongest binding energy in this subset is only 5.20 kcal mol⁻¹, and hence PBE fails severely for this subset. The addition of Grimme's dispersion terms reduces the unsigned error to 0.58 kcal mol⁻¹. Due to the importance of "long-range" electron correlation in these complexes, neither M05-2X or M06-2X produce binding energies as accurate as PBE-D. M05-2X/aug-cc-pVDZ and M06-2X/aug-cc-pVDZ have mean unsigned errors of 1.23 and 1.08 kcal mol⁻¹, respectively. Thus interstrand base pairs are

an example of a chemically interesting system where “medium-range” electron correlation is not sufficient to compute accurate binding energies. For both interstrand and hydrogen-bonded base pairs, Grimme’s simple DFT-D approach appears to provide more reliable results than meta-GGA’s which hope to effectively capture “medium-range” electron correlation effects through the addition of terms depending on the electronic kinetic energy density and through significant parametrization. It might be noted that, to our knowledge, no theoretical connection between electronic kinetic energy density and dispersion interactions has been demonstrated.

4. Conclusions

We have shown that M05–2X and M06–2X provide significant improvements over traditional density functionals for the noncovalent interactions exemplified by the JSCH-2005 test set. The apparent ability of these functionals to capture “medium-range” (≤ 5 Å) electron correlation allows them to describe stacking interactions between base pairs accurately, especially in the case of M06–2X. However, in hydrogen-bonded and interstrand base pairs, much of the dispersion interaction is “long-range” (> 5 Å) and is not captured by M05–2X and M06–2X. The addition of Grimme’s empirical dispersion terms to the PBE functional provided a better description of the interactions between base pairs. Dispersion interactions can be modeled accurately with an R^{-6} term. Although M05–2X and M06–2X represent a significant step forward in density functionals able to describe noncovalent interactions, more improvement will be required before a density functional can outperform DFT-D methods which add dispersion empirically. Approaches which include terms explicitly tailored to capture the physics of long-range dispersion interactions^{25–28,30} appear to be the most promising.

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Supporting Information Available: Binding energies for hydrogen bonded, interstrand, and stacked base pairs. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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