

# Benchmarking of London Dispersion-Accounting Density Functional Theory Methods on Very Large Molecular Complexes

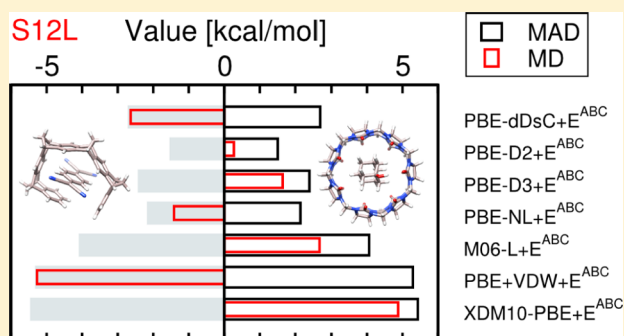
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**S** Supporting Information

**ABSTRACT:** A new test set (S12L) containing 12 supramolecular noncovalently bound complexes is presented and used to evaluate seven different methods to account for dispersion in DFT (DFT-D3, DFT-D2, DFT-NL, XDM, dDsC, TS-vdW, M06-L) at different basis set levels against experimental, back-corrected reference energies. This allows conclusions about the performance of each method in an explorative research setting on “real-life” problems. Most DFT methods show satisfactory performance but, due to the largeness of the complexes, almost always require an explicit correction for the nonadditive Axilrod–Teller–Muto three-body dispersion interaction to get accurate results. The necessity of using a method capable of accounting for dispersion is clearly demonstrated in that the two-body dispersion contributions are on the order of 20–150% of the total interaction energy. MP2 and some variants thereof are shown to be insufficient for this while a few tested D3-corrected semiempirical MO methods perform reasonably well. Overall, we suggest the use of this benchmark set as a “sanity check” against overfitting to too small molecular cases.



## 1. INTRODUCTION

Noncovalent interactions and their correct description are of high importance in many areas of chemistry (and the fields building on it). This is due to the ubiquity of these interactions as the main source of attraction for nonpolar systems or at large intramolecular distances.<sup>1</sup> Although frequently termed “weak,” especially the London dispersion force can account for a large percentage of the interaction energy of molecular complexes of modest size, easily outranking electrostatic and hydrogen bonding contributions.<sup>2</sup>

Quantum chemistry can model the dispersion interaction (as well as the other parts of noncovalent interactions) using correlated methods of high quality, for instance CCSD(T) using large basis sets or extrapolating the results to the basis set limit. However, these correlated methods often prove to be too expensive due to their inherent computational cost, which scales as  $N^5$ ,  $N^7$ , or even higher, where  $N$  is a measure of the system size. Density functional theory according to Kohn and Sham (here referred to as DFT), on the other hand, has shown itself to be a cost-efficient method for many applications of quantum chemistry. However, it is well established that standard approximations to the exchange-correlation functional of DFT cannot describe the dispersion interaction correctly, especially not at large distances.<sup>3–6</sup>

Several different ways to account for dispersion forces have been devised in the past years. For reviews, see refs 7 and 8. Of course, the performance of the methods is not known *a priori*;

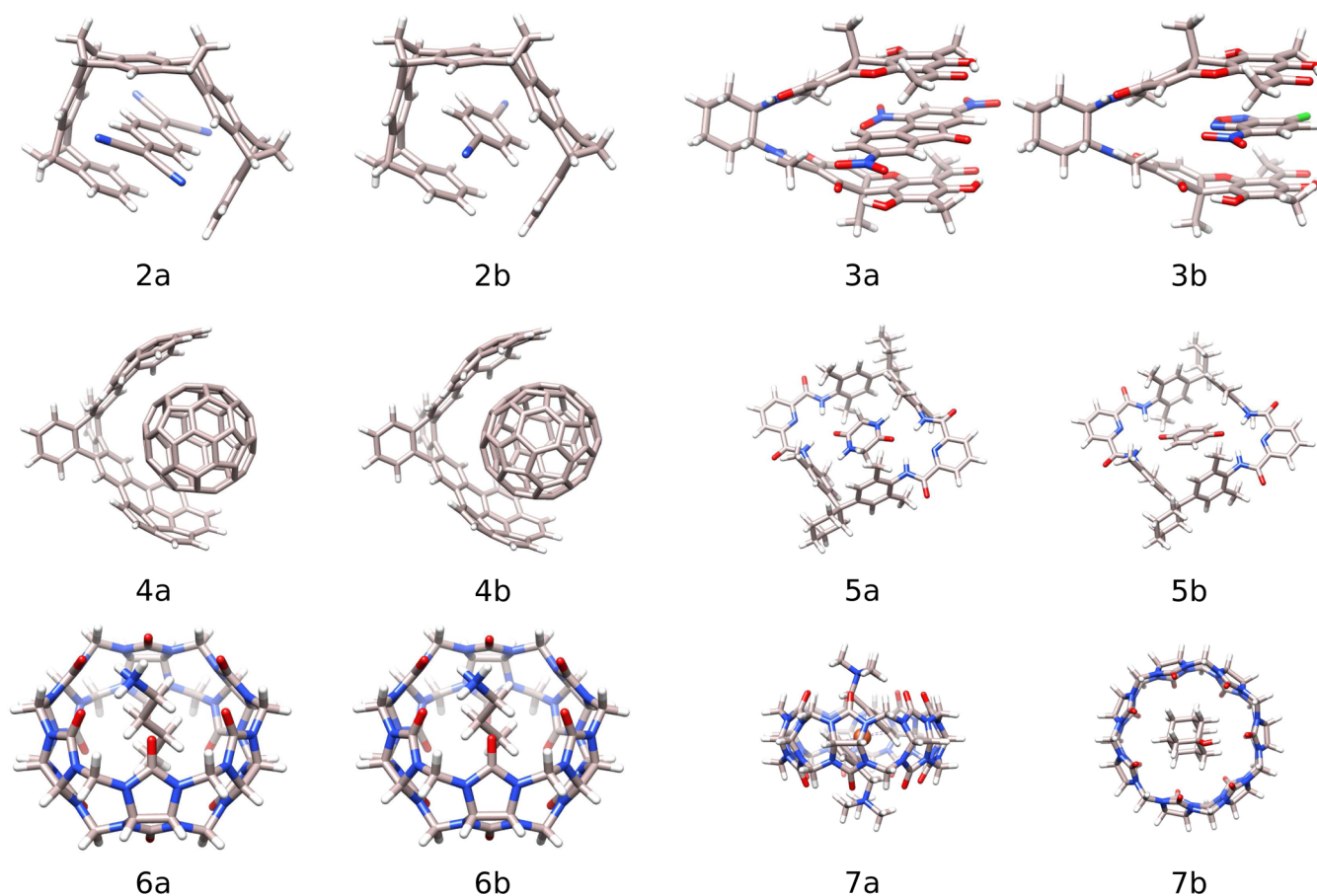
thus benchmarking is warranted, also due to the large variety of competing schemes. In this study, we shall undertake the benchmarking of a range of methods on very large (so-called supramolecular) noncovalently bound complexes for the first time. The methods evaluated are the atom pair wise corrections known as DFT-D2 and DFT-D3 by Grimme et al.,<sup>9–11</sup> the density dependent dispersion correction (dDsC) by Steinmann and Corminboeuf,<sup>12</sup> DFT+vdW by Tkatchenko and Scheffler,<sup>13</sup> the exchange-hole dipole moment method (XDM) by Becke et al.,<sup>14–16</sup> one Minnesota class density functional (and one for comparison) by Truhlar and Zhao,<sup>17,18</sup> and a dispersion density functional based on VV10 by Vydrov and van Voorhis<sup>19</sup> (as extended to standard functionals by Hujo and Grimme<sup>20</sup>). These approaches will be briefly explained, *vide infra*.

A multitude of test sets have been compiled to facilitate benchmarking, for instance by the groups of Hobza<sup>21–23</sup> and Truhlar.<sup>24,25</sup> Most of these tests employ the above-mentioned correlated methods (mostly CCSD(T)) to establish reference values. This leads to the following characteristics: The reference values are very accurate for diverse interactions and prototypical cases from different fields of chemistry; for example, saturated and unsaturated hydrocarbon dimers are described and covered just as well as water clusters and interactions of primarily biological importance (e.g., DNA base

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**Figure 1.** Structures of the molecular complexes used for the S12L test set. Note that the numbering is chosen to conform with ref 27; i.e. the benzene dimer has been dropped. Color Code: hydrogen - white, carbon - brown, nitrogen - blue, oxygen - red, chlorine - green, iron - orange.

pairs). Nevertheless, the individual complexes are usually rather small, at most reaching medium size in the case of the nucleobase dimers. This leads to the principal problem of uncertainty concerning the performance of dispersion-accounting methods for larger molecules but also implies doubts regarding the correct description of dispersion on varying length scales. The latter problem has been addressed recently with the publication of the S66x8 and X40x10 test sets,<sup>23,26</sup> which consist of complexes in the usual minima structures and structures in which the intermolecular separation has been scaled. However, the problem of a lack of testing opportunities on large systems remains. Perhaps more disquieting is the fact that most dispersion-accounting methods have been parametrized to reproduce the values of the mentioned test sets. This means that large systems are at least underrepresented in the fit sets for said methods.

In this study, we intend to overcome the size limitations present in most test sets for noncovalent interactions by using experimental values for binding affinities which have been corrected back to yield gas-phase interaction energies (instead of free interaction enthalpies in solution). These values have been published in ref 27. They are termed “empirical” and will serve as the reference. Our test set, named S12L, consists of 12 supramolecular complexes which can be described in terms of host–guest chemistry as six hosts with two different guests each, see Figure 1. The molecules are a “tweezer” complex consisting of phenyl and norbornyl units with cyano-substituted benzene guests (2), a “pincer” complex composed of substituted dibenzofurane units joined by 1,2-diaminocyclohex-

ane with a small and a medium sized aromatic compound (3), a “buckycatcher” (two flexibly connected coronene units) with  $C_{60}$  and  $C_{70}$  (4), an amide macrocycle containing pyridine and mesitylene derivatives with a single ring heterocycle and an aromatic ring (5), and the six- and seven-membered cucurbiturils, with primary ammonium ions (6) and ferrocene/adamantane derivatives (7), respectively. These supramolecular complexes and others similar to them continue to attract considerable research interest. For recent studies, see refs 28–32. We note that, *a priori*, it is not clear whether our attempt to construct such a test set, consisting of large molecular complexes and using back-corrected experimental values, will be successful and yield values amenable to benchmarking.

We will focus on DFT methods that we perceive to be affordable in explorative research for large to very large cases. This precludes the broad use of hybrid functionals or even more sophisticated approaches (with the exception of the VV10-style DFT-NL functionals, used as post-SCF corrections). In the case of the Minnesota class of density functionals, we checked the results of the pure meta-GGA M06-L against the hybrid M06-2X commonly used for weak interactions. Second-order Møller–Plesset perturbation theory and scaled variants thereof are included due to their unabated popularity.

The rest of this article is organized as follows: We will give a short introduction on each of the methods evaluated herein, ensued by the general approach of our study and the technical details, which are of some importance due to the sheer size of the complexes and our philosophy to provide accurate and

conclusive results. A presentation of the results for each method follows, accompanied by a reasoned pick of technical variations for further comparison. Such comparisons are then made and discussed, before conclusions are drawn.

**1.1. Evaluated Methods.** We now proceed to give a short overview of each of the dispersion-accounting methods considered in this study. For more details, see the original publications. The largest group of dispersion corrections considered in this study and overall are those based on atom pair wise interactions. The overall success of these approaches<sup>7</sup> aside from this article confirms the soundness of its first, core approximation: that the dispersion interaction energy can be modeled additively from atom pair interactions. All these approaches are based on an on-top correction  $E_{\text{disp}}^{\text{APW}}$  (APW: atom pair wise) to the total DFT energy  $E^{\text{DFT}}$  of each molecule considered in the complexation:

$$E_{\text{total}}^{\text{APW}} = E^{\text{DFT}} + E_{\text{disp}}^{\text{APW}} \quad (1)$$

The correction is primarily dependent on the distance  $R_{AB}$  between the two atoms considered in each unique pair  $AB$ . All corrections employ a  $1/R_{AB}^6$  term; some employ higher powers of  $R_{AB}$  (which influence the short to medium range behavior) as well:

$$E_{\text{disp}}^{\text{APW}} = - \sum_{A>B} \sum_{n=6(8,10)} s_n \cdot \frac{C_n^{AB}}{R_{AB}^n} \cdot f_{\text{damp}}(R_{AB}) \quad (2)$$

where  $C_n^{AB}$  is a dispersion coefficient (see below) and  $f_{\text{damp}}$  is a damping function, which facilitates the transition between regions where dispersion is part of the employed exchange-correlation density functional and the more distant region where the functional is no longer able to describe any correlation. The dispersion coefficient can be obtained from experimental data or be computed exactly (in principle), be set to a fixed value or be made system-dependent. The approaches under consideration here primarily differ in the way the  $C_n^{AB}$  are constructed. We consider the van der Waals radii, that are usually used in the damping, to be a part of an effective  $C_6$  and note that several competing schemes to obtain them are in existence. However, we refrain from further discussion of these methods here.

DFT-D2 uses fixed values for the  $C_6^{AA}$  and generates  $C_6^{AB}$  using the geometric mean; i.e., there is no system dependence for the damping or the coefficients.<sup>9</sup>

The more advanced DFT-D3 utilizes a fractional coordination number easily gotten from the geometry of the system to interpolate the  $C_n$  between different, tabulated states of hybridization.<sup>10,11</sup> The dispersion coefficients were obtained from the Casimir–Polder relation

$$C_6^{M_1 M_2} = \frac{3}{\pi} \int_0^\infty d\omega \alpha^{M_1}(i\omega) \alpha^{M_2}(i\omega) \quad (3)$$

wherein the dynamic fragment polarizabilities  $\alpha$  are evaluated over all imaginary frequencies  $i\omega$  using an appropriate DFT method. In the case of DFT-D3, hydrides of all elements (from which the hydrogenic contribution was subtracted) were used as fragments  $M_1$  and  $M_2$  to obtain the  $C_6$ . Higher order dispersion coefficients are attained by recursion.

The evaluated implementation of DFT+vdW restricts itself to  $C_6 R^{-6}$  terms.<sup>13</sup> The required  $C_6$  stem from self-interaction corrected TD-DFT using the Casimir–Polder relation for atoms and are subsequently modified by the Hirshfeld partitioned volume of the free atom and the atom in the

system. This is motivated by the proportionality relation between volume and polarizability. A short-range Fermi-type damping is applied to circumvent singularities in the dispersion energy.

The dispersion correction devised by Becke et al. is termed XDM (for exchange dipole moment).<sup>14–16</sup> The basic idea is to obtain  $C_n$  coefficients from the dipole moment created by a reference electron and its corresponding exchange hole (for which a model has to be applied) using a variant of second-order perturbation theory. This is done separately for each atom in the molecule under consideration. Similarly to DFT+vdW, the atom-in-molecule Hirshfeld volume is used to supply additional system dependence. The higher order  $C_n$  are also dependent on the quadrupole and octupole moments of the exchange hole. A simple rational damping function employing the approximate van der Waals radii is applied, which yields a finite nonzero contribution for short interaction lengths. Note that basically the same damping expression is used in DFT-D3 as the now-default, dubbed BJ-damping in previous papers.<sup>11</sup> Two different variants of the XDM model have been published, dubbed XDM6 and XDM10 after the highest order term in the central expression, analogously to eq 2. Following the recommendation by Otero-de-la-Roza and Johnson,<sup>33</sup> we decided to evaluate the XDM10 model in this study.

The dDsC dispersion correction by Steinmann and Corminboeuf attempts to improve on the XDM model by introducing a more sophisticated damping function by Tang and Toennies that also has some electron density dependence.<sup>12</sup> The employed  $C_n$  coefficients are obtained in a similar manner as in XDM, but using a GGA-like model.<sup>34</sup>

The two other methods to account for dispersion under investigation in this work are not atom pair based in principle (although DFT-NL makes use of the Casimir–Polder relation in its derivation). The first one is the extension of standard density functionals with a term devised by Vydrov and van Voorhis,<sup>19</sup> termed DFT-NL:<sup>20</sup>

$$E_{\text{total}}^{\text{DFT-NL}} = E_X^{\text{DFT}} + E_C^{\text{DFT}} + E_C^{\text{NL}} \quad (4)$$

which takes the form

$$E_C^{\text{NL}} = \frac{1}{2} \int d\mathbf{r} d\mathbf{r}' \rho(\mathbf{r}) \Phi(\mathbf{r}, \mathbf{r}') \rho(\mathbf{r}') \quad (5)$$

This term, additive to the standard DFT exchange and correlation energies  $E_X^{\text{DFT}}$  and  $E_C^{\text{DFT}}$ , is dependent on the electron density  $\rho$  and a correlation kernel  $\Phi$  based on local approximations to the dipole polarizability of an implicit fragment of the system.<sup>7</sup> In turn, the kernel is dependent on the electron density and its gradient at the Cartesian positions  $\mathbf{r}$  and  $\mathbf{r}'$ . One can show that the particular kernel employed yields the correct long- and short-range limits. Note that the energy expression implies that the double integral of eq 5 be evaluated for each iteration of the SCF procedure. However, as Langreth et al. have shown, it is also possible to use such a correction in a single-step post-SCF fashion, reducing the computational cost.<sup>35,36</sup> The last method is the Minnesota class of functionals designed by Zhao and Truhlar. These functionals, made flexible by form and by employing 30+ fitting parameters, are trained on a set composed with a significant weighting of noncovalent interactions.<sup>17,37</sup> Thus, it is argued that these functionals recover almost all short-range type dispersion (called overlap-dispersive interaction in ref 38) because dispersion, at its core, stems from correlation. However, it must be noted that this



cannot be true for the long-range limit because semilocal functionals fail to describe dispersion correctly at large distances, as stated before. Of the Minnesota functionals, the meta-GGA M06-L was chosen as the primarily evaluated functional due to the diminished cost compared to the hybrid density functionals, whose exact exchange proves too expensive to be used for explorative calculations in general.

**1.2. Approach.** The basic idea of this work is the evaluation of different dispersion-accounting methods in the context of DFT. Given the nature of most methods, this amounts to choosing a standard exchange-correlation density functional (along a basis set) and applying the correction after the calculation. We wish to treat the first step as consistently as possible and thus use, whenever appropriate, the PBE functional. The reasons for doing so are as follows: We believe that PBE constitutes a prototypical density functional that is widely used and is available in basically any quantum chemistry code.

We hope to achieve a fair, unbiased comparison in this way. The alternative, which is to always follow the respective authors' recommendation, is frequently not feasible in a typical research setting because a given, specific approach may not be available. Since we intend the simulation of explorative research to be a part of this paper, we decided against using many different density functionals for the main part of this paper. The influence of different functionals has been evaluated to some extent in ref 27 and in section 3.3.

Another issue to consider is the three-body dispersion interaction energy  $E^{ABC}$ . As shown by von Lilienfeld and Tkatchenko, the three-body interaction energy becomes significant for large, dense systems.<sup>39,40</sup> In DFT-D3, the pair wise two-body interaction can be corrected by a form equal to the Axilrod–Teller–Muto term:

$$E_{\text{disp}}^{ABC} = \sum_{A < B < C} C_9^{ABC} \frac{3 \cos \theta_a \cos \theta_b \cos \theta_c + 1}{(R_{AB} R_{AC} R_{BC})^3} f_{\text{damp}} \quad (6)$$

where the  $\theta_{a,b,c}$  are the internal angles of the ABC triangle. The appropriate coefficient  $C_9^{ABC}$  can be derived using a formula similar to the Casimir–Polder formula referenced in eq 3:

$$C_9^{M_1 M_2 M_3} = \frac{3}{\pi} \int_0^\infty d\omega \alpha^{M_1}(i\omega) \alpha^{M_2}(i\omega) \alpha^{M_3}(i\omega) \quad (7)$$

which is valid for fragments  $M_1$ ,  $M_2$ , and  $M_3$ .

In DFT-D3, the  $C_9^{ABC}$  coefficient is approximated from the corresponding  $C_6$  coefficients<sup>10</sup>

$$C_9^{ABC} = -\sqrt{C_6^{AB} C_6^{AC} C_6^{BC}} \quad (8)$$

whereas the damping function is similar to the one of the two-body term but uses the geometric mean of the distances involved. A positive contribution and thus weaker bonding will result when there are many small internal angles in the complex. This is generally the case except in planar arrangements such as the Watson–Crick orientation of nucleobases.

For many small complexes, the three-body contribution can be neglected without a detectable loss of accuracy. In a large, dense system, the number of summands in eq 6 will become significantly larger than the number of summands in eq 2. Even though the two-body contribution will remain the dominant term, the influence of the three-body term may become significant, as can for instance be seen in the case of a bilayer of graphene, for which the magnitude of the three-body

contribution is described to be sizable.<sup>39</sup> In our case of large test systems, we also expect a significant three-body term.

None of the methods under consideration use an explicit three-body term as a default. Other developers of dispersion-accounting methods have hinted at the necessity of such a term, but if defined, the term has yet to be implemented at the time of this writing.<sup>19,39</sup> One would expect that the parametrization of most of the atom pair wise dispersion corrections and certainly the one of the two other methods is flexible enough to incorporate the three-body effect implicitly. Yet for this to happen, the fit set used would have to include large van der Waals complexes, which is usually not the case.

For these reasons, we will employ the same  $E^{ABC}$  correction of eq 6 to all DFT-based dispersion-accounting methods evaluated in this paper and try to deduce the significance of the correction from a comparison with uncorrected results.

We will briefly consider the counterpoise correction (CP) to correct for the basis set superposition error (BSSE). While many researchers would probably suggest the use of the CP correction, its benefits in the current context are not a foregone conclusion, since experience shows that the CP scheme may yield an overcorrection.<sup>41</sup> For explorative purposes, the additional necessary computational time may be an impediment, especially for geometry optimizations. Note that the geometries considered in this study have been obtained earlier at the uncorrected TPSS-D3/def2-TZVP level.<sup>27</sup>

## 2. COMPUTATIONAL DETAILS

All calculations were performed on the original Cartesian coordinates as published in ref 27. No further geometry optimizations were carried out. Care was taken to select meaningful SCF convergence criteria for each method employed.

The functionals used in this study are PBE<sup>42</sup> (as implemented in each program), BLYP<sup>43</sup> (as implemented in ORCA 2.9, see below), M06-L,<sup>17</sup> and M06-2X<sup>18</sup> (using ORCA 2.9, see below).

Some of the values have been counterpoise corrected according to the scheme of Boys and Bernardi,<sup>44</sup> which will be indicated by “CP” and “CP\*,” respectively. The asterisk signifies that the CP correction values of PBE/def2-TZVP have been applied. The same settings as for the DFT-D2 and -D3 calculations were used, see below. In convergence studies of the counterpoise correction, additional basis sets were used: SV(P),<sup>45</sup> def1-TZVP,<sup>46</sup> cc-pVTZ,<sup>47–49</sup> def2-QZVPD,<sup>50,51</sup> and SZ. The latter was constructed from a partly decontracted def2-QZVP basis set<sup>51</sup> together with some of the polarization functions of cc-pVSZ.<sup>47–49</sup> SZ is listed in the Supporting Information.

Some of the values have been corrected by the three-body interaction energy  $E^{ABC}$  of DFT-D3. The parametrization is functional-independent and uses the “zero”-damping.<sup>10</sup>

All DFT-D, i.e. PBE-D2<sup>9</sup> and -D3,<sup>10</sup> calculations were carried out using Turbomole 6.4<sup>52</sup> in combination with the standalone DFT-D3 program as available via the Grimme group Web site.<sup>53</sup> For the D3 term, the damping of Johnson and Becke was employed.<sup>11</sup> The employed basis sets are def2-TZVP<sup>54,55</sup> and def2-QZVP' (def2-QZVP from which all g-functions have been dropped).<sup>51</sup> Where omitted, the def2 prefix is implied. The RI-J approximation was used<sup>56,57</sup> with the “universal” auxiliary basis set.<sup>58</sup> The m5 numerical quadrature grid was used.<sup>57</sup>

All DFT-NL calculations were carried out using ORCA 2.9<sup>59</sup> employing the Grimme group implementation of the VV10

scheme.<sup>19,20</sup> The RI-J approximation was used analogously as for the DFT-D calculations. The analog of the mS grid was used. The NL energy was calculated after the SCF had converged, i.e. nonself-consistently and on a size 3 grid. For PBE-NL, the  $b$  parameter was fitted with the same procedure as was used in ref 20 employing the S22 set, resulting in a value of 6.4.<sup>60</sup>

All calculations employing the dispersion correction of Corminboeuf and Steinmann (dDsC)<sup>12</sup> were carried out using ADF 2012.01.<sup>61–63</sup> The therein implemented Slater-type basis sets termed TZ2P and QZ4P were used.<sup>64</sup> For the numerical integration, a high precision value of 6.0, recommended for frequencies, was set.

All XDM calculations were carried out using Q-Chem 4.0.<sup>65</sup> The basis sets used are cc-pVTZ(seg-opt)<sup>66</sup> and TZV.<sup>46</sup> For technical reasons, it is not possible to employ non-hard-coded basis sets in XDM calculations using the Q-Chem version available. Thus, the interaction energies reported as PBE-XDM/mixedTZ are cc-pVTZ(seg-opt) values except for the complex containing iron. In this case, the value of PBE-XDM/TZV is reported. For completeness, the TZV values are reported in the Supporting Information. The larger of the two standard grids for the XC-integration (“SG-1”) was used.<sup>67</sup> The Fourier Transform Coulomb method (FTC) was used to speed up the calculations.<sup>68–70</sup> The XDM<sup>14–16</sup> energy was added as a post-SCF correction. The XDM10 variant, referring to the  $C_6/R^6 + C_8/R^8 + C_{10}/R^{10}$  formula, was chosen to be evaluated. The dipole moment of the exchange hole was calculated from the Becke–Roussel model, which was solved numerically.<sup>71</sup> The exception to this is the counterpoise correction for PW86PBE/mixedTZ, which was obtained using ORCA 2.9 and the settings described in the DFT-NL section but without the RI approximation.

All M06-L and M06-2X calculations were carried out using ORCA 2.9 and the xcfun module<sup>72</sup> using the analog of the mS grid and tight SCF convergence criteria. The RI-J approximation was used together with the appropriate basis sets.

All calculations using the dispersion correction of Tkatchenko and Scheffler (PBE+vdW)<sup>13</sup> were carried out using FHI-AIMS (version 071711).<sup>73</sup> The calculations were done without periodic boundary conditions using the “reallytight” presets for the calculation, employing the tier 2 basis. The SCF procedure was considered converged if the root-mean-square change of the electron density was below  $10^{-5}$  au and the absolute total energy change was below  $10^{-6}$  eV.

All MP2 and related calculations were carried out using Turbomole 6.4, using the frozen core approximation. We employed Dunning’s cc-pVDZ and cc-pVTZ<sup>47–49</sup> basis sets and the appropriate auxiliary basis sets<sup>58,74</sup> for the use of RI-MP2 and RI-J algorithms. In the case of cc-pVDZ for Fe, it was necessary to substitute the auxiliary c-basis by the cc-pVTZ c-basis because the double- $\zeta$  variant is not defined. Hartree–Fock energy and MP2 correlation energies were extrapolated separately according to Helgaker’s two-point extrapolation schemes.<sup>75,76</sup> Some calculations were carried out using the 6-31G\*(0.25) basis set, which is the 6-31G\* basis set<sup>77,78</sup> where the standard augmentation function has been replaced by one with an exponent of 0.25. All resulting interaction energies were fully counterpoise corrected.

All VDW3<sup>79</sup> calculations were done using an in-house implementation. All PM6<sup>80</sup> and PM6-DH2<sup>81</sup> calculations were carried out using MOPAC2012.<sup>82</sup> All OM2<sup>83</sup> and OM3<sup>84</sup>

calculations were carried out using MNDO2005.<sup>85</sup> All DFTB3<sup>86</sup> calculations were done using DFTB+ Release 1.2.<sup>87</sup>

We use the statistical measures mean deviation (MD), mean absolute deviation (MAD), and signed relative deviations (indicated by percentage values).  $\Delta E$  is the gas phase interaction energy defined as

$$\Delta E = E^{\text{complex}} - E^{\text{host}} - E^{\text{guest}} \quad (9)$$

where  $E$  is the total energy of the system.

### 3. RESULTS AND DISCUSSION

In Table 1, the reference values used in this study are listed. A rather large spread of reference values is used in this test set,

**Table 1. Empirical Reference Energies<sup>27</sup> of the S12L Test Set, Obtained by Back-Correcting Experimental Results<sup>a</sup>**

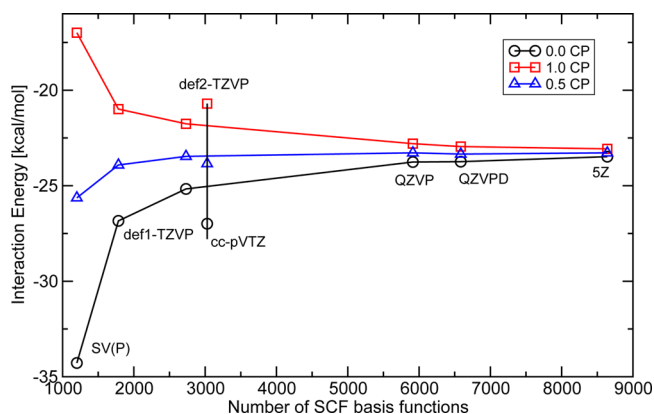
| complex | $\Delta E_{\text{emp}}$ | $\Delta E_{\text{DFT}}$ | $\Delta E^{\text{ABC}}$ |
|---------|-------------------------|-------------------------|-------------------------|
| 2a      | −29.9                   | −0.6                    | 1.8                     |
| 2b      | −20.5                   | 1.7                     | 1.2                     |
| 3a      | −24.3                   | 0.3                     | 1.8                     |
| 3b      | −20.4                   | −6.5                    | 0.7                     |
| 4a      | −27.5                   | 11.8                    | 3.2                     |
| 4b      | −28.7                   | 13.5                    | 3.5                     |
| 5a      | −34.8                   | −14.8                   | 1.0                     |
| 5b      | −21.3                   | −5.2                    | 1.0                     |
| 6a      | −77.4                   | −63.2                   | 2.2                     |
| 6b      | −77.0                   | −62.7                   | 1.8                     |
| 7a      | −131.5                  | −86.6                   | 4.6                     |
| 7b      | −22.6                   | 1.2                     | 3.3                     |

<sup>a</sup>For perspective, pure PBE/QZVP’ interaction energies (denoted  $\Delta E_{\text{DFT}}$ ) and the three-body correction (*vide supra*) are provided. All values are in kcal/mol.

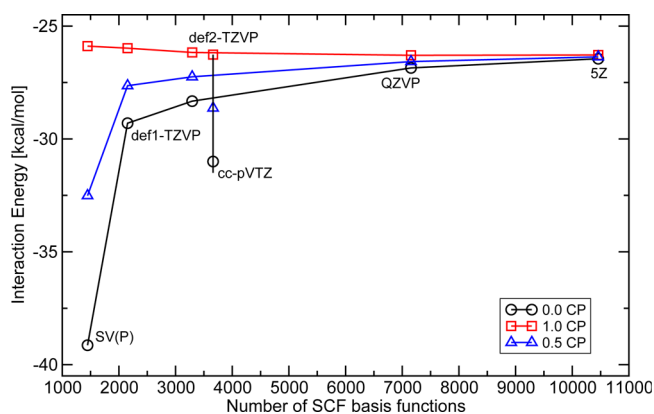
ranging from −20.4 to −131.5 kcal/mol. The  $\Delta E_{\text{DFT}}$  values tabulated in the same table have been obtained at the pure PBE/QZVP’ level and demonstrate that a conventional density functional fails completely for the calculation of these interaction energies. Note that we restrict our discussion mostly to deviations in terms of signed and unsigned absolute values; i.e., we do not explicitly discuss relative deviations. However, there is very little difference in our analysis when considering percentage deviations.

**3.1. Counterpoise Correction and Three-Body Correction.** The first issue to be considered is the possible inclusion of the counterpoise correction, which can also be scaled by a factor differing from 1. To do this, we calculated the interaction energies, both with and without counterpoise correction for four different complexes using Ahlrichs’ basis sets and cc-pVTZ at the PBE-D3 level. The two cases shown in Figures 2 and 3, 3a and 7b, are the two extreme examples of the cases investigated in that 3a suggests a large overestimation of the BSSE by a standard full CP correction while 7b shows that the full CP correction is superior to the common alternative of applying half the CP correction. The other two cases not shown here (available in the Supporting Information) point to a intermediate fraction of CP correction as the optimal choice.

We are thus facing the problem that there is no unambiguously best option when choosing a fraction of CP to be used. In any event, a fraction between 0.5 and 1.0 improves the valence triple- $\zeta$  results and lowers the BSSE. We make the decision to use 0.5 to avoid artificial over-repulsive results.



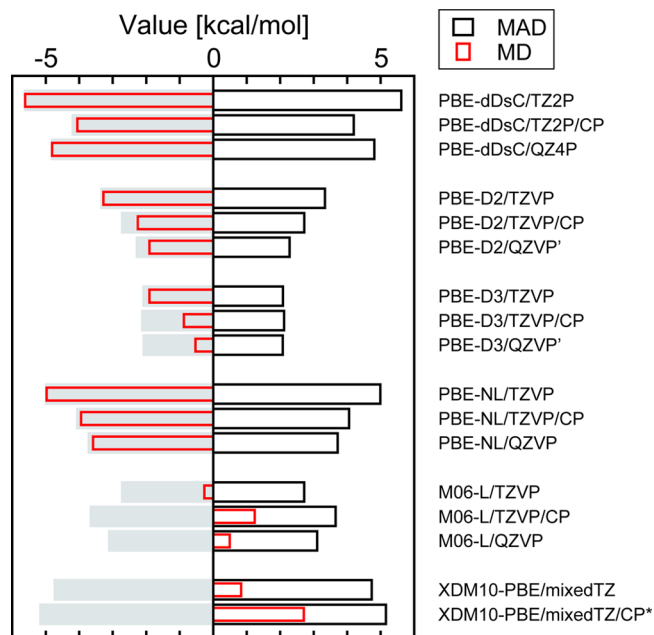
**Figure 2.** Interaction energies of **3a** calculated with different basis sets using the PBE-D3 functional. The connecting lines are drawn merely to guide the eye.



**Figure 3.** Interaction energies of **7b** calculated with different basis sets using the PBE-D3 functional. The connecting lines are drawn merely to guide the eye.

To validate our choice, we investigate the effect of half the CP correction on the valence triple- $\zeta$  results with respect to the valence quadruple- $\zeta$  results. The relevant statistical data are plotted in Figure 4. All methods considered gain accuracy compared to the valence quadruple- $\zeta$  results, with the exception of PBE-dDsC, which appears to be overcorrected even with half the CP correction and, similarly, M06-L. However, since both uncorrected and corrected results are equally far from the large-basis set result in either case, we decided to keep the methodology consistent and ascribe the tiny MD of M06-L/TZVP to fortuitous error cancellation. From this point forward, all valence triple- $\zeta$  DFT results will include 0.5 CP, whether or not noted explicitly. The exception to this are the so far unconsidered MP2/CBS(DT) results, as it is known that correlated methods suffer more heavily from BSSE than SCF methods. We thus decided to keep the full CP correction.

The next topic to be considered is the three-body correction of eq 6. Since these values are identical for all methods considered, the contribution of the three-body correction has been listed in Table 1. At this point, it is already clear that this contribution is not constant but largely dependent on the system considered (compare entries **2a** at 1.8 kcal/mol and **4b** at 3.5 kcal/mol, but with similar reference total interaction energies of  $-29.9$  and  $-28.7$  kcal/mol, respectively). The relative contribution with respect to the reference varies

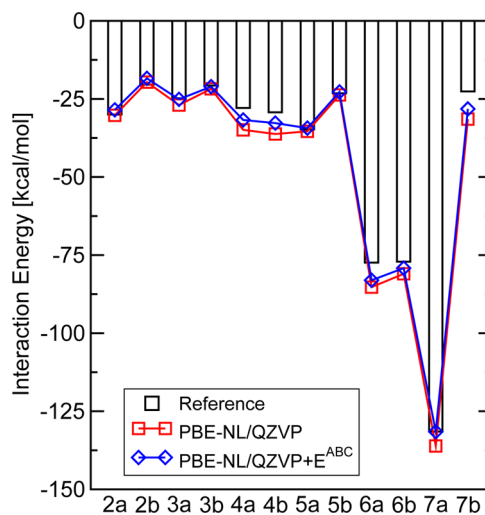


**Figure 4.** Comparison of uncorrected valence triple- $\zeta$  DFT results to those with the CP correction. Valence quadruple- $\zeta$  results are shown where available. Deviations from reference are shown; a negative MD means overbinding. The gray bars mirror the MAD to the negative for better comparability.

between 2.3 and 14.6%, showing that the three-body correction will certainly have an influence.

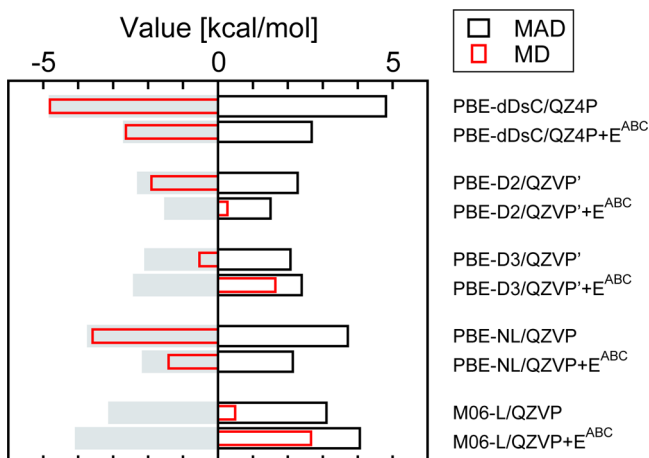
For the purpose of illustration, the reference values have been plotted in Figure 5 along the results of a prototypical method (PBE-NL/QZVP), showing the effect of the three-body correction.

We will now try to decide whether it is advisable to include the three-body energy  $E^{ABC}$ . For this, we will compare the DFT valence quadruple- $\zeta$  results with and without the three-body correction in Figure 6, because these results are virtually free of BSSE. Comparing the MAD and MD for the  $E^{ABC}$ -uncorrected



**Figure 5.** Empirical interaction energies serving as the reference values. PBE-NL/QZVP is shown as a prototypical example, with and without the three-body correction applied. The connecting lines are drawn merely to guide the eye.



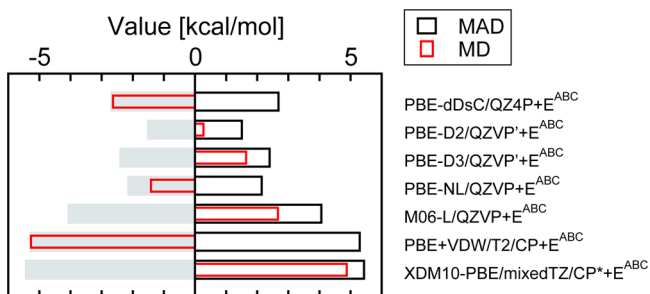


**Figure 6.** Comparison of valence quadruple- $\zeta$  DFT results with and without the repulsive three-body dispersion interaction term. Deviations from reference are shown; a negative MD means overbinding. The gray bars mirror the MAD to the negative for better comparability.

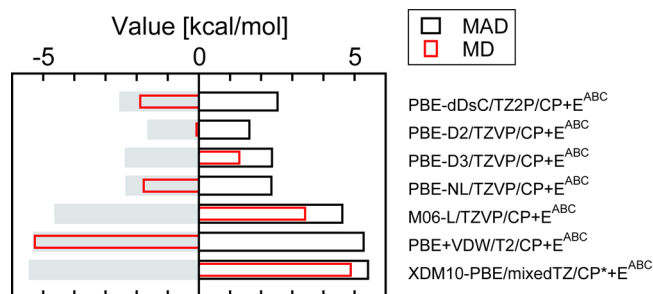
methods reveals that for all methods, almost all complexes are overbound. With the exception of PBE-D3/QZVP' and M06-L/QZVP, the inclusion of  $E^{ABC}$  improves the results in both MD and MAD. Because we believe the three-body interaction to be important, we opt for keeping our methodology consistent, including the three-body correction henceforth and returning to this issue at a later stage.

**3.2. DFT-Based Methods.** At this point, we have decided to include the three-body contribution to the dispersion energy as a correction to all DFT methods and to use half of the CP correction. We will now take a closer look at the performance for each method. In doing so, we define a “best estimate,” representing the most advanced choices one can reasonably make while using the method. Even more important, we define a “workable” approach, which typically consists of using a smaller basis set plus the CP correction, and whose resource usage is probably closer to what is realistic in an explorative research setting. In some cases, the two defined approaches will be the same, because a larger basis set than a valence triple- $\zeta$  (or equivalent) was beyond our capabilities for technical reasons. The statistical data of either category are visualized in Figures 7 and 8, respectively.

We begin by looking at the performance of PBE-D2, where the workable approach is PBE-D2/TZVP/CP+E<sup>ABC</sup>. This method shows a tiny MD of  $-0.1$  kcal/mol; especially when



**Figure 7.** The best quality calculations “best estimate” available for each dispersion-accounting method. Deviations from the reference are shown; a negative MD means overbinding. The gray bars mirror the MAD to the negative for better comparability.



**Figure 8.** The “workable” approaches possible with each dispersion-accounting method. Deviations from the reference are shown; a negative MD means overbinding. The gray bars mirror the MAD to the negative for better comparability.

considering the simplicity of this dispersion correction, the small overbinding is surprising and must be ascribed to the small test set size and fortuitous error cancellation. The largest relative deviation is found for **3a** (12%). For the best estimate, PBE-D2/QZVP'+E<sup>ABC</sup>, the MD stays almost at zero (0.3 kcal/mol). The worst relative deviation is now found for **3a** ( $-11\%$ ). We note that this method gives the lowest MAD (1.5 kcal/mol) of all methods considered in either category.

Next, we consider PBE-D3. The workable approach, PBE-D3/TZVP+E<sup>ABC</sup>, is outperformed by D2 with a MAD that is 50% higher and a MD that is more than 1 kcal/mol more underbinding. Similarly to D2, **3a** yields the largest relative error at 13%. For the best estimate method, PBE-D3 is outperformed by PBE-D2 in both measures as well. This substantiates the earlier conclusion that D2 may benefit from error cancellation in this case. For PBE-D3/QZVP'+E<sup>ABC</sup>, the largest relative deviation is found for **3a** (12%), as for D2.

For PBE+vdW, the best estimate and the workable approach are the same. Among the methods chosen for either comparison, it is one of the worst performers at a MD of  $-5.3$  kcal/mol. The method is overbinding for almost all complexes, showing relative deviations above 40% for complexes **7b** (49%) and **4a** and **4b** (42% each). For other complexes, deviations below 5% are found. [In a private communication, Alexandre Tkatchenko provided us with interaction energies calculated with a new method dubbed “PBE+fMBD,”<sup>88</sup> which corrects some of the overbinding (MD =  $-2.9$  kcal/mol, MAD = 3.3 kcal/mol). Notably, the interaction energy of **4a** is much improved.] The tier 2 basis set used is described to yield results comparable to aug-cc-pVQZ and thus should be sufficient for this test set.<sup>89</sup> We also note that the CP scheme yielded very small, albeit beneficent corrections in this case.

The next method investigated is XDM, which is used as XDM-PBE/mixedTZ+E<sup>ABC</sup> for both workable and best estimates. The MAD obtained (5.4 kcal/mol) is similar to the one of PBE+vdW (5.3 kcal/mol), and the MD is only slightly smaller in magnitude at +4.8 kcal/mol, but pointing in the opposite direction. Looking at the performance for the individual systems, a clear trend is found: for complexes **2a,b**–**5a,b**, sometimes large underbinding is found (up to 38%), whereas the remaining complexes are much better described with overbindings ranging from 1% to 9%. This does not perfectly correlate with system size but with the chemical nature of the complexes, as complexes **6a,b** and **7a,b** are cucurbituril-based. Given the large underbinding for almost all

cases, we note that the XDM-PBE/mixedTZ/0.5CP\* statistical data are as follows: MD = 2.7 kcal/mol, MAD = 5.2 kcal/mol.

We now turn our attention toward dDsC, for which the workable method is PBE-dDsC/TZ2P+E<sup>ABC</sup>. It improves strongly upon the XDM method by cutting both MAD and MD to less than half (−1.9 and 2.5 kcal/mol). Since the sign of the MD changes, one may guess that problems with the basis set may remain in either variant of XDM or dDsC under consideration. However, dDsC may indeed be regarded as an improvement over XDM. The best estimate method is PBE-dDsC/QZ4P+E<sup>ABC</sup>, which gives a result slightly inferior to PBE-D3 in terms of MAD and significantly worse in MD (larger in magnitude by 1 kcal/mol). The distribution of deviations for each member of the test set of the workable and best estimate variant is fairly similar with both methods yielding the largest deviation for **7b** (42% and 30%, respectively).

We now address the first method that does not rely on atom pair wise additive corrections: PBE-NL. The workable variant yields a MAD on par (2.3 kcal/mol) with the best methods in its class. The deviations reveal a small tendency toward overbinding with the exception of the tweezer complexes **2a,b**. The largest relative deviation is found for **7b** (27%). The best estimate method is PBE-NL/QZVP+E<sup>ABC</sup>, which results in a slightly smaller MD and MAD (−1.4 and 2.1 kcal/mol). Again, the largest deviation is found for complex **7b** (24%).

Finally, we consider the M06-L density functional, for which the best estimate variant is M06-L/QZVP, producing a MD of 2.6 kcal/mol and a MAD of 4.1 kcal/mol. The performance worsens decidedly toward underbinding in the workable case (MD = 3.4 kcal/mol, MAD = 4.6 kcal/mol). The largest deviation is found for **4b** at 29% and 33%, respectively.

We now turn to a comparison within the “best estimate” collection of methods. In essence, we find two classes of performance. The first one is comprised of PBE+VDW and XDM-PBE, which show rather disappointing performance with MDs of magnitudes greater than 3 kcal/mol and large MADs. For neither of the two methods is a single dominating outlier or an indication of what causes the large deviations discernible. We also note that the PBE/TZVP CP correction used for XDM is unlikely to be responsible for the large underbinding because it is probably on the small side for the actual basis set used (cf. Figures 2 and 3).

The second class of performance consists of PBE-D3, PBE-dDsC, PBE-NL, PBE-D2, and M06-L. The former three approaches show basically the same level of accuracy with MADs around 2.5 kcal/mol and MDs around 1.5 kcal/mol (with the exception of PBE-dDsC and M06-L, which are more strongly underbinding/overbinding, respectively). In the case of M06-L, doubts whether the long-range dispersion is correctly accounted are still valid. However, given that M06-L without E<sup>ABC</sup> performs at a much better level (MD = 0.5 kcal/mol, yet a comparatively high MAD of 3.1 kcal/mol), it may also be the case that the fit set used for the functional is representative enough for van der Waals interactions in large systems and does not need the three-body correction after all, as long as complexes near their equilibrium geometry are considered. Because of the simplicity of the scheme and the widespread availability of D3, we recommend it for further use, but note the good alternatives present. We reiterate that the very good performance of D2 is by all estimates a fluke because the D3 scheme has shown itself to be superior in our evaluations.<sup>10</sup>

When comparing the “workable” and the “best estimate” results (as far as they differ), we observe a large similarity in the

quality of results (which we believe to validate the choice of 0.5 CP made earlier). Minor alterations on the order of 0.2 kcal/mol toward a degradation are found for PBE-NL and the already mentioned deterioration for M06-L, while the other methods actually improve slightly. We consider this good news for the exploring researcher because results close to “complete basis set limit” quality seem to be within reach even with moderate computational resources.

All in all, it is heartening that all methods considered predict the correct sequence of energies for each guest of a given complex. In most cases, the difference of the complexation energies between the two complexes of each host is basically correct, as well. Thus, it seems that DFT-based quantum chemistry has its place in an explorative research setting for supramolecular chemistry.

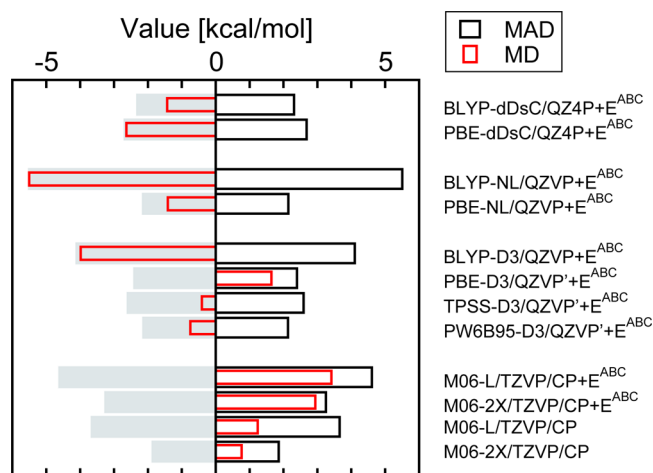
To evaluate whether clear outlier complexes exist, we ranked the percentage error of each case and collected the worst three performers for every method. They were then given one to three penalty points according to the rank, and penalty points were summed over all methods for each complex. This method yields the following three cases: **7b**, **4b**, and **3a**. We are unable to draw further conclusions from this, since the partner complexes **4a** and **3b** are very similar yet perform much better in this evaluation, and **7b** has no special structure.

Finally, we conclude that the attempt to create a new test set composed of large molecular complexes mentioned in the Introduction was in fact successful. We believe that the unexpected high accuracy of most methods shows that the procedure to obtain the reference values does not yield large systematic errors and thus validates the procedure. Separately from this work, an investigation into the different rotamers and their influence is being carried out. At this point and throughout this study, we refrain from giving concrete values for the accuracy of the reference values because we are lacking the necessary detailed experience with the back-correction approach outlined in ref 27. However, an independent DMC calculation<sup>89</sup> found an interaction energy of  $-26 \pm 2$  kcal/mol for **4a**, which is in reasonable agreement with our reference value of  $-27.5$  kcal/mol. Similarly, the same study found a DMC interaction energy of  $-33.4 \pm 1.5$  kcal/mol for **5a**, where our reference value is  $-34.8$  kcal/mol. This further supports the notion that the reference values herein presented are reasonably accurate.

**3.3. Comparison of Density Functionals.** The GGA density functional BLYP plus a dispersion correction shows up frequently as a viable alternative to higher rung functionals if the test set emphasizes or is exclusively composed of noncovalent interactions.<sup>90</sup> We thus decided to evaluate the DFT-D3, dDsC, and DFT-NL corrections with this functional, yielding the values visualized in Figure 9. In the cases of DFT-NL and DFT-D3, the results of BLYP are significantly worse than those of PBE, but retaining the relative order of the two. For dDsC, a similar MAD is obtained, but the total trend is less overbinding. Given this increased accuracy, it may be worthwhile to test XDM-BLYP, which is closely related to the dDsC correction.

Given the disappointing performance of XDM-PBE, it was suggested to us to evaluate XDM-PW86PBE. Unfortunately, we were unable to converge all the necessary calculations and thus present the partial results in Table 2. Inspection reveals that the differences between the two functionals are rather small albeit improvements are found. As for XDM-PBE, the absence of the “good fit” of XDM and PW86PBE is thus unlikely to be the





**Figure 9.** Visualization of different dispersion-accounts methods with an emphasis on different functionals. The values for TPSS and PW6B95 have been taken from ref 27. Deviations from the reference are shown; a negative MD means overbinding. The gray bars mirror the MAD to the negative for better comparability.

**Table 2.** The Reference Energies of the Test Set and the Interaction Energies of XDM-PBE/mixedTZ/CP\* and XDM-PW86PBE/mixedTZ/CP\*

| complex | $\Delta E_{\text{emp}}$ | $\Delta E(\text{PBE/mixedTZ})$ | $\Delta E(\text{PW86PBE/mixedTZ})$ |
|---------|-------------------------|--------------------------------|------------------------------------|
| 2a      | −29.9                   | −20.9                          | −20.2                              |
| 2b      | −20.5                   | −13.2                          | −12.7                              |
| 3a      | −24.3                   | −15.3                          | −14.8                              |
| 3b      | −20.4                   | −13.9                          | −13.2                              |
| 5a      | −34.8                   | −29.0                          | −28.3                              |
| 5b      | −21.3                   | −18.1                          | −18.1                              |
| 6a      | −77.4                   | −79.9                          | −79.5                              |

\*Values that could not be obtained have been omitted. All values are in kcal/mol.

reason for the performance shown in this evaluation. As of this writing, the true reason remains unknown.

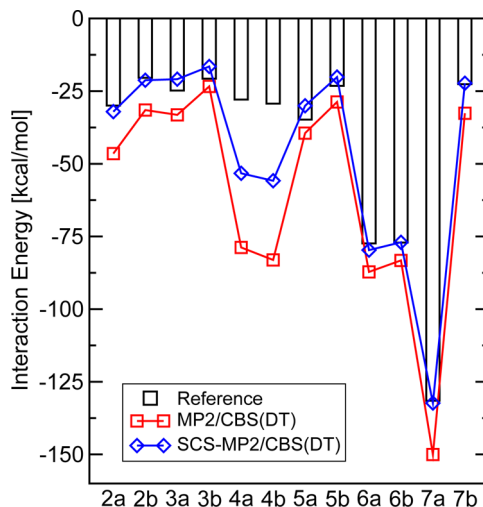
A comparison of functionals combined with the DFT-D3 correction shows that PBE-D3 is inferior to both TPSS and PW6B95 for this test set when considering the MD. However, in terms of MAD, the three functionals are basically on par with each other and thus equally reliable.

Overall, we note that some differences due to the actual functional chosen are present and to be expected. However, we believe that our general choice of PBE was not a flawed one.

As for the Minnesota class of functionals, we observe that M06-2X/TZVP without the three-body correction outperforms the other Minnesota-based approaches and reaches one of the best MADs in the entire study. We thus conclude, that albeit very costly, the use of M06-2X may be necessary to obtain meaningful results if one is determined to use a Minnesota functional. As already mentioned, given the equilibrium nature of the complexes under consideration, the good performance of M06-2X and M06-L is perhaps not very surprising to some observers. It may be for the same reason that the three-body correction is not beneficial to these functionals.

**3.4. MP2-Based Methods.** For comparison, we calculated the interaction energies using the only standard wave function approaches possible in an acceptable computational time, which are MP2-based. We evaluated standard MP2 as well as the scaled variant SCS-MP2 using Helgaker's extrapolation

formulas and the full CP correction. Other scaled approaches (SOS-MP2 SCS(MI)-MP2, SSS(MI)-MP2, and SOS(MI)-MP2; for a review, see ref 91) did not yield an improvement over SCS-MP2. All relevant values are reported in the Supporting Information to allow other researchers to undertake further investigations. In Figure 10, MP2 shows the expected



**Figure 10.** Counterpoise corrected, to the basis set limit extrapolated MP2 and SCS-MP2 interaction energies compared to the empirical reference. The connecting lines are drawn merely to guide the eye.

overestimation of the aromatic interaction in the cases of the buckycatcher complexes **4a,b**. While SCS-MP2 is unable to correct this error completely, it improves considerably upon MP2 but is ultimately no match for DFT-based approaches. This is substantiated by the statistical data available (MP2: MD = −16.5, MAD = 16.5; SCS-MP2: MD = −3.5, MAD = 6.2; all values in kcal/mol). Recently, Steinmann and Corminboeuf reported that MP2/6-31G\*(0.25) was the “best approximation” in their evaluation on a set of neutral and radical building blocks of organic electronics.<sup>92</sup> We have thus tested the CP corrected variant of this method on a subset (Complexes **2a** through **6b**) of the current benchmark set and found its performance lacking ( $N = 10$ , MD = −6.4, MAD = 12.2). We note that the superior performance of the DFT-based methods is partially due to the simple electronic structure of the cases under consideration, whereas Steinmann and Corminboeuf's set contained radical cations, for which DFT can show serious errors.

### 3.5. Semi-Empirical MO Methods and Total Ranking.

Table 3 summarizes the MAD values of the tested methods in condensed form for convenient future reference. It includes furthermore some interesting results obtained with modern semiempirical MO methods which are often used in practice for complexes of this large size.<sup>27,93</sup> The Density Functional Tight-Binding approach with third-order corrections (DFTB3<sup>86</sup>), NDDO-type methods with orthogonalization corrections (OM2<sup>83</sup> and OM3<sup>84</sup>), or in dispersion- and hydrogen-bond corrected form (PM6-DH2<sup>80,81</sup>) as well as an intermolecular force-field (VDW3<sup>79</sup>) were tested. All methods except plain PM6 also contain the  $E^{\text{ABC}}$  term, and the short-range D3 parameters for DFTB3, OM2, and OM3 were obtained by a standard fit to the S66x8 data set.<sup>23</sup>

According to this summary, the better dispersion corrected DFT methods span a relatively narrow MAD range of 2–4

**Table 3. Some of the Methods Mentioned in This Paper, Ranked by MAD<sup>a</sup>**

| "workable" methods      | MAD  |
|-------------------------|------|
| PBE-D2/TZVP             | 1.6  |
| PBE-NL/TZVP             | 2.3  |
| PBE-D3/TZVP             | 2.3  |
| PBE-dDsC/TZ2P           | 2.5  |
| M06-2X/TZVP             | 3.3  |
| M06-L/TZVP              | 4.6  |
| PBE+vdW/T2              | 5.3  |
| PBE-XDM/mixedTZ         | 5.4  |
| "best estimate" methods | MAD  |
| PBE-NL/QZVP             | 2.1  |
| PBE-D2/QZVP'            | 2.3  |
| PBE-D3/QZVP'            | 2.4  |
| PBE-dDsC/QZ4P           | 2.7  |
| M06-L/QZVP              | 4.1  |
| MP2-based methods       | MAD  |
| SCS-MP2/CBS             | 6.2  |
| MP2/CBS                 | 16.5 |
| semiempirical methods   | MAD  |
| OM2-D3                  | 3.8  |
| OM3-D3                  | 4.1  |
| PM6-DH2                 | 5.5  |
| DFTB3-D3                | 6.2  |
| VDW3                    | 8.3  |
| PM6                     | 17.2 |

<sup>a</sup>All DFT-based and semi-empirical methods are  $E^{ABC}$ -corrected. In the case of basis sets smaller than quadruple- $\zeta$  for DFT- and MP2-based methods, a CP correction has been applied.

kcal/mol which we consider as being accurate. Only SCS-MP2 can come close to the performance of the worst DFT methods ( $MAD = 5\text{--}6$  kcal/mol), and these methods can be considered as being borderline, i.e. applicable but not really accurate. Surprisingly, the best semiempirical methods OM2-D3 and OM3-D3 perform almost as good as the reliable DFT methods. DFTB3-D3 and PM6-DH2 also provide reasonable results similar to SCS-MP2 (but for a very tiny fraction of computational cost) but much better than MP2. All these low-cost methods show the largest errors as expected for the charged complexes with deviations of typically 10–20 kcal/mol (20–30% of  $\Delta E$ ), meaning that their performance for the neutral systems is even better than suggested by the MAD. Because OM2/3-D3 and DFTB3-D3 also perform well for the broad S66x8 database containing very many different non-covalent interactions ( $MAD$  of about 0.8 kcal/mol), we can recommend these methods for exploratorial investigations, huge complexes, or the computation of vibrational frequencies for statistical thermodynamic corrections.

#### 4. CONCLUSION

Perhaps the most relevant point of this paper is the fact that most dispersion-accounting methods of DFT work well not only for small complexes but also for the large supramolecular complexes presented herein. Also important is the finding that the three-body dispersion energy, which rises with system size, becomes too important to be neglected when dealing with complexes of the size considered in this study. We find that basis sets of valence triple- $\zeta$  quality are clearly sufficient for explorative calculations. We then suggest the use of half the counterpoise correction for DFT calculations. When doing so,

we find a similar performance of valence triple- $\zeta$  and valence quadruple- $\zeta$  basis sets, putting explorative research on complexes of the size considered in this study within reach of many users of DFT. From the present results and our point of view, we can recommend the DFT-D3, DFT-dDsC, and DFT-NL approaches for large complexes. For neutral complexes, D3-corrected semiempirical MO methods represent a viable alternative in some applications.

For further analysis, we suggest the evaluation of more functional/dispersion correction combinations because different density functionals work well with different corrections. While the size of the complexes on the one hand and the number of complexes on the other possibly render this set less useful for straight fitting or testing purposes, we believe that it is useful as a "sanity check" for a given method because we believe that this set may be able to detect overfitting to too small cases.

#### ■ ASSOCIATED CONTENT

##### Supporting Information

All referenced interaction energies and statistical data thereof (including RMSD), the absolute energies used for the MP2/CBS values, the D3 parameters for some of the semiempirical methods, and the SZ basis set are available. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

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##### Notes

The authors declare no competing financial interest.

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