Accuracy of Quantum Chemical Methods for Large Noncovalent Complexes

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Ⓢ *Supporting Information*

ABSTRACT: We evaluate the performance of the most widely used wave function, density functional theory, and semiempirical methods for the description of noncovalent interactions in a set of larger, mostly dispersion-stabilized noncovalent complexes (the L7 data set). The methods tested include MP2, MP3, SCS-MP2, SCS(MI)-MP2, MP2.5, MP2.X, MP2C, DFT-D, DFT-D3 (B3-LYP-D3, B-LYP-D3, TPSS-D3, PW6B95-D3, M06-2X-D3), and M06-2X, and semiempirical methods augmented with dispersion and hydrogen bonding corrections: SCC-DFTB-D, PM6-D, PM6-DH2, and PM6-D3H4. The test complexes are the octadecane dimer, the guanine trimer, the circumcoronene···adenine dimer, the coronene dimer, the guanine-cytosine dimer, the circumcoronene···guanine-cytosine dimer, and an amyloid fragment trimer containing phenylalanine residues. The best performing method is MP2.5 with relative root-mean-square deviation (rRMSD) of 4%. It can thus be recommended as an alternative to the CCSD(T)/CBS (alternatively QCISD(T)/CBS) benchmark for molecular systems which exceed current computational capacity. The second best non-DFT method is MP2C with rRMSD of 8%. A method with the most favorable "accuracy/cost" ratio belongs to the DFT family: BLYP-D3, with an rRMSD of 8%. Semiempirical methods deliver less accurate results (the rRMSD exceeds 25%). Nevertheless, their absolute errors are close to some much more expensive methods, such as M06-2X, MP2, or SCS(MI)-MP2, and thus their price/performance ratio is excellent.

INTRODUCTION

Noncovalent interactions, such as hydrogen bond, halogen bond, π···π stacking, etc., play an important role in processes like the molecular recognition, crystal packing, protein folding, vapor−liquid condensation, stacking of nucleobases, etc. Although these interactions are at least by an order of magnitude weaker than covalent interactions, they accumulate for larger systems and their impact on structure and function of biomolecules is fundamental.[1−3]

Different binding motifs require different levels of theory to reach a given accuracy. Interactions driven mostly by electrostatics, such as the hydrogen bonding,[4,5] are (at least qualitatively) described properly already at the Hartree−Fock (HF) level. However, neither Hartree−Fock theory nor traditional local or semilocal density functional theories include dispersion,[6−8] and not even highly parametrized exchange-correlation functionals are able to describe dispersion in the asymptotic limit,[9] leading to an underestimation of the stability of dispersion dominated complexes at the density functional (DFT) and semiempirical levels of theory. The simplest method which accounts for dispersion *for the right reason,* second order Møller−Plesset perturbation theory (MP2), strongly overestimates dispersion for π systems.[10] In many cases, accurate results are obtained only at the computationally expensive coupled cluster level with the perturbative inclusion of triple excitations in extended basis sets. Two, unfortunately mutually contradictory goals govern the method development.

Figure 1. Structures of the investigated complexes.

The first one is to achieve maximum accuracy, while the second one is the ability to describe large molecular systems efficiently. Significant effort was spent in the past decade to develop methods that strike a reasonable compromise between accuracy and computational cost for dispersion-dominated interactions.[11] Some examples are empirical scaling of different contributions in wave function-based methods,[12−15] parametrizing exchange-correlation functionals to account for dispersion,[16] combining short-range DFT correlation with long-range MP2 (MP2C)[17] or RPA[18] and adding explicit dispersion terms to conventional DFT.[19] Other promising approaches are local electron correlation theories,[20] Symmetry-Adapted Perturbation Theory[21] based on DFT,[22,23] modification of the core potentials to mimic dispersion,[24,25] and methods aiming at incorporating the physics of dispersion in DFT.[26−28] Although many of these methods are very promising, we will focus on the following classes of methods: (a) post-HF wave function theory (WFT) methods containing empirical parameters, (b) DFT based methods with added dispersion terms, and (c) semiempirical quantum mechanical methods augmented with empirical corrections for noncovalent interactions.

The first group is represented by the SCS-MP2, SCS(MI)-MP2, MP2C, MP2.5, and MP2.X methods.[12,14,17,29,30] The formal scaling of these methods is $O(N^5)$, for the MP2-based, and $O(N^6)$ for MP3-based methods, where N is proportional to the size of the system (assuming constant basis set quality). Perturbational methods such as MPn are noniterative and are thus about an order of magnitude more efficient than iterative methods, and they are also more readily parallelized.

The most widely used family of quantum chemical methods, local or semilocal density functional theory (DFT) does not account for the dispersion interaction.[6−8] Dispersion can be included by empirical corrections[19,31,32] or by fitting the exchange-correlation functional to reproduce dispersion near the van der Waals minimum[33] (note, however, that these methods fail to represent the long-range behavior of dispersion). DFT-based methods have advantages over post-HF methods: smaller basis set superposition error (BSSE) and more favorable scaling. The DFT functionals investigated in

this work scale one or two powers lower than post-Hartree−Fock methods, $O(N^3)$−O (N^4) versus $O(N^5)$−$O(N^6)$.

The third group contains semiempirical methods[34] augmented with empirical corrections, such as the dispersion correction of Martin and Clark.[35] We focus on the PM6 method[36] enhanced with empirical corrections for dispersion and hydrogen bonding.[37,38] Empirical corrections used in this group are usually obtained from minimization of the root-mean-square deviation relative to high-quality benchmark data.

The design of reference data is of a crucial importance. They should be obtained by state-of-the-art methods, such as CCSD(T) in extended basis set or even extrapolated to the complete basis set (CBS) limit. They should also be available for a large, balanced set of molecules. Several such benchmark data sets for noncovalent complexes are available. The S22 set,[39] developed in Hobza's group, has become one of the most commonly used data sets for testing and parametrization of methods focused on the noncovalent interactions. This data set is now being replaced by larger and more balanced data sets, such as S22 × 5,[40] S22+,[41] and S66.[42] Super databases (databases containing several data sets) such as GMTKN[43,44] or NCIE[45−48] are also available.

All the data sets above share the same restriction: only medium-sized systems (less than ∼30 atoms) are included. The only exception is the recent study of Risthaus and Grimme,[49] where the performance of different dispersion-accounting DFT methods is tested with respect to experimental data on the S12L set (set of large molecular clusters). It is a tacit assumption that the accuracy of methods parametrized for small complexes/clusters is preserved for larger ones. This, however, may not be the case if a method works well near the van der Waals minimum but is deficient for distant interactions because larger molecules have more long-range dispersion terms. The potential accumulation of errors with increasing system size is not yet fully understood. Thus there is a need to test the accuracy of recent methods on larger systems. In the present paper, we provide benchmark data for noncovalent complexes considerably larger than those in S22 or S66 data sets: this data set is called L7. We test the performance of WFT, DFT, and semiempirical methods on a set of seven large

molecular complexes: "CBH", the octadecane dimer in stacked parallel conformation (representative of aliphatic dispersion-dominated interaction); "GGG", a stacked guanine trimer arranged as in DNA (representative of the aromatic stacking $\pi\cdots\pi$ dispersion interaction with implicit account for the three-body interaction, the binding energy of one of the outer guanine monomers is evaluated); "C3A", a stacked circum-coronene⋯adenine dimer (representative of strong aromatic dispersion interaction with implicit account for three-body interaction); "C3GC", a stacked circumcoronene and Watson—Crick hydrogen-bonded guanine-cytosine dimer (representative of a strong aromatic dispersion interaction with implicit account for H-bonding-stacking nonadditivity, the binding energy of circumcoronene and guanine—cytosine base pair is calculated); "C2C2PD", a parallel displaced stacked coronene dimer (representative of strong aromatic dispersion inter-action); "GCGC", a stacked Watson—Crick H-bonded guanine-cytosine dimers arranged as in DNA (representative of strong aromatic dispersion interaction with implicit three- and four-body interactions, the binding energy of two guanine-cytosine base pairs is evaluated); and "PHE", an amyloid fragment, a trimer of phenylalanine residues in mixed H-bonded-stacked conformation (representative of "mixed-character" interaction with implicit account for many-body interactions. The binding of one of the "outer" residues is evaluated). Structures of all complexes are shown in Figure 1. The full geometry information of all seven complexes along with explicit specification of interacting subsystems is available in the Supporting Information. Their size ranges from 48 to 112 atoms and they are intentionally selected to be mostly dispersion dominated. The motivation is simple: it is to assemble a set of noncovalent complexes, the accurate description of which is a challenge for the contemporary computational chemistry. The data set includes a representative of aliphatic hydrocarbon dimers, which are, similarly to the $\pi\cdots\pi$ stacking complexes, dispersion dominated, but of a different flavor. Aliphatic dispersion interactions are important because their abundance in proteins[48] and membranes but their accurate description is problematic as well.[50,51] The dispersion originating from saturated hydrocarbons scales linearly with system size in the asymptotic limit, as opposed to interactions in aromatic systems, because of intrinsically local character of aliphatic hydrocarbons and a significant HOMO—LUMO gap. It still requires high-level ab initio methods to be described accurately. We believe that the complexes included in the data set are representative of the most important motifs dominated by dispersion in biological chemistry.

■ METHODS

Geometries. Geometries of the CBH, C3A, C3GC, and PHE systems were determined at the TPSS-D/TZVP level[32] with no constrains. The structures of GCGC and C2C2PD complexes were taken from Pitoňák et al.[52] and Janowski et al.,[53] respectively. The GCGC geometry was taken from crystal X-ray data,[52] and the C2C2PD structure was optimized at the QCISD(T) level of theory. The cc-pVDZ basis set for all atoms and the corresponding diffuse (aug-cc-pVDZ) basis set for every other, neighboring carbon atom were used. The GGG geometry was extracted from the 1ZF9 structure[54] with hydrogen atoms added using xleap,[55] one of the Amber software package tools. Subsequently, the coordinates of the hydrogen atoms only were optimized at the TPSS-D/TZVP level.[32] Cartesian coordinates of all the complexes studied in

this work are included in the Supporting Information, as well as on the www.begdb.com[56] web page.

Interaction Energy Calculations. Interaction energies for all of the complexes investigated were calculated for geometries optimized at lower level (see above) without considering the deformation energy (so-called rigid monomer approximation was used). With the exception of semiempirical and DFT results, all calculation used the frozen core approximation and were corrected for BSSE by the counterpoise correction.[57]

QCISD(T)/CBS as the Reference. The QCISD(T)/CBS method was chosen as the reference method, because of an advantage in efficiency over CCSD(T) in the PQS program package[58] and the fact that the QCISD(T) results closely agree with "gold standard" CCSD(T) for the noncovalent interactions of closed-shell complexes.[59] The hybrid scheme of Sherrill et al.[10] and Jurečka and Hobza[60] was used to extrapolate the results to the Complete Basis Set limit

$$\Delta E(\text{QCISD(T)/CBS})$$
$$= \Delta E(\text{MP2/CBS})' + \Delta\text{QCISD(T)}|\text{small basis} \quad (1)$$

where $\Delta E(\text{MP2/CBS})'$ is a CBS limit estimate of the MP2 interaction energy, obtained as described further, and $\Delta\text{QCISD(T)}|\text{small basis}$ is a QCISD(T) correction term covering the higher-order correlation effects, determined in small sized basis set. The physical basis of this approximation is that the extra correlation energy provided by the large basis originates from highly oscillatory, high-energy basis functions which are well described by low-level perturbation theory. The most time-consuming part of the total interaction energy assembly is clearly the calculation of the $\Delta\text{QCISD(T)}$ correction term. The small basis set is defined as a 6-31G*(0.25) basis set.

$$\Delta\text{QCISD(T)}|_{\text{small basis}}$$
$$= [\Delta E(\text{QCISD(T)}) - \Delta E(\text{MP2})]|_{6-31G*(0.25)} \quad (2)$$

The exponents of the diffuse d functions, used in this modified 6-31G* basis set, were changed from their original value of 0.8 to 0.25.[61] This basis set and the 6-31G**-(0.25,0.15) basis[61] were designed for the treatment of noncovalent interactions. They have been extensively validated for hydrogen bonded and stacked DNA base pairs in Hobza's group,[62] and surprisingly, good performance was demonstrated also for more diverse data sets[63,64] containing noncovalent interactions. The QCISD(T)/CBS method constructed as described above was used for all complexes with exception of GCGC and C2C2PD ones where slightly different method-ology was applied (see later).

The $\Delta E(\text{MP2/CBS})'$ term was calculated slightly differently from the routinely used cubic extrapolation of Halkier et al.[65,66] Typically, a different two-point extrapolation is performed for the HF and post-HF terms, usually using Dunning's[67,68] aug-cc-pVXZ (aXZ) basis sets with X = 2 (D) and 3(T)

$$E(\text{HF}/X) = E(\text{HF/CBS}) + A\exp(-\alpha X), \alpha = 1.43 \quad (3)$$

and

$$E(\text{corr}/X) = E(\text{corr/CBS}) + BX^{-3} \quad (4)$$

The use of augmented basis set for extended cluster fragments (or monomers) is problematic, if not impossible. The reason is not so much excessive computational time and storage requirements but numerical instabilities caused by

overcompleteness of the atomic basis set. The overcompleteness problem can be overcome in the most straightforward way by excluding the linear dependent basis functions from the basis set. Doing so, the numerical problems usually disappear, but the error with respect to the complete basis set is unpredictable and discontinuities may occur on the potential energy surface. One of the methods of eliminating this problem, as used in this work, is to scale the $\Delta E(MP2/CBS)$ term obtained from extrapolation using nonaugmented Dunning's[67−69] cc-pVXZ (XZ) basis sets, so that the value is close to that obtained from the augmented basis set series. The scaling factors were determined for four model complexes which are simplified representatives of a particular complex category, and for which the $\Delta E(MP2/CBS)$ term could be rigorously calculated in both nonaugmented and augmented basis sets. The four model complexes were created in accordance with the character of interaction of complexes in the data set: coronene···adenine (C2A) as a representative of C3A, C3CG, GCGC, and C2C2PD; guanine···guanine (GG) as a representative of GGG; and PHE and octane dimers (C8 dimer) as representatives of PHE trimer and CBH, respectively. The structures of the model complexes are shown in Figure 2 and
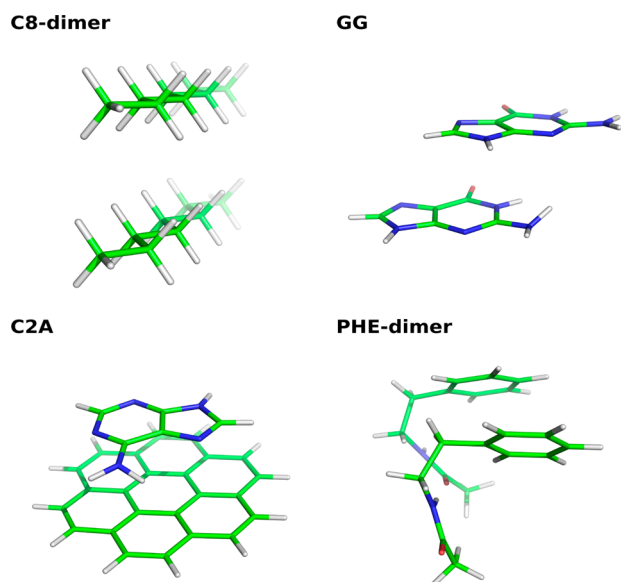
Figure 2. Structures of the four simplified (model) complexes.

the complete geometry is available in the Supporting Information. Two $\Delta E(MP2/CBS)$ values were calculated for each complex, obtained from two-point aDZ → aTZ and DZ → TZ extrapolation. To our surprise the scaling factors obtained vary only a little, from 1.01 for C8(CBH) to 1.05 for GG(GGG), thus an average value for the scaling coefficient could have been used as well. The values of other two scaling coefficients are 1.02 for C2A model complex and 1.03 for the PHE dimer. The $\Delta E(MP2/CBS)$ values are summarized in Table 1.

Higher-order correlation correction for the GCGC and C2C2PD complexes were calculated slightly differently than for the other systems, these numbers were taken from our previous publications (ref 52 and 53). The GCGC was calculated at the CCSD(T)/6-31G**(0.25,0.15) level.[52] The C2C2PD complex at QCISD(T) level with basis set augmented with diffuse functions (aug-cc-pVDZ) on every second carbon atom only,

Table 1. MP2/CBS Interaction Energies (in kcal/mol) of the Simplified (Model) Complexes (See Figure 2) Calculated Using Nonaugmented and Augmented Dunning's (aug-)cc-pVXZ, X = D, T, Basis Sets

complex/method	MP2[CBS] (DZ → TZ)[a]	MP2[CBS] (aDZ → aTZ)[a]	MP2[CBS] (aDZ → aTZ)/ MP2[CBS] (DZ → TZ)δ[b]
C2A	−20.51	−20.82	1.02
GG	−5.56	−5.86	1.05
PHE-dimer	−13.26	−13.67	1.03
C8-dimer	−4.73	−4.80	1.01

[a]Two-point cubic extrapolation according to eqs 3 and 4. [b]The average value of the scaling factor is 1.03.

the rest of carbon atoms together with hydrogen atoms were described with nonaugmented basis set (cc-VDZ).[53] These two levels provide results similar to QCISD(T)/6-31G*(0.25), which was used for the rest of the complexes. This statement is supported by an observation that QCISD(T) and CCSD(T) methods deliver practically identical results for the interaction energies for similar systems,[59] as well as by extensive benchmarking of the 6-31G**(0.25,0.15) and 6-31G*(0.25) basis sets.[62,64] It is less obvious that the aDZ basis performs similarly to the 6-31G*(0.25) basis. Nevertheless, for larger complexes the results match surprisingly well.[63] We did not recalculate these two complexes at QCISD(T) level used for remaining complexes, because of high similarity between QCISD(T) and CCSD(T) techniques.

The presented strategy of obtaining reference binding energy has some limitations that should be mentioned. First, it is the accuracy of the MP2/CBS energies. For such large molecular systems there is not much evidence how effective is the counterpoise correction and whether it should be used or not. Our tests suggest that the CP correction should be applied, for more details see Tables S5 and S6 in the Supporting Information material and the discussion therein. Second, the scaling of the resulting MP2/CBS values also brings some degree of uncertainty. Nevertheless, we are convinced that the scaling improves the result, and that it is a legitimate approach since (a) the scaling is based on similar model systems that differ only in size (typically one-half or two-thirds of the size of the original molecule from the L7 set, octane is used as a model for octadecane, guanine dimer for guanine trimer, coronene for circumcoronene, amyloid chain dimer for amyloid chain trimer) and (b) the procedure is done separately for each specific molecule from the set. Finally, the calculation of the correction term, where the relatively small 6-31G*(0.25) basis set is used, is another potential source of uncertainty, but we should bear in mind that use of bigger basis set would not be feasible for cluster of presented size and that this basis set has been proven to work well in smaller systems. We may speculate that the same basis set should, in principle, provide better description of larger systems. This opinion is based on the observation that large basis sets, which provide satisfactory description in small systems tend to become overcomplete and numerically unstable in larger systems. The same effect should diminish undercompleteness of small basis sets, when applied to large molecules.

Explicitly Correlated MP2-F12 Methods. The explicitly correlated RI-MP2-F12 calculations with cc-pVDZ and cc-pVTZ basis set were utilized to estimate error in scaled MP2/CBS values (see above). Because of computational complexity

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of these calculations along with extended size of the studied complexes explicitly correlated calculations were carried out only for GGG and GCGC complexes. The RI-MP2-F12/CBS values were obtained utilizing the Schwenke general type of extrapolation.[70]

MP2 and Scaled-MP2 Methods. MP2 along with its spin component scaled variants SCS-MP2 and SCS(MI)-MP2 were tested. The procedure for obtaining the MP2/CBS values is described in the previous paragraph. For calculation of the CBS value of the spin-component scaled MP2 methods, we refer to DiStasio et al.[14] The following scaling coefficients were used for the opposite-spin (os, "singlet") and same-spin (ss, "triplet") terms: SCS-MP2 $c_{os} = 1.20$, $c_{ss} = 0.33$; SCS(MI)-MP2 $c_{os} = 0.29$, $c_{ss} = 1.46$, regardless of the basis set.

Higher-Order Correlation Methods. The performance of several methods, which go beyond the MP2 level (marked as post-MP2): MP3, MP2.5, MP2.X, MP2C (not exactly a WFT method), and QCISD were investigated. The extrapolation procedure followed for these methods toward the CBS limit was the same as for the QCISD(T) benchmark, eq 1

$$\Delta E(\text{post-MP2/CBS})$$
$$= \Delta E(\text{MP2/CBS})' + \Delta(\text{post-MP2} - \text{MP2})|_{\text{small basis}} \quad (5)$$

To facilitate the discussion, we group the WFT methods into two categories: "non-empirical", QCISD, MP3, MP2C, and "empirical", MP2.5 and MP2.X.

Both QCISD and MP3 are traditional methods based on approximating the molecular wave function, while the MP2C method of Hesselmann[17,71] is slightly different. It combines time-dependent DFT with supramolecular MP2 energy, and therefore it cannot be correctly categorized as a nonempirical WFT method. However, it improves the MP2 results significantly with only a minor computational overhead, thus represents a promising strategy for noncovalent interaction calculations.[42,50]

The group of empirical methods includes methods with the inclusion of the third-order correlation contribution, MP2.X and MP2.5. The MP2.5 method, proposed by Pitoňák et al.,[72] takes advantage of the error cancellation between the MP2 (overestimation) and the MP3 (underestimation) binding energies.[11] The MP2.5 binding energy is obtained according to eq 6 (the "small size basis set" used in the correction term is consistent with reference QCISD(T) calculation for each complex):

$$\Delta E(\text{MP2.5/CBS}) = \Delta E(\text{MP2/CBS})'$$
$$+ c[\Delta E(\text{MP3}) - \Delta E(\text{MP2})]|_{\text{small basis}} \quad (6)$$

with $c = 0.5$. Riley et al.[30] optimized the parameter c for the S66 data set and different basis set. For large basis sets c converges to 0.5 and for extended basis it is almost exactly 0.5. The MP2.X method is analogous to MP2.5, however, the coefficient c is optimized for a specific basis set. Excellent stabilization energies were obtained already for 6-31G*(0.25) basis set with $c = 0.62$.[30]

DFT Methods. In this group, the following approaches have been investigated: (a) Grimme's[71] DFT-D3 using the BLYP/def2-QZVP, B3-LYP/def2-QZVP, TPSS/def2-QZVP, PW6B95/def2-QZVP, and M06-2X/def2-QZVP combinations of the functional and the basis set.[15] These methods were tested

with both the "zero" and the Becke–Johnson damping.[73−76] According to previous studies, these methods provide reasonably accurate description of dispersion interaction.[77] (b) Jurecka's DFT-D method with the TPSS/TZVP combination of the functional/basis set,[32] and (c) Truhlar's M06-2X functional with the def2-QZVP basis set.[33]

Semiempirical Quantum Chemical Methods. The PM6[36] based methods augmented with the empirical correction for the dispersion and the H-bonding interactions (PM6-D,[37] PM6-DH2,[78] and PM6-D3H4[38]) as well as the SCC-DFTB-D[79,80] method were investigated.

Computational Details. The DFT calculations (with the exception of M06-2X), and MP2 calculations were carried out using TURBOMOLE program package, versions 6.0, 6.1, and 6.4.[81] The single point calculations and gradient optimizations were done with a convergence threshold imposed on the change in energy between consecutive SCF iterations, and was set to 10^{-7} E_h; the geometry convergence criteria were unchanged from default values: energy change of 10^{-5} E_h and maximum gradient norm of 10^{-3} E_h/a_0. The integral neglect threshold was set by the program automatically: between 10^{-11} and 10^{-13} E_h and Turbomole grid m3 was used for all the calculations.

QCISD(T) calculations were done using the PQS program.[58] The integral neglect threshold was set to 10^{-15} E_h. The reason for such a tight threshold was to prevent any numerical problems resulting from possible linear dependencies in the basis set. The QCISD convergence criteria were set to 10^{-6} E_h for the maximum change in energy and the same threshold was imposed on the largest QCISD residuum element.

MP2C and RI-MP2-F12 calculations were performed using MOLPRO version 2009.[82] The integral neglect threshold was set to 10^{-12} E_h and 10^{-11} E_h for one-electron and two-electron integrals, respectively. The energy threshold and orbital threshold for the SCF procedure was set to 10^{-8} E_h. The maximum allowed eigenvalue of the overlap matrix was set to 10^{-8} E_h. The grid accuracy (per atom) in TDDFT part of MP2C calculation was set to 10^{-8} E_h. Density fitting approximation in MP2-F12 calculations (RI-MP2-F12) was done with cc-pVD(T)Z/JKFIT and cc-pVD(T)Z/MP2FIT basis sets and the following thresholds: neglect of contracted 3-index integrals in AO basis (10^{-10} E_h), neglect of half-transformed 3-index integrals (10^{-9} E_h), Schwarz screening threshold (10^{-5} E_h), neglect of 2-index integrals in AO basis (10^{-12} E_h), product screening threshold for first half trans-formation (10^{-9} E_h) and screening threshold for F12 integrals (10^{-8} E_h). Further, the 3C(FIX) *Ansatz* with geminal Slater exponent set to 1.0 were used.

MP3 calculations were performed using MOLCAS program package.[83] The Cholesky decomposition of two-electron integrals[84] was applied, with the integral threshold set to 10^{-5} E_h. The thresholds for the energy change, RMSD of the density matrix and RMSD of the Fock matrix were set to 10^{-5} E_h, 10^{-4} E_h, and 10^{-4} E_h, respectively.

The M06-2X calculations were carried out using Gaussian09[85] program package with the thresholds for the energy change and RMSD of the density matrix set to 10^{-5} and 10^{-7} E_h, respectively. The default grid with 75 radial shells and 302 angular points per shell was used in all the calculations.

PM6 calculations were carried out with MOPAC2009[86] program, the SCF convergence was set to 1.6×10^{-7} E_h. SCC-DFTB-D calculations were done via DFTB+[79,80] program, here

Table 2. Interaction Energies in kcal/mol of the Investigated Complexes at Different Levels of Theory[a]

method/basis set//complex	CBH	C2C2PD	C3A	C3GC	GCGC	GGG	PHE
QCISD(T)/CBS	−11.06	−24.36[b]	−18.19	−31.25	−14.37[c]	−2.40	−25.76
QCISD/CBS	−9.53	−	−14.52	−24.79	−	−1.30	−24.23
MP2.X/CBS	−10.63	−22.15	−15.52	−26.65	−12.26	−1.85	−25.24
MP2.5/CBS	−10.88	−22.80	−17.85	−30.40	−13.41	−2.34	−25.46
MP2C/CBS	−11.29	−20.88	−16.89	−28.71	−12.89	−2.22	−24.82
MP3/CBS	−9.84	−6.61	−8.15	−14.77	−8.61	−0.32	−24.56
MP2/CBS	−11.92	−38.98	−27.54	−46.02	−18.21	−4.36	−26.36
SCS(MI)-MP2/CBS[d]	−9.64	−31.71	−22.92	−37.92	−14.08	−2.23	−26.16
SCS-MP2/CBS[d]	−7.87	−27.53	−19.61	−32.07	−11.70	−1.79	−22.77
B3-LYP-D3/def2-QZVP[e]	−12.96	−23.22	−17.99	−31.29	−15.48	−2.10	−25.99
BLYP-D3/def2-QZVP[e]	−14.34	−22.82	−18.12	−31.79	−16.44	−2.48	−25.56
TPSS-D3/def2-QZVP[e]	−12.35	−21.19	−16.71	−28.58	−13.38	−1.87	−24.23
PW6B95-D3/def2-QZVP[e]	−10.01	−19.93	−16.63	−29.71	−12.48	−1.70	−24.07
M06−2X-D3/def2-QZVP[f]	−8.23	−20.55	−15.96	−29.00	−14.28	−1.71	−25.63
M06−2X/def2-QZVP	−4.71	−16.85	−12.88	−23.68	−11.59	−0.65	−23.38
TPSS-D/TZVP	−14.49	−18.69	−16.53	−27.78	−13.69	−2.19	−24.46
PM6-D3H4/SMB[g]	−9.64	−17.53	−16.01	−26.47	−19.87	−3.50	−25.43
PM6-DH2/SMB[g]	−9.96	−21.99	−18.04	−30.25	−22.55	−4.18	−24.91
PM6-D/SMB[g]	−9.96	−21.99	−18.04	−30.03	−20.99	−3.85	−22.80
SCC-DFTB-D/SMB[g]	−13.26	−18.7	−14.52	−24.41	−15.57	−1.08	−20.17

[a]The CBS limit is obtained according to eqs 1−6. [b]Correction term (cf., eq 2) was determined at QCISD(T) level using cc-pVDZ basis set for all atoms and the corresponding aug-cc-pVDZ basis set for every other, neighboring carbone atom. [c]Correction term (cf., eq 2) was determined at CCSD(T)/6-31G**(0.25,0.15) level of theory. [d]CBS limit calculated using cc-pVDZ and the cc-pVTZ basis sets. [e]Becke Johnson damping of the dispersion correction used. [f]Zero damping of the dispersion correction used. [g]SMB stands for "subminimal" basis set.

Table 3. Signed Errors (in kcal/mol) and the Respective Relative Values (in %) for the Investigated Complexes at Different Level of Theory[a]

method/bases//complex	CBH	C2C2PD	C3A	C3GC	GCGC	GGG	PHE
QCISD/CBS	1.53/13.8	−	3.67/20.2	6.46/20.7	−	1.10/45.9	1.53/5.9
MP2.X/CBS	0.43/3.9	2.20/9.1	2.67/14.7	4.61/14.7	2.11/14.7	0.54/22.7	0.52/2.0
MP2.5/CBS	0.18/1.6	1.56/6.4	0.34/1.9	0.86/2.7	0.96/6.7	0.06/2.5	0.30/1.2
MP2C/CBS	−0.24/−2.1	3.48/14.3	1.30/7.2	2.54/8.1	1.48/10.3	0.17/7.2	0.94/3.7
MP3/CBS	1.22/11.0	17.74/72.9	10.04/55.2	16.48/52.7	5.75/40.0	2.08/86.8	1.20/4.7
MP2/CBS	−0.86/−7.8	−14.63/−60.1	−9.35/−51.4	−14.77/−47.3	−3.84/−26.7	−1.96/−81.8	−0.60/−2.3
SCS(MI)-MP2/CBS[b]	1.41/12.8	−7.35/−30.2	−4.73/−26.0	−6.67/−21.4	0.29/2.0	0.16/6.8	−0.40/−1.6
SCS-MP2/CBS[b]	3.18/28.8	−3.17/−13.0	−1.42/−7.8	−0.82/−2.6	2.67/18.6	0.60/25.2	2.99/11.6
MP2/CBS[b]	−0.74/−6.7	−13.86/−56.9	−8.81/−48.4	−13.87/−44.4	−3.48/−24.2	−1.75/−73.1	0.17/0.7
B3-LYP-D3/def2-QZVP[c]	−1.90/−17.2	1.1/4.7	0.20/1.1	−0.03/−0.1	−1.1/−7.8	0.30/12.4	−0.23/−0.91
BLYP-D3/def2-QZVP[c]	−2.35/−21.3	−1.05/−4.3	−0.61/−3.3	−1.91/−6.1	−2.14/−14.9	−0.16/−6.8	0.80/3.1
TPSS-D3/def2-QZVP[c]	−1.29/−11.7	3.16/13.0	1.48/8.1	2.67/8.5	−0.99/−6.9	−0.53/−22.0	1.52/5.9
PW6B95-D3/def2-QZVP[c]	1.04/9.5	4.42/18.2	1.56/8.6	1.55/5.0	1.89/13.2	−0.70/−29.1	−1.68/−6.5
M06−2X-D3/def2-QZVP[d]	2.83/25.6	3.81/15.6	2.23/12.2	2.25/7.2	0.09/0.6	0.69/28.7	0.13/0.5
M06−2X/def2-QZVP	6.35/57.4	7.51/30.8	5.31/29.2	7.57/24.2	2.80/19.5	1.75/72.9	2.38/9.2
TPSS-D/TZVP	−3.43/−31.0	5.67/23.3	1.66/9.1	3.47/11.1	0.68/4.7	0.21/8.7	1.30/5.0
PM6-D3H4/SMB[e]	1.42/12.8	6.83/28.0	2.18/12.0	4.78/15.3	−5.50/−38.3	−1.10/−46.0	0.33/1.3
PM6-DH2/SMB[e]	1.10/9.9	2.37/9.7	0.15/0.8	1.00/3.2	−8.18/−57.0	−1.78/−74.4	0.85/3.3
PM6-D/SMB[e]	1.10/9.9	2.37/9.7	0.15/0.8	1.22/3.9	−6.62/−46.1	−1.45/−60.6	2.96/11.5
SCC-DFTB-D/SMB[e]	−2.20/−19.9	5.66/23.2	3.67/20.2	6.84/21.9	−1.20/−8.4	1.32/55.0	5.59/21.7

[a]Negative sign (−) indicates overestimation of the interaction energy. The CBS limit is obtained according to eqs 5−6. [b]CBS limit constructed using cc-pVDZ and cc-pVTZ basis sets. [c]Becke Johnson damping of the dispersion correction used. [d]Zero damping of the dispersion correction used. [e]SMB stands for "subminimal" basis set.

the threshold for self-consistent charge (SCC) procedure was set to 10^{-5} e.

All the calculations presented in this study, except for the semiempirical ones, were done using spherical basis functions, if not explicitly stated otherwise.

Error Analysis. The performance of the studied methods with respect to the benchmark results is measured by the following statistical indicators: root mean square deviation (RMSD), mean unsigned error (MUE), mean signed error (MSE), and maximum unsigned error (MAX). RMSD and MUE characterize the overall accuracy of a method. MSE provides information about systematic errors. MAX identifies the worst described entity and thus it measures the robustness of the method. The total binding energies for the noncovalent complexes investigated vary significantly, from 2 to 32 kcal/mol. Hence, the relative (percentage) values marked with prefix

"r", defined as $100 \times (\Delta E_{method} - \Delta E_{reference})/\Delta E_{reference}$ are more appropriate for the comparison across the whole data set.

■ RESULTS AND DISCUSSION

Table 1 summarizes the MP2/CBS interaction energies for four model complexes, obtained from extrapolating the augmented and nonaugmented cc-pVXZ, X = D, T basis sets to the basis set limit. The extrapolated values of stabilization energies follow the expectations that the former are larger than the later ones, thus leading to the scaling coefficients above one. The variation of the scaling coefficients, as already noted, is surprisingly small, in orders of only few percent (1−5%). This is most likely the consequence of the basis set saturation already at the nonaugmented level due to the extended size of the investigated complexes.

Interaction energies obtained at various levels of theory for all seven complexes are listed in Table 2. Signed errors and the corresponding relative values are shown separately in Table 3. Statistical quantities, that is, RMSD, MSE, MUE, and MAX for the tested methods are summarized in Table 4. In Figure 3, the

Table 4. Set of Statistical Measures (in kcal/mol) Calculated with Respect to the Reference (QCISD(T)/CBS) Data for the Investigated Complexes[a]

method/basis set//statis. measure	RMSD	MUE	MSE	MAX
QCISD/CBS[b]	3.50	2.86	2.86	6.46
MP2.X/CBS	2.34	1.87	1.87	4.61
MP2.5/CBS	0.79	0.61	0.61	1.56
MP2C/CBS	1.83	1.45	1.38	3.48
MP3/CBS	10.19	7.79	7.79	17.74
MP2/CBS	8.78	6.57	−6.57	14.77
SCS-MP2/CBS[c]	2.37	2.12	0.58	3.18
SCS(MI)-MP2/CBS[c]	4.20	3.00	−2.47	7.35
B3-LYP-D3/def2-QZVP[d]	0.95	0.70	−0.24	1.90
BLYP-D3/def2-QZVP[d]	1.60	1.39	−1.16	2.36
TPSS-D3/def2-QZVP[d]	1.87	1.66	−1.29	3.16
PW6D95-D3/def2-QZVP[d]	2.15	1.83	−1.83	4.42
M06−2X-D3/def2-QZVP[e]	2.17	1.72	1.72	3.81
M06−2X/def2-QZVP	5.33	4.81	4.81	7.57
TPSS-D/TZVP[f]	2.95	2.34	1.36	5.67
PM6-D3H4/SMB[g]	3.92	3.16	1.28	6.83
PM6-DH2/SMB[g]	3.35	2.20	−0.64	8.18
PM6-D/SMB[g]	3.00	2.27	0.04	6.62
SCC-DFTB-D/SMB[g]	4.33	3.78	2.81	6.84

[a]The CBS limit is obtained according to eqs 5 and 6. [b]Statistical measures are calculated only for five out of seven complexes (C2C2PD and GCGC complexes omitted). [c]CBS limit constructed using cc-pVDZ and cc-pVTZ basis sets. [d]Becke Johnson damping of the dispersion correction used. [e]Zero damping of the dispersion correction used. [f]Jurecka's dispersion correction. [g]SMB stands for "subminimal" basis set.

relative signed errors for the best performing method within the specific subgroup (for more details see Error Analysis section) are visualized, while Figure 4 depicts the relative RMSD for all methods.

Only the results obtained using the largest basis set for a particular complex and theoretical method are discussed below, separately for each group of methods. To emphasize the effect of large cluster size, presented data are compared to results obtained for the S66 data set which contains smaller systems.
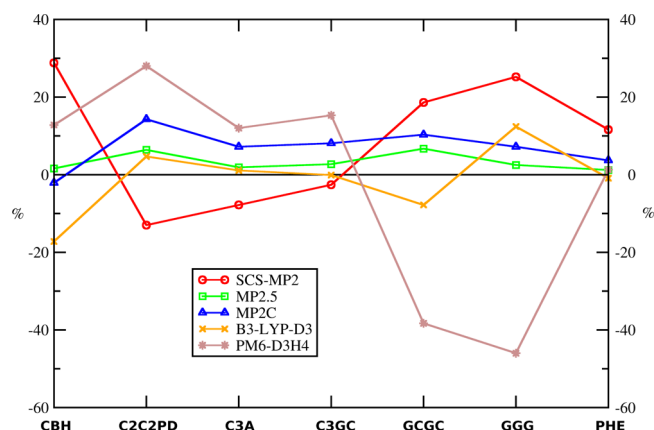

Figure 3. Relative signed errors (in %) of SCS-MP2, MP2.5, MP2C, BLYP-D3 (Becke−Johnson damping), and PM6-D3H4 methods for the investigated complexes. Negative sign (−) indicates overestimation of the interaction energy. Methods listed are the best performing methods within each category of methods: (a) post-HF wave function theory (WFT) methods containing empirical parameters (SCS-MP2, MP2.5, MP2C), (b) DFT based methods with added dispersion terms (BLYP-D3 (Becke-Johnson damping)), and (c) semiempirical quantum mechanical methods augmented with empirical corrections for noncovalent interactions (PM6-D3H4).
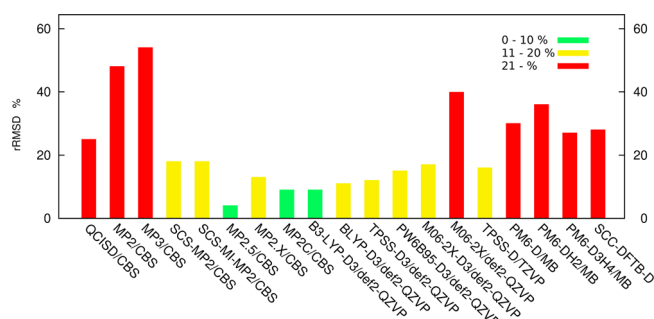

Figure 4. Relative RMSD (rRMSD in %) with respect to the reference (QCISD(T)/CBS) for the investigated methods.

QCISD. Comparison of the QCISD values (Table 2) with the reference QCISD(T) data (provided only for 5 complexes, see QCISD(T)/CBS as the Reference section) confirms the well-known fact that the contribution of the triples is substantial. The RMSD and rRMSD values are rather large, 3.5 kcal/mol and 25%, respectively (cf., Table 4 and Figure 4). For the C3GC complex, the error even exceeded 6 kcal/mol (20%) (cf., Table 3).

MP2. The accuracy of the MP2 method, documented by RMSD value of 8.8 kcal/mol, is poor (cf., Table 4). This is a consequence of the data set being dominated by $\pi\cdots\pi$ stacked interactions. The span of relative errors for $\pi\cdots\pi$ dispersion dominated complexes is large 27−82% (see Table 3). However, signed errors of −0.9 kcal/mol (8%) for the CBH complex and −0.6 kcal/mol (2%) for the PHE trimer (cf., Table 3) confirms that MP2 properly describes the aliphatic dispersion and hydrogen bonding.[7,32]

The explicitly correlated RI-MP2-F12 calculations with cc-pVDZ and cc-pVTZ basis set were utilized in order to estimate error in scaled MP2/CBS values (cf. Methods; for more information see Table S6 in the Supporting Information material). The absolute (relative) underestimation of scaled MP2/CBS stabilization energy with respect to RI-MP2-F12/

CBS values is 0.39 (9%) and 1.57 (9%) kcal/mol for GGG and GCGC complexes, respectively. On the basis of these values, we can estimate the relative error in scaled MP2/CBS values.

Scaled MP2. Empirically scaling the spin components in MP2 improves the description of noncovalent interactions,[12] particularly for π stacking. Our RMSD and relative RMSD values for MP2, SCS-MP2, and SCS(MI)-MP2[52] are 8.8 (48%), 2.4 (18%), and 4.2 (18%), respectively (cf., Table 4 and Figure 4). However, the performance for some dispersion dominated complexes is still inadequate, for example, the signed error for C2C2PD at the SCS(MI)-MP2 level is −7.4 kcal/mol (−30%) (cf. Table 3). According to the results in Table 4, SCS(MI)-MP2 performs worse than the original SCS-MP2. This is surprising, considering that SCS(MI)-MP2 was, unlike SCS-MP2, parametrized toward the best performance on interaction energies. Comparing the performance of both methods for dispersion dominated complexes in the S66 set, the opposite conclusion in obtained. The relative RMSD of SCS(MI)-MP2 and SCS-MP2 are 18% and 26%, respectively,[42] which indicates that the size of the investigated molecular cluster has a significant effect. SCS-MP2 underestimates the bonding between aliphatic species.[87,51] The relative error, roughly 30% for the aliphatic CBH complex, is among the largest from all the methods within the group (cf., Table 3 and Figure 3) confirms this observation.

MP3, MP2.5, MP2.X, and MP2C. The performance of the plain MP3 method is poor, perhaps comparable with MP2 in the RMSD, MUE, and MAX values (cf. Table 4). Typical feature of the MP3 method is underestimation of the aromatic dispersion interaction (MSE about 7.8 kcal/mol, cf. Table 4), contrary to MP2 (MSE about −6.6 kcal/mol, cf. Table 4). However, both MP2 and MP3 describe hydrogen bonded complexes very well. The error cancellation between MP2 and MP3 is responsible for substantially higher accuracy of MP2.5, with RMSD of only about 0.8 kcal/mol (4%, cf. Table 4 and Figure 4). A statistical evaluation of the MP2.X performance gives 2.3, 1.9, and 4.6 kcal/mol and 13% for RMSD, MUE, MAX, and rRMSD, respectively (cf. Table 4), which is quite good. MP2.X outperforms both scaled-MP2 variants. However, its performance is worse than MP2.5, in spite of the optimization of the mixing parameter (cf. Table 3 and 4). This is most likely a consequence of parametrization toward substantially smaller molecular clusters in the S66 data set.

The MP2C method shows a real improvement over MP2. In terms of the relative errors, it is the second best performer among the WFT methods evaluated in this work with an rRMSD of about 8% (1.8 kcal/mol, cf. Table 4 and Figure 4) and an rMAX of 14% (3.5 kcal/mol) (for the coronene dimer, cf. Table 3 and 4).

DFT Methods. The performance of the group of functionals augmented with the Grimme's D3 correction utilizing the Becke-Johnson (B-J) damping is better in comparison with the Zero damping (cf., Table S1−S4 in Supporting Information). These results are consistent with findings of Grimme, where the use of the DFT-D3 methods with B−J damping yield better results for most of the functionals.[77] Hence, in this paper, we will discuss almost exclusively DFT-D3 methods using B-J damping procedure. The M06-2X-D3 method will be discussed in combination with Zero damping, because there are no B−J damping parameters for the D3 correction. The best performing functional is the B3-LYP followed by the BLYP, TPSS, PW6B95, and M06-2X. Corresponding RMSD in kcal/mol (rRMSD in %) are 1.0 (9), 1.6 (11), 1.9 (12), 2.2 (15), and 2.2

(17), cf. Table 4 and Figure 4. The performance of the PW6B95 and the M06−2X are almost equivalent (cf. Table 4). In Grimme's study, where different DFT functional were tested against the S66 data set, the best performing functional for the dispersion bounded subset was B3-LYP.[77] This is consistent with our findings. The relative ordering of other functionals in this paper is different compared to Grimme's study.[77] However, the absolute differences in performance of functionals are, in both studies, of order of tenths of kcal/mol. Hence, any definitive conclusions about the general performance based on these results would be questionable.

The M06-2X method in combination with zero damping form of the D3 correction leads to the RMSD value of 2.2 kcal/mol (17%) as already mentioned. The plain M06-2X functional provides substantially larger value of the RMSD 5.3 kcal/mol or 40% (cf. Table 4). All the statistical indicators are reduced, two to three times, after applying D3 correction (cf. Table 4). This result serves as the proof that functionals which were fitted to reproduce dispersion near van der Waals minimum (for example M06-2X) are not able to cover long-range dispersion interaction. This feature was already demonstrated by Grimme.[77]

On the basis of the findings from Grimme's study, the double-hybrid functionals should provide even better performance than the B3-LYP.[88] Moreover, it was shown that double-hybrids as DSD-BLYP-D3 or PWPB95-D3 outperform scaled variants of MP2 such as SCS-MP2, S2-MP2, and SOS-MP2 methods.[88] However, we should bear in mind that the computational complexity of the double-hybrids is higher when compared with other groups of functionals. Methods involving double-hybrid functionals include nonlocal perturbation correction for the correlation part; hence their scaling is equivalent to the regular MP2 method.

The magnitude of the many-body nonadditivity term is by an order of magnitude smaller than the interaction energies.[52,89] It is believed that the three-body (Axilrod−Teller−Mutto) correction term is non-negligible for extended molecular systems.[19,49] When it is implemented as described in ref 19 and is added to the Becke−Johnson and zero-damped dispersion, it weakens the interaction. Because it is not known much about the 3-body correction and its impact on the accuracy of a method, the results are only listed in Supporting Information (cf., Table S1−S4), without any further discussion. In general the accuracy of the DFT-D3 methods after applying the 3-body correction deteriorates. The only exception is the BLYP functional in combination with B-J damping. The RMSD is reduced from 1.6 kcal/mol (11%) to 1.1 kcal/mol (9%), cf., Table S4 in Supporting Information. The same correction, when added to the zero-damped results, raises the overall error to 2.0 kcal/mol (12%), cf., Table S4 in Supporting Information. . In Grimme's study,[49] it was shown that the three-body correction is not negligible, and it correlates positively with the size of a molecule. In the S12L set, this effect varies between 2% and 15% of the total stabilization energy. Moreover, the inclusion of three-body correction in the DFT values of binding energies at quadruple-ζ level improves the overall performance of the investigated methods even in smaller systems (for more details see ref 49.).

The TPSS-D/TZVP method of Jurečka et al.[32] performs slightly worse than tested density functionals with D3 correction but clearly better than the M06−2X/def2-QZVP method of Zhao and Truhlar, with RMSD of 3.0 kcal/mol (16%) and 5.3 kcal/mol (40%) (cf. Table 4 and Figure 4),

respectively. The direct comparison of the TPSS-D/TZVP with the TPSS-D3/def2-QZVP reveals that the latter method is slightly more accurate. However, this comparison is not completely fair because of the unequal quality of the used basis sets. The def2-QZVP basis set is of better quality than TZVP which could be the reason for the higher accuracy. The TPSS-D/TZVP combination of the functional and the basis set was chosen as the best feasible. The use of the TPSS-D/6-311++G(3df,3pd) method, which should provide best results for dispersion bounded complexes,[32] was not possible, due to problems with linear dependences in the basis set in the case of the coronene dimer and circumcoronene. This issue is discussed in the Interaction Energy Calculation subsection.

DFT methods describe H-bonding (or electrostatic dominated interactions in general) fairly well (see Table 3 and Figure 3), and empirically corrected DFT-D and DFT-D3 methods share a similar feature. Signed errors for the H-bonded PHE complex (ranging from 0.2 to 2.4 kcal/mol, that is, 1−9%, cf., Table 3) are significantly lower than for other complexes. Dispersion dominated interactions are described less accurately. The largest signed errors of Grimme's (DFT-D3) methods are: 4.4 kcal/mol (18%) in the case of C2C2PD complex for PW6D95 functional and −2.1 kcal/mol (8%) in the case of GCGC complex for BLYP functional (see Table 3). The latter one is the largest negative error for all DFT methods considered here. Aliphatic dispersion, for instance in the CBH complex, is even worse: the signed errors range from −1.3 kcal/mol up to 6.4 kcal/mol (see Table 3).

Semiempirical Methods. The PM6 method,[36] corrected for dispersion[37] (PM6-D) gives an RMSD of 3.0 kcal/mol, see Table 4. Correction for hydrogen bonding[38,78] (PM6-DH2, PM6-D3H4) does not, however, increase of accuracy further (RMSD of 3.4 and 3.9 kcal/mol, respectively) (cf., Table 4). The correction for hydrogen bonding is most likely the source of undesirable errors, and it is responsible for slightly worse correlation with the benchmark data for complexes stabilized by dispersion interaction. On the other hand, errors decrease significantly for the PHE complex upon inclusion of the hydrogen bonding correction: the signed error drops from 3.0 (PM6-D) to 0.9 (PM6-DH2) and 0.3 (PM6-D3H4) kcal/mol, respectively (cf., Table 3). The SCC-DFTB-D method[79,80] is comparable with that of PM6-D3H4 (cf., Table 4). In terms of relative RMSD, the ordering of the semiempirical methods we tested is the following: SCC-DFTB-D and PM6-D3H4, roughly equal, are the most accurate, followed by PM6-D and PM6-DH2 (cf., Figure 4). The rRMSD and rMAX values vary between 26−36% and 46−74%, respectively (cf., Table 4). Nevertheless, the absolute errors of the semiempirical methods are comparable with some of more sophisticated methods such as M06-2X/def2-QZVP, MP2/CBS, MP3/CBS, or SCS(MI)-MP2 (see Table 4).

CONCLUSIONS

Seven extended molecular complexes, stabilized mostly by dispersion interaction, were investigated with a number of modern quantum chemical methods. This set of molecules, called the L7 set, includes the octadecane dimer, the circumcoronene···adenine dimer, the circumcoronene···guanine−cytosine dimer, the coronene dimer, the guanine−cytosine dimer, the guanine trimer, and a trimer of amyloid residues containing phenylalanine. These complexes are representative of dispersion-dominated supramolecular associations in biological systems, although a few systems have also

significant hydrogen bonding. The methods include wave function-based, density functional based and semiempirical methods, spanning a wide range of accuracy and computational cost. We have included both fully nonempirical wave function methods, such as MP2, MP3, and QCISD, and methods which contain adjustable parameters. The parametrized methods perform in general better, justifying their use for larger molecular clusters. The performance of the methods was evaluated by comparing them to high-level QCISD(T) (and CCSD(T)) results. These benchmark results, along with the geometries of the L7 complexes, are available online in the BEGDB database (www.begdb.com).

The results of this large-molecule test set differ from earlier results for smaller complexes, most likely because the large molecule test set emphasizes longer-range interactions. The best method in this study in absolute performance is MP2.5, delivering binding energies with an average error of 4% relative to QCISD(T). The performance of the MP2.X method, parametrized toward noncovalent interactions, is surprisingly slightly worse. MP2C provides fairly accurate results, with an average relative error of 8%. It has a clear computational advantage over the MP2.5 by being an order of magnitude faster. The SCS-MP2 and SCS-(MI)-MP2 methods are rather disappointing, although they perform better for this test set than for the S66 data set of medium-sized noncovalent complexes. SCS-MP2 does not resolve fully the overbinding of MP2 for π stacking, while it underestimates dispersion between σ systems.

Among density functional based methods, DFT-D3 is clearly superior to other approaches tested in this work. It represents the best trade-off between the accuracy and computational cost and, at an average relative error of only 11%, it outperforms some more sophisticated methods, such as SCS(MI)-MP2 or M06-2X.

The accuracy of the semiempirical quantum mechanical methods, with empirical corrections for dispersion or hydrogen bonding is less satisfactory. The best are SCC-DFTB-D and PM6-D3H4, and their relative standard deviation exceeds 25%. Nevertheless, the performance of these methods is not much worse than that of dramatically more expensive ones, such as M06-2X, MP2, or SCS(MI)-MP2, and thus their price/performance ratio is excellent.

ASSOCIATED CONTENT

ⓢ Supporting Information
Detailed DFT-D3 results for presented complexes together with their full geometry information are provided. This material is available free of charge via Internet at http://pubs.acs.org/.

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Notes
The authors declare no competing financial interest.

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