

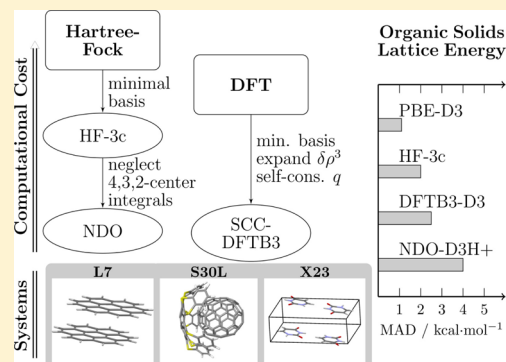
Low-Cost Quantum Chemical Methods for Noncovalent Interactions

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S Supporting Information

ABSTRACT: The efficient and reasonably accurate description of non-covalent interactions is important for various areas of chemistry, ranging from supramolecular host–guest complexes and biomolecular applications to the challenging task of crystal structure prediction. While London dispersion inclusive density functional theory (DFT-D) can be applied, faster “low-cost” methods are required for large-scale applications. In this Perspective, we present the state-of-the-art of minimal basis set, semiempirical molecular-orbital-based methods. Various levels of approximations are discussed based either on canonical Hartree–Fock or on semilocal density functionals. The performance for intermolecular interactions is examined on various small to large molecular complexes and organic solids covering many different chemical groups and interaction types. We put the accuracy of low-cost methods into perspective by comparing with first-principle density functional theory results. The mean unsigned deviations of binding energies from reference data are typically 10–30%, which is only two times larger than those of DFT-D. In particular, for neutral or moderately polar systems, many of the tested methods perform very well, while at the same time, computational savings of up to 2 orders of magnitude can be achieved.



The description of noncovalent interactions (NCIs) has gained increasing importance in quantum chemistry in the past decade.^{1–3} Although NCIs, such as hydrogen bonding, π – π stacking, and van der Waals interactions, are typically an order of magnitude weaker than covalent bonds, they play an important role in various domains of chemistry and biology. For instance, the structure of biomacromolecules like DNA, RNA, and proteins, molecular recognition processes, and crystal packing are dominated by NCIs.^{4–6} In this context, the prediction of organic crystal structures is a very active research field.^{7–9}

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The development of new or improved methods for the description of NCIs is driven by a compromise between efficiency and routine applicability for large molecular and crystalline systems on the one hand and the necessity to keep a certain accuracy level on the other. Concerning the latter point, one should further distinguish between absolute accuracy for basic properties (binding or lattice energies, equilibrium

structures) and relative energies (conformational energies, affinity trends, polymorphism). In Figure 1, we give a general classification of the different theoretical levels. One typically distinguishes between ab initio wave function theory, first-principles density functional theory (DFT), semiempirical molecular orbital (MO)-based methods, and classical methods that do not treat electrons explicitly (atomistic and coarse-grained force fields and continuum mechanics). Depending on

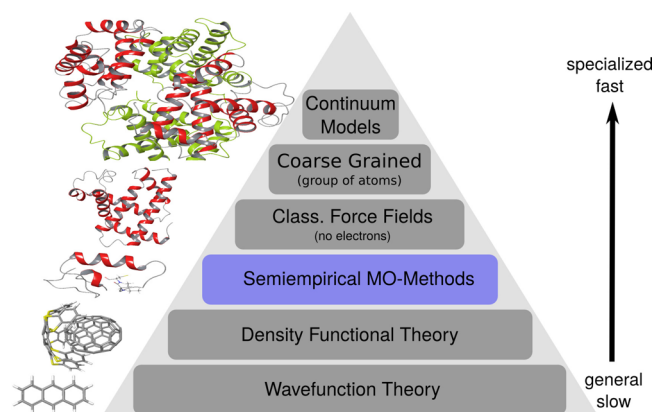


Figure 1. Classification of “quantum” chemical methods according to their computational cost and generality.

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the system size and the available computational resources, one has to choose an appropriate method for the desired application. While wave function theory is rather general, it is inapplicable to many interesting systems due to the huge computational cost, although some steps into the “100 atom regime” have been made recently.¹⁰ DFT can routinely describe and optimize larger systems of up to 10^3 atoms. When the electronic structure is still of importance and DFT is too expensive, “low-cost” methods like various semiempirical MO schemes¹¹ represent a viable alternative. At this level, huge systems (up to approximately 10^3 – 10^4 atoms) can be treated routinely in a reasonable time, allowing, for example, a high-throughput screening of different polymorphs.^{12,13}

The description of NCIs involves different levels of complexity. Electrostatic (ES), induction (IND), Pauli exchange repulsion (EXR), and London dispersion (DISP) interactions have to be treated accurately. Following the above classification, high-level, electron correlation including wave function theory like CCSD(T) seamlessly covers all interactions. In DFT, electron correlation is typically expressed in a local framework. Because DISP is a nonlocal, long-range electron correlation effect, standard DFT approximations cannot describe it properly.^{14–16} The same holds for the (mean field) Hartree–Fock (HF) approach, which lacks all Coulomb correlation effects. Significant progress has been made in recent years to solve the dispersion problem. Various approaches providing very good accuracy are available and are becoming now the standard in the field.^{17–21} For overviews on these dispersion-corrected, so-called London dispersion inclusive density functional theory (DFT-D) methods, see, for example, refs 22–24. The semiempirical MO methods are approximations to DFT or HF. As such, the above-mentioned dispersion problem is also present with the same rather general solution.²⁵ However, the semiempirical integral and basis set approximations lead to further errors in ES, IND, and EXR terms. The repulsion term is typically repaired by empirical, element-specific pair potentials. The poor description of ES and IND interactions, leading for instance to a bad description of hydrogen bonds, is another well-known problem in all semiempirical methods.^{26–28} In this field, geometry-dependent hydrogen bond corrections became popular.^{29,30}

Two general classes of semiempirical approaches exist in the literature. They have in common that minimal AO basis sets are used to expand the MOs, which is a prerequisite for computationally efficient methods. One can start from a Kohn–Sham DFT total energy expression and expand it with respect to charge density fluctuations. The resulting density functional tight-binding (DFTB) Hamiltonian was actively developed by the groups of Frauenheim, Elstner, and Seifert.^{31–33} Recently, we coupled the third-order variant of the DFTB Hamiltonian to the D3 DISP correction and showed its good performance for noncovalent complexes and crystals.³⁴

Another starting point is the HF approach. We combined it in a small (MINIX) Gaussian basis set with the D3 dispersion model and two basis set corrections. This method (denoted as HF-3c) showed stable and good performance for molecular complexes and also for organic solids.³⁵ For larger speedups, three- and four-center two-electron integrals have to be neglected in the HF formalism, as realized in the so-called neglect-of-differential-overlap (NDO)-type semiempirical methods.¹¹ This is done with slightly different strategies in the OMx, PMx, or MSINDO methods.^{36–38} To correct the

arising errors, adjusted one-electron contributions and element-specific pair potentials are introduced.

In the present Perspective, the presentation of the vast field of low-cost quantum chemical methods cannot be complete. Nevertheless, we try to give a comprehensive view on the available minimal basis set MO methods and highlight both success and some failures. Fragmentation and similar methods that are applied to the system of interest are not considered here. We first give an overview on the different general strategies and then try to validate the methods on various standard benchmarks. The focus is on the computation of absolute interaction energies. Improving the performance for those more or less automatically makes relative energies better. However, the performance for NCI is not necessarily correlated to those for other properties like molecular structures or chemical reaction energies, which should be kept in mind when general conclusions are made.

Covered Methods. A classification of different semiempirical methods is sketched in Figure 2 and will be discussed in the

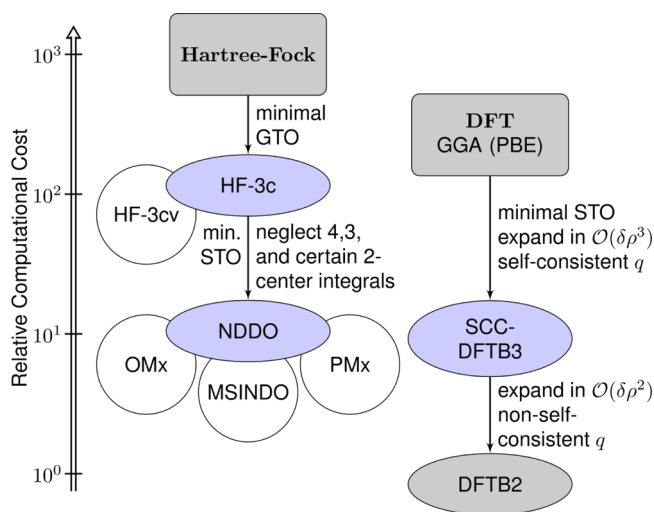


Figure 2. Classification of low-cost, minimal basis set based quantum chemical methods according to their specific approximations.

following subsections. The computational cost decreases in the order DFT/“CBS” > HF-3c > HF-3cv > NDDO \approx SCC-DFTB3 > DFTB2. On standard workstations and for typical applications, the HF-3c single-point calculation is a factor of about 10–15 faster than the DFT computation near the basis set limit (“CBS”). HF-3cv gains a factor of 40–50 compared to DFT/“CBS”, and both NDDO and SCC-DFTB3 are even a factor of 100–1000 faster. The non-self-consistent DFTB2 method reduces the timings by an additional factor of 5–10.

HF-3c. HF lacks the chemically important Coulomb correlation effects but has several advantages. It is, by construction, (one-electron) self-interaction error free, analytical, and naturally includes reasonably accurate density response leading to correct ES and IND interactions. The EXR effects, which together with the ES describe the repulsive behavior of the potential at short interatomic distances, are treated correct to first-order in HF. The clear downside is that very many two-electron repulsion integrals have to be computed. The simplest way to speed up a HF computation is by reducing the one-particle basis set. This introduces errors, which are corrected in the HF-3c^{35,39} (and HF-3cv; see below) methods by two additional (D3 dispersion is already included)

physically plausible atom pairwise correction terms. For correcting the basis set superposition error (BSSE), the geometrical counterpoise correction (gCP) scheme^{40,41} is used, and in order to account for short-ranged basis set incompleteness (SRB) effects, another correction is added

$$E_{\text{HF-3c(v)}} = E_{\text{HF}} + E_{\text{D3}} + E_{\text{gCP}} + E_{\text{SRB}} \quad (1)$$

In the gCP scheme, the Boys–Bernardi counterpoise correction is mapped onto a semiempirical, repulsive pair potential, which decays exponentially with the interatomic distance. Due to the small size of the basis set, bond lengths of electronegative elements in molecular structures are systematically too long. We correct this with a short-ranged basis set correction (SRB). In total, HF-3c has nine global empirical parameters, which is comparable to common density functionals.

In order to demonstrate how far one can push this approach, we developed a “valence variant” denoted HF-3cv. Here, the core electrons of all elements are implicitly described by the standard Stuttgart–Dresden (relativistic) effective core potentials.^{42,43} The HF equations of the valence electrons are evaluated in a minimal basis with only two Gaussian functions per shell. This leads to an additional speedup compared to HF-3c by about 2–4 in typical applications. In this context, the SRB has to be slightly modified, and element-dependent potentials are introduced. The method is parametrized for all elements H–Rn with 11 global and 1 element-specific parameters. In the progress of this work, the HF-3c method (together with HF-3cv) has been implemented into the CRYSTAL14 software package and will be available in its next release (details can be found in the Supporting Information (SI)).

NDO Approximations. Neglect of differential overlap (NDO) methods are typically based on HF evaluated in a minimal basis of Slater-type orbitals (STOs). A significant speedup compared to, for example, HF-3c is achieved by neglecting many-center two-electron integrals. This rather broad method family was pioneered by Pople, Zerner, Dewar, and Thiel.^{44–46} Different strategies in the integral neglect, such as neglect of diatomic differential overlap (NDDO) and intermediate NDO (INDO), leads to the various variants like MNDO, OMx, PMx, and MSINDO.^{36,46–48}

The arising errors are corrected by adjusted one-electron contributions and element-specific pair potentials. Because some of those NDDO methods are expanded in an orthogonalized AO basis and hence solve a special eigenvalue problem (opposed to DFTB, which solves the “right” problem including overlap), EXR effects are incompletely accounted for. Special-empirical (two-body) potentials are designed to repair this in MNDO and PMx. In OMx^{36,49} and MSINDO,^{38,48} explicit orthogonalization corrections are included.

The NDO methods are empirically parametrized on theoretical or experimental reference data. The possible strategies are nicely outlined by Stewart in his latest variant (PM7⁵⁰). One focus of the latter method is the inclusion of noncovalent complexes in the fit set. However, as shown here, this does not automatically lead to a more consistent description of these systems. While OM2 parameters only exist for the first- and second-row elements, PM6/7 and MSINDO are more extensively parametrized for larger parts of the periodic table.

While in principle all methods can be used in a Γ -point approach for periodic systems, only MSINDO has an easy usable periodic implementation. The periodicity is accounted for in the real-space cyclic cluster model (CCM).⁵¹

DFTB. DFT has several advantages over HF, and it is reasonable to develop approximations to a certain density functional in a minimal STO basis. An expansion of the total DFT energy in charge density fluctuations to second order $O(\delta\rho^2)$ results in a standard tight-binding model. The most widespread variant is the DFTB Hamiltonian of Frauenheim, Seifert, and Elstner derived from the PBE density functional.⁵² This Hamiltonian consists of contributions from the free atoms, precalculated kinetic energy integrals, and atom pair potentials. These pair potentials have to be precomputed for all element combinations.

More recent developments take into account third-order density fluctuations. Additionally, a self-consistent charge redistribution (SCC) is introduced by coupling of the atomic charges to the Hubbard derivatives (chemical hardness).^{53,54} The long-range limit from the nuclei is a pure Coulomb potential, while at short range, it resembles an on-site repulsion. The set of coupled equations is solved self-consistently. This leads to computational costs comparable to those of the NDO methods. Up to this point, exclusively precomputed data were used. However, the description of hydrogen bonds is poor, and an additional damping of all hydrogen-containing pair potentials with an empirical exponent is introduced. This SCC-DFTB3 (and XH damping) will be abbreviated as DFTB3 in the following. Periodic boundary conditions are available with a standard k -space sampling and the corresponding solution of the Bloch equations.

DISP Interaction. Being approximations to HF and semilocal DFT, respectively, all of the above methods cannot describe long-range electron correlation effects. The DISP interaction (also referred to as the attractive part of the van der Waals interaction) is of utmost importance for extended systems. In principle, several DISP corrections can be applied. For instance the exchange-dipole model XDM,¹⁸ the Tkatchenko–Scheffler model TS,¹⁹ the many-body dispersion (MBD) model,²⁰ and the nonlocal DFT kernel VV10²¹ all provide reasonable accuracies. However, here we focus on intrinsically fast electronic structure methods, where the computationally least-demanding D3 approach is probably the best choice. Further, the mentioned methods depend explicitly on the electron density, which is typically not very accurate in a minimal basis set representation. Because of these reasons, the D3 correction is very prominent in the low-cost field of quantum chemistry and is a reasonable choice for methods that employ a minimal basis. Except for PM7, all of the tested method use the D3 scheme.

The DISP energy between two fragments can be calculated in the large distance limit as a frequency integral over their dynamic polarizabilities.

$$E_{\text{disp}}^{\alpha\beta}(r_{\alpha\beta} \gg 1) = \frac{3}{\pi} \int_0^\infty \alpha^\alpha(i\omega) \alpha^\beta(i\omega) d\omega \times \frac{1}{r_{\alpha\beta}^6} \quad (2)$$

This is known as Casimir–Polder relation.⁵⁵ In the standard D3 DISP correction, this is mapped on an atom-pairwise scheme

$$E_{\text{D3}} = -\frac{1}{2} \sum_{n=6,8} \sum_{\alpha,\beta} s_n \frac{C_n^{\alpha\beta}}{\|\mathbf{r}_{\alpha\beta}\|^n + f(R_0^{\alpha\beta})^n} \quad (3)$$

where $C_{6/8}^{\alpha\beta}$ are the leading order dipole–dipole and dipole–quadrupole dispersion coefficients, respectively, and $r_{\alpha\beta}$ is the distance between the atom pair α, β .¹⁷ The s_6 scaling coefficient is set to unity to ensure the correct long-range behavior. The

Becke–Johnson⁵⁶ rational damping function $f(R_0^{ab})$ is used to match the long- and medium-range dispersion contributions from D3 with the basic electronic potential.⁵⁷ The C_6 dispersion coefficients depend geometrically on the molecular environment and are precalculated by time-dependent DFT utilizing the Casimir–Polder relation. A nonadditive Axilrod–Teller–Muto three-body dispersion (ATM-3B) is also available. The corresponding C_9 coefficients are approximated as averages from the C_6 coefficients. Similar to the two-body term, the ATM-3B contribution is evaluated in an atom-*tripletwise* scheme.

The good performance for small systems is certainly “good news” but an insufficient condition to be applicable to much larger complexes or solids, which are the “true” target for such low-cost methods.

Current research is dedicated to analyze the importance of dispersion contributions beyond the pairwise model. Tkatchenko and co-workers significantly contributed to this field, which is reviewed in ref 58. However, the importance of these contributions (competing with higher multipole or anisotropy effects) is still an active debate.^{59,60} According to our experience, three-body dispersion is in fact important for binding energies of extended systems. For instance, the ATM-3B contribution to the lattice energy of typical organic solids is 2–7%, while its effect on structure is negligible.^{39,61} Because the impact on the final energy can be significant and improves the results of nearly all tested methods, the three-body contribution is included in the single-point energy of all large systems (L7, S30L, X23). The influence for the small molecule test sets (S22, S66x8, X40, WATER14) is negligible. The ATM-3B term is the same for all tested methods and not adjusted empirically.

Hydrogen-Bonding Correction. As mentioned in the introduction, the neglect of two-electron integrals and the applied minimal basis set in both the NDO and DFTB methods leads to a bad description of ES and IND effects. This is most important in hydrogen-bonded systems where the binding is

typically underestimated. This can be partially cured in DFTB by introducing an additional damping of certain pair potentials. In the NDO-based methods, explicit geometry-dependent hydrogen-bonding corrections are commonly used together with D3 in an additive scheme

$$E_{\text{NDO-D3H+}} = E_{\text{NDO}} + E_{\text{D3}} + E_{\text{H+}} \quad (4)$$

where E_{NDO} is the uncorrected SCF energy. Korth has developed a series of slightly different corrections; the final version is dubbed D3H+.²⁹ The geometric arrangement of acceptor, donor, and hydrogen atoms is used to calculate the hydrogen bond energy

$$E_{\text{H+}} = \frac{C_{\text{AD}}}{r_{\text{AD}}^2} f_{\text{AHD}} f_{\text{damp}} \quad (5)$$

with the hydrogen-bonding strength parameter C_{AD} as the arithmetic mean of the empirical acceptor and donor parameters C_{A} and C_{D} and their distance r_{AD} . The other terms are the angle-dependent and damping functions f_{AHD} and f_{damp} , respectively. Within this work, the D3H+ correction was implemented in the CCM model of MSINDO. A slightly modified version was recently published by Hobza to ensure smooth energy surfaces and a more consistent repulsive potential.³⁰ This method in combination with PM6, D3, and a halogen bond correction, dubbed PM6-D3H4X, showed most promising results.⁶² Results with older variants of both dispersion correction and hydrogen-bonding corrections have been analyzed in the past. Also, some additional variants of the here-presented semiempirical methods, namely, OM3, AM1, and SCC-DFTB2, are covered.²²

Technical Setup. The HF-3c(v) calculations are conducted with a developer version of CRYSTAL14.⁶³ The MSINDO-D3H+ results are obtained with the MSINDO program version 3.7. Tight SCF convergence thresholds ($\Delta E < 10^{-8}$ Eh), geometry convergence (maximum nuclear gradient $< 10^{-4}$ au), and integral neglect thresholds were applied. Some organic crystals with convergence problems are disregarded in the statistics (see the SI). All individual binding energies are given in the SI. To put these values into perspective, we compare with other well-established semiempirical methods and the PBE density functional⁶⁴ evaluated in the estimated complete basis set limit (CBS). The PM6, PM7, OM2, and DFTB energies are calculated with the MOPAC2012, MNDO2005, and DFTB+

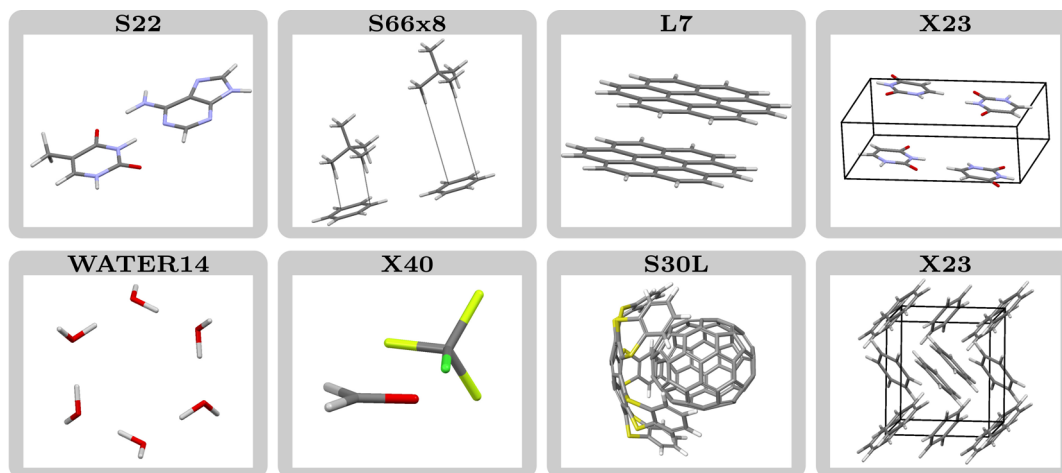


Figure 3. Prototypical system from each investigated benchmark set.

programs, respectively.^{46,65} For DFTB, the 3OB parameters are used.⁶⁶ For the H4 correction, we use the H_bonds4 program with default parameters. For the PM6-D3H+ and PM6-D3H4X method combinations, the D3 correction is used in its zero-damping variant as parametrized by Korth and Hobza, respectively.^{29,62} All other methods are treated in the rational Becke–Johnson damping scheme.

The molecular systems are treated in a single-point energy approach in order to allow a direct comparison with the reference energies. For the WATER14 subset, we give the binding energies per water molecule because of the large spread of interaction energies. Because the resolution of X-ray structures is not accurate enough (especially for the position of hydrogen atoms), we optimized at each level the atomic positions of all X23 solids with fixed (experimental) unit cell parameters. The solid-state HF-3c(v) and DFTB3-D3 calculations were carried out using the standard Bloch function approach with dense k -point grids ($<0.05 \text{ \AA}^{-1}$). For MSINDO, the CCM approach with supercells with a minimum lattice vector length of 10 Å are used. Note that the reported interaction energies sometimes but not always include the fragment relaxation energy, and we always apply the sets as originally published.

A broad range of test sets, including ones for the interaction of small- and medium-sized and large molecular complexes as well as for molecular crystals, were investigated to test the performance of the methods in various situations. Prototypical systems from each analyzed benchmark set are shown in Figure 3. We first summarize the computational details and then introduce the benchmark systems and discuss the results.

Small Molecular Systems. The S22,⁶⁷ S66x8,⁶⁸ and X40⁶⁹ test sets compiled by the group of Hobza served as references for the interaction of small- and medium-sized molecular gas-phase dimers. The S22 set consists of 22 complexes with typical NCIs like hydrogen bonds, dispersion interactions, and mixed ES–DISP interactions. The S66x8 test set is similar to S22, but with slightly larger molecules and less emphasis on nucleobases. In addition to the equilibrium structures, seven points along the center-of-mass dissociation curve of each complex are available. The X40 test set contains small- and medium-sized complexes of noncovalently bound organic halides, halohydrides, and halogen molecules. Besides the typical NCIs, the X40 test set includes halogen bonding. Because water plays a dominant role in many fields, we include the uncharged systems of the WATER27 set compiled by Goddard, dubbed WATER14 in the following.⁷⁰ It consists of water oligomers of varying size (up to 20 molecules). The reference energies for these four sets refer to the estimated CCSD(T)/CBS level of theory.

The strategy of separately adjusting the short-range electronic potentials and the noncovalent corrections seems to be superior to an overfitting-prone determination of all parameters on a huge reference set.

We give the statistical data for the different methods in Table 1 and highlight the two best-performing low-level methods for each set. In order to put the semiempirical methods into a broader perspective and to judge their overall performance, we

included a widely used density functional (PBE) with and without DISP correction (and evaluated with single-particle basis sets close to the variational limit) for comparison. In the SI, we additionally give PBE values evaluated in a smaller basis set of double- ζ quality. The arising BSSE is huge (in fact, larger than that in the HF/MINIX calculation in HF-3c), and even with decent corrections (PBE-D3-gCP), the results are on average worse than those for HF-3c.

As expected, the plain PBE functional can not describe the long-range correlation effects and systematically underbinds the NCI complexes. The inclusion of D3 DISP correction clearly improves the results. The semiempirical methods also perform well. The mean absolute errors (MADs) on the S66 \times 8 set are 0.5–1.2 kcal/mol, while the MADs for the S22 set are slightly larger with 0.6–1.7 kcal/mol. The larger errors on the S22 set can be seen for nearly all DFT and semiempirical methods. This is due to the emphasis of the stronger bound hydrogen-bonded systems in S22 compared to S66. In the following discussion, one should also keep in mind that all of the discussed methods are (partly) parametrized on S22 or S66 sets. For the newly implemented HF-3cv and MSINDO methods, we show the individual binding energies of the S22 test set in Figure 4. The errors for the X40 test set are overall larger but still acceptable in a 1.2–2.1 kcal/mol range. The more involved ES and IND contributions challenge all semiempirical methods. Most of the tested methods bind the X40 systems too strongly, most clearly for the HF-based schemes. In this regard, the good performance of MSINDO-D3H+ for the X40 set with the smallest MAD of 1.4 kcal/mol is notable.

The reduced WATER14 set is an exception, where the uncorrected PBE functional performs surprisingly well. This is due to a systematic overestimation of the hydrogen bond energy, which compensates partly for the missing DISP. Inclusion of the physically correct dispersion term deteriorates the result due to short-range double-counting effects. The PBE functional should be avoided if strong hydrogen bonds are present. We recommend the meta GGA functional TPSS-D3 in such cases. The performance of the semiempirical methods for the water clusters is good. The best-performing methods are DFTB3-D3 and PM7 with MADs of only 0.4 and 0.5 kcal/mol, respectively, which corresponds to about 10% deviation per water monomer. Interestingly, the methods with explicit hydrogen-bonding corrections do not outperform the other schemes.

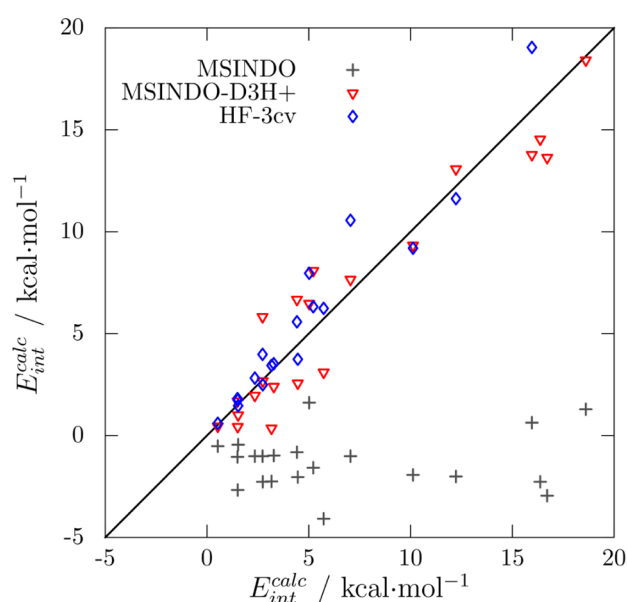
In summary, all semiempirical methods perform reasonable well on these small systems. HF-3c and PM6-D3H4X have the smallest average overall MAD well below 1 kcal/mol. The good performance for small systems is certainly “good news” but an insufficient condition to be applicable to much larger complexes or solids. This is the “true” target for such low-cost methods. However, the worse description of halogen-bonded systems with a more complicated electronic structure is apparent. In passing, it is noted that more explicit halogen-bonding corrections exist which, however, they have not been considered here.^{69,71–73}

Large Molecular Complexes and Organic Solids. In this section, first the L7⁷⁴ set by Hobza and the S30L set, which both contain large molecular complexes, are examined. The L7 set is composed of seven large noncovalently bound molecular complexes of organic molecules. We use new DLPNO-CCSD(T)/ Δ CBS/CP reference values (to be published elsewhere), which are more consistent than the original

Table 1. Performance of the Low-Cost Quantum Chemical Methods for Small- to Medium-Sized NCI Dimers Verified on the Benchmark Sets S22, S66x8, X40, and WATER14^a

	S22		S66x8		X40		WATER14		all
	MAD	MD	MAD	MD	MAD	MD	MAD	MD	MAD
PBE ^b	2.6	−2.6	1.5	−1.5	1.0	−0.9	0.5	0.5	1.4
PBE-D3 ^b	0.6	0.1	0.5	0.2	0.5	0.3	1.3	1.3	0.7
HF-3c ^c	0.6	0.0	0.4	0.0	1.4	0.8	1.1	1.1	0.9
HF-3cv	1.7	1.5	0.5	0.1	2.1	1.4	2.3	2.3	1.7
OM2-D3 ^d	0.9	−0.9	0.8	−0.4			0.9	−0.9	0.9
PM6-D3H+	0.6	−0.2	0.6	−0.0	1.6	0.1	1.6	1.6	1.1
PM6-D3H4X	0.7	−0.4	0.5	0.1	1.2	−0.9	0.7	−0.7	0.8
PM7 ^b	0.8	−0.0	0.7	−0.1	1.8	−1.4	0.5	0.4	1.0
MSINDO-D3H+ ^d	1.5	−0.5	1.1	−0.2	1.4	0.4	1.5	1.5	1.4
DFTB3-D3 ^b	0.9	−0.8	0.8	−0.2	1.8	0.9	0.4	−0.4	1.0

^aFor each set the two best performing methods are highlighted in bold. The mean absolute deviation (MAD) and mean deviation (MD, >0 denotes overbinding) are given in kcal/mol. For WATER14, the interaction energy is divided by the number of water molecules in each complex. ^bFrom ref 34. ^cFrom ref 35. ^dX40 systems are neglected due to missing parameters.

**Figure 4.** Interaction energies for the S22 set on MSINDO, MSINDO-D3H+, and HF-3cv levels in comparison with the CCSD(T)/CBS reference.

values.⁷⁴ The S30L test set consists of 30 supramolecular host–guest complexes. It is an extension of the S12L set, which was the first benchmark set of supramolecular complexes in the literature.⁷⁵ Together, these systems are certainly challenging for any molecular electronic structure method. In passing, it is noted that most empirical force fields fail badly on these tests either due to missing parametrization or totally inconsistent results, as discussed recently.⁷³ The reference interaction energies vary between 20 and 150 kcal/mol, multiple hydrogen bonds are present, and nine systems have a positive charge between 1 and 4. The reference binding energies are obtained from experimental data that are explicitly back-corrected for thermodynamic and solvent effects to ensure direct comparability to electronic energies; for details, see ref 75. This procedure has been independently verified by comparison to high-level DMC results.⁷⁶

The statistical data for these complexes are shown in Table 2. The analysis of the deviations reveals similar trends as discussed in the previous paragraph. The overall interaction energies are

Table 2. Performance of the Low-Cost Quantum Chemical Methods for Large Complexes Verified on the Benchmark Sets L7 and S30L^{a,b}

	L7		S30L		all
	MAD	MD	MAD	MD	MAD
PBE ^b	15.6	−15.6	31.1	−28.6	23.3
PBE-D3 ^b	2.0	−0.8	6.6	−1.0	4.3
HF-3c ^c	1.2	0.4	6.5	1.5	3.9
HF-3cv	2.4	2.3	7.4	−0.4	4.9
OM2-D3 ^c	2.9	−1.8	6.7	1.1	4.8
PM6-D3H+	3.5	−0.2	6.2	1.2	4.8
PM6-D3H4X	2.9	0.0	7.4	1.9	5.2
PM7 ^b	6.5	6.5	16.0	15.7	11.3
MSINDO-D3H+	5.7	3.9	9.5	5.3	7.6
DFTB3-D3 ^b	1.7	0.2	6.2	0.9	3.9

^aMAD and MD (>0 denotes overbinding) are given in kcal/mol. ^bThe D3 correction includes the ATM-3B energy. ^cFour systems in S30L are neglected due to missing parameters.

larger, and therefore, also the absolute deviations are larger. Again, almost no binding is obtained by the uncorrected PBE functional. With inclusion of the D3 dispersion correction, a significant improvement is apparent. More sophisticated functionals like the meta-GGA TPSS-D3 or the hybrid PBE0-D3 (not discussed here) improve these results even further.

Most of the low-cost methods work very reasonably well, with errors sometimes even below those of PBE-D3. Only PM7 is far off and cannot be recommended. Figure 5 shows individual interaction energies for the S30L set. At the MSINDO level, some problems with large π systems are apparent (e.g., the bucky “catcher” 9–12). Except for PM7, the other methods perform better. DFTB3-D3 has the smallest MAD of 6.0 kcal/mol closely followed by PM6-D3H+. For L7, HF-3c and DFTB3-D3 have the smallest errors of 1.2 and 1.7 kcal/mol, respectively. These deviations are below 12% of the mean binding energy, which is even better than the dispersion-corrected PBE functional. Somewhat expected, the charged systems are the main error source in all of the minimal basis set approaches. These errors can be reduced by applying counterions, as discussed in ref 77. The statistic with exclusion of the charged systems is shown in Figure 8 as S30Ln (neutral). The relative errors in the binding energies of the joint L7 and S30L sets are shown in Figure 6. We converted the statistical

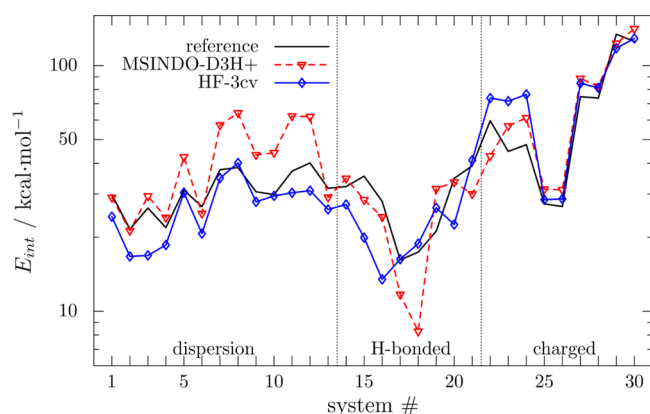


Figure 5. Interaction energies for the S30L set on the MSINDO-D3H+ and HF-3cv level in comparison with the back-corrected experimental interaction energies. Note the logarithmic energy scale.

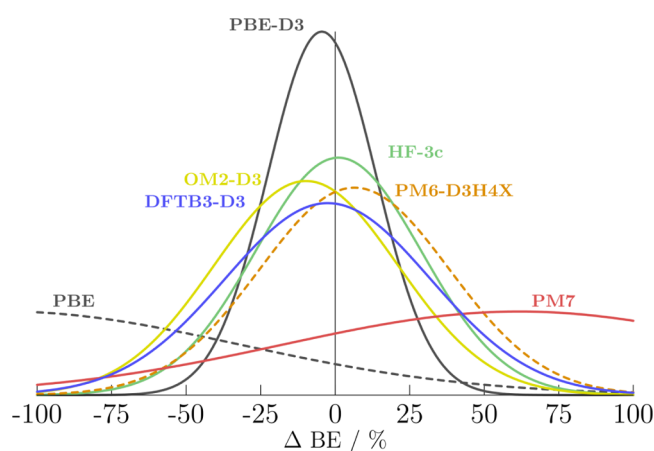


Figure 6. Relative deviations of the computed binding energies ΔBE from the reference for the joint L7 and S30L set. The statistical results are converted into normal error distributions. The deviations for the L7 set were upscaled by a factor of 4 in order to ensure a balanced weighting.

data into normal error distributions. While PM7 and plain PBE are far off, the other methods perform rather similar. Especially for PBE-D3, HF-3c, and DFTB3-D3, no systematic shift is found.

As the most critical test for long-range interactions, the X23⁷⁸ set of organic solids was considered. The original test set of 21 molecular crystals was set up by Johnson⁷⁹ and later refined by Tkatchenko et al.⁷⁸ The crystal structures were taken from low-temperature X-ray diffraction, and the reference energies were based on experimental sublimation energies, which were back-corrected to get electronic lattice energies. The results are given in Table 3, and the corresponding normal error distributions are shown in Figure 7.

The remarkable performance of HF-3c and DFTB3-D3 has been noted before.^{39,34} The MADs of 2.2 and 2.4 kcal/mol, respectively, are close to the DFT-D results at significantly lower costs. However, HF-3c is the least empirical and most expensive of the here-investigated low-cost methods. Further basis set reduction in the HF-3cv scheme gives slightly worse results without systematic over- or underbinding. The MAD of 3.1 kcal/mol is still reasonable to allow explorative or screening investigations. While HF-3cv has a larger MAD compared to DFTB3-D3 and is even computationally more expensive, its

Table 3. Performance of the Low-Cost Quantum Chemical Methods for the X23 Set of Organic Crystals^{a,b}

	MAD	MD
PBE	11.7	−11.7
PBE-D3	1.1	0.4
HF-3c	2.2	−1.3
HF-3cv	3.1	−1.4
MSINDO-D3H+ ^c	6.6(3.9)	1.9(−1.6)
DFTB3-D3	2.4	−0.9

^aFor each set, the two best performing methods are highlighted. MAD and MD (>0 denotes overbinding) are given in kcal/mol. ^bThe D3 correction includes the ATM-3B energy in the final energy. ^cIn parentheses: four outliers neglected.

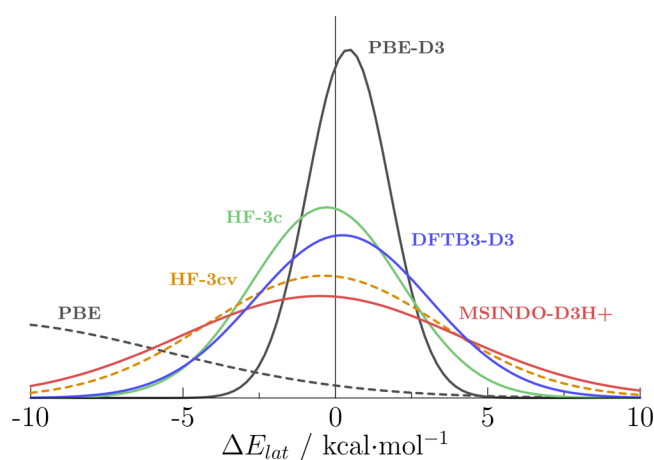


Figure 7. Absolute deviation of the computed lattice energies ΔE_{lat} from the references for the X23 set. The statistical data are converted into normal error distributions.

empirical adjustment is much less involved, and therefore, the method is readily available for the whole periodic table. Though the D3H corrections lead to a clear improvement for MSINDO-D3H+ of about 70%, its overall error is rather large. The high MAD of 6.6 kcal/mol is particularly caused by four systems (benzene, CO₂, oxalic acid α , β). If these systems are neglected, the MAD diminishes to 3.9 kcal/mol. The bad description of the very strong hydrogen-bonded systems and the pure π -systems could already be seen for large molecular complexes of similar structure in S30L.

Regarding the overall picture, we lose a factor of about two in accuracy for the semiempirical methods compared to first-principle DFT results. At the same time, a computational speedup of 2 orders of magnitude is achieved.

We considered several well-established low-cost quantum chemical methods ranging from minimal basis set HF to semiempirical MO-based schemes for the calculation of general NCIs. We have developed a computationally more efficient valence variant of the HF-3c method and augmented the MSINDO method with corrections for DISP and hydrogen-

bonding interactions. Both schemes were implemented in generally available program packages. The proposed methods were tested in comparison to other semiempirical approaches (DFTB3-D3, OM2-D3, PM6-D3H+, PM6-D3H4X, and PM7) regarding their performance for NCIs in various systems.

A summary of our investigations is shown in Figure 8 as MADs in kcal/mol. In order to easily judge the results, we give

	S22	S66x8	X40	WATER14	L7	S30L	S30Ln	X23
PBE-D3/'CBS'	0.6	0.4	0.5	1.3	2.0	6.6	4.7	1.1
HF-3c	0.6	0.4	1.4	1.1	1.2	6.5	4.0	2.2
HF-3cv	1.7	0.5	2.1	2.3	2.4	7.4	5.3	3.1
DFTB3-D3	1.0	0.8	1.8	0.4	1.7	6.2	3.6	2.4
OM2-D3	0.9	0.8	—	0.9	2.9	6.7	3.7	—
PM6-D3H4X	0.7	0.5	1.2	0.7	2.9	6.7	4.8	—
PM6-D3H+	0.6	0.6	1.5	1.6	2.6	6.2	4.6	—
MSINDO-D3H+	1.5	1.1	1.4	1.5	5.7	9.5	8.8	6.6
PM7	0.8	0.7	1.8	0.5	6.5	16	11	—

MAD / kcal·mol⁻¹

relative error: ■ < 12.5% ■ < 25% ■ < 37.5% ■

Figure 8. MADs in kcal/mol for various low-cost methods on all investigated benchmark sets. The color code highlights the error relative to the mean binding energy of the corresponding test set.

the errors relative to the mean binding energy of the corresponding test set in the color code. To put these values into perspective, we also added values for a commonly used dispersion-corrected density functional (PBE-D3) in the estimated basis set limit ("CBS").

For the small organic systems (S22, S66x8) most methods perform well with MAD values close to or below 1 kcal/mol. Note, however, that such values here correspond to typical relative errors of about 20–30%, while a MAD of <0.5 kcal/mol is required to bring the typical error down to a more acceptable 5–10% range. The halogenated systems are problematic for all minimal basis set methods, which probably can only be reduced by special correction schemes. The larger molecular complexes (L7, S30L) are more challenging, but most of the methods give very reasonable results in particular for neutral complexes. HF-3c and DFTB3-D3 perform excellent with relative errors below about 10%. Though PM7 was presented as a successor of PM6, we cannot recommend it for large noncovalently bound systems with relative errors close to 50%. The strategy of separately adjusting the short-range electronic potentials and the noncovalent corrections (as conducted in HF-3c and DFTB3-D3) seems to be superior to an overfitting-prone determination of all parameters on a huge reference set. The X23 set of organic solids is most sensitive to the correct treatment of long-range interactions. All technically feasible and converging computations give good results with relative errors for sublimation energies ranging from 10 to 20%. The MAD increases in the order PBE-D3, HF-3c, DFTB3-D3, MSINDO-D3H+.

Regarding the overall picture, we lose a factor of about 2 in accuracy for the semiempirical methods compared to first-

principle DFT results. At the same time, a computational speedup of 2 orders of magnitude is achieved. While we have analyzed the interaction energies in huge data sets, future benchmarks should also examine structures (molecular complexes as well as unit cells) provided by the low-cost methods in more detail. We have recently shown that the rotational constants of medium-sized molecules are well-described by dispersion-corrected DFT and dispersion-corrected semiempirical methods.⁸⁰ PM6 and PM7 geometries were also investigated for small NCI dimers.⁸¹ This should be extended to larger and periodic systems because geometry optimization represents a main area of application of low-cost methods.

Due to the improved accuracy and meanwhile relative broad range of applicability, the future for low-cost quantum chemical methods for investigating non-covalent interactions in all of their aspects seems bright.

In conclusion, the here-presented methods are ideally suited for large-scale applications as either prescreening tools or in a multilevel approach by combining ab initio electronic energies with semiempirically derived thermostistical corrections. In any case, due to the improved accuracy and meanwhile relative broad range of applicability, the future for low-cost quantum chemical methods for investigating NCIs in all of their aspects seems bright.

■ ASSOCIATED CONTENT

Supporting Information

Global and element-specific parameters of the HF-3c(v) and MSINDO-D3H+ method, tables of individual interaction energies, and geometries of the optimized organic crystals are given. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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