Application of London dispersion corrected density functional theory for non-covalent ion-π interactions

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Abstract

The strongly attractive non-covalent interactions of charged atoms or molecules with π-systems are important bonding motifs in many chemical and biological systems. These so-called ion-π interactions play a major role in enzymes, molecular recognition, and for the structure of proteins. To model ion-π interactions with DFT, it is crucial to include London dispersion interactions, whose importance for ion-π interactions is often underestimated. In this work, several dispersion-corrected DFT methods are evaluated for inter- and intramolecular anionic- and anion-π interactions in larger and practically relevant molecules. We compare the DFT results with MP2, while highly accurate (local) coupled cluster values are provided as reference. The latter can also be a great help in the development and validation of approximate methods. We demonstrate that dispersion-uncorrected DFT underestimates ion-π interactions significantly, even though electrostatic interactions dominate the overall binding. Accordingly, the new charge dependent D4 dispersion model is found to be consistently better than the standard D3 correction. Dispersion-corrected DFT clearly outperforms MP2/CBS whereby the best performers come close to the accuracy limit of the reference values at considerably smaller computational cost. Due to its low cost, D4 can be combined very well with semi-empirical QM and force field methods, which is important in the development of more accurate methods for modeling large (bio)chemical systems (e.g. proteins). Another important aspect in modeling these charged systems with DFT is the self-interaction error (SIE). However, we do not find it to constitute a significant problem. Overall, the double hybrid PWPB95-D4/QZ turned out to be the most reliable among all assessed methods in predicting ion-π interactions, which opens up new perspectives for systems where coupled cluster calculations are no longer computationally feasible.

Introduction

Ion-π interactions refer to strongly attractive non-covalent interactions (NCIs) between ions and mostly organic π-systems.[1,2] They are of crucial importance for many processes in chemistry and biology, *e.g.*, for controlling the regio- and stereoselectivity in various organic reactions,[3,4] enabling important biological processes,[5–9] and for the structures of molecules and proteins.[10–13] A deeper understanding of this NCI class is achieved by symmetry adapted perturbation theory[14–16] (SAPT), which allows the separation into different energy components namely electrostatics, Pauli repulsion, induction, and London dispersion (LD). Previous SAPT studies revealed[17] that ion-π systems incorporate strong electrostatic and inductive interactions. For highly polarizable systems, however, also LD were identified as a crucial part of the ion-π interaction.[18]

In the last decades, the development of computationally quite efficient yet accurate LD-corrected density functional theory (DFT) methods led to their establishment as a standard tool in computational chemistry.[19,20] Nevertheless, also DFT methods have well-known weaknesses, like the one- and many-electron self-interaction error (SIE),[21,22] which is particularly pronounced in ionic systems.[23,24] Even modern density-functional approximations (DFAs) are affected by SIE, which may lead to severe SCF convergence problems,[25] artificial charge-transfer (CT),[26,27] and inaccurate NCI energies for larger inter-fragment distances. This is in contrast to Hartee–Fock (HF) theory and MP2, which are SIE free because the exchange integrals exactly cancel the self-interaction contributions from the Coulomb integrals. This behavior is exploited by hybrid DFAs where a fraction of exact exchange (also called Fock exchange) is mixed in, partially cancelling the SIE. While large amounts of Fock exchange reduce the SIE, the resulting hybrid DFAs also inherit general shortcomings of HF, *e.g.*, a lacking description of dynamical and in particular static electron correlation. For a more general discussion on the one-electron SIE in DFT see, *e.g.*, Ref. 28, and for the related many-electron SIE, see e.g. Ref. 22.

Also MP2 (see e.g. Refs.[29,30]) and variants thereof[31] are popular in modeling ion-π interactions, although there are severe and well-known problems. The main issue is that MP2 generally overestimates NCI involving π-systems particularly for π-π interactions.[32–36] Furthermore, similar to other post-HF correlation methods, MP2 is highly susceptible to the basis set superposition error[37,38] (BSSE) which leads to systematic overbinding with small and medium sized basis sets.

As has been shown in previous studies,[39,40] well performing LD-corrected DFAs are able to reproduce coupled cluster reference interaction energies for cation-anion complexes, representing the building blocks of ionic liquids. These chemically often rather saturated systems are less prone to the SIE. Good results for small charged systems could also be obtained with DFT-D methods in Refs. 16 and 41 though the benchmark sets discussed in these studies are composed of rather small ion-π systems. In this work, we investigate the importance of LD corrections for obtaining accurate interaction and relative energies for prototypical systems and larger systems of practical relevance composed of cations/anions and π-systems. The common believe is that such ion-π systems are dominated by electrostatic and inductive interactions[18] but little attention has been paid so far to the importance of LD in this context. In the present work, we will put a particularly focus on the latter in the framework of LD-corrected DFT. Due to persisting popularity of MP2 in NCI studies (see e.g. Refs. 42,43), it is chosen as a competitor method.

To evaluate the performance of the methods mentioned above, reliable reference values of high accuracy are needed since otherwise a meaningful evaluation of the already quite good DFA methods would be impossible. For small to medium sized systems (up to about 30 atoms) explicitly correlated coupled cluster composite schemes such as the Weizmann protocols[44] (W1-F12 and W2-F12) have proven to yield highly accurate reference values. Yet, the respective computational cost are considerable. For larger systems (up to about 150 atoms), domain based local pair natural orbital coupled cluster theory (DLPNO-CCSD(T))[45,46] is still computational feasible and was already successfully applied,[47,48] even though the high precision of the Wn-F12 protocols cannot be fully achieved. To reduce the additional errors due to the local (DLPNO) approximations, very tight threshold settings have to be applied[49] in addition to a proper CBS extrapolation which in turn also makes these calculations quite computationally demanding. To assess faster but more approximate methods such as MP2 or DFAs, the high-level reference values calculated in this work can also be very useful in the development and validation of low-cost methods, e.g., of special force-fields (FF),[50,51] since hardly any reliable coupled-cluster reference values for ion-π interactions energies of larger molecules exist so far[52] and neither have them been calculated with such an accurate setup.[53] The development of such FFs and respective workflows is an emerging field of research, especially with respect to the efficient description of ion-π interactions in proteins.[54,55]

After a brief survey of the employed semi-classical LD-correction schemes, the results for diverse ion-π systems are presented and discussed for LD uncorrected DFAs, LD-corrected DFAs, and MP2/CBS. Finally, general conclusions and method recommendations will be given.

Semi-classical London dispersion corrections

To account for the missing LD interactions in the framework of DFT, we apply two closely related semi-classical LD-correction schemes. First, the widely used DFT-D3 method[56–58] with two-body contributions (only $E_{\text{disp}}^{(2)}$) and the standard Becke–Johnson (BJ) rational damping[59,60] is applied. Second, we consider the default version of the recently introduced DFT-D4 scheme[61,62] including also three-body Axilrod–Teller–Muto[63,64] (ATM) contributions

$$E_{\text{disp}}^{\text{DFT-D4}} = E_{\text{disp}}^{(2)} + E_{\text{disp}}^{\text{ATM}}. \tag{1}$$

The basic formula for two-body dispersion interactions is the same in the D3 and D4 model, where the BJ rational damping form for the interatomic pair sum is employed,

$$E_{\mathrm{disp}}^{(2)} = -\sum_{\mathrm{AB}} \left[\frac{C_6^{\mathrm{AB}}}{R_{\mathrm{AB}}^6 + f\left(R_{\mathrm{AB}}^0\right)^6} + s_8 \frac{C_8^{\mathrm{AB}}}{R_{\mathrm{AB}}^8 + f\left(R_{\mathrm{AB}}^0\right)^8} \right], \tag{2}$$

with the three fitted damping and scaling parameters a_1, a_2, and s_8. Here, AB labels atom pairs, and $f(R_{\mathrm{AB}}^0) = a_1 R_{\mathrm{AB}}^0 + a_2$ is the BJ damping function with appropriate covalent radii.[57]

In both methods, the C_6 (and C_8) coefficients are obtained from precalculated frequency-dependent time-dependent DFT dipole polarizabilities.[65] In addition to the coordination number dependence in DFT-D3, classical atomic partial charges are included in DFT-D4. Hence, D4 dispersion coefficients are improved also for "normal" (neutral) organic molecules (deviation from experimental reference data is about 3% instead of 5% for DFT-D3).[61] For metallic and ionic systems significantly improved polarizabilities, cohesive energies and reaction energies are obtained compared to the DFT-D3 ones (for details, see Refs. 66,67). According to many tests on neutral organic systems, DFT-D3 and DFT-D4 methods provide both accurate asymptotic dispersion energies of roughly coupled-cluster accuracy[58] while D4 is somewhat superior for ionic or metallic cases.[61,66] If this also holds for the important class of ion-π complexes is one main questions of the present work.

Other popular LD correction schemes exist, *e.g.*, the exchange-hole dipole method,[68–71] the many-body dispersion model,,[72,73] the non-local electron density dependent dispersion correction termed VV10 or DFT-NL,[74–76] or the van der Waals family of density functionals.[77] However, previous studies revealed that the D3 and D4 LD correction schemes exhibit the best accuracy to cost ratio[61,66,67,78] making them also suitable for low-cost methods including force-fields,[79–82] which is the reason why we have exclusively assessed these methods in the present study. For an in-depth analysis of other LD corrections and a more general discussion on the importance of LD effects for chemical bonding, see *e.g.* Refs. 58,83.

Computational details

Typical DFAs from different classes of Jacob's ladder[84,85] employed with the large def2-QZVPP basis set[86,87] are evaluated. The DFA selection is based on promising results in previous benchmark studies[41] and on their popularity in the computational chemistry community.[88] Accordingly, we selected the double hybrid PWPB95,[89] the hybrids PBE0[90] and B3LYP,[91,92] the meta-GGA TPSS,[93] and the GGA PBE.[94]

All DFT calculations except PWPB95 were performed using the TURBOMOLE 7.2.1 program package.[95,96] Computations of energies and geometry optimizations were performed analytically using the `ridft` and `jobex` programs of TURBOMOLE, respectively. The resolution-of-identity (RI) approximation for the Coulomb integrals was always applied using matching default auxiliary basis sets.[97,98] For the integration of the exchange-correlation contribution, the numerical quadrature grid $m4$ was employed. The default convergence criteria (10^{-7} E_h for energies and 10^{-5} E_h/Bohr for gradients) were used throughout. Dispersion corrections were calculated with the `dftd3` and `dftd4` standalone programs. Lowest energy molecular conformers were obtained from the advanced conformer rotamer ensemble sampling tool[99] (CREST) at the GFN2-xTB[100] level followed by DFT geometry re-optimizations at the PBEh-3c[101] level of theory.

All PWPB95/def2-QZVPP, MP2, and local coupled cluster calculations were carried out with the ORCA 4.2.1 program package[102,103] and employ the frozen core and RI approximations for the correlation part as well as *TightSCF* convergence criteria for the HF energy. The domain based pair natural orbital local coupled cluster method[45] in its sparse maps[46] iterative triples[104] implementation (DLPNO-CCSD(T1)) employing *VeryTightPNO*[49] threshold settings was applied. An aug-cc-pVTZ/aug-cc-pVQZ[105] and def2-TZVPP/def2-QZVPP CBS extrapolation according to the schemes proposed by Helgaker/Klopper[106] (aug-cc basis sets) or Neese/Valeev[107] (def2 basis sets) was carried out for MP2 and DLPNO-CCSD(T1) as indicated below. Matching auxiliary basis sets were applied for the density fitting. For the largest test system (a cyclophane complex hosting a cationic N-alkylated quinoline guest, *vide supra*), a slightly more approximate CBS extrapolation scheme was employed for the local coupled cluster correlation energy since the full def2-QZVPP calculation was computationally unfeasible with the latter method. It is labelled as CBS/'def2-TZVPP/def2-QZVPP' in the following and refers to a multiplicative scaling of the DLPNO-CCSD('T1') correlation energy by the quotient of the respective CBS(def2-TZVPP/def2-QZVPP) and def2-TZVPP MP2 correlation energies. A similar CBS protocol was already successfully employed in Ref. 47. Note that the iterative correction to the triples correlation energy is calculated with the smaller def2-SVP[87] basis set (labelled as 'T1') for this test system which, however, should not introduce a significant error considering the estimated error range of ± 2 $\mathrm{kcal\,mol^{-1}}$ for the association energy of this supramolecular complex. The high-level composite explicitly correlated coupled cluster protocols W1-F12 and W2-F12[44] were applied with the Molpro program package V. 2015.1.[108,109]

Results and discussion

In the following, the performance of LD-uncorrected and LD-corrected DFAs as well as MP2/CBS is assessed with respect to newly calculated high-level (local) coupled cluster reference values for several (bio)chemical ion-π systems.

Definitions of the employed statistical measures (mean deviation (MD), mean absolute deviation (MAD), standard deviation (SD), and the absolute maximum deviation (AMAX)) are given in the supporting information (SI).

Dissociation of ion-π complexes

First, we focus on intermolecular ion-π interactions, where usually ions or small ionic molecules binding to the π-system of a neutral, rigid molecule are studied. Figure 1 shows dissociation curves of two ion-π complexes, where the reference interaction curves (black lines) for rigid monomers are computed in both cases at the W1-F12 level (abbreviated as "reference";

estimated error range: ± 0.5 kcal mol^{-1}).

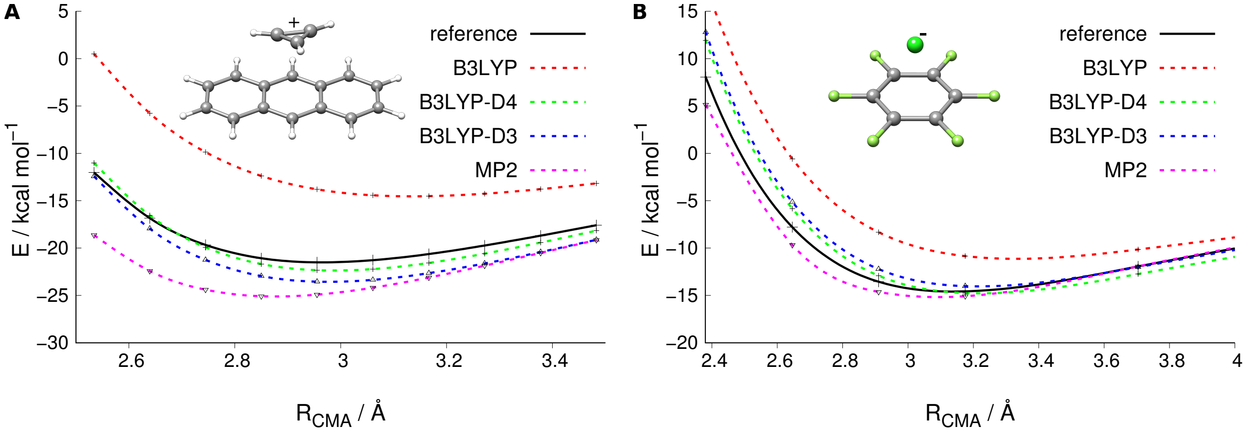

Figure 1: **A** Intermolecular potential energy curve of anthracene and the cyclopropenyl cation ($C_3H_3^+$) calculated with B3LYP (red dashed), B3LYP-D3 (blue dashed), B3LYP-D4 (green dashed), MP2/CBS (violet dashed), and W1-F12 (reference, black solid). **B** Intermolecular potential energy curve of C_6F_6 and the chloride anion (Cl^-) obtained with the same methods as in **A**.

Figure 1A shows B3LYP (with and without LD corrections) dissociation curves for anthracene and the cyclopropenyl cation ($C_3H_3^+$) in comparison to the reference. More statistical data for the assessed DFAs are listed in Table 1. Since D4 corrected DFAs consistently outperform their D3 counterparts for ion-pi interactions, the latter data are only given in the SI. References interaction energies were calculated for ten center-of-mass (CMA) distances in the range of 2.5 - 3.5 Å . As expected for a rather repulsive DFA, B3LYP (red dashed line) strongly underestimates the reference interaction energy (MD and MAD of 7.8 kcal mol^{-1}). Especially for short distances, it is too repulsive resulting in a large AMAX value of 12.5 kcal mol^{-1} . B3LYP-D3 (blue dashed line) reasonably reproduces the reference (MD = −1.6, MAD = 1.6, AMAX = 2.1, all in kcal mol^{-1}), however, the interaction energy is slightly overestimated. Replacing D3 by D4 (green dashed line) improves the asymptotic region of the interaction and lowers several statistical measures (MD = −0.4, MAD = 0.7, AMAX = 1.0, all in kcal mol^{-1}). However, the position of the minimum is still slightly shifted to larger distances compared to the reference.

As mentioned in the Introduction, the SIE can be problematic for the GGA and meta-GGA classes of DFAs especially for systems including ions. Table 1 (for further details, see Tables S1 and S2 in the SI) reveals that hybrid DFAs (PBE0 and B3LYP) yield lower statistical errors compared to DFAs incorporating only approximate DFT exchange (TPSS and PBE), which tend to overbind due to some artificial CT. MP2/CBS (violet dashed line) overbinds even more strongly especially for short CMA distances, however, for a different reason (overestimation of π-π interactions). The highest accuracy among the tested DFAs is obtained with the LD-corrected double-hybrid PWPB95-D4, presumably also due to its high amount (50%) of Fock exchange.[89]

Table 1: Statistical measures of several methods for the dissociation of (A) anthracene$\cdots$ $C_3H_3{}^+$ and (B) $C_6F_6 \cdots$ Cl^- relative to W1-F12 reference values. Values for uncorrected methods are given in parentheses and D3 corrected values are provided in the SI. All measures are given in kcal mol^{-1} .

	MD		MAD		SD		AMAX	
Method	A	B	A	B	A	B	A	B
PWPB95	−0.7(1.9)	0.1(1.3)	0.7(1.9)	0.4(1.3)	0.6(0.3)	0.5(0.9)	1.8(2.1)	0.7(2.6)
B3LYP	−0.4(7.8)	0.8(4.7)	0.7(7.8)	1.4(4.7)	0.6(2.7)	1.9(3.4)	6.2(12.5)	3.9(9.7)
PBE0	−1.3(3.8)	0.9(3.2)	1.3(3.8)	1.0(3.2)	0.3(0.8)	1.0(1.8)	1.7(5.0)	2.4(5.6)
TPSS	−2.7(4.5)	0.6(4.0)	2.7(4.5)	0.8(4.0)	1.1(0.8)	0.9(2.2)	4.6(5.4)	1.8(6.8)
PBE	−2.6(2.9)	0.9(3.4)	2.6(2.9)	1.2(3.4)	0.6(0.8)	1.3(2.2)	3.6(3.9)	2.6(6.3)
MP2/CBS	−3.5	−1.0	3.5	1.1	1.7	1.2	6.6	2.9

Figure 1B shows various B3LYP dissociation curves of C_6F_6 and the chloride anion (Cl^-) in comparison to the reference for six different CMA distances within a range of 2.4 - 4.2 Å . B3LYP (red dashed line) underbinds especially for short CMA distances (MD and MAD= 6.5, SD= 4.4 and AMAX= 12.6 all in kcal mol^{-1}). Analogous to the results obtained for the anthracene$\cdots$ $C_3H_3{}^+$ dissociation curve, D3 (blue dashed line) and D4 (green dashed line) corrected B3LYP both reproduce the reference reasonably well whereby B3LYP-D4 achieves the lowest statistical errors.

For this system the SIE seems to be less severe since the (meta-) DFAs are able to compete with the hybrid functionals (cf. PBE vs. PBE0). To better understand this observation we conducted energy decomposition analyses[110] (EDA) for PBE-D3 and PBE0-D3 to investigate the effect of Fock exchange at four CMA distances taken from the dissociation curve in Fig.

1B from 2.65 to 4.23 Å (5 to 8 Bohr, see Table 2).

Table 2: Energy decomposition analyses of the $C_6F_6\cdots Cl^-$ complex for PBE-D3 and PBE0-D3. The total interaction energy (INT), the electrostatic (ES), the Pauli repulsion (REP), the short-range DFA correlation (CORR), and the LD contributions are listed. All values are given in kcal mol^{-1} .

	CMA distance of $C_6F_6\cdots Cl^-$							
	2.65 Å (5 a_0)		3.17 Å (6 a_0)		3.70 Å (7 a_0)		4.23 Å (8 a_0)	
DFA	PBE	PBE0	PBE	PBE0	PBE	PBE0	PBE	PBE0
INT	−5.1	−5.6	−13.4	−13.5	−11.7	−11.5	−8.7	−8.5
EL	−34.0	−33.5	−12.2	−12.4	−6.1	−6.5	46.3	−4.4
REP	55.8	53.8	13.8	12.9	3.1	2.9	−47.7	0.5
CORR	−24.4	−23.5	−13.1	−12.2	−7.6	−6.7	−6.8	−3.9
LD‡	−2.5	−2.4	−1.9	−1.8	−1.2	−1.2	−0.7	−0.7
$\Delta^{\mathrm{ref}\ \dagger}$	2.7	2.2	1.2	1.1	0.2	0.4	−0.1	0.1

† $\Delta^{\mathrm{ref}} = E^{\mathrm{calc}}_{\mathrm{INT}} - E^{\mathrm{ref}}_{\mathrm{INT}}$. ‡ LD contribution calculated with D3.

For all tested CMA distances, PBE0-D3 is only slightly more accurate with an MAD of 1.0 kcal mol^{-1} than PBE-D3 (1.1 kcal mol^{-1}). The EDA interaction energy (INT) is calculated as the sum of electrostatics (EL), Pauli repulsion (REP), DFA correlation (CORR), and LD contributions. Table 2 lists deviations from W1-F12 reference interaction energies (denoted as $\Delta^{\mathrm{ref}} = E^{\mathrm{calc}}_{\mathrm{INT}} - E^{\mathrm{ref}}_{\mathrm{INT}}$) for both DFAs. At CMA distances of 5, 6, and 7 Bohr no significant SIE related issues occur and the energetic contributions of PBE-D3 and PBE0-D3 are on the same order of magnitude. This changes, however, for the largest CMA distance of 8 Bohr, where PBE-D3 predicts nonphysical contributions for EL (repulsive) and REP (attractive) of 46.3 and -47.7 kcal mol^{-1} respectively. This error is probably due to a violation of the Perdew–Parr–Levy–Balduz condition,[111–115] meaning that the total electronic energy as a function of electron number under a fixed external potential is not interpolating straight between integers. For GGA methods, this usually results in intrinsic delocalization errors.[21,116] Interestingly, despite the nonphysical contributions for EL and REP, an accurate PBE-D3 total interaction energy is obtained based on fortuitously error compensation, hence we get the right answer for the wrong reasons.

Of all tested LD-corrected DFA combinations, PWPB95-D4 obtains the lowest statistical errors. MP2/CBS (violet dashed line) slightly overestimates the interaction energies for this system and is *on par* with the statistical measures of PBE0-D4 (*i.e.*, MAD, SD, and AMAX). Note that for both dissociation curves, most statistical deviations are significantly reduced (typically by about 50 %) for all tested DFAs when applying an LD correction (either D3 or D4).

Additivity of anion-π interactions

The next test system is taken from a study on designing receptors for molecular recognition where the additivity of anion-π interactions for 1:1, 1:2, and 1:3 (anion:π) complexes of trifluoro-1,3,5-triazine ($C_3F_3N_3$) with Cl^- ions[117] (see Figure 2) was investigated.

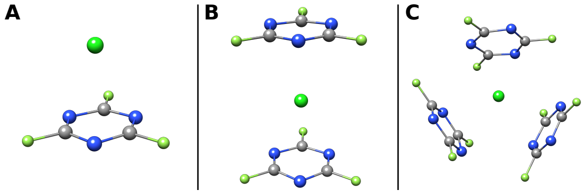

Figure 2: Complex of trifluoro-1,3,5-triazine (monomer in **A**, dimer in **B**, and trimer in **C**) with a Cl^- anion.

This observation is confirmed by W2-F12 (A) and DLPNO-CCSD(T) / *VeryTightPNO* / CBS(aug-cc-pVTZ/aug-cc-pVQZ) (B, C) reference interaction energies (abbreviated as “reference”): 1:1 ($E_{\text{int}}^{\text{ref}} = -18.6 \pm 0.2$ kcal mol^{-1}), 1:2 ($E_{\text{int}}^{\text{ref}} = -33.7 \pm 1.0$ kcal mol^{-1}), and 1:3 ($E_{\text{int}}^{\text{ref}} = -45.3 \pm 1.0$ kcal mol^{-1}). Compared to purely additive interactions (see below), the reference interaction energies decrease by 9.4% and 18.8% for the dimer (Figure 2B) and trimer (Figure 2C) complex with Cl^-, respectively. Table 3 lists interaction energies for the 1:1 complex (Figure 2A) calculated with several D4-corrected DFAs and MP2 / CBS(aug-cc-pVTZ/aug-cc-pVQZ). Additionally, relative deviations of the 1:2 (Δ^2) and 1:3 (Δ^3) interaction energies with respect to purely additive interactions are presented. Relative deviations were calculated according to Eq. 3,

$$\Delta^X = \frac{E_{\text{int}}^X - X\,E_{\text{int}}}{X\,E_{\text{int}}}\,100\%, \tag{3}$$

where E_{int} denotes the interaction energy of the monomer complex and E_{int}^X is the one of the dimer complex ($X = 2$) and the trimer complex ($X = 3$), respectively. Note that Table 3 lists only LD-uncorrected and D4-corrected values since the respective D3-corrected results for Δ^x are very similar to the latter.

Table 3: Interaction energies (E_{int}, in kcal mol^{-1}) of the $\text{Cl}^-\cdots\text{C}_3\text{F}_3\text{N}_3$ complex for several D4-corrected DFAs (LD-uncorrected values in parenthesis) and for MP2 / CBS(aug-cc-pVTZ/aug-cc-pVQZ). Relative deviations (in %) with respect to purely additive interactions for the 1:2 (Δ^2) and 1:3 (Δ^3) complexes.

Method	E_{int} / kcal mol^{-1}	Δ^2 / %	Δ^3 / %
Reference	-18.6	-9.4	-18.8
PWPB95-D4	-18.4 (-16.9)	-8.6 (-8.4)	-17.8 (-17.3)
PBE0-D4	-17.7 (-15.2)	-9.0 (-8.9)	-18.6 (-19.4)
B3LYP-D4	-17.9 (-13.5)	-8.9 (-8.1)	-17.9 (-18.6)
TPSS-D4	-18.0 (-14.3)	-10.0 (-10.0)	-20.0 (-21.3)
PBE-D4	-17.7 (-15.0)	-9.7 (-9.8)	-20.5 (-21.5)
MP2/CBS	-19.1	-7.1	-15.0

The double-hybrid PWPB95 and both hybrids (PBE0 and B3LYP) closely match the trend of the reference. DFAs with approximate DFT exchange (TPSS and PBE) slightly overestimate this trend, while MP2/CBS underestimates anti-cooperativity, likely as a consequence of the increasing π-π character of the (1:2 and 1:3) complexes.

Additionally, the accuracy in reproducing the reference interaction energies for all three complexes was analyzed. Figure 3 shows the minimum (min.), the maximum (max.), and the mean deviation (mean) for the assessed DFAs with respect to the reference interaction energies for the 1:1, 1:2, and 1:3 complexes.

LD-uncorrected DFAs (see Fig. 3A) slightly (PWPB95) to strongly (TPSS) underestimate the interaction energies (w.r.t. the reference, MAD values for PBE/TPSS/PBE0-/PWPB95 are 6.7/8.0/5.9/2.6 respectively, all in kcal mol^{-1}). Adding the D3 correction to

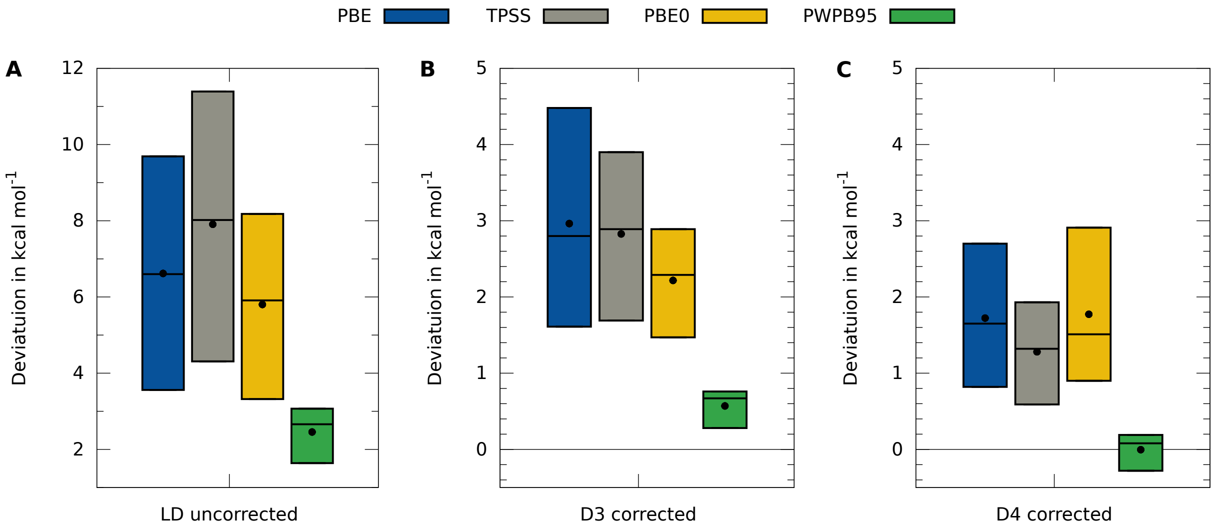

Figure 3: Statistical errors with respect to W2-F12 (1:1 complex) and DLPNO-CCSD(T1) / *VeryTightPNO* / CBS(aug-cc-pVTZ/aug-cc-pVQZ) (1:2, 1:3 complex) reference values for calculated interaction energies using different theoretical levels of theory for $Cl^{-}\cdots(C_3F_3N_3)_X$ (X = 1, 2, 3). The minimum deviation and maximum deviation for the three complexes are shown as the range of the box plot. Additionally, the mean and median deviation are depicted as dot and vertical bar, respectively. In A, values of LD uncorrected DFAs are shown. In B and C, the values of D3 and D4 corrected DFAs, respectively.

the tested DFAs (see Fig. 3B) significantly improves most of the statistical measures (MAD values for PBE/TPSS/PBE0/PWPB95 are 2.9/2.9/2.3/3.0 respectively, all in kcal mol^{-1}). The minimum deviations of D3-corrected DFAs come close to the estimated error margin that represents an MAD of ± 1.0 kcal mol^{-1} for the 1:2 and 1:3 complex. The error margin for the 1:1 complex, calculated by W2-F12 is smaller with a range of ± 0.2 kcal mol^{-1}. For simplicity, error margins are not shown in Fig. 3. D4-corrected DFAs (see Fig. 3C) overall perform best (MAD values for PBE/TPSS/PBE0/PWPB95 are 1.8/1.4/1.5/0.1 respectively, all in kcal mol^{-1}), indicating a small trend of under binding. Note that for the tested DFAs the worst DFA-D4 combination is still more accurate in terms of MAD values than the best DFA-D3 combination.

Furthermore, the influence of including many-body dispersion contributions approximately via the ATM three-body term is investigated for DFA-D3 combinations. The ATM contribution does not significantly improve the DFA-D3 accuracy for the investigated π-anion complexes, as can be seen from MAD values for PBE/TPSS/PBE0/PWPB95 (3.0/2.9/2.3-

/2.9 $\mathrm{kcal\,mol^{-1}}$) and hence, the included three-body LD contributions are not responsible for the better DFA-D4 performance (see Figure 3). Instead, the better performance of the D4 model can be attributed to its charge dependency.

Overall, D4-corrected DFAs yield accurate interaction energies, especially, PWPB95-D4 closely approaches the reference with errors in the sub-$\mathrm{kcal\,mol^{-1}}$ range (see the SI). Considering all tested DFAs, we notice that LD-uncorrected DFAs show on average an about 5 $\mathrm{kcal\,mol^{-1}}$ larger MAD compared to the D4-corrected ones.

MP2/CBS overestimates the interaction energies with increasing deviation for the larger complexes (-0,5/-1.3/-3.2 $\mathrm{kcal\,mol^{-1}}$ for A, B, and C) showing statistical errors that are comparable to PBE-D4 (all other tested DFA-D4 combinations yield lower statistical errors).

Intermolecular host-guest complexes

As revealed by Wang and co-workers,[118] the electron-deficit and cavity self-tunable macrocyclic host tetraoxacalix[2]arene[2]triazine (Figure 4A, abbreviated as "calixarene" in the following) forms 1:1 complexes with small anions in gas phase, solution, and solid state. These larger NCI complexes constitute representative supramolecular anion-π systems and hence, are considered in our study.

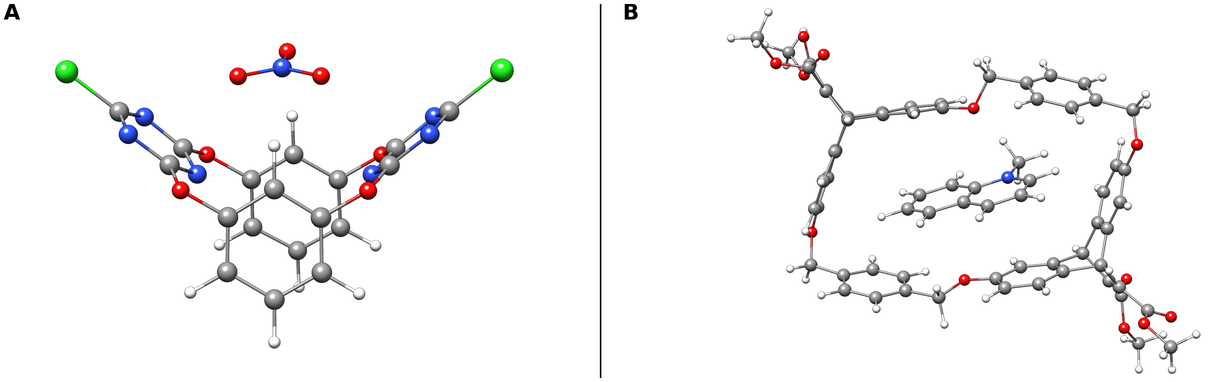

Figure 4: **A** Calixarene molecule with anionic binding partners X^- ($X^- = NO_3{}^-$ or SCN^-). Shown is the $NO_3{}^-$ complex. **B** Supramolecular cyclophane host-guest complex with a cationic N-alkylated quinoline guest.

Two calixerene (c) host-guest complexes serve as test sytems, each having a polyatomic anion namely NO_3^- and SCN^-. Very accurate theoretical reference association energies (i.e., including geometry relaxation) at the DLPNO-CCSD(T1)/ *VeryTightPNO* / CBS(aug-cc-pVTZ/aug-cc-pVQZ) level (abbreviated as "reference") are consistent with experimental results[118] and show that the $c\cdots NO_3^-$ system (-29.4 ± 1.0 kcal mol^{-1}) is more stable than the $c\cdots SCN^-$ system (-26.7 ± 1.0 kcal mol^{-1}). LD-uncorrected DFAs correctly reproduce the relative stability between these two anion-π complexes, but overall strongly underestimate the magnitude of the reference association energies. Deviations of LD-uncorrected DFAs range from 3.7 kcal mol^{-1} (PWPB95 for $c\cdots NO_3^-$) up to 10.1 kcal mol^{-1} (B3LYP for $c\cdots SCN^-$). The smaller deviation of PWPB95 compared to the other tested hybrid and (meta-)GGA DFAs may be attributed to its MP2 part which captures the LD interactions to some extent. Averaged absolute deviations $\overline{\Delta}$ for five tested DFAs from the GGA/meta-GGA/hybrid/double hybrid classes are 6.7 kcal mol^{-1} for $c\cdots NO_3^-$ and 7.5 kcal mol^{-1} for $c\cdots SCN^-$, respectively. The D3 correction significantly lowers the deviations for all assessed DFAs to $\overline{\Delta}$ values of 1.2 kcal mol^{-1} ($c\cdots NO_3^-$) and 3.6 kcal mol^{-1} ($c\cdots SCN^-$), respectively. Once more, replacing D3 by D4 is beneficial for both anion complexes lowering the averaged deviation of D3 again by 0.8 kcal mol^{-1} for both complexes, resulting in $\overline{\Delta}$ values of 0.4 kcal mol^{-1} ($c\cdots NO_3^-$) and 2.7 kcal mol^{-1} ($c\cdots SCN^-$), respectively. Again, the double-hybrid PWPB95-D4 obtains the lowest statistical error among all tested DFAs. Hybrid (PBE0 and B3LYP) association energies are not significantly more accurate than the ones obtained from (meta-)GGAs (PBE and TPSS) revealing no clear trend with respect to SIE related issues. This may be explained by the fact that such errors become more pronounced for larger (non-equilibrium) inter-fragment distances, as already discussed for the $Cl^-\cdots C_6F_6$ system (*vide supra*). MP2/(aug-cc-pVTZ/aug-cc-pVQZ) association energies are overestimated by 3.3 kcal mol^{-1} ($c\cdots NO_3^-$) and by 5.0 kcal mol^{-1} ($c\cdots SCN^-$), thus does not reach the accuracy of LD-corrected DFAs for predicting supramolecular binding thermodynamics of such larger anion-π complexes. The mean deviation of the respective association energies calculated with the tested methods from the reference (Δ^{ref}) for $c\cdots NO_3^-$ and $c\cdots SCN^-$ is shown in Figure 5.

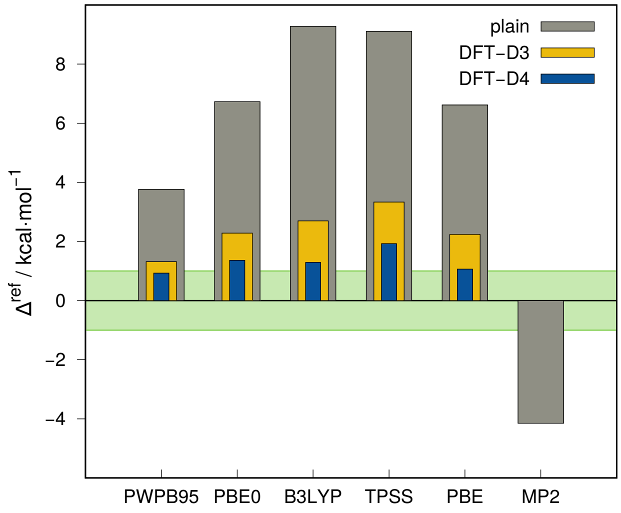

Figure 5: Mean deviation in interaction energies Δ^{ref} between the respective plain method, D3 and D4 LD-corrected DFAs, and the DLPNO-CCSD(T1) / *VeryTightPNO* / CBS(aug-cc-pVTZ/aug-cc-pVQZ) reference values for $c\cdots NO_3^-$ and $c\cdots SCN^-$. Values are given in kcal mol^{-1}. The estimated error range of the reference (± 1 kcal mol^{-1}) is indicated in green.

The excellent performance of the dispersion-corrected double hybrid becomes even more impressive when one compares the required computational wall times. A PWPB95-D4/def2-QZVPP single point energy calculation for $c\cdots NO_3^-$ took just about one hour on ten Intel© Xeon E5-2660 v4 @ 2.00 GHz CPUs, while the corresponding MP2/aug-cc-pVQZ and DLPNO-CCSD(T1) / *VeryTightPNO* / aug-cc-pVQZ calculations took about 149 hours and three months.

The supramolecular cyclophane host-guest complex depicted in Fig. 4B is another interesting test system of practical relevance. This complex is able to catalyse N-alkylation to form cationic products *via* the Menschutkin reaction,[119] where it is assumed that the cation-π interaction plays a central role in catalysis and that it is important for the understanding of several biological methylation reactions.[120] For a cyclophane hosting a cationic N-alkylated quinoline (see Figure 4B) a strongly attractive DLPNO-CCSD('T1') / *VeryTightPNO* / 'CBS(def2-TZVPP/def2-QZVPP)' reference association energy (abbreviated as "reference", see the subsection Computational Details) of −37.1 ± 2.0 kcal mol^{-1} is obtained.

The larger error range of the reference is mainly due to the more approximate CBS protocol and to a lesser extent to the approximate correction for iterative triples, both of which were necessary due to the larger system size. The assessed LD-uncorrected DFAs strongly underestimate this association energy by 27.0 kcal mol^{-1} on average and rather repulsive DFAs as, e.g., B3LYP predict the cationic N-alkylated quinoline ligand as only weakly bound (-1.8 kcal mol^{-1}) by the cyclophane cage. Hence, it is mandatory to include LD corrections for hybrid and (meta-)GGA DFAs to be able to reliably calculate such systems. LD-uncorrected PWPB95, which achieved overall reasonably small deviations from the reference for the systems discussed above, deviates by more than one third (12.7 kcal mol^{-1}) from the reference for the cyclophane host-guest system. Hence, it is clearly recommended to apply also double hybrid DFAs with LD correction, especially for larger systems with sizeable LD contribution to the association energy. Moreover, it causes practically no additional computational cost. When incorporating any of the tested LD corrections (either D3 or D4), the deviations of the association energies calculated with the respective DFA-D3 and -D4 methods is much smaller (averaged absolute deviations $\overline{\Delta}$ of 2.6 kcal mol^{-1} and 2.0 kcal mol^{-1}, respectively). Note the outstanding performance of PBE-D3 and PWPB95-D4, which both reproduce the reference very accurately (deviation below 0.2 kcal mol^{-1}), especially considering the larger error bar (± 2 kcal/mol) of the latter. Due to the larger systems size, a CBS(aug-cc-pVTZ/aug-cc-pVQZ) extrapolation was computationally unfeasible with MP2 and hence, an analogous CBS extrapolation employing the def2-TZVPP and def2-QZVPP basis sets was carried out. The MP2/CBS errors are large, similar (on a relative scale) to the π-stacked anthracene$\cdots$C$_3$H$_3$$^+$ system discussed above, overestimating the reference by more than 15 kcal mol^{-1}. This is in accordance to other studies for similar systems,[121,122] where also spin-component scaled versions[123] of MP2 could only partially mitigate this error.[124]

Intramolecular cation-π interactions

Since intramolecular ion-π interactions are also of great importance.[47] Two test cases were chosen, in which cation-π interactions contribute significantly to the stability of conformations. The first example is based on a study of Dougherty *et al.*[125] who proposed that the neurotransmitter acetylcholine can bind to acetylcholinesterase through cation-π interactions. A simplified system is taken from Ref. 126 and exemplified in Figure 6A, where the folded ester conformation (right side of Figure 6A) is proposed to be more stable than the unfolded one. For the isosteric 3,3-dimethylbutyl indole-3-acetate (i.e., replaced ammonium nitrogen with carbon), an analogous folding is not observed. This implies that the cationic nature of the quaternary trimethylammonium group is responsible for this preferable association with the indole ring through cation-π interactions. Folded and unfolded conformations were generated with the recently published CREST algorithm (see subsection Computational Details), and subsequently re-optimized at the PBEh-3c level. Reference DLPNO-CCSD(T1) / *VeryTightPNO* / CBS(aug-cc-pVTZ/aug-cc-pVQZ) conformational energies confirm that the folded arrangement is energetically favored by about 5 ± 0.5 $\mathrm{kcal\,mol^{-1}}$ in gas phase. Strongly directional short-range covalent interactions are also crucial for good relative energies of conformers, but here we focus on the intramolecular NCIs.

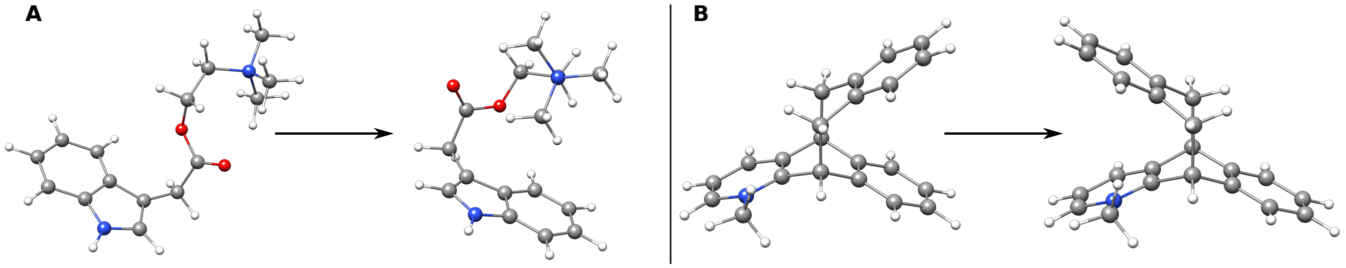

Figure 6: **A** Cation-π interactions influence the conformation of the indole-3-acetic acid choline ester. **B** Competitive behaviour between π-π (left) and cation-π (right) interactions within a seesaw balance.

LD-uncorrected DFAs correctly compute the folded conformer as being more stable but the magnitude of conformational energy is clearly underestimated. For LD-uncorrected DFAs, an averaged absolute deviation $\overline{\Delta}$ of 2.6 $\mathrm{kcal\,mol^{-1}}$ is observed which corresponds to a large error given the relatively small energy difference of the two conformers. The respective individual deviations range from 0.9 kcal mol^{-1} (PWPB95) up to 3.8 kcal mol^{-1} (TPSS). Again, applying LD corrections considerably reduces these errors and small $\overline{\Delta}$ values of only 0.3 kcal mol^{-1} for D3 and 0.2 kcal mol^{-1} for D4-corrected DFAs, respectively, are obtained. The MP2/CBS conformational energy is overestimated by more than 1 kcal mol^{-1} , i.e., it performs clearly inferior to LD-corrected DFAs.

The second example (see Fig. 6B) contains multiple interaction motifs that are able to compete with each other. This seesaw balance[127] adopts two distinct conformations that are either stabilized by cation-π or by π-π interactions. Experimental ^{1}H-NMR studies[43,128] in solution proposed that the cation-π bound conformer is stabilized by about 1.5 kcal mol^{-1} . The gas phase reference conformational energy calculated with the high-level DLPNO-CCSD(T1) / *VeryTightPNO* / CBS(aug-cc-pVTZ/aug-cc-pVQZ) method confirms that the cation-π bonded conformer is stabilized by 2.4 ±0.2 kcal mol^{-1} . LD-uncorrected DFAs qualitative correctly predict the latter to be more stable. Somewhat surprisingly, PWPB95 yields a deviation of only 0.2 kcal mol^{-1} but this is most likely due to fortuitous compensation of errors in predicting the strongly directional short-range covalent interactions and the missing part of the long-range, intramolecular non-covalent LD interactions not covered by MP2. For the other tested DFAs, larger deviations of up to 1.0 kcal mol^{-1} are observed which again represents a huge relative error given the small relative energy of both conformers and compared to the thermal energy at room temperature (0.6 kcal mol^{-1}).

Applying the DFAs together with the D3 or D4 LD corrections again reduces the error significantly, i.e. large deviations (1.0 kcal mol^{-1} for TPSS) are lowered significantly by more than 50% (0.4 kcal mol^{-1} for TPSS-D3 and 0.3 kcal mol^{-1} for TPSS-D4) and already good performing DFAs become even more accurate (0.1 kcal mol^{-1} for PWPB95-D3 and PWPB95-D4, respectively). Overall, the $\overline{\Delta}$ value of 0.7 kcal mol^{-1} for LD-uncorrected DFAs drops to a remarkably small value of only 0.2 kcal mol^{-1} for LD-corrected DFAs (for both LD corrections schemes).

MP2/CBS(aug-cc-pVTZ/aug-cc-pVQZ) describes the relative energy between both conformers accurately denoting the cation-π bounded conformer to be stabilized by 2.7 kcal mol^{-1} . The combined mean deviation in conformational energies (Δ^{ref}) for the indole-3-acetic acid choline ester and the seesaw balance from the reference are illustrated in Figure 7.

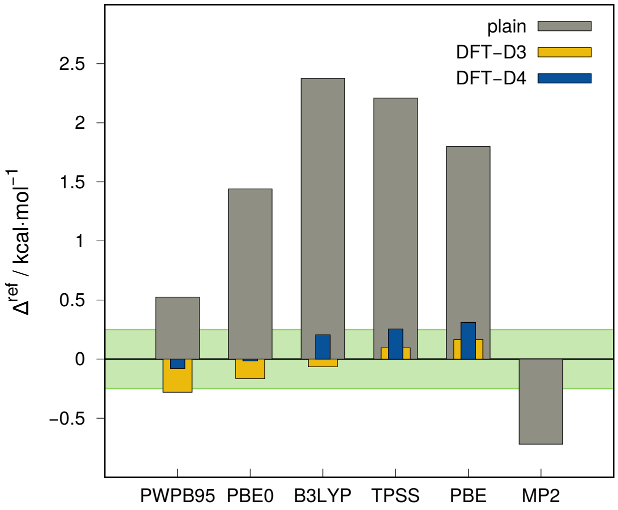

Figure 7: Mean deviation in conformation energies Δ^{ref} (in kcal mol^{-1}) of the respective LD-uncorrected, D3, and D4 LD-corrected DFAs from the DLPNO-CCSD(T1) / *VeryTightPNO* / CBS(aug-cc-pVTZ/aug-cc-pVQZ) reference values for the indole-3-acetic acid choline ester and the seesaw balance. The error range of ± 0.25 kcal mol^{-1} is indicated in green.

Combined Δ^{ref} values for LD-uncorrected, D3, and D4 LD-corrected DFAs from the DLPNO-CCSD(T1) / *VeryTightPNO* / CBS(aug-cc-pVTZ/aug-cc-pVQZ) reference values are given and the error range of ± 0.25 kcal mol^{-1} is indicated in green.

Conclusions

In this work, the importance of London dispersion (LD) for the accurate description of inter- and intramolecular ion-π interactions was analyzed for a diverse set of (bio)chemically relevant molecules, also of larger size. The performance of several popular density functional approximations (DFAs: PBE, TPSS, B3LYP, PBE0, and PWPB95) applied with the large def2-QZVPP basis set and in combination with the D3 and D4 dispersion correction schemes were assessed. Second-order Møller-Plesset perturbation theory (MP2) extrapolated to the complete basis set (CBS) limit was evaluated as computationally more expensive but self-interaction error (SIE) free competitor. Reference interaction and association energies were generated with high-level coupled cluster (W1-F12, W2-F12, and DLPNO-CCSD(T1) / *VeryTightPNO* / CBS) protocols. These data may also be valuable for future studies on the development and validation of low-cost methods, e.g., specialized force fields (FF) for the efficient calculations of ion-π interactions in proteins.

Dissociation curves were considered for two prototypical complexes (anthracene$\cdots C_3H_3^+$ and $C_6F_6\cdots Cl^-$) to estimate how much the SIE reduces the accuracy of the respective DFA (specifically (meta-)GGAs) for ion-π systems. Our investigations revealed that DFAs with Fock exchange (hybrids) are not generally superior to DFAs with approximate DFT exchange ((meta)GGAs), e.g., for the $Cl^-\cdots C_6F_6$ system the tested (meta)GGAs are *on par* with the tested hybrids. However, energy decomposition analyses (EDA) results showed that PBE-D3 suffers from delocalization errors at larger CMA distances while still a reasonably accurate total interaction energy is predicted due to fortuitous error compensation. Furthermore, for the dissociation of anthracene$\cdots C_3H_3^+$ the assessed LD-corrected (meta-)GGA DFAs overbind significantly and yield a too short inter-molecular equilibrium distance which is accompanied by artificial charge-transfer. For the other intermolecular complexes considered in this study, no significant worsening influence of the SIE on the results was found, but also only relative energies at intermolecular equilibrium distance were evaluated.

As further test case, we investigated the additivity of anion-π interactions analyzing the monomer, dimer, and trimer complexes of trifluoro-1,3,5-triazine ($C_3N_3F_3$) with Cl^-. The coupled cluster reference interaction energies decreased by 9.4% and 18.8% for the dimer and trimer in complex with Cl^-, respectively compared to the purely additive monomer interactions with the latter. All computational methods under consideration (LD-uncorrected DFAs, LD-corrected DFAs, and MP2/CBS) were able to reproduce this trend accurately.

Supramolecular ion-π interactions were investigated for larger supramolecular host-guest complexes. An accurate description was found for all tested DFAs provided (LD interaction were properly taken into account by the D3 or D4 correction) while MP2/CBS significantly overestimates the respective association energies.

Intramolecular cation-π interactions were assessed for two examples, an indole-3-acetic acid choline ester featuring cation-π interactions and a molecular seesaw balance with two distinct conformations stabilized by cation-π and π-π interactions, respectively. For the former, all tested computational methods predict the folded ester conformer to be more stable than the unfolded one. For the seesaw balance, the cation-π bounded conformer is consistently predicted by all tested methods to be more stable.

Throughout all tested systems the trend of Jacob's ladder was mostly preserved among the tested DFAs meaning that the performance of (meta-)GGAs was on average improved by hybrids, whereas the highest accuracy was reached most of the time by the double hybrid PWPB95. Generally, an accuracy close to that of the high-level reference was only obtained by adding LD-correction. Overall, the best performance was obtained for all DFAs when coupled to the charge-dependent D4 LD-correction which includes also approximate many-body LD interactions by default. Specifically, PWPB95-D4/def2-QZVPP reaches in many cases an accuracy that is remarkably close to the high-level coupled cluster reference values but at up to two orders of magnitude lower computational cost than MP2/CBS(aug-cc-pVTZ/aug-cc-pVQZ). And even more importantly, the PWPB95-D4/def2-QZVPP is also significantly more accurate (MD = 0.3 $\mathrm{kcal\,mol^{-1}}$, MAD = 0.4 $\mathrm{kcal\,mol^{-1}}$ over all systems tested without the dissociation curves) compared to the MP2/CBS, which systematically and significantly overestimates ion-π interactions (MD = MAD = -5.0 $\mathrm{kcal\,mol^{-1}}$). Therefore, we generally recommend the use of PWPB95-D4/def2-QZVPP for calculating reference interaction energies of larger (100-250 atoms) ion-π systems in favor of MP2/CBS which is still relatively widely used for this purpose. This also extends the possibilities for generating reliable reference values for larger systems, which are essential for the development of low-cost methods to describe ion-π interactions in very large systems such as proteins. This clear and physically meaningful trend only really becomes apparent when larger systems are considered than those assessed in, for example, the ion-π benchmark sets in the GMTKN55 database.

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Supporting Information Available

Information about the availability of employed program packages, definition of the applied statistical measures, detailed results (relative energies and error statistics) (si.pdf); Cartesian atomic coordinates (XYZ) of all geometries of the investigated molecules (geometries.zip).

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