

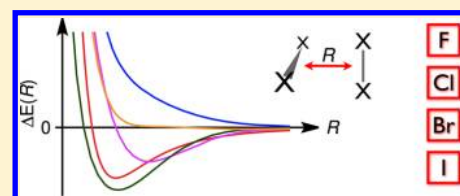
# Intricacies of Describing Weak Interactions Involving Halogen Atoms within Density Functional Theory

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**S** Supporting Information

**ABSTRACT:** In this work we assess the performance of different dispersion-corrected density functional theory (DFT) approaches (M06, M06-2X, DFT-D3, and DCACP) in reproducing high-level wave function based benchmark calculations on the weakly bound halogen dimers  $X_2 \cdots X_2$  and  $X_2 \cdots \text{Ar}$  (for  $X = \text{F}, \text{Cl}, \text{Br}, \text{and I}$ ), as well as the prototype halogen bonded complexes  $\text{H}_3\text{CX} \cdots \text{OCH}_2$  ( $X = \text{Cl}, \text{Br}, \text{I}$ ). In spite of the generally good performance of all tested methods for weakly bound systems, their performance for halogen-containing compounds varies largely. We find maximum errors in the energies with respect to the CCSD(T) reference values of 0.13 kcal/mol for DCACP, 0.22 kcal/mol for M06-2X, 0.47 kcal/mol for BLYP-D3, and 0.77 kcal/mol for M06. The root-mean-square deviations are 0.13 kcal/mol for DCACP and M06-2X, 0.44 kcal/mol for M06, and 0.51 kcal/mol for BLYP-D3.



## 1. INTRODUCTION

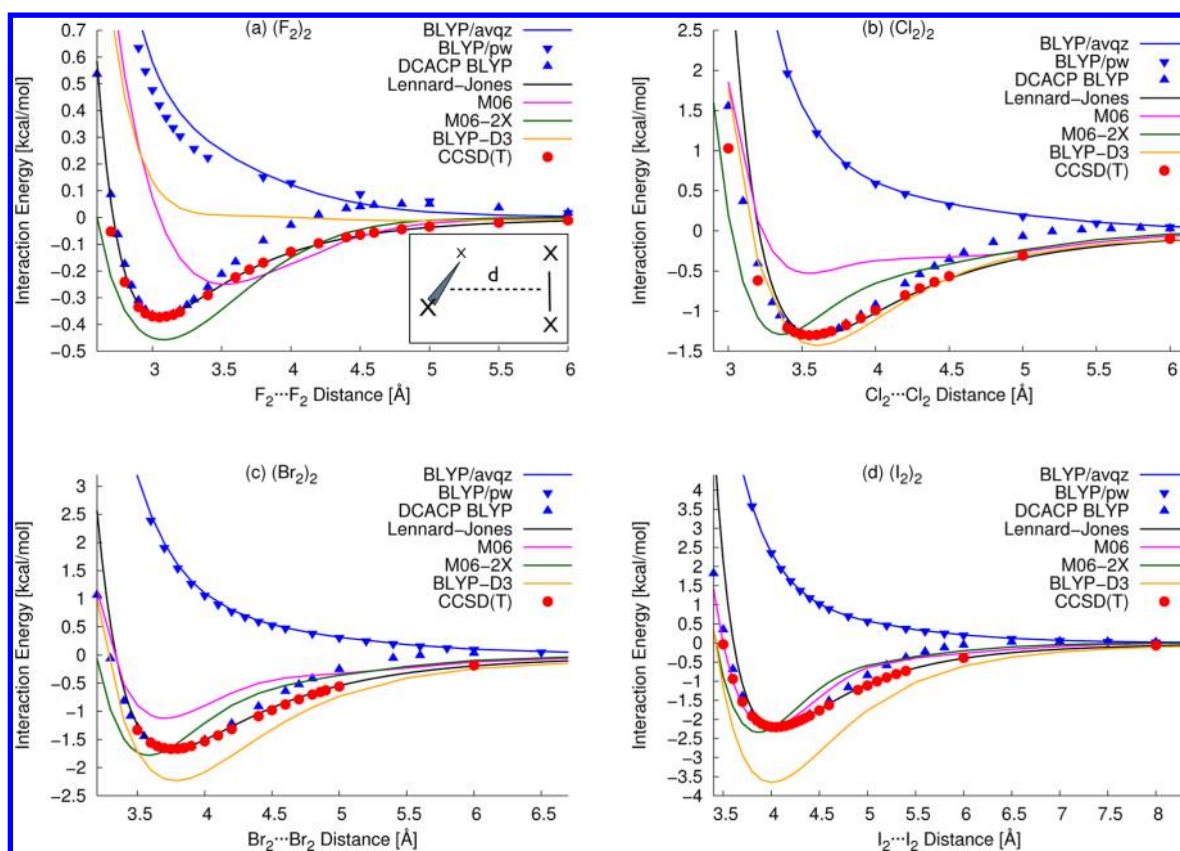
The understanding of noncovalent interactions involving halogen atoms is pivotal for a variety of fields, ranging from stratospheric chemistry,<sup>1–5</sup> materials science and engineering,<sup>6–13</sup> to biological systems<sup>14–17</sup> and medicinal chemistry.<sup>18–22</sup> The importance of halogens for pharmacology seems surprising at first, since only a few natural processes are known in the human body that involve halogen atoms. Chloride ions appear in the stomach acid, some membrane ion channels involved in signal transductions are selective to chloride ions,<sup>23</sup> and iodine is used by the thyroid gland to produce thyroxine.<sup>24</sup> On the other hand, the scarcity of halogens in natural systems might to some extent explain the potency of halogenated drug molecules since their particular chemical properties can be less interfered with or screened by naturally occurring mechanisms. For example, halogenation can render molecules more lipophilic and therefore more transmissible through lipid membranes.<sup>21</sup> Furthermore, replacing a C–H group by C–F inverts the dipole moment of the group and therefore represents a powerful tool in fine-tuning the electrostatic properties of a given lead compound.<sup>25</sup> The greater strength of the C–F bond (~110 kcal/mol) is an additional important factor, since the group becomes less reactive.<sup>19</sup>

In addition, a special noncovalent interaction involving halogens is observed between covalently bound halogen atoms (R–X) and Lewis bases (A):  $\text{R}-\text{X} \cdots \text{A}$ , which has been termed halogen bond,<sup>6,13,26,27</sup> in analogy to the hydrogen bond.<sup>28–31</sup> Much scientific interest has been devoted to the understanding of the underlying physical forces of halogen bonding, both from the experimental and theoretical side. In the emerging picture, the dominating interactions are of electrostatic origin, where a region of positive electrostatic potential located at the end of the R–X bond, called a “ $\sigma$ -hole”, interacts with a region of negative electrostatic potential located on A. However, it has

been shown recently that besides electrostatic effects, dispersion seems to play an important role as well.<sup>32</sup>

For a computational modeling of these types of weak, nonbonded interactions it is well established that high level ab initio methods with a balanced description of electron correlation are necessary,<sup>33</sup> with the coupled cluster method involving single, double, and a perturbative treatment of the triple excitations [CCSD(T)] being the current gold standard. Unfortunately, the high computational cost associated with these methods allows the treatment of only relatively small-sized systems. Computationally more expedient methods would be highly desirable, since halogen bonding is important in biological systems, which are notoriously large. Density functional theory (DFT) methods represent a good trade-off between computational cost and accuracy. Unfortunately, popular exchange-correlation (xc) functionals in the local density approximation (LDA) and generalized gradient approximation (GGA) show severe shortcomings in the description of nonbonded interactions, such as London dispersion forces<sup>34–36</sup> since they depend on local quantities (density and density gradient) only and therefore fail to account for intrinsically nonlocal correlation effects of the electron density. A number of different strategies to overcome this problem in DFT methods have been proposed in the recent literature. The incorporation of dispersion interactions directly via nonlocal density functionals<sup>37,38</sup> shows promising results but is computationally not tractable for large-scale applications. Alternatively, classical two-body potentials with  $C_6/R^6$  dependence can be added to the DFT energy, where the  $C_6$  coefficient is determined either empirically,<sup>39–42</sup> derived from atomic polarizabilities as functional of the in situ atomic electron density,<sup>43</sup> or calculated from the instantaneous dipole

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**Figure 1.** Interaction energies of the  $X_2 \cdots X_2$  dimers ( $X = \text{F}, \text{Cl}, \text{Br}, \text{I}$ ) in perpendicular configuration, as shown in the inset of part a, using DCACP augmented BLYP, M06, M06-2X, and BLYP-D3. For comparison, the CCSD(T) references, the uncorrected BLYP interaction energies, and Lennard-Jones curves fitted to the respective DCACP minima are also shown.

moment of the exchange hole.<sup>44–46</sup> Furthermore impressive results have been obtained using highly parametrized meta-hybrid-GGA xc functionals.<sup>47–50</sup> Alternatively, in the DCACP approach dispersion interactions are captured by an empirical correction term to the total Kohn–Sham potential which is decomposed into atom-centered nonlocal contributions.<sup>51</sup> In a number of preceding communications it has been demonstrated that DCACPs are highly transferable and show a great improvement in the description of weak interactions over popular GGA xc functionals in systems as different as inert gases,<sup>52</sup> aliphatic and aromatic hydrocarbons,<sup>53</sup> stacked base pairs,<sup>54</sup> hydrogen-bonded complexes,<sup>54,55</sup> and bulk water.<sup>56</sup>

In view of the great importance of a reliable description of systems involving halogen atoms, we calculated interaction energy curves for the  $X_2 \cdots X_2$  and  $X_2 \cdots \text{Ar}$  (for  $X = \text{F}, \text{Cl}, \text{Br}, \text{I}$ ) dimers, as well as for the halogen bonded prototype complexes  $\text{H}_3\text{CX} \cdots \text{OCH}_2$  ( $X = \text{Cl}, \text{Br}, \text{I}$ ) with a variety of DFT approaches. We assessed the performance of the uncorrected Becke–Lee–Yang–Parr (BLYP)<sup>57,58</sup> xc functional as well as the dispersion-corrected DFT approaches DCACP augmented BLYP, BLYP-D3,<sup>59</sup> M06,<sup>60</sup> and M06-2X<sup>60</sup> in reproducing high-level wave function based benchmark calculations. These performance tests show that uncorrected BLYP is not able to describe these interactions and dispersion-corrected methods have to be employed. The DCACP results are in excellent agreement with the CCSD(T) reference values with a maximum error (MAX) of 0.13 kcal/mol and root-mean-square deviation (RMSD), mean signed error (MSE), and mean unsigned error (MUE) below 0.1 kcal/mol. M06-2X has the best performance among all other tested DFT approaches

but with MAX 0.22 kcal/mol and RMSD 0.13 kcal/mol has essentially twice as large errors as DCACPs. BLYP-D3 performs well on some systems but shows large significant errors for a few halogen containing systems resulting in an overall performance of MAX 0.47 kcal/mol, RMSD 0.51 kcal/mol, MSE −0.13 kcal/mol, and MUE 0.32 kcal/mol. M06 has relative errors above 50% in more than half of the systems considered in this work (MAX 0.77 kcal/mol, RMSD 0.44 kcal/mol, MSE 0.34 kcal/mol, and MUE 0.36 kcal/mol).

## 2. METHODS

**2.1. DCACPs and Calibration.** The underlying theory of the DCACP methodology has been discussed in detail elsewhere,<sup>51,52,61</sup> we therefore restrict this section to a brief recapitulation. The formalism introduces a general correction term to the total Kohn–Sham potential which is decomposed in atom-centered contributions. It has been shown from a formal point of view that the multiatom-centered potential approach is a valid expansion for the corrections to the approximated universal density functional.<sup>61</sup> This formalism is completely general, and the correction potential can be expressed in any desirable functional form that features the necessary flexibility. For practical reasons, we have adopted an analytic functional form of atom-centered angular-momentum-dependent potentials identical to the nonlocal part of the atomic pseudopotentials developed by Goedecker et al.<sup>62</sup>

$$\hat{v}_l^{\text{DCACP}}(\mathbf{r}, \mathbf{r}') = \sum_{l=0}^{l_{\max}} \sum_{m=-l}^{+l} Y_{lm}(\hat{\mathbf{r}}) p_l(r) \sigma_l p_l(r') Y_{lm}^*(\hat{\mathbf{r}}') \quad (1)$$

with the normalized projector  $p_l(r) \propto r^l \exp[-r^2/(2\sigma_2^2)]$ . Here  $r = |\mathbf{r} - \mathbf{R}_I|$  is the distance from the position of nucleus  $I$ ,  $\hat{\mathbf{r}}$  is the unit vector in the direction of  $\mathbf{r} - \mathbf{R}_I$  and  $Y_{lm}$  denotes a spherical harmonic. In the current generation of DCACPs, only one channel,  $l = 3$ , is employed. However, with as few as two angular-momentum components in the expansion, it is also possible to achieve the correct  $r^{-6}$  asymptotic behavior.<sup>61</sup> It is important to notice that despite of this particular functional form, DCACPs are not additions or corrections to the *ab initio* pseudopotentials, since they model completely different physical effects at different scales of energy and nucleus–electron separation. On the other hand, due to their functional form they are tailored for pseudopotential plane-wave and mixed Gaussian-plane-wave codes with only a small computational overhead but the benefit of describing interaction energies at essentially CCSD(T) accuracy.

The two element specific tuning parameters  $\sigma_1$  and  $\sigma_2$  are determined by minimizing the penalty function

$$\begin{aligned} \min_{\sigma_i} \mathcal{P}(\mathbf{r}) = & \min_{\sigma_i} [ |E^{\text{ref}}(\mathbf{r}_{\min}) - E(\mathbf{r}_{\min}, \{\sigma_i\})|^2 \\ & + w_m |E^{\text{ref}}(\mathbf{r}_{\text{mid}}) - E(\mathbf{r}_{\text{mid}}, \{\sigma_i\})|^2 \\ & + \sum_I w_I |E_I(\mathbf{r}_{\min}, \{\sigma_i\})|^2 ] \end{aligned} \quad (2)$$

that depends on the difference of the intermolecular energy  $E(\mathbf{r})$  at the equilibrium and the midpoint distance ( $E(\mathbf{r}_{\min})$  and  $E(\mathbf{r}_{\text{mid}})$ ) with respect to a given high-level reference calculation on a suitably chosen reference system.  $E^{\text{ref}}(\mathbf{r})$  is the reference interaction energy at  $\mathbf{r}$ . Furthermore the penalty function contains a contribution of the forces along the intermolecular axis at the minimum position. The weighting factor  $w_I$  is set in such a way as to scale the force contributions to the same order of magnitude as the energy contributions.

DCACPs are a general correction to the approximate Kohn–Sham potential<sup>61</sup> and can, in principle, also include short-range contributions beyond dispersion. Therefore, the reference system is chosen such that its interaction energy is dominated by dispersion. This ensures that the energy-scale and spatial domain of the DCACPs are characteristic for dispersion dominated interactions. Furthermore, the reference system should be small to allow the application of high-level *ab initio* methods in combination with large basis sets to obtain accurate reference energies. Another prerequisite for the calibration system is that it is preferably homo-atomic in order to exclude interference effects from other elements.

The current library of DCACPs comprises the inert gases and the elements hydrogen, carbon, oxygen, nitrogen, sulfur, and phosphorus.<sup>52,63,64</sup> In this work, DCACPs for BLYP were calibrated for fluorine, chlorine, bromine, and iodine. The choice of the BLYP functional is motivated by the fact that it is a well-established GGA functional in the context of organic and biochemical systems and, moreover, does not have any spurious dispersion interactions, e.g. the interaction of rare gas dimers is fully repulsive. The obtained parameters for the dispersion correction are therefore more transferable than for GGAs with spurious dispersion interactions, such as the Perdew–Burke–Ernzerhof functional (PBE).<sup>65</sup> We have chosen the halogen dimers  $X_2 \cdots X_2$  in the perpendicular orientation shown in Figure 1a as dispersion-dominated reference systems. The interaction energies shown in Figure 1 were computed along the intermolecular axis varying the distance  $d$  between the bond midpoints, while keeping the monomer bond lengths fixed at

the equilibrium distance of the respective isolated molecules, 1.41 Å for fluorine, 1.988 Å for chlorine, 2.28 Å for bromine, and 2.67 Å for iodine. Coupled Cluster reference interaction energy curves were computed at the CCSD(T)/(pp-)aug-cc-pVQZ level of theory, which feature minima for all four complexes with binding energies of  $\sim 0.4$ –2.2 kcal/mol. The DCACPs were obtained by calibration against these reference energies at two critical intermolecular distances for the corresponding weakly bound  $(X_2)_2$  dimers ( $X = \text{F, Cl, Br, I}$ ):  $\mathbf{r}_{\min}$  and  $\mathbf{r}_{\text{mid}}$  in eq 2. The calibration was performed in such a way as to obtain optimal accuracy around the equilibrium geometries while less emphasis was put on the accurate reproduction of the reference data far from equilibrium. It has already been demonstrated that the correct asymptotic behavior at large intermolecular distances can easily be achieved by adding a second channel,<sup>61</sup> and a library of DCACPs with improved asymptotic behavior is currently in preparation.<sup>66</sup> The weighting factors  $w_I$  were therefore set to

$$w_I = \begin{cases} 1.0 & \text{if } \mathcal{F} > 1.0 \times 10^{-9} \\ 0.01 & \text{otherwise} \end{cases} \quad (3)$$

with  $\mathcal{F} = \sum_I |E_I(\mathbf{r}_{\min}, \{\sigma_i\})|^2$ . Here  $w_m$  was set to

$$w_m = \begin{cases} 1.0 & \text{if } |E^{\text{ref}}(\mathbf{r}_{\min}) - E(\mathbf{r}_{\min}, \{\sigma_i\})| \\ & \geq 0.01 |E^{\text{ref}}(\mathbf{r}_{\min})| \\ 0.01 & \text{if } |E^{\text{ref}}(\mathbf{r}_{\min}) - E(\mathbf{r}_{\min}, \{\sigma_i\})| \\ & < 0.01 |E^{\text{ref}}(\mathbf{r}_{\min})| \end{cases} \quad (4)$$

if  $\mathcal{F} \leq 1.0 \times 10^{-9}$ , and  $w_m = 0.0$  otherwise. The DCACP parameters determined in this work are listed in Table 1 and the resulting DCACP-BLYP interaction energies closely match the CCSD(T) references (see Table 2 and Figure 1).

**Table 1.** DCACP Parameters for the  $l = 3$  Channel in Equation 1 for the Elements F, Cl, Br, and I in Conjunction with the BLYP xc Functional in Atomic Units

	$\sigma_1 [10^{-4}]$	$\sigma_2$
F	−7.03	2.4
Cl	−16.00	2.6709
Br	−14.08	2.9997
I	−22.22	3.0463

**2.2. Computational Details.** For the interaction energy between two monomers (K and L) in a dispersion bound dimer (KL), we apply the definition  $E_{\text{int}}(\text{KL}) = E_{\text{KL}} - (E_{\text{K}} + E_{\text{L}})$ . For the calculation of the interaction energy, no zero point energies or thermal corrections were included. In all calculations, the monomers were kept fixed at the respective equilibrium geometries, as described in the Results and Discussion section. All plane wave (pw) DFT calculations were performed with the software package CPMD<sup>67</sup> with the self-consistent field (SCF) convergence criterion for the Kohn–Sham orbitals set to  $10^{-7}$  a.u. The scalar relativistic pseudopotentials of Goedecker et al.<sup>62,68,69</sup> were employed using pw cutoffs of 600 (for fluorine), 150 (for chlorine), and 120 Ry (for bromine and iodine containing systems). These calculations were carried out in isolated cubic cells with edge lengths of 16 ( $(\text{F}_2)_2$ ), 17 ( $\text{F}_2\text{Ar}$ ), 18 ( $(\text{Cl}_2)_2$  and  $\text{Cl}_2\text{Ar}$ ), 20 ( $(\text{X}_2)_2$  and  $\text{X}_2\text{Ar}$ ,  $\text{X} = \text{Br, I}$ ), and 28 Å ( $\text{H}_3\text{CX} - \text{OCH}_3$ ,  $\text{X} = \text{Cl, Br, I}$ ), using the Hockney Poisson solver as implemented in CPMD.<sup>70</sup>



**Table 2.** Equilibrium Distances (Å) and Interaction Energies in Brackets (kcal/mol) for the Calibration Systems  $X_2 \cdots X_2$  ( $X = \text{F, Cl, Br, I}$ )

element X	CCSD(T)	BLYP	BLYP + DCACP	BLYP-D3	M06	M06-2X
F	3.05 (−0.37)	(0.42) <sup>a</sup>	3.05 (−0.37)	(0.10) <sup>a</sup>	3.55 (−0.25)	3.10 (−0.46)
Cl	3.55 (−1.30)	(1.37) <sup>a</sup>	3.60 (−1.31)	3.60 (−1.43)	3.55 (−0.53)	3.35 (−1.29)
Br	3.75 (−1.67)	(1.71) <sup>a</sup>	3.75 (−1.68)	3.80 (−2.23)	3.70 (−1.12)	3.60 (−1.78)
I	4.05 (−2.20)	(1.02) <sup>a</sup>	4.05 (−2.23)	4.00 (−3.65)	3.95 (−2.21)	3.85 (−2.34)

<sup>a</sup>For repulsive interaction curves, the quoted interaction energy is calculated at the equilibrium distance of the corresponding CCSD(T) complex.

For the coupled cluster reference values, energies for the  $(X_2)_2$  dimers were computed at the CCSD(T)<sup>71,72</sup> level of theory with the aug-cc-pVQZ<sup>73,74</sup> (avqz) basis sets as implemented in MOLPRO 2006.1.<sup>75</sup> We also tested different extrapolation schemes to the CBS limit (see the Supporting Information). To account for relativistic effects in iodine, pseudopotentials, consistent with the respective correlation consistent basis sets, were applied (pp-aug-cc-pVQZ).<sup>76</sup>

The M06/(pp)-aug-cc-pVQZ and M06-2X/(pp)-aug-cc-pVQZ calculations were performed using the Gaussian G09<sup>77</sup> software package employing tight convergence criteria and an especially fine grid for integral evaluation ([350,770] for F and [350,590] for Cl, Br, I). See the Supporting Information for a benchmark of different grid sizes and ref 78 for a discussion of the effect of the grid spacing on the smoothness of the potential energy curves of dispersion bound complexes in meta-GGA calculations. For the BLYP-D3<sup>59</sup> calculations, BLYP/(pp)-aug-cc-pVQZ energies from Gaussian G09 were augmented with the results from Grimme's DFT-D3 program<sup>79</sup> employing Becke–Johnson damping.<sup>80</sup> All calculations of interaction energies involving atom-centered basis sets were corrected for the basis set superposition error employing the counterpoise correction.<sup>81</sup>

**2.3. Statistical Quantities.** In order to compare the performance of the various DFT methods on the test set for weak interactions involving halogens, we compute the maximum error (MAX, eq 5), root-mean-square deviation (RMSD, eq 6), mean signed error (MSE, eq 7), and mean unsigned error (MUE, eq 8) as follows:

$$\text{MAX} = \max\{E_{\text{int}}^{\text{DFT}}(\text{KL}) - E_{\text{int}}^{\text{ref}}(\text{KL})\}_N \quad (5)$$

$$\text{RMSD} = \sqrt{\frac{1}{N} \sum_N (E_{\text{int}}^{\text{DFT}}(\text{KL}) - E_{\text{int}}^{\text{ref}}(\text{KL}))^2} \quad (6)$$

$$\text{MSE} = \frac{1}{N} \sum_N E_{\text{int}}^{\text{DFT}}(\text{KL}) - E_{\text{int}}^{\text{ref}}(\text{KL}) \quad (7)$$

$$\text{MUE} = \frac{1}{N} \sum_N |E_{\text{int}}^{\text{DFT}}(\text{KL}) - E_{\text{int}}^{\text{ref}}(\text{KL})| \quad (8)$$

where  $E_{\text{int}}^{\text{DFT}}(\text{KL})$  represents the interaction energy in the dimer KL computed at the respective DFT method and  $E_{\text{int}}^{\text{ref}}(\text{KL})$  is the reference CCSD(T) value. We evaluate the errors for all  $N = 11$  dimers KL in  $X_2 \cdots X_2$  ( $X = \text{F, Cl, Br, I}$ ),  $X_2 \cdots \text{Ar}$  ( $X = \text{F, Cl, Br, I}$ ) and  $\text{H}_3\text{CX} \cdots \text{OCH}_2$  ( $X = \text{Cl, Br, I}$ ) of the test set. These error quantities provide complementary information. RMSD is a measure for the average performance over the test set with a comparably large weight on outliers. MAX shows the variability of the error and possible unpredictable behavior. MUE is a similar measure like the RMSD but does not stress strong outliers. MSE contains additional information about possible

systematic trends, e.g. negative values indicating a systematic overestimation of the interaction energy.

### 3. RESULTS AND DISCUSSION

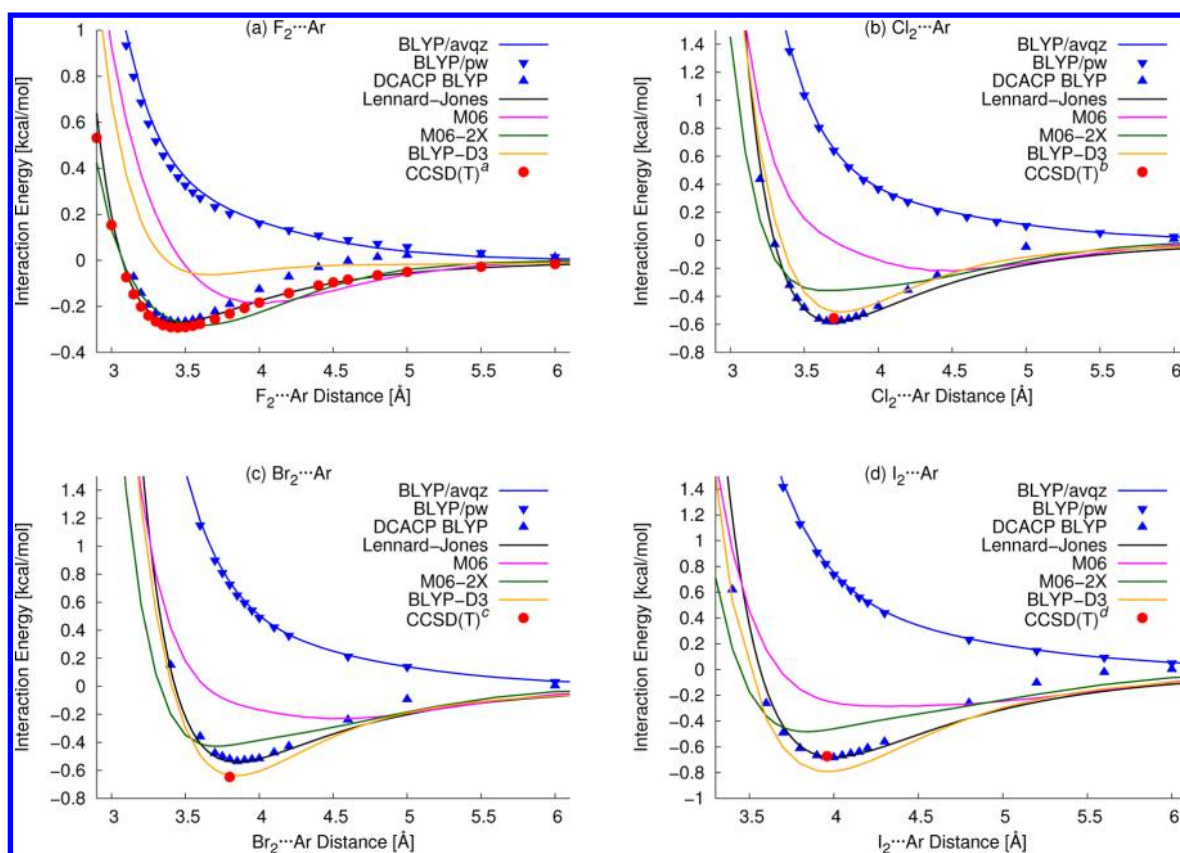
**3.1. Performance for  $X_2 \cdots X_2$  Complexes.** The interaction energy curves of the  $X_2 \cdots X_2$  complexes at various levels of theory are shown in Figure 1. For all intermolecular separations the monomer bond lengths were kept fixed at 1.41 Å for fluorine, 1.988 Å for chlorine, 2.28 Å for bromine, and 2.67 Å for iodine. The CCSD(T) reference curves feature a minimum for all four complexes, which extends to larger intermolecular distance (3.05–4.05 Å) and larger binding energy (0.37–2.2 kcal/mol) when moving down the group (Table 2). As expected, uncorrected BLYP fails in all four cases to describe this interaction, predicting purely repulsive interaction energy curves. This is a strong indication that the dominant interaction is indeed dispersion. For the calibration of the DCACP parameters, only the interaction energies at the reference equilibrium distance and the midpoint were used. Therefore, the interaction energies at the other distances are already a first test for transferability. The DCACP-BLYP binding energy curves match well the CCSD(T) references. The reference equilibrium distances are accurately reproduced, only the  $\text{Cl}_2 \cdots \text{Cl}_2$  distance is 0.05 Å too long. The largest relative error in the well depth amounts to ~1% in  $(\text{I}_2)_2$ . For comparison, also Lennard-Jones 12–6 potentials with minima at the respective DCACP-BLYP positions are shown. Furthermore, we tested the performance of M06, M06-2X, and BLYP-D3 for the closed-shell interhalogen interactions. Tables 2 and 3 summarize the numerical results, and the

**Table 3.** Unsigned Error in Percent with Respect to the CCSD(T) References of the Binding Energy of the  $X_2 \cdots X_2$  ( $X = \text{F, Cl, Br, I}$ ) Systems

element X	BLYP	BLYP + DCACP	BLYP-D3	M06	M06-2X
F	213.5 <sup>a</sup>	0.1	126.4 <sup>a</sup>	32.0	24.3
Cl	205.4 <sup>a</sup>	0.6	10.0	59.4	0.8
Br	202.4 <sup>a</sup>	0.9	33.9	32.8	6.6
I	146.4 <sup>a</sup>	1.0	65.7	0.5	6.4

<sup>a</sup>For repulsive interaction curves, the error is calculated at the equilibrium distance of the corresponding CCSD(T) complex.

relative percentage errors in the interaction energy minimum are reproduced graphically in Figure 4. M06 performs worst among these methods. The overall trend of increasing well depth and longer equilibrium distance for the heavier elements is correctly reproduced. However, the errors in the equilibrium distance range from an overestimation by 0.5 Å in case of the fluorine complex to an underestimation by 0.1 Å in case of the iodine complex. The well depth is generally underestimated by ~30–60%, with the exception of an overestimation of 1% in  $(\text{I}_2)_2$ . M06-2X shows a more balanced and overall better



**Figure 2.** Interaction energies in the weakly bound  $X_2 \cdots \text{Ar}$  complexes. DCACP augmented BLYP versus standard BLYP, M06, BLYP-D3, and CCSD(T) references. See caption of Table 4 for details and citations of the CCSD(T) references.

**Table 4.** Equilibrium Distance (Å) and Binding Energies in Brackets (kcal/mol) for the  $X_2 \cdots \text{Ar}$  Systems

element X	CCSD(T)	BLYP	BLYP + DCACP	BLYP-D3	M06	M06-2X
F	3.45 (−0.29) <sup>b</sup>	(0.36) <sup>a</sup>	3.45 (−0.27)	3.70 (−0.06)	4.05 (−0.19)	3.60 (−0.28)
Cl	3.70 (−0.56) <sup>c</sup>	(0.64) <sup>a</sup>	3.70 (−0.58)	3.75 (−0.51)	4.35 (−0.22)	3.70 (−0.36)
Br	3.80 (−0.65) <sup>d</sup>	(0.73) <sup>a</sup>	3.85 (−0.54)	3.85 (−0.64)	4.50 (−0.23)	3.70 (−0.43)
I	3.96 (−0.67) <sup>e</sup>	(0.82) <sup>a</sup>	4.00 (−0.68)	3.95 (−0.79)	4.30 (−0.29)	3.85 (−0.48)

<sup>a</sup>For repulsive interaction curves, the quoted interaction energy is calculated at the equilibrium distance of the corresponding CCSD(T) complex. References for the X = F, Cl, Br, I systems at the CCSD(T) level of theory are available employing different types of basis sets. <sup>b</sup>Aug-cc-pVQZ (this work). <sup>c</sup>Aug-cc-pVQZ.<sup>82</sup> <sup>d</sup>SDD+G(3df) for Br and aug-cc-pVQZ+(3s3p2d2f1g) for Ar.<sup>83</sup> <sup>e</sup>Stuttgart (SDD)/+ (sp) + (3df) for I, aug-cc-pVQZ + (3s3p2d2f1g) for Ar.<sup>84</sup>

agreement with respect to the CCSD(T) references. The relative errors in the well depths range from 24% in case of fluorine to 1% in case of chlorine. The equilibrium distance of  $(F_2)_2$  is in almost perfect agreement with the CCSD(T) value, while for the remaining elements it is slightly underestimated by  $\sim 0.2$  Å. For BLYP-D3, the interaction energy curve of the  $F_2 \cdots F_2$  complex is purely repulsive, adding only a marginal dispersion contribution onto the BLYP energies. The  $X_2 \cdots X_2$  complexes for the heavier elements, on the other hand, are all bound, but the interaction energies are overestimated by 10–66%. The equilibrium distances are predicted within 0.05 Å.

**3.2. Performance for  $X_2 \cdots \text{Ar}$  Complexes.** In order to assess the performance of uncorrected BLYP, DCACP augmented BLYP, M06, M06-2X, and BLYP-D3 on a heteronuclear test system, we computed the interaction energy curves of  $X_2 \cdots \text{Ar}$  complexes (in a T-shaped arrangement) along the distance between the center of mass of  $X_2$  and Ar while keeping the monomer bond lengths fixed at the equilibrium distance of the respective isolated molecule (1.41 Å  $F_2$ , 1.988 Å  $Cl_2$ ,

2.28 Å  $Br_2$ , and 2.67 Å  $I_2$ ). From Figures 2b and d, it can be seen that as expected standard BLYP is not able to describe these interactions predicting repulsive interaction energy curves for all four complexes. DCACP augmented BLYP, on the other hand, reproduces very well the equilibrium distances and interaction energies of the CCSD(T) reference data. The overall trend of larger binding energies and longer equilibrium distances toward the heavier halogens is also correctly reproduced. The errors in the well depths range from 2–17%. M06 predicts for all  $X_2 \cdots \text{Ar}$  complexes a bonded interaction energy curve but underestimates the interaction energy by as much as 36–64% in parallel with an overestimation of the equilibrium distances by  $\sim 0.4$  Å. M06-2X performs better than M06, both in terms of well depth and equilibrium distance. It underestimates the interaction energy by 3% ( $F_2 \cdots \text{Ar}$ ) to 36% ( $Cl_2 \cdots \text{Ar}$ ). BLYP-D3 predicts correctly the overall trend of stronger binding energies and longer equilibrium distances toward the heavier halogens; however, it clearly underestimates the dispersion contribution of fluorine,

producing a relative error in the well depth of 79% in the case of the  $F_2 \cdots Ar$  complex. The errors in the remaining systems are of the same order of magnitude as for BLYP-DCACP. The numerical results are summarized in Tables 4 and 5, and the relative energetic errors are plotted in Figure 4 for comparison.

**Table 5. Unsigned Error in Percent with Respect to the CCSD(T) References of the Binding Energy of the  $X_2 \cdots Ar$  ( $X = F, Cl, Br, I$ ) Systems**

element X	BLYP	BLYP + DCACP	BLYP-D3	M06	M06-2X
F	224.1 <sup>a</sup>	6.9	79.3	34.5	3.5
Cl	214.3 <sup>a</sup>	3.6	8.9	60.7	35.7
Br	212.3 <sup>a</sup>	16.9	1.5	64.6	33.9
I	222.4 <sup>a</sup>	1.5	17.9	56.7	28.4

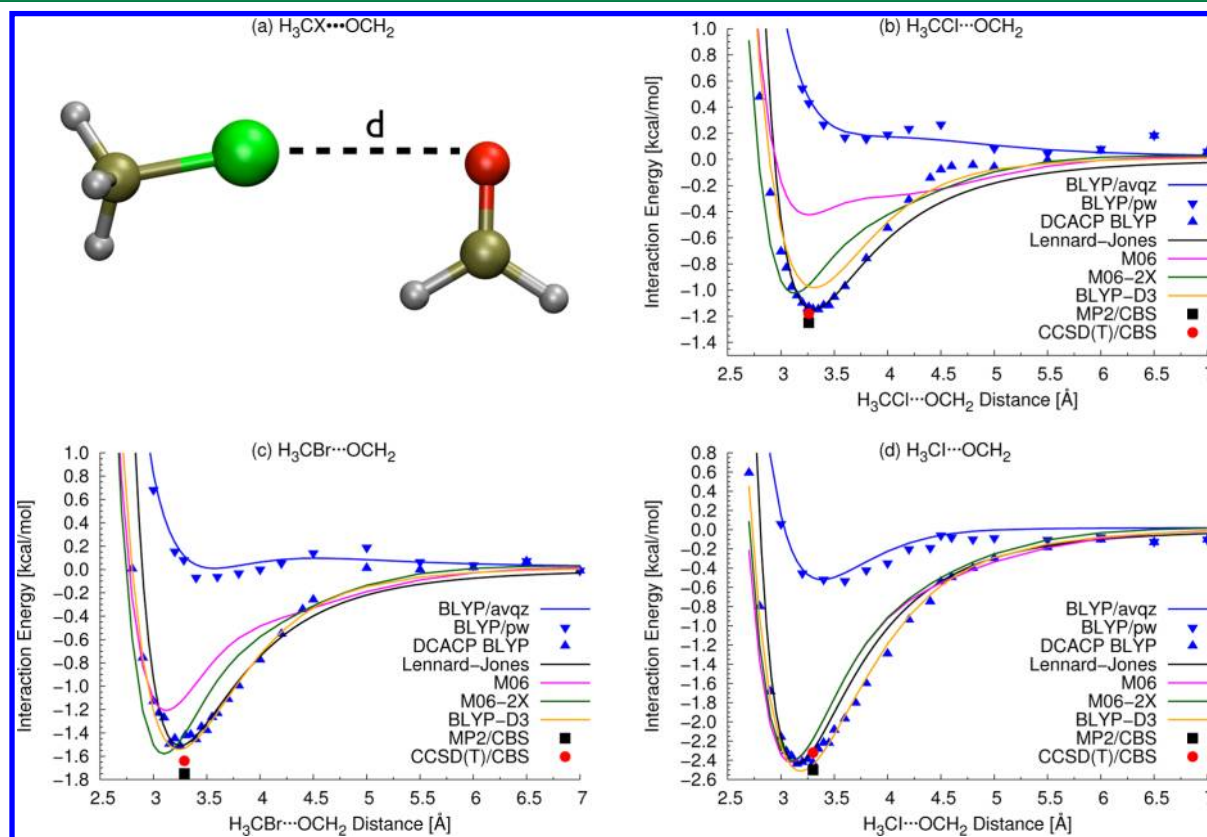
<sup>a</sup>For repulsive interaction curves, the error is calculated at the equilibrium distance of the corresponding CCSD(T) complex.

**3.3. Performance for the  $H_3CX \cdots OCH_2$  Complexes.** As a second family of test systems for weak interactions involving halogens, we selected the halomethane-formaldehyde complexes  $H_3CX \cdots OCH_2$  ( $X = Cl, Br, I$ ), which are considered as prototype systems for halogen bonding. This is expected to be a more serious test since the binding is due to a delicate interplay between several types of weak interactions besides dispersion.<sup>32</sup> The interaction energy curves along the  $X \cdots O$  axis ( $d$  in 2) were computed at the BLYP, DCACP, BLYP-D3, M06, and M06-2X level of theory (Figure 3) keeping the monomers fixed at the MP2 equilibrium geometries from ref 85. Reference values at the MP2 complete basis set limit (CBS) and

CCSD(T)/CBS level of theory for the interaction energy at the MP2 equilibrium geometry are taken from ref 32. At the CCSD(T) level, all complexes are weakly bound with slightly increasing well depths along the group from 1.18 kcal/mol for  $X = Cl$ , to 1.64 kcal/mol for  $Br$  and 2.32 kcal/mol for  $I$ . At the same time, the equilibrium distance remains almost the same around 3.3 Å. Uncorrected BLYP produces a purely repulsive interaction energy curve for the  $H_3CCl \cdots OCH_2$  complex, and overall, it is not able to capture the interactions governing halogen bonding in these model complexes. DCACP augmented BLYP, on the other hand, reproduces well the reference equilibrium distances and interaction energies. The errors in the interaction energy minima range from 3–8%. BLYP-D3 performs comparably well with errors in the binding energy of 6–17%. M06-2X results are only marginally better than BLYP-D3 in the interaction energies and the equilibrium distances are 0.1 Å too short for all complexes. For M06 the errors in the interaction energies span a large range from 4% to 64% with a systematic improvement from  $X = Cl$  to  $Br$  and  $I$ . The equilibrium distance is in perfect agreement with the reference for the chlorine complex but 0.2 Å too short for the remaining two systems. See Tables 6 and 7 for the details and Figure 4 for the graphical representation of the error distribution.

Reference values at the MP2 complete basis set limit (CBS) and CCSD(T)/CBS level of theory for the interaction energy at the MP2 equilibrium geometry are taken from ref 32.

**3.4. Summary of the Performance of the Different Methods.** For comparison, Figure 4 shows the relative error in the interaction energy at the equilibrium distance of all tested



**Figure 3.** Interaction energies in the halogen bonded  $H_3CX \cdots OCH_2$  complexes ( $X = Cl, Br, I$ ) along the  $X \cdots O$  axis (a). DCACP augmented BLYP versus standard BLYP, M06, BLYP-D3, and CCSD(T) references.<sup>32</sup>

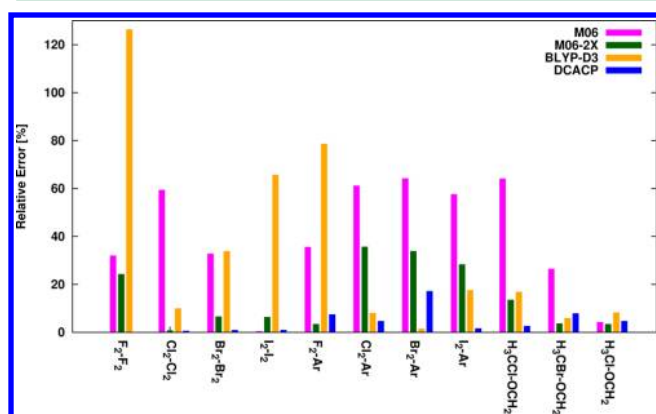


**Table 6.** Interaction Energy Minima Positions (Å) and Energies in Brackets (kcal/mol) for the  $\text{H}_3\text{CX}\cdots\text{OCH}_2$  systems ( $\text{X} = \text{Cl}, \text{Br}, \text{I}$ ) with Fixed Monomer Geometries as Optimized at the MP2/CBS Level in Reference 32<sup>a</sup>

element X	CCSD(T)/CBS <sup>32</sup>	BLYP	BLYP + DCACP	BLYP-D3	M06	M06-2X
Cl	3.26 (−1.18)	3.80 (0.16)	3.35 (−1.15)	3.30 (−0.98)	3.26 (−0.42)	3.15 (−1.02)
Br	3.29 (−1.64)	3.40 (−0.07)	3.25 (−1.51)	3.25 (−1.54)	3.10 (−1.21)	3.10 (−1.58)
I	3.30 (−2.32)	3.60 (−0.53)	3.15 (−2.44)	3.20 (−2.51)	3.10 (−2.42)	3.10 (−2.40)

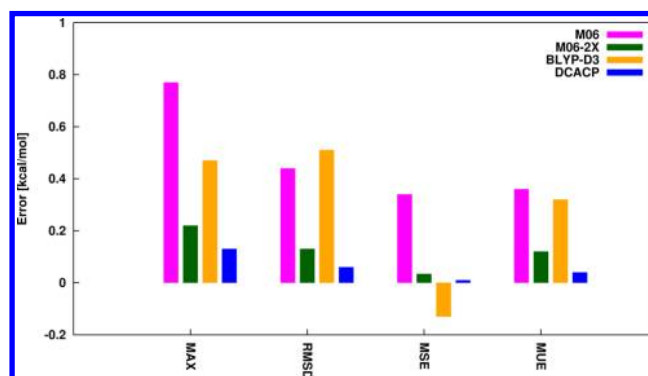
<sup>a</sup>The CCSD(T) energies are reproduced from ref 32.**Table 7.** Unsigned Error in Percent with Respect to the CCSD(T) References of the Binding Energy of the  $\text{H}_3\text{CX}\cdots\text{OCH}_2$  Systems ( $\text{X} = \text{Cl}, \text{Br}, \text{I}$ )

element X	BLYP	BLYP + DCACP	BLYP-D3	M06	M06-2X
Cl	136.4 <sup>a</sup>	2.5	17.0	64.4	13.6
Br	95.7 <sup>a</sup>	7.9	6.1	26.2	3.7
I	77.2 <sup>a</sup>	5.2	8.2	4.3	3.5

<sup>a</sup>For repulsive interaction curves, the error is calculated at the equilibrium distance of the corresponding CCSD(T) complex.**Figure 4.** Relative percentage error of the interaction energy well depth with respect to CCSD(T) for all weakly bound complexes considered in this work.

methods with respect to the CCSD(T) values. BLYP-D3 does not predict a minimum for the  $\text{F}_2\cdots\text{F}_2$  complex. For this case the relative energy difference at the CCSD(T) equilibrium distance was considered for the calculation of the relative error. In summary, M06 results in relative errors above 50% for more than half of the systems considered in this work. For BLYP-D3, the errors are surprisingly large, ranging from 10 to over 120% for the homonuclear complexes ( $\text{X}_2$ )<sub>2</sub>, although these are the simplest systems and no cross-coupling between different element-specific parameters sets should interfere. In addition, the large error for the  $\text{F}_2\text{Ar}$  (79%) complex indicates a general problem in the description of dispersion interactions involving fluorine. In the remaining systems  $\text{X}_2\cdots\text{Ar}$  and  $\text{H}_3\text{CX}\cdots\text{OCH}_2$  ( $\text{X} = \text{Cl}, \text{Br}, \text{I}$ ) the relative errors are of the same order as for DCACP. M06-2X performs better than BLYP-D3 in almost all systems, except  $\text{X}_2\text{Ar}$  ( $\text{X} = \text{Cl}, \text{Br}, \text{I}$ ). Overall, DCACP shows the best performance.

Figure 5 summarizes the maximum error, root-mean-square deviation, mean signed error, and mean unsigned error (eqs 5–8) of the binding energies with respect to the CCSD(T) reference for DCACP, M06, M06-2X, and BLYP-D3 on the test systems considered in this work. These errors have to be interpreted with respect to the relatively small binding energy scale covered by the test systems, which ranges from 0.37 kcal/mol ( $\text{F}_2$ )<sub>2</sub> to 2.32 kcal/mol ( $\text{H}_3\text{Cl}\cdots\text{OCH}_2$ ) with an average

**Figure 5.** Maximum error (MAX), root-mean-square deviation (RMSD), mean signed error (MSE), and mean unsigned error (MUE) of the interaction energy well depth with respect to the CCSD(T) references on the weakly bound complexes considered in this work.

value of 1.18 kcal/mol. This small energy scale poses exceptionally high demands on the accuracy of the computational method. The excellent performance of DCACPs is demonstrated with a maximum error of 0.13 kcal/mol and RMSD, MSE, and MUE below 0.1 kcal/mol. M06-2X follows as second in this ranking with slightly larger errors (MAX 0.22 kcal/mol, RMSD 0.13 kcal/mol, MSE 0.03 kcal/mol, and MUE 0.12 kcal/mol). BLYP-D3 is less accurate in all of these measures (MAX 0.47 kcal/mol, RMSD 0.51 kcal/mol, MSE −0.13 kcal/mol, and MUE: 0.32 kcal/mol). The negative MSE indicates an overall overestimation of the interaction, in contrast to the other methods. M06 performs the worst with MAX 0.77 kcal/mol, RMSD 0.44 kcal/mol, MSE 0.34 kcal/mol, and MUE 0.36 kcal/mol. Only the RMSD is slightly better than the one of BLYP-D3. These errors are substantial compared to the overall energy scale of the test set.

We also compare the computational cost of the different dispersion corrected methods with respect to an uncorrected GGA calculation. For all of the methods, we measured the time required for a single point calculation of the ( $\text{F}_2$ )<sub>2</sub> dimer at an intermolecular distance of 3.5 Å on an 8 core 2.26 GHz Intel Nehalem node with 72 GB of shared memory. Table 8 gives the computational overhead of the different methods with respect to the uncorrected BLYP calculation. For DCACP, we compared to the standard BLYP calculation with the same plane wave cutoff and box size (same number of SCF cycles). In this case the computing time increased by a factor of 1.1. For DFT-D3, the time for the evaluation of the dispersion energy with the DFT-D3 program<sup>59</sup> is negligible (below 1 s). In contrast, for the meta-hybrid-GGA functionals M06 and M06-2X, the necessity of an extremely fine integration grid to eliminate oscillations in the interaction energy curves of such weakly bound systems has a non-negligible impact on the computational costs. For example, our benchmarks showed that for the ( $\text{F}_2$ )<sub>2</sub> complex a pruned grid with 350 radial shells and

**Table 8. Difference of Number of SCF Cycles and Multiplicative Factor for the Computational Time of the Dispersion Corrections with Respect to an Uncorrected GGA Calculation<sup>a</sup>**

reference method	DCACP/ pw	D3	M06/ AC	M06/ AC/G	M06- 2X/AC	M06-2X/ AC/G
	BLYP/ pw		BLYP/AC			
$\Delta N(\text{SCF})$	0	0	−1	−2	−1	−2
factor comp time	1.1	~1.0	1.9	4.1	1.9	3.9

<sup>a</sup>Single point calculation of the  $(\text{F}_2)_2$  dimer at an intermolecular distance of 3.5 Å. pw: plane wave calculation (CPMD) with isolated cubic box of 16 Å edge length. AC: atom-centered basis set (Gaussian G09) aug-cc-pVQZ. G: (350,770) pruned integration grid instead of the default (75,302) grid.

770 angular points (350,770) in Gaussian G09 is necessary (see the Supporting Information), while for BLYP the default fine grid (75,302) was sufficient. For this relatively small system, the M06 and M06-2X functionals in combination with the (75,302) grid are, due to the exact exchange and kinetic energy contributions, a factor of 1.9 more expensive than the BLYP calculation, although one SCF cycle less is needed to converge. However, increasing the number of grid points to (350,770), necessary for converged results with the meta-hybrid-GGA functionals, essentially doubles the computational cost and renders the calculations four times more expensive than BLYP (75,302). In summary, D3 is the most economical dispersion correction, however, not performing reliably for the systems tested here, while DCACP leads to a marginal increase of the computational costs and the M06/M06-2X methods are the most costly ones.

#### 4. CONCLUSION

With the aim to identify a DFT method capable of reliably describing weak interactions involving halogen atoms, we have assessed the performance of BLYP, DCACP augmented BLYP, BLYP-D3,<sup>59</sup> M06,<sup>60</sup> and M06-2X<sup>60</sup> compared to CCSD(T) references. To this end, we have calculated the full interaction energy curves for the  $(\text{X}_2)_2$  and  $\text{X}_2\text{--Ar}$  (for  $\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}$ ) dimers, as well as for the prototype halogen bonded complexes  $\text{H}_3\text{CX--OCH}_2$  ( $\text{X} = \text{Cl}, \text{Br}, \text{I}$ ). The small energy scale of this test set and the subtle interplay between different types of interactions in the heteronuclear complexes represent serious challenges for the different computational methods. Uncorrected BLYP fails in describing these interactions, and dispersion-corrected approaches have to be employed. We have therefore extended the DCACP library for BLYP to include the halogens. The parameters were obtained by calibration with respect to CCSD(T) references at two critical points of the interaction energy curves of the dispersion-dominated model complexes  $\text{X}_2\cdots\text{X}_2$  ( $\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}$ ). DCACP results are in excellent agreement with the CCSD(T) reference values on the full test set, showing a maximum error of 0.13 kcal/mol and RMSD, MSE, and MUE values below 0.1 kcal/mol. M06-2X produces errors slightly larger than DCACP (MAX 0.22 kcal/mol, RMSD 0.13 kcal/mol, MSE 0.03 kcal/mol, and MUE 0.12 kcal/mol). While for BLYP-D3 the errors are MAX (0.47 kcal/mol), RMSD (0.51 kcal/mol), MSE (−0.13 kcal/mol), and MUE (0.32 kcal/mol), with main contributions from the fluorine containing complexes and the homonuclear  $(\text{X}_2)_2$  ( $\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}$ ) systems. M06 performs

with relative errors above 50% in more than half of the systems considered in this work (MAX 0.77 kcal/mol, RMSD 0.44 kcal/mol, MSE 0.34 kcal/mol, and MUE 0.36 kcal/mol). These are relatively large errors compared to the overall very small energy scale of the test set of halogen containing weakly bound complexes. Concerning the computational cost, it is not surprising that D3 is the most economical dispersion correction, while DCACP leads to a marginal increase in computational costs and M06/M06-2X are the most costly ones, compared to uncorrected BLYP.

In conclusion, this study has revealed the challenges related to the accurate description of weak interactions involving halogen atoms at the DFT level. These are reflected in the largely varying performance among the different methods tested here (DCACP, BLYP-D3, M06 and M06-2X). At the same time, we have made a significant step toward the identifications of computational expedient and yet accurate methods to model halogen containing systems in material science, biology, and medicinal chemistry. For the small test set considered here, DCACPs feature the best ratio of accuracy versus computational costs.

#### ■ ASSOCIATED CONTENT

##### Supporting Information

DCACP parameter files for the halogens in Goedecker–Teter–Hutter format, a test of extrapolation schemes to the CBS limit of the CCSD(T) interaction energies, and a benchmark of the grid size for the interaction energy curves of  $(\text{F}_2)_2$  at the M06 level of theory. This material is available free of charge via the Internet at <http://pubs.acs.org/>. The complete library of DCACP parameters in analytic and numerical formats is available free of charge from our Web site.<sup>66</sup>

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##### Notes

The authors declare no competing financial interest.

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