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Investigations into the Nature of Halogen Bonding Including Symmetry Adapted Perturbation Theory Analyses

Kevin E. Riley and Pavel Hobza*

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic and Center for Biomolecules and Complex Molecular Systems, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic

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Abstract: In recent years it has been recognized that, because of their unique properties, halogen bonds have tremendous potential in the development of new pharmaceutical compounds and materials. In this study we investigate the phenomenon of halogen bonding by carrying out *ab initio* calculations on the halomethane-formaldehyde complexes as well as the fluorine substituted $F_nH_{3-n}CX\cdots OCH_2$ dimers, where the halogen bonding halogens (X) are chlorine, bromine, and iodine. Coupled cluster (CCSD(T)/aug-cc-pVTZ) calculations indicate that the binding energies for these type of interactions lie in the range between −1.05 kcal/mol ($H_3CCl\cdots OCH_2$) and −3.72 kcal/mol ($F_3CI\cdots OCH_2$). One of the most important findings in this study is that, according to symmetry adapted perturbation theory (SAPT) analyses, halogen bonds are largely dependent on both electrostatic and dispersion type interactions. As the halogen atom involved in halogen bonding becomes larger the interaction strength for this type of interaction also gets larger and, interestingly, more electrostatic (and less dispersive) in character. Halogen bonding interactions also become stronger and more electrostatic upon substitution of (the very electronegative) fluorines onto the halomethane molecule.

Introduction

In recent years halogen bonding has been implicated as an important type of interaction in many different types of physical systems and are especially interesting within the fields of biochemistry[1−11] and material science.[12−23] These interactions play roles in a wide variety of biochemical phenomena such as protein−ligand complexation[1,2,4−6,9,19] and are responsible for many novel properties of materials;[14,17,19−21] these types of interactions, many believe, promise to be of great importance in the design of novel drugs and materials.

A halogen bond is defined as a short-range $C - X\cdots Y - Z$ interaction (where X is typically chlorine, bromine, or iodine, Y is an electron donor such as oxygen, nitrogen, or sulfur, and $Y - Z$ represents a side group such as a hydroxyl or carbonyl group), where the $X\cdots Y$ distance is less than sum of the van der Waals radii of X and Y.[1] Halogen bonds share numerous physical properties with the more commonly encountered hydrogen bonds and are often treated analogously to their ubiquitous counterparts.[1,19] There is a broad range of reported halogen bond interaction energies with values varying from about 1.2 kcal/mol (Cl···Cl) to about 43.0 kcal/mol ($I_3^-\cdots I_2$).[19]

Considering the fact that halogen atoms as well as halogen bond electron donors (Y) are negatively charged, the existence of halogen bonds is surprising and counterintuitive. However, studies of the electrostatic potentials of halogen bonding systems by Auffinger et al.,[1] Clark et al.,[24] and Politzer et al.[25] show that a large halogen bound to carbon tends to form an electropositive crown, which is distal to the carbon, an electroneutral ring, which surrounds the crown, and an electronegative belt, which goes around the circumference of the halogen atom in the plane that is perpendicular to the $C - X$ bond (see Figure 3). In the works by Clark and Politzer, the electropositive crown is referred to as the

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* Corresponding author e-mail: pavel.hobza@uochb.cas.cz.

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σ-hole to denote the region of positive charge on the halogen surface. Halogen bonding can be, at least partially, attributed to the favorable interaction that exists between a halogen's electropositive σ-hole and an electronegative atom, such as oxygen.[1,19,24−27] A halogen's σ-hole becomes larger and gains a higher degree of elctropositivity as the size of the halogen increases, with a corresponding tendency for the halogen bond to become stronger. Fluorine, the smallest (and most electronegative) halogen, does not form an electropositive crown and thus does not participate in halogen bonding.[1,24,25] It has also been observed that the size and charge of the σ-hole tends to increase as electronegative substituents are added to a halogen containing molecule.[1,24,25]

There have been several theoretical[1,23−40] and experimental[16,17,28,41−54] studies seeking to characterize the geometric and energetic properties of halogen bonds. For example, Valerio et al. performed *ab initio* calculations on the $CH_{n-3}F_nX{\cdots}NH_3$ ($X = I,Br,Cl$) halogen bonded complexes, and it was found in this study that substitution of successive fluorines substituents results in $X{\cdots}N$ halogen bonds that are shorter and stronger.[40] The strongest halogen bond found in this study occurs for the $CF_3I{\cdots}NH_3$ complex with a binding energy of 5.8 kcal/mol. Riley and Merz characterized halogen bonds involving chlorine, bromine, and iodine, and carbonyl oxygens as a function of the halogen bonding distance and the $X{\cdots}O$ - C halogen bonding angle. In this work it was found that the optimum halogen bond angle is generally within the range from 95° to 115°, corresponding to an interaction between the halogen σ-hole and the lone pair of electrons on oxygen.[27] Lommerse et al. carried out intermolecular perturbation theory calculations on several halogen bonding systems containing chlorine as the halogen bond donor and both nitrogen and oxygen as the halogen bond acceptors.[26] In this study it is concluded that the attractive nature of halogen bonds is mostly attributable to electrostatic effects although dispersion, polarization, and charge-transfer effects seem to also play a role in these interactions. It should be pointed out that these studies were carried out with the 6-31G basis set, which is not large enough to describe dispersion effects, and it would be expected that the use of this small basis set would result in an underestimation of the dispersion energy by about an order of magnitude. On the experimental side, Corradi et al. determined the binding energy for a halogen bonded complex of 1-iodoperflourohexane and 2,2,6,6-tetramethylpiperidine to be 7.4 kcal/mol.[17]

Halogen bonds involving oxygen as the halogen bond acceptor are especially interesting in biochemistry because they are, by a large margin, the most common types of halogen bonds involved in protein−ligand interactions. Recently Auffinger and co-workers carried out a database survey of short halogen-oxygen interactions, and in this study it was found that 81 out of 113 $X{\cdots}O$ interactions involved carbonyl oxygens (the data set contained 66 protein structures and 6 nucleic acid structures from the protein data bank).[1] These interactions generally involved a protein's backbone carbonyl group (78 out of 81 interactions). Interactions involving hydroxyl groups were also fairly common, with 18 $X{\cdots}O$ interactions involving hydroxyl oxygens. As has been shown in several studies, a nitrogen atom can act as an efficient halogen bond acceptor, and one might expect that nitrogen atoms found in proteins (both in the backbone and in sidechains) might tend to be involved in halogen bonding with roughly the same frequency as oxygen atoms. Auffinger's work shows that there are only a handful of halogen bonds involving nitrogen, and seemingly these atoms are somehow inaccessible to halogen atoms. Our main interest is in halogen bonds as they pertain to biological systems, and for this reason we have chosen to focus on $X{\cdots}O$ halogen bonds in this study, as they seem to be the most biologically relevant examples of these types of interactions.

In this work we carry out systematic studies of C - $X{\cdots}O$ - Z halogen bonds, where the O - Z group represents a carbonyl group. The model systems used here are the halomethane-formaldehyde dimers. Because the binding energies of halogen bonds are comparable to those of hydrogen bonding, very accurate quantum mechanical procedures should be adopted to describe them. It has recently been shown that the CCSD(T) method, extrapolated to the complete basis set limit (CBS), provides a very accurate description of intermolecular interactions.[55] In order to more fully understand the nature of halogen bonding we need, in addition to accurate binding energies, physically meaningful, well-defined interaction energy components, which can be obtained using symmetry adapted perturbation theory (SAPT).[56] We have also obtained accurate interaction energies and performed SAPT analyses of the fluorine substituted halogen bonding dimers ($F_nH_{3-n}CX{\cdots}O$ - Z) in order to gain insight into the effects of electron withdrawing substituents on the strength and character of halogen bonds. In order to compare these, relatively poorly characterized, interactions with their more ubiquitous counterparts, hydrogen bonds, we have performed SAPT calculations on the methane-formaldehyde and ethyne-water dimers, which exemplify C - $H{\cdots}O$ type hydrogen bonds.

The recently developed density functional theory combined with the symmetry adapted perturbation theory (DFT-SAPT) method uses electronic densities determined using DFT methods (instead of Hartree−Fock).[57−61] This method promises to yield results that are similar to those of the Hartree−Fock based scheme with a much smaller computational cost. In this work we have performed calculations using both SAPT and DFT-SAPT in order to compare the results obtained with each method.

Methods

In order to gain insight into the origin and nature of halogen bonds we have employed several computational methods in this study. Very accurate interaction energies are obtained with the coupled cluster method (CCSD(T)) using several different basis sets, the largest of which is the aug-cc-pVQZ quadruple-ζ basis of Dunning. Møller-Plesset (MP2) and Hartree−Fock (HF) interaction energies are also computed with several basis sets. Symmetry adapted perturbation theory calculations are carried out in order to discern the relative contributions of the interaction energy components. Natural bond order (NBO) analyses are done for some halogen bonded dimers so that the role of electron sharing effects, such as hyperconjugation, can be studied.[62]

The geometries of the halomethane-formaldehyde complexes were optimized on the counterpoise corrected geometric hypersurface at the MP2 level. For systems containing chlorine and bromine the cc-pVTZ basis[63] was used for optimization, while for complexes containing iodine a mixed basis set approach was used; here the large halogens are described using the pseudopotential based cc-pVTZ-PP basis,[64−67] and the other atoms are described using the cc-pVTZ basis set. The MP2/cc-pVTZ method is used for these optimizations because it has been shown that the cc-pVTZ basis set yields the most well balanced description of intermolecular interactions, in terms of describing electrostatic and dispersion type interactions, when paired with MP2.[68] In the case of fluorine substituted systems, the positions of the carbon, oxygen, and halogen bonding halogen atom were kept fixed (at the positions obtained for the unsubstituted complexes), while the positions of the hydrogen and fluorine atoms were optimized at the B3LYP/3-21G* level of theory.

Interaction energies for all halogen bonding systems have been computed using the HF, MP2, and CCSD(T) methods. The CCSD(T) method describes correlation effects very well and is the most accurate modern technique for the determination of interaction energies of noncovalently bound complexes; when combined with large basis sets this method provides accurate values for molecular properties such as stabilization energies, geometries, and vibrational frequencies. The MP2 method describes some correlation effects and is much less computationally intensive than higher order techniques such as the configuration interaction and coupled cluster methods. HF describes interactions derived from electrostatic forces fairly well but greatly underestimates the binding energies of dispersion bound systems. Thus, HF interaction energies can be used to qualitatively determine whether an interaction is attributable chiefly to electrostatic or dispersive forces.

For complexes containing chlorine, the aug-cc-pVxZ (x = D,T,Q) basis sets of Dunning have been employed.[63] For systems containing iodine we have used a somewhat different strategy, whereby the iodine atom is treated using the pseudopotential based aug-cc-pVxZ-PP[64−67] (x = D,T,Q) bases, while all other atoms in these systems are described using the standard aug-cc-pVxZ basis sets. There are two main reasons that this strategy has been adopted, first, there are very few high quality all-electron basis sets available for iodine, and, second, the aug-cc-pVxZ-PP basis implicitly takes relativistic effects into account. Given the large size of an iodine atom, it seems that relativistic effects might play a role in its halogen bonding behavior. For systems containing bromine calculations have been carried out using both the aug-cc-pVxZ (on all atoms) and mixed aug-cc-pVxZ-PP/aug-cc-pVxZ (for bromine/all other atoms) basis sets. This is done in order to estimate the role that relativistic effects play in these halogen bonding complexes. For all of these systems the MP2 and CCSD(T) interaction energies have also been determined at the extrapolated complete basis set limit (CBS). The electronic energies of all monomers and dimers were extrapolated to the complete basis set limit from aug-cc-pVTZ and aug-cc-pVQZ values using the technique of Helgaker and co-workers.[69]

The SAPT method allows for the separation of interaction energies into physically meaningful components such as those arising from dispersion, electrostatics, induction, and exchange. The SAPT interaction energy is given as

$$E_{\mathrm{int}} = E_{pol}{}^{1} + E_{ex}{}^{1} + E_{ind}{}^{2} + E_{ex-ind}{}^{2} + E_{disp}{}^{2} + E_{ex-disp}{}^{2}$$

Some of these terms can be combined in order to define values that correspond to commonly understood physical quantities. In this work we define the following equalities

$$E(elec.) = E_{pol}{}^{1}$$

$$E(ind.) = E_{ind}{}^{2} + E_{ex-ind}{}^{2}$$

$$E(disp.) = E_{disp}{}^{2} + E_{ex-disp}{}^{2}$$

and

$$E(exch.) = E_{ex}{}^{1}$$

These four quantities refer to the electrostatic, induction, dispersion, and exchange contributions (respectively) to the overall interaction energy.

In this work we have carried out SAPT analyses for all of the halogen bonding systems. Calculations were carried out using the aug-cc-pVxZ and aug-cc-pVxZ/aug-cc-pVxZ-PP basis sets (x = D,T,Q). Estimated complete basis set results were also obtained by extrapolating each of the interaction energy terms (as well as the SAPT interaction energy) from values obtained with aug-cc-pVTZ and aug-cc-pVQZ using the extrapolation technique of Helgaker and co-workers.[69]

We have performed NBO analyses for all of the halogen bonding systems considered in this work at the DFT/B3LYP/aug-cc-pVDZ level of theory. The interaction between filled orbitals in one subsystem and unfilled orbitals of another represents a deviation of the complex from its Lewis structure and can be used as a measure of the intermolecular delocalization, also called hyperconjugation. The hyperconjugative interaction energy can be deduced from the second-order perturbation approach

$$E(2) = -\eta_{\sigma} \frac{\langle \sigma^{*}|F|\sigma \rangle}{\epsilon_{\sigma^{*}} - \epsilon_{\sigma}} = \eta_{\sigma} \frac{F_{ij}{}^{2}}{\Delta E}$$

where F_{ij} is the Fock matrix element between the i and j NBO orbitals, ϵ_{σ} and $\epsilon_{\sigma^{*}}$ are the energies of σ and σ^{*}, and n_{σ} is the population of the donor σ orbital.

The DFT-SAPT method provides the same type of interaction energy decomposition as SAPT but at a much lower computational cost, which makes it a useful tool for computations on very large systems. The DFT-SAPT interaction energy is given as

$$E_{\mathrm{int}} = E_{pol}{}^{1} + E_{ex}{}^{1} + E_{ind}{}^{2} + E_{ex-ind}{}^{2} + E_{disp}{}^{2} + E_{ex-disp}{}^{2} + \delta HF$$

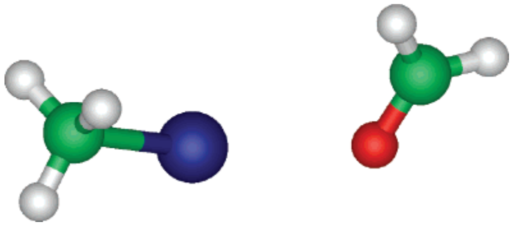

Figure 1. Geometrical configuration of the iodomethane-formaldehyde dimer.

where all but the last term are identical to the SAPT interaction energy components. The δHF term is a Hartree–Fock correction for higher order contributions to the interaction energy that are not included within the other DFT-SAPT terms.

In order to compare DFT-SAPT to SAPT we have performed DFT-SAPT calculations on the bromomethane-formaldehyde complex. These computations were carried out using the aug-cc-pVxZ/aug-cc0pVxZ-PP ($x = D,T,Q$) basis sets.

All single point CCSD(T), MP2, HF, SAPT, and DFT-SAPT calculations were performed using the MOLPRO version 2006.1 suite of molecular electronic structure programs,[70] while the NBO analysis and geometry optimizations were carried out using the Gaussian electronic structure package.[71] Here we will note that binding energies are given as the negative value of interactions (i.e. $\Delta E(\text{binding}) = -\Delta E(\text{interaction})$), so that a positive binding energy refers to a bound complex.

Results and Discussion

In this article we describe computations carried out for the set of halomethane-formaldehyde dimers. We will note here that some calculations were also done for the halomethane-methanol dimers and that the results for these complexes were very similar to those obtained for the halomethane-formaldehyde dimers. Tables and figures describing the halomethane-methanol data are given as Supporting Information. Most of the data presented for the bromomethane-formaldehyde dimer described in this text refer to calculations carried out using the aug-cc-pVDZ/aug-cc-pVDZ-PP mixed basis set approach, and results computed using the aug-cc-pVDZ basis set (on all atoms) are also available as Supporting Information.

Geometries. Figure 1 shows the optimized structure of the iodomethane-formaldehyde dimer, and in this figure it can be seen that the iodine atom is positioned in such a way that its σ-hole can interact with the lone pair electrons on the methanol oxygen atom. The geometrical structures of the bromomethane-methanol and chloromethane-methanol complexes are similar to that of the iodomethane-methanol system, with the halogen atom σ-holes pointing in the direction of the oxygen lone pair electrons. Table 1 gives the important geometric quantities for the halomethane-formaldehyde complexes. One interesting aspect of the data presented in this table is the fact that the bonding distance of the systems tends to increase as the size of the halogen increases, with the bromine and iodine substituted systems having roughly the same bond distance. The $C - X\cdots O$ angle for bromine and iodine containing complexes is about the same (≈172°), while it is smaller for the chlorine system (≈167°). This trend may be attributable to the fact that the interaction between chlorine and oxygen is the weakest among those seen in halogen bonding and is largely based on dispersion forces (see below). Thus, the alignment of the σ-hole with the oxygen lone pair is not as critical as in the case of bromine and iodine based halogen bonds. Increasing the size of the halogen bonding halogen results in an increase in the $X\cdots O - C$ angle from 91.3° (for chlorine) to 107.6° (for iodine).

Table 1. Geometric Parameters (Å and deg) for Optimized Structures of Halogen Bonding Complexes Considered in This Work

	$H_3CCl\cdots OCH_2$	$H_3CBr\cdots OCH_2$	$H_3CI\cdots OCH_2$
$d(X\cdots O)$	3.26	3.29	3.30
$\theta(C-X\cdots O)$	166.8	171.2	172.9
$\theta(X\cdots O-C)$	91.3	97.1	107.6

Table 2. Interaction Energies (kcal/mol) for $H_3CX\cdots OCH_2$ Complexes (kcal/mol)[a]

	a-pVDZ	a-pVTZ	a-pVQZ	CBS
	$H_3CCl\cdots OCH_2$ (a-pVxZ)			
HF	0.63	0.66	0.65	
MP2	−0.86	−1.11	−1.19	−1.25
CCSD(T)	−0.78	−1.05	−1.12	−1.18
	$H_3CBr\cdots OCH_2$ (a-pVxZ)			
HF	0.29	0.36	0.37	
MP2	−1.37	−1.61	−1.69	−1.75
CCSD(T)	−1.24	−1.49	−1.58	−1.64
	$H_3CBr\cdots OCH_2$ (a-pVxZ-PP)			
HF	0.20	0.27	0.28	
MP2	−1.44	−1.68	−1.76	−1.82
CCSD(T)	−1.32	−1.57	−1.65	−1.71
	$H_3CI\cdots OCH_2$ (a-pVxZ-PP)			
HF	−0.33	−0.21	−0.21	
MP2	−2.08	−2.34	−2.43	−2.50
CCSD(T)	−1.87	−2.15	−2.25	−2.32

[a] Note that a-pVxZ denotes a aug-cc-pVxZ basis set, parenthetical notation refers to the basis set used to describe the halogen atom, and CBS refers to the extrapolated complete basis set limit.

Interaction Energies. The halogen bonding interaction energies for all of the $H_3CX\cdots OCH_2$ complexes are shown in Table 2. As expected, the magnitudes of the binding energies increase with increasing halogen size. Focusing on the CCSD(T)/aug-cc-pVQZ (aug-cc-pVTZ/aug-cc-pVTZ-PP for the bromine and iodine substituted complexes) results, which are available for each type of system considered, it can be seen that the $H_3CI\cdots OCH_2$ complex is bound about 27% more strongly than $H_3CBr\cdots OCH_2$, which binds about 32% more strongly than $H_3CCl\cdots OCH_2$.

Considering the halogen-bonded complexes discussed above, the HF method greatly underestimates all of the binding energies and, in the cases of chlorine and bromine substituted systems, predicts the dimers to be unbound. This indicates that dispersion must play a large role in the stabilization of halogen bonded complexes. The fact that HF interaction energies for iodine containing halogen bonding

Table 3. SAPT Decomposition of the Interaction Energies (kcal/mol) for the $H_3CCl\cdots OCH_2$, $H_3CBr\cdots OCH_2$, and $H_3CI\cdots OCH_2$ Complexes[a]

	aug-cc-pVDZ	aug-cc-pVTZ	aug-cc-pVQZ	CBS
		$H_3CCl\cdots OCH_2$		
$E(elec.)$	−1.01	−0.96	−0.96	−0.96
$E(ind.)$	−0.22	−0.23	−0.23	−0.23
$E(disp.)$	−1.55	−1.81	−1.89	−1.96
$E(exch.)$	2.03	2.02	2.02	2.02
ΔE_{int}^{SAPT}	−0.75	−0.98	−1.07	−1.13
		$H_3CBr\cdots OCH_2$		
$E(elec.)$	−1.56	−1.47	−1.46	−1.45
$E(ind.)$	−0.36	−0.37	−0.37	−0.37
$E(disp.)$	−1.69	−1.98	−2.08	−2.15
$E(exch.)$	2.12	2.12	2.11	2.11
ΔE_{int}^{SAPT}	−1.49	−1.70	−1.80	−1.86
		$H_3CI\cdots OCH_2$		
$E(elec.)$	−2.77	−2.61	−2.61	−2.60
$E(ind.)$	−0.77	−0.78	−0.78	−0.79
$E(disp.)$	−1.91	−2.31	−2.44	−2.54
$E(exch.)$	3.01	3.01	2.98	2.96
ΔE_{int}^{SAPT}	−2.45	−2.67	−2.85	−2.96

[a] Chlorine is described using the aug-cc-pVxZ basis sets, while bromine and iodine are described using the augcc-pVxZ-PP basis sets; CBS refers to the extrapolated complete basis set limit.

complexes are negative suggests that these interactions may depend more on electrostatic effects than those occurring between the smaller halogen atoms and oxygen. It should also be noted that the MP2 binding energies are all slightly higher than those of CCSD(T) as computed using any given basis set and that the difference between MP2 and CCSD(T) binding energies increases as the size of the halogen substituent increases.

In terms of basis sets, it can be seen that for all of the $H_3CX\cdots OCH_2$ complexes that the MP2 and CCSD(T) binding energies display convergent behavior. One interesting aspect of the data presented here is that, for all of the chlorine and bromine containing halogen bonding systems, the difference between the MP2 and CCSD(T) interaction energies remains roughly constant (within 0.02 kcal/mol) for each of the basis sets employed here.

The binding energies obtained for the bromomethane-formaldehyde complex with the mixed aug-cc-pVxZ/aug-cc-pVxZ-PP basis sets are consistently higher (by about 0.1 kcal/mol) than those computed using the aug-cc-pVxZ bases. This indicates that relativistic effects do play a non-negligible role in halogen bonding complexes involving bromine. The binding energy for this complex as computed using the aug-cc-pVQZ/aug-cc-pVQZ-PP mixed bases is 0.07 kcal/mol higher than that obtained with the aug-cc-pVQZ basis on all atoms.

SAPT Interaction Energy Decomposition. Table 3 gives the symmetry adapted perturbation theory interaction energy decomposition results for the halomethane-formaldehyde complexes. One of the most striking features of these data is the fact that the stabilities of the $Cl\cdots O$ and $Br\cdots O$ halogen bonds are predicted to be attributable chiefly to dispersion, while electrostatic forces, which have been widely believed to be responsible for these types of interactions, play a smaller role in stabilizing these complexes. In contrast to the $Cl\cdots O$ and $Br\cdots O$ type halogen bonds, for the $I\cdots O$ halogen bond, the most stabilizing interaction energy component is the electrostatic one.

Considering the results obtained with the large aug-cc-pVQZ (aug-cc-pVQZ/aug-cc-pVQZ-PP) basis set, dispersion forces account for about 61% and 52% of the overall attraction in the chlorine and bromine substituted dimers respectively. By comparison, the electrostatic components of these interactions represent about 31% and 39% of the total attractive forces, while induction contributes 7% and 10% to the stability of these complexes (for $X = Cl$, Br respectively). Thus it can be said that the halogen bonding interactions that occur for the chloromethane-formaldehyde and bromomethane-formaldehyde complexes are dependent on both electrostatic and dispersive forces, with dispersion playing the largest role in their stability. For the iodomethane-formaldehyde dimer the electrostatic term accounts for 54% of the attractive interaction, while dispersion represents about 33% of the attractive forces within this dimer. Induction plays a larger role in the $I\cdots O$ halogen bonding interaction than in the cases of the $Cl\cdots O$ and $Br\cdots O$ type halogen bonds, accounting for about 13% of the overall attractive interaction. It is interesting to note that, although these types of interactions are largely dependent on dispersive forces, the electrostatic interaction between the halogen σ-hole and the oxygen lone pair electrons seems to play a large role in determining the geometric structures of these complexes.

As the size of the halogen substituent increases the dispersion interaction would be expected to increase, whereas the larger halogen substituents should also allow for a larger sigma-hole, which would tend to increase the magnitude of the electrostatic interaction. Comparing the data for the chlorine, bromine, and iodine substituted halogen bonding systems, it can be seen that both the dispersion and electrostatic components of the interaction energy increase with increasing halogen size. Interestingly, there is a larger increase in the electrostatic interaction, going from chlorine to bromine to iodine, than in the dispersion interaction.

The quality of results obtained with the SAPT method, like those of other molecular structure methods, is highly dependent on the size of basis set employed. In terms of halogen bonding, Table 3 shows that the overall SAPT interaction energies as well as the interaction energy components tend to converge as larger basis sets are used. While the induction and exchange parts of the interaction energies vary very little with basis set size, the dispersion and, to a lesser extent, electrostatic components display more basis set dependence. For each of the systems considered here the electrostatic portion of the interaction energy decreases by about 5% going from aug-cc-pVDZ to aug-cc-pVTZ but does not decrease any more when the aug-cc-pVQZ basis is used. The dispersion component of the interaction energies, for each of these halogen-bonded complexes, decreases significantly (by between 10% and 15%) going from aug-cc-pVDZ to aug-cc-pVTZ and then decreases by about 5% going from aug-cc-pVTZ to aug-cc-pVQZ. Looking at the extrapolated complete basis set limit results it can be seen that each of the SAPT interaction energy

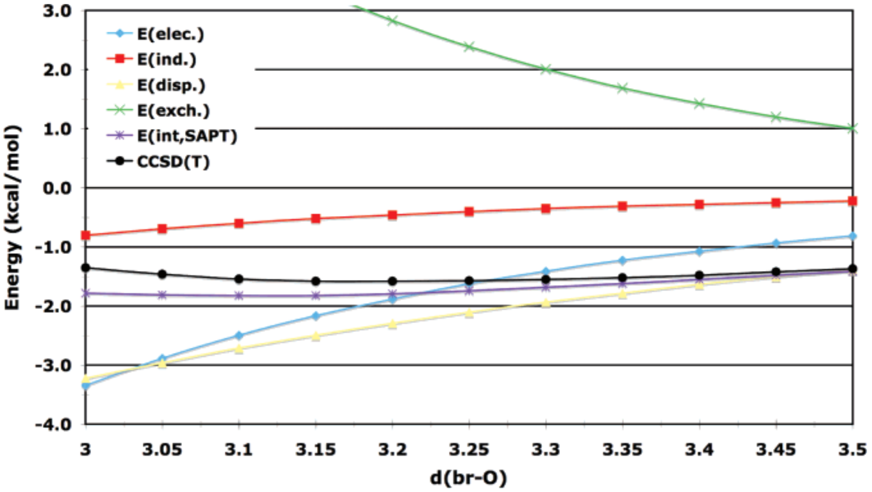

Figure 2. CCSD(T) and SAPT interaction energies as well as SAPT interaction energy components, for the bromomethane-formaldehyde dimer as a function of the bromine-oxygen separation distance *d(Br⋯O)*.

components, with the exception of the dispersion term, converges (to within 0.01 kcal/mol) at the aug-cc-pVQZ basis set. The CBS dispersion terms are about 0.06−0.08 kcal/mol lower than the aug-cc-pVQZ dispersion values; this is not a surprising result, as it is well-known that it is necessary to use very large basis sets to treat dispersion properly.

The SAPT interaction energies for the chloromethane-formaldehyde complex (for which no pseudopotential based basis sets are used) are generally in good agreement with those obtained using the CCSD(T) method. The SAPT interaction energies for complexes containing larger halogens generally do not agree with CCSD(T) results as well. The SAPT results for the iodomethane-formaldehyde complex compare particularly poorly to CCSD(T), with the SAPT/aug-cc-pVQZ(aug-cc-pVQZ-PP) binding energy being 0.60 kcal/mol higher than that calculated using the CCSD(T) with the same basis set. It is interesting to note that, in the case of the $Cl\cdots O$ type halogen bond, all SAPT binding energies are underestimated in relation to CCSD(T), while binding energies for the $Br\cdots O$ and $I\cdots O$ halogen bonds are always overestimated. It should also be noted that when standard (nonpseudopotential based) basis sets are used for the bromomethane-formaldehyde complex the SAPT and CCSD(T) interactions energies are generally in much better agreement, with SAPT binding energies always being lower than those of CCSD(T) (see the Supporting Information).

Distance Dependence of Halogen Bonds. Figure 2 shows the CCSD(T) interaction energies and SAPT interaction energy components, as calculated with the aug-cc-pVTZ/aug-cc-pVTZ-PP basis set, for several points near the potential energy minimum of the $H_3CBr\cdots OCH_2$ complex. Here it can be seen that the potential energy curve for this interaction is fairly shallow with a minimum CCSD(T) binding energy of −1.58 at a $d(Br\cdots O)$ distance of 3.20 Å. The SAPT interaction energies are in relatively good agreement with those determined using CCSD(T), although they tend to deviate at small values of $d(Br\cdots O)$.

One of the most interesting aspects of the data depicted in Figure 2 is the increasing contribution of the electrostatic interaction to the overall stability of the complex with decreasing halogen bond distances. At a separation distance of 3.50 Å the electrostatic contribution to the interaction energy (−0.81 kcal/mol) is about half that of the dispersion contribution (−1.39 kcal/mol), while at a separation of 3.00 kcal/mol the contributions of these two binding components are roughly the same (electrostatic = −3.34 kcal/mol, dispersion = −3.22 kcal/mol). The contribution from induction effects also increases with decreasing values of $d(Br\cdots O)$, with a minimum value of −0.22 at a separation of 3.50 Å and a maximum value of −0.80 kcal/mol at a separation of 3.00 Å. The different behavior of the electrostatic and dispersion interaction terms can likely be explained on the basis of the difference in their dependence on reciprocal distances (i.e. r^{-3} for electrostatic and r^{-6} for dispersion).

Table 4. Interaction Energies (kcal/mol) of the $F_nH_{3-n}CX\cdots OCH_2$ Complexes as a Function of the Number of Fluorine Substituents[a]

	n=0	n=1	n=2	n=3
	$F_nH_{3-n}CCl\cdots OCH_2$ (aug-cc-pVTZ)			
HF	0.66	0.32	−0.03	−0.45
MP2	−1.11	−1.34	−1.58	−1.87
CCSD(T)	−1.05	−1.29	−1.54	−1.84
	$F_nH_{3-n}CBr\cdots OCH_2$ (aug-cc-pVTZ-PP)			
HF	0.27	−0.18	−0.69	−1.24
MP2	−1.68	−1.98	−2.28	−2.61
CCSD(T)	−1.57	−1.89	−2.23	−2.58
	$F_nH_{3-n}CI\cdots OCH_2$ (aug-cc-pVTZ-PP)			
HF	−0.21	−0.89	−1.60	−2.50
MP2	−2.34	−2.72	−3.22	−3.77
CCSD(T)	−2.15	−2.58	−3.16	−3.72

[a] aug-cc-pVTZ for Cl complexes, aug-cc-pVTZ/aug-cc-pVTZ-PP for Br and I complexes.

Effects of Fluorine Substitution. Fluorine is a very electronegative atom and, when substituted onto halogen bonding systems, such as the set of $F_nH_{3-n}CX\cdots OCH_2$ complexes, has the effect of drawing electron density away from the halogen bonding halogen. The HF, MP2, and CCSD(T) interactions for the fluorine substituted halomethane-formaldehyde complexes, as calculated with the aug-cc-pVTZ basis set, are given in Table 4. Here it can be seen that successive fluorine substitution results in a continuous

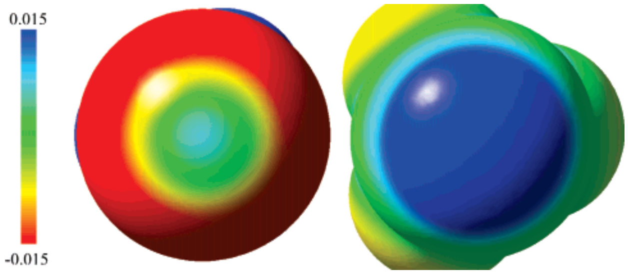

Figure 3. Molecular electrostatic potential for H_3CBr (left) and F_3CBr (right) at the 0.001 electrons Bohr^{-3} isodensity surface.

decrease in the interaction energies of these systems. It is expected that this decrease in the binding energy is caused by an increase in the electrostatic interaction between the halogen's σ-hole and the oxygen's lone pair electrons. The fact that the HF binding energies go from being positive, for the unsubstituted chlorine and bromine containing complexes, to being negative as fluorine substituents are added indicates that this assertion is correct. Figure 3 shows electrostatic potential isosurfaces for H_3CBr and F_3CBr; here it can be seen that the σ-hole for the fluorine substituted system is significantly larger than that of the unsubstituted molecule.

Inspection of Table 4 shows the MP2 and CCSD(T) interaction energies for the $F_nH_{3-n}CX\cdots OCH_2$ complexes as a function of the number of substituted fluorines. Two features of these data that are clearly depicted in this figure are that the steepness of the curves increases with increasing halogen size and that the MP2 interaction energies approach those of CCSD(T) as more fluorine substituents are added. The most likely explanation for the stronger effect of fluorine substitution on the interactions of systems containing larger halogens is that, because the electronegativity of halogens decreases with size, the larger ones tend to lose electron density more easily and are able to form larger σ-holes. The MP2 method, when paired with a large basis set, is known to yield accurate results for electrostatically bound complexes, such as in the case of hydrogen bonding. The fact that the MP2 interaction energies become increasingly accurate (compared to those of CCSD(T)) with successive fluorine substitution is another indicator that fluorine substitution into these types of halogen bonding systems produces interactions that are more electrostatic in nature.

Table 5 gives the SAPT interaction energy decompositions for the sets of $F_nH_{3-n}CX\cdots OCH_2$ complexes. One key aspect of these results is the fact that, as expected, the electrostatic interactions are strongly modulated by the addition of fluorine substituents in these types of systems. Somewhat surprisingly, there are also non-negligible changes in the exchange and dispersion terms upon successive fluorine substitution. The exchange terms decrease with an increasing number of fluorine substituents, a trend that is probably caused by the decrease in electron density on the halogen bonding halogen, and tends to stabilize structures containing more fluorines. The addition of fluorine substituents tends to cause a decrease in the dispersion interaction terms, which tends to destabilize the fluorinated halogen bonding complexes. This increase in the dispersion term may be related to a change in the polarizability of the halomethane upon fluorine substitution.

Table 5. SAPT Interaction Decomposition Terms (kcal/mol) for the $F_nH_{3-n}CCl\cdots OCH_2$ and $F_nH_{3-n}CCBr\cdots OCH_2$ Complexes as a Function of the Number of Fluorine Substituents[a]

	n=0	n=1	n=2	n=3
		$F_nH_{3-n}CCl\cdots OCH_2$		
E(elec.)	−0.96	−1.22	−1.47	−1.73
E(ind.)	−0.22	−0.21	−0.22	−0.24
E(disp.)	−1.81	−1.77	−1.73	−1.68
E(exch.)	2.02	1.93	1.81	1.70
ΔE_{int}^{SAPT}	−0.98	−1.27	−1.60	−1.96
		$F_nH_{3-n}CBr\cdots OCH_2$		
E(elec.)	−1.47	−1.84	−2.17	−2.50
E(ind.)	−0.37	−0.38	−0.4	−0.45
E(disp.)	−1.98	−1.94	−1.89	−1.83
E(exch.)	2.12	2.04	1.90	1.74
ΔE_{int}^{SAPT}	−1.70	−2.12	−2.56	−3.04
		$F_nH_{3-n}CI\cdots OCH_2$		
E(elec.)	−2.61	−3.11	−3.62	−4.04
E(ind.)	−0.78	−0.82	−0.88	−0.95
E(disp.)	−2.30	−2.26	−2.21	−2.14
E(exch.)	3.01	2.90	2.73	2.48
ΔE_{int}^{SAPT}	−2.68	−3.29	−3.98	−4.65

[a] aug-cc-pVTZ for Cl Complexes aug-cc-pVTZ/aug-cc-pVTZ-PP for Br and I Complexes.

It is interesting to note that the magnitudes of the electrostatic interaction energy components for the $F_3CCl\cdots OCH_2$, $F_2H_1CBr\cdots OCH_2$, and $F_3CBr\cdots OCH_2$ complexes as well as for all of the halogen bonding systems containing iodine exceed those of the dispersion components.

NBO Analysis. We would like to note that extensive NBO analyses of halogen bonding systems have been carried out by Clark and co-workers, who show that the electronic configuration of the unshared electron pairs on a halogen bonding halogen approximates $s^2p_x^2p_y^2$ (where the C - X bond lies along the z-axis).[24] This electronic configuration leads to an electron density deficiency in the region of the halogen that is distal to the carbon in the C - X bond and leads to the formation of the halogen's σ-hole. The goal of the NBO analysis carried out here is to determine the role of hyperconjugation in halogen bonding. We will note here that the concept of hyperconjugation has successfully been used to interpret the electronic structure and properties of hydrogen bonds.[72] In hydrogen bonding the main contribution to hyperconjugation is derived from charge transfer between the proton acceptor's lone pair orbital and the X - H antibonding orbital.

Natural bond order analysis of the $F_nH_{3-n}CX\cdots OCH_2$ halogen bonding complexes reveals non-negligible values of the Fock matrix elements, F_{ij}, between the C - X antibonding and oxygen lone pair natural orbitals, indicating a delocalization, or hyperconjugation, of the electron density between these orbitals. It is interesting to note that the hyperconjugation observed for these halogen bonds is of the same type as that seen in the case of hydrogen bonding. Table 6 shows the F_{ij} matrix element values for these complexes, where i represents the C - X antibonding orbital and j represents the oxygen lone pair orbital. Here it can be seen that the degree of hyperconjugation increases with increasing

Table 6. NBO Fock Matrix Elements (kcal/mol) between the C−X Antibonding Orbital and the Oxygen Lone Pair Orbital for the $F_nH_{3-n}CX\cdots OCH_2$ and $F_nH_{3-n}CX\cdots OHCH_3$ Complexes and the Changes of Electron Density in the C−X σ^* Antibonding Orbital upon Complexation of Halogen Bonding Pairs[a]

	$F_nH_{3-n}CX\cdots OCH_2$			
	n = 0	n = 1	n = 2	n = 3
X = *Cl*	0.31 (0.0020)	0.33 (0.0014)	0.35 (0.0010)	0.40 (0.0007)
X = *Br*	0.65 (0.0044)	0.69 (0.0029)	0.76 (0.0019)	0.87 (0.0020)
X = *I*	1.23 (0.0095)	1.36 (0.0070)	1.51 (0.0054)	1.76 (0.0071)

[a] Given in parentheses (B3LYP/aug-cc-pVDZ).

halogen size and with higher degree of fluorination. The hyperconjugation increase leads to a decrease in the interaction energy. In the SAPT decomposition this increase is reflected primarily in the decrease of the induction term, which includes charge transfer.

$C - H\cdots X$ hydrogen bonds exhibit both red and blue shifts of the $C - H$ stretching frequency upon formation of the hydrogen bond. Vibrational shifts for the present (unfluorinated) halogen bonded complexes have been computed, and we have found that these shifts are negligible (maximum ± 3 cm^{-1}). All of the halomethane monomers exhibit a positive derivative of the dipole moment as a function of the $C - X$ distance (i.e., the dipole moment increases when the $C - X$ bond is elongated), which indicates a red shift of the $C - X$ stretching frequencies. The electron density of the σ^* antibonding orbital of the $C - X$ bond systematically increases upon complexation, which also indicates a red shift of the $C - X$ stretching frequencies. On the other hand the s-character of the carbon atom in the $C - X$ bond increases upon dimerization, which indicates a blue shift of the $C - X$ stretching frequencies. Evidently, the cumulative effect of all the factors considered above is to leave the $C - X$ stretching frequencies largely unchanged upon complexation of these halogen bonding dimers.

Comparison of Halogen Bonds to Hydrogen Bonds. Halogen bonds are often compared to, the much more ubiquitous, hydrogen bonds, with which they share some properties. Here we will compare the SAPT (aug-cc-pVTZ) interaction energy decomposition results for the, halogen bonding, $H_3CCl\cdots OCH_2$, $H_3CBr\cdots OCH_2$, $F_1H_2CI\cdots OCH_2$, and $F_3CI\cdots OCH_2$ complexes to those obtained for $H_3CH\cdots OCH_2$ and $HCCH\cdots OH_2$, which exemplify typical $C - H\cdots O$ type hydrogen bonds.

Table 7 gives the SAPT interaction energy decomposition values for $H_3CCl\cdots OCH_2$, $H_3CBr\cdots OCH_2$, $F_1H_2CI\cdots OCH_2$, and $F_3CI\cdots OCH_2$, $H_3CH\cdots OCH_2$, and $HCCH\cdots OH_2$. The binding energy of the ethyne-water dimer (−3.25 kcal/mol) is roughly comparable to that of $F_1H_2CI\cdots OCH_2$ (−3.29 kcal/mol) and is higher than that of $H_3CBr\cdots OCH_2$ (−1.70 kcal/mol). Overall, the $C - H\cdots O$ interaction is more electrostatic (and less dispersive) in nature than the $C - X\cdots O$ interactions, with the electrostatic term accounting for 68.5% of the overall attractive interaction in the $HCCH\cdots OH_2$ complex. For the $F_1H_2CI\cdots OCH_2$ complex, to which the hydrogen-bonding systems can be most closely compared, the electrostatic component is responsible for 50.2% of the attractive interaction, while for the (unfluorinated) bromomethane-formaldehyde dimer, this term yields only 38.5% of the attractive interaction. When the SAPT decomposition results for the $HCCH\cdots OH_2$ (68.5% electrostatic) dimer are compared to those of the $F_3CI\cdots OCH_2$ (56.8% electrostatic) complex, which exemplifies the strongest halogen bonding complex considered in this work (SAPT binding energy of −4.65 kcal/mol), it can be seen that the hydrogen-bonding complex displays much more of an electrostatic character.

The hydrogen bonding $H_3CH\cdots OCH_2$ complex, with a binding energy of −0.70 kcal/mol, can most closely be compared to the $H_3CCl\cdots OCH_2$ complex, which has a binding energy of −0.98 kcal/mol. The interaction between methanol and formaldehyde is not dominated by the electrostatic interaction as in the case of the ethyne-water complex; nonetheless, electrostatics play a larger role in the $H_3CH\cdots OCH_2$ complex (38.5% of the attractive interaction) than in the $H_3CCl\cdots OCH_2$ complex (32.2% of the attractive interaction). In terms of SAPT interaction energy contributions the methane-formaldehyde complex is most similar to the bromomethane-formaldehyde system, whose electrostatic term corresponds to 38.5% of the total attractive interaction.

Overall it can be said that, in terms of SAPT interaction energy components, halogen bonds are similar in character to the weak $C - H\cdots O$ type hydrogen bond found in the $H_3CH\cdots OCH_2$ complex. Both halogen bonds and this weak hydrogen bond depend largely on both electrostatic and dispersive forces. The strong $C - H\cdots O$ hydrogen bond found in the $HCCH\cdots OH_2$ complex is very electrostatic in nature and, in terms of the SAPT interaction decomposition, does not resemble a halogen bonding interaction.

Comparison of DFT-SAPT and SAPT. Table 8 gives the DFT-SAPT and SAPT interaction energy decomposition results with the aug-cc-pVxZ/aug-cc-pVxZ-PP basis set for the $H_3CBr\cdots OCH_2$ complex. The binding energies obtained by SAPT and DFT-SAPT agree remarkably well, with the largest deviation of 0.05 kcal/mol occurring for the aug-cc-pVDZ/aug-cc-pVDZ-PP basis set. Here it can be seen that, for a given basis set, the DFT-SAPT method slightly overestimates the electrostatic and dispersion values, while it slightly underestimates the exchange values compared to standard SAPT. The DFT-SAPT values for the induction components of the binding energies agree with those of SAPT perfectly (out to two decimal places). In terms of basis sets, the same trends are seen for the DFT-SAPT method as for SAPT, as the basis set becomes larger the interaction between the two molecules within a complex gets stronger, the dispersion component increases and the electrostatic term decreases.

At present it is only possible to use the DFT-SAPT/aug-cc-pVDZ method to treat large systems, such as biological complexes. While this method can be used to obtain a qualitative description of these types of interactions, it should be kept in mind that dispersion contributions are generally underestimated by 15%-20% and that electrostatic contributions are usually overestimated by 5%-10%.

Table 7. Comparison of SAPT Results for Several Halogen Bonding and Hydrogen Bonding Complexes[a]

	$H_3CCl\cdots OCH_2$	$H_3CBr\cdots OCH_2$	$F_1H_2Cl\cdots OCH_2$	$F_3Cl\cdots OCH_2$	$H_3CH\cdots OCH_2$	$HCCH\cdots OH_2$
E(*elec.*)	−0.96 (32.2)	−1.47 (38.5)	−3.11 (50.2)	−4.04 (56.7)	−0.55 (38.5)	−3.78 (68.5)
E(*ind.*)	−0.23 (7.5)	−0.37 (9.7)	−0.82 (13.2)	−0.95 (13.3)	−0.16 (11.0)	−0.51 (9.3)
E(*disp.*)	−1.81 (60.3)	−1.98 (51.8)	−2.26 (36.5)	−2.14 (30.0)	−0.72 (50.5)	−1.23 (22.2)
E(*exch.*)	2.02	2.12	2.90	2.48	0.72	2.27
ΔE_{int}^{SAPT}	−0.98	−1.70	−3.29	−4.65	−0.70	−3.25

[a] kcal/mol (numbers in parentheses indicate the relative contribution (in %) to the total attractive interaction).

Table 8. Comparison of SAPT and DFT-SAPT Results for the $H_3CBr\cdots OCH_2$ Complex[a]

	$H_3CBr\cdots OCH_2$			
DFT-SAPT	a-pVDZ	a-pVTZ	a-pVQZ	CBS
E(*elec.*)	−1.63	−1.56	−1.56	−1.56
E(*ind.*)	−0.36	−0.37	−0.37	−0.37
E(*disp.*)	−1.74	−2.06	−2.13	−2.18
E(*exch.*)	2.29	2.29	2.26	2.23
δHF	0.00	−0.01	−0.01	−0.01
ΔE_{int}^{SAPT}	−1.44	−1.71	−1.81	−1.89
SAPT	a-pVDZ	a-pVTZ	a-pVQZ	CBS
E(*elec.*)	−1.56	−1.47	−1.46	−1.45
E(*ind.*)	−0.36	−0.37	−0.37	−0.37
E(*disp.*)	−1.69	−1.98	−2.08	−2.15
E(*exch.*)	2.12	2.12	2.11	2.11
ΔE_{int}^{SAPT}	−1.49	−1.70	−1.80	−1.86

[a] kcal/mol (note that a-pVxZ = aug-cc-pVxZ/aug-cc-pVxZ-PP).

Conclusions

In this work we have performed HF, MP2, CCSD(T), NBO, SAPT, and DFT-SAPT calculations, using several large basis sets, on the (fluorinated and unfluorinated) halomethane-formaldehyde complexes. It is found that, as the halogen bonding halogen's size increases, the halogen bond becomes stronger and longer. SAPT analyses of halogen bonds in systems containing chlorine and bromine indicate that halogen bonding interactions involving these halogen atoms are principally dispersive in nature, although electrostatic contributions to halogen bonds are not negligible. The electrostatic contribution to the interaction energy in halogen bonding increases as the size of the halogen bonding halogen increases. The most dominant physical component of interactions for systems containing iodine is the electrostatic one, which accounts for slightly more than half of the total binding energy. Upon substitution of fluorine atoms, which are very electronegative, onto the halomethanes, halogen bonds become more stable and more electrostatic (and less dispersive) in nature. The weakest halogen bond observed in this study is for the $H_3CCl\cdots OCH_2$ complex, whose CCSD(T)/aug-cc-pVTZ binding energy is −1.05 kcal/mol. The strongest halogen bond occurs for the $F_3CI\cdots OCH_2$ complex, with a CCSD(T)/aug-cc-pVTZ interaction energy of −3.72 kcal/mol.

The most significant result obtained in this study is the fact that, according to SAPT analysis, halogen bonds are largely dependent on both electrostatic and dispersion forces. The electrostatic nature of halogen bonds increases with the increasing size of the halogen involved, while the dispersive contribution to the halogen bonding interaction decreases with increasing halogen size. The largest SAPT interaction energy component for (unfluorinated) systems containing chlorine and bromine is dispersion, while the electrostatic term accounts for slightly more than half of the attractive interaction for the iodomethane-formaldehyde complex. It should be noted that, even in cases where the electrostatic contribution to the interaction energy is smaller than that of dispersion, electrostatic effects probably play a large role in determining the geometries of halogen bonding systems, as the halogen's positive σ-hole tends to line up with the negative lone electron pair on oxygen. The contribution of induction effects to halogen bonding interactions is relatively small and generally accounts for about 5%-15% of the attractive interaction.

The addition of fluorine substituents to the halomethane molecules in our model complexes tends to draw electron density away from the halogen bonding halogen atoms, which results in halogen atoms that have significantly larger (and more positive) σ-holes. The overall effect of successive fluorine substitution onto the halomethane systems is to produce halogen bonds that are both stronger and more electrostatic in character.

Halogen bonds are often compared to, the much more commonly encountered, hydrogen bonds. Here we have shown that, in terms of SAPT interaction energy terms, halogen bonds share many common features with weak C - $H\cdots O$ type hydrogen bonds. Halogen bonds are not very similar to strong C - $H\cdots O$ hydrogen bonds, which exhibit interactions that are much more electrostatic in nature. One common feature of halogen bonds and hydrogen bonds is the hyperconjugation that occurs between the C - X (where X represents either a halogen or hydrogen) antibonding orbital and the oxygen lone pair orbital. The magnitude of this hyperconjugation increases with larger halogen atoms and with the addition of fluorine substituents onto the halomethane systems.

Among the many scientific fields in which halogen bonds have been implicated as important types of interactions is the study of protein−ligand interactions. It has been shown in this work, and in several other studies, that halogen bonding interactions are sufficiently strong to be considered as relevant in biological complexes and that, because of their unique properties, halogen bonds might be used in the development of, for example, new pharmaceutical compounds.

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Supporting Information Available: Tables and figures describing the halomethane-methanol data and results computed using the aug-cc-pVDZ basis set (on all atoms). This material is available free of charge via the Internet at http://pubs.acs.org.

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