

Halogen bond tunability I: the effects of aromatic fluorine substitution on the strengths of halogen-bonding interactions involving chlorine, bromine, and iodine

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Abstract In the past several years, halogen bonds have been shown to be relevant in crystal engineering and biomedical applications. One of the reasons for the utility of these types of noncovalent interactions in the development of, for example, pharmaceutical ligands is that their strengths and geometric properties are very tunable. That is, substitution of atoms or chemical groups in the vicinity of a halogen can have a very strong effect on the strength of the halogen bond. In this study we investigate halogen-bonding interactions involving aromatically-bound halogens (Cl, Br, and I) and a carbonyl oxygen. The properties of these halogen bonds are modulated by substitution of aromatic hydrogens with fluorines, which are very electronegative. It

is found that these types of substitutions have dramatic effects on the strengths of the halogen bonds, leading to interactions that can be up to 100% stronger. Very good correlations are obtained between the interaction energies and the magnitudes of the positive electrostatic potentials (σ -holes) on the halogens. Interestingly, it is seen that the substitution of fluorines in systems containing smaller halogens results in electrostatic potentials resembling those of systems with larger halogens, with correspondingly stronger interaction energies. It is also shown that aromatic fluorine substitutions affect the optimal geometries of the halogen-bonded complexes, often as the result of secondary interactions.

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Introduction

Halogen bonding has emerged in recent years as one of the most interesting types of noncovalent interactions [1–4], with unique properties that can only be understood by examination of the molecules' electrostatic potentials. These interactions are extremely tunable, meaning that changing neighboring atoms or chemical groups can have a dramatic impact on the strengths of the halogen bonds. This property makes halogen bonds a very promising mode of interaction for the design of novel materials and pharmaceutical ligands [2, 5–9]. In this study, we investigate halogen bond tunability by examining the effects of aromatic fluorine substitution on the strengths and characters of the interactions.

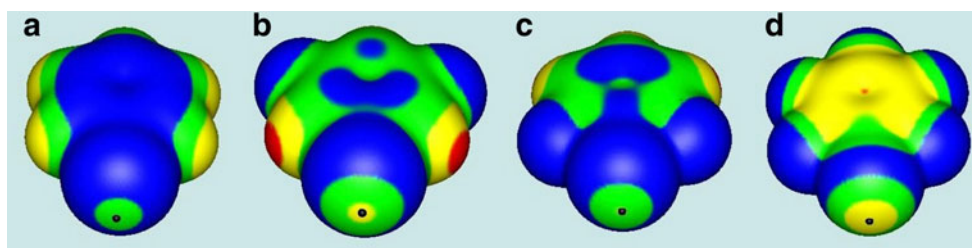


Fig. 1 Computed electrostatic potentials on 0.001 au molecular surfaces of the chlorobenzene monomers: chlorobenzene (a), *meta*-difluorochlorobenzene (b), *ortho*-difluorochlorobenzene (c), pentafluorochlorobenzene (d). Color ranges, in kcal mol⁻¹, are: red, greater than 20; yellow, between 20 and 10; green, between 10 and 0; blue, negative. Black hemispheres denote the positions of the chlorine $V_{S,max}$

Halogen bonds can be depicted as RX...YZ interactions, where RX is usually an organic halide (almost always a chloride, bromide, or iodide) and YZ is a Lewis base, Y generally having a lone pair of electrons. Halogen bonds are considered to be analogous to hydrogen bonds, RH...YZ, and the same terminology is used to describe both types of interactions; for example RX is commonly described as the halogen bond donor (in analogy to the hydrogen bond donor RH) and the Lewis base YZ is the halogen bond acceptor. A halogen bond typically has an X...Y distance that is shorter than the sum of the van der Waals radii of the respective atoms.

Since the participants in a halogen bond, X and Y, are both normally considered to be negative in character, their attractive interaction may appear to be counterintuitive. The explanation can be found through examination of the electrostatic potentials of various organic halogens [3, 4, 10–15]. Such studies show that the larger halogens (Cl, Br, and I) bound to carbon (and possibly other atoms) generally have a region of positive potential along the extension of the covalent bond to the halogen atom (see Figs. 1, 2, 3). There is also typically a belt of negative potential on the halogen, around its lateral sides. So even if the halogen overall is considered to be negative, it does have distinct regions of both positive and negative potential. The positive potential on the halogen is usually referred to as the σ -hole [16]. It reflects an anisotropic distribution of the electronic charge on the halogen [17–22]. The principal origin of

halogen bonding interactions, and the force leading to their directionalities [14], is the electrostatic attraction between the halogen σ -hole and the negative Lewis base.

Many properties of halogen bonds have now been elucidated [3, 4]. A halogen's σ -hole tends to become larger and more positive with increasing size of the halogen, Cl < Br < I. The smallest halogen, fluorine, only forms a σ -hole in very special instances, such as the fluorine molecule (F₂) [3]. A halogen's chemical environment also plays a large role in determining the size and potential of the σ -hole. For example, bromine has a much larger and more positive σ -hole in F₃C-Br than in H₃C-Br [11, 23], due to the electron-withdrawing effect of the fluorines. Similarly, the bromine in 5-bromo-4,6-dicyano pyrimidine is more positive than the corresponding one in 5-bromopyrimidine [13]. Such modulation of the σ -hole can produce halogen bonding interactions that are stronger and more electrostatic in character, as has been discussed for brominated benzene and pyrimidine derivatives in relation to their complexes with acetone in an earlier study [13]. For more detailed discussions of the origins of σ -holes and the factors that determine their properties, see Politzer et al. [3] and Murray et al. [4].

Analyses of halogen bonds in terms of density functional symmetry-adapted perturbation theory (DFT-SAPT) suggest that these interactions involve dispersion as well as electrostatic contributions [13, 23]. This is supported by the fact that both Hartree-Fock and density functional theory

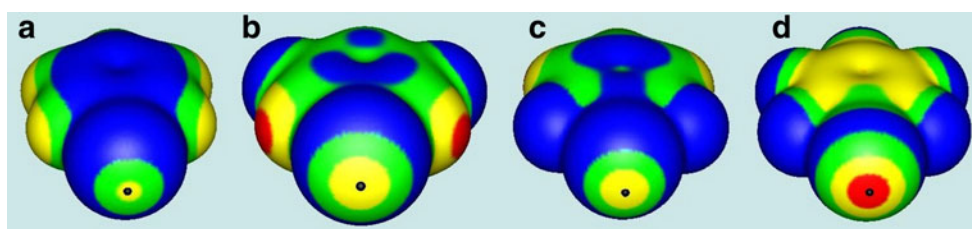


Fig. 2 Computed electrostatic potentials on 0.001 au molecular surfaces of the bromobenzene monomers: bromobenzene (a), *meta*-difluorobromobenzene (b), *ortho*-difluorobromobenzene (c), pentafluorobromobenzene (d). Color ranges, in kcal mol⁻¹, are: red,

greater than 20; yellow, between 20 and 10; green, between 10 and 0; blue, negative. Black hemispheres denote the positions of the bromine $V_{S,max}$

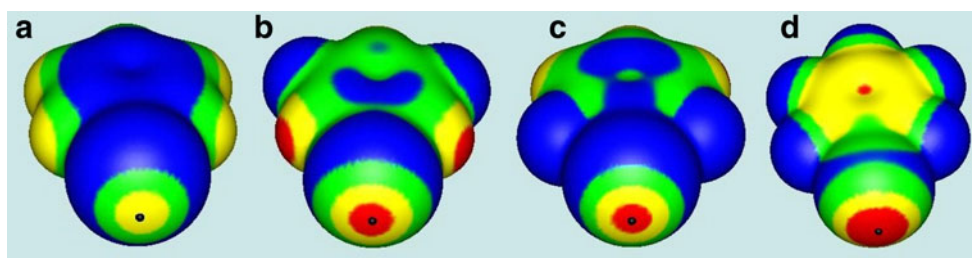


Fig. 3 Computed electrostatic potentials on 0.001 au molecular surfaces of the iodobenzene monomers: iodobenzene (**a**), *meta*-difluoriodobenzene (**b**), *ortho*-difluoriodobenzene (**c**), pentafluor-

iodobenzene (**d**). Color ranges, in kcal mol⁻¹, are: red, greater than 20; yellow, between 20 and 10; green, between 10 and 0; blue, negative. Black hemispheres denote the positions of the iodine $V_{S,max}$

(DFT) treatments of halogen bonding generally yield binding energies that are too low [23]. (There are a few DFT methods that have been found to give fairly accurate binding energies for halogen bonds, but there is no systematic way to predict this [24].) The degree to which electrostatics and dispersion contribute to the overall halogen bonding interaction depends on the identity of the halogen and the specific chemical environment in which the halogen is found [13].

As noted above, one of the key properties of halogen bonding interactions that makes them so attractive for the design of new materials is that they are highly tunable, i.e., their binding properties can be strongly modulated by substituting various atoms or chemical groups into neighboring positions [3, 4, 13]. A modification that can have a dramatic effect on the electron density of a system is the substitution of hydrogens by fluorine atoms. The latter are highly electronegative and will tend to increase the positive characters of atoms in their proximities. Such substitution has been shown to strongly modify the properties of many different types of noncovalent interactions. The method of fluorine-scanning, in which hydrogens are substituted with fluorines (one at a time, or in groups), has been used in studies of protein-ligand complexes and has yielded ligands that bind much more strongly than their unfluorinated counterparts [25–27]. It is common in medicinal chemistry to substitute fluorines for hydrogens in order to enhance ligand binding to proteins [25–28]. Fluorine is an isosteric substitution for hydrogen and is isoelectronic with hydroxyl groups, properties that make it very suitable for substitution into small molecule ligands. Hence, a fluorinated small molecule ligand should be capable of binding in generally the same location as a nonfluorinated one, but the chemical properties of the modified ligand may affect and impact protein-ligand affinity and selectivity.

More specifically, fluorine substitution on a halobenzene has a marked effect on the positive character of the halogen's σ -hole [13], and thus on the strength of any halogen bond. Modulating halogen bonds by aromatic fluorine substitution may have a dramatic impact on

protein-ligand interactions involving such bonds. It can also be useful in the design of new crystals and materials exhibiting halogen-bonding interactions [5, 6].

In this study, we use computational methods to investigate the consequences of aromatic fluorine substitution on halogen-bonding interactions. The calculated electrostatic potentials of the halogen bond donors reveal the sizes and positive characters of the halogen σ -holes. The strengths of the interactions are then related to the characteristic properties of the σ -holes in order to determine the role that these play in modulating the halogen bonding.

Computational methods

The systems studied are halobenzene–acetone complexes involving chlorine, bromine, or iodine as the halogen. These are the three that have been shown to participate in halogen bonds under normal circumstances. Three types of fluorine substitution patterns are used for each of the halobenzene systems. Two of these patterns have two fluorine substituents and one has five. The difluoro systems will be denoted as the X-benz-*meta*-2 F and X-benz-*ortho*-2 F configurations (where X could be Cl, Br, or I). These correspond to 3,5-difluorohalobenzene and 2,6-difluorohalobenzene, respectively. The third substitution pattern, labeled X-benz-5 F, represents the pentafluorinated case (2,3,4,5,6-pentafluorohalobenzene). The unsubstituted halobenzenes will be designated X-benz. Acetone is chosen as the halogen bond acceptor because it has been previously shown to form strong halogen bonds [13] and because it is among the simplest models of a carbonyl-containing molecule that can mimic the chemical environments of carbonyl groups in biological systems [13].

We have studied different aspects of these interactions in order to reveal the various factors that contribute to attractive forces in halogen bonds and the way that these forces change when fluorine atoms are substituted onto the halobenzene ring. Interaction energy calculations were carried out using the MP2 procedure. The basis set was, for the most part, aug-cc-pVDZ; for the bromine and iodine atoms, however, it was

necessary to use the aug-cc-pVDZ-PP, which contains pseudopotentials and implicitly accounts for relativistic effects, which are important for larger atoms. All MP2 binding energy calculations include the counterpoise corrections of Boys and Bernardi in order to account for basis set superposition error (BSSE) [29]. All MP2 interaction energy calculations were made using the MOLPRO 2008 suite of molecular electronic structure programs [30].

The electrostatic potential $V(\mathbf{r})$ that is created by the nuclei and electrons of a system at any point \mathbf{r} is given by,

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \quad (1)$$

in which Z_A is the charge on nucleus A, located at \mathbf{R}_A , and $\rho(\mathbf{r})$ is the total electronic density. The sign of $V(\mathbf{r})$ in any region depends upon whether the positive contribution of the nuclei or the negative one of the electrons is dominant there. The electrostatic potential is a real physical property, a physical observable. It can be determined experimentally, by diffraction techniques [31, 32], as well as computationally.

While $V(\mathbf{r})$ is of fundamental importance in several different areas [33, 34], our present interest is in its well-established effectiveness in analyzing and predicting non-covalent interactions [34–36]. For this purpose, $V(\mathbf{r})$ is now usually computed on the molecular “surface,” taking this to be an outer contour of the electronic density, generally the 0.001 au (electrons/bohr³), as proposed by Bader et al. [37]. The potential computed on this surface is designated $V_S(\mathbf{r})$ [38]; its most positive and most negative values (its maxima and minima) are labeled $V_{S,\max}$ and $V_{S,\min}$. There may be several of each on a given molecular surface.

Electrostatic potentials for all 12 halobenzenes were computed at the B3PW91/6-311 G* level with the WFA-Surface Analysis Suite [38]; the input wave functions (for the optimized halobenzene geometries) were computed using Gaussian 09 [39]. The B3PW91 density functional was used for these electrostatic potential calculations (instead of the B3LYP) in order to maintain consistency with earlier studies [3, 4, 12, 13, 15].

The global minimum energy configurations of the halobenzene...acetone complexes, as well as their fluorinated counterparts will not necessarily correspond to the minimum energy halogen bond configurations of these complexes. This is because secondary (non-halogen bonding) interactions that exist between the monomers can strongly influence the final structure of the dimers. In this study our primary interest has been to investigate the effects of aromatic substitution on interactions that are in their ideal [i.e., $a(\text{C-X}\dots\text{O})=180^\circ$] halogen bonding configurations. As such, we have not carried out gradient-based minimizations on these complexes, but have optimized the dimers using the manual procedure described below.

The geometries of the individual monomers were obtained at the B3LYP/6-31+G* level of theory. The structures of the complexes were then obtained by manual optimizations in which two intermolecular parameters were adjusted individually (one at a time). These were the X...O distance, $d(\text{X}\dots\text{O})$, and the X...O=C angle, $a(\text{X}\dots\text{O}=\text{C})$; see Fig. 4. These are the two parameters that have the strongest effects on the strengths and characters of halogen-bonding interactions. The C-X...O angles were fixed at a value of 180° . The X...O distances were determined to within 0.1 Å, the X...O=C angles to within 2.5° . The importance of the X...O=C angle is that it determines the extent to which the halogen σ -hole will interact with an oxygen lone pair. When this angle is 180° , the σ -hole is pointing *between* the two oxygen lone pairs; the strongest interaction is expected to be when it is pointing *toward* one of them, so that $a(\text{X}\dots\text{O}=\text{C}) < 180^\circ$.

The first step in the manual optimization procedure was to produce a potential energy curve along the X...O axis at an X...O=C angle of 180° . Next, a potential energy curve was generated for the bending of the complex about the X...O=C angle, at the minimum energy separation as determined in the first potential energy scan (to within 0.1 Å). Finally, another potential energy curve along the X...O axis was produced at the optimum X...O=C angle (to within 2.5°). Results will be presented for both this optimum angle and for $a(\text{X}\dots\text{O}=\text{C})=180^\circ$. Tabulated geometric results are the minima for the potential energy curves as obtained from data fitted using cubic splines.

Results and discussion

General trends

In Table 1 are listed the most positive electrostatic potentials (the $V_{S,\max}$) associated with the halogen σ -holes

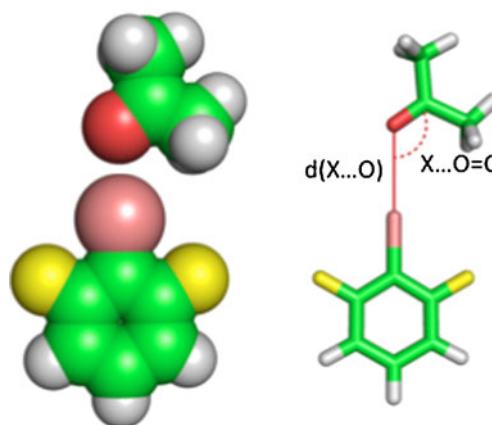


Fig. 4 Schematic models of halogen bonding complexes studied in this work

Table 1 Halogen $V_{S,max}$ values in halobenzenes, MP2/aug-cc-pVDZ(-PP) interaction energies, equilibrium intermolecular separations, and optimum equilibrium $X...O=C$ angles for all of the systems studied in this work. Energies are in kcal mol^{-1} , distances in \AA and angles in degrees

System	At $a(X...O=C)=180^\circ$			At optimum $X...O=C$ angle		
	$V_{S,max}$	ΔE	$d(X...O)$	ΔE	$d(X...O)$	$a(X...O=C)$
Cl-benz	5.3	-0.75	3.13	-1.30	3.16	118
Cl-benz- <i>meta</i> -2 F	11.9	-1.35	3.09	-1.74	3.10	120
Cl-benz- <i>ortho</i> -2 F	10.2	-1.32	3.04	-2.00	3.04	119
Cl-benz-5 F	18.9	-2.14	3.00	-2.63	3.00	121
Br-benz	12.2	-1.58	3.10	-2.23	3.13	122
Br-benz- <i>meta</i> -2 F	18.4	-2.22	3.05	-2.78	3.04	123
Br-benz- <i>ortho</i> -2 F	18.0	-2.37	3.00	-3.17	2.98	123
Br-benz-5 F	27.2	-3.34	2.96	-4.09	2.91	124
I-benz	17.3	-2.44	3.18	-3.22	3.14	125
I-benz- <i>meta</i> -2 F	26.1	-3.38	3.09	-4.13	3.05	128
I-benz- <i>ortho</i> -2 F	25.5	-3.64	3.05	-4.71	3.00	126
I-benz-5 F	35.9	-4.88	2.99	-5.97	2.91	128

of the chloro-, bromo- and iodobenzenes included in this study. They show the expected trends of increasing with the number of electron-attracting fluorines on the ring and with the size of the halogen ($\text{Cl} < \text{Br} < \text{I}$).

Each halobenzene was allowed to form two halogen-bonded complexes with acetone. One of these was at an imposed $X...O=C$ angle of 180° ; the other was for an optimized $a(X...O=C)$, which ranged from 118° to 128° . The interaction energies are in Table 1, and the respective potential energy profiles are in Figs. 5 and 6 for the chlorobenzenes, Figs. 7 and 8 for the bromobenzenes and Figs. 9 and 10 for the iodobenzenes.

In an earlier analysis of the electrostatic potential of acetone [13], the most negative values associated with the oxygen were observed to be at points that would correspond to $X...O=C$ angles of $\pm 127^\circ$. These presumably reflect the lone pairs of the oxygens. The complexes at $X...O=C$ angles of 180° can accordingly be interpreted as the

halogen σ -hole interacting with the negative region between the lone pairs, while the ones at the optimized $X...O=C$ angles have the σ -holes interacting more directly with just one of the lone pairs. The latter complexes are invariably slightly more strongly bound (Table 1), but the differences are small, because the lone pair potentials are not much more negative than the region between them [13]. In Fig. 11, the interaction energies of each type of complex are plotted against the respective $V_{S,max}$. Good linear correlations are obtained: $R^2=0.975$ and 0.942 . These results are consistent with previous work showing the electrostatically-driven nature of halogen bonding [3, 13, 14].

A striking feature of Fig. 11 is that each line has three clusters of closely-spaced points, with $V_{S,max}$ of ~ 10 – 12 kcal mol^{-1} , 17 – 19 kcal mol^{-1} and 25 – 27 kcal mol^{-1} . These clusters reflect some marked similarities between certain members of the three families of halobenzenes, that

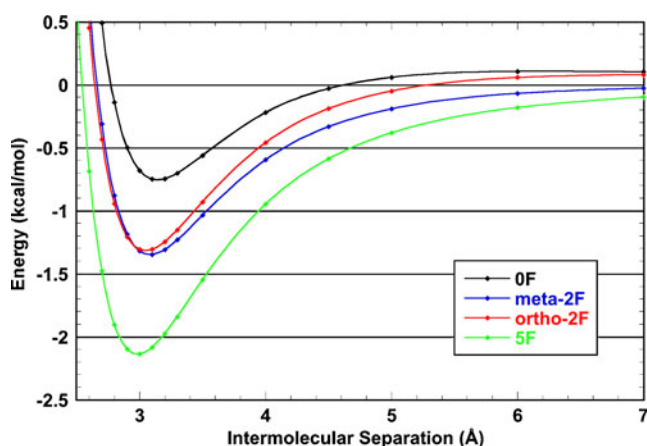


Fig. 5 MP2 potential energy curves for fluorinated chlorobenzenes complexed with acetone at a $\text{Cl}...O=C$ angle of 180°

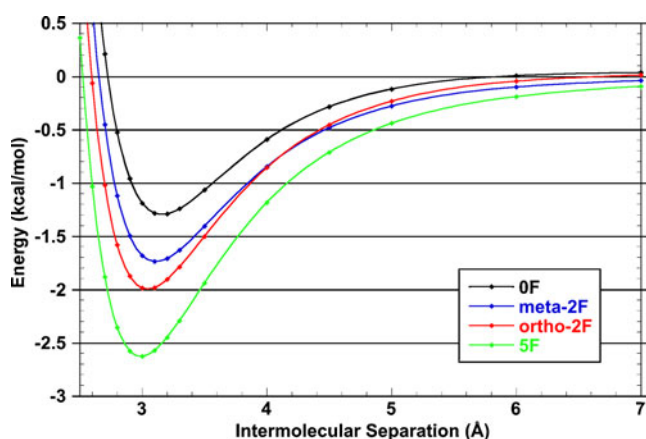


Fig. 6 MP2 potential energy curves for fluorinated chlorobenzene... acetone complexes at the optimum $\text{Cl}...O=C$ angles

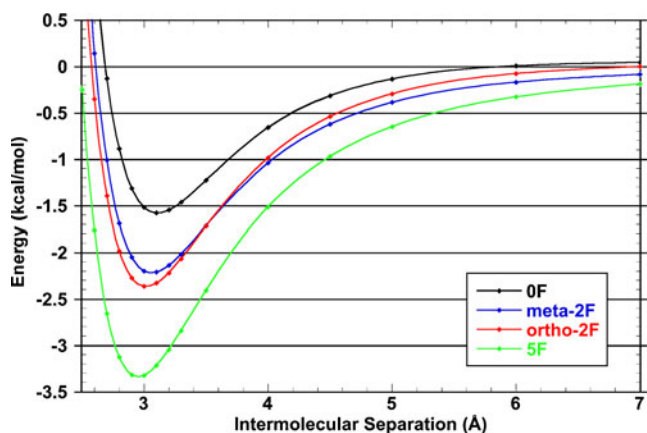


Fig. 7 MP2 potential energy curves for fluorinated bromobenzenes complexed with acetone at a Br...O=C angles of 180°

are revealed by Table 1. The presence of two fluorines in chlorobenzene (bromobenzene) produces approximately the same $V_{S,max}$ as in bromobenzene (iodobenzene). The presence of five fluorines in chlorobenzene (bromobenzene) results in about the same $V_{S,max}$ as two fluorines in bromobenzene (iodobenzene). Figures 1, 2, 3 show that the halogen electrostatic potentials of each of the pairs described above are quite similar, with comparable σ -holes. The interaction energies follow very much the same patterns.

The clusters with $V_{S,max}$ values between 17 and 19 kcal mol⁻¹ are especially interesting, since they correspond to interactions involving all three halogens: chlorine, bromine, and iodine. For the linear complexes, the range of interaction energies in this cluster is only between -2.14 and -2.44 kcal mol⁻¹; for the optimized complexes, it is somewhat larger.

The trends described above give an excellent demonstration of the tunability of halogen bonding. For instance, if halogen bonding via iodobenzene is not feasible (perhaps

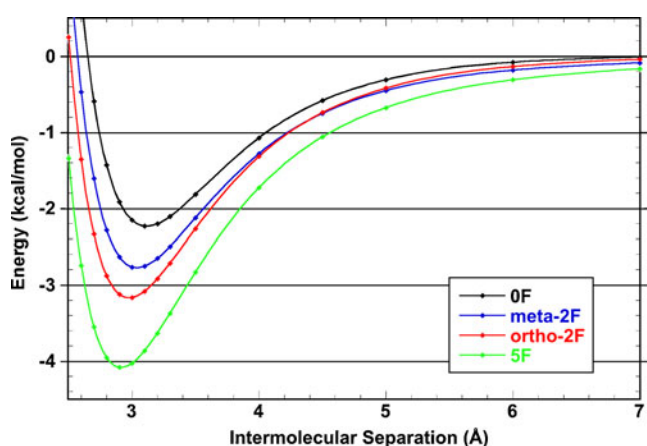


Fig. 8 MP2 potential energy curves for fluorinated bromobenzene... acetone complexes at their optimum Br...O=C angles

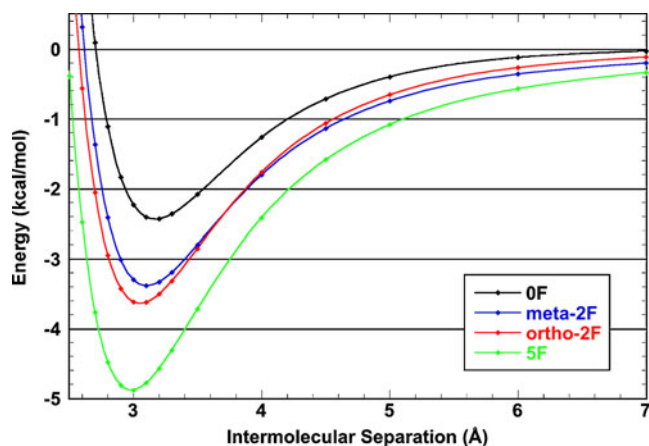


Fig. 9 MP2 potential energy curves for fluorinated iodobenzenes complexed with acetone at an I...O=C angle of 180°

for steric reasons), doubly-fluorinated bromobenzene may serve instead. In this sense, it becomes possible to think of a substituted system as an electrostatic analog of an unsubstituted one containing a larger halogen. For example, the chlorine in Cl-benz-2 F system (either *meta* or *ortho*) can be viewed as a pseudo-bromine, in that the electrostatic potentials (and $V_{S,max}$ values) of the chlorine in Cl-benz-2 F and the bromine in bromobenzene are very similar, as are their interaction energies.

For a given halogen, the X...O distances in its halobenzene-acetone complexes decrease as the number of fluorines increases (Table 1). This can be anticipated; with more fluorines, the $V_{S,max}$ becomes more positive and the interaction stronger. For the doubly-fluorinated systems, the *ortho* substituted always have shorter X...O separations than the *meta*. We attribute this to secondary interactions, as shall be discussed.

Comparisons should be made cautiously, however, when different halogens are involved. Their differing sizes may counteract the effect of the strength of the interaction. Thus

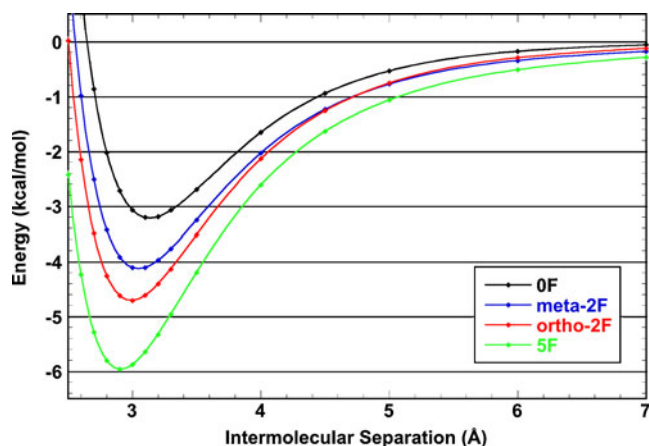


Fig. 10 MP2 potential energy curves for fluorinated iodobenzene... acetone complexes at their optimum I...O=C angles

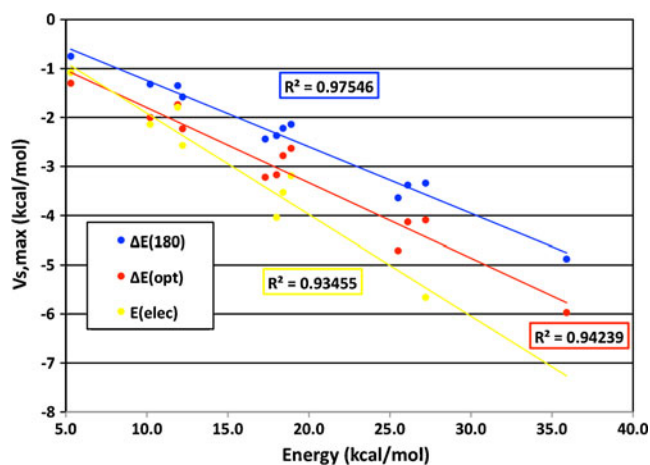


Fig. 11 Plots of interaction energies vs. halogen $V_{S,max}$ at $a(X...O=C)=180^\circ$ (blue) and at optimum $X...O=C$ angles (red). Interactions are given for complexes containing chlorine (X), bromine (solid circle), and iodine (hollow circle)

the $I...O$ distances in Table 1 are usually greater than the $Br...O$, for a given number of fluorines, despite the former complexes being more tightly bound. This can be ascribed to the greater van der Waals radius of iodine compared to bromine, 1.96 Å vs. 1.85 Å [40]. On the other hand, the $Br...O$ separations are all less than the $Cl...O$, even though the chlorine van der Waals radius is 0.09 Å less than the bromine. Again, secondary interactions may be involved.

A final trend of interest in Table 1 is that the $X...O=C$ angles tend to increase as the complexes become more strongly bound. For the iodo systems, these angles are in the neighborhood of those corresponding to the most negative oxygen potentials ($\pm 127^\circ$) [13]. This point needs to be elucidated; it may involve several factors, including the larger sizes and stronger σ -holes of the iodines.

The role of possible secondary interactions, in addition to the primary halogen-bonding one, should not be overlooked. We shall now consider these in some detail, starting with the bromobenzene complexes, then moving on to the chloro- and iodo- analogues. Substituted bromobenzenes and bromopyrimidines were the topic of an earlier extensive study [13] and thus the bromo series provides a good starting point for examining secondary interactions.

Halogen bonds involving bromine

Figure 2 displays the electrostatic potentials on the 0.001 au surfaces of the four bromobenzenes: Br-benz, Br-benz-*meta*-2 F, Br-benz-*ortho*-2 F, and Br-benz-5 F. Figure 2 and the $V_{S,max}$ values in Table 1 show that successive fluorine substitution results in bromine σ -holes that are larger and more positively charged, as has been observed in earlier work [13]. Among the two doubly-fluorinated systems, Br-benz-*meta*-2 F and Br-benz-*ortho*-2 F, the former has a

larger σ -hole and a slightly higher $V_{S,max}$. However Table 1 and Figs. 7 and 8 reveal that the Br-benz-*ortho*-2 F...acetone complex binds marginally more strongly. At the optimum $Br...O=C$ angle, the interaction energy of the Br-benz-*ortho*-2 F complex is 0.39 kcal mol⁻¹ more negative than that of Br-benz-*meta*-2 F. This minor inconsistency seems to be attributable to secondary (non-halogen bonding) interactions. It can be seen in Fig. 4, which depicts the halogen-bonding complexes studied here, that there is a relatively short distance between the acetone hydrogens and the X-benz-*ortho*-2 F fluorines. In the Br-benz-*ortho*-2 F...acetone complex, these distances are 4.57 Å, which is close enough to indicate a substantial attractive interaction. Another possible explanation for Br-benz-*ortho*-2 F binding slightly more strongly to acetone than Br-benz-*meta*-2 F is a secondary interaction occurring between the acetone hydrogens and the ring of negative potential encircling the bromine (Fig. 2). Because the Br-benz-*ortho*-2 F σ -hole is smaller than that of Br-benz-*meta*-2 F, the ring is larger and is better able to interact with the acetone hydrogens. A third conceivable secondary interaction is a repulsion between the *ortho* hydrogens and the acetone hydrogens in the Br-benz-*meta*-2 F...acetone complex. This could destabilize it relative to the Br-benz-*ortho*-2 F...acetone system. It is likely that all of these types of secondary interactions are involved in the extra stabilization observed for the optimum Br-benz-*ortho*-2 F...acetone complex. Analogous secondary interactions are likely to affect the overall stabilization of the Br-benz-5 F...acetone complex as well.

At a $Br...O=C$ angle of 180° , Br-benz-*ortho*-2 F still binds more strongly to acetone than does Br-benz-*meta*-2 F (Table 1), but only by 0.15 kcal mol⁻¹. As at the optimum $Br...O=C$ angles, this is likely due to secondary interactions between the acetone hydrogens and both of the *ortho* fluorines and the bromine negative ring. In this case, the separations are much larger ($d(H...F)=6.90$ Å), which accounts for the extra stabilization of the Br-benz-*ortho*-2 F...acetone complex being much smaller.

In order to further investigate the role of secondary interactions in the *ortho*-substituted case, we produced rotational potential energy curves for a singly *ortho*-substituted bromobenzene...acetone complex. Starting with $a(Br...O=C)=180^\circ$, Br-benz-*ortho*-1 F was rotated in both directions, such that the substituted fluorine was either approaching or retreating from the nearest acetone methyl group. Figure 12 shows that both rotations produce an energy minimum, when the bromine σ -hole is interacting most directly with one of the oxygen lone pairs (i.e., pointing toward it). However the minimum is deeper for the rotation in which the fluorine is approaching a methyl group. The latter interaction is stronger than in the case of the optimum Br-benz-*meta*-2 F...acetone complex (Fig. 12). This clearly indicates that there are secondary

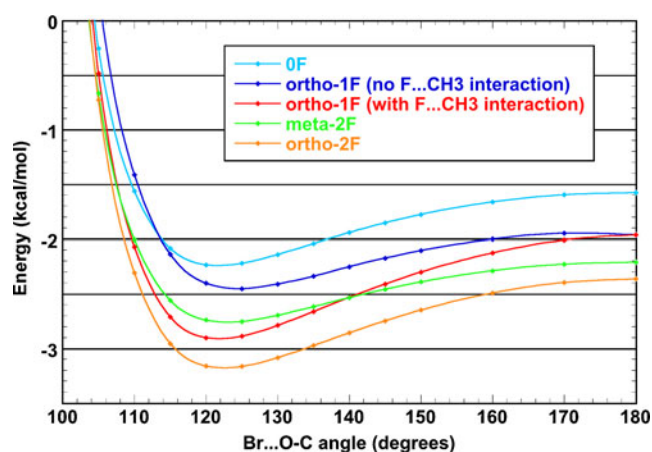


Fig. 12 Potential energy curve for rotation about the Br...C=O angle of singly- and doubly-fluorinated bromobenzene...acetone complexes

interactions occurring that contribute to the overall stability of the system. The relative shallowness of the minima for the fluorine-retreating Br-benz-*ortho*-1 F...acetone and the Br-benz-*meta*-2 F...acetone complexes may indicate the importance of repulsions between *ortho* hydrogens on the bromobenzene systems and methyl hydrogens on acetone.

Halogen bonds involving chlorine

Figure 1 presents the electrostatic potentials on the 0.001 au surfaces of the four chlorobenzenes. Figure 1 and the $V_{S,max}$ values in Table 1 show that the σ -holes of these systems are all smaller and less positive than those of their bromobenzene counterparts (Table 1 and Fig. 2). This is expected, since it is well known that the sizes and positive potentials of halogen σ -holes increase with the size of the halogen [3, 4, 12, 15]. As for the bromobenzenes (Fig. 2 and Table 1), successive aromatic fluorine substitution results in larger and stronger σ -holes.

The effects of successive fluorine substitution in the chlorobenzene...acetone complexes are a contraction of the interaction distances and an increase in the strengths of the interactions (Table 1 and Figs. 5 and 6). These trends have been observed in other fluorinated (aliphatic and aromatic) halogen-bonding systems [12, 13], including the fluorinated bromobenzene...acetone complexes in this study (Table 1 and Figs. 7 and 8), and can be attributed to the changes in the sizes and positive characters of the σ -holes. The interactions of the chlorobenzenes are substantially weaker than those of the bromo- and iodobenzenes (Table 1). The Cl-benz...acetone complex is especially weak, with an interaction energy (MP2/aug-cc-pVTZ) of $-1.30 \text{ kcal mol}^{-1}$ at the optimum geometry and $-0.75 \text{ kcal mol}^{-1}$ at a Cl...O=C angle of 180° . The most negative interaction energy in this set is $-2.63 \text{ kcal mol}^{-1}$ for the Cl-benz-5 F...acetone complex.

As in the case of the bromobenzenes, Cl-benz-*meta*-2 F has a larger and more positive σ -hole than Cl-benz-*ortho*-2 F. However Table 1 and Fig. 6 show that, at their respective optimum angles, the Cl-benz-*ortho*-2 F...acetone complex is slightly more strongly bound than the Cl-benz-*meta*-2 F...acetone. The most likely explanation is once again the presence of secondary interactions analogous to those occurring for the bromobenzene...acetone systems. These are apparently no longer significant when the Cl...O=C angle is 180° (Table 1 and Fig. 5), since the interaction energies are essentially the same. This may be because the Cl...O halogen bonds are somewhat longer than their Br...O counterparts, making the distances between the acetone methyl groups and the chlorobenzenes longer.

Inspection of Fig. 5 brings out an interesting feature. At large intermolecular separations, the interaction can become repulsive. In the case of the benz-Cl...acetone complex with $a(\text{Cl...O=C})=180^\circ$, this repulsion has an interaction energy of $+0.11 \text{ kcal mol}^{-1}$ at a separation of approximately 6 \AA . Since the acetone methyl groups are very distant from the Cl-benz molecule, it seems unlikely that secondary interactions are causing this repulsion. A possible explanation is that because the σ -hole is so small for Cl-benz, the negative potential on the sides of the chlorine begins to dominate at long distances. In other words, the acetone carbonyl oxygen is no longer interacting primarily with the chlorine σ -hole at these separations, but also quite significantly with the negative lateral sides of the chlorine atom. This repulsion acts over very long distances and is still non-zero at an intermolecular separation of 13 \AA (see supplementary material Fig. S4). Such repulsion is also observed for the Br-benz...acetone complex at a separation of 7 \AA (Fig. 7), but its magnitude is smaller ($0.04 \text{ kcal mol}^{-1}$). (It was thought that these repulsions might be an artifact of the counterpoise correction, but the corrected and uncorrected potential energy curves both show the repulsion.)

Halogen bonds involving iodine

It is well known that larger halogens tend to form more positive σ -holes, resulting in stronger halogen-bonding interactions. Figure 3 shows that the four (fluorinated and unfluorinated) iodobenzenes considered in this study have larger and more positive σ -holes than their chlorobenzene and bromobenzene counterparts. As for the latter, the successive substitution of aromatic hydrogens by fluorines increases the σ -holes and their $V_{S,max}$ (Table 1). The potential energy curves in Figs. 9 and 10 confirm that this results in progressively stronger halogen-bonding interactions, with the I-benz-5 F...acetone system having the most negative interaction energy of all the complexes considered in this work ($-5.97 \text{ kcal mol}^{-1}$). Once again it can be seen

that despite the $V_{S,max}$ of I-benz-*meta*-2 F (26.1 kcal mol⁻¹) being slightly higher than that of I-benz-*ortho*-2 F (25.5 kcal mol⁻¹), the I-benz-*ortho*-2 F...acetone complex is bound marginally more tightly than the I-benz-*meta*-2 F...acetone. This is believed to be attributable to the same types of secondary interactions as were described for the complexes involving doubly-fluorinated chloro- and bromobenzenes. As before, the difference between the binding energies of the two doubly-fluorinated systems is lower at an I...O=C angle of 180° (0.26 kcal mol⁻¹) than at the optimum “bent” angle (0.58 kcal mol⁻¹); the secondary interactions become more relevant as an acetone methyl group approaches the iodobenzene aromatic ring.

Conclusions

The main conclusion to be drawn from the results presented here is that halogen bonds are highly tunable interactions whose strengths and characters are heavily influenced by aromatic fluorine substitution. The electron-withdrawing effects of the electronegative fluorine atoms serve to increase the sizes and positive potentials of the halogen σ -holes, which leads to stronger halogen bonds. Very good correlations were obtained between the interaction energy (at both the optimal X...O=C angles and for X...O=C angles set to 180°) and the $V_{S,max}$ of the halogen.

The consequences of fluorine substitution can be quite dramatic; for example, the binding energy for the Cl-benz-5 F...acetone complex is 102% higher than that of the Cl-benz...acetone. The corresponding bromine and iodine systems show binding energy increases of about 85% when all of the aromatic hydrogens are substituted with fluorines. Particularly notable and relevant to tunability are the relationships *between* halogen families. For instance, the presence of five fluorines on bromobenzene gives rise to a bromine $V_{S,max}$ that is very similar to the iodine $V_{S,max}$ resulting from two fluorines on iodobenzene.

The geometries of the halobenzene complexes are heavily influenced by the positive characters of the halogen σ -holes, and thus the degrees of aromatic substitution. Halogen bonds generally contract and strengthen with increasing σ -hole $V_{S,max}$. The optimum X...O=C angles are within the range 118° to 128°. These angles generally increase as the σ -hole potentials become more positive, which may be due to a tendency for σ -holes that are more positive to align more directionally with one of the acetone oxygen lone pairs.

Secondary interactions appear to play a non-negligible (but not dominant) role in determining the geometries and energetics of the systems studied here. These interactions seemingly have the strongest effects on halobenzene complexes with fluorines in the *ortho* positions. The types

of secondary interactions that have been discussed can be expected to accompany halogen bonding involving aromatically-bound halogens, as in protein-ligand interactions and in nanostructural applications.

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