Insights into the Strength and Origin of Halogen Bonding: The Halobenzene−Formaldehyde Dimer

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The observation of short halogen−carbonyl oxygen interactions in protein−ligand complexes has spurred us to use computational tools to better understand the strength of halogen bonding interactions. In this study we have produced potential energy curves for the halogen bonding interactions of several halobenzene−formaldehyde complexes. It was found that, for most halogen substituents, a halobenzene and formaldehyde form stable halogen bonded complexes with interaction energies that increase as the size of the halogen substituent increases.

Introduction

Halogen bonding is of considerable interest in many fields within chemistry and material science because these noncovalent interactions play roles in a wide variety of chemical phenomena.[1−15] Halogen bonds are of particular interest in biochemistry and medicinal chemistry because they are often involved in protein−ligand interactions that are either biologically detrimental, as in the case of interactions involving organohalogens found in the environment, or beneficial, because of their potential usefulness in the design of novel ligands that interact with proteins in a very specific way.[1,2,5−7,9,12]

A halogen bond is defined as a short-range C−X···Y−Z interaction (where X is typically chlorine, bromine, or iodine, Y is typically oxygen, nitrogen, or sulfur, and Y−Z represents a side group such as a hydroxyl or carbonyl group), where the X···Y distance is less than sum of the van der Waals radii of X and Y (please see Figure 1 for relevant van der Waals radii).[1] Halogen bonds share numerous physical properties with the more commonly encountered hydrogen bonds and are often treated analogously to their ubiquitous counterparts.[1,12] 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^-···I_2).[12]

Organohalogens that are present in the environment, mainly as a byproduct of the commercial production of chemicals, are thought to lead to adverse biological effects in animals and humans.[5] An example of a hormone transport protein whose ability to function properly is hindered by halogen bond forming organohalogens is transthyretin, which is responsible for the transport of thyroid hormones in the blood plasma.[5,16] In vitro binding studies with several groups of organohalogens have shown that polychlorinated biphenyls and polybrominated biphenyls are able to bind to transthyretin at least as strongly as the natural ligand thyroxine.[17,18] The binding of these halogenated phenyl molecules is attributable, at least in part, to halogen bonding.[5]

An example of the utilization of halogen bonds in the context of drug design is the development of R165481, a pyridinone derivative that acts as a non-nucleoside inhibitor of HIV-1 reverse transcriptase. This compound exhibits strong inhibition of wild type HIV-1 reverse transcriptase and several of its drug resistant variants, including the commonly found Tyr181Cys and Lys103Asn mutants. R221239 contains an iodine atom that forms a halogen bond with a carbonyl group on HIV-1 reverse transcriptase (with the backbone carbonyl of residue Tyr188); this interaction is thought to be one of the key interactions leading to the overall protein−ligand binding affinity.[6]

One type of halogen bond that is of great interest in biochemistry is one that involves the interaction between a halogen and the oxygen in a carbonyl group. In a recent database survey of short halogen−oxygen interactions it was found that 78 out of 113 X···O interactions involved carbonyl groups (data set contained 66 protein structures and 6 nucleic acid structures from the protein data bank).[1] Given that carbonyl oxygens seem to be the most common electron donor in C−X···O−Z halogen bonding, we have chosen to focus on this type of interaction in the present study.

There have been several theoretical[8,19−24] and experimental[19,25−28] studies seeking to characterize the geometric and energetic properties of halogen bonds. For example, Valerio et al. performed ab initio calculations on the $CH_{n-3}F_nX$···NH_3 (X = I, Br, Cl) halogen bonded complexes, it was found in this study that substitution of successive fluorines substituents results in X···N halogen bonds that are shorter and stronger. The strongest halogen bond found in this study occurs for the CF_3I···NH_3 complex with of binding energy of 5.8 kcal/mol. On the experimental side, Corradi et al. determined the binding energy for a halogen bonded complex of 1-iodoperfluorohexane and 2,2,6,6-tetramethylpiperidine to be 7.4 kcal/mol.

In this work we seek to characterize the strength of halogen−carbonyl bonds as a function of two geometric parameters, the halogen−oxygen distance ($d_{X\cdots O}$) and the halogen−oxygen−carbon angle ($\Theta_{X\cdots O-C}$), a diagram illustrating these parameters is given in Figure 2. The model systems used in this study are the halobenzene−formaldehyde complexes, the halogen substituents used here are fluorine, chlorine, bromine, and iodine. Calculations were also made using hydrogen as the substituent (i.e., an unsubstituted benzene) for the purpose of comparing the halogen bond strengths to that of a hydrogen bond. The reason that halobenzenes are used is that, because of the electron withdrawing properties of the aromatic ring, halogen bonds associated with aromatic compounds should be stronger than those formed with their aliphatic counterparts.[1]

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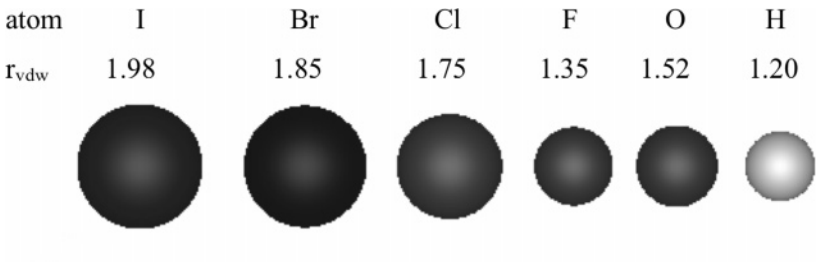

Figure 1. Van der Waals radii (in angstroms) of atoms relevant to halogen and hydrogen bonding in biological systems. r_{vdw} from ref 54.

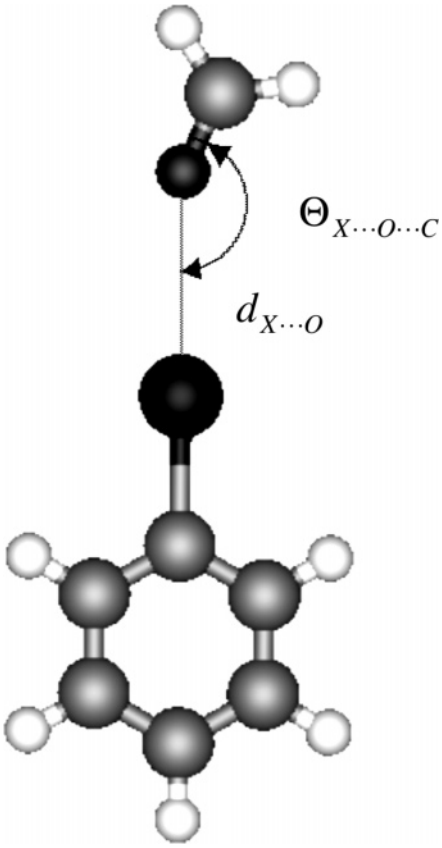

Figure 2. Schematic diagram of the halobenzene−formaldehyde interaction. In this study the halogen atoms used are fluorine, chlorine, bromine, and iodine (the hydrogen atom is also used for the purpose of comparison with hydrogen bonds).

Most of the chemistry that is of major biological interest occurs either in solution or within the environment of a protein or nucleic acid. For this reason, we have carried out calculations to estimate the binding energies of the halobenzene−formaldehyde systems when they are in such environments.

Methods

All ab initio calculations in this work were carried out using the Gaussian 03 program.[29] Second-order perturbation theory (MP2) methods were employed in order to account for electron correlation effects.[30] In order to correct for the basis set superposition error (BSSE) the counterpoise method of Boys and Bernardi was employed for gas-phase complexes.[31]

For each of the potential energy curves the geometries of both of the monomers within the dimer system were optimized and then held fixed in the dimer calculations, that is to say that only $d_{X\cdots O}$ and $\Theta_{X\cdots O-C}$ were varied. This type of approximation has been made in previous works and introduces negligible error.[32,33] In order to validate the accuracy of this approximation we have carried out a full optimization of the iodobenzene−formaldehyde complex with $d_{I\cdots O}$ fixed at 3.3 Å and ($\Theta_{I\cdots O-C} = 180°$) and compared the obtained interaction energy to the single point result. It was found that the interaction energy of the fully optimized complex (1.72 kcal/mol) is within 0.02 kcal/mol of the single point value (1.74 kcal/mol). When one considers the significant expense of performing full optimizations of these complexes at each point along the potential energy curve, the approximation of using single point geometries (with the geometric configurations obtained by optimizing each of the monomers) seems very reasonable.

At this point, we will say a word about the relative orientations of the formaldehyde−halobenzene complexes used in this study. We have chosen to carry out all of our calculations in an orientation such that all of the atoms in both the formaldehyde and the halobenzene molecules are in the same plane. There is some possibility that a different choice of orientation, such as putting the hydrogen atoms in formaldehyde in a plane perpendicular to the plane formed by the benzene atoms, might affect the interaction energies. In order to gain some understanding of these orientation effects, at least in a preliminary way, we have performed a calculation for the formaldehyde−iodobenzene dimer in which the planes formed by the individual monomers are perpendicular, this test was carried out at an iodine−oxygen−carbon angle of 160° ($\Theta_{X\cdots O-C} = 160°$). It was found that the difference in the interaction energies between the parallel (1.82(0) kcal/mol) and perpendicular (1.82(2) kcal/mol) configurations is only 0.002 kcal/mol, this energy difference can be said to be negligible for the purposes of this study.

Large halogens such as iodine and bromine are not commonly encountered in organic and biological chemistry, for this reason there are relatively few basis sets available for these atoms. In order to treat systems containing iodine and bromine we have used a mixed basis set scheme in which the halogen atoms are described using the aug-cc-pVDZ-PP[34−37] basis set while all other atoms are described using the commonly used aug-cc-pVDZ[38] basis. Each of these bases is of double-z quality with the key difference between the two being that aug-cc-pVDZ-PP uses pseudopotentials to describe the inner core orbitals. For systems containing fluorine and chlorine, the aug-cc-pVDZ basis set is used for all atoms.

Currently it is not possible in Gaussian, or any other molecular electronic structure package that we are aware of, to perform calculations using both the counterpoise correction, to account for the basis set superposition error, and an implicit solvation method, to model the effects of a surrounding solvent on the interaction between two chemical species. In order to account for both the basis set superposition error and solvation effects in our halogen bonded systems we have carried out counterpoise corrected calculations in vacuum and then added solvation

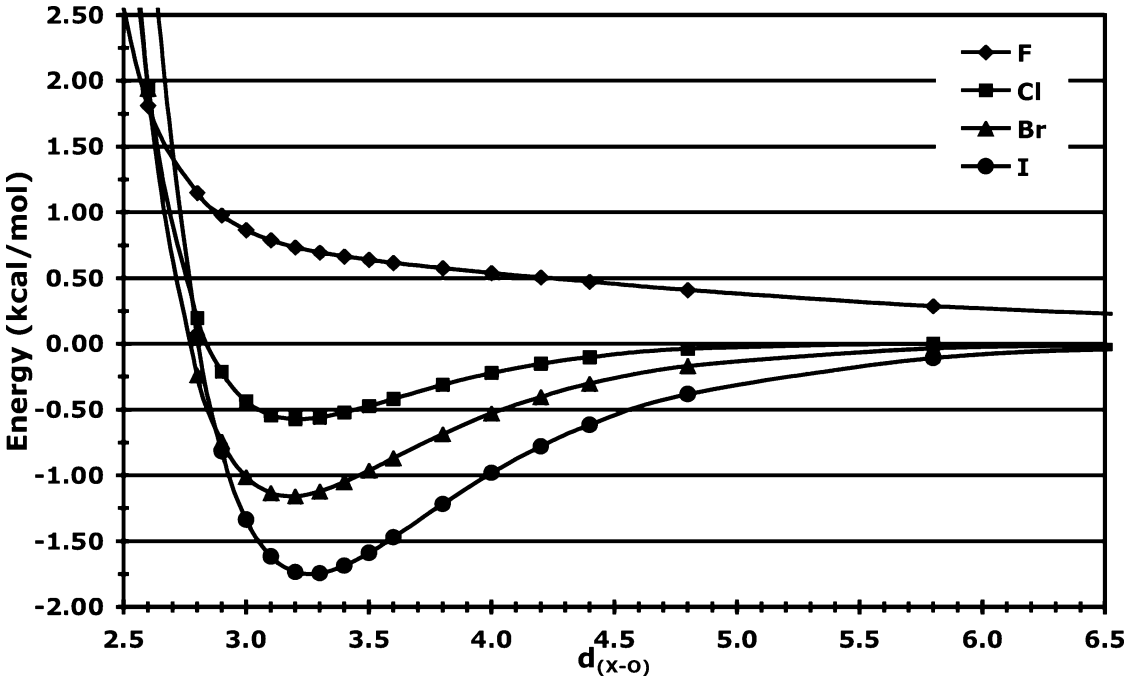

Figure 3. In vacuo potential energy curves of halobenzene−formaldehyde interactions as a function of the halogen−oxygen separation distance, $d_{X\cdots O}$.

corrections, $\Delta\Delta G_{solv}$, to the resulting interaction energies. The total interaction energy in solvent is given as

$$\Delta E_{solv}^{CP} = \Delta E_{vac}^{CP} + \Delta\Delta G_{solv}$$

The solvation correction, $\Delta\Delta G_{solv}$, is calculated as the difference between the interaction energies in solvent and in vacuum:

$$\Delta\Delta G_{solv} = \Delta G_{solv} - \Delta E_{vac}^{no-CP}$$

It should be noted here that ΔE_{vac}^{CP} is the interaction energy of the halogen bonded complex as calculated in vacuum and corrected for the basis set superposition error (BSSE), whereas ΔE_{vac}^{no-CP} and ΔG_{solv} are interaction energies with no BSSE corrections.

Solvation effects are modeled using the polarizable continuum method (PCM),[39] a method that has been well validated and is the subject of several reviews.[40−42] In order to gain insight into the effects of solvation within protein and nucleic systems we have carried out our calculations with two different solvents; the first of these is ether ($\epsilon = 4.335$), and the second is water ($\epsilon = 78.39$). Ether is used because its dielectric constant is taken to represent the overall dielectric constant in the interior of a protein.[43−45]

Results

Figure 3 shows the gas-phase potential energy curves (ΔE_{vac}^{CP}) of each of the halobenzene−formaldehyde dimers as a function of the halogen−oxygen separation. Here a clear trend can be seen where the system containing the largest halogen, iodine, is most strongly bound, with a binding energy of 1.74 kcal/mol ($d_{X\cdots O} = 3.3$ Å) and the system containing the smallest halogen, fluorine, is unbound. Bromobenzene and chlorobenzene both form stable complexes with formaldehyde, with interaction energies that are progressively smaller as the size of the halogen decreases, their respective binding energies are 1.15 kcal/mol ($d_{X\cdots O} = 3.2$ Å) and 0.57 kcal/mol ($d_{X\cdots O} = 3.2$ Å). This trend is consistent with the findings of Auffinger et al., who found

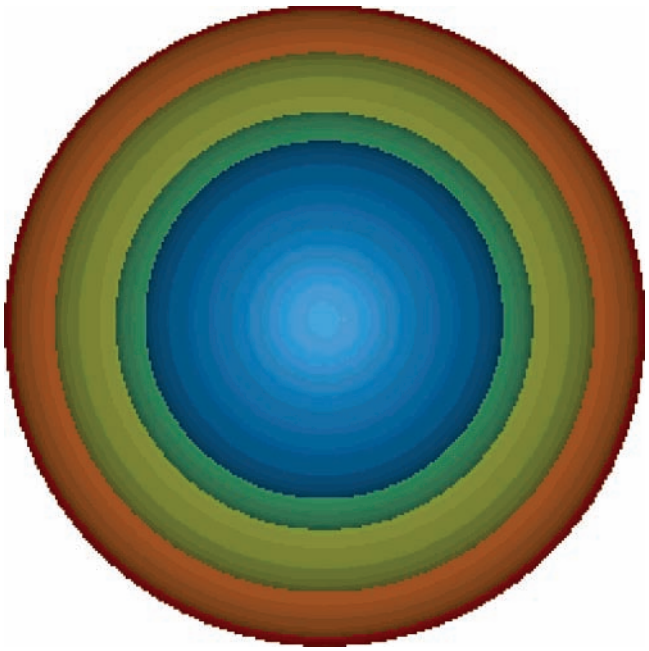

Figure 4. Schematic representation of crown−ring−belt structure of halogens bound to carbon. Here the blue region represents the electropositive crown, the green region represents the electroneutral ring, and the orange/red region represents the electronegative belt. This representation is based on electrostatic isosurface plots published by Auffinger et al.[1]

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 (please see Figure 4 for a schematic representation of the halogen crown−ring−belt).[1] Halogen bonding can be attributed to the favorable interaction that exists between a halogen's electropositive crown and an electronegative atom, such as oxygen. A halogen's crown becomes larger and gains a higher degree of elctropositivity as the size of the halogen increases, with a

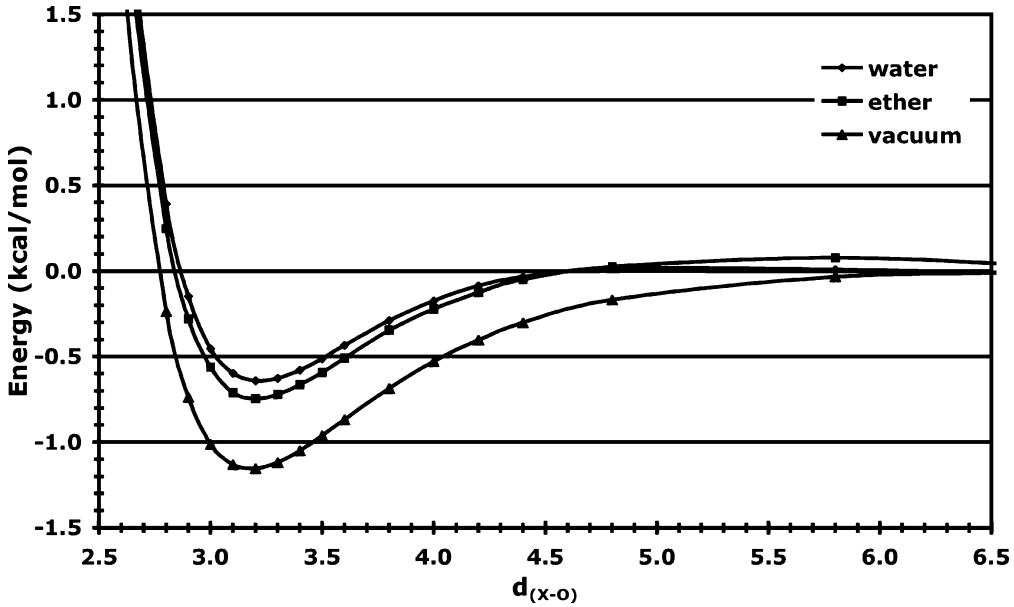

Figure 5. Potential energy curves of the bromobenzene−formaldehyde interaction in vacuum, water, and ether.

corresponding tendency for the halogen bond to become stronger. Fluorine, the smallest halogen, does not form an electropositive crown. The optimum halogen bonding distances are also in good agreement with those of the PDB survey study carried out by Auffinger et al. In this study it was found that the average halogen−oxygen distances are 3.06, 3.15, and 3.24 Å for chlorine, bromine, and iodine respectively.

Interestingly, there are some discrepancies between the calculated and experimentally (PDB) derived optimal halogen−oxygen distances. It should be kept in mind that the PDB distances take into account the chemical and physical environments of the halogen bonded species explicitly while the computational values are obtained using model systems, which are "unaware" of any particular (protein) environment. For example, the PDB derived average halogen−oxygen optimal distance for systems containing iodine is larger than that for systems containing chlorine, this might be explained by the fact that, because iodine is so much larger than chlorine, the iodine containing systems are sterically obstructed from forming halogen bonds with halogen−oxygen distances as short as those of chorine containing systems.

In order to compare the halogen bond strengths to that of a hydrogen bond we have carried out calculations on the benzene−formaldehyde complex, the binding energy of this complex as a function of the hydrogen−oxygen separation is given as Supporting Information (Sup-Figure 1). The hydrogen bond interaction energy is equivalent to that of a bromine−oxygen halogen bond, with a value of 1.15 kcal/mol, but the potential energy minimum occurs at a much shorter interatomic distance of 2.5 Å. It is interesting that the iodine−oxygen halogen bond is significantly stronger than the hydrogen−oxygen hydrogen bond, though, it should be noted that this C−H···O hydrogen bond is not particularly strong. It is not surprising that the hydrogen−oxygen distance is shorter than the halogen−oxygen distances because the van der Waals radius of hydrogen is much smaller than those of the halogen atoms.

Figures 5 and 6 show the potential energy curves in vacuum, ether, and water for the bromine and iodine substituted halobenzene−formaldehyde complexes respectively. Here it can be seen that the introduction of both solvents destabilizes the dimers by a significant amount. In the case of the iodobenzene−formaldehyde system, the binding energy goes from 1.74 kcal/mol in vacuum to 0.81 kcal/mol in water, representing a destabilization of 0.93 kcal/mol. The bromine substituted complex displays a less dramatic effect with a destabilization of 0.51 kcal/mol going from vacuum (1.15 kcal/mol) to water (0.64 kcal/mol). As one might expect, the halogen bonds have a higher degree of destabilization when water, which is highly polar, is used as the solvent as compared to ether, which is nonpolar. Sup-Figure 2 shows the potential energy curve for the binding of the chlorobenzene−formaldehyde complex, which displays trends that are similar to those of iodine and bromine substituted systems in terms of solvation destabilization. Binding energies for iodine, bromine, and chlorine substituted halobenzene−formaldehyde complexes in vacuum, ether, and water are given in Table 1.

It is interesting to note that the difference in binding energies between water solvated and ether solvated complexes is substantially larger for the iodine substituted system than for the bromine substituted complex (i.e., $\Delta DE^{\text{solvent}}_{\text{iodine}} > \Delta\Delta E^{\text{solvent}}_{\text{bromine}}$, with $\Delta\Delta E^{\text{solvent}} = |\Delta E^{\text{CP}}_{\text{ether}}| - |\Delta E^{\text{CP}}_{\text{water}}|$). The same type of behavior is observed for chlorine substituted systems, that is to say, $\Delta\Delta E^{\text{solvent}}_{\text{bromine}} > \Delta\Delta E^{\text{solvent}}_{\text{chlorine}}$. A possible explanation for this phenomenon is that, in water, as the polarity of the halogen atom increases, the charge density around that halogen atom will also increase due to the presence of the polar solvent. This buildup of charge in water interferes with the halogen−oxygen interaction. In an nonpolar solvent such as ether, there is no tendency for more charge to build up around the halogen atom as the polarity of that halogen increases, thus one would expect that the destabilization of the halogen−oxygen interaction would generally depend only on the total strength of the gas phase interaction. In order to test this idea, we have calculated a quantity that we call the fractional solvation destabilization, this quantity is given as

$$\%\Delta D^{\text{solv}}_{\text{solvent}} = \frac{|\Delta E^{\text{CP}}_{\text{vac}}| - |\Delta E^{\text{CP}}_{\text{solv}}(\text{solvent})|}{|\Delta E^{\text{CP}}_{\text{vac}}|} \times 100$$

where $\Delta E^{\text{CP}}_{\text{solv}}(\text{solvent})$ is simply $\Delta E^{\text{CP}}_{\text{solv}}$ for a given solvent (in the present study, either ether or water). One would expect that the value of $\%\Delta D^{\text{solv}}_{\text{ether}}$ should be approximately the same for iodine, bromine, and chlorine substituted complexes whereas

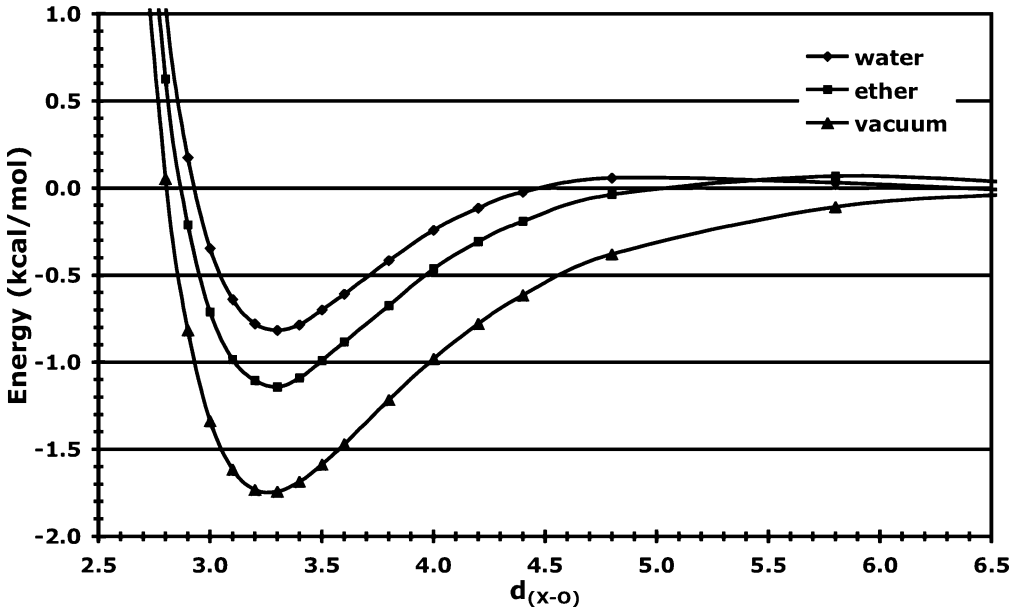

Figure 6. Potential energy curves of the iodobenzene−formaldehyde interaction in vacuum, water, and ether.

TABLE 1: Binding Energies (kcal/mol) and Optimum X−O Separation Distances (Å) for Linear Configurations of Formaldehyde−Halobenzene Complexes

	substituent		
quantity	Cl	Br	I
ΔE_{vac}^{CP}	0.57	1.15	1.74
ΔE_{solv}^{CP}(ether)	0.38	0.75	1.14
ΔE_{solv}^{CP}(water)	0.35	0.64	0.81
$d_{X\cdots O}^{vac}$(min)	3.2	3.2	3.3
$d_{X\cdots O}^{ether}$(min)	3.3	3.2	3.3
$d_{X\cdots O}^{water}$(min)	3.3	3.2	3.3

TABLE 2: Fractional Solvation Destabilizations for Linear Configurations of the Formaldehyde−Halobenzene Complexes Considered in This Work[a]

	substituent		
	Cl	Br	I
$\%\Delta D_{ether}^{solv}$	33	35	34
$\%\Delta D_{water}^{solv}$	39	44	53

[a] The fractional solvation destabilization is given as

$$\%\Delta D_{solvent}^{solv} = \frac{|\Delta E_{vac}^{CP}| - |\Delta E_{solv}^{CP}(solvent)|}{|\Delta E_{vac}^{CP}|} \times 100$$

the value of $\%\Delta D_{water}^{solv}$ should increase as the size of the halogen substituent increases. Table 2 gives values of $\%\Delta D_{ether}^{solv}$ and $\%\Delta D_{water}^{solv}$, here it can be seen that indeed the value of $\%\Delta D_{ether}^{solv}$ varies only slightly while the value of $\%\Delta D_{water}^{solv}$ increases for larger halogen substituents.

Figures 7 and 8 show the potential energy curves as a function of the halogen−oxygen−carbon angle at several halogen−oxygen separation distances for the bromine and iodine substituted halobenzene−formaldehyde complexes respectively. Here it is seen that, for both systems, distinct energy minima are present for halogen−oxygen separations between 3.0 Å and 3.6 Å, these minima generally occur at angles in the range from 95° to 115°. The global energy minima (for the parameters considered here) for both the iodine and bromine substituted complexes are obtained at halogen−oxygen separation distances of 3.2 Å, the optimum angle for the bromine system at this separation distance is 105° and for the iodine system is 110°. There is a significant increase in the interaction energies of the halogen bonding systems when the angle $\Theta_{X\cdots O-C}$ is allowed to vary. At an intermolecular separation of 3.2 Å the bromine substituted complex interaction energy increases by 0.59 kcal/mol (from 1.09 kcal/mol to 1.68 kcal/mol) compared to the linear configuration ($\Theta_{X\cdots O-C} = 180°$) while the interaction energy of the iodine substituted complex increases by 0.66 kcal/mol (from 1.73 kcal/mol to 2.39 kcal/mol).

The range of angles at which the minimum energies occur is in relatively good agreement with the PDB survey results of Auffinger et al. who determined the average X···O−C angle to be 113°.[1] The occurrence of energy minima within this range of angles suggests that the preferred geometry of these halogen bonds corresponds to an alignment of the electropositive halogen crowns with the lone pair electrons on the oxygen atom. In the case of halogen−carbonyl interaction, it has also been suggested that there might be a favorable interaction between the electropositive halogen crown and the p system associated with the C═O bond.[1]

There are two prominent trends that can be discerned from Figures 7 and 8 along with Sup-Figure 3 (given in Supporting Information), which gives angular potential energy curves for the chlorobenzene−formaldehyde complex. The first of these trends has to do with the relationship between the halogen−oxygen separation and the halogen−oxygen−carbon angle. For all three halobenzene−formaldehyde complexes it was found that as the halogen−oxygen separation increases, the angle at which the minimum energy occurs becomes smaller. An example of this trend can be seen for the bromobenzene−formaldehyde complex, the optimal angle for this system at a bromine−oxygen separation of 3.0 Å is found to be 110° whereas at a separation of 3.6 Å the optimal angle is 95°. The second trend that can be seen in these Figures deals with the size of the halogen substituent in the halobenzene−formaldehyde complex and its effect on the optimum angle at a given halogen−oxygen separation. As the size of a halogen substituent increases the angle at which the minimum energy occurs also increases, this is true for all halogen−oxygen separation distances for which a distinct angular minimum exists. For example, at a halogen−oxygen separation of 3.2 Å, the angular minima for chlorine, bromine, and iodine occur at 95°

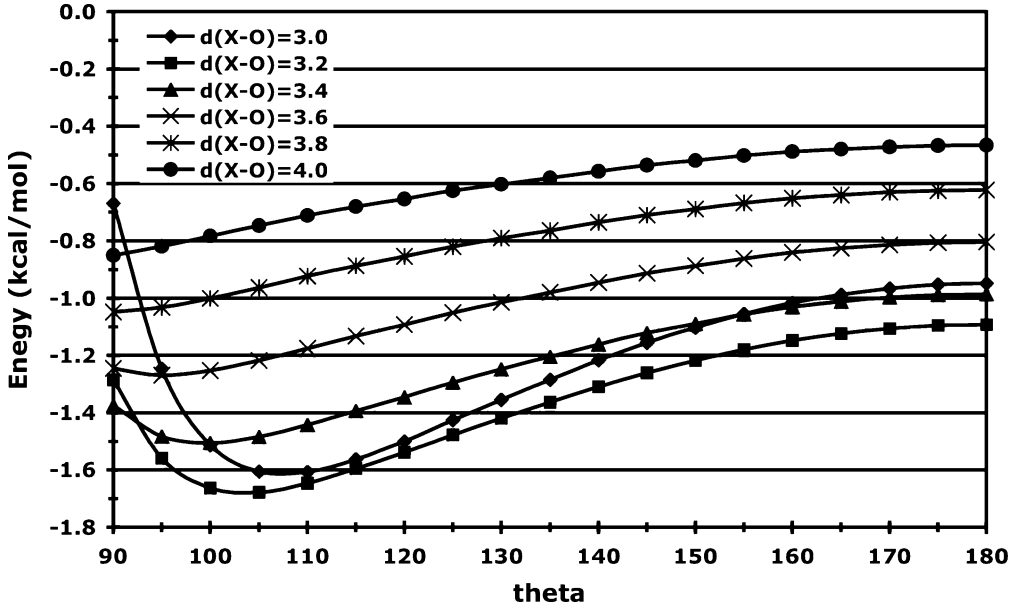

Figure 7. In vacuo potential energy curves of bromobenzene−formaldehyde interactions as a function of the bromine−oxygen−carbon angle, $\Theta_{Br\cdots O-C}$, at several bromine−oxygen separation distances, $d_{Br\cdots O}$.

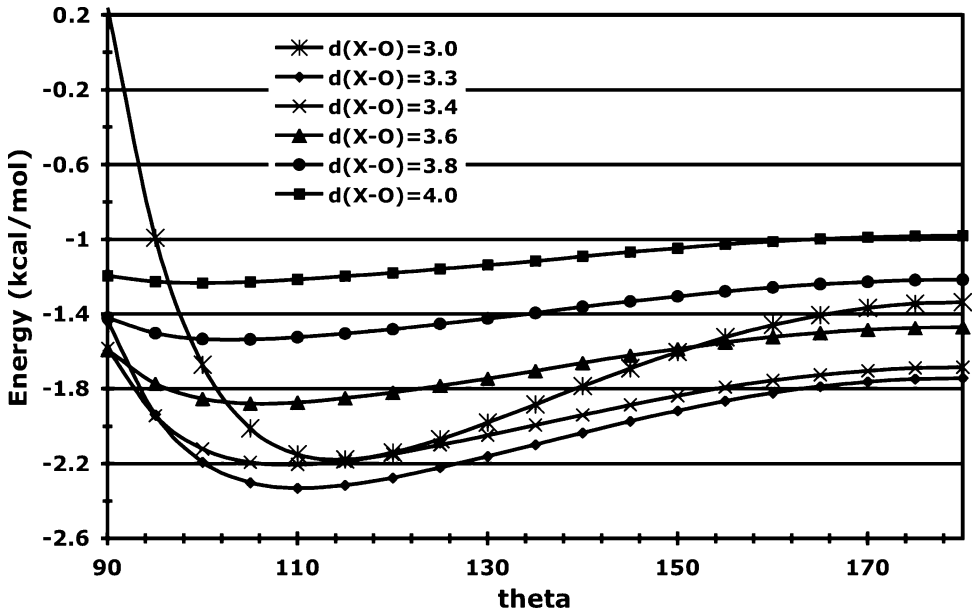

Figure 8. In vacuo potential energy curves of iodobenzene−formaldehyde interactions as a function of the iodine−oxygen−carbon angle, $\Theta_{I\cdots O-C}$, at several iodine−oxygen separation distances, $d_{I\cdots O}$.

(−1.06 kcal/mol), 110° (−1.68 kcal/mol), and 115° (−2.39 kcal/mol) respectively.

Conclusions

In this work, we have shown that halobenzenes containing chlorine, bromine, and iodine substituents will tend to form a bound complex with the oxygen from a carbonyl group with binding energies that increase as the size of the halogen substituent increases. These systems are destabilized when solvent is introduced, for the halobenzene−formaldehyde complexes containing the larger halogen substituents, bromine and iodine, the destabilization is significantly more pronounced when water is used as solvent as opposed to ether. The preferred halogen−oxygen−carbon angle for halobenzene−formaldehyde complexes is in the range between 95 and 115°; this is probably due to a favorable interaction of the electropositive halogen crowns with the lone pair electrons on the oxygen atom.

One of the key reasons for studying the strengths of halogen bonds as a function of geometrical parameters is to determine the contribution that these types of interactions can make to protein−ligand interactions, which may be important in many fields within biological chemistry, including drug design. One way to gain some insight into the relative importance of these types of interactions is to compare them with similar, more commonly studied noncovalent interactions. C−H···O hydrogen bonds are generally recognized as weak interactions that play important roles in such phenomena as protein stability[44,46−50] and the stability of protein ligand systems.[51−53] In a recent study of the strengths of C−H···O hydrogen bonds in various configurations of a glycine dimer−formamide complex, ab initio calculations were carried out in vacuum at the MP2/6-31+G** level of theory using the counterpoise method to account for the basis set superposition error.[46] In this work it was found that, for two distinct conformations of this dimer, the intermo-

lecular interaction energies are 2.81 and 2.25 kcal/mol. In the current study the interaction energy of most strongly bound halogen bonding system was found to be 2.39 kcal/mol (iodobenzene−formaldehyde, $d_{I\cdots O} = 3.2$ Å, $Q_{I\cdots O-C} = 110°$), a binding energy that seems to be in register with those of the C−H···O hydrogen bonds. The lowest interaction energy for the bromobenzene−formaldehyde complex is 1.68 kcal/mol ($d_{I\cdots O} = 3.2$ Å, $\Theta_{I\cdots O-C} = 105°$), which represents an interaction that is 75% as strong as the weakest C−H···O hydrogen bond. These data, along with other experimental evidence,[1,5−7,9] indicate that, although they are not particularly strong interactions, halogen bonds play a role in the binding of a ligand to a protein. Hence, given the presence of a carbonyl moiety as well as the space necessary to accommodate the presence of a large halogen atom like iodine, the use of carbonyl−halogen interactions would be beneficial in the design of selective small molecule inhibitors.

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Supporting Information Available: Figures showing potential energy curves for benzene−formaldehyde and chlorobenzene−formaldehyde complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Auffinger, P.; Hays, F. A.; Westhof, E.; Ho, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101* (48), 16789−16794.
(2) Battistutta, R.; Mazzorana, M.; Sarno, S.; Kazimierczuk, Z.; Zanotti, G.; Pinna, L. A. *Chem. Biol.* **2005**, *12*, 1211−1219.
(3) Caronna, T.; Liantonio, R.; Logothetis, T. A.; Metrangolo, P.; Pilati, T.; Resnati, G. *J. Am. Chem. Soc.* **2004**, *126*, 4500−4501.
(4) Forni, A.; Metrangolo, P.; Pilati, T.; Resnati, G. *Cryst. Growth Des.* **2004**, *4* (2), 291−295.
(5) Ghosh, M.; Meerts, I. A. T. M.; Cook, A.; Bergman, A.; Brouwer, A.; Johnson, L. N. *Acta Crystallogr., Sect. D: Biol. Crystallogr.* **2000**, *56*, 1085−1095.
(6) Himmel, D. M.; Das, K.; Clark, A. D.; Hughes, S. H.; Benjahad, A.; Oumouch, S.; Guillemont, J.; Coupa, S.; Poncelet, A.; Csoka, I.; Meyer, C.; Andries, K.; Nguyen, C. H.; Grierson, D. S.; Arnold, E. *J. Med. Chem.* **2005**, *48*, 7582−7591.
(7) Jiang, Y.; Alcaraz, A. A.; Chen, J. M.; Kobayashi, H.; Lu, Y. J.; Snyder, J. P. *J. Med. Chem.* **2006**, *49*, 1891−1899.
(8) Lommerse, J. P. M.; Stone, A. J.; Taylor, R.; Allen, F. H. *J. Am. Chem. Soc.* **1996**, *118*, 3108−3116.
(9) Lopez-Rodriguez, M. L.; Murcia, M.; Benhamu, B.; Viso, A.; Campillo, M.; Pardo, L. *J. Med. Chem.* **2002**, *45*, 4806−4815.
(10) Lucassen, A. C. B.; Vartanian, M.; Leitus, G.; van der Boom, M. E. *Cryst. Growth Des.* **2005**, *5*, 1671−1673.
(11) Mele, a.; Metrangolo, P.; Neukirch, H.; Pilati, T.; Resnati, G. *J. Am. Chem. Soc.* **2005**, *127*, 14972−14973.
(12) Metrangolo, P.; Neukirch, H.; Pilati, T.; Resnati, G. *Acc. Chem. Res.* **2005**, *38*, 386−395.
(13) Ouvrard, C.; Le Questel, J. Y.; Berthelot, M.; Laurence, C. *Acta Crystallogr., Sect. B: Struct. Sci.* **2003**, *59*, 512−526.
(14) Pigge, F. C.; Vangala, V. R.; Swenson, D. C. *Chem. Commun.* **2006**, 2123−2125.
(15) Resnati, G.; Neukirch, H.; Metrangolo, P.; Pilati, T. *Abstr. Pap. Am. Chem. Soc.* **2005**, *230*, U3142−U3143.
(16) Brouwer, a.; Morse, D. C.; Lans, M. C.; Schuur, A. G.; Murk, A. J.; Klasson-Wehler, E.; Bergman, A.; Visser, T. J. *Toxicol. Ind. Health* **1998**, *14* (1−2), 59−84.
(17) Lans, M. C.; Klassonwehler, E.; Willemsen, M.; Meussen, E.; Safe, S.; Brouwer, A. *Chem. Biol. Interact.* **1993**, *88* (1), 7−21.
(18) Lans, M. C.; Spiertz, C.; Brouwer, A.; Koeman, J. H. *Eur. J. Pharmacol.-Environ. Toxicol. Pharm. Sect.* **1994**, *270* (2−3), 129−136.
(19) Glaser, R.; Chen, N. J.; Wu, H.; Knotts, N.; Kaupp, M. *J. Am. Chem. Soc.* **2004**, *126*, 4412−4419.
(20) Romaniello, P.; Lelj, F. *J. Phys. Chem. A* **2002**, *106*, 9114−9119.
(21) Valerio, G.; Raos, G.; Meille, S. V.; Metrangolo, P.; Resnati, G. *J. Phys. Chem. A* **2000**, *104*, 1617−1620.
(22) Wang, W. Z.; Tian, A. M.; Wong, N. B. *J. Phys. Chem. A* **2005**, *109*, 8035−8040.
(23) Wang, W. Z.; Wong, N. B.; Zheng, W. X.; Tian, A. M. *J. Phys. Chem. A* **2004**, *108*, 1799−1805.
(24) Zou, J. W.; Jiang, Y. J.; Guo, M.; Hu, G. X.; Zhang, B.; Liu, H. C.; Yu, Q. S. *Chem.−Eur. J.* **2005**, *11*, 740−751.
(25) Corradi, E.; Meille, S. V.; Messina, M. T.; Metrangolo, P.; Resnati, G. *Angew. Chem.-Int. Ed.* **2000**, *39*, 1782.
(26) Larsen, D. W.; Allred, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 1216−1219.
(27) Larsen, D. W.; Allred, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 1219−1226.
(28) Larsen, D. W.; Allred, A. L. *J. Phys. Chem.* **1965**, *69*, 2400−2401.
(29) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Chesseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Forseman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; AlLoham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 03*, Gaussian Inc.: Wallingford, CT, 2003.
(30) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.
(31) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19* (553).
(32) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tenabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 104−112.
(33) Sinnokrot, M. O.; Sherrill, C. D. *J. Am. Chem. Soc.* **2004**, *126*, 7690−7697.
(34) Metz, B.; Schweizer, M.; Stoll, H.; Dolg, M.; Liu, W. J. *Theor. Chem. Acc.* **2000**, *104* (1), 22−28.
(35) Metz, B.; Stoll, H.; Dolg, M. *J. Chem. Phys.* **2000**, *113*, 2563−2569.
(36) Peterson, K. A. *J. Chem. Phys.* **2003**, *119*, 11099−11112.
(37) Peterson, K. A.; Figgen, D.; Goll, E.; Stoll, H.; Dolg, M. *J. Chem. Phys.* **2003**, *119*, 11113−11123.
(38) Dunning, T. H. *J. Chem. Phys.* **1989**, *90*, 1007−1023.
(39) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *106*, 5151−5158.
(40) Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161−2200.
(41) Tomasi, J.; Cammi, R.; Mennucci, B.; Cappelli, C.; Corni, S. *Phys. Chem. Chem. Phys.* **2002**, *4*, 5697−5712.
(42) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027−2094.
(43) Dwyer, J. J.; Gittis, A. G.; Karp, D. A.; Lattman, E. E.; Spencer, D. S.; Stites, W. E.; Garcia-Moreno, B. *Biophys. J.* **2000**, *79*, 1610−1620.
(44) Scheiner, S.; Kar, T. *J. Phys. Chem. B* **2005**, *109*, 3681−3689.
(45) Simonson, T.; Perahia, D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 1082−1086.
(46) Scheiner, S. *J. Phys. Chem.. B* **2005**, *109*, 16132−16141.
(47) Lee, K. M.; Chang, H. C.; Jiang, J. C.; Chen, J. C. C.; Kao, H. E.; Lin, S. H.; Lin, I. J. B. *J. Am. Chem. Soc.* **2003**, *125*, 12358−12364.
(48) Manikandan, K.; Ramakumar, S. *Proteins−Struct. Funct. Bioinformatics* **2004**, *56*, 768−781.
(49) Babu, M. M.; Singh, S. K.; Balaram, P. *J. Mol. Biol.* **2002**, *322*, 871−880.
(50) Singh, S. K.; Babu, M. M.; Balaram, P. *Proteins−Struct. Funct. Genetics* **2003**, *51*, 167−171.
(51) Pierce, A. C.; ter Haar, E.; Binch, H. M.; Kay, D. P.; Patel, S. R.; Li, P. *J. Med. Chem.* **2005**, *48*, 1278−1281.
(52) Sarkhel, S.; Desiraju, G. R. *Proteins−Struct. Funct. Genetics* **2004**, *54*, 247−259.
(53) Cotesta, S.; Stahl, M. *J. Mol. Model.* **2005**, *12*, 436−444.
(54) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.