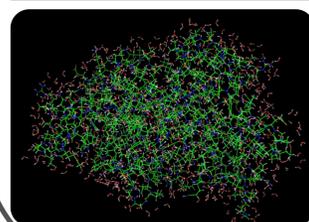
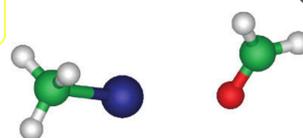
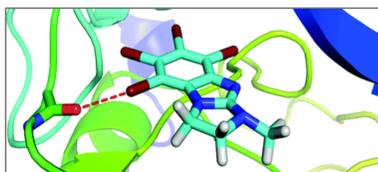


## Diving into C-X... $\pi$ Interactions

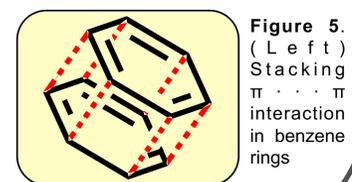
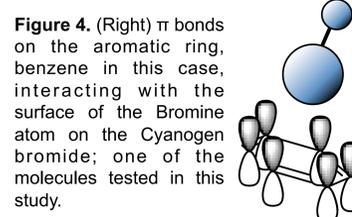
Halogen bond interactions have grown in the past decade due to their behavior analogous to weak hydrogen bonds when in contact with electronegative atoms.<sup>[1,2,3,4,5,6]</sup> Due to recent investigations, our study demonstrates interaction between a halogen and a benzene ring that may be found in proteins (Fig. 1 and 2),<sup>[1]</sup> crystal design,<sup>[3]</sup> anion transport,<sup>[3]</sup> phosphorescent cocrystal activation,<sup>[3]</sup> and supramolecular gelation.<sup>[3]</sup> Their main attraction is due to the tunability, directionality (Fig. 3), hydrophobicity, and donor atom size<sup>[1,3]</sup>. Our study is between methyl bromide and a nonsubstituted benzene ring and through substitution of hydrogen by fluorine atoms the strengths of these interactions increase with each substitution, Fig 4. Benzene has been chosen due to the noncovalent nature of the  $\pi$ ... $\pi$  stacking among rings, Fig 5. By replacing hydrogen by fluorine atoms there is an increase in the interactions from -1.68 to -3.21 kcal/mol demonstrating the effect fluorine atoms have on the electronegative density of bromine affecting the sigma hole. When placing a cyano group with the Bromine, there was an enlarged sigma hole compared to the trifluorinated methyl bromide which lowered the interaction energy to -4.21 kcal/mol. Comparisons of different Hartree-Fock methods such as Coupled-cluster with Single and Double and perturbative Triple excitations (CCSD(T)), Møller-Plesset (MP2), and symmetry-adapted perturbation theory (SAPT) coupled with the density functional theory (DFT), demonstrate that dispersion and electrostatic play a major role in the interactions between the two molecules.



**Figure 1.** (To the left) Computational model of the protein Liver X receptor (LXR- $\beta$ ) and ligand in an optimized hydration shell. **Figure 2.** (Right) An example of halogen bonding interactions in the protein between the protein and the ligand.



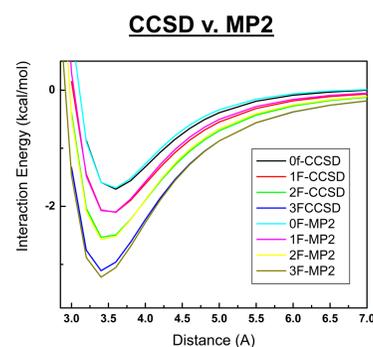
**Figure 3.** (Above) Methyl Bromide creating a halogen bond with the lone pairs on the oxygen of the formaldehyde demonstrating the directionality characteristic of halogen bonds.



**Figure 5.** (Left) Stacking  $\pi$ ... $\pi$  interaction in benzene rings

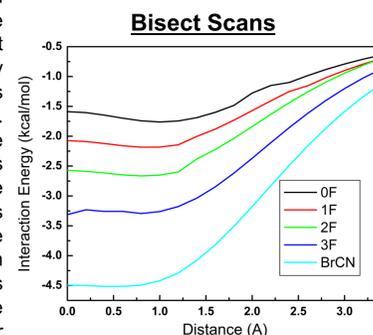
### Comparing MP2 and CCSD(T)

The SCS MP2 method is very comparable to the more accurate and more expensive CCSD(T) calculation method. The two methods resulted in almost identical results, and validates the use of the less computationally intensive MP2 method for the other sets of calculations.

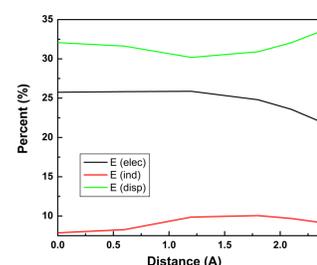


### Bisect Scan Results

As the C-X molecule moved away from the axis of the benzene at a constant height, the interaction energy was relatively unchanged, as can be seen to the right. From the center of the benzene to the C-C bond is 1.2 Å, and within 1.2 Å, the interaction energy is relatively steady. Outside the benzene ring, the interaction energy intuitively tends towards zero as the molecules move further apart.



### 0F SAPT



### SAPT

This method breaks down the contribution of each interaction to the total interaction energy. These interactions include electrostatic, exchange, induction, and dispersion. In the above figures are the percentage of the total binding energy (excluding exchange energies) of each interaction in a bisect scan. In the 0F case, dispersion interaction is the dominating interaction holding this complex together compared to the electrostatic.

In the BrCN case, electrostatic and dispersion interactions make almost equivalent contributions. Induction is clearly not nearly as impactful as dispersion or electrostatic interactions, and only makes a significant contribution outside the benzene ring.

### Angle Test Results

In each case in Table 2, an angle of 180 degrees resulted in the minimum interaction energy. However, the difference between 180 and 140 was less significant than was expected. This could indicate that C-X... $\pi$  interactions are slightly less directional than originally thought.

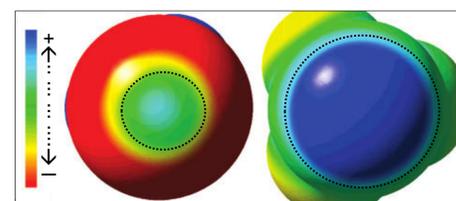
Angles (degrees)	140°	150°	160°	170°	180°
0F (kcal/mol)	1.86	1.54	1.27	1.09	1.02
BrCN (kcal/mol)	-3.88	-4.14	-4.35	-4.49	-4.54

**Table 2.** Angle comparison between the smallest  $\sigma$ -hole and largest  $\sigma$ -hole molecules

## Design and Operation

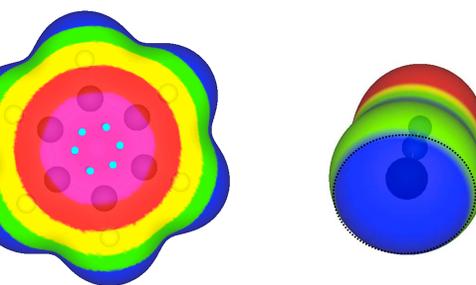
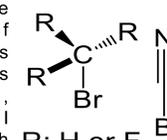
Studies of halogen bonds have shown their ability to form sigma holes due to polarizability of the surface of the halogens. The size of the sigma hole can be varied if the attached molecule to the halogen includes electronegative withdrawing groups pulling the electronegative density off of the halogen and redirecting the distribution towards themselves, Fig 6. Fig. 7 demonstrates the different systems we worked with 0F-3F, in the results section, referring to different degrees of fluorinated methyl bromide and BrCN to the Cyanogen bromide molecule.

Due to the inability of Hartree-Fock to describe dispersion in halogen bonds precisely, similar but more accurate calculations such as CCSD(T) and MP2 methods, Equation 1, were applied along DFT-SAPT, Equation 2. CCSD/adz produces accurate and reliable calculations with a drawback of being magnitudes more expensive than MP2. However, MP2 methods shown in the study were reasonably comparable to CCSD calculations and coupling the two methods gave the inputs of the first equation giving a final product close to CCSD/aqz. DFT-SAPT allowed us to see each individual interaction that contributes to the total interaction. All calculations such as geometry optimization, binding energies, and DFT-SAPT interaction were through the Molpro 2010.



**Figure 6.** (Above)  $H_3CBr$  (left),  $F_3CBr$  (Right) Frontal view of the effects of substituted Fluorine atoms on methyl Bromide and how it affects the  $\sigma$ -hole size, emphasized by dotted black line.

**Figure 7.** (Right) the variety of systems studied in this publication, methyl bromide with R representing Hydrogen or Fluorine atoms and Cyanogen bromide.



**Figure 8.** (Above) In the benzene image on the left, the teal dots indicate a local potential minima—above these minima is where we would expect the greatest interaction energies. On the cyanogen to the right, the sigma hole is clearly much larger than the other molecules we tested, such as those in Figure 6.

Molecule	0F	1F	2F	3F	BrCN	Benzene
$V_s$ max. (kcal/mol)	5.69	10.41	15.48	23.2	42.03	-14.95

**Table 1.** The maximum electrostatic potential for each sigma hole on each molecule tested including the electron acceptor, benzene.

**Equation 1.** (Above) is applied to compute the interaction energy for the coupled cluster augmented quintuplet zeta basis set.

**Equation 2.** (Below) is applied to compute the SAPT calculations going from a double basis set to a triple basis set.

$$\text{Eq. 1) } \Delta E_{\text{CCSD(T)}/\text{aqz}} = \Delta E_{\text{MP2}/\text{aqz}} + \Delta E_{\text{CCSD(T)}}$$

$$\text{Eq. 2) } \Delta E_{\text{CCSD(T)}/\text{adz}} = \Delta E_{\text{CCSD(T)}/\text{adz}} - \Delta E_{\text{MP2}/\text{adz}}$$

$$E_{\text{corr, CBS}} = \frac{(E_{\text{corr}, X+1}(X+1)^P - E_{\text{corr}, X} \times X^P)}{((X+1)^P - X^P)}$$

Double basis set  $\rightarrow$  Triple basis set  
P = 2.868

J. Chem. Theory Comput. 2011, 7, 685-689

Although the direction or distance of the brominated molecule from the center of the benzene ring did not produce a dramatic change of interaction energy; it gives insight on predicting outcomes of behavior in larger systems with similar interactions. There are still some additional tests needed to reassure the conclusions we have come to. Similar tests with other halogens—iodine or chlorine—would help determine the role that the size of the atom interacting with benzene plays.

C-X... $\pi$  interactions are not quite as directional as traditional halogen bonds<sup>[1,2,4,5,6]</sup>. Though it is clear that these interaction can be geometrically adjusted and tuned to produce specific interaction energies, they are not as sensitive to direction or location above the benzene as expected prior to this examination. This may explain pi interaction existence in protein structures. Due to these results, development of future applications bode well for protein analysis, crystal structures, and smart organic materials.

## Concluding Remarks

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## Calculation Outcomes

