Effects of Fluorine Substitution on the Edge-to-Face Interaction of the Benzene Dimer

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To gain some insight into the effects of fluorination on the aromatic−aromatic interactions found in protein−ligand complexes, like those observed in the set of *N*-(4-sulfamylbenzoyl)benzylamine (SBB) inhibitors bound to Human Carbonic Anhydrase II (HCAII), we have produced potential energy curves for the edge-to-face interactions of a set of fluorinated benzene dimer compounds. All calculations were carried out at the MP2/aug-cc-pVDZ level of theory using the counterpoise method of Boys and Bernardi (Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553) to account for the basis set superposition error. Fluorine substitutions are made onto the face molecule of the edge-to-face benzene dimer. As one might expect, the substitution of additional fluorines into this system generally resulted in a decrease of the binding energy. It was also found that the positioning of the fluorine substituents on isosubstituted compounds has a large effect on the total binding energy of these types of systems. More specifically, complexes with fluorines that are substituted closer to the hydrogen atoms of the edge benzene will tend to be stabilized by an electrostatic interaction between the partially negative fluorine atoms and the partially positive hydrogen atoms. However, our findings do not explain the recent crystallographic findings for the SBB-HCAII protein−ligand complex, where increased fluorination resulted in closer edge-to-face contacts, which suggests that there are factors, other than edge-to-face aromatic interactions, influencing this system's behavior.

Introduction

Aromatic−aromatic interactions play a key role in a broad range of intermolecular and intramolecular complexes.[1−8] In particular, in biological systems, aromatic−aromatic interactions are observed in globular proteins and in protein−ligand complexes, with the former being important in understanding protein folding and stability,[1,4,7] while the latter is of import to modern drug-design efforts.[6,8] Most protein−small molecule complexes contain interactions involving aromatic amino acid side chains of the receptor and/or aromatic and heteroaromatic rings of the ligand.[6] Numerous experimental[9−12] and theoretical[13−26] studies have been carried out over the course of the last few decades seeking to explain the nature of aromatic−aromatic interactions.

The substitution of fluorine atoms for hydrogen atoms is commonly exploited in medicinal chemistry to enhance ligand binding to proteins.[12] Fluorine is an isosteric substitution for hydrogen and is isoelectronic with hydroxyl which, along with its relative stability, makes it a very suitable atom 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 ligand, but the chemical properties of the modified fluorine substituted ligand may impact protein−ligand affinity and selectivity.[27]

One example of a protein−ligand system that demonstrates aromatic interactions is the set of fluorine substituted *N*-(4-sulfamylbenzoyl)benzylamine (SBB) inhibitors bound to Human Carbonic Anhydrase II (HCAII). HCAII is a zinc metalloenzyme that catalyzes the hydration of carbon dioxide releasing bicarbonate and a proton. Inhibition of HCAII is of clinical importance and can be useful in the treatment of various diseases such as glaucoma.[28] The substitution of fluorine atoms in the benzyl group of the SBB inhibitor modifies the edge-to-face interaction between Phe131 and the benzyl group of SBB and thus influences the affinity of the SBB inhibitor for HCAII. In this work, we wish to further elucidate the effects of fluorination on edge-to-face aromatic interactions and relate this insight to the SBB/HCAII system.

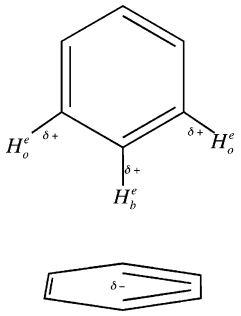

Figure 1. Benzene dimer. Here, the bonding edge hydrogen, H_b^e, along with the ortho edge hydrogens, H_o^e, are shown.

The edge-to-face aromatic interaction is an example of a quadrupole−quadrupole interaction in which the partial positive charge on the ring hydrogen of the upper (edge) benzene (see Figure 1) interacts favorably with the partial negative charge above the aromatic ring of the lower (face) benzene.[29] Substitution of fluorine onto the lower benzene molecule diminishes the partial negative character of the π cloud above the ring, thereby reducing the attractive forces between the two benzene molecules. Using this model, one would expect that the addition of further fluorine substituents would result in an increase in the intercentroid separation and a decrease in the binding energy of the benzene dimer system.

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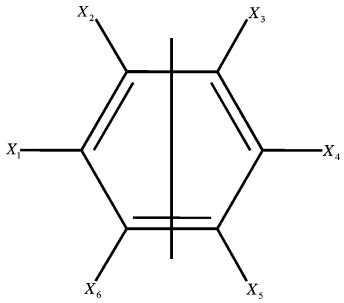

Figure 2. Top downview of the edge-to-face benzene dimer. Here, the solid line through the middle of the figure represents the upper (edge) benzene. The X's represent the various positions onto which fluorine can be substituted.

Kim et al. have performed high-resolution X-ray crystallographic work on five SBB-HCAII complexes with varying degrees of fluorination on the aromatic portion of Phe131.[12] In these studies, it was found that various fluorine substitution patterns modulated the enzyme−inhibitor affinity by a factor of 10. The range of intercentroid separations observed was 3.4−6.5 Å, a range of distances associated with quadrupole−quadrupole interactions. Surprisingly, it was found in these studies that the fluoroaromatic ring of each inhibitor tended to shift closer to Phe-131 with increasing fluorination. These observations contradict the expected behavior of these types of fluoronated aromatic systems.

It is now possible to make calculations on large systems such as proteins using semiempirical, density functional, and Hartree−Fock methods.[30−33] These techniques, however, lack the precision needed to describe weak interactions such as those between aromatic systems. To understand the behavior of aromatic complexes in proteins, it becomes necessary to carry out higher level calculations on smaller model systems chosen to mimic the aromatic moieties found within the system of interest. The behavior of these smaller model systems can then be related back to the original, larger, systems.

Previously, Sinnokrot and Sherrill carried out studies in which several substituents were introduced to a benzene dimer system using the MP2, CCSD(T), and SAPT[34] methods.[17] Fluorine substitution onto the lower ring (corresponding to a 1-fluorobenzene system as in Figure 2) generally resulted in a negligible change in intercentroid separation and a decrease in the binding energy by about half a kcal/mol. SAPT studies show that this decrease in binding energy is principally due to electrostatic effects and is caused by the diminished π electron density in the lower 1-fluorobenzene ring. However, they have not investigated more extensive fluorine substitution, so we are not able to draw on their work to better understand the SBB/HCAII system.

In this study, we produce potential energy curves for the interaction energies of a set of edge-to-face (T-shaped) fluorine substituted benzene dimers in an attempt to clarify the counterintuitive role of fluorination on the aromatic interactions found within the SBB-HCAII complex. The interaction between these aromatic systems may depend not only on the number of fluorine substituents present but also on the particular placement of the substituents, and as such, we have used a set of fluorinated dimers that is complete in the sense that all symmetrically unique fluorination patterns have been considered.

Materials and Methods

All ab initio calculations in this work were carried out using the Gaussian 03 program.[35] Second-order perturbation theory (MP2) methods were employed to account for electron correlation effects.[36] The basis set used for all calculations in this work is the augmented double-ζ basis set of Dunning (aug-cc-pVDZ).[37] To correct for the basis set superposition error (BSSE), the counterpoise method of Boys and Bernardi was employed.[38] Atomic charges were calculated using the electrostatic potential (ESP) model of Merz and Kollman.[39]

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 the intercentroid separations were varied. This type of approximation has been made in previous works and introduces negligible error.[17−19]

Given the weakness of the attractions between aromatic systems, a very high level of theory is needed to accurately describe these types of interactions. Sinnokrot and Sherrill carried out studies on the benzene dimer using both MP2 and CCSD(T) methods along with various augmented correlation consistent basis sets.[18] In these studies, it was found that the MP2 method obtains binding energies that are too high with respect to the higher level CCSD(T) interaction energies. In the case of the edge-to-face benzene dimer, however, the MP2/aug-cc-pVDZ interaction energies near the potential energy minimum were found to be reasonably close to those of the highest level CCSD(T) method with a minimum value that is 0.4 kcal/mol too low. In related work, Sinnokrot and Sherrill note that the MP2/aug-cc-pVDZ method yields a very similar result to the best estimated CCSD(T)/aug-cc-pVTZ method when the stability of the 1-fluorobenzene dimer system relative to the benzene dimer was calculated.[17] The MP2 value for this quantity is −0.51 kcal/mol, while the CCSD(T) value is −0.49 kcal/mol. The primary focus of this work is to evaluate the binding energies of the various fluorination configurations relative to one another, and as such, the previous result indicates that our MP2/aug-cc-pVDZ calculations should give accurate values. Overall, MP2/aug-cc-pVDZ calculations can be regarded as being at least semiquantitative, with a computational expense significantly smaller than that of CCSD(T).

Discussion

Figure 3 shows selected potential energy curves for several fluorine substituted benzene dimer systems. It is clear from this figure that the addition of fluorine substituents generally decreases the binding affinity and slightly increases the optimum intercentroid separation between the two monomers. However, the trend of decreasing binding affinity with additional fluorine substitution does not always hold true. For example, the triply substituted 1,3,5-trifluorobenzene has a binding affinity that is significantly lower than the doubly substituted 1,4-difluorobenzene. Table 1 gives the values for the binding affinities for each of the symmetrically unique substitution patterns considered in this study at an intercentroid separation of five Å. From these calculations, it can be seen that there is a wide variation in the binding affinity between systems containing the same number of substituents.

Figure 4 shows potential energy curves for the both unique combinations of singly substituted benzene dimer systems along with the unsubstituted benzene dimer; here, it can clearly be seen that fluorine substitution destabilizes this dimer. This destabilization agrees with the model proposed previously, in which the fluorine substituents will tend to draw electron density away from the π ring and reduce the electrostatic interaction between the negative π ring on the lower benzene and the positive hydrogens on the upper benzene. Interestingly, there

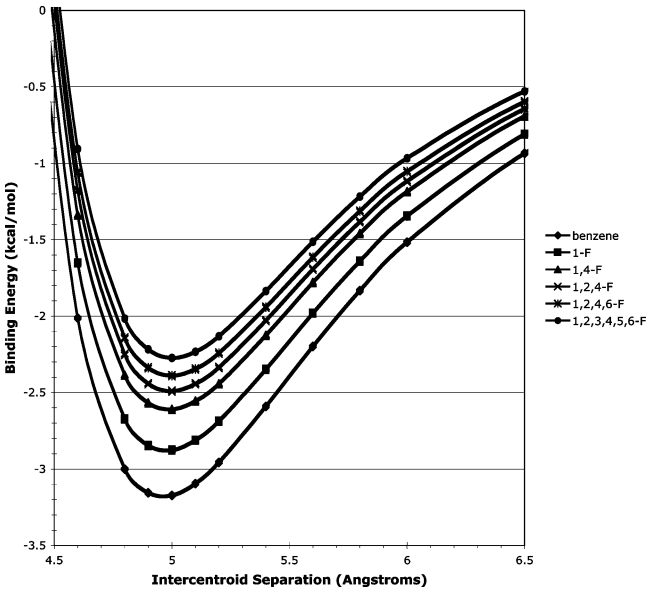

Figure 3. Potential energy curves for the binding energy of various fluorinated benzene dimer systems as a function of the intercentroid separation. The abbreviation F is used for the suffix *n*-fluorobenzene (i.e., 1,4-F represents 1,4-difluorobenzene).

TABLE 1: Binding Energies (in kcal/mol) of All Symmetrically Unique Fluorinated Benzene Dimers Considered in this Study at an Intercentroid Separation of 5.0 Å

benzene	3.17
1-F	2.87
2-F	2.97
1,2-F	2.73
1,3-F	2.70
1,4-F	2.60
2,3-F	2.82
3,5-F	2.80
2,5-F	2.80
1,2,3-F	2.60
1,2,4-F	2.49
1,2,5-F	2.58
1,3,5-F	2.58
2,3,5-F	2.67
3,4,5-F	2.60
1,2,3,4-F	2.40
1,2,3,5-F	2.48
1,2,3,6-F	2.49
2,3,5,6-F	2.57
1,2,4,5-F	2.38
1,2,4,6-F	2.38
1,2,3,4,5-F	2.32
2,3,4,5,6-F	2.41
1,2,3,4,5,6-F	2.27

is a substantial difference in binding energy between 1-fluorbenzene and 2-fluorobenzene substituted structures with the 1-F system having a binding energy significantly smaller than that of 2-fluorobenzene.

A possible explanation for the difference in binding energy between the 1-fluorobenzene and the 2-fluorobenzene systems is the fact that, in the 2-fluorobenzene system, the fluorine is substituted at a position that lies closer to one of the partially positive charged hydrogens, H_o^e, that is ortho to the hydrogen of the upper benzene whose bond is pointed at the lower benzene ring, H_b^e (see Figure 2). Because of its high electronegativity, the fluorine will tend to have a partially negative charge; thus, there will be an attractive interaction between the fluorine and the H_o^e, and this attractive interaction will tend to stabilize the

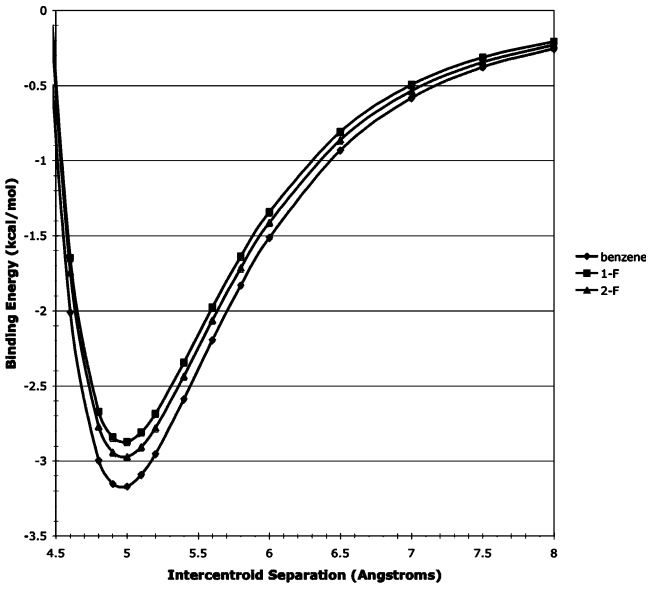

Figure 4. Potential energy curves for the nonsubstituted and monosubstituted benzene dimer systems.

dimer system. The distances between the substituted fluorine atoms and the nearest H_o^e atom for the 1-fluorobenzene and 2-fluorobenzne systems at an intercentroid separation of 5 Å are 5.11 and 3.99 Å, respectively. The Merz−Kollman charge density analysis indicates that the fluorine has a charge of −0.27 while the nearest H_o^e has a charge of +0.14 for both the 1-fluorobenzene and 2-fluorobenzene systems. Henceforth, in this work we will refer to the first and fourth positions (as in Figure 1) as outer substituent positions and the second, third, fifth, and sixth positions as the inner substituent positions (see Figure 5).

Figure 6 shows the binding energies for all of the doubly substituted benzene dimer systems along with the triply substituted 2,3,5-trifluorobenzene system. Here, it can be seen that the most strongly bound dimer, 2,3-difluorobenzene, has a binding affinity that is 0.22 kcal/mol higher than the most weakly bound dimer, 1,4-difluorobenzene. Another interesting point is that the doubly substituted 1,4-difluorobenzene compound is bound more weakly than the triply substituted 2,3,5-trifluorobenzene compound.

The main pattern that can be discerned from looking at the difluorinated dimers in Figure 6 is that the more fluorine substituents a system has in the outer substituent positions, the lower the binding energy of that system will be. This pattern can be ascribed to the same type of effect that was seen in the singly substituted systems where the dimer was stabilized more by inner substituent fluorines because they tend to have a stronger attraction for the hydrogen atoms on the upper ring than the outer substituent fluorines.

The inner/outer substitution model seems to describe the basic trends in binding energy patterns fairly well for disubstituted compounds. There are, however, some slight differences in binding energy that cannot be explained by this model. For instance, using our model, one would predict that the 1,2- and 1,3-difluorobenzene compounds would have the same binding energies. Our studies indicate, however, that the 1,2-difluorobenzene system is more stable than the 1,3-difluorobenzene system by about 0.02 kcal/mol. This small difference in binding energy may be attributed to the fact that two adjacent fluorine substituents might deform the π ring of the lower benzene molecule in a different way than two fluorine substituents that are meta to each other.

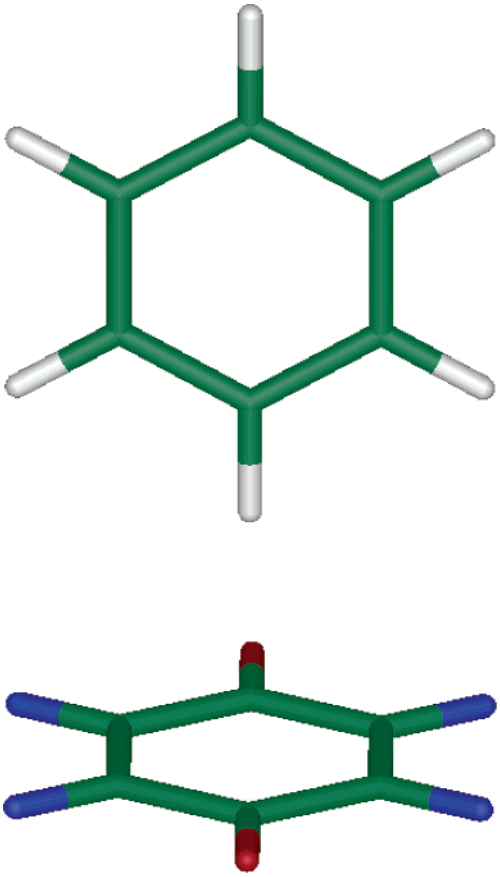

Figure 5. Inside/outside substitution patterns. Inside substituent positions (blue) are closer to the H_o^e hydrogens on the edge benzene molecule than the outside subtituent positions (red).

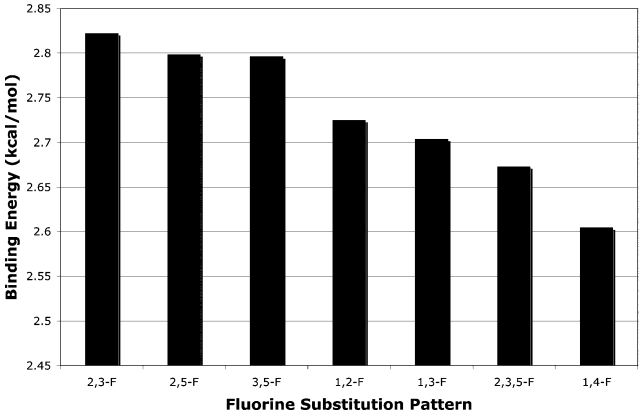

Figure 6. Binding energies of the disubstituted and 2,3,5-F benzene dimer systems.

The binding energies for all of the triply substituted benzene dimer complexes along with the 2,3,5,6- and 1,2,3,5-tetrafluorobenzene compounds are given in Figure 7. Here, the difference between the most strongly bound system, 2,3,5-fluorobenzene, and the most weakly bound system, 1,2,4-fluorobenzene, is about 0.19 kcal/mol. Clearly, the inner/outer model proposed for the singly and doubly substituted systems also holds true for these systems as well.

It is interesting to note that two tetra-substituted molecules, 2,3,5,6- and 1,2,3,5-tetrafluorobenzene, bind more favorably to benzene than the triply substituted 1,2,4-trifluorobenzene. Also, both 3,4,5- and 1,3,5-trifluorobenzene complexes have binding energies of 2.58 kcal/mol, while the 2,3,5,6-tetrofluorobenzene system has a binding energy of 2.57 kcal/mol.

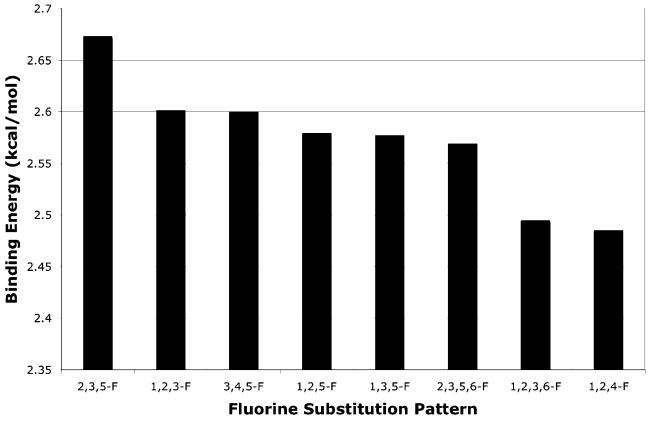

Figure 7. Binding energies of the trisubstituted, 2,3,5,6-F, and 1,2,3,5-F benzene dimer systems.

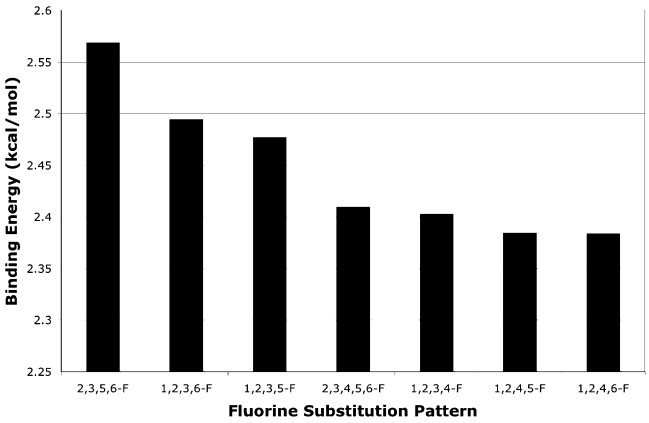

Figure 8. Binding energies of tetrasubstituted and 2,3,4,5,6-F benzene dimer systems.

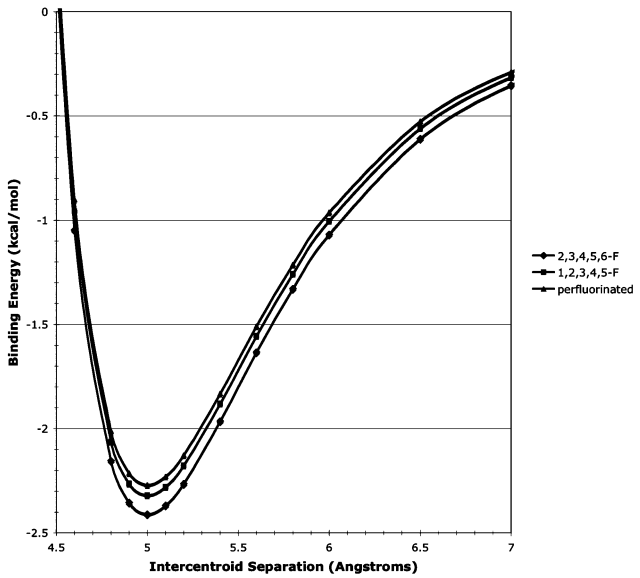

Figure 9. Potential energy curves for pentafluorinated and perfluorinated benzene dimer complexes.

It can be seen in Figure 8 that the type of binding energy pattern observed for the doubly and triply substituted systems is also present for the tetra-substituted systems. The 2,3,5,6-tetrafluorobenzene compound, containing fluorines only on the inner substitution positions, has a binding energy that is 0.19 kcal/mol higher than the 1,2,4,5-tetrafluorobenzene system, which contains two fluorine substituents on the outer substitution positions. There are three unique tetra-substituted systems that

have fluorine atoms on both outer substitution positions, and each of these has a binding energy that is lower than the penta-substituted 2,3,4,5,6-pentafluorobenzene dimer system, which has only one fluorine on an outer substitution position.

It should be noted that there are some small discrepancies in the binding energy for the tetra-substituted systems that cannot be explained by the inside/outside fluorine substituent model. For example, the 1,2,3,5-tetrafluorobenzene system is more stable than the 1,2,3,6-tetrafluorobenzene system by about 0.02 kcal/mol. As was stated in regard to the doubly substituted systems, these small differences might be caused by the nature of the deformation of the π ring that the various fluorination patterns impose.

The potential energy curves for the two penta-substituted fluorine systems along with the perfluorinated compound are given in Figure 9. As expected, the 2,3,4,5,6-pentafluorobenzene compound, with its single outer substituted fluorine, is more stable than the 1,2,3,4,5-pentafluorobenzene complex, which has two outer substituted fluorines. The perfluorinated system, 1,2,3,4,5,6-hexafluorobenzene, is the least stable of all the edge-to-face complexes studied in this paper.

Conclusions

In this work, we have found that, generally, the substitution of successive fluorine atoms into an edge-to-face benzene dimer complex will result in a decrease in the binding energy between the two monomers in the system. We have also shown that the differences in binding energy between isosubstituted systems can be explained, in large part, by the inside/outside fluorine substitution model. In this model, fluorine atoms that are substituted onto the two, three, five, and six positions will tend to interact favorably with the H_o^e hydrogens and stabilize the dimer relative to systems with fluorine substituents on the one or four positions. It should be noted that there are some very small binding energy discrepancies of about 0.02 kcal/mol that cannot be explained using this model. Another result that can be taken from our study is that successive fluorine substitution does not have any large impact on the optimal intercentroid separation for these types of systems.

This last statement seems to contradict the findings of Kim et al., who determined that in the SBB-HCAII system, the addition of fluorine substituents tends to decrease the intercentroid separation between the two edge-to-face aromatic rings.[12] It should be remembered, however, that there are many interactions within the SBB-HCAII system that could be responsible for this shortening of the intercentroid distance; for instance, there are several other residues within the protein−ligand complex that lie within a few angstroms of the SBB aromatic ring. Another factor that might have an affect on the position of the aromatic portion of the SBB molecule is the presence of water molecules within the crystal.

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