DOI: 10.1002/chem.200501316

The Effect of Multiple Substituents on Sandwich and T-Shaped π–π Interactions

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Abstract: Sandwich and T-shaped configurations of substituted benzene dimers were studied by second-order perturbation theory to determine how substituents tune π–π interactions. Remarkably, multiple substituents have an additive effect on the binding energy of sandwich dimers, except in some cases when substituents are aligned on top of each other. The energetics of substituted T-shaped configurations are more complex, but nevertheless a simple model that accounts for electrostatic and dispersion interactions (and direct contacts between substituents on one ring and hydrogen atoms on the other), provides a good match to the quantum mechanical results. These results provide insight into the manner by which substituents csan be utilized in supramolecular design.

Keywords: ab initio calculations · molecular recognition · pi interactions · substituent effects · supramolecular chemistry

Introduction

Noncovalent π–π interactions are involved in a wide variety of chemical and biological processes,[1] ranging from self-assembly of synthetic molecules[2] to drug intercalation into DNA.[3] However, these important interactions are weak and feature shallow potential energy landscapes. Substituents can significantly alter the energy landscape and provide a way to tune π–π interactions. An understanding of how substituents can be used to adjust π–π interactions could be helpful in crystal engineering and the design of supramolecular architectures.

A few experiments have probed the effect of substituents on π–π interactions by using NMR techniques. Cozzi, Siegel, and co-workers[4–6] have measured barriers to rotation in substituted 1,8-diarylnaphthalenes featuring a nearly face-to-face (sandwich) configuration. Other experiments by Rashkin and Waters,[7] Hunter and co-workers,[8,9] and Wilcox and co-workers[10,11] examined π–π interactions in other (parallel-displaced and T-shaped) configurations. Other studies have examined the structures of benzene–hexafluorobenzene dimers or 1:1 crystals.[12,13] None of these experiments were performed in the gas phase, so characterizing the intrinsic binding energy is difficult due to the inevitable presence of secondary interactions and solvent effects.[14,15] Unfortunately, these experiments do not agree about how substituents alter π-π interactions: some indicate that electrostatic effects are dominant,[4–6,8,9] while others argue for dispersion effects.[10,11]

Approximately perpendicular and offset parallel configurations are frequently observed in the crystal structures of simple aromatic compounds,[16,17] and interacting side chains in proteins exhibit both orientations.[18,16] Tsuzuki and coworkers[19] have noted in their examination of toluene dimers that unlike benzene dimers, toluene dimers favor parallel-displaced over T-shaped configurations, and the sandwich and T-shaped configurations become nearly isoenergetic. Here we will focus on sandwich and T-shaped configurations of substituted benzene dimers, and parallel-displaced configurations will be considered in future work.

Conventional wisdom about geometric and substituent effects in π–π interactions is currently based upon the Hunter–Sanders model,[20] which argues that although dispersion effects are important to the total binding energy, changes due to geometry or substitution are governed by electrostatic forces. This simple model describes an aromatic

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. The Supporting Information contains cartesian coordinates and total energies of substituted sandwich and T-shaped configurations.

ring as a positively charged σ framework and a negatively charged π cloud. For sandwich configurations of substituted benzenes, this model predicts that electron-withdrawing substituents strengthen the interaction because they decrease the electrostatic repulsion between the negatively charged π clouds. The reverse effect is predicted for electron-donating substituents. Our recent high-level theoretical studies of substituted benzene dimers[21,22] demonstrate that *all* substituted sandwich benzene dimers have a stronger attraction than the unsubstituted benzene dimer, regardless of the electron-donating or electron-withdrawing nature of the substituent, in contradiction to the Hunter–Sanders rules. Geerlings and co-workers[23] find similar results in their theoretical study of the interaction between monosubstituted benzenes with pyrimidine and imidazole. Our unconventional prediction that electron-donating substituents *increase* binding in face-to-face π–π interactions seems to have been confirmed in a recent study by Mei and Wolf.[24] These workers have synthesized a new, highly congested 1,8-diacridylnapthalene system to serve as a more robust experimental model of face-to-face π–π interactions. They find that oxides of their parent system feature increased π–π interactions, in agreement with our predictions.

We previously analyzed the binding energies of substituted sandwich and T-shaped benzene dimers by using symmetry-adapted perturbation theory (SAPT),[25,26] which provides the electrostatic, dispersion, induction, and exchange–repulsion components of the interaction energy. This analysis showed that not only is dispersion more important than electrostatics in the overall binding, but it can also be more important in determining substituent effects.[22] This conclusion is supported by previous studies of substituent effects in solute–solvent interactions in nematic liquid crystals by Williams and Lemieux.[27]

So far, we have studied only monosubstituted benzene dimers. Here we extend our work to explore the effect of multiple substituents on sandwich and T-shaped configurations. Experimental work on multiple fluorination of 1,8-diarylnaphthalenes by Cozzi, Siegel, and co-workers[6] suggests that substituent effects in π–π interactions may be additive: these workers measured the barrier to rotation of phenyl groups about the naphthyl–phenyl bond, which they argue is related to the strength of the π–π interaction between phenyl groups.[28] In their studies of mono- through trifluorinated phenyl rings, they found that each fluorine contributes about 0.5 kcal mol^{-1} to the barrier to rotation. This is a remarkable result and suggests that, if additivity holds more generally, it might be possible to predict the energy change in π–π interactions based simply on the number and type of substituents by using tabulated substituent values and/or a very simple equation involving molecular quantities for the monomers. In recent theoretical work, Kim and co-workers[29] demonstrated additivity in a single example in which they substituted both aromatic rings in a T-shaped benzene dimer and found that the change in total interaction energy was nearly equal to the sum of the changes caused by the individual substitutions. However, by considering only a single disubstituted dimer, this work did not address the question of additivity in a general fashion. While the present paper was in preparation, Riley and Merz[30] demonstrated the need to carefully consider direct hydrogen–substituent interaction in their extensive study of fluorosubstituted dimers, in which they consider every possible substitution pattern through hexasubstitution for T-shaped benzene–*n*-fluorobenzene dimers. In this work, we present a broader investigation of the additivity of substituent effects on π–π interactions by considering sandwich and T-shaped dimers of benzene that are up to hexasubstituted for five different substituents. Further, we develop a mathematical model to predict relative interaction energies for substituted dimers that is a function of parameters correlating to electrostatic and dispersion contributions of the substituents.

Computational Methods

All computations were performed using second-order Møller–Plesset perturbation theory (MP2) in conjunction with Dunning's augmented polarized correlation-consistent basis set aug-cc-pVDZ.[31] The aug- prefix denotes that this basis set has an extra set of diffuse functions for each angular momentum appearing in the basis. This basis set was chosen because the low symmetry of the dimers in this study, ranging in size from 24 to 33 atoms, limited the level of theory that could be applied. Previous work[32] on the benzene dimer indicates that it is more important to include additional diffuse functions rather than use a triple-ζ-quality basis set. Fortunately, our previous study of the relative changes caused by substitution of the benzene dimer shows that the *change* in interaction energy due to the substituents can be accurately determined at this computational level,[22] even though the *total* binding energies are not as reliable as those computed by using coupled-cluster theory with large basis sets. Monomers (Ph−X$_n$ in which X = H, F, CH$_3$, OH, NH$_2$, and CN; Figure 1) were optimized at the MP2/aug-cc-pVDZ level of theory, and sandwich dimers were constructed by maintaining these monomer geometries and varying the distance between the monomers over the range 3.0–4.0 Å. For the T-shaped configurations, the monomers were aligned at a 90° angle as shown in Figure 2, and the distance between the centers of the rings was varied over the range 4.5–5.5 Å. The monomer separation was initially varied by 0.2 Å increments to give the general shape of the potential energy curve, and then the resolution of the curve was increased to 0.05 Å near the equilibrium point. When substituting the benzene ring, the symmetrical substitution patterns, illustrated in Figure 1, were used. Disubstituted systems were substituted in the *para*-1,4-positions, and trisubstitutions were in the 1,3,5-positions. Hexasubstituted systems were also considered in some cases.

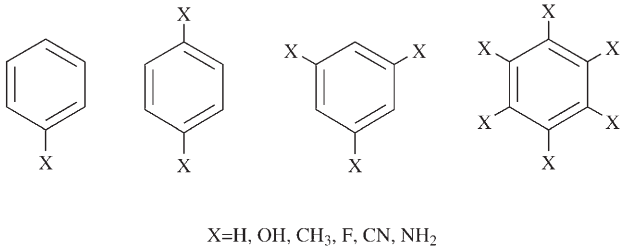

Figure 1. Symmetric substitution patterns for substituted dimers.

In the sandwich configurations, the monomers were aligned at their centers, such that the C−X bonds of the substituted benzene were coplanar

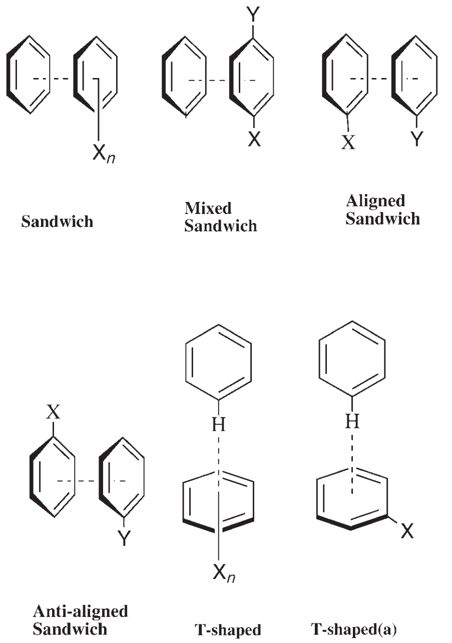

Figure 2. Dimer construction configurations for sandwich and T-shaped configurations.

to the C–H bond of benzene. In this procedure, we used the geometric center of each ring for alignment.[33] This configuration was chosen as representative and is of course not the only possibility, but rotation of the sandwich dimer caused no more than 0.01 kcal mol^{-1} difference in the total interaction energy, even in the hexasubstituted dimers. Rotation of the lower ring in the T-shaped configurations is discussed below. The CH_3 substituents had nearly free rotation around the C–C single bond, so the C_s configuration with one hydrogen atom up and two hydrogen atoms down was chosen as representative. For the amino-substituted systems, the configuration in which the hydrogen atoms are directed away from the other benzene ring was chosen.

Most of the dimers in this study are heterodimers between a benzene moiety and a substituted benzene molecule in which the substituents are all of the same type. However, we have also considered several "mixed" sandwich dimers with two different types of substituents; these are depicted in Figure 2. These dimers allow us to evaluate, among other factors, the possible importance of direct interactions between substituents on different rings. We considered mixed sandwiches of benzene and *para*-disubstituted benzene and also dimers of two different monosubstituted benzenes. In the latter case, we allowed the substituents to be aligned on top of each other or to be opposite each other in an "anti-aligned" configuration (see Figure 2).

Our previous work on the benzene dimer[32,22] demonstrates that interaction energies converge more rapidly when the Boys–Bernardi counterpoise correction[34] is employed (although this is not necessarily the case for all weakly bound systems); hence, we apply the counterpoise correction to all results reported here. Optimizations of monomer geometries were performed using Q-Chem 2.1,[35] and dimer computations were performed using MOLPRO.[36]

Symmetry-adapted perturbation theory (SAPT)[25,26] was applied by using the program package SAPT2002[37] to selected dimers to analyze their total interaction energies in terms of electrostatic, induction, dispersion, and exchange energies. The total interaction energy can be represented by the sum given in Equation (1) in which $E_{\mathrm{int}}^{\mathrm{HF}}$ describes the interactions at the Hartree-Fock level. This term can be further expanded to yield Equation (2).

$$E_{\mathrm{int}} = E_{\mathrm{int}}^{\mathrm{HF}} + E_{\mathrm{int}}^{\mathrm{CORR}} \qquad (1)$$

$$E_{\mathrm{int}}^{\mathrm{HF}} = E_{\mathrm{elst}}^{(10)} + E_{\mathrm{exch}}^{(10)} + E_{\mathrm{ind,resp}}^{(20)} + E_{\mathrm{exch\text{-}int,resp}}^{(20)} + \delta E_{\mathrm{int,resp}}^{\mathrm{HF}} \qquad (2)$$

The superscripts (ab) indicate the order of the perturbation with respect to the intermolecular and intramonomer parts of the Hamiltonian, respectively. The subscript "resp" indicates that the term contains contributions from the coupled-perturbed Hartree–Fock response.

In the SAPT2 method employed here, the contribution of electron correlation to the interaction energy is nearly equivalent to that from a supermolecular MP2 computation and can be represented as Equation (3) in which ${}^{t}E_{\mathrm{ind}}^{(22)}$ represents the part of $E_{\mathrm{ind}}^{(22)}$ that is not included in $E_{\mathrm{ind,resp}}^{(20)}$.

$$E_{\mathrm{int}}^{\mathrm{CORR}} = E_{\mathrm{elst,resp}}^{(12)} + E_{\mathrm{exch}}^{(11)} + E_{\mathrm{exch}}^{(12)} + {}^{t}E_{\mathrm{ind}}^{(22)} + {}^{t}E_{\mathrm{exch\text{-}ind}}^{(22)} + E_{\mathrm{disp}}^{(20)} + E_{\mathrm{exch\text{-}disp}}^{(20)} \qquad (3)$$

To simplify our discussion of the SAPT results, the exchange–induction and exchange–dispersion cross terms will be considered as induction and dispersion contributions, respectively. Additionally, the $\delta E_{\mathrm{int,resp}}^{\mathrm{HF}}$ term, which includes the third- and higher-order induction and exchange–induction contributions, is counted as induction. To make the SAPT computations feasible, we used a less expensive basis set, denoted cc-pVDZ+, which is the cc-pVDZ basis for hydrogen and an aug-cc-pVDZ basis minus diffuse d functions for all other atoms.

Results and Discussion

Sandwich dimers: We first consider sandwich heterodimers consisting of one benzene and one substituted benzene (left-most dimer of Figure 2). The optimum intermonomer distances are presented in Table 1 along with the change in the interaction energy (relative to the benzene dimer) due to substitution. As seen in our previous work[21,22] all substituted sandwich dimers have a greater interaction energy than the sandwich benzene dimer, regardless of the electron-donating or electron-withdrawing nature of the substituent. It is remarkable that the energy lowering due to two substituents is very nearly twice the energy lowering due to one substituent in all cases; that is, the substituent effects are nearly additive for these sandwich heterodimers. Moreover, this additivity persists up through hexasubstituted dimers. This result is illustrated more clearly by Figures 3 and 4, which show the total interaction energy versus the number of substituents. The average change in the interaction energy per substituent can be determined from the slope of the best fit line for each functional group (-OH, 0.50; -CH_3, 0.66; -F,

Table 1. Optimum intermonomer distances [R in Å] and changes in the interaction energy [in kcal mol^{-1}, relative to benzene dimer] due to n substituents for sandwich heterodimers of benzene with multiply substituted benzenes.[a]

	$n=1$		$n=2$		$n=3$		$n=6$	
	R[b]	$\Delta\Delta E_{\mathrm{int}}$	R[b]	$\Delta\Delta E_{\mathrm{int}}$	R[b]	$\Delta\Delta E_{\mathrm{int}}$	R[b]	$\Delta\Delta E_{\mathrm{int}}$
H	3.80	0.00						
OH	3.70	−0.49	3.65	−1.05	3.60	−1.50		
CH_3	3.70	−0.70	3.65	−1.23	3.60	−1.98		
F	3.70	−0.60	3.65	−1.24	3.60	−1.89	3.45	−4.29
CN	3.65	−1.58	3.60	−3.28	3.55	−4.82	3.40	−10.46
NH_2	3.65	−0.64	3.60	−1.39	3.50	−2.20		

[a] All data computed at MP2/aug-cc-pVDZ level of theory; interaction energy of benzene dimer at this level is −2.90 kcal mol^{-1}. [b] Equilibrium monomer separation (using rigid monomers).

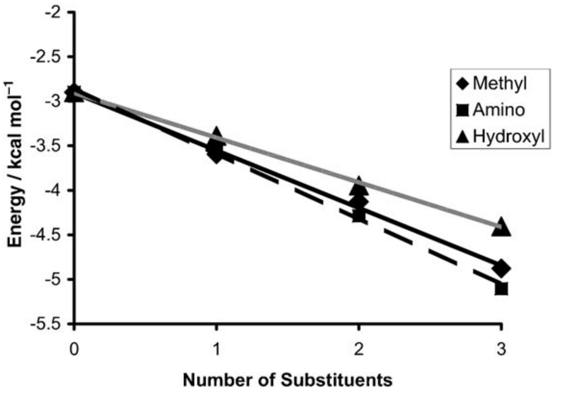

Figure 3. Total interaction energy versus number of substituents (through trisubstitution) for sandwich configurations.

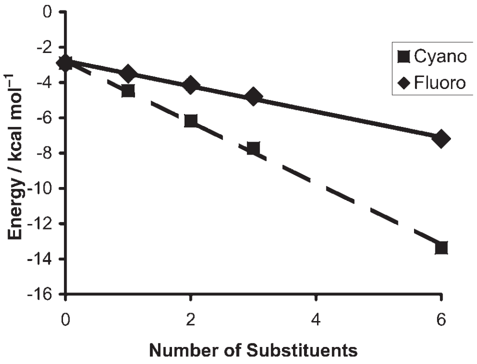

Figure 4. Total interaction energy versus number of substituents (through hexasubstitution) for sandwich configurations.

0.64; -CN, 1.61; -NH_2, 0.69 kcal mol^{-1}). These values are in good agreement with the value simply determined from the monosubstituted system by subtracting the total interaction energy of benzene dimer from the interaction energy of the monosubstituted dimer (see Table 1). This indicates that interaction energies of these heterodimers might be accurately estimated by using only information from the monosubstituted dimers. The results for multiple fluorination are of particular interest, because they relate to the NMR experiments on multiply fluorinated, biarylnaphthalenes by Cozzi, Siegel, and co-workers.[6] Those experiments indicated that the barrier to rotation about the aryl–naphthyl bond was increased by 0.5 kcal mol^{-1} for each fluorine substituent (presumably due to increased π–π interactions between the two aryl groups). We also find a near-linearity in the energies for multiple fluorinations, with the π–π interaction increasing by 0.6 kcal mol^{-1} per fluorine substituent, in excellent agreement with experiment.

Like the changes in the energies, the optimum geometries also show a systematic pattern with respect to the number of substituents. For monosubstituted dimers, the optimized distance between the rings ranges from 3.80 (benzene dimer) to 3.65 Å (benzene–benzonitrile and benzene–aniline). However, in nearly all cases, each additional substituent, regardless of type, decreases the equilibrium distance between the rings by 0.05 Å (note that this is the resolution used in determining the potential curves); for example, the equilibrium distance in benzene–hexacyanobenzene is 0.25 Å less than that in benzene–benzonitrile, which has five fewer CN substituents.

Table 2 presents the SAPT results for the benzene dimer and several fluorinated dimers. In agreement with the MP2/aug-cc-pVDZ supermolecule computations, the SAPT2/cc-pVDZ+ results show that one fluorine substituent in the sandwich fluorobenzene–benzene dimer stabilizes the complex by about 0.6 kcal mol^{-1} relative to the benzene dimer sandwich, and two fluorine atoms in the 1,4-difluorobenzene–benzene dimer lead to almost twice this stabilization. One might suppose that this doubling of the stabilization might be reflected in each of the SAPT energy components, but this is not the case. For example, considering the electrostatic stabilization of substitution relative to the sandwich benzene dimer, we find that it is −1.145 kcal mol^{-1} for the 1,4-difluorobenzene–benzene dimer, which is significantly more than twice the stabilization of −0.395 kcal mol^{-1} found for the fluorobenzene–benzene dimer. On the other hand, the change in the induction term relative to benzene dimer is almost the same for both fluorinated dimers. Both the exchange–repulsion and dispersion terms are much larger in magnitude for the 1,4-difluorobenzene–benzene sandwich, because its shorter intermonomer distance leads to greater overlap between the π clouds.

Although the effect of substituents on the individual SAPT components is not additive, the additivity of substituent effects on the total interaction energies for the sandwich dimers remains very encouraging. However, so far we have considered only dimers in which one ring has been substituted and which feature only one type of substituent. Let us now consider mixed sandwich dimers with two different types of substituents (Figure 2) and/or substituents on both

Table 2. Physical components [in kcal mol^{-1}] of total interaction energy determined using SAPT for benzene and substituted fluorobenzene dimers.[a,b]

	R	Elst.	Exch.	Ind.	Disp.	SAPT2
benzene–benzene(S)	3.70	−0.974	6.034	−0.331	−6.528	−1.799
fluorobenzene–benzene(S)	3.70	−1.369	5.890	−0.305	−6.630	−2.414
difluorobenzene–benzene(S)	3.65	−2.119	6.425	−0.311	−7.012	−3.017
fluorobenzene–fluorobenzene(S aligned)	3.70	−1.066	5.582	−0.237	−6.538	−2.259
fluorobenzene–fluorobenzene(S anti)	3.65	−2.068	6.412	−0.285	−7.013	−2.954
benzene–benzene(T)	4.90	−2.244	4.865	−0.670	−4.367	−2.416
fluorobenzene–benzene(T)	5.00	−1.639	3.777	−0.487	−3.876	−2.225
fluorobenzene–benzene(T(a))[c]	5.00	−1.748	3.778	−0.483	−3.867	−2.320
difluorobenzene–benzene(T)	5.00	−1.368	3.706	−0.420	−3.834	−1.916

[a] All data computed by using cc-pVDZ+ with optimized MP2/aug-cc-pVDZ monomer geometries with optimum intermonomer separations. [b] S = sandwich configuration; T = T-shaped configuration. [c] Configuration depicted by rightmost dimer in Figure 2.

rings. Table 3 presents equilibrium intermonomer distances and changes in the interaction energy due to substitution for five mixed sandwiches. The table also includes the change in the interaction energy, which would be predicted by adding the average energy lowering of each substituent derived from the slopes of the graphs in Figures 3 and 4. For the dimers of benzene with *para*-disubstituted benzene, the predicted energy lowering is very close to that which is explicitly computed (within 0.1 kcal mol^{-1}). However, when the substituents are placed on two different monomers, significant deviations from the predicted values appear for the aligned CN/F, CN/CN, F/F, and NH_2/F cases. We note that the strongest deviations from the ideal values are observed when both substituents are strongly electron donating or strongly electron withdrawing; mixed cases involving methyl substituents follow the ideal behavior.

Table 3. Optimum intermonomer distances [R in Å] and changes in interaction energies [in kcal mol^{-1}, relative to benzene dimer] for mixed-substituent sandwich heterodimers.[a]

	Predicted[b]	1,4-Substitution		Aligned		Anti-aligned	
	$\Delta\Delta E_{int}$	R[c]	$\Delta\Delta E_{int}$	R[c]	$\Delta\Delta E_{int}$	R[c]	$\Delta\Delta E_{int}$
NH_2 and CH_3	−1.35	3.65	−1.33	3.75	−1.30	3.65	−1.32
CN and CH_3	−2.30	3.65	−2.25	3.75	−2.23	3.65	−2.20
CN and F	−2.28	3.60	−2.25	3.65	−0.98	3.60	−2.10
CN and CN	−3.28	3.60	−3.28	3.70	−0.75	3.60	−2.89
NH_2 and F	−1.33	3.60	−1.26	3.70	−0.52	3.60	−1.34
F and F	−1.28	3.65	−1.24	3.70	−0.49	3.65	−1.17

[a] All data computed at MP2/aug-cc-pVDZ level of theory; interaction energy of benzene dimer at this level is −2.90 kcal mol^{-1}. [b] Determined by adding the average change in interaction energies for each substituent as determined from Figures 3 and 4. [c] Equilibrium monomer separation (using rigid monomers).

To determine the cause of this deviation from the predicted additivity, we again turn to SAPT analysis to obtain the physical components of the total interaction energy. The aligned fluorobenzene–fluorobenzene dimer was taken as representative of a nonadditive case, and SAPT results for the aligned and anti-aligned configurations of this dimer are compared to the 1,4-difluorobenzene–benzene dimer in Table 2. Comparing the three cases, all components of the 1,4-substituted and the anti-aligned dimers are almost identical, thus they have nearly the same total interaction energy. However, for the aligned dimer, the electrostatic contribution is less stabilizing than the 1,4-substituted or the anti-aligned dimer by approximately 1 kcal mol^{-1}, despite the fact that two fluorine atoms in any configuration should withdraw electron density from the π cloud in about the same way. We attribute this difference to the direct fluorine–fluorine interaction of the aligned dimer, which would have a much less favorable electrostatic contribution than a fluorine–hydrogen interaction in the 1,4-substituted or anti-aligned dimers. Partially compensating for this electrostatic destabilization is the significant reduction in the exchange–repulsion term (0.8 kcal mol^{-1}) due to the greater intermonomer separation in the aligned dimer. However, the greater distance also leads to a significant decrease (0.5 kcal mol^{-1}) in the dispersion stabilization, so that the aligned case is about 0.7 kcal mol^{-1} destabilized relative to the anti-aligned case. We note that all of the aligned sandwich dimers have intermonomer distances that are at least 0.05 Å greater than those of the corresponding anti-aligned dimers.

T-shaped dimers: As we have discussed previously,[22] the effect of substituents on the binding energies of T-shaped dimers might be thought of, to a first approximation, in terms of the favorable electrostatic interaction between the negatively charged π cloud of the lower ring and the positively charged hydrogen atom of the other ring above it. One might then expect substituents on the lower ring to strengthen or weaken this interaction depending on how they tune the negative charge of the π cloud. Our previous analysis[22] shows that this picture is somewhat oversimplified. First, the nominally electron-donating substituent −OH does not lead to any significant change in binding (although this is consistent with the electrostatic potential of phenol, which is very similar to that of benzene in the middle of the ring); second, $-CH_3$ substitution leads to significantly increased binding due to changes in the dispersion term, not the electrostatic term. T-shaped interactions are also sometimes described in terms of their favorable quadrapole–quadrapole interactions, but our analysis shows a lack of correlation between calculated quadrapole moments and the electrostatic component of the interaction.

Theoretical results for multiply substituted T-shaped dimers are summarized in Table 4 and Figures 5 and 6. Unlike the corresponding figures for the sandwich configurations, the energy shows significant nonlinearity as the number of substituents (n) increases from 0 to 6. However, the plots in Figures 5 and 6 are nearly linear through disubstitution (n = 0–2), suggesting that a new effect becomes operative for dimers with three or more substituents. In the T-shaped configuration, there is a possibility for direct interactions between the functional groups of the substituted benzene rings and the hydrogen atoms of the upper benzene ring that would cause deviations from additivity. Such interactions would not be present in the mono- and disubstituted dimer configurations we considered, but two interactions would be present in the trisubstituted dimers and four such

Table 4. Optimum intermonomer distances [in Å] and changes in interaction energies [in kcal mol^{-1}, relative to benzene dimer] for T-shaped heterodimers of benzene with multiply-substituted benzenes[a]

	$n=1$		$n=2$		$n=3$		$n=6$	
	R[b]	$\Delta\Delta E_{int}$	R[b]	$\Delta\Delta E_{int}$	R[b]	$\Delta\Delta E_{int}$	R[b]	$\Delta\Delta E_{int}$
H	5.00	0.00						
OH	4.95	−0.02	4.95	−0.09	4.95	−0.22		
CH_3	4.90	−0.39	4.90	−0.72	4.85	−0.99		
F	5.00	0.33	5.00	0.56	5.00	0.64	5.00	0.90
CN	4.95	0.39	4.95	0.57	4.95	0.32	5.00	−0.68
NH_2	4.95	−0.16	4.90	−0.22	4.90	−0.90		

[a] All data computed at MP2/aug-cc-pVDZ level of theory; interaction energy of benzene dimer at this level is −3.16 kcal mol^{-1}. [b] Equilibrium monomer separation (using rigid monomers).

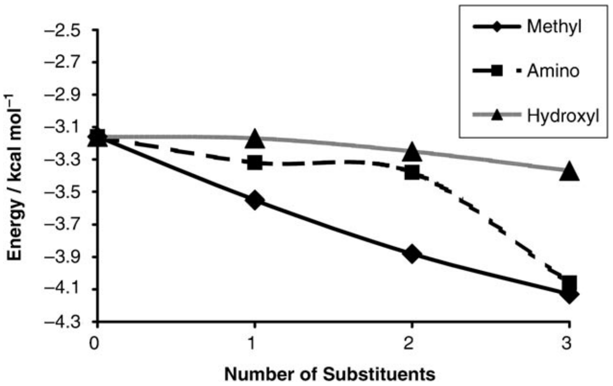

Figure 5. Total interaction energy versus number of substituents (through trisubstitution) for T-shaped configurations.

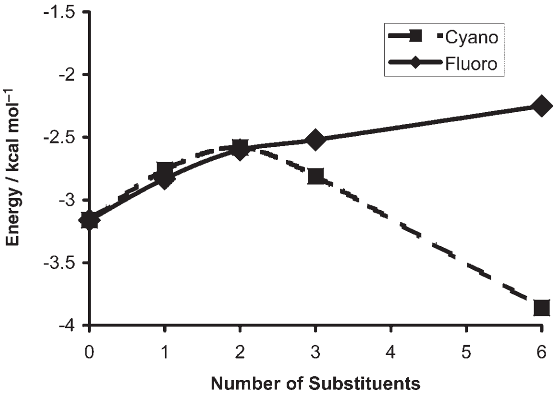

Figure 6. Total interaction energy versus number of substituents (through hexasubstitution) for T-shaped configurations.

interactions for hexasubstituted dimers (see Figures 1 and 2). This type of direct substituent interaction would cause an electrostatic stabilization with respect to an otherwise identical dimer, the geometry of which did not provide such an interaction. SAPT analysis comparing the T-shaped and T-shaped(a) configurations (Figure 2) of the fluorobenzene–benzene dimer is presented in Table 2. The exchange, induction, and dispersion contributions to the total interaction energy are the same for both configurations, but the electrostatic contribution is stabilized by approximately 0.1 kcal mol^{-1}, which is consistent with a direct interaction between a partially positive hydrogen and a partially negative fluorine atom.

SAPT energy analysis also reveals important differences in the ways that substituents affect different dimer configurations. Comparing results for the T-shaped fluorobenzene–benzene and 1,4-difluorobenzene–benzene dimers from Table 2, the only component that changes significantly with the addition of the second fluorine atom is the electrostatic contribution, with a destabilization of almost 0.30 kcal mol^{-1} that accounts for essentially the entire difference in the total interaction energy. Interestingly, the exchange–repulsion contribution, which changes by about 0.6 kcal mol^{-1} with the addition of a second fluorine atom in the sandwich configuration dimers, is now largely unchanged by the second fluorination in a T-shaped configuration. We attribute this difference to the sandwich configurations of these dimers having different intermonomer separations, whereas the T-shaped configurations do not.

Because the T-shaped dimers do not exhibit full additivity through hexasubstitution, a simple extrapolation of interaction energies from monosubstituted dimers will not capture the correct trend as it did for the sandwich dimers. One factor we must account for is the number of direct interactions between substituents on one ring and the hydrogen atoms of the other ring, as discussed above (in the sandwiches we considered, this direct interaction is *always* present). However, even after these direct interactions are accounted for, we fail to observe a linear relationship between substituent effects on binding and the number of substituents; we therefore considered somewhat more complex models. In our previous work,[22] we used a linear model to fit interaction energies of monosubstituted T-shaped benzene dimers to the Hammett constants of the substituents, but we found only a rough correlation with σ_m. Because SAPT analysis showed that the two components of interaction energy most relevant in determining changes caused by substituents are dispersion and electrostatic energies, in this work we develop a physically motivated multilinear model that uses parameters corresponding to both these interactions. Williams and Lemieux[27] advanced a similar idea in a study in which they measured the shift in clearing point caused by dopant–host interactions in nematic liquids. Taking this shift as a measure of the interaction, they used a multilinear model to describe this clearing point shift as a function of the HOMO energy for the dopant molecule and the calculated molecular polarizability. Our model predicts the strength of the π–π interaction directly by fitting to the Hammett σ_m parameters to describe the electrostatic character of the substituent and experimentally determined molecular polarizabilities to account for the dispersive interaction. The σ_m parameters primarily capture a substituent's inductive effect, and they roughly correlate with the electrostatic potentials of substituted benzenes and with the electrostatic components of π–π interactions;[22] Mecozzi, West, and Dougherty found similar results in studies for cation–π interactions.[38]

The interaction energies (relative to benzene dimer) of the substituted, T-shaped Ph−X$_n$–benzene dimers (with substituents on the lower ring) were fitted to a linear combination of these parameters [Eq. (4)].

$$\Delta\Delta E_{\text{int}} = a \sum \sigma_{\text{m}} + b\,\Delta\alpha + d\,\delta \tag{4}$$

In Equation (4) $\Sigma\sigma_m$ is the sum of the Hammett parameters for all substituents, $\Delta\alpha$ is the change in the experimentally determined scalar molecular polarizability (in 10^{-24} cm^3) relative to benzene, and δ is a parameter to account for the direct interactions between substituents of one ring and hydrogen atoms of the other, as described above. The coefficient *d* designates the number of these direct interactions, which for our configurations are $d=2$ for trisubstituted dimers and $d=4$ for hexasubstituted dimers. The experimental scalar polarizability values[39] were obtained from reference [40]. To determine the value of the δ parameter, the total interaction energy was determined for another series of monosubstituted dimers in which the functional group of the substituted ring was placed closer to the interacting hydrogen atoms of the other ring (see rightmost dimer of Figure 2), but the rest of the geometry, including the intermonomer separation, was kept constant. The difference in the interaction energies of this configuration and the original T-shaped configuration is taken as value of a direct interaction (δ) and shown in Table 5.

Table 5. Interaction energies [kcal mol^{-1}] used to determine the direct interaction parameter (δ).

	T-shaped[a]	T-shaped(a)[b]	δ[c]
OH	−3.17	−3.10	0.07
CH_3	−3.55	−3.47	0.08
F	−2.83	−2.93	−0.10
CN	−2.76	−2.95	−0.19
NH_2	−3.32	−3.48	−0.16

[a] From Table 4. [b] Interaction energy of configuration shown in Figure 2 using intermonomer separations of T-shaped configuration from Table 4. [c] Determined as the difference between the T-shaped and T-shaped(a) configurations.

The coefficients a and b were determined by fitting to the MP2/aug-cc-pVDZ $\Delta\Delta E_{int}$ values for all substituted T-shaped dimers for which experimental monomer polarizabilities were available. This yielded values of $a=0.708$ kcal mol^{-1} and $b=-0.052$ kcal mol^{-1} 10^{24} cm^{-3}.

Figure 7 compares the predictions of the model to the explicitly computed MP2/aug-cc-pVDZ results. We obtain an R^2 of 0.83 for the line $y=x$, which would indicate a perfect coincidence of the $\Delta\Delta E_{int}$ values predicted by the model with those computed by the MP2 method. This value is rather similar to the R^2 of 0.81 obtained by Williams and Lemieux[27] in their fit of clearing point shifts due to substituents effects in π–π interactions in nematic liquids crystals. The largest discrepancy is for benzene–dimethylbenzene, for which the model predicts a $\Delta\Delta E_{int}$ of −0.31 compared to a value of −0.72 kcal mol^{-1} computed at the MP2/aug-cc-pVDZ level of theory. Given the crudity of the model and its reliance on experimental polarizabilities, which may be off by as much as 30%,[40] the quality of the fit is quite good, and we believe it may be useful in providing semiquantitative estimates of how substituents may tune the strength of T-shaped π–π interactions.

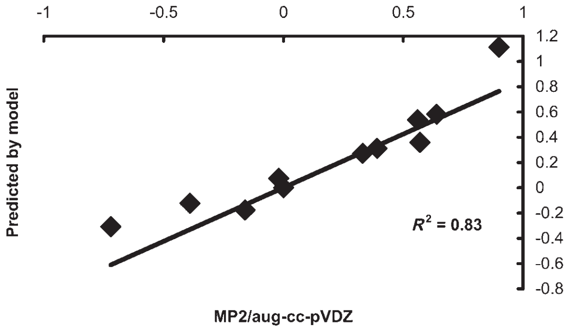

Figure 7. $\Delta\Delta E_{int}$ predicted by the simple model versus $\Delta\Delta E_{int}$ explicitly computed at the MP2/aug-cc-pVDZ level of theory.

Conclusion

In this work, we have explored how multiple substituents may tune π–π interactions. Such knowledge is foundational for rational drug design, crystal engineering, and supramolecular chemistry. We have used reliable ab initio quantum-mechanical methods to assess how substitution changes intermolecular geometries and binding energies in face-to-face (sandwich) and edge-to-face (T-shaped) configurations of substituted benzene dimers. Perhaps surprisingly, substituent effects are nearly additive in many sandwich configurations, allowing one to predict the results of any combination of substituents simply from the changes due to each substituent individually. An exception to this rule is the case in which substituents on different rings are aligned on top of each other, which can cause deviations from additivity. The situation for T-shaped configurations is somewhat more complex, in part because there is the additional complication of having to account for how many contacts a substituent on one benzene ring might make with hydrogen atoms of the other ring. Nevertheless, a simple model involving Hammett σ_m parameters and experimentally determined scalar polarizabilities provides a good fit to the ab initio data for the T-shaped configurations, once again suggesting that the effect of multiple substitution may be simply predicted. Our results underscore the importance of accounting for direct interactions between an aromatic ring and substituents on another ring, as pointed out earlier in experimental studies of parallel-displaced interactions by Rashkin and Waters.[7] The data presented here should provide valuable guidance in how to tune π–π interactions.

Acknowledgements

A.L.R. acknowledges an NSF Graduate Research Fellowship. R.P.L. acknowledges a Georgia Tech PURA fellowship. C.D.S. acknowledges an NSF CAREER Award (Grant No. CHE-0094088). The Center for Computational Molecular Science and Technology is funded through a Shared University Research (SUR) grant from IBM and by Georgia Tech.

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Received: October 21, 2005