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FEATURE ARTICLE

High-Accuracy Quantum Mechanical Studies of $\pi-\pi$ Interactions in Benzene Dimers

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Although supramolecular chemistry and noncovalent interactions are playing an increasingly important role in modern chemical research, a detailed understanding of prototype noncovalent interactions remains lacking. In particular, $\pi-\pi$ interactions, which are ubiquitous in biological systems, are not fully understood in terms of their strength, geometrical dependence, substituent effects, or fundamental physical nature. However, state-of-the-art quantum chemical methods are beginning to provide answers to these questions. Coupled-cluster theory through perturbative triple excitations in conjunction with large basis sets and extrapolations to the complete basis set limit have provided definitive results for the binding energy of several configurations of the benzene dimer, and benchmark-quality ab initio potential curves are being used to calibrate new density functional and force-field models for $\pi-\pi$ interactions. Studies of substituted benzene dimers indicate flaws in the conventional wisdom about substituent effects in $\pi-\pi$ interactions. Three-body and four-body interactions in benzene clusters have also been examined.

I. Introduction

Supramolecular chemistry, or chemistry "beyond the molecule", has been one of the fastest-growing fields of chemical research since the Nobel prize was awarded to Cram, Lehn, and Pedersen in 1987. Broadly defined, supramolecular chemistry encompasses host−guest interactions including drug binding, self-assembly of natural and artificial systems, molecular devices, and crystal engineering.[1,2] Instead of the usual covalent or ionic bonds, a wide variety of weaker intermolecular forces govern supramolecular chemistry. These include hydrogen bonding, $\pi-\pi$, and cation$-\pi$ interactions, among others. Often, several types of noncovalent interactions are operative simultaneously. For example, the anti-Alzheimer's drug Aricept utilizes $\pi-\pi$, O−H/π, and cation$-\pi$ interactions in its binding.[3] Here, we will consider primarily those noncovalent interactions involving aromatic rings, the subject of an excellent recent review by Meyer, Castellano, and Diederich.[3]

These interactions are difficult to study experimentally because they often occur in complex systems where secondary interactions and solvent effects can complicate the interpretation of results.[4,5] Additionally, precise gas-phase studies of small model systems are often challenging[6−11] because of the weak binding and the flatness of the potential energy landscape, which can lead to rapid interconversion of structures which are close in energy. These difficulties mean that our understanding of noncovalent interactions is far from complete. As pointed out by Hunter,[12]

> Noncovalent interactions play a major role in determining the structures and properties of molecular assemblies in biology, chemistry, and materials science. However, they are not well understood. When molecular scientists obtain an unexpected result in a system which contains π systems, they tend to invoke the mythical powers of the "$\pi-\pi$ interaction", "π-stacking", "charge transfer" (CT), "π-acid/π-base", or "electron donor acceptor (EDA) interaction".

Interactions between aromatic groups are among the most important but least understood of the noncovalent interactions. The structures of DNA, RNA, and proteins are stabilized by $\pi-\pi$ interactions,[13−15] and it has been estimated that around 60% of aromatic side chains in proteins participate in $\pi-\pi$ interactions.[14] These $\pi-\pi$ interactions also influence the structures of many host−guest complexes,[16−19] self-assembled supramolecular architectures,[20,21] and organic crystals.[22,20] Many drugs, including anticancer agents which intercalate into DNA,[23] utilize $\pi-\pi$ interactions in their binding.

An improved understanding of noncovalent interactions would greatly aid the rational design of supramolecular architectures, crystal engineering, and drug design. In principle, theoretical quantum mechanical models are very useful in this regard because they can directly provide the intrinsic strength and geometrical preferences of these interactions as found in small model systems. They can also determine the relative importance of the fundamental forces that make up these interactions: electrostatic, induction, dispersion, and exchange−repulsion forces. In practice, the theoretical modeling of intermolecular interactions, even using advanced ab initio quantum mechanical methods, is very challenging, as discussed in several recent

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reviews.[11,24−26] The present article describes our efforts to understand the fundamental aspects of $\pi-\pi$ interactions using a variety of ab initio methods, including at times those which approach the exact solution to the electronic Schrödinger equation (the "ab initio limit").

After describing the theoretical and technical challenges in obtaining reliable theoretical results for noncovalent interactions, we will discuss high-level computations of potential energy curves for the benzene dimer, the simplest model of aromatic $\pi-\pi$ interactions. We also discuss the additivity of $\pi-\pi$ interactions as determined by studies of benzene trimers and tetramers. Studies of substituted benzene dimers allow us to learn how substituents can tune $\pi-\pi$ interactions, a critical topic for the rational design of supramolecular systems. Our theoretical findings are at odds with the most commonly used qualitative model of $\pi-\pi$ interactions, the Hunter−Sanders model.[27] They are, however, in accord with some recent experiments.[28,29] We conclude by summarizing our experience with the model systems considered and by commenting on the prospects for more computationally affordable models of these interactions.

Although this article focuses on recent contributions from our own laboratory, we would like to emphasize that a large number of theoretical studies have examined $\pi-\pi$ interactions in general and the benzene dimer in particular. Among many important contributions, in 1996, Jaffe and Smith[30] provided a rather extensive study of the potential energy landscape of the benzene dimer at reasonable levels of theory [MP2/6-311G-(2d,2p) and better]. This study, and also key studies by Hobza et al.[31] and by Tsuzuki et al.,[32,33] demonstrated that MP2 overestimates the effects of electron correlation in such systems. In more recent work, a number of high-quality studies of the benzene dimer[34] or nucleic acid dimers[35−39] have been performed by Hobza, Šponer, and co-workers. Very accurate computations of the benzene dimer have also been reported by Tsuzuki et al.;[40,41] these studies neglect "explicitly correlated" (R12) terms and use somewhat less extensive basis sets compared to our studies, but they yield results in good agreement with ours. Tsuzuki has published an excellent high-level study of the toluene dimer,[42] and the more general question of substituent effects has also been considered by K. S. Kim and co-workers.[43] There are, of course, many other informative studies in this area which are simply too numerous to list here; the interested reader is referred to review articles by Hobza, Selzle, and Schlag;[44] by Kim, Tarakeshwar, and Lee;[24] and by Meyer, Castellano, and Diederich.[3]

II. Theoretical Methods

As mentioned above, even ab initio quantum mechanical methods have difficulty in properly modeling intermolecular interactions. The primary problem is that London dispersion forces (van der Waals forces) are important or even dominant in many of these interactions, yet they are absent from many popular ab initio models. Dispersion forces are caused by favorable instantaneous multipole/induced multipole charge fluctuations. Hartree−Fock molecular orbital theory describes the motion of each electron in the *average* field of the other electrons, so it is incapable of describing the instantaneous correlated motions of electrons which give rise to dispersion forces. Although current implementations of Kohn−Sham density functional theory[45] (DFT) include some description of electron correlation, they do not include long-range, nonlocal terms necessary to properly model dispersion interactions.[33,46,47] Hence, Hartree−Fock and DFT methods should not be used in studies of intermolecular interactions unless it is known that dispersion interactions are relatively unimportant in the systems of interest (a criterion which seems hard to confirm without explicit computations using better theoretical methods). This shortcoming of DFT has captured the interest of several theorists who have begun working on modified density functional methods which are capable of describing dispersion effects.[48−53] Many of these studies have leveraged our high-quality ab initio results for the benzene dimer as a useful benchmark.

Any ab initio quantum mechanical modeling of noncovalent interactions, then, ought to include a description of electron correlation in order to capture the dispersion interactions. This can be accomplished most easily using second-order Møller−Plesset perturbation theory (MP2), which approximately accounts for uncoupled, two-body electron correlations. Previous ab initio studies, however, indicate that MP2 tends to overestimate binding in noncovalent interactions.[30−33] One way to improve upon the MP2 model of electron correlation is to include the coupling between electron pairs via coupled-cluster theory with single and double substitutions (CCSD).[54] Further improvements are afforded by the perturbative estimate of three-body correlations included in the CCSD(T) method.[55] So long as there are no electronic near-degeneracies, such as those that occur in bond-breaking reactions or first-row transition metals, the CCSD(T) method is very reliable and has been referred to as a "gold standard" of quantum chemistry. A recent study of small, weakly bound dimers by Hopkins and Tschumper indicates that CCSD underbinds about as much as MP2 overbinds and only CCSD(T) is capable of providing very accurate binding energies.[56] These authors also estimated that the effect of four-body electron correlation, which is neglected in the CCSD(T) method, is very small but perhaps not completely negligible (this contribution to the binding energy of some small dimers was on the order of 0.1 kcal mol^{-1}, or around 5%). It is unfortunate, then, that highly accurate ab initio studies of noncovalent interactions would seem to require using the CCSD(T) approach, which is very expensive computationally; the time required to perform the computation scales as $\mathcal{O}(N^7)$, where N is proportional to the size of the molecule. This indicates that a calculation that runs in 1 day for a monomer would require on the order of 128 days for the dimer!

Yet another challenge for theoretical studies of weakly bound systems is that the dispersion energy is related to the polarizability of the monomers, and accurate estimates of polarizabilities can require very large basis sets including multiple polarization and diffuse functions. Several studies of weak interactions indicate the importance of using large basis sets (e.g., refs 30, 33, 57−59), but when we began our investigations of $\pi-\pi$ interactions, no studies of those systems had used a basis set large enough to give one confidence that the complete basis set (CBS) limit had been closely approximated. In principle, a complete treatment of electron correlation and a complete basis set would constitute an exact numerical solution to the electronic Schrödinger equation, which is what we will term the "ab initio limit". Theoretical predictions approaching this quality are extremely reliable, having an error comparable to experimental errors in some cases (see, e.g., refs 60−65). Although it is currently impossible to directly estimate the ab initio limit for most of the interesting prototypes of noncovalent interactions, due to the prohibitive computational cost of electron correlation methods going beyond CCSD(T), the results of Hopkins and Tschumper[56] indicate that estimates of the CCSD(T) CBS limit will only miss the ab initio limit for binding energies by about 5% or less.

One of our goals, then, has been to obtain the first reliable estimates of the CCSD(T) CBS limit for prototypes of $\pi-\pi$ and other noncovalent interactions. The literature suggests at least two ways to obtain good estimates of the CCSD(T) CBS limit. First, Dunning and co-workers have introduced a family of basis sets, the "correlation-consistent" basis sets,[66−70] which are specifically designed to systematically approach the CBS limit as larger and larger basis sets from the family are employed (see ref 26 for an excellent review). The convergence behavior of these basis sets is often so smooth that the correlation energy can be extrapolated to the CBS limit using results from two or more of these basis sets.[71] Second, the "explicitly correlated, linear-R12" methods of Kutzelnigg and Klopper[72−74] provide a way to accelerate the convergence of correlated methods to the CBS limit. Unfortunately, the advantages of this approach are not achieved until one has already used rather large basis sets, but promising new algorithms have been proposed over the past few years.[75−79]

In principle, either CCSD(T)-R12 computations or a series of CCSD(T) computations with increasingly larger correlation-consistent basis sets would provide good estimates of the CCSD(T) CBS limit. In practice, for most interesting prototypes of noncovalent interactions, the CCSD(T) computations are too difficult to perform except with small basis sets. To solve this problem, we employ an "additive" approach, which rests on the fact that higher-order electron correlation effects tend to be very insensitive to improvements in the basis (this is the foundation of the Gaussian-*n* approach to thermochemistry[80,81] and of the "focal point" approach of Allen and co-workers).[82,83] We therefore expect that the energy difference between CCSD(T) and MP2, denoted as ΔCCSD(T), will not change significantly when computed with larger and larger basis sets, so long as a certain minimum quality in the basis set is achieved. This allows us to estimate energies for CCSD(T) in a large basis by computing the MP2 energy in the large basis and adding the "coupled-cluster correction", ΔCCSD(T), computed in a smaller basis:

$$E_{\mathrm{CCSD(T)}}^{\mathrm{large-basis}} \approx E_{\mathrm{MP2}}^{\mathrm{large-basis}} + \Delta\mathrm{CCSD(T)} \quad (1)$$

$$\Delta\mathrm{CCSD(T)} = E_{\mathrm{CCSD(T)}}^{\mathrm{small-basis}} - E_{\mathrm{MP2}}^{\mathrm{small-basis}} \quad (2)$$

In a recent study of the benzene dimer,[84] we demonstrate that this correction is very well converged (to within a few hundredths of a kcal mol^{-1}) when one uses a basis set as small as aug-cc-pVDZ for C and cc-pVDZ for H, but moderate basis sets which lack any diffuse functions at all (such as cc-pVDZ and cc-pVTZ) are insufficient to converge ΔCCSD(T).

Although the coupled-cluster correction, ΔCCSD(T), converges rapidly with respect to the basis set, the overall CCSD(T) or MP2 binding energies for weakly bound complexes do not. The basis set superposition error, which results from the use of an incomplete basis set, can have a particularly large effect on the binding energies of weakly bound complexes. Binding is artificially strengthened (and intermonomer distances are artificially shortened) in finite-basis computations of complexes because each monomer moves closer to the others in an attempt to access some of their basis functions. One remedy for this is the Boys−Bernardi counterpoise correction,[85] which is a simple procedure for estimating the size of the basis set superposition error. Unfortunately, theorists and computational chemists often have strongly conflicting opinions about the efficacy of the counterpoise correction for weakly interacting systems. Dunning[26] has noted that counterpoise-corrected energies often converge more smoothly to the CBS limit, but "overcorrection" can lead to larger errors for smaller basis sets. Indeed, this behavior is observed for hydrogen-bonded complexes.[59] However, the performance of the counterpoise correction differs from system to system, and our own experience clearly demonstrates that the counterpoise-corrected energies converge much more rapidly for the benzene dimer.[84,86] All results discussed in this article have been obtained using the counterpoise correction unless otherwise noted.

We have performed large-scale conventional MP2 and CCSD(T) computations using several program packages: MOLPRO,[87] PSI3,[88] Q-Chem,[89] ACES II,[90] and MPQC.[91,92] In addition, to more fully explore convergence toward the CBS limit, Kutzelnigg and Klopper's MP2-R12/A approach[72] was implemented[86] in a shared-memory parallel algorithm in PSI3 to allow large-scale computations on the benzene dimer.

In addition to obtaining converged binding energies, we also wish to analyze the results in terms of the fundamental intermolecular forces: electrostatics, dispersion, exchange−repulsion, and induction. For this purpose, we have found symmetry-adapted perturbation theory (SAPT)[93] to be very helpful. In SAPT, the dimer Hamiltonian is composed of three operators: $H = F + W + V$, where F is the Fock operator, written as the sum of Fock operators for separate monomers; W is the intramonomer correlation operator; and V is the intermolecular correlation operator. The SAPT interaction energy may be represented as

$$E_{\rm int} = E_{\rm int}^{\rm HF} + E_{\rm int}^{\rm corr} \tag{3}$$

where $E_{\rm int}^{\rm HF}$ is the Hartree−Fock level of description which can be represented as

$$E_{\rm int}^{\rm HF} = E_{\rm elst}^{(10)} + E_{\rm exch}^{(10)} + E_{\rm ind,resp}^{(20)} + E_{\rm exch-ind,resp}^{(20)} + \delta E_{\rm ind,resp}^{\rm HF} \tag{4}$$

The superscripts (nm) denote orders in perturbation theory with respect to the operators V and W, respectively. The subscript "resp" indicates the inclusion of the coupled-perturbed Hartree−Fock response.[94] Note that, in addition to electrostatic, exchange, and induction terms, there is also an "exchange−induction" cross term. The final term contains third- and higher-order HF induction and exchange−induction contributions.

Our SAPT studies to date have treated the correlation energy using second-order many-body perturbation theory, which is technically designated as SAPT2.[93] The correlation energy obtained is equivalent to the supermolecular MP2 correlation energy and can be represented as

$$E_{\rm int}^{\rm corr} = E_{\rm elst,resp}^{(12)} + E_{\rm exch}^{(11)} + E_{\rm exch}^{(12)} + {}^{t}E_{\rm ind}^{(22)} + {}^{t}E_{\rm exch-ind}^{(22)} + E_{\rm disp}^{(20)} + E_{\rm exch-disp}^{(20)} \tag{5}$$

The particular meaning of each of these terms is discussed fully in ref 93, but note that the dispersion interaction first appears in $E_{\rm int}^{\rm corr}$ and note again the presence of cross terms (exchange−induction and exchange−dispersion). Our analyses to date have chosen (somewhat arbitrarily) to categorize the SAPT2 terms as follows:

$$E(\text{electrostatic}) = E_{\rm elst}^{(10)} + E_{\rm elst,resp}^{(12)} \tag{6}$$

$$E(\text{exchange}) = E_{\rm exch}^{(10)} + E_{\rm exch}^{(11)} + E_{\rm exch}^{(12)} \tag{7}$$

$$E(\text{induction}) = E_{\rm ind,resp}^{(20)} + E_{\rm exch-ind,resp}^{(20)} + \delta E_{\rm int,resp}^{\rm HF} + {}^{t}E_{\rm ind}^{(22)} + {}^{t}E_{\rm exch-ind}^{(22)} \tag{8}$$

$$E(\text{dispersion}) = E_{\rm disp}^{(20)} + E_{\rm exch-disp}^{(20)} \tag{9}$$

All of our SAPT2 results have been performed using the SAPT2002 program.[95]

III. Results and Discussion

A. $\pi-\pi$ Interactions in the Benzene Dimer. Perhaps surprisingly, the simplest example of aromatic−aromatic $\pi-\pi$ interactions, the benzene dimer, was not definitively characterized until recently.[86] The previous section outlines some of the theoretical challenges. Many excellent theoretical studies have shed light on the benzene dimer (see, for example, refs 30−33, 40, 58, and 96), and the importance of using large basis sets[30,33,58] and extensive treatments of electron correlation[30−33] in particular have been highlighted. However, previous work had not applied highly correlated methods such as CCSD(T) in conjunction with truly large basis sets (including multiple diffuse functions) large enough to give one confidence that the CBS limit had been reached. Experimentally, its small binding energy (2−3 kcal mol^{-1}) makes the benzene dimer stable only at low temperatures, and mass selection techniques must be used to select only dimers and not larger clusters. Various experimental studies have yielded seemingly contradictory results which are consistent only if there are two or more low-energy minima or if the system is highly fluxional with low barriers.[30] Experimental studies of the binding energy (measured indirectly from the dissociation energy of the cation and the ionization potentials of the dimer and monomer) give answers ranging from $D_0 = 1.6 \pm 0.2$ kcal mol^{-1} (Krause et al.[97]) to 2.4 ± 0.4 kcal mol^{-1} (Grover et al.[98]), a large difference for this weak interaction.

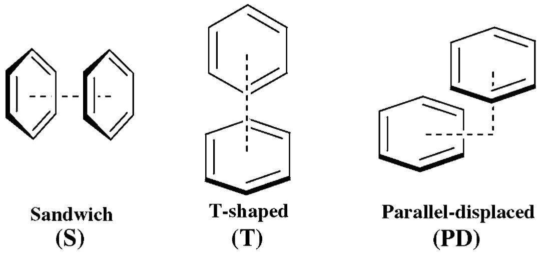

Figure 1. Selected configurations of the benzene dimer.

Most studies discuss three prototype configurations, which are displayed in Figure 1. The sandwich (S) configuration places both benzenes on top of each other, the T-shaped (T) configuration has one benzene pointed at the center of the other ring, and the parallel-displaced (PD) configuration is reached from the sandwich configuration by a parallel shift of one ring away from the other. The sandwich configuration, having maximal overlap, might appear to be the most favorable for maximizing dispersion interactions, but it is rarely (if ever) observed in systems containing phenyl rings, whereas approximately perpendicular or parallel-displaced configurations are often seen in the crystal structures of small aromatic compounds[15,22] or in pairs of interacting aromatic side chains in proteins.[14,15] We should note that, when the monomers are at their equilibrium separation, many minor variations in the geometries of these prototype configurations (e.g., eclipsed vs staggered hydrogens in the sandwich) are not energetically significant.

Molecular beam electric resonance studies by Klemperer and co-workers[99,100] indicated a T-shaped configuration for the benzene dimer, and a rotational spectrum of this configuration was measured by Arunan and Gutowsky,[101] giving a separation between the centers of the rings of 4.96 Å. However, because these experiments were sensitive only to molecules with dipole moments, they did not rule out the possible existence of the parallel-displaced or sandwich configurations. Spectra obtained by Felker et al.[6] using mass-selected stimulated Raman spectroscopy were consistent with configurations without symmetry-equivalent monomers (e.g., the T-shaped form). However, optical absorption spectra by Bernstein and co-workers[102] and multiphoton ionization studies by Schlag and co-workers[103] supported configurations with symmetry-equivalent monomers. Hole-burning experiments[104] were consistent with the existence of three different dimer configurations.

The experimental account of the benzene dimer clearly leaves many fundamental questions about energetics and geometric dependence unanswered, providing a challenging opportunity for theory. In our first study of the benzene dimer,[86] one question we addressed was the basis set dependence of the potential energy as a function of intermonomer distance. After conducting tests which indicated that monomer geometries relax very little in the dimer, we computed MP2 potential energy curves using rigid monomers for the three configurations in Figure 1. The potentials were evaluated using both aug-cc-pVDZ and aug-cc-pVTZ basis sets, the latter being by far the largest basis set used to that point to investigate geometry effects in the benzene

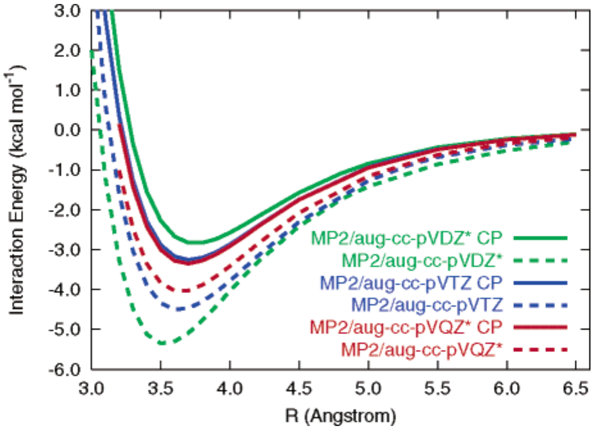

Figure 2. Effect of basis set and counterpoise (CP) correction on MP2 potential energy curves for the sandwich configuration of the benzene dimer.

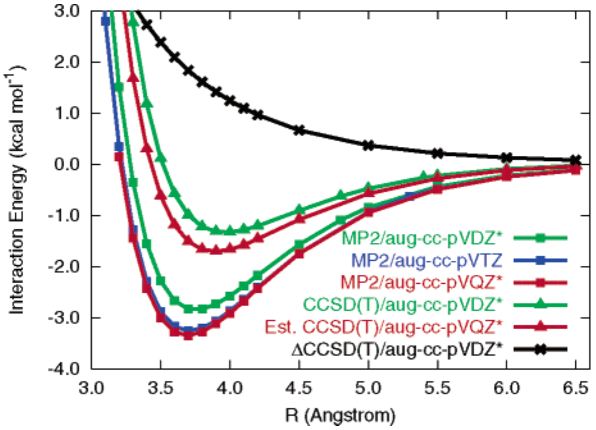

Figure 3. MP2 and CCSD(T) potential energy curves for the sandwich configuration of the benzene dimer. ΔCCSD(T) denotes the difference between CCSD(T) and MP2. All results reflect counterpoise correction.

dimer. Our results indicated that although binding energies are very sensitive to basis set, the intermolecular geometries are not, so long as the counterpoise correction is applied.

More recently, we have obtained[84] MP2 potential curves using a considerably larger basis set which we denote as aug-cc-pVQZ*, which is the usual aug-cc-pVQZ basis without g functions on carbon and f functions on hydrogen. We also considered a truncated aug-cc-pVDZ basis, denoted aug-cc-pVDZ*, which neglects diffuse functions on hydrogen, for the purpose of speeding up the CCSD(T) computations. Our results indicate that these truncations make little difference to the interaction energy for the benzene dimer relative to the full basis sets, consistent with a recent study of truncations of the correlation-consistent basis sets by Mintz, Lennox, and Wilson.[105] MP2 potential curves with the aug-cc-pVDZ*, aug-cc-pVTZ, and aug-cc-pVQZ* basis sets are presented in Figure 2 for the sandwich configuration. At least two conclusions are immediately apparent from the figure: (1) the counterpoise-corrected energies are much more rapidly convergent than the uncorrected energies; (2) there is a significant improvement in binding energies on going from double-ζ to triple-ζ basis set, but the counterpoise-corrected triple-ζ results already appear to be converged to within a few tenths of 1 kcal mol^{-1}.

As mentioned above, MP2 is known to significantly overbind some van der Waals complexes, and this has also been observed for the benzene dimer.[30−33] Hence, it is important to use highly correlated models such as CCSD(T). Figure 3 compares the MP2 and CCSD(T) results for the sandwich benzene dimer. There is a very large difference between MP2 and CCSD(T) in this case, much larger than the changes in the MP2 energies when larger basis sets are used. Hence, theoretical studies of $\pi-\pi$ interactions which stop at the MP2 model of electron correlation must be treated with caution. The difference between CCSD(T) and MP2 in the aug-cc-pVDZ* basis, which is our coupled-cluster correction, ΔCCSD(T), is also displayed in the figure. It is much larger for smaller distances (where electrons are closer together and correlation effects are more significant), and it dies off rapidly to zero at large distances. This correction is accurately determined in the aug-cc-pVDZ* basis, as demonstrated in ref 84 (although if one neglects diffuse functions, significant errors can occur). When this correction is added to the MP2/aug-cc-pVQZ* energies, we approximate the CCSD(T)/aug-cc-pVQZ* results, which should be very accurate indeed.

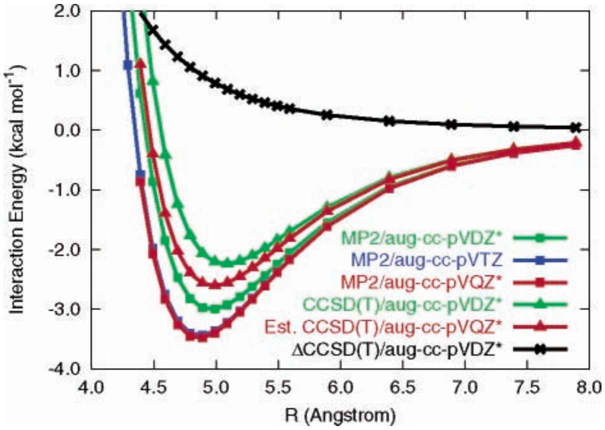

Figure 4. MP2 and CCSD(T) potential energy curves for the T-shaped configuration of the benzene dimer. ΔCCSD(T) denotes the difference between CCSD(T) and MP2. All results reflect counterpoise correction.

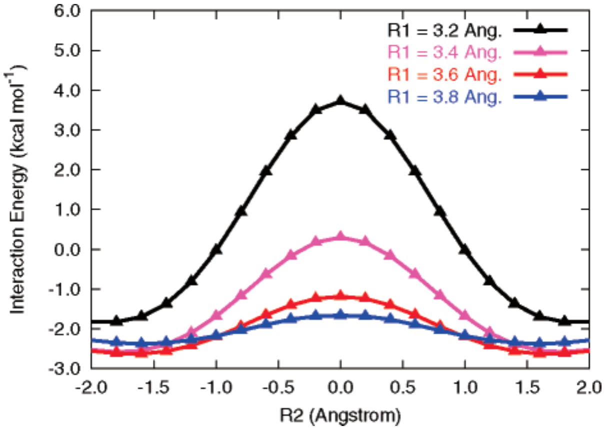

Figure 5. Potential energy curves for the parallel-displaced configuration of the benzene dimer at the (counterpoise-corrected) estimated CCSD(T)/aug-cc-pVQZ* level of theory.

Estimated CCSD(T)/aug-cc-pVQZ* results have also been obtained for the T-shaped and parallel-displaced configurations,[84] and the results are displayed in Figures 4 and 5. The relationships among the different levels of theory appear qualitatively similar in the case of the T-shaped configuration as they do for the sandwich. For the parallel-displaced configuration, we varied both the vertical distance between the rings and the horizontal displacement. We observe that the sandwich configuration, which corresponds to a horizontal displacement of $R2 = 0$, is a saddle point connecting two equivalent lower-energy parallel-displaced configurations. The barrier to interconversion is much higher for smaller vertical distances, $R1$,

TABLE 1: Interaction Energies (kcal mol^{-1}) for the Benzene Dimer[a]

method	basis	S	T	PD
MP2	aug-cc-pVDZ*[b]	−2.83	−3.00	−4.12
	aug-cc-pVTZ	−3.25	−3.44	−4.65
	aug-cc-pVQZ*[c]	−3.35	−3.48	−4.73
CCSD(T)	aug-cc-pVDZ*[b]	−1.33	−2.24	−2.22
estd CCSD(T)/aug-cc-pVQZ*		−1.70	−2.61	−2.63
estd CBS CCSD(T)[d,e]		−1.81	−2.74	−2.78

[a] Unless otherwise noted, all computations used intermonomer distances optimized at each level of theory with rigid monomers ($r_{\text{CC}} = 1.3915$ Å and $r_{\text{CH}} = 1.0800$ Å, ref 106). The data were taken from ref 84 except where noted. [b] This is aug-cc-pVDZ for carbon and cc-pVDZ for hydrogen. [c] This is aug-cc-pVQZ less g functions for carbon and less f functions for hydrogen. [d] At the MP2/aug-cc-pVTZ optimized intermonomer distance (ref 86) with the rigid monomer geometry of ref 106. [e] Estimated as discussed in ref 86.

but for all values of $R1$ considered, the potential becomes fairly flat for horizontal separations, $R2$, around 1.5 Å or larger.

The optimal intermonomer distances for each configuration are presented in ref 84; at our best level of theory, estimated CCSD(T)/aug-cc-pVQZ*, they are 3.9 (S), 5.0 (T), and $R1 = 3.6$ Å and $R2 = 1.6$ Å (PD). Given that our geometries were only resolved to 0.1 Å, we observe excellent agreement with the experimental value for the T-shaped configuration (4.96 Å).[101] Unfortunately, no other experimental geometric data is available for direct comparison; however, our vertical distance of 3.6 Å agrees well with the observation[22] that crystals of many aromatic molecules form stacks with approximately parallel molecular planes separated by 3.3−3.6 Å.

Benzene dimer interaction energies at various levels of theory are presented in Table 1. The table clarifies that the differences between the MP2 energies using the aug-cc-pVTZ and aug-cc-pVQZ* basis sets are only about 0.1 kcal mol^{-1} or less at equilibrium, and the differences between the estimated CCSD(T)/aug-cc-pVQZ* and the more expensive CBS CCSD(T) estimates using MP2-R12 data are only around 0.15 kcal mol^{-1} or less. The observed convergence of our theoretical data gives us confidence that our best estimates of the binding energies are within a few tenths of 1 kcal mol^{-1} of the true values. The most frequently quoted experimental binding energy,[97] $D_0 = 1.6 \pm 0.2$ kcal mol^{-1}, is thus clearly too low. However, the older experimental value[98] of 2.4 ± 0.4 kcal mol^{-1} is well-supported by our data. Note that, contrary to conventional wisdom, our computations do not support the T-shaped configuration being the lowest in energy. Rather, this and the parallel-displaced configurations are nearly isoenergetic; this is consistent with the observation that interacting pairs of phenylalanines in proteins are found in mostly T- and PD-like configurations, although they sample a wide range of conformational space with no strongly preferred single orientation.[15] Of course, the benzene dimer itself will be highly fluxional without a rigid structure.[10]

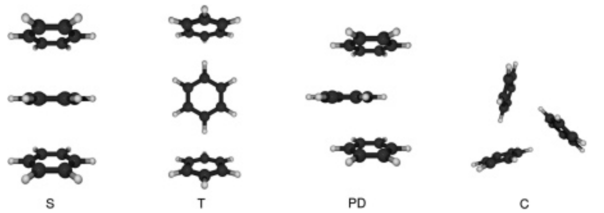

Figure 6. Prototype benzene trimer configurations.

TABLE 2: Total, Two-Body, and Three-Body Interaction Energies (kcal mol^{-1}) of Benzene Trimers at the CCSD(T)/cc-pVDZ+ Level of Theory[a]

	S	PD	T	C
$\Delta^2E(12)$	−0.48	−0.92	−1.62	−1.61
$\Delta^2E(13)$	0.02	−0.01	0.02	−1.61
$\Delta^2E(23)$	−0.48	−0.92	−1.62	−1.61
Δ^2E	−0.94	−1.85	−3.22	−4.84
Δ^3E	0.038	0.014	0.072	−0.250
E_{total}	−0.90	−1.84	−3.14	−5.09
E_{dimer}[b]	−0.86	−1.72	−3.20	−4.62

[a] Data from ref 107. [b] E_{dimer} is the estimated interaction energy based on a sum of nearest-neighbor benzene dimer energies. The interaction energies of the dimer at this level of theory are −0.43 (S), −0.86 (PD), −1.60 (T), and −1.54 kcal mol^{-1} (C).

B. Additivity of π−π Interactions. The previous section discussed the benzene dimer as the simplest prototype of π−π interactions between aromatic rings. However, according to Burley and Petsko, around 80% of aromatic pairs are part of a larger "pair network" involving three or more aromatic rings.[14] To cite just one example, the carp parvalbumin protein (P3CPV) contains a cluster of seven phenylalanines. In such cases, it is conceivable that the presence of a third aromatic ring could significantly polarize the electron distribution in a π−π pair and alter the nature of the interaction. We recently investigated this question[107] by studying benzene trimers and tetramers to see whether their binding departed significantly from what would be expected on the basis of isolated pairs of π−π interactions.

Figure 6 displays a few arbitrarily chosen prototype configurations for the benzene trimer. Experimentally, the cyclic (C) form is thought to be the lowest-energy configuration of the trimer,[108] and indeed, this form has the lowest energy of those considered in our computations. Table 2 presents interaction energies at the CCSD(T)/cc-pVDZ+ level of theory, broken down into their two-body and three-body components. The cc-pVDZ+ basis denotes cc-pVDZ plus the diffuse s and p functions from aug-cc-pVDZ for non-hydrogen atoms. We observed that, due to favorable cancellations of errors, this level of theory provides interaction energies within a few tenths of 1 kcal mol^{-1} of our best estimates for the benzene dimer.[107] From the table, we see that in the linear sandwich (S), T-shaped (T), or parallel-displaced (PD) configurations, the 1−3 pair energy is essentially zero because the monomers are too far apart (it is slightly larger at the MP2 level of theory, which overestimates these interactions). The 1−2 pair energies are essentially the same as they are in the benzene dimer. The three-body interaction is less than 0.1 kcal mol^{-1} for all but the cyclic trimer, where it is 0.25 kcal mol^{-1}. Overall, if we estimate the energies of these trimers as a simple sum of nearest-neighbor benzene dimer energies with these same geometries and at the same level of theory, we obtain values which are remarkably similar to the results for the full trimer computations. The largest deviation, 0.5 kcal mol^{-1}, is found for the cyclic trimer where the three-body effects are largest. In studies of tetramers, we found that four-body effects were always negligible for the linear stacks considered, as were three-body terms including any non-nearest neighbors. Although long-distance two-body interactions and nearest-neighbor three-body terms are not necessarily negligible (and will have a cumulative effect in larger clusters), π−π interactions in benzene clusters do not differ greatly from what would be expected by thinking of the cluster as a collection of individual, nearest-neighbor benzene dimers.

C. Substituent Effects in π−π Interactions. Because π−π interactions can be so important in supramolecular chemistry and host−guest chemistry (including drug binding), it would be valuable to understand how their strength might be *tuned* by substituents. Indeed, this question would seem to be central for future advances in supramolecular design. Nevertheless, to date, only a few experiments have addressed this issue. Most of these experiments have used NMR techniques to measure equilibrium constants for the interconversion of different configurations of substituted $\pi-\pi$ systems. For example, Wilcox and co-workers have presented[109,110] a "molecular torsion balance" which can adopt a "closed" form featuring a T-shaped $\pi-\pi$ interaction or an "open" form with no $\pi-\pi$ interaction. Hunter and co-workers have also investigated substituent effects in T-shaped interactions; they deduce substituent effects through double-mutant cycle studies of molecular zipper complexes.[111,112] Cozzi, Siegel, and co-workers[113-115] have studied rotation constants in 1,8-biarylnaphthalenes in which substituted aryl groups can adopt an approximate sandwich configuration. Rashkin and Waters have reported[116] a study of substituent effects in model systems featuring a parallel-displaced configuration. Unfortunately, it has proven difficult to discern the true nature of substituent effects from these studies. The papers by Hunter[111,112] come to qualitatively different conclusions than those of Wilcox[109,110] for the T-shaped interaction. Additionally, the interpretation of these experiments is complicated by secondary interactions or solvation effects. The paper by Rashkin and Waters[116] suggests that *direct* interactions between the substituent on one π system and the hydrogens of another can also be significant. Nakamura and Houk used molecular mechanics models to show that the substituent effects in Wilcox's molecular torsion balance are damped out due to more favorable solvation for the open form than the closed form;[4] subsequent ab initio and DFT studies of this issue were reported by Ribas et al.,[5] who suggested that the backbone in Wilcox's compounds could also play a non-negligible role in the conformational energetics.

The prevailing framework for understanding the nature of substituent effects in $\pi-\pi$ interactions is that presented in a 1990 *J. Am. Chem. Soc.* article by Hunter and Sanders.[27] These authors recognize that dispersion interactions contribute significantly to $\pi-\pi$ interactions, but on the basis of experiments and a very simple mathematical model, they argue that electrostatic effects dominate substituent effects. This view appears to be supported by experiments by Hunter[112] and by Cozzi and Siegel,[113-115] but not by the experiments of Wilcox.[109,110] In an attempt to better understand substituent effects in $\pi-\pi$ interactions and to remove factors which complicate analysis of the experiments, we have performed ab initio computations on substituted T-shaped and sandwich benzene dimers.[117-119] Additional theoretical work along these lines has been reported by K. S. Kim and co-workers for the case of T-shaped interactions.[43]

Let us first consider the monosubstituted heterodimers displayed in Figure 7, where for the T-shaped configurations we have substituted both the top ("edge") and bottom ("face") rings. These are among the simpler substituted dimers that might be studied; note that the substituents in the T-shaped configurations are placed as far away as possible from the other ring to avoid direct interactions between them. We have examined both electron-donating (CH_3, OH) and electron-withdrawing substituents (F, CN). Estimates of the CCSD(T)/aug-cc-pVTZ binding energies, relative to the benzene dimer, are presented in Table 3.

Theoretical results for the sandwich dimers are in surprising contradiction to what would be expected from the Hunter–Sanders rules; namely, the electron-donating OH and CH_3 substituents cause the dimers to be *more stable* than the unsubstituted benzene dimer. Two items are important for understanding this result. First, although OH and CH_3 are typically thought of as "electron-donating" substituents (e.g., they both have negative Hammett parameters, σ_p), phenol and toluene have approximately the same electrostatic potential as benzene in the middle of the ring, as displayed in Figure 8. It must be kept in mind that Hammett parameters were derived from benzoic acid dissociation constants, and it seems that they have more to do with the stabilization of the carboxylate ion of the dissociated acid than with the electron distribution of the reactant. Similar observations have been made by Dougherty and co-workers in studies of cation–π interactions.[120] Consistent with Figure 8, the electrostatic contributions to the binding of benzene dimer, benzene–phenol, and benzene–toluene sandwiches are all very similar.[118] Second, in contradiction to the Hunter–Sanders rules, differential dispersion effects *can* dominate substituent effects, and they do so in these two cases. The changes in the electrostatic, exchange–repulsion, dispersion, and induction contributions to the interaction energies can be found in Figure 9 for these sandwich dimers as computed by symmetry-adapted perturbation theory.

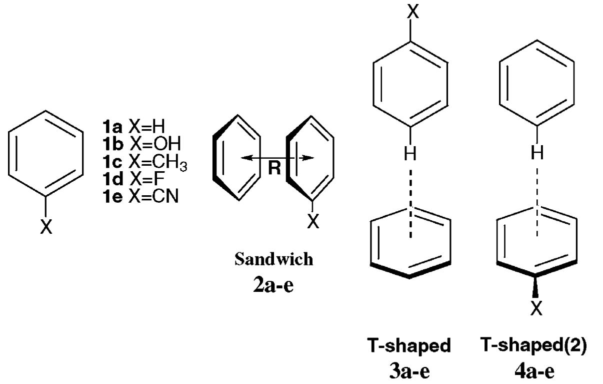

Figure 7. Monosubstituted benzene dimers.

TABLE 3: Interaction Energies Relative to the Benzene Dimer for Heterodimers of Benzene with Monosubsituted Benzenes [Estimated CCSD(T)/aug-cc-pVTZ Results][a]

X	S	T	T(2)
H	0.00	0.00	0.00
OH	−0.37	0.04	−0.05
CH_3	−0.47	0.07	−0.33
F	−0.49	−0.15	0.24
CN	−1.25	−0.63	0.42

[a] Reflecting the counterpoise correction and using the geometries and additivity schemes of ref 118.

Experiments by Williams and Lemieux support the idea that both electrostatics and dispersion can be important for substituent effects in $\pi-\pi$ interactions.[28] In these experiments, the nematic liquid crystal host 4′-(pentyloxy)-4-biphenylcarbonitrile was doped with a series of substituted biphenyl, phenylpyridine, and bypyridine derivatives. The effect of the dopants on the nematic–isotropic phase transition temperature of the liquid crystal phase was quantified and found to depend on both dispersion and electrostatics. More recently, in 2005, Mei and Wolf presented rigid, highly congested 1,8-diacridylnaphthalenes as improved experimental models of $\pi-\pi$ interactions where steric constraints lock in a sandwich configuration.[29] The authors found that oxidation of these compounds to form *N*,*N*′-dioxides led to stronger $\pi-\pi$ interactions. They suggest that, because the oxygens are π electron rich, they should increase the π electron density of the aromatic rings; an increased $\pi-\pi$

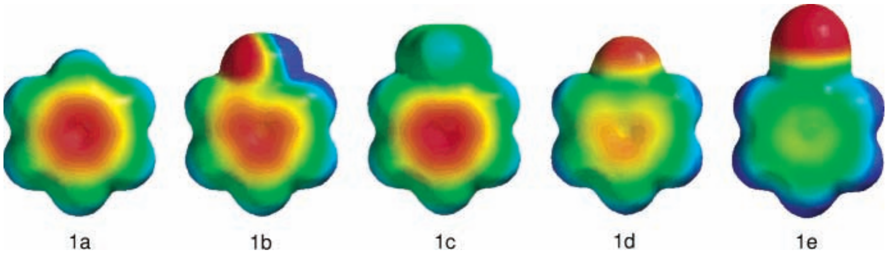

Figure 8. Electrostatic potentials computed using Hartree−Fock and a 6-31G* basis set with a scale of −25 to +25 kcal mol^{-1}.

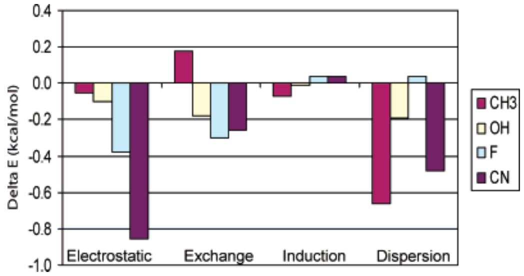

Figure 9. Changes to interaction energy relative to the benzene dimer for heterodimers of benzene with monosubstituted benzenes in sandwich configurations. Computed at the SAPT2/aug-cc-pVDZ′ level of theory (ref 118).

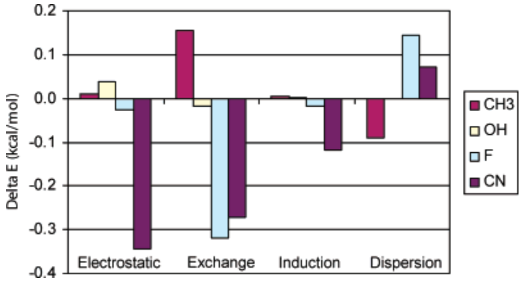

Figure 10. Changes to interaction energy relative to the benzene dimer for heterodimers of benzene with monosubstituted benzenes in T-shaped configurations. Computed at the SAPT2/aug-cc-pVDZ′ level of theory (ref 118).

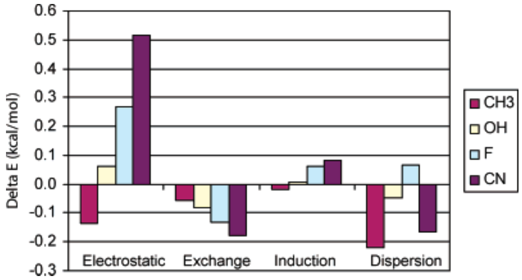

Figure 11. Changes to interaction energy relative to the benzene dimer for heterodimers of benzene with monosubstituted benzenes in T-shaped(2) configurations. Computed at the SAPT2/aug-cc-pVDZ′ level of theory (ref 118).

interaction in such a situation would contradict the Hunter−Sanders rules but would be in agreement with our predictions that *most* substituents—whether electron donating or electron withdrawing—increase the strength of $\pi-\pi$ interactions. Indeed, N-oxidation of heteroaryl compounds causes them to undergo electrophilic aromatic substitution reactions more easily, which is consistent with the notion that they have a greater π electron density.[121] On the other hand, as we have just discussed, phenol is activated with respect to electrophilic aromatic substitution compared to benzene, yet we do not observe any greater π electron density in the electrostatic potentials. Our preliminary computations suggest that the electrostatic potential above the middle of the ring is actually less negative in pyridine *N*-oxide than in pyridine (possibly due to the formal positive charge on nitrogen in the oxide). Thus, the experiments by Mei and Wolf might not provide a definitive experimental contradiction of the Hunter−Sanders rules, but nevertheless, they are still in accord with our predictions.

Turning to the T-shaped configurations, the results of Table 3 indicate that the dimer is stabilized by the CN and F substituents and weakly destabilized by the OH and CH_3 substituents. Here, it may be more tempting to ascribe these trends to electrostatic effects, and indeed, a rough correlation is seen when plotting the energy changes against the Hammett σ_m parameters. Nevertheless, the symmetry-adapted perturbation theory results in Figure 10 suggest that such a correlation is fortuitous and demonstrate that changes in the exchange−repulsion terms dominate for all but the CN substituent. These changes in the exchange−repulsion terms may result from changes in $\pi-\pi$ overlap as substituents increase or decrease the π density in the vertical ring. The much larger electrostatic stabilization of benzene−benzonitrile compared to the other T-shaped dimers is consistent with a much larger increase in the partially positive charge of the hydrogen closest to the negatively charged π cloud of the ring below.

Finally, considering the T-shaped(2) configurations, in which we substitute the horizontal ring of the T-shaped interaction, Table 3 indicates that, again, substituents can either increase or decrease the binding. Substituents on the horizontal ring have the opposite effect that they do on the vertical ring, where now the dimer is *destabilized* by the F and CN substituents and *stabilized* by CH_3 and OH. Again, it is tempting to explain these effects in electrostatic terms. The electron-withdrawing F and CN substituents decrease the amount of negative π density in the horizontal ring, decreasing its favorable electrostatic interaction with the partially positive sigma framework of the vertical ring. Indeed, the differential electrostatic contributions in Figure 11 are consistent with this interpretation and are the dominant terms for the F and CN substituents. If we continue to think of OH and CH_3 as being π donating substituents (in contrast to Figure 8), we would predict a more favorable electrostatic interaction, leading to the stronger binding, which is observed. However, Figure 11 indicates that, for OH, the electrostatic term is slightly *less* favorable than that in the benzene dimer and that the increase in binding for this substituent is actually due to changes in the exchange−repulsion and dispersion terms (all of which are fairly small). For CH_3 substitution, the electrostatic term is favorable, but the dispersion term is even more favorable. Hence, even for the T-shaped(2) configurations, electrostatic considerations do not quite capture the complete picture.

So far, we have been discussing how a single substituent affects binding in $\pi-\pi$ interactions. How does the situation change if we allow *multiple* substitutions? Limited experimental evidence suggests that substituent effects may be, to some extent, additive. For example, Cozzi, Siegel, and co-workers have studied 1,8-biarylnaphthalenes in which the aryl groups are

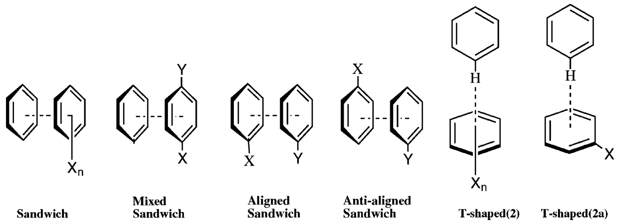

Figure 12. Multiply substituted benzene dimers.

substituted.[113] These authors measure the barrier to rotation about the aryl−naphthyl bond, which they argue is related to the strength of the $\pi-\pi$ interaction between the aryl groups when they are in a cofacial geometry. Remarkably, in studies where one of the aryl groups is substituted with one to three fluorines, each fluorine contributes a constant ~0.5 kcal mol^{-1} to the rotation barrier. Could such a result hold more generally? In recent work,[119] we investigated this question for sandwich and T-shaped configurations. Although T-shaped and parallel-displaced configurations are favored over sandwiches for the benzene dimer, substituents can alter the energy landscape; Tsuzuki and co-workers[42] have noted that toluene dimers favor parallel-displaced over T-shaped configurations, while the sandwich configuration becomes nearly isoenergetic with the T-shaped form. We are unaware of any previous systematic study of multiple substituent effects in benzene dimers, although a recent theoretical study by Riley and Merz[122] carefully examines T-shaped dimers of benzene with fluorinated benzene dimers. Additionally, a theoretical study of monosubstituted benzene dimers conducted independently by Kim and co-workers included an example of a disubstituted dimer.[43]

We have studied[119] the multiply substituted sandwich and T-shaped configurations displayed in Figure 12. We considered several configurations where one monomer remained unsubstituted and the other had one, two, or three substituents of the same type (CH_3, OH, or NH_2). For the substituents F and CN, hexasubstituted rings were also considered. We chose configurations in which the substituents were distributed symmetrically (i.e., para-1,4 substitution for two substituents and 1,3,5 substitution for three substituents). In addition to these dimers between benzene and multiply substituted benzenes, we also considered some sandwich dimers with two different substituents, where the two substituents could be on the same ring ("mixed sandwich") or on two different rings in an "aligned" or "anti-aligned" fashion (see Figure 12). CCSD(T) computations with a reasonable basis set would be very difficult for these systems with current programs and computers; fortunately, however, in earlier studies, we found *relative* energies (compared to the benzene dimer) are fairly accurately predicted at the MP2/aug-cc-pVDZ level of theory.[118]

Figures 13 and 14 present the MP2/aug-cc-pVDZ interaction energies for sandwiches of benzene with multiply substituted benzenes. In agreement with the experimental findings of Cozzi, Siegel, and co-workers,[113] we observe a nearly additive effect for multiple fluorination in sandwich dimers; moreover, we deduce an average energy lowering per fluorine of 0.6 kcal mol^{-1}, in excellent agreement with the experimental value of 0.5 kcal mol^{-1}. More importantly, we also observe an additive effect for all of the other substituents considered. This is very encouraging and suggests that understanding and predicting substituent effects in sandwich $\pi-\pi$ interactions is much easier than might have been expected. For example, one could suppose that adding a second fluorine to yield para-difluorobenzene might increase the binding energy by much less than the first fluorine; after all, fluorobenzene has a dipole moment, allowing dipole-induced dipole interactions, whereas para-difluorobenzene removes this interaction. However, our previous symmetry-adapted perturbation theory study[118] demonstrates that dipole-induced dipole terms and other induction interactions are actually very small in these systems.

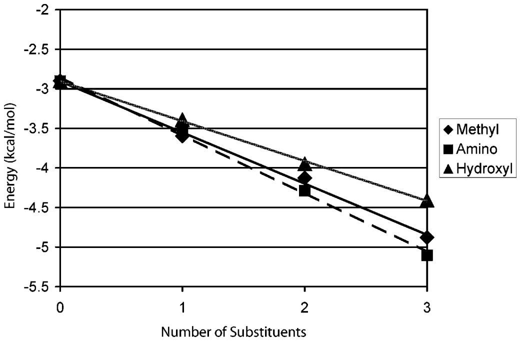

Figure 13. Interaction energies (MP2/aug-cc-pVDZ) for sandwich heterodimers of benzene with multiply substituted benzenes, through trisubstitution (data from ref 119).

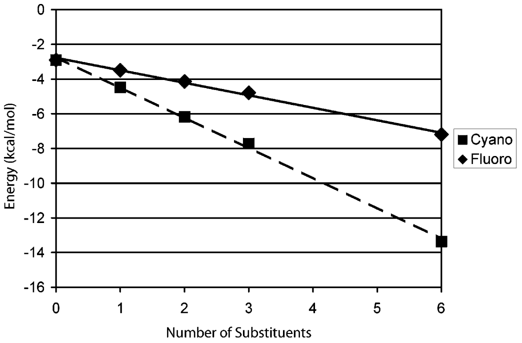

Figure 14. Interaction energies (MP2/aug-cc-pVDZ) for sandwich heterodimers of benzene with multiply substituted benzenes, through hexa-substitution (data from ref 119).

TABLE 4: Changes in Interaction Energies (in kcal mol^{-1}, Relative to the Benzene Dimer) for Mixed-Substituent Sandwich Heterodimers[a]

	predicted[b]	1,4 substitution	aligned	anti-aligned
NH_2 and CH_3	−1.35	−1.33	−1.30	−1.32
CN and CH_3	−2.30	−2.25	−2.23	−2.20
CN and F	−2.28	−2.25	−0.98	−2.10
CN and CN	−3.28	−3.28	−0.75	−2.89
NH_2 and F	−1.33	−1.26	−0.52	−1.34
F and F	−1.28	−1.24	−0.49	−1.17

[a] All data computed at the MP2/aug-cc-pVDZ level of theory; the interaction energy of benzene dimer at this level is −2.90 kcal mol^{-1}; data from ref 119. [b] Determined by adding the average change in interaction energies for each substituent as determined from Figures 13 and 14.

Let us turn to the mixed, aligned, and anti-aligned sandwiches in Figure 12, where up to two types of substituents are considered. To the extent that the substituent effects are truly additive, we might predict the energy lowering relative to the benzene dimer by adding the average stabilization due to each substituent as deduced from Figures 13 and 14. These predicted changes to the interaction energies are compared to explicitly computed (MP2/aug-cc-pVDZ) values in Table 4. There is a remarkable agreement between the additivity-predicted values and the computed values (typically within 0.1 kcal mol^{-1}) in all cases except for the aligned sandwiches. Here, there can be significant deviations if both substituents are strongly electron donating or withdrawing. We attribute this deviation to direct

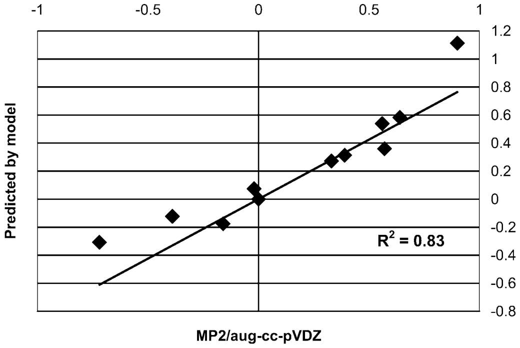

Figure 15. Comparison of explicitly computed values versus those from a bilinear model for the substituent effect on the interaction energy for T-shaped(2) configurations of multiply substituted benzene dimers (see Figure 12). Results from ref 119.

substituent−substituent interactions; further discussion of this topic, with accompanying symmetry-adapted perturbation theory analysis, is presented in ref 119.

Unfortunately, these simple additivity schemes—in which we estimate substituent effects merely by adding tabulated substituent values—do not work very well for the T-shaped(2) configurations in which we substitute the bottom (horizontal) ring. However, we were able to fit the quantum mechanical data with a rather simple model incorporating three factors: (1) electrostatic effects, crudely modeled as the sum of Hammett σ_m parameters; (2) dispersion effects, modeled by the change in polarizability of the substituted ring compared to benzene; (3) direct interactions between substituents on the horizontal ring and hydrogens of the vertical ring, which can come into relatively close contact (there are two such contacts in our trisubstituted dimers and four such contacts for the hexasubstituted cases). The fit of this model versus the explicitly computed results is presented in Figure 15; the results seem good, given the simplicity of the model. It is our hope that these and future studies will give insight into how substituents influence $\pi-\pi$ interactions and that this insight will be useful in designing supramolecular systems or in adjusting drug binding affinities.

D. Prospects for Computationally Inexpensive Modeling of Noncovalent Interactions. As we noted above, unfortunately it appears that definitive theoretical results for $\pi-\pi$ interactions require very expensive CCSD(T) computations in conjunction with large basis sets including multiple polarization and diffuse functions. Such computations do not appear feasible for systems much larger than the benzene dimer, but some of the most interesting examples of $\pi-\pi$ interactions appear in very large systems such as organic crystals or biomolecules. This raises the question of how one might accurately model $\pi-\pi$ interactions in larger systems.

It is very tempting to try to use density functional theory for these problems because of its tremendous success in so many areas of chemistry. However, as we have stated, the DFT methods which are widely available at present fail completely for these interactions.[33,46,47] For example, a recent study of 25 different density functionals found that *none* of them could come within 1 kcal mol^{-1} (∼30−50%) of our benchmark-quality binding energies of the sandwich, T-shaped, and parallel-displaced configurations of the benzene dimer.[47] For the sandwich dimer, all but two functionals failed to predict binding at all. These failures occur because the current set of popular DFT methods, even if they include gradients or higher-order derivatives of the density, are really “local” or at least “semilocal” theories, whereas dispersion is an inherently long-range, nonlocal phenomenon.[46] Exact density functional theory would, of course, include dispersion and all other necessary effects, but the exact density functional is currently unknown (and even if it were known, it would likely have a dramatically greater computational cost than current approximate models).

Various approximate solutions to this deficiency of modern density functional methods are being vigorously pursued by theorists; unfortunately, we have time to discuss only a few. One simple but somewhat effective solution[35,48,123−127] is to simply add damped interatomic potentials of the form $-C_6r^{-6}$. An extensive recent study by Grimme[48] indicates that this approach dramatically improves over standard DFT methods and yields binding energies which are typically within 30% of benchmark ab initio values for noncovalent interactions in small molecules. A more general approach has been advocated by Röthlisberger and co-workers, who have used effective atom-centered nonlocal potentials fitted to ab initio data for small dimers.[51,52] Langreth, Lundqvist, and co-workers have improved over standard DFT by adding nonlocal terms to the correlation energy functional.[49] This functional has been tested both for the benzene dimer[128] and for monosubstituted benzene dimers.[129] Although the sandwich configuration is significantly overbound by this van der Waals density functional (vdW-DF), results for T-shaped and parallel-displaced configurations are fairly good. In all cases, results are vastly improved over standard DFT methods, most of which fail to bind the sandwich configuration at all. Shifts in binding energies due to substitution are somewhat easier to compute than the total binding energies themselves,[118] and Langreth and co-workers obtain results[129] which are typically within 0.1 kcal mol^{-1} of our values for the changes in binding due to substitution for monosubstituted T-shaped and sandwich configurations. Combinations of symmetry-adapted perturbation theory with Kohn−Sham density functional theory look promising; these evaluate the dispersion term via the frequency-dependent density susceptibility functions of time-dependent DFT.[53,130] Alternatively, Becke seems to have uncovered a remarkable connection between dispersion and the dipole moment generated by an electron and its corresponding exchange hole; these considerations lead to very practical computational methods which can be more accurate than large-basis MP2 for weak interactions.[131−133] Finally, we note that several authors have also explored new parametrizations of currently available density functionals; we are pessimistic about these approaches working generally, because they do not add new physics to the local (or semilocal) functionals, yet dispersion is a nonlocal effect.

Another kind of approach which has been compared to our benchmark results for $\pi-\pi$ interactions in the benzene dimer is the “multicoefficient extrapolated density functional theory” of Truhlar and co-workers,[134] which is a composite method similar to the Gaussian-*n* methods[80,81] but which includes DFT energies as well as energies from wave-function-based methods (the use of DFT geometries and vibrational frequencies in a modified G3 method has been examined by Baboul et al.)[135] Various versions of Truhlar’s approach have been applied to the benzene dimer.[136] The N^7 composite methods [which include small-basis QCISD(T) computations and large-basis MP2 computations, similar to our strategy of combining small-basis CCSD(T) with large-basis MP2] give binding energies which agree within a few tenths of 1 kcal mol^{-1} of our more rigorous results, but at a reduced cost. Truhlar’s composite N^6 methods also give reasonable results for the T-shaped and parallel-displaced configurations but have difficulty for the sandwich configuration.

For larger-scale modeling of $\pi-\pi$ interactions in crystals or biomolecules, even DFT computations may become prohibitive. Here force-field methods are often computationally feasible, and these do include empirical terms for van der Waals dispersion interactions. However, it remains unclear at present how well these methods do at describing noncovalent interactions, and one of our future goals is to investigate this question by comparison to high-quality ab initio results. Already Hobza and co-workers have compared[36] the AMBER force field to MP2 with a modified 6-31G* basis set for the interaction of a few intercalators with nucleic acid base pairs (this study also considers modified DFT methods); the AMBER results in this case were good but only after some of the terms had been modified. Macias and MacKerell[137] recently refined the CHARMM force field and found reasonably good agreement (within a few tenths of 1 kcal mol^{-1}) for the binding energies and relative energies of the benzene dimer. More flexible approaches, such as polarizable force fields, are being developed by a number of researchers. The recent polarizable force field of Friesner, Berne, and co-workers[138] appears to yield a good agreement (within a few tenths of 1 kcal mol^{-1}) with our benchmark results for the binding energy of the benzene dimer.

IV. Conclusions

State-of-the-art electronic structure methods, extrapolated toward the ab initio limit, are beginning to enable definitive computations of $\pi-\pi$ interactions. These results, coupled with analysis via symmetry-adapted perturbation theory, are clarifying the strength, geometrical dependence, and physical nature of $\pi-\pi$ interactions. Substituent effects, which may provide a convenient handle for tuning $\pi-\pi$ interactions for applications in crystal engineering or drug design, do not appear to fit the conventional wisdom of the Hunter–Sanders rules, which state that these effects can be predicted based solely on electrostatic considerations. Results from quantum computations are beginning to paint a more complete picture of how substituents affect $\pi-\pi$ interactions. Benchmark-quality computations on the benzene dimer and similar systems are proving to be of great value in fitting and calibrating new methods for simulations of large-scale systems, such as organic crystals or biomolecules, incorporating $\pi-\pi$ interactions. These interactions are of fundamental importance in supramolecular chemistry, and as our ability to accurately model them increases, new opportunities will open up in the rational design of supramolecular systems.

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