

LETTERS

Unexpected Substituent Effects in Face-to-Face π -Stacking Interactions

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State-of-the-art electronic structure methods have been applied to obtain the first high-quality theoretical results for substituent effects in π -stacking interactions. The sandwich configurations of benzene dimer, benzene–phenol, benzene–toluene, benzene–fluorobenzene, and benzene–benzonitrile have been studied using correlation consistent basis sets augmented by multiple diffuse functions, namely aug-cc-pVDZ and aug-cc-pVTZ, at the second-order perturbation theory (MP2) level. Coupled-cluster computations with perturbative triples [CCSD(T)] were performed and combined with the above MP2 calculations to estimate the CCSD(T)/aug-cc-pVTZ binding energies, which should be accurate within several tenths of a kcal mol⁻¹. All substituted dimers bind more strongly than benzene dimer, with benzene–benzonitrile binding the most strongly. Both electrostatic and dispersion interactions contribute to the increased binding of the monosubstituted dimers.

Intermolecular interactions between π systems are one of the principal noncovalent forces governing molecular recognition and biomolecular structure.¹ These interactions play a major role in phenomena as diverse as base-pair stacking in DNA,² the tertiary structures of proteins,³ host–guest complexes,⁴ and self-assembly of synthetic molecules.⁵ Despite the widely recognized importance of π – π interactions, a detailed understanding of their strength and orientational preferences has been a challenging problem for both experiment and theory due to the shallowness of the potential energy surfaces. An understanding of these issues, as well as how substituents may tune π – π interactions, is of prime importance for molecular design.

As the simplest prototype of π – π interactions, the benzene dimer has been the subject of intense experimental and theoretical interest.^{1,6,7} Using explicitly correlated MP2–R12/A wave functions,⁸ we recently estimated the complete basis set limit for second-order Møller–Plesset perturbation theory (MP2) gas-phase binding energies.⁷ After correction for higher-order

correlation effects via coupled-cluster theory including perturbative triple substitutions [CCSD(T)], the resulting binding energies should approach the ab initio limit within a few tenths of a kcal mol⁻¹. The results demonstrate that the perpendicular T-shaped configuration and the parallel-displaced (offset-stacked) configuration are nearly isoenergetic ($D_e = 2.7$ and 2.8 kcal mol⁻¹, respectively), while the face-to-face sandwich configuration is a saddle point on the potential energy surface and is significantly higher in energy (1.8 kcal mol⁻¹). However, substituents may substantially alter the energy landscape: for the toluene dimer, stacked configurations appear to be preferred, and this preference is observed both in the gas phase and in aqueous solution.⁹

Very little is known about substituent effects in π – π interactions.^{10–12} Cozzi, Siegel, and co-workers have used ¹H NMR techniques to study substituent effects in 1,8-diarylnaphthalenes which force a face-to-face arrangement. The barrier to rotation about the aryl–naphthyl bond, which should increase as the π – π interaction becomes more favorable, showed a linear relationship with the sum of the Hammett parameters σ_{para} of

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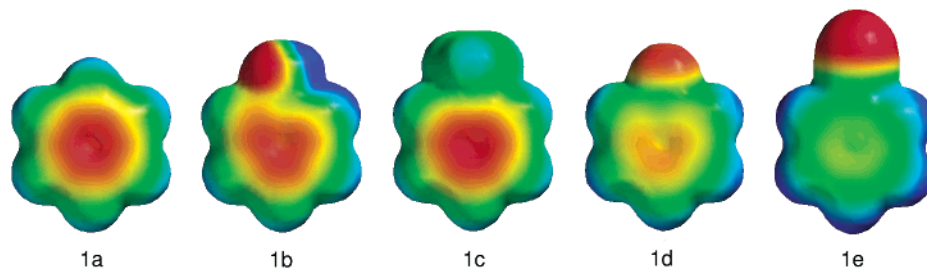
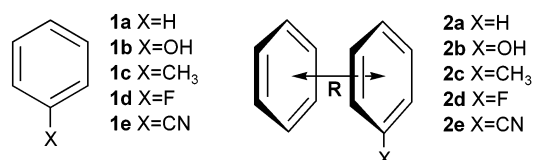


Figure 1. Electrostatic potentials computed using Hartree-Fock and a 6-31G* basis set with a scale of -25 to $+25$ kcal mol $^{-1}$. Potentials using B3LYP/6-31G* appear very similar.

CHART 1



the substituents.¹⁰ This suggests that electron-withdrawing substituents stabilize the transition state by decreasing the repulsion between the π electrons on each aryl ring, while electron-donating substituents destabilize the transition state by increasing the repulsion between the two π systems, and that the electron donating or withdrawing character of the substituents is reasonably described by the σ parameter. Such an analysis is consistent with the Hunter-Sanders rules,¹³ which make qualitative predictions of π - π interactions by focusing on electrostatics and considering the π electron cloud to have a negative charge and the σ framework to have a positive charge.

Here we present preliminary results from the first ab initio study of substituent effects in face-to-face π - π interactions. Dimers of benzene with substituted benzenes have been considered, with substituents OH, CH₃, F, and CN (Chart 1). The centers of the two rings were aligned in an eclipsed configuration. Monomer geometries were optimized using MP2 with the aug-cc-pVDZ and aug-cc-pVTZ basis sets, where the aug- prefix denotes one set of diffuse functions for each angular momentum in the basis. With frozen monomer geometries, the distance between the centers of the rings was optimized with the aug-cc-pVDZ and aug-cc-pVTZ basis sets and counterpoise-corrected MP2 energies. Results using the larger, aug-cc-pVTZ basis set are taken as more reliable, and these are corrected for higher-order correlation effects by CCSD(T) using an aug-cc-pVDZ basis in which diffuse functions have been removed from hydrogen (denoted aug-cc-pVDZ'). This procedure, which approximates aug-cc-pVTZ CCSD(T), underestimates the binding energy for benzene dimer by approximately 0.2 kcal mol $^{-1}$ when compared to the more complete MP2-R12/A + Δ CCSD(T) approach,⁷ which is currently impractical for the lower-symmetry substituted dimers. We anticipate that remaining errors due to incompleteness of the basis set or correlation treatment are small and will approximately cancel when considering differences among the dimers. The PSI 3.2 and MOLPRO programs were used in the present study.^{14,15}

Theoretical results are summarized in Table 1. The optimized distance between monomers, R , is relatively insensitive to the basis set, but using the larger basis set makes binding significantly more favorable. The Δ CCSD(T) corrections are very large, and they account for the known overbinding of van der Waals complexes by the MP2 method. The most striking result from Table 1 is that *all* of the substituted dimers bind more strongly than benzene dimer, even though the substituents are

TABLE 1: Interfragment Distances (\AA) and Binding Energies (kcal mol $^{-1}$) for Face-to-Face Dimers of Benzene with Substituted Benzenes^a

dimer	method	R^b	ΔE_{int}
benzene-benzene	MP2/aug-cc-pVDZ ^c	3.80	-2.90
	MP2/aug-cc-pVTZ ^c	3.70	-3.26
	MP2/aug-cc-pVQZ ^{c,d}		-3.37
	MP2-R12/A ^{c,d}		-3.64
	Δ CCSD(T)/aug-cc-pVDZ'		1.65
benzene-phenol	estd CCSD(T)/aug-cc-pVTZ		-1.60
	Δ CCSD(T)/aug-cc-pVDZ ^{c,d}		1.83
	estd CCSD(T)/CBS ^{c,d}		-1.81
	MP2/aug-cc-pVDZ	3.70	-3.40
	MP2/aug-cc-pVTZ	3.60	-3.75
benzene-toluene	Δ CCSD(T)/aug-cc-pVDZ ^e		1.90
	estd CCSD(T)/aug-cc-pVTZ ^e		-1.85
	MP2/aug-cc-pVDZ	3.70	-3.58
	MP2/aug-cc-pVTZ	3.65	-3.94
	Δ CCSD(T)/aug-cc-pVDZ ^e		1.90
benzene-fluorobenzene	estd CCSD(T)/aug-cc-pVTZ ^e		-2.04
	MP2/aug-cc-pVDZ	3.70	-3.50
	MP2/aug-cc-pVTZ	3.70	-3.81
	Δ CCSD(T)/aug-cc-pVDZ ^e		1.61
	estd CCSD(T)/aug-cc-pVTZ ^e		-2.20
benzene-benzonitrile	MP2/aug-cc-pVDZ	3.70	-4.49
	MP2/aug-cc-pVTZ	3.60	-4.86
	Δ CCSD(T)/aug-cc-pVDZ ^e		2.07
	estd CCSD(T)/aug-cc-pVTZ ^e		-2.79

^a All computations include the counterpoise correction. ^b Distance between centers of rings optimized with frozen monomers. ^c Reference 7. ^d Using the best estimate of monomer geometry and MP2/aug-cc-pVTZ interfragment distance. ^e Using MP2/aug-cc-pVTZ monomer and interfragment geometry.

typically characterized as ranging from strongly electron donating (OH) to strongly electron withdrawing (CN). This contrasts with the previously mentioned results of Cozzi, Siegel, and co-workers for biaryl-naphthalenes, which correlated with σ parameters.

It is tempting to ascribe the increased attraction for all substituents considered to dipole-induced dipole interactions, which are absent in benzene dimer. The differences in binding energies, however, do not correlate very well with the dipole moments of the substituted monomers (toluene, 0.375; phenol, 1.224; fluorobenzene, 1.60; and benzonitrile, 4.18 D).¹⁶ It may also be noted that all the substituted benzenes should have larger dispersion interactions with benzene.

An alternative approach to understanding the electrostatic contribution to binding is afforded by the electrostatic potentials of the monomers **1a-e** (Figure 1), obtained using the SPARTAN program with a density isosurface of 0.002 electrons au $^{-3}$.¹⁷ According to the Hunter-Sanders rules, the most important consideration for a face-to-face sandwich configuration would be the negative π -electron charge at the ring center. Figure 1 indicates that this charge is greatest for benzene, toluene, and phenol, and followed by fluorobenzene and

benzonitrile. The observed order, **2a** < **2b** < **2c** < **2d** < **2e** shows benzene to bind somewhat more weakly and toluene somewhat more strongly compared to phenol. The sequence **2a** < **2b** < **2c** is consistent with the order of the polarizabilities¹⁸ and the expected order of increasing dispersion interactions.

The electrostatic potentials do not necessarily correspond to the classical electron donating or withdrawing effects observed in electrophilic aromatic substitution reactions. OH is a strongly activating (electron-donating) substituent in electrophilic aromatic substitutions, yet phenol displays no more π -electron charge in the ring than benzene. This suggests that the electron donating effect of OH is seen in the transition state and not the ground state of the substitution reaction. This observation has been made by Dougherty and co-workers in studies of cation- π binding.¹⁹

We expect that an increased understanding of substituent effects in π - π interactions will aid molecular design efforts. Soon, we hope to report on additional configurations and a more detailed analysis using energy decomposition methods.

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Supporting Information Available: A .txt file of Cartesian coordinates of dimers. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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