

Substituent Effects in Sandwich Configurations of Multiply Substituted Benzene Dimers Are Not Solely Governed By Electrostatic Control

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Noncovalent interactions between π systems are central to understanding protein folding and the stability of DNA. Moreover, they frequently influence drug binding, and understanding how these interactions can be tuned by substituents or heteroatoms would be valuable for rational drug design. Considerable controversy exists about whether substituent effects in π - π interactions can be understood purely on the basis of electrostatic interactions,¹⁻³ as posited by the Hunter-Sanders rules,⁴ or whether electrostatic effects are not sufficient to understand observed trends.⁵⁻⁸ The first systematic, high-level theoretical examination of this question^{9,10} studied monosubstituted, face-to-face (sandwich) benzene dimers and found that the binding energy increased for *all* substituents considered, whether they were electron-donating or electron-withdrawing; this indicates the critical importance of both electrostatics and London dispersion interactions.

In a recently published communication,¹¹ Wheeler and Houk revisited monosubstituted sandwich benzene dimers, this time considering many more types of substituents using a more economical computational approach, namely, the density functional approximation M05-2X.¹² When the unsubstituted case (benzene dimer) was not included, the relative interaction energies showed a reasonably good linear correlation with the Hammett parameter σ_m^X for each substituent X, which represents that substituent's electron-donating or electron-withdrawing character. However, the M05-2X results also corroborated previous findings⁹ that all substituents increase the interaction energy (E_{int}) relative to that of the benzene dimer. The authors suggest that this is due to a relatively constant dispersion stabilization for all of the substituents considered. Because most substituents lead to larger dispersion interactions than hydrogen, this has the effect of shifting the relative interaction energies downward (i.e., increasing the stabilization), so the line determined from the linear fit ($E_{int} = 2.71\sigma_m^X - 0.57$ kcal mol⁻¹) does not cross through the origin but instead has a negative intercept. However, when the effect of dispersion was explicitly subtracted using previously published results for four of the substituted dimers,¹⁰ the linear model nicely fit not only those points but also that for the parent benzene dimer.

Although the dispersion contributions complicate the picture somewhat, the linear correlation with Hammett parameters led Wheeler and Houk to conclude that "the trend in substituent effects can be qualitatively understood in terms of the electron-donating or withdrawing character of the substituents." This is certainly true for the data presented in that work, but we will show here that it is not true for π - π interactions in general.

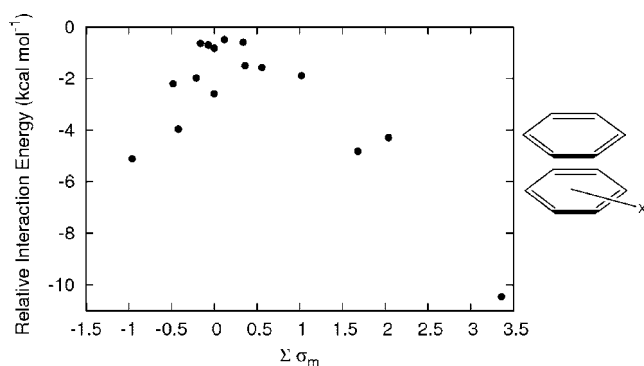


Figure 1. Interaction energies (relative to benzene dimer) vs $\sum\sigma_m$ for multiply substituted face-to-face benzene dimers (including monosubstituted, 1,3,5-trisubstituted, and hexasubstituted cases).

Instead, differential dispersion effects can be so large that even molecules with wildly different electrostatic potentials can exhibit similar attractions to benzene.

Here we present an analysis similar to that given by Wheeler and Houk but for multiply substituted sandwich benzene dimers. We considered monosubstituted, 1,3,5-trisubstituted, and hexasubstituted benzene complexes for six different substituents: CH₃, F, OH, NH₂, CH₂OH, and CN (the hexasubstituted cases for OH and CH₂OH were not included). Interaction energies were determined using counterpoise-corrected second-order Møller-Plesset perturbation theory (MP2) in conjunction with the aug-cc-pVDZ basis set. This method is sufficient to provide reliable relative interaction energies, as benchmarked against higher-level coupled-cluster results.¹⁰ Figure 1 plots the interaction energies (relative to benzene dimer) versus the sum of the Hammett parameters ($\sum\sigma_m$) for all of the substituents. Previous work¹³ has shown that an additivity rule is applicable when using Hammett parameters to capture inductive effects for multiple substituents in quinuclidine and bicyclo[2.2.2]octane carboxylic derivatives, and a summation of Hammett parameters has been used to represent the electrostatic character of multiply substituted complexes in other work that calculated π - π interactions.^{3,14} A linear correlation between the relative interaction energies and $\sum\sigma_m$ is not observed in Figure 1, and the data provides striking evidence that substituent effects in face-to-face π - π interactions are not governed solely by electrostatic control.

To further examine the relationship between the electrostatic nature of the substituted systems and the interaction energy, Hartree-Fock/6-31G* electrostatic potential maps were computed for three of the molecules having similar interaction energies with

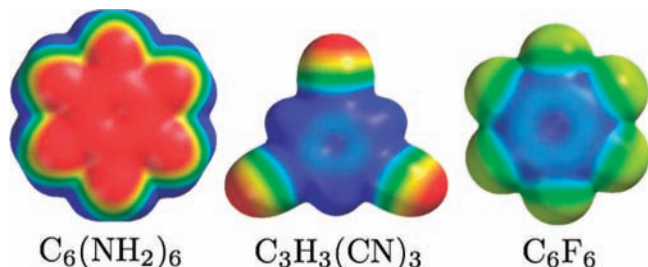


Figure 2. Hartree-Fock/6-31G* electrostatic potential maps [-25 kcal mol $^{-1}$ (red) to $+25$ kcal mol $^{-1}$ (blue)] of hexaamino-, 1,3,5-tricyano-, and hexafluoro-substituted benzene. All three molecules have similar (within 1 kcal mol $^{-1}$) interaction energies with benzene.

benzene (Figure 2). The hexa-substituted NH₂ complex, with six highly electron-donating groups, still is more strongly bound than benzene dimer, with an interaction energy that is 5.1 kcal mol $^{-1}$ more negative. Such a result is impossible to explain on the basis of the Hunter-Sanders rules, which posit that electron-donating substituents increase the negative charge in the π -electron cloud and thus lead to less favorable electrostatic interactions with an unsubstituted benzene. The electrostatic potential map (Figure 2) confirms an electron-rich π cloud for the hexaamino-substituted benzene, whereas the tricyano-substituted complex (more strongly bound than benzene dimer by 4.8 kcal mol $^{-1}$) and the hexafluoro-substituted complex (more strongly bound than benzene dimer by 4.3 kcal mol $^{-1}$) have similar interaction energies with benzene but noticeably depleted electron density in the center of the substituted rings.

The notable stabilization of the hexaamino-substituted complex demonstrates the significant effect that the differential dispersion effects can have on the overall stability of the substituted complex. Changes in the dispersion energy due to substituents in monosubstituted sandwich benzene dimers, while relatively small, are neither roughly constant nor even always stabilizing. The relative dispersion contributions (in kcal mol $^{-1}$) for the monosubstituted cases are -0.66 (CH₃), 0.039 (F), -0.192 (OH), and -0.482 (CN) at the SAPT/aug-cc-pVDZ' level of theory.¹⁰ As demonstrated in prior work,¹³ the relative interaction energy is additive for increasing numbers of substitutions in sandwich configurations; thus, it is likely that the dispersion contribution is also additive, which would mean that the differences in the dispersion contributions of various substituents would become magnified for multiply substituted dimers and that correlations with electrostatic parameters would be erased for multiply substituted dimers unless explicit account of the dispersion contribution is also included.

The overall nature of substituent effects on π stacking involves the interplay of several competing factors, including electrostatics, dispersion, and direct substituent-ring interactions,^{11,14} in addition to effects from the surrounding chemical environment (e.g., solvent effects). In complex chemical systems where π - π interactions play a role in the overall stability of the system, all of these factors must be evaluated to predict the overall nature of the substituent effect. Simple models that account for only one type of interaction cannot capture the complexity of substituent effects. It will be interesting to study how these interactions contribute to substituent effects in other geometric configurations, such as T-shaped and parallel-displaced geometries.

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Supporting Information Available: Hammett parameters, relative interaction energies, total energies, graphical structures, and optimized coordinates for all of the substituted benzene complexes. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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