

Origin of the Surprising Enhancement of Electrostatic Energies by Electron-Donating Substituents in Substituted Sandwich Benzene Dimers

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S Supporting Information

ABSTRACT: A recent study of substituted face-to-face benzene dimers by Lewis and co-workers [*J. Am. Chem. Soc.* **2011**, *133*, 3854–3862] indicated a surprising enhancement of electrostatic interactions for *both* electron-withdrawing and electron-donating substituents. Here we demonstrate that charge penetration (an attractive electrostatic interaction arising from the overlap of the electron densities on the two monomers) is the cause of this counterintuitive effect. These charge penetration effects are significant at typical π – π interaction distances, and they are not easily described by multipole models. A simple measure of a substituent's electron-donating or electron-withdrawing character, such as the Hammett parameter σ_m , is unlikely to capture subtle charge penetration effects. Indeed, correlation of the relative total energies or relative electrostatic energies with $\Sigma\sigma_m$ breaks down for multiply substituted face-to-face benzene dimers.

The influence of π – π interactions on protein folding and many drug binding complexes has been reported,^{1,2} and such interactions are critical for stabilizing the structure of DNA and RNA.³ Understanding how π – π interactions can be modified by substituents is of fundamental importance for advances in drug design, exploration of non-natural nucleic acid analogues, and crystal engineering of organic materials. The conventional wisdom, inferred from numerous experiments, is encoded in the Hunter–Sanders rules,⁴ which state that substituent effects can be understood in terms of how substituents change electrostatic energies by donating or withdrawing electron density from the π cloud. Theoretical studies of gas-phase monosubstituted benzene dimers, however, indicated that *both* electron-donating and electron-withdrawing substituents increase the attraction between two benzenes in an idealized face-to-face (sandwich) orientation,⁵ contradicting this picture. Moreover, symmetry-adapted perturbation theory (SAPT)⁶ analysis indicates that, for substituents like methyl, the majority of the substituent effect is due to dispersion, not electrostatics.⁵ T-shaped and parallel-displaced configurations are more prevalent in actual chemical systems, and some studies have explored their substituent effects as well.^{7–11} Nevertheless, near-sandwich configurations are observed in some model systems,^{12–15} and the sandwich structures have remained popular in theoretical studies because they are simpler geometrically.

Wheeler and Houk made the amazing discovery that computed substituent effects in sandwich $C_6H_5X \cdots C_6H_6$ complexes are essentially the *same* as they are in $HX \cdots C_6H_6$ complexes in corresponding geometries.¹⁶ That is, the substituent effects are due to direct substituent– π interactions and not to tuning of the π – π interaction itself. For an expanded collection of substituents, a good correlation was observed between stabilization due to substituent and the Hammett parameter σ_m of the substituent, suggesting that electrostatic effects do determine the trend with respect to substituents, while dispersion merely serves to shift the trend line down from the origin (stabilizing even complexes with electron-donating substituents, in agreement with earlier theoretical studies).

However, if dispersion effects are noticeable in monosubstituted benzene dimers, then they should become large in multiply substituted benzene dimers. Indeed, Ringer and Sherrill¹⁷ showed that the correlation between relative binding energy and $\Sigma\sigma_m$ is destroyed for multiply substituted sandwich dimers. Moreover, several monomers with radically different electrostatic potentials all exhibited similar binding to benzene. These data appear to support the hypothesis that differential dispersion effects can be large in multiply substituted benzene dimers, and that electrostatics effects alone are not sufficient to understand substituent effects in sandwich benzene dimers. However, energy decompositions were not reported.

While an energy component analysis was being performed in our laboratory, a similar study was published by Lewis and co-workers.¹⁸ Their study found a good correlation between computed binding energies and a model containing σ_m and M_r values, where M_r is the molar refractivity, taken to describe the polarizability of a substituent (which should be proportional to its dispersion contribution). However, SAPT analysis indicated that the sum of dispersion, exchange repulsion, and induction was relatively constant for the substituted dimers (variations of a few tenths of one kcal mol^{–1}), whereas changes in the electrostatic term were much larger. Counterintuitively, the electrostatic term itself was found to be more favorable than in benzene dimer for *all* substituents. While increased binding for electron-donating substituents is easy to rationalize as arising from dispersion terms, it is not obvious how electron-donating substituents could lead to increased binding in the electrostatic term itself. Here we explain this surprising result.

SAPT0/aug-cc-pVDZ' interaction energies were computed for substituted sandwich benzene dimers using a development version of the PSI4 program.^{19,20} This level of theory can

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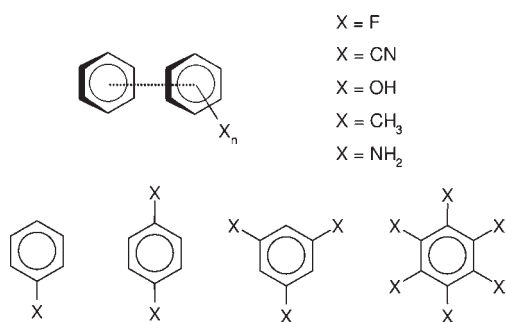


Figure 1. Depiction of the substituted sandwich benzene dimers considered. Only one of the benzene rings is substituted, according to the substitution pattern displayed. Only hexahydroxybenzene is omitted.

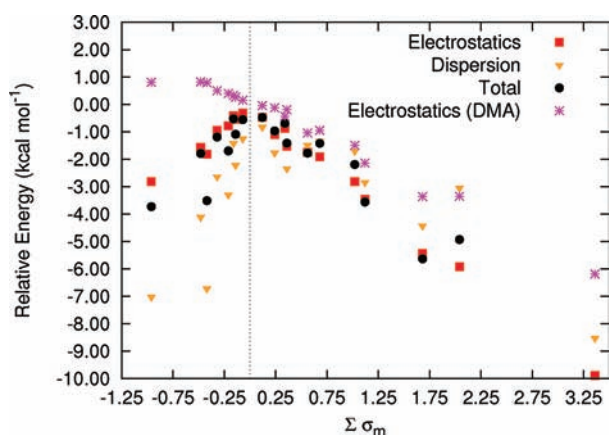


Figure 2. SAPT electrostatic, dispersion, and total interaction energies of substituted benzene dimers relative to the unsubstituted benzene dimer at their respective equilibrium geometries. For comparison, relative electrostatic energies computed from a distributed multipole analysis (DMA) are also included.

accurately predict benzene dimer interaction energies.²¹ The benzene and substituted benzene monomer geometries are optimized at the MP2/aug-cc-pVDZ level of theory using Q-Chem 3.2.²² The sandwich configurations of the substituted benzene dimers from ref 17 are considered and are aligned on the geometric center of the benzene rings. The specific substituents and geometries considered are shown in Figure 1.

In Figure 2, we present the SAPT electrostatic, dispersion, and total interaction energies of each substituted benzene dimer relative to the unsubstituted benzene dimer, each at their equilibrium geometries. We also include relative electrostatic energies estimated by a distributed multipole analysis (DMA), to be discussed below. The reader may notice that the relative energies and dispersion energies for dimers with $\Sigma\sigma_m < 0$ appear to form two separate trend lines: one line results from dimers with various numbers of $-\text{NH}_2$ substituents, and the other line results from dimers with various numbers of $-\text{CH}_3$ substituents (substituent effects in sandwich dimers tend to be additive²³). Dimers with more total electron-withdrawing character (positive $\Sigma\sigma_m$) have stronger interactions, and the electrostatic energies behave similarly to the total interaction energies for these substituents. These results are in accord with the Hunter–Sanders rules.⁴ Dimers with more electron-donating character are also more strongly bound, in agreement with

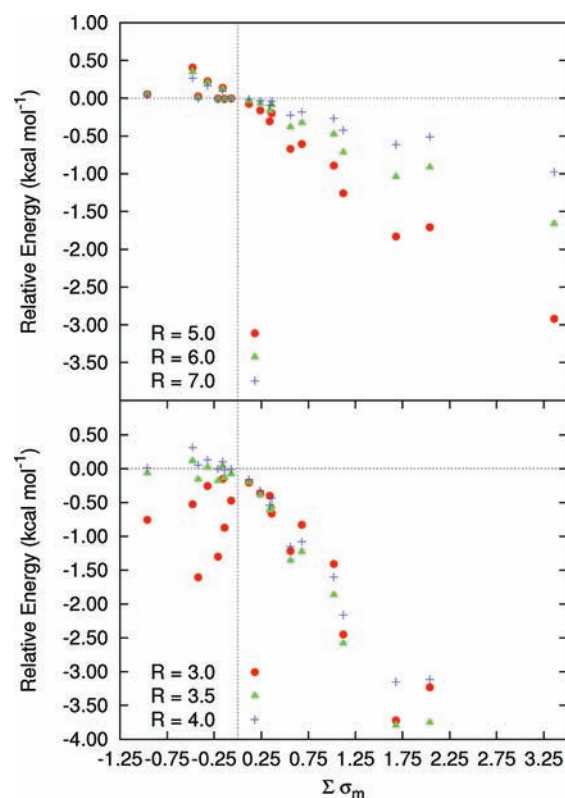


Figure 3. SAPT electrostatic energies of substituted benzene dimers relative to the unsubstituted benzene dimer at fixed intermolecular displacements (given in Å).

ref 17 but in contradiction to the Hunter–Sanders rules. This increase in binding is consistent with the stronger dispersion terms exhibited by all substituents (which grow with the number of substituents), as anticipated by ref 17. The surprising result is that the SAPT electrostatic energy itself also becomes more attractive with more strongly electron-donating substituents, as reported by Lewis and co-workers.¹⁸

In order to understand the origin of this curious effect, the multipole picture of electrostatics must be abandoned. As monomer electron densities begin to overlap, charge penetration effects become important.²⁴ These are attractive electrostatic interactions due to the interaction of the electrons of one monomer with the nuclei of the other, and they increase with orbital overlap. At long range, the sandwich benzene dimer has repulsive electrostatics due to unfavorable quadrupole–quadrupole interactions. At short range, however, it has attractive electrostatic interactions due to charge penetration. Any typical multipole-based description of the electrostatics in the benzene dimer would incorrectly predict repulsive electrostatics at short range. To demonstrate the limitations of the multipole model explicitly, DMA²⁵ was performed on Hartree–Fock/6-311G** densities for all the monomer geometries considered here, using the Molpro program.²⁶ Electrostatic energies based on the multipole analysis were computed for the unsubstituted and substituted benzene dimers, including terms through quadrupole–quadrupole. Figure 2 compares the DMA-predicted electrostatic energies vs the more rigorous SAPT electrostatic energies. We clearly see that the DMA electrostatic energies fail to capture the charge penetration terms that become important at the equilibrium intermolecular separations. Figures S9–S14 in the Supporting Information

present a comparison of the SAPT and DMA electrostatic contributions relative to the benzene dimer. There are large differences between the two estimates for several substituted dimers at short intermolecular distances, but the agreement becomes better as the intermolecular distance increases, just as one would expect, because the charge penetration terms are strongly dependent on the extent of orbital overlap. The small remaining differences at large intermolecular separations are due to the truncation of our DMA at quadrupole terms and our use of a different basis set for the DMA (because the DMA procedure can be unstable for basis sets including diffuse functions).

The fact that all substituents lead to an increased electrostatic interaction at equilibrium separations is a direct result of increased charge penetration. Any substituent increases the spatial extent of the substituted benzene's electron density and thus increases the overlap with the unsubstituted benzene (with the possible exception of fluorine). Therefore, both electron-donating and electron-withdrawing substituents increase the electrostatic interaction as a result of increased charge penetration.

The effect of charge penetration on the results in Figure 2 is, perhaps, exaggerated because all substituted benzene dimers have shorter intermolecular distances than the unsubstituted benzene dimer. To simplify the analysis, in Figure 3 we present relative electrostatic energies at various fixed intermolecular distances. At long range, 5–7 Å, the electrostatic interactions in the substituted benzene dimers correlate with $\Sigma\sigma_m$ (as might be predicted by the Hunter–Sanders rules). The electron-withdrawing substituents have attractive electrostatic interactions that become stronger as the inter-monomer separation is reduced; the electron-donating substituents have repulsive electrostatic interactions that become more repulsive at shorter inter-monomer separations. At short range, 3–4 Å, the correlation falls apart. The electron-withdrawing substituents continue to behave as expected, but the electron-donating substituents have increasingly more attractive electrostatic interactions as the inter-monomer separation is reduced. At long range, there is very little charge penetration present; multipole–multipole interactions dominate the electrostatic interaction. As the separation is reduced and orbital overlap increases, charge penetration begins to dominate the electrostatic interaction. Notably, the equilibrium geometries here are all in the region where charge penetration effects are very important (3.45–3.95 Å, see Table S1 in the Supporting Information).

Although Figure 2 emphasizes the two most important attractive forces (electrostatics and dispersion), it is worth commenting on the other SAPT components, induction and exchange repulsion. The Supporting Information presents tables of the complete SAPT data and figures of the contributions relative to benzene dimer for equilibrium intermolecular separations and for fixed separations from 3.0 to 7.0 Å. In previous work,^{7,23,27} we have found that although substituents or heteroatoms create a dipole not present in unsubstituted benzene, the resulting dipole–induced dipole forces (included in the induction term) are relatively weak. Figures S1–S7 in the Supporting Information show that variations in the induction term due to substituents are quite modest (typically a few tenths of one kcal mol⁻¹) and are generally much smaller than variations in the other energy components.

For π – π interactions, the dispersion and exchange repulsion terms are often of roughly equal magnitude (but opposite sign), leading them to approximately cancel.^{7,27} This is not a general phenomenon, as exchange repulsion will tend to cancel whatever the dominant attraction is in the complex; for hydrogen-bonded systems, exchange is closer in magnitude to the dominant

electrostatic term than it is to the dispersion term.²⁸ Figure S1 shows that exchange roughly cancels dispersion at equilibrium, although there are significant differences (up to 2.9 kcal mol⁻¹) in some cases. However, much of this appears to be a geometry effect arising because the substituted benzene dimers are bound more strongly and achieve shorter intermolecular separations. At fixed separations of 3.0–4.0 Å, the substituted dimers usually feature *less* unfavorable exchange repulsion than in the benzene dimer. This is surprising given that, according to the Wheeler–Houk view,^{10,16,29} the main effect of the substituent should be direct exchange repulsion between the substituent and the unsubstituted benzene, which one would imagine as always being more repulsive than in the benzene dimer. We hypothesize that because exchange repulsion is such a short-range phenomenon and so sensitive to the orbital overlap, it remains dominated by small changes in the π -electron density induced by substituents. All electron-withdrawing substituents considered here lead to reduced exchange repulsion, whereas the electron-donating methyl groups lead to enhanced exchange repulsion. (Curiously, the electron-donating amine group breaks this pattern and leads to reduced exchange repulsion.) Although the behavior of the relative exchange repulsion term is hard to reconcile with the Wheeler–Houk view, the magnitude of this term is typically comparable to or smaller than the relative dispersion and electrostatic terms (see Figures S2–S7), so that substituent effects on the total interaction energy may remain well-described by the Wheeler–Houk picture.

Finally, we explore further the other intriguing finding of Lewis and co-workers,¹⁸ that the sum of all non-electrostatic terms is roughly constant (thus commending the electrostatic term as the primary descriptor for substituent effects). Similar results have been noted^{8,11} for parallel-displaced configurations of substituted benzene dimers at their equilibrium positions. For the present sandwich systems at their equilibrium separations, Figure S8 plots the relative electrostatic, non-electrostatic (exchange + induction + dispersion), and total SAPT energies vs $\Sigma\sigma_m$. Consistent with the findings of Lewis and co-workers,¹⁸ the electrostatic energies generally track the total interaction energies (although there are differences as large as 3.6 kcal mol⁻¹), and the non-electrostatic terms are roughly constant and near zero (although they can be as large as 1.7 kcal mol⁻¹). We find a good correlation ($R^2 = 0.94$, see Table S8) between the SAPT electrostatic energies and the total SAPT energies.

Unfortunately, however, the quality of this correlation degrades significantly for non-equilibrium geometries. π – π and other non-covalent interactions often occur in the context of larger systems, where backbone constraints or competing interactions prevent individual contacts from reaching what would otherwise be their optimal geometries. Hence, for a correlation to remain useful, it must hold at a range of geometries. As shown in Figures S9–S14, for fixed separations, the relative non-electrostatic energies are no longer nearly constant, varying as much as 6.0 kcal mol⁻¹ at 3.5 Å or as much as 3.2 kcal mol⁻¹ at 4.0 Å for C₆(CN)₆ (Tables S3 and S4). As shown in Table S8, the R^2 metric of the correlation between the relative electrostatic and total energies reduces to 0.81 at 4.0 Å, and to only 0.76 at 3.5 Å (where the correlation with the non-electrostatic components, 0.69, starts to become as good). The correlation between relative interaction energies and electrostatic energies improves at larger distances where other contributions start to die off. Interestingly, the good correlation noted by Lewis and co-workers¹⁸ between relative interaction energies and the sum of the *absolute values* of

the Hammett parameters, $\Sigma|\sigma_m|$, persists here (although somewhat diminished in quality), with R^2 ranging from 0.85 to 0.92, depending on the intermolecular distance. However, as there is no precedent or theoretical justification for using $\Sigma|\sigma_m|$ as a descriptor of interaction energies, without additional testing we are unsure whether it will prove useful in future studies.

The present study has shown that charge penetration effects are crucial for understanding the electrostatic component of π - π interactions and their substituent effects. There is no reason to expect that Hammett σ_m parameters should be capable of describing complicated effects such as charge penetration, and indeed at shorter ranges, the correlation between the electrostatic energy and $\Sigma\sigma_m$ breaks down. As shown previously,¹⁷ for multiply substituted sandwich benzene dimers, there is not a good correlation between relative binding energies and $\Sigma\sigma_m$ (see also Table S8). In agreement with Lewis and co-workers,¹⁸ we find a fairly good correlation between relative binding energies and $\Sigma|\sigma_m|$, but we are reluctant to advocate use of these parameters without further study.

Although additional questions remain, we are optimistic that the main fundamental concepts necessary for understanding substituent effects in the simplest π - π model system (gas-phase sandwich benzene dimer) are now recognized: (a) Except at large intermolecular separations (~ 6 Å or more), all substituents lead to increased binding, regardless of electron-donating or electron-withdrawing character.⁵ (b) Substituent effects are largely due to direct substituent- π interactions, not an indirect modulation of π density¹⁶ (although, as indicated here, this may not be true for the particular contribution from exchange). (c) Substituents influence not only electrostatic contributions but also exchange, induction, and London dispersion contributions.⁷ Although substituent effects in sandwich and parallel-displaced configurations correlate well with just the (SAPT) electrostatic contribution at equilibrium,^{8,11,18} at other geometries this correlation is not nearly as good. (d) The electrostatic contributions are modified by a substituent not only through changes in dipoles, quadrupoles, etc., but also through charge penetration effects that are not easily modeled by multipoles (and certainly not by atom-centered charges³⁰). To demonstrate this point, a simplified electrostatic model complete through quadrupole-quadrupole interactions was shown to fail at reproducing the more rigorous SAPT electrostatic energy. We stress that parallel π - π interactions are often observed for interplanar distances of 3.6 Å or less (3.3 Å in B-DNA) and that charge penetration effects are large (i.e., multipole models fail) at these distances. It now remains to explore how these fundamental concepts in the physics of π - π interactions play out in other geometrical arrangements, for larger systems, and in the presence of solvent.

■ ASSOCIATED CONTENT

Supporting Information. All equilibrium geometries, symmetry-adapted perturbation theory energy components, graphs of various energy components vs $\Sigma\sigma_m$, correlations between various quantities and relative binding energies, and complete refs 22 and 26. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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