

Local Nature of Substituent Effects in Stacking Interactions

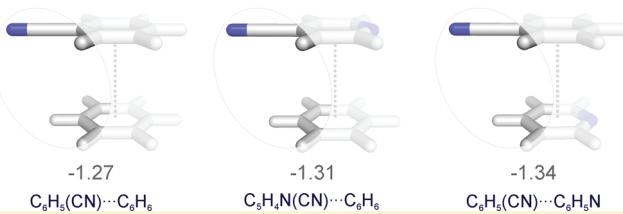
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 Supporting Information

ABSTRACT: Popular explanations of substituent effects in π -stacking interactions hinge upon substituent-induced changes in the aryl π -system. This entrenched view has been used to explain substituent effects in countless stacking interactions over the past 2 decades. However, for a broad range of stacked dimers, it is shown that substituent effects are better described as arising from local, direct interactions of the substituent with the proximal vertex of the other ring. Consequently, substituent effects in stacking interactions are additive, regardless of whether the substituents are on the same or opposite rings. Substituent effects are also insensitive to the introduction of heteroatoms on distant parts of either stacked ring. This local, direct interaction viewpoint provides clear, unambiguous explanations of substituent effects for myriad stacking interactions that are in accord with robust computational data, including DFT-D and new benchmark CCSD(T) results. Many of these computational results cannot be readily explained using traditional π -polarization-based models. Analyses of stacking interactions based solely on the sign of the electrostatic potential above the face of an aromatic ring or the molecular quadrupole moment face a similar fate. The local, direct interaction model provides a simple means of analyzing substituent effects in complex aromatic systems and also offers simple explanations of the crystal packing of fluorinated benzenes and the recently published dependence of the stability of protein–RNA complexes on the regiochemistry of fluorinated base analogues [J. Am. Chem. Soc. 2011, 133, 3687–3689].

Effect of CN Substituents on Stacking Interactions (kcal mol⁻¹)



I. INTRODUCTION

Stacking interactions between aromatic rings are central to many areas of chemistry, materials science, and molecular biology (e.g., Figure 1).^{1,2} Although individually these interactions are relatively weak, they exert significant influence over many key chemical and biological processes. Indeed, these subtle effects are invoked in studies of such disparate areas as the structures of organic electronic materials,³ the basis of sequence selectivity in protein–DNA interactions and DNA intercalation phenomena,⁴ and the origin of stereoselectivity in organocatalyzed reactions.⁵ In each of these cases, the strength and geometry of the stacking interactions can be finely tuned through substituent effects, providing a powerful tool for everything from drug design and crystal engineering to the development of novel materials.^{1–3} For example, Anthony and co-workers^{3,6} demonstrated that fluorination can be used to enhance the stacking interactions and charge-carrier mobilities of bis(triisopropylsilylethynyl)pentacenes for use in organic field effect transistors (Figure 1b). A sound understanding of the nature of substituent effects in stacking interactions will help elucidate their role in myriad chemical contexts and will also enable more refined exploitation in many practical applications.

The most popular view of substituent effects in stacking interactions depends on the polarization of the π -system of the substituted ring (Figure 2a). In particular, the polar/ π model of Cozzi and Siegel^{7–9} and the related model championed by Hunter and co-workers^{10–14} posit that electron-withdrawing

substituents enhance stacking interactions by depleting the π -electron density of the substituted ring. This π -electron depletion relieves some of the electrostatic repulsion between the two aryl π -clouds. Electron donors are said to hinder stacking interactions through the opposite mechanism. Although these two models^{7–14} share many concepts, there are fundamental differences that come to light when considering stacking interactions in which both interacting rings bear substituents. These differences will be discussed below.

Experimental probes of substituent effects in stacking interactions generally support these intuitive electrostatic models,^{8,9,12–18} and clearly indicate that electron donors destabilize stacking interactions, while electron acceptors stabilize stacked rings. Moreover, that substituents on one ring in a stacked dimer can modulate the effect of a substituent on the other ring is often cited as evidence of π -polarization effects.¹⁴ For example, Hunter and co-workers¹⁴ found that replacing an electron-donating group with an electron acceptor on one ring in a stacked dimer reversed the effect of substituents on the other ring. Similar results have been reported by Hunter et al.^{13,14} and many other groups^{9,19–21} in the case of perfluorinated arenes.

Support of these intuitive, π -polarization-based views^{7–14} also stems from the use of plots of electrostatic potential (ESP) surfaces in analyses of noncovalent interactions (Figure 2b). In

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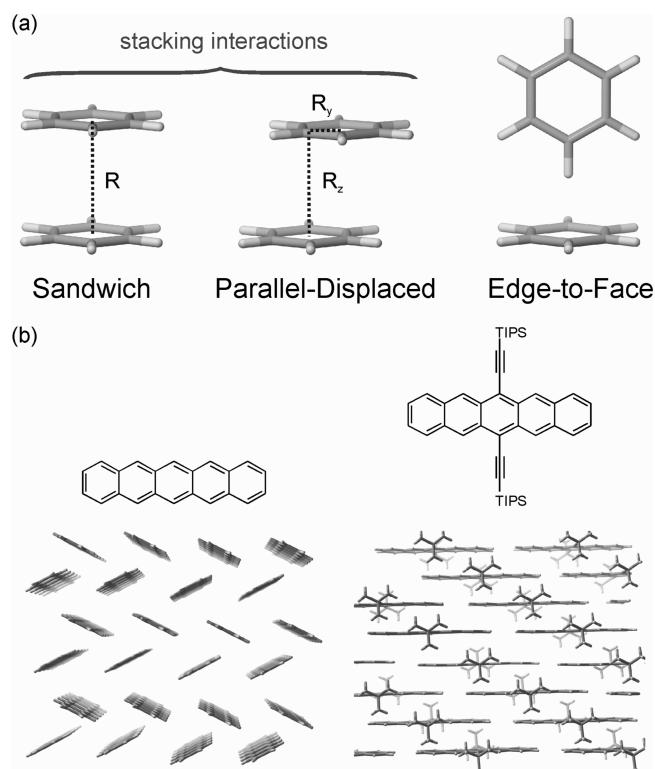


Figure 1. (a) Prototypical benzene dimer configurations, of which the sandwich and parallel-displaced are considered stacking interactions. (b) Intermolecular edge-to-face and stacking interactions in the solid state for pentacene and bis(triisopropylsilyl)pentacene (TIPS-pentacene).

particular, that the ESP above the center of an aryl ring tends to change upon substitution is often touted as evidence of underlying changes in the aryl π -electron density.^{22–26} However, we recently showed²⁷ that changes in the ESP above an aryl ring do not necessarily reflect underlying changes in the π -electron density. We will show below that considering only the sign of the ESP above the center of aryl rings in analyses of stacking interactions can lead to expectations in conflict with accurate computational predictions.

Related discussions of substituent effects in stacking interactions are cast in terms of molecular quadrupole moments. For example, the disparate nature of substituent effects in $C_6H_5X \cdots C_6F_6$ dimers compared to the benzene dimer is generally attributed^{19,28–30} to differences in the quadrupole moments of C_6H_6 and C_6F_6 , which are roughly equal in magnitude but opposite in sign. Similarly, the stacking interaction between C_6F_6 and benzene in the solid state is often explained in terms of quadrupole moments.^{1,11,29,31} Dunitz, in 2004, highlighted flaws of such quadrupole-based analyses in this context.³² For example, 1,3,5-trifluorobenzene, which has a negligible quadrupole moment, exhibits stacking interactions in the solid state quite similar to those seen in C_6F_6/C_6H_6 .^{33,34}

Although the venerable model depicted in Figure 2a has been used countless times to explain experimental trends in substituent effects on stacking interactions,^{8,9,12–18} recent computational investigations have pinpointed flaws in this simple electrostatic picture.^{22–25,28,35–39} For example, Sherrill and co-workers^{22,24,25,35} and Kim et al.³⁶ both showed that, in the gas phase, all substituents stabilize the benzene dimer, not just

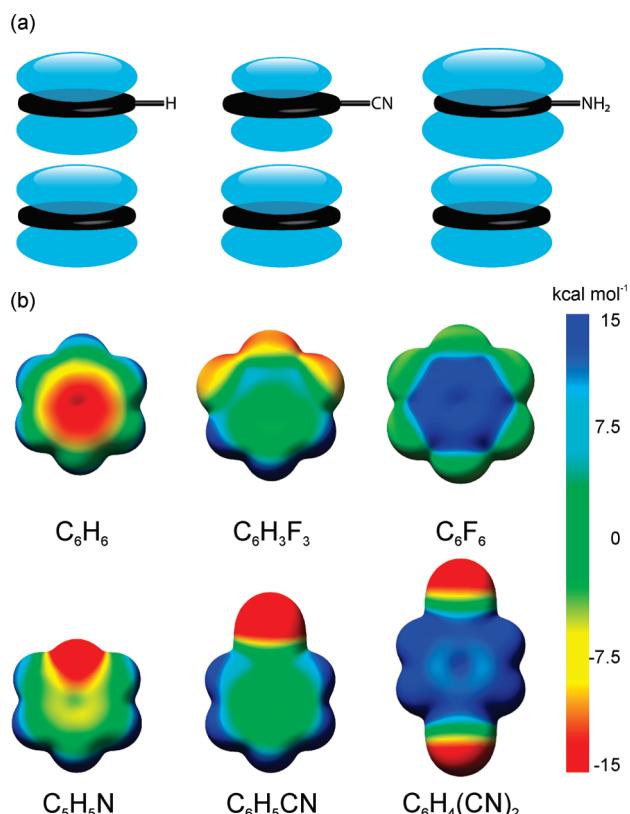


Figure 2. (a) Prevailing view^{7–14} of substituent effects in stacking interactions; electron withdrawing groups (e.g., CN, middle) deplete the aryl π -electron density and relieve the electrostatic repulsion with the π -electron cloud of the unsubstituted ring, while electron donors (e.g., NH₂, right) hinder stacking interactions via the opposite mechanism. (b) ESP plots for benzene, 1,2,3-trifluorobenzene, hexafluorobenzene, pyridine, cyanobenzene, and *p*-dicyanobenzene.

electron acceptors. This year, Lewis and co-workers⁴⁰ published an extensive study of substituent effects in the benzene sandwich dimer, showing that although the overall binding energy is dominated by dispersion interactions, substituent effects are due primarily to electrostatic effects. Seo et al.⁴¹ had shown previously that substituent effects in parallel-displaced benzene dimers are well-described by electrostatic terms alone. However, these electrostatic interactions do not always follow the trends predicted by the model depicted in Figure 2a, and both electron donors and acceptors can lead to attractive electrostatic interactions.⁴⁰

In 2008, Wheeler and Houk proposed^{38,42} that substituent effects in the benzene sandwich dimer arise from direct interactions between the substituent and the other ring, not π -polarization effects. This was based on results from a simple model system in which the substituted ring in the sandwich dimer was replaced by a hydrogen atom (i.e., replacing C_6H_5X in $C_6H_5X \cdots C_6H_6$ with XH, to yield $HX \cdots C_6H_6$), with no discernible effect on substituent effects.³⁸ This direct interaction model was later extended^{38,43} to edge-to-face arene–arene interactions, cation/ π , interactions, and anion/ π interactions. Rashkin and Waters¹⁵ had previously suggested that direct interactions between substituents and the hydrogens of the other ring could explain anomalies in experimental stacking free energies. Similarly, Sherrill et al. invoked²⁴ direct interactions to explain

computed interaction energies for some substituted T-shaped²⁵ and parallel-displaced benzene dimers.²⁵ Tsuzuki and Fujii proposed⁴⁴ direct substituent-ring interactions in CH/π complexes, and Clements and Lewis⁴⁵ suggested a role for direct interactions in the case of anion/π interactions.

Results from one recent experimental probe of substituent effects in stacking interactions⁴² are consistent with the direct interaction model,^{38,42} primarily because they indicate that OMe enhances stacking interactions, despite being a π-electron donor. Recent experimental data from Gung and co-workers⁴⁶ provided more compelling support of this model by showing that the strength of stacking interactions is dependent on the relative position of the substituents (*vide infra*). However, subsequent work on CH/π interactions from Gung et al.⁴⁷ has called the direct interaction model into question, claiming that because “a dominant molecular dipole should place a partial positive charge on the hydrogen in the molecular fragment X–H”, what were described as direct interactions by Wheeler and Houk^{38,42} were actually X–H···π interactions in the HX···C₆H₆ model system. This analysis, however, seems to be based on a fundamental misunderstanding of the computational model of Wheeler et al.^{38,42} In particular, the polarization of the X–H bond was an integral part of the original direct interaction model,^{38,39,42} and the direct interactions were described as arising from the “local dipole induced by the substituent” (i.e., including the polarization of the X–H σ-bond).^{27,38,39,42,43}

Conceptual, predictive models of molecular phenomena are a cornerstone of chemistry and related fields. Here we introduce a simple means of understanding and predicting substituent effects in general stacking interactions, emphasizing their *local*, direct nature. The utility of this viewpoint is demonstrated by examining substituent effects in a range of stacked dimers that are difficult to explain in terms of changes in the aryl π-system.^{7–14} Because the primary focus in the present work is substituent effects, not absolute interaction energies, relative energies are presented almost exclusively and many of the dimers studied are not in their optimal arrangements. As such, consideration of fully relaxed dimers, which in general are not exactly parallel, would likely lead to more complex, and possibly different, qualitative trends in substituent effects. Regardless, the proposed qualitative model should provide sound predictions suitable for the analysis of stacking interactions in diverse and complex aromatic systems.

II. THEORETICAL METHODS

Geometries for 25 monosubstituted pyridines and mono- and disubstituted benzenes were optimized at the B97-D/TZV(2d,2p) level of theory.^{48–50} The substituents considered span the gamut of electron donors and acceptors: NHCH₃, NH₂, N(CH₃)₂, CH₃, NHOH, CH₂OH, SiH₃, OH, OCH₃, SCH₃, CCH, SH, BF₂, F, CHO, COOCH₃, COOH, COCH₃, OCF₃, CF₃, SiF₃, CN, NO, and NO₂. B97-D, when paired with the TZV(2d,2p) basis set along with density fitting techniques, has been shown to provide an economical and practical means of predicting accurate interaction energies for dispersion-dominated complexes, including stacking interactions.^{50,51} Except for the substituted pentacene dimers, interaction energies for all stacked dimers were computed within the fixed monomer approximation using the supramolecular approach. Dimer geometries were optimized along only one (for sandwich configurations) or two (for parallel-displaced configurations) intermolecular distances, indicated in Figure 1a. All other coordinates were fixed. For many of the substituents considered, multiple rotamers are possible. In each system, the monomer geometries utilized correspond to the lowest-energy rotamer at the B97-D/

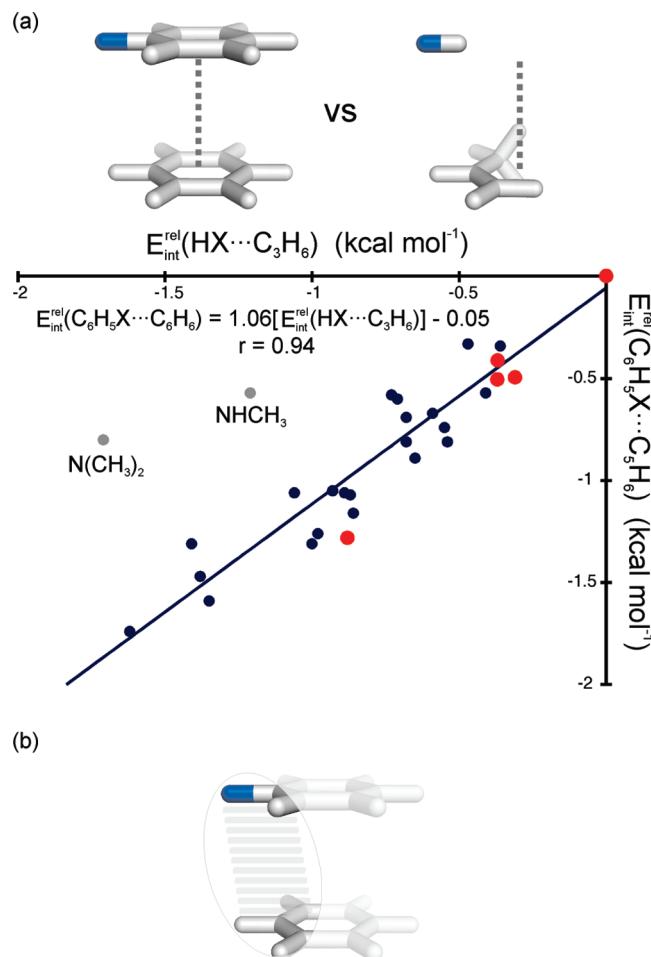


Figure 3. (a) CCSD(T) (red dots) and B97-D (blue dots) interaction energies (kcal mol⁻¹, relative to X = H) for C₆H₅X···C₆H₆ sandwich dimers versus HX···C₃H₆ complexes. The two outliers [N(CH₃)₂ and NHCH₃, gray] were not included in the linear fit. (b) The local, direct interaction model of substituent effects in stacking interactions. Only the substituent and the closest end of the other ring need to be considered when comparing substituent effects in stacking interactions; changes to the other parts of the two rings (faded region) can be ignored.

TZV(2d,2p) level of theory, and the orientations of the monomers in the stacked dimers are those that give the most favorable interaction energy. Except where noted otherwise, all interaction energies presented were evaluated at the dimer geometry optimized at the given level of theory. For the pentacene dimers, full, unconstrained B97-D optimizations were performed. B97-D energies were not corrected for basis set superposition error (BSSE).

Benchmark CCSD(T) interaction energies were computed for selected systems to validate and corroborate the B97-D results and to provide more accurate interaction energies and optimized geometries. In this case, CCSD(T)/AVTZ energies were estimated by appending a basis set correction evaluated at the MP2 level of theory to CCSD(T)/AVDZ' energies,

$$E[\text{CCSD(T)}/\text{AVTZ}] \approx E[\text{CCSD(T)}/\text{AVDZ}'] + E[\text{MP2}/\text{AVTZ}] - E[\text{MP2}/\text{AVDZ}']$$

where AVTZ denotes the standard aug-cc-pVTZ basis set⁴⁹ and AVDZ' is a truncated basis³⁵ comprising cc-pVDZ on H and aug-cc-pVDZ without diffuse d-functions on all other atoms. CCSD(T) and MP2 energies were corrected for BSSE via the counterpoise correction.⁵² As

with the B97-D optimizations, only one or two intermolecular distances were optimized, and monomers were fixed at MP2/AVTZ optimized geometries. Core orbitals were frozen in all correlated computations.

Uncertainties in the slopes of the linear regressions are quoted at the 95% confidence interval. Electrostatic potential plots were made using UCSF Chimera⁵³ by mapping the ESP onto electron density isosurfaces ($\rho = 0.001 \text{ e}/\text{au}^3$) and were computed at the B97-D/TZV(2d,2p) level of theory. Density fitting was used in all B97-D computations, which were carried out using Gaussian09.⁵⁴ Molpro 2009 was used for the MP2 and CCSD(T) computations.⁵⁵

III. LOCAL, DIRECT INTERACTION MODEL OF SUBSTITUENT EFFECTS IN STACKING INTERACTIONS

Previous work by Wheeler and Houk³⁸ on the benzene sandwich dimer revealed that the effects of a broad range of substituents can be reproduced using a simple model system in which the substituted phenyl ring in the equilibrium dimer geometry is replaced with a hydrogen atom. We now consider an even simpler model system to demonstrate the local nature of substituent effects in stacking interactions—the interaction of XH with propene. These complexes were constructed such that all of the atoms of the substituent X are coincident with the corresponding positions in the equilibrium substituted benzene sandwich dimer geometry and the carbon framework of propene is coincident with the nearest vertex of the unsubstituted benzene (Figure 3a). The positions of all added hydrogens were optimized. Remarkably, there is a strong correlation ($r = 0.94$, excluding the two outliers marked in gray) between B97-D predicted relative interaction energies in the intact substituted sandwich dimers and $\text{HX}\cdots\text{C}_3\text{H}_6$ (Figure 3a). This trend is also reproduced at the CCSD(T) level of theory (red dots, Figure 3a). The two outliers, $\text{N}(\text{CH}_3)_2$ and NHCH_3 , both feature methyl groups that protrude to the sides, and it is therefore unsurprising that capturing the substituent effects in these two systems requires more than just the three closest carbons of the nonsubstituted ring.

That the substituent effects in the benzene sandwich dimer are captured by $\text{HX}\cdots\text{C}_3\text{H}_6$ complexes suggests a simple model of substituent effects in stacking interactions in which the effects depend only on the interaction of the substituent (including the first polarized σ -bond, as approximated by H—X) with the closest vertex of the other aromatic ring (as approximated by propene in Figure 3a). This model is depicted in Figure 3b and will be validated below. In this model, the effect of a given substituent is not influenced by changes to either aromatic ring *as long as these changes are not in the local environment of the substituent or involve the closest three carbons of the other ring*.

The physical basis of this local, direct interaction model can be understood qualitatively in terms of local dipoles. Specifically, substituent effects in stacking interactions are consistent with the interaction of the dipole induced by the substituent (including the polarization of the first σ -bond) with the local C—H dipoles on the nearest end of the other arene. These local interactions will be relatively unperturbed by changes to distant parts of either ring.

Sandwich dimers of disubstituted benzenes with benzene and monosubstituted benzene homodimers provide a convenient proving ground for qualitative models of substituent effects in stacking interactions. The π -polarization models^{7–14} predict additivity of substituent effects in the case of sandwich dimers

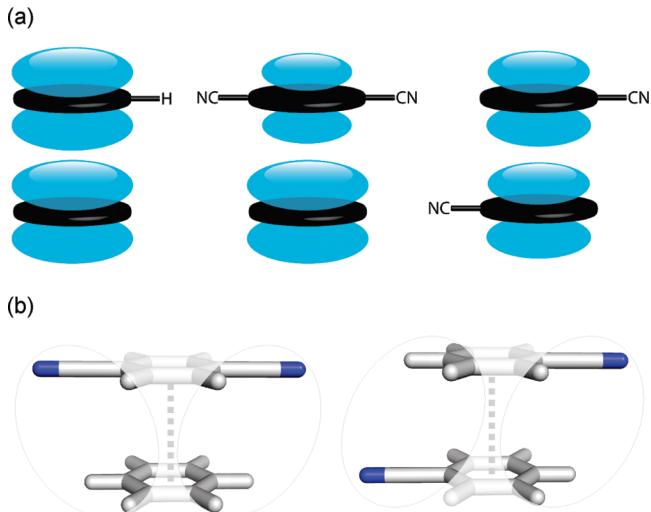


Figure 4. (a) π -polarization model and (b) local, direct interaction model applied to the *p*-dicyanobenzene–benzene sandwich dimer and cyanobenzene sandwich homodimer. From b, it is clear that the local, direct interactions are identical in the two dimers and that the stacking interaction energies should be equal.

of a disubstituted benzene with benzene (Figure 4a), because it is assumed that each substituent will act on the aryl π -system independently. This additivity has been confirmed by experiment and theory.^{21,24} For example, Sherrill and co-workers²⁴ found almost quantitative additivity of substituent effects in sandwich dimers of polysubstituted benzenes with benzene for a small number of substituents at the MP2/AVDZ level of theory.

For stacked dimers in which each ring bears a substituent, e.g., $\text{C}_6\text{H}_5\text{X}\cdots\text{C}_6\text{H}_5\text{Y}$, the predictions of π -polarization-based models of Cozzi et al. and Hunter and co-workers differ.^{7–14} Cozzi et al.⁷ argued in one of their pioneering papers on the polar/ π model that “the Coulombic repulsion should be minimized for the interaction between two electron-poor rings, maximized for two electron-rich rings, and intermediate for one electron-rich and one electron-poor ring.” In the case of monosubstituted homodimers (i.e., $\text{C}_6\text{H}_5\text{X}\cdots\text{C}_6\text{H}_5\text{X}$), this analysis indicates additivity of effects, analogous to those seen in the dimers of disubstituted benzene with benzene. Hunter and co-workers,^{11,14} on the other hand, argue that stacking interactions should be maximized when one ring bears an electron-donating group and the other an electron acceptor and that “like-polarized” aromatic rings, as in monosubstituted homodimers, should repel one another.

B97-D and CCSD(T) stacking energies for selected $\text{C}_6\text{H}_5\text{X}\cdots\text{C}_6\text{H}_6$, $\text{C}_6\text{H}_4\text{X}_2\cdots\text{C}_6\text{H}_6$, and $\text{C}_6\text{H}_5\text{X}\cdots\text{C}_6\text{H}_5\text{X}$ sandwich dimers are presented in Table 1. B97-D data for 20 additional substituents are provided in Supporting Information Tables S1–S3. As previously observed at lower levels of theory,²⁴ interaction energies for $\text{C}_6\text{H}_4\text{X}_2\cdots\text{C}_6\text{H}_6$ dimers are almost exactly twice the interaction energy of the corresponding $\text{C}_6\text{H}_5\text{X}\cdots\text{C}_6\text{H}_6$ dimers at the estimated CCSD(T)/AVTZ level of theory. This additivity is also exhibited by the B97-D data for the full set of substituents (see Supporting Information Figure S1), with a correlation coefficient of 0.997 and a best fit line with a slope of 2.04 ± 0.06 .

However, as seen from Table 1 and Figure 5a, computed interaction energies for $\text{C}_6\text{H}_5\text{X}\cdots\text{C}_6\text{H}_5\text{X}$ homodimers are also

Table 1. B97-D/TZV(2d,2p) and Estimated CCSD(T)/AVTZ Relative Interaction Energies ($E_{\text{int}}^{\text{rel}}$, kcal mol⁻¹) and Optimized Interring Distances (R , R_y , and R_z , Å) for Selected Substituted Benzene Sandwich and Parallel Displaced Dimers^a

| X | sandwich dimer | | | | parallel-displaced dimer | | | | | | | |
|--|----------------|-------------------------------|---------|-------------------------------|--------------------------|-------|-------------------------------|-------|-------|-------------------------------|--|--|
| | B97-D | | CCSD(T) | | B97-D | | CCSD(T) | | | | | |
| | R | $E_{\text{int}}^{\text{rel}}$ | R | $E_{\text{int}}^{\text{rel}}$ | R_y | R_z | $E_{\text{int}}^{\text{rel}}$ | R_y | R_z | $E_{\text{int}}^{\text{rel}}$ | | |
| $\text{C}_6\text{H}_5\text{X} \cdots \text{C}_6\text{H}_6$ | | | | | | | | | | | | |
| H ^b | 3.95 | 0.00 | 3.83 | 0.00 | 1.82 | 3.50 | 0.00 | 1.69 | 3.52 | 0.00 | | |
| CN | 3.82 | -1.31 | 3.79 | -1.27 | 1.61 | 3.43 | -1.38 | 1.55 | 3.46 | -1.26 | | |
| F | 3.89 | -0.58 | 3.83 | -0.50 | 1.72 | 3.47 | -0.65 | 1.61 | 3.48 | -0.52 | | |
| CH ₃ | 3.88 | -0.57 | 3.84 | -0.49 | 1.70 | 3.44 | -0.58 | 1.61 | 3.48 | -0.50 | | |
| NH ₂ | 3.91 | -0.34 | 3.80 | -0.41 | 1.79 | 3.42 | -0.57 | 1.65 | 3.44 | -0.61 | | |
| $\text{C}_6\text{H}_4\text{X}_2 \cdots \text{C}_6\text{H}_6$ | | | | | | | | | | | | |
| CN | 3.67 | -2.73 | 3.70 | -2.62 | 1.60 | 3.37 | -2.80 | 1.46 | 3.41 | -2.64 | | |
| F | 3.78 | -1.22 | 3.76 | -1.06 | 1.70 | 3.39 | -1.34 | 1.54 | 3.44 | -1.10 | | |
| CH ₃ | 3.78 | -1.17 | 3.78 | -0.98 | 1.65 | 3.37 | -1.12 | 1.55 | 3.43 | -1.01 | | |
| NH ₂ | 3.77 | -0.87 | 3.71 | -0.92 | 1.77 | 3.34 | -1.32 | 1.61 | 3.37 | -1.34 | | |
| $\text{C}_6\text{H}_5\text{X} \cdots \text{C}_6\text{H}_5\text{X}$ | | | | | | | | | | | | |
| CN | 3.69 | -2.50 | 3.74 | -2.17 | 1.50 | 3.40 | -2.44 | 1.45 | 3.43 | -2.26 | | |
| F | 3.79 | -1.17 | 3.78 | -0.86 | 1.62 | 3.40 | -1.27 | 1.54 | 3.44 | -1.02 | | |
| CH ₃ | 3.79 | -1.05 | 3.80 | -0.86 | 1.64 | 3.40 | -1.23 | 1.55 | 3.44 | -1.06 | | |
| NH ₂ | 3.83 | -0.63 | 3.72 | -0.65 | 1.81 | 3.36 | -1.01 | 1.65 | 3.37 | -1.15 | | |

^aB97-D data for 20 other substituents is available in Supporting Information Tables S1, S2, S8, and S10. ^bFor the benzene sandwich dimer, absolute $E_{\text{int}} = -1.80$ and -1.79 kcal mol⁻¹ with B97-D and CCSD(T), respectively. For the parallel-displaced benzene dimer, absolute $E_{\text{int}} = -2.74$ and -2.78 kcal mol⁻¹ with B97-D and CCSD(T), respectively.

strongly correlated with the interaction energies in $\text{C}_6\text{H}_4\text{X}_2 \cdots \text{C}_6\text{H}_6$ sandwich dimers at both levels of theory ($r = 0.99$, slope = 1.03 ± 0.07). Although this behavior is consistent with the analysis of Cozzi et al.,⁷ the correlation is more readily explained in terms of local, direct interactions, with no involvement of π -polarization effects. In both $\text{C}_6\text{H}_5\text{X} \cdots \text{C}_6\text{H}_5\text{X}$ and $\text{C}_6\text{H}_4\text{X}_2 \cdots \text{C}_6\text{H}_6$, the local interactions are equivalent (Figure 4b), and as a result the substituent effects in these two types of dimers are identical. These data are in stark contrast to the model of Hunter and co-workers,^{11,14} which clearly predicts repulsive interactions in monosubstituted homodimers.^{11,14}

Substituent effects in the parallel-displaced benzene dimer have received considerably less attention than the sandwich dimer in the computational literature,²⁵ even though the parallel-displaced configuration is the one that is a stable minimum.²³ Sherrill and co-workers²⁵ presented accurate CCSD(T) computations of substituted parallel-displaced dimers, showing complex interaction potentials with multiple minima. These complex potentials were attributed in part to direct interactions between the substituents and the other ring. In this case, such direct interactions were unsurprising, because the rings were displaced in a direction parallel to the benzene-substituent bond and the substituent was located directly above the other ring.

Here we consider parallel-displaced dimers in which the displacement is perpendicular to the benzene-substituent bonds.

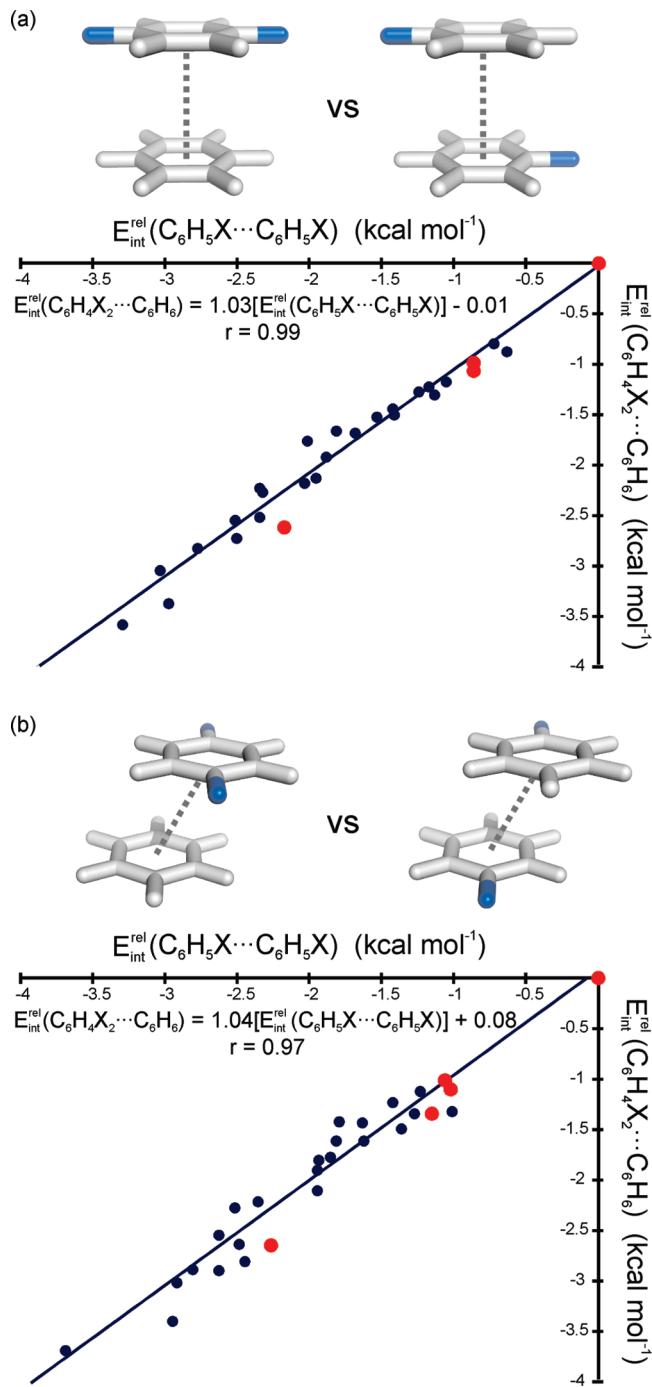


Figure 5. CCSD(T) (red dots) and B97-D (blue dots) interaction energies (kcal mol⁻¹, relative to X = H) for $\text{C}_6\text{H}_4\text{X}_2 \cdots \text{C}_6\text{H}_6$ versus $\text{C}_6\text{H}_5\text{X} \cdots \text{C}_6\text{H}_5\text{X}$ in a sandwich (a) and parallel-displaced configuration (b).

In this case, conventional views would predict no appreciable direct interaction between the substituent and the other ring. B97-D and CCSD(T) results for selected monosubstituted and disubstituted parallel-displaced benzene dimers are presented in Table 1 (additional B97-D is available in the Supporting Information). Substituents have a significant impact on the extent of parallel displacement (R_y), with B97-D predicting distances ranging from 1.56 (for COOCH₃) to 1.83 Å (for CF₃); the equilibrium value of R_y for the unsubstituted dimer at this level of

theory is 1.82 Å. The effect of substituents on the vertical displacement (R_z) is somewhat less severe, with values ranging from 3.39 Å for NO_2 to 3.50 Å. As with the disubstituted benzene–benzene sandwich dimers, substituent effects in the parallel-displaced dimers are additive, with a strong correlation ($r = 0.98$, best fit line with slope of 1.98 ± 0.15 ; see Figure S2 of the Supporting Information) between the parallel-displaced monosubstituted benzene–benzene and *p*-disubstituted benzene–benzene dimers.

Overall, substituent effects in the parallel-displaced configuration mimic those in the sandwich configuration. Indeed, there is a strong correlation between interaction energies in these parallel-displaced dimers and those for the sandwich dimers ($r = 0.96$; see Supporting Information Figure S3), with a best-fit line with slope 0.95 ± 0.11 . That the substituent effects in these two cases are essentially identical is seemingly at odds with conventional

π -polarization-based views.^{7–14} This is because in the parallel-displaced dimers there should be an interaction between the π -cloud of the substituted ring and the partially positively charged hydrogens of the other ring, which, if any appreciable π -polarization were occurring, would lead to substituent effects in opposition to those in the sandwich dimer. Moreover, substituent effects in monosubstituted parallel-displaced homodimers are strongly correlated with substituent effects in disubstituted parallel-displaced dimers ($r = 0.97$, slope = 1.04 ± 0.11 , Figure Sb), as was observed in the case of sandwich dimers (Figure 5a). That this additivity is independent of which rings bear the substituents can again be explained readily in terms of local, direct interactions.

Extension to mixed monosubstituted dimers, $\text{C}_6\text{H}_5\text{X} \cdots \text{C}_6\text{H}_5\text{Y}$, enables the examination of a broader range of complexes and provides a more stringent test of available models. In terms of the π -polarization model of Hunter and co-workers,^{7–14} one would expect a strong coupling between substituents X and Y in $\text{C}_6\text{H}_5\text{X} \cdots \text{C}_6\text{H}_5\text{Y}$ sandwich dimers. Specifically, according to Hunter et al.,^{11,14} if Y is an electron acceptor, the most favorable interaction is expected when X is a donor, and vice versa. The analysis of Cozzi et al.⁷ instead indicates additivity of substituent effects, regardless of which ring the substituents are attached to,

Scheme 1

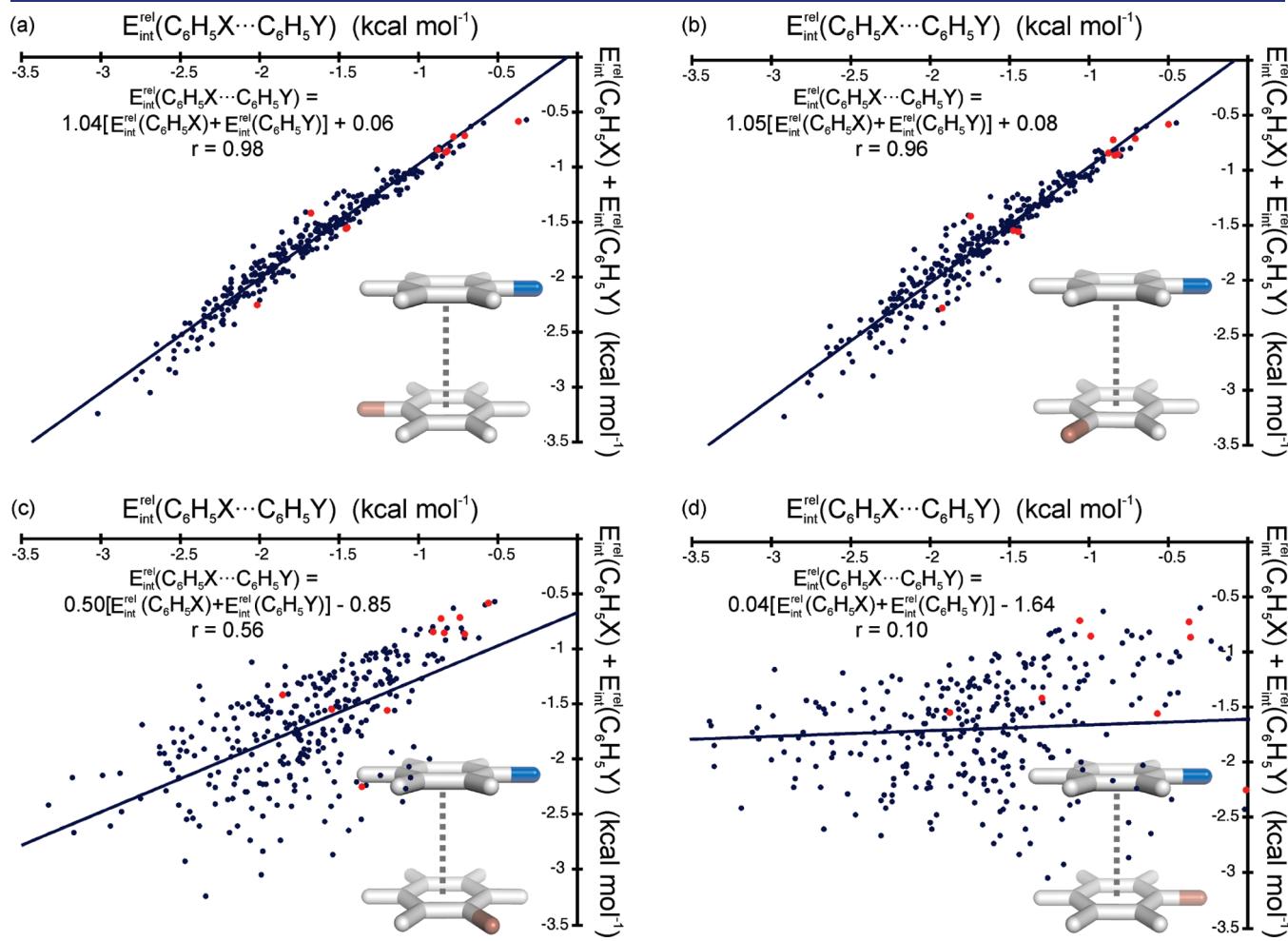
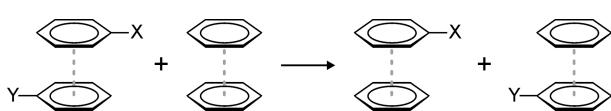


Figure 6. CCSD(T) (red dots) and B97-D (blue dots) interaction energies for $\text{C}_6\text{H}_5\text{X} \cdots \text{C}_6\text{H}_5\text{Y}$ dimers (kcal mol⁻¹, relative to X, Y = H) versus the sum of the interaction energies of the corresponding $\text{C}_6\text{H}_5\text{X} \cdots \text{C}_6\text{H}_6$ and $\text{C}_6\text{H}_5\text{Y} \cdots \text{C}_6\text{H}_6$ dimers (kcal mol⁻¹, relative to X, Y = H) for substituents oriented at (a) 180, (b) 120, (c) 60, and (d) 0° relative to one another. For simplicity, all dimers were computed at ring separations of 4 Å. Interaction energies for the 1200 B97-D and 40 CCSD(T) data points plotted above are reported in Supporting Information Tables S11 and S12.

as does the local, direct interaction picture. In other words, on the basis of the local, direct interaction view and that of Cozzi et al.,⁷ the homodesmotic transformation⁵⁶ in Scheme 1 should be thermoneutral.

As seen in Figure 6a, for a set of 300 unique $C_6H_5X \cdots C_6H_5Y$ sandwich dimers in which the two substituents are oriented at 180° relative to one another, there is no coupling between the substituents and there is a very strong correlation ($r = 0.98$, slope $= 1.04 \pm 0.03$) between the total substituent effect in $C_6H_5X \cdots C_6H_5Y$ and the sum of substituent effects in $C_6H_5X \cdots C_6H_6$ and $C_6H_5Y \cdots C_6H_6$. This excellent correlation is also exhibited by the CCSD(T) data and cannot be readily explained in terms of the π -polarization model of Hunter et al.^{11,14} This additivity of substituent effects is a natural consequence of the local, direct interaction model and has previously been noted by Sherrill and co-workers.²⁴

If the two substituents in $C_6H_5X \cdots C_6H_5Y$ are oriented at a 120° angle (Figure 6b), then there is still nearly quantitative additivity and little coupling between the two substituents. It is not until the two substituents are in close proximity, as in Figure 6c,d, that the substituent effects are coupled. Indeed, for the $C_6H_5X \cdots C_6H_5Y$ dimers in which the angle between the two substituents is zero, there is essentially no correlation (Figure 6d, $r = 0.10$, slope $= 0.04 \pm 0.05$) between the substituent effect in the mixed dimer and the sum of individual substituent effects for X and Y. This is due to the direct substituent–substituent interactions that are possible in this case (and to a lesser extent in the orientation in Figure 6c), but not in the complexes where the substituents are at 120 and 180° . Sherrill and co-workers previously noted these direct substituent–substituent interactions in monosubstituted sandwich heterodimers in which the two substituents were aligned.²⁴ Such orientation dependence of substituent effects in mixed disubstituted dimers is not expected on the basis of the polar/ π model of Cozzi et al.⁷

That many experimental studies^{14,16} have shown a coupling between substituent effects in stacked aromatic rings is seemingly in conflict with the above results. However, closer examination of these experimental probes^{14,16} reveals that they are akin to the orientation depicted in Figure 6d, in which the substituents on the two rings are in close proximity. In other words, the experimental observation of coupling between substituent effects might simply be due to direct substituent–substituent interactions, not any effect transmitted through the aryl π -systems as assumed.^{14,16} The present, high-level computations clearly predict that substituents operate independently of one another, as long as they are on distant ends of the two stacked rings.

IV. APPLICATIONS OF THE LOCAL, DIRECT INTERACTION MODEL

Below, we examine substituent effects in more diverse stacked dimers to gauge the utility of the local, direct interaction model depicted in Figure 3b. In each case, this model provides clear, unambiguous predictions that are consistent with interaction energies computed at both the B97-D/TZV(2d,2p) and estimated CCSD(T)/AVTZ levels of theory, or with experimental results. For many of these systems, the substituent effects are difficult to reconcile with the prevailing π -polarization-based viewpoint.^{7–14}

A. Benzene–1,2,3-Trifluorobenzene Dimers. According to the consensus view,^{7–14} substituent effects in the perfluorobenzene–benzene dimer differ from those in the nonfluorinated

Table 2. B97-D/TZV(2d,2p) and Estimated CCSD(T)/AVTZ Relative Interaction Energies (E_{int}^{rel} , kcal mol⁻¹) and Optimized Interring Distances (R, Å) for Selected Substituted Benzene–Perfluorobenzene and Benzene–1,2,3-Trifluorobenzene Sandwich Dimers^a

| X | B97-D | | CCSD(T) | |
|---|-------|-----------------|---------|-----------------|
| | R | E_{int}^{rel} | R | E_{int}^{rel} |
| $C_6H_5X \cdots C_6F_6$ | | | | |
| H ^b | 3.52 | 0.00 | 3.53 | 0.00 |
| CN | 3.53 | 0.43 | 3.56 | 0.83 |
| F | 3.52 | 0.11 | 3.54 | 0.46 |
| CH ₃ | 3.52 | -0.85 | 3.55 | -0.55 |
| NH ₂ | 3.54 | -0.95 | 3.51 | -0.74 |
| $C_6H_5X \cdots C_6H_3F_3$ (Substituent over the Fluorinated End) | | | | |
| H ^c | 3.65 | 0.00 | 3.70 | 0.00 |
| CN | 3.64 | 0.09 | 3.70 | 0.47 |
| F | 3.64 | 0.03 | 3.71 | 0.35 |
| CH ₃ | 3.63 | -0.93 | 3.69 | -0.63 |
| NH ₂ | 3.67 | -0.57 | 3.68 | -0.32 |
| $C_6H_5X \cdots C_6H_3F_3$ (Substituent over the Non-fluorinated End) | | | | |
| CN | 3.60 | -1.29 | 3.64 | -1.08 |
| F | 3.60 | -0.69 | 3.64 | -0.52 |
| CH ₃ | 3.59 | -0.65 | 3.65 | -0.51 |
| NH ₂ | 3.61 | -0.97 | 3.60 | -0.97 |

^a B97-D data for 20 other substituents is available in Supporting Information Tables S6 and S7. ^b For the $C_6H_5 \cdots C_6F_6$ sandwich dimer, the absolute $E_{int} = -6.27$ and -5.59 kcal mol⁻¹ at the B97-D and CCSD(T) levels of theory, respectively. ^c For the $C_6H_5 \cdots C_6H_3F_3$ sandwich dimer, the absolute $E_{int} = -3.74$ and -3.44 kcal mol⁻¹ at the B97-D and CCSD(T) levels of theory, respectively.

benzene dimer because of the opposite sign of the C_6F_6 and C_6H_6 quadrupole moments.^{9,13,14,19–21} Substituted benzene–1,2,3-trifluorobenzene dimers provide an example of the utility of the local, direct interaction view of substituent effects in stacking interactions and reveal a major weakness in quadrupole-based description of perfluoroarene–arene interactions.^{9,13,14,19–21} In terms of the local, direct interaction viewpoint, if the benzene substituent is oriented over the nonfluorinated end of $C_6H_3F_3$, one would expect substituent effects to resemble those in the monosubstituted benzene sandwich dimer. Similarly, if the substituent is oriented over the fluorinated end of the ring, the local interactions are the same as those in the $C_6H_5X \cdots C_6F_6$ dimer and a correlation is expected between the relative energies in these two systems.

B97-D and CCSD(T) data for selected $C_6H_5X \cdots C_6F_6$ dimers and two orientations of the $C_6H_5X \cdots C_6H_3F_3$ dimer are provided in Table 2. Substituent effects in $C_6H_5X \cdots C_6F_6$ dimers are of similar magnitude to those in the benzene dimer, and in this case electron-withdrawing groups destabilize this dimer as has been shown previously.^{9,19–21,38} However, $C_6H_5X \cdots C_6H_3F_3$ complexes show the same substituent effects, as long as the substituent is located over the fluorinated end of trifluorobenzene ($r = 0.97$, slope $= 0.82 \pm 0.09$, Figure 7a). There is also a correlation ($r = 0.91$, slope $= 0.80 \pm 0.16$, Figure 7b) between substituent effects in the benzene sandwich dimer and the $C_6H_5X \cdots C_6H_3F_3$ dimer if the substituent is oriented over

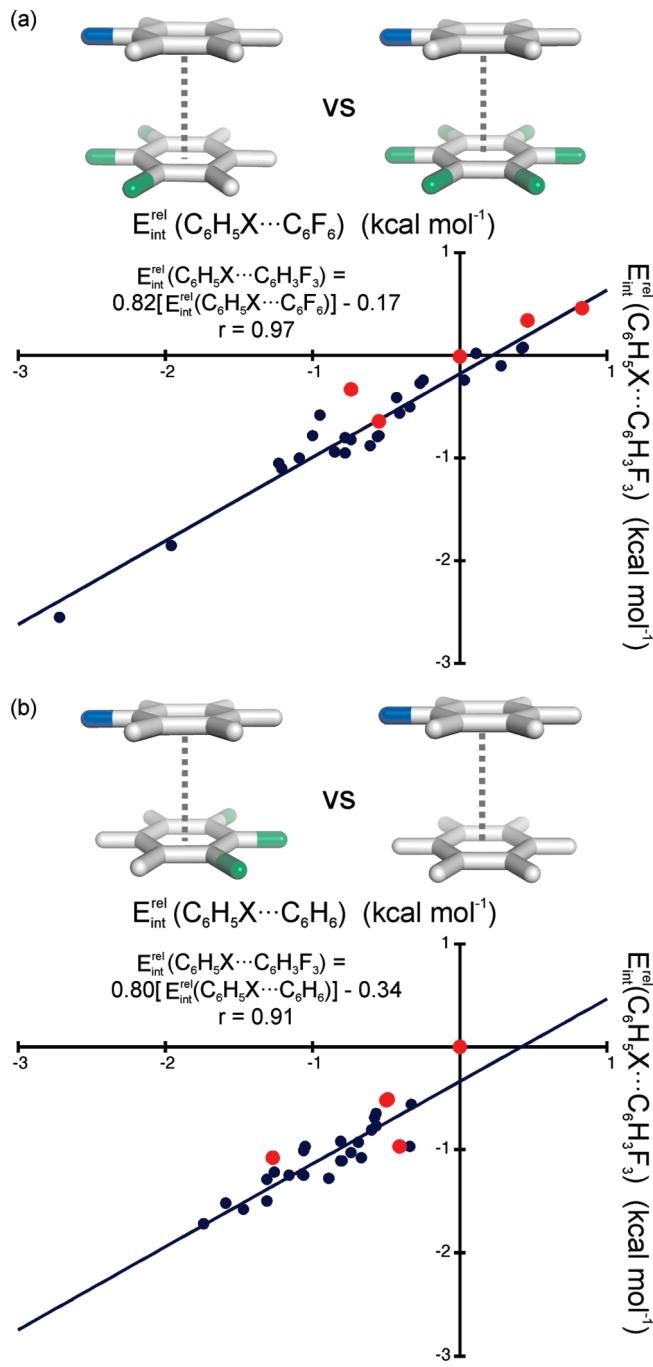


Figure 7. CCSD(T) (red dots) and B97-D (blue dots) interaction energies (kcal mol⁻¹, relative to X = H) in $C_6H_5X \cdots C_6H_3F_3$ sandwich dimers compared to (a) $C_6H_5X \cdots C_6F_6$ and (b) $C_6H_5X \cdots C_6H_6$.

the nonfluorinated end of trifluorobenzene. In both cases, the slope of the best-fit lines are not exactly unity, suggesting some systematic deviation between the substituent effects in $C_6H_5X \cdots C_6H_3F_3$ and the perfluorobenzene and nonfluorinated benzene dimers. Regardless, there is certainly qualitative agreement, which is in stark contrast to the behavior expected on the basis of molecular quadrupole moments, π -polarization effects, or computed electrostatic potentials (vide infra). In both cases, the substituent effects arise from local, direct interactions between the substituent and the local C–H or C–F dipoles. This

Table 3. B97-D/TZV(2d,2p) and Estimated CCSD(T)/AVTZ Relative Interaction Energies ($E_{\text{int}}^{\text{rel}}$, kcal mol⁻¹) and Optimized Interring Distances (R , Å) for Selected Substituted Benzene–Pyridine Sandwich Dimers^a

| X | B97-D | | CCSD(T) | |
|--------------------------|-------|-------------------------------|---------|-------------------------------|
| | R | $E_{\text{int}}^{\text{rel}}$ | R | $E_{\text{int}}^{\text{rel}}$ |
| $C_6H_6 \cdots XC_5H_4N$ | | | | |
| H ^b | 3.88 | 0.00 | 3.81 | 0.00 |
| CN | 3.71 | -1.37 | 3.72 | -1.31 |
| F | 3.79 | -0.63 | 3.75 | -0.55 |
| CH ₃ | 3.78 | -0.62 | 3.77 | -0.52 |
| NH ₂ | 3.77 | -0.27 | 3.73 | -0.37 |
| $C_6H_5X \cdots C_5H_3N$ | | | | |
| CN | 3.71 | -1.44 | 3.72 | -1.34 |
| F | 3.79 | -0.61 | 3.76 | -0.52 |
| CH ₃ | 3.78 | -0.49 | 3.77 | -0.38 |
| NH ₂ | 3.77 | -0.50 | 3.72 | -0.59 |

^a B97-D data for 20 other substituents is available in Supporting Information Tables S4 and S5. ^b For the pyridine–benzene sandwich dimer, the absolute $E_{\text{int}} = -2.23$ and -2.24 kcal mol⁻¹ at the B97-D and CCSD(T) levels of theory, respectively.

implies that the differences in substituent effects^{9,13,14,19–21} in C_6H_6 versus the perfluorinated benzenes can be explained solely on the basis of differences in the polarity of C–F and C–H bonds, and discussions cast in terms of molecular quadrupole moments are unwarranted.

B. Benzene–Pyridine Dimers. The local, direct interaction model also provides a simple means of understanding substituent effects in stacking interactions involving heterocyclic aromatic systems, which have received far less attention in the literature. Hohenstein and Sherrill presented²⁶ a detailed quantum mechanical analysis of the benzene–pyridine and pyridine–pyridine sandwich dimers, providing key insight into the differences between these complexes and the benzene dimer. Notably, it was shown that dispersion, exchange, and induction effects are reduced in these two dimers compared to the benzene dimer, and the pyridine–benzene stacking interaction is 0.4 kcal mol⁻¹ more favorable than that in the benzene sandwich dimer. Also, parallel-displaced configurations were shown to be significantly favored over T-shaped arrangements for both pyridine–benzene and pyridine–pyridine, while for the benzene dimer the parallel-displaced and T-shaped configurations are essentially isoenergetic.^{23,57} In 2004, Geerlings et al.⁵⁸ studied parallel-displaced dimers of substituted benzenes with pyridine using MP2, showing a strong correlation between hardness and polarizabilities with predicted interaction energies. To our knowledge, there has been no systematic study of dimers of substituted pyridines with benzenes.

B97-D and CCSD(T) results for selected substituted dimers are presented in Table 3, including data for substituents on both the benzene and pyridine. B97-D data for 20 additional substituents are provided in Supporting Information. The local, direct interaction model presented in section III predicts that substituent effects in the benzene–pyridine sandwich dimer should be the same as those in the benzene sandwich dimer, provided that the substituent is oriented away from the pyridine nitrogen. Indeed, both CCSD(T) and B97-D computations reveal a

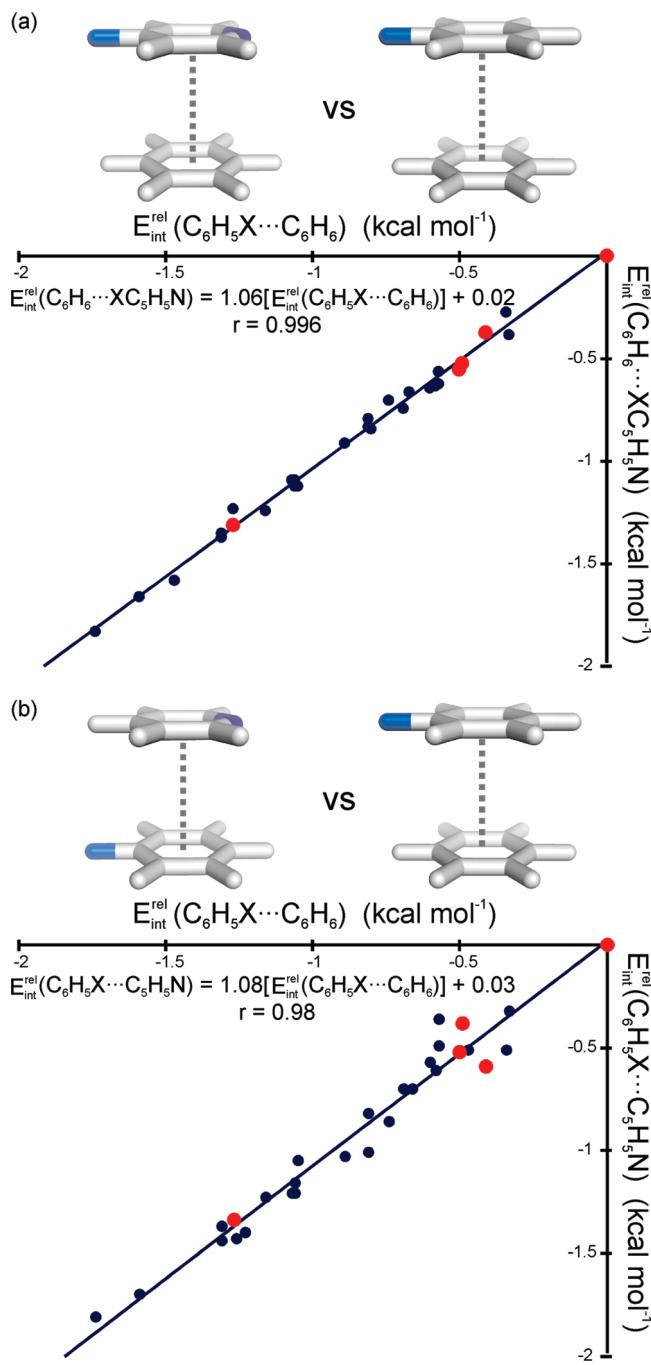


Figure 8. CCSD(T) (red dots) and B97-D (blue dots) interaction energies (kcal mol⁻¹, relative to X = H) for $C_6H_5X \cdots C_6H_6$ versus (a) $C_6H_5X \cdots C_5H_5N$ and (b) $C_6H_6 \cdots XC_5H_5N$.

striking correlation between substituent effects in pyridine–benzene dimers and monosubstituted benzene dimers ($r = 0.996$, slope = 1.06 ± 0.04 and $r = 0.98$, slope = 1.08 ± 0.11 ; see Figure 8), regardless of whether the benzene or pyridine bears the substituent. That nitrogen has no discernible bearing on the substituent effects lends further support to the local, direct interaction model presented in section III and provides a glimpse of the power offered by the transferability of substituent effects predicted by this model. In particular, substituent effects are unaffected by the presence of heteroatoms in either the substituted

or nonsubstituted ring, as long as the local, direct interactions are unaltered. Such behavior is contrary to expectations based on considerations of the π -system, which will be altered by the presence of a nitrogen anywhere in the ring.

Gung et al.⁵⁹ published experimental data for stacking interactions of substituted benzenes with pyridine that are seemingly in conflict with the above results. In particular, Gung showed⁵⁹ that compared to the benzene–benzene interaction, the stacking interaction of a heterocycle with benzene was far less sensitive to substituent effects. However, in the triptycene-derived molecular balances utilized by Gung and co-workers,⁵⁹ the substituents were located directly above the heteroatom (i.e., equivalent to the pyridine rotated 180° in Figure 8b). In that case, the local interactions in the benzene–benzene and benzene–pyridine dimers were not the same, and differences in substituent effects are expected.

C. Pentacene Dimers. The performance and properties of organic electronic materials are inextricably linked with material morphology and molecular architecture.^{60,61} Recently, there has been increased attention afforded to the role of substituents in tuning the structure and charge-carrier mobility of these materials.^{61,62} For example, Tang and Bao⁶³ recently reviewed halogenation as a means of tuning HOMO–LUMO gaps and engineering molecular packing to maximize the performance of organic semiconductors in electronic applications. Anthony and co-workers⁶ and Swager et al.⁶⁴ have demonstrated that partial fluorination of oligoacenes leads to enhanced stacking interactions in the solid state and improved charge-carrier mobilities.³

Inspired by these advances,^{3,6,64} we examined the fluorinated pentacene dimers depicted in Figure 9 as a demonstration of the utility of the local, direct interaction model applied to more complex systems. We note that the B97-D optimized dimer configurations in Figure 9 are not necessarily global minima but were chosen to mimic the dimer interactions present in crystal structures for similar fluorinated pentacenes.⁶ The effect of fluorination impacts the stacking interaction in these complexes, enhancing the interaction energy by 3.0 kcal mol⁻¹. The relative displacement of the two pentacenes is also affected by the substitution, resulting in a 0.3 Å increase in the displacement along the length of the pentacene and a 0.4 Å decrease in the displacement perpendicular to the long axis of pentacene. The latter change can be understood in terms of local dipole interactions; the decrease in the degree of displacement perpendicular to the long axis upon fluorination increases the favorable electrostatic interactions between the local C–H and C–F dipoles.

Most notably, the effect on the stacking interaction of adding four fluorines to the pentacene dimer does not depend on which acene the fluorines are attached to, in accord with the above results for substituted benzene dimers (e.g., Figure 5). Thus, the effects of substituents on the stacking interactions of oligoacenes can be understood by considering only the individual local interactions, with no regard for coupling between substituents through the π -system, as long as there are no close substituent–substituent contacts.

D. Other Fluorinated Systems. While the above example focuses on an application of the local, direct interaction model to stacking interactions in polycyclic aromatic molecules, this model can be similarly applied to stacking interactions in any context, including crystal engineering and molecular biology. For example, as previously mentioned, Boese and co-workers³³ demonstrated that, in the solid state, 1,3,5-trifluorobenzene exhibits

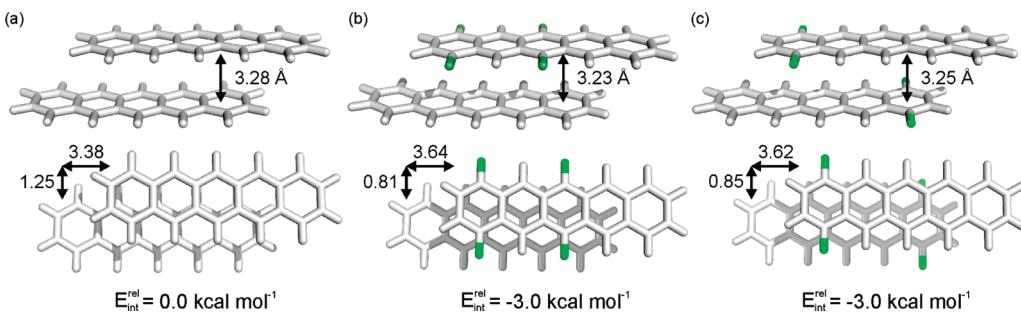


Figure 9. B97-D/TZV(2d,2p) optimized (a) pentacene dimer, (b) 1,4,6,13-tetrafluoropentacene–pentacene homodimer, and (c) 1,4-difluoropentacene homodimer. The absolute binding energy for the pictured pentacene dimer is predicted to be $-16.9 \text{ kcal mol}^{-1}$.

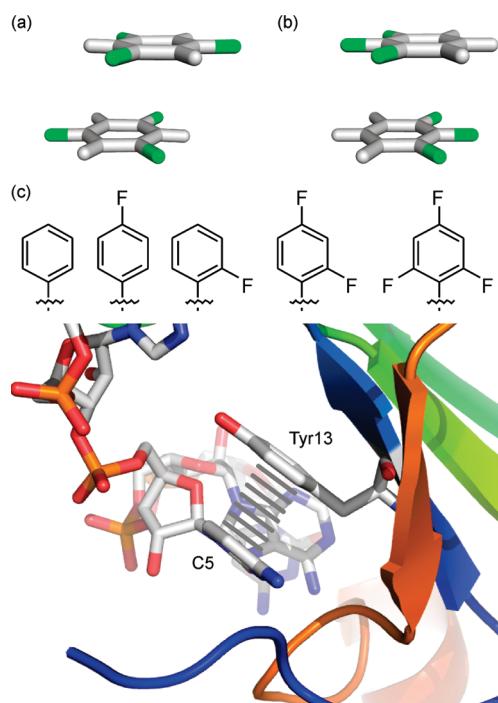


Figure 10. Stacking interactions present in (a) 1,3,5-trifluorobenzene and (b) 1,2,3-trifluorobenzene in the solid state.^{33,65} (c) Fluorinated phenyl groups used as base analogues in the study by Benitex and Baranger,⁶⁷ along with the stacking interaction between cytosine (C5) and tyrosine (Tyr13) in the native protein–RNA complex.⁶⁸

stacking interactions analogous to those observed in $\text{C}_6\text{F}_6/\text{C}_6\text{H}_6$ co-crystals (Figure 10a), which is contrary to expectations based solely on molecular quadrupole moments.³² More recent results from Boese et al.⁶⁵ show that 1,2,3-trifluorobenzene exhibits similar stacking interactions (Figure 10b), even though 1,2,3-trifluorobenzene and 1,3,5-trifluorobenzene have very different molecular dipole moments, and both have negligible quadrupole moments. In both systems, the two rings are oriented so that each C–H bond is located over a C–F bond. In terms of local, direct dipole–dipole interactions, the behavior of both of these trifluorinated rings is unsurprising, because these stacking arrangements maximize favorable direct interactions between the local C–F and C–H dipoles.⁶⁶

On the biological front, Benitex and Baranger recently published⁶⁷ an elegant study of the effects of fluorinated base analogues on the stability of a complex between a modified SL2 RNA and the U1A protein,⁶⁸ coming to the initially confounding

conclusion that the effects of fluorine are strongly dependent on the regiochemistry of fluorinated base analogues (Figure 10c). Agreement between computed stacking energies for phenol with these fluorinated base analogues indicated that the observed changes in the stability of the protein–RNA complex were primarily a result of changes in the stacking interaction between the base analogue and Tyr13. The dependence of the stacking interaction in this protein–RNA complex on the regiochemistry of the fluorinated base analogues is consistent with the local, direct interaction model. For base analogues in which the fluorine is aligned with the OH in Tyr13, direct interactions between the OH and F will dominate, while for other regioisomers there will be direct substituent–CH interactions. This orientational dependence is analogous to that seen for model stacked dimers in Figure 6 and in the experimental results of Gung et al.⁴⁶

V. PITFALLS OF ELECTROSTATIC POTENTIAL PLOTS

Plots of molecular electrostatic potentials are ubiquitous in studies of stacking interactions,^{1,14,18,20,22,23,26,35,67,69} with strong emphasis placed on the sign of the ESP above the center of the aryl ring. The supposed merit of these plots in this context is that they are said to provide a qualitative predictor of the strength and preferred orientation of arenes engaged in stacking interactions. However, because changes in ESPs do not reflect just local changes in the electron density,²⁷ ESP plots do not necessarily provide reliable information about the strength of the electrostatic component of stacking interactions.

The pitfalls of relying on the sign of the ESP above the center of an aryl ring become clear when considering the examples detailed in section IV. In many of these cases, examining the sign (color) of the ESP above the ring center yields expectations that are in discord with computational predictions. For example, on the basis of the ESPs above the centers of benzene, benzonitrile, and *p*-dicyanobenzene (Figure 2b), one would expect a very favorable electrostatic interaction between benzene and dicyanobenzene, and a repulsive electrostatic interaction in the cyanobenzene homodimer. Instead, CCSD(T) computations indicate that the stacking interaction in the cyanobenzene homodimer is comparable to that in the dicyanobenzene–benzene dimer (see Table 1). This is because the substituent effects are dominated by local, direct interactions, and in general, these effects are matched in $\text{C}_6\text{H}_4\text{X} \cdots \text{C}_6\text{H}_6$ and $\text{C}_6\text{H}_5\text{X} \cdots \text{C}_6\text{H}_5\text{X}$ (Figure 4).

For the benzene–pyridine dimer, differences between the ESPs of benzene and pyridine (e.g., the ESP for benzene is largely negative above the ring center, while the negative region of the

pyridine ESP is localized near the nitrogen) similarly suggest that substituent effects should differ in these two dimers. One would also expect substituent effects in the pyridine–benzene dimer to depend on whether the substituent was attached to the pyridine or the benzene ring. However, as seen in Figure 8, $C_6H_5X \cdots C_6H_6$, $C_6H_5X \cdots C_5H_5N$, and $C_6H_6 \cdots XC_5H_4N$ exhibit essentially identical substituent effects, despite these differences in the ESPs above the benzene and pyridine.

The ESPs of 1,2,3-trifluorobenzene and hexafluorobenzene (Figure 2b) provide the most striking example of the dangers of relying on the sign of the ESP above the center of an aryl ring to predict stacking interactions. The ESP above the ring center changes from negative in benzene to positive in hexafluorobenzene. For trifluorobenzene the ESP is essentially zero above the ring center, and, on the basis of these ESPs alone, one would expect substituent effects in 1,2,3-trifluorobenzene to be small. Instead, as seen in Figure 7, the substituent effects in $C_6H_5X \cdots C_6H_3F_3$ dimers are substantial and mimic those in the benzene–benzene or perfluorobenzene–benzene dimers, depending on which end of trifluorobenzene the substituent is located near. Distilling this behavior solely from the ESP above the ring centers is impossible. Although ESP plots provide a powerful tool for analyzing cation/ π interactions,⁷⁰ their utility in the context of stacking interactions is limited, and the information gleaned from these plots is often misleading.

VI. SUMMARY AND CONCLUSIONS

Traditional views of substituent effects in stacking interactions, which rely on the polarization of the aryl π -system by the substituent, are deeply engrained in the chemical literature.^{8,9,12–18} Unfortunately, these models have not held up under closer computational scrutiny.^{22–25,28,35–39} Moreover, when applied to more complex systems beyond monosubstituted benzene dimers, expectations based on these π -polarization viewpoints become murky and cannot be reconciled with accurate computational data. Analyses of stacking interactions based on molecular quadrupole moments or the sign of the ESP above the aromatic ring lead to similar difficulties. A more satisfactory view of substituent effects arises from the consideration of *local* dipoles (and higher order local multipoles).⁷¹

We have presented a comprehensive view of substituent effects in stacking interactions based on the local, direct interaction model depicted in Figure 3b. This simple, intuitive viewpoint provides clear, unambiguous predictions of substituent effects in myriad stacking interactions that are in full agreement with accurate DFT and new benchmark CCSD(T) interaction energies. In essence, substituent effects can be understood in terms of local, direct interactions between the substituent and the closest vertex of the other ring. The introduction of substituents or heteroatoms on the other end of either monomer has little bearing on these substituent effects. The application of this local, direct interaction model to a wide range of substituted stacked dimers, including model systems and more complex stacked dimers from the literature, demonstrates the predictive power and utility of this viewpoint. Specifically, it was shown that substituent effects in many stacked dimers exhibit nearly identical trends as long as the local interactions are matched. Moreover, the common practice of considering only the sign of the ESP above the center of aryl rings was shown to yield expectations regarding stacking interactions that are in conflict with accurate computational predictions.

This new model represents a drastic departure from a well-entrenched viewpoint.^{7–14} However, when both approaches are applied to the panoply of stacked dimers considered here, the local, direct interaction picture provides much more clear and reliable predictions. The primary practical ramifications of this new paradigm are 3-fold:

(1) There is broad *additivity* of substituent effects in stacking interactions, regardless of the ring to which the substituents are attached, as long as local, direct interactions are conserved.

(2) There is *transferability* of substituent effects between different stacking interactions in which the local, direct interactions are congruent.

(3) In stacking interactions in which both rings bear substituents, the substituent effects depend on the relative position of the substituents.

This model suggests that substituent effects in stacking interactions between complex aromatic systems can be understood in terms of individual, local interactions. Such an approach provides a simpler means of tackling substituent effects in large aromatic systems with multiple heteroatoms and many substituents than do traditional models based on π -polarization.^{7–14}

Another implication of the present work concerns the development of force-field representations of arene–arene interactions. In particular, the above results obviate the need to account for polarization of the aryl π -system in empirical force fields applied to stacking interactions and suggest that as long as the polarization of the substituent–arene bond is sufficiently well-described, then at least semiquantitative recapitulation of substituent effects in stacking interactions is expected. The present results also bode well for the development of empirical potentials for substituents that should be highly transferable among diverse stacking interactions.

As mentioned above, although robust ab initio methods were used, the present work involves a number of approximations. Most importantly, these gas-phase energy computations neglect the potentially significant solvent and entropy effects, which will come into play in realistic systems. Also, even though the proposed local, direct interaction model provides reliable predictions of substituent effects across a broad range of stacked dimers, the underlying physics has not been fully elucidated. Such clarification will require detailed energy decompositions to unveil the various effects that must be balanced in order for this simple model to perform as demonstrated. Furthermore, effects beyond those described in the simple model of Figure 3b will contribute to substituent effects, and in some systems these other effects may become dominant. However, the above results demonstrate for a broad range of stacked dimers that, in general, substituent effects are well-described by this simple model.

Finally, each of the dimers examined is amenable to experimental observation. Thus, carefully designed experimental probes of the relative strength of any of these stacked dimers should provide significant insight into the origin of substituent effects in stacking interactions and enable an evaluation of the relative merits of the prevailing π -polarization models^{7–14} and the local, direct interaction model presented here.

■ ASSOCIATED CONTENT

S Supporting Information. Full citations for refs 54 and 55, figures showing interaction energies, and tables listing absolute energies, optimized geometries, and absolute and relative interaction

energies for all systems studied. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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