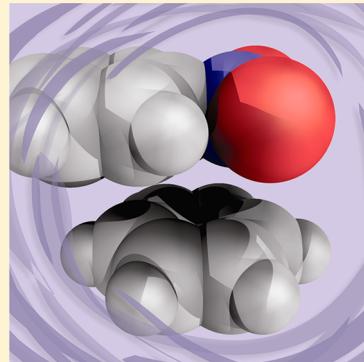


Toward a More Complete Understanding of Noncovalent Interactions Involving Aromatic Rings

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ABSTRACT: Noncovalent interactions involving aromatic rings, which include π -stacking interactions, anion– π interactions, and XH– π interactions, among others, are ubiquitous in chemical and biochemical systems. Despite dramatic advances in our understanding of these interactions over the past decade, many aspects of these noncovalent interactions have only recently been uncovered, with many questions remaining. We summarize our computational studies aimed at understanding the impact of substituents and heteroatoms on these noncovalent interactions. In particular, we discuss our local, direct interaction model of substituent effects in π -stacking interactions. In this model, substituent effects are dominated by electrostatic interactions of the local dipoles associated with the substituents and the electric field of the other ring. The implications of the local nature of substituent effects on π -stacking interactions in larger systems are discussed, with examples given for complexes with carbon nanotubes and a small graphene model, as well as model stacked discotic systems. We also discuss related issues involving the interpretation of electrostatic potential (ESP) maps. Although ESP maps are widely used in discussions of noncovalent interactions, they are often misinterpreted. Next, we provide an alternative explanation for the origin of anion– π interactions involving substituted benzenes and N-heterocycles, and show that these interactions are well-described by simple models based solely on charge-dipole interactions. Finally, we summarize our recent work on the physical nature of substituent effects in XH– π interactions. Together, these results paint a more complete picture of noncovalent interactions involving aromatic rings and provide a firm conceptual foundation for the rational exploitation of these interactions in a myriad of chemical contexts.



I. INTRODUCTION

Noncovalent interactions involving aromatic rings (π -stacking, cation/ π , anion– π , X-H/ π , etc., see Figure 1a) play vital roles in many chemical and biochemical phenomena.^{1–4} For example, Figure 1b shows the binding site of a sequence selective, single-stranded DNA binding autoantibody that is involved in the autoimmune disease systemic lupus erythematosus (SLE).⁵ The dinucleotide binding site involves extensive π -stacking and edge-to-face interactions between the DNA bases and aromatic amino acid side chains, which are largely responsible for the sequence selectivity of this antibody.⁶ A sound understanding of the nature of these noncovalent interactions, as well as means by which these interactions can be tuned, is vital for understanding their role in many contexts and for harnessing their power in chemical applications. This is particularly important in the design of pharmaceuticals and organic materials, for which precise control of both the strength and geometry of intermolecular interactions is key.^{7–13} Moreover, there is growing emphasis on using favorable noncovalent interactions in the design of organocatalysts for asymmetric reactions,^{14–21} and a more thorough understanding of the operative noncovalent interactions can facilitate the rational design of more effective organocatalysts.²¹ Among noncovalent interactions involving aromatic rings, π -stacking interactions have received the most attention in recent years.

Most discussions of π -stacking interactions are cast in terms of the Hunter–Sanders model.²² This seminal work, published in 1990, provided a simple conceptual framework for under-

standing the nature of π -stacking interactions between aromatic rings, as well as the impact of substituents and heteroatoms. The original Hunter–Sanders model²² was based on the idea that each atom of an aromatic ring could be treated as a local quadrupole comprising the positively charged nucleus and a pair of negative charges located a distance d above and below the molecular plane. As such, in the context of heteroatom effects, Hunter and Sanders²² emphasized the locality of heteroatom-induced changes in the aryl π -electron distribution, which were viewed as more important than the overall molecular properties. Hunter and Sanders presented a simple set of rules that could be used to rationalize and predict both the strength and geometries of stacking interactions involving various aromatic systems. In subsequent work by Hunter and co-workers,²³ a simpler view of stacking interactions emerged in which the distributed quadrupoles of the original Hunter–Sanders model²² were replaced with the “ π -electron system.” In the electrostatic model presented in this and subsequent work (Figure 2a),^{23–26} substituents modulate the strength of π -stacking interactions through their impact on the π -electron density of the aromatic ring. In particular, electron-accepting substituents (e.g., CN, NO₂, etc.) deplete the aryl π -electron density through π -resonance effects, reducing the electron–electron repulsion between the π -electron clouds of the stacked rings and enhancing

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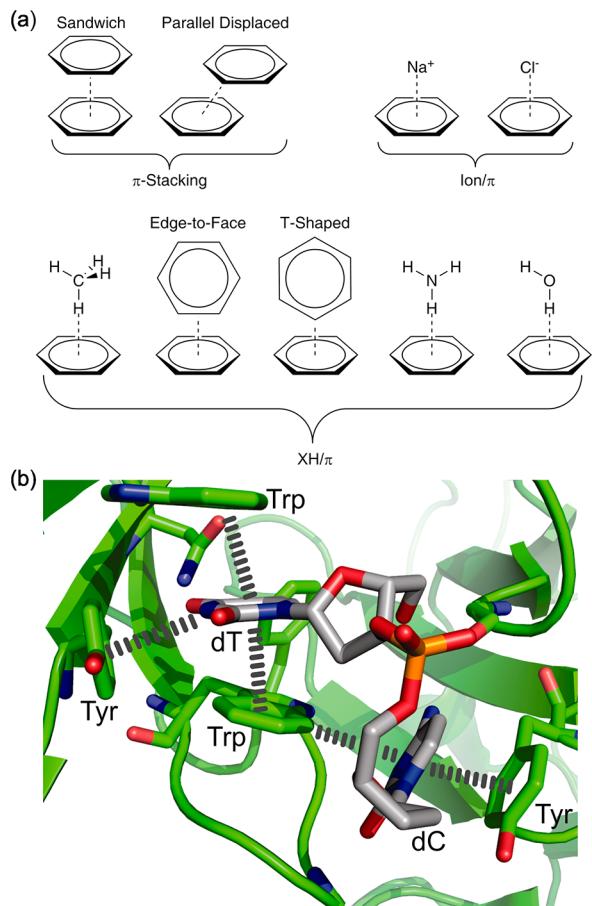


Figure 1. (a) Model noncovalent interactions involving aromatic rings and (b) 5'-dTdC binding site of a single-stranded DNA binding autoantibody⁵ in which π -stacking and edge-to-face interactions play key roles in the 5'-base selectivity. Panel (b) adapted from ref 6. Copyright 2014 American Chemical Society.

π -stacking interactions. Electron-donating substituents are said to hinder π -stacking interactions through the opposite mechanism. A related model from Cozzi and Siegel,^{27–31} the Polar/ π model, is cast in terms of molecular quadrupole moments.

The importance of π -resonance based changes in the aryl π -electron density in noncovalent interactions is seemingly supported by electrostatic potential (ESP) maps. At a given point in space, the ESP is a measure of the electrostatic interaction of a positive test charge with the molecule. ESPs are typically mapped onto electron density isosurfaces, and these ESP maps are widely used in analyses of noncovalent interactions.^{32–35} Notably, ESP maps show significant variation above the centroids of substituted aromatic rings and heterocyclic systems, and many chemists conflate these changes in ESP with changes in the π -electron density. This arises in part because these changes in ESPs follow expected trends based on conventional views of the nature of the substituents. For example, arenes with electron-withdrawing substituents (CN, NO₂, etc.) typically exhibit positive ESPs above the rings, whereas electron-donating substituents (CH₃, NH₂, etc.) result in more negative ESPs. As discussed below, however, these views stem from a misinterpretation of ESPs and likely underlie the misplaced emphasis on π -electron densities in many discussions of noncovalent interactions (*vide infra*).

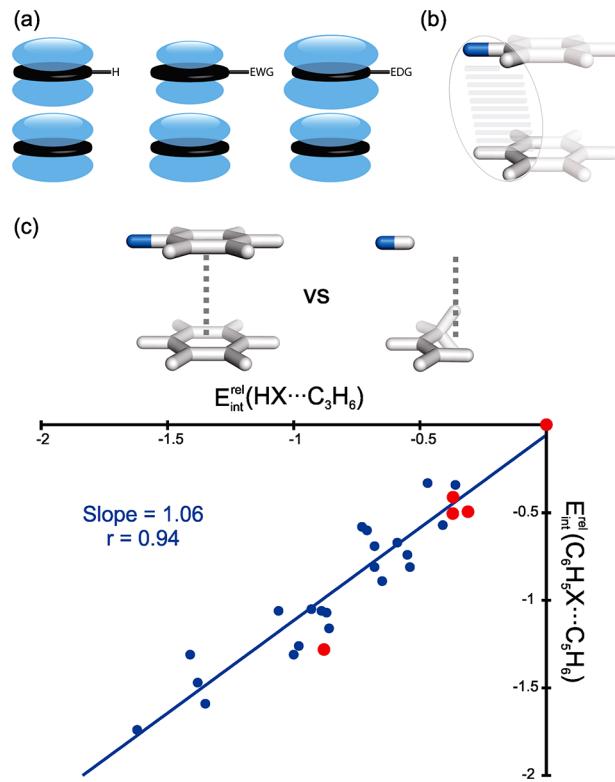


Figure 2. (a) Conventional view^{4,9,23–25} of substituent effects in π -stacking interactions (EWG = electron-withdrawing group; EDG = electron-donating group) and (b) the local, direct interaction model.^{36,37} (c) B97-D/TZV(2d,2p) (blue) and estimated CCSD(T)/aug-cc-pVTZ (red) interaction energies (kcal mol^{−1}) for C₆H₅X···C₆H₆ vs HX···C₃H₆ complexes for 23 substituents X [only five substituents are treated at the CCSD(T) level]. The best fit line applies only to the B97-D data. Adapted from ref 36. Copyright 2011 American Chemical Society.

The venerable models of Hunter and Sanders^{4,9,23–25} and Cozzi and Siegel,^{27–31} as well as associated discussions of electrostatic potentials in terms of π -electron densities, have proved invaluable in both the prediction and rationalization of countless noncovalent complexes. The Hunter–Sanders model underlies the well-worn mantra that strong stacking interactions arise between arenes with complementary electrostatic character; that is, electron-rich rings stack preferentially with electron-poor rings. However, there are deficiencies in these models, and none hold up under closer scrutiny.^{12,14,16,17,29–39} Moreover, there are many examples of strong self-stacking interactions involving electron-deficient arenes (e.g., naphthalene diimides, NDIs)³⁸ that seemingly contradict the notion that stacking arises from complementary electrostatic character.

Starting in the early 2000s, Sherrill and co-workers,^{39–48} Kim et al.,⁴⁹ and others,^{50–52} embarked on an ambitious quest to provide robust, gas-phase, ab initio interaction energies for prototypical π -stacking interactions, including substituted benzenes. This resulted in a physically sound view of π -stacking interactions in the benzene dimer. In particular, it is now well-established that the sandwich and parallel displaced configurations are bound primarily by dispersion interactions, while the resulting decrease in exchange-repulsion renders the parallel displaced dimer about one kcal mol^{−1} more favorable than the sandwich dimer.³⁹ However, many questions remain regarding the nature of these noncovalent interactions.^{38,53,54} For example,

the noncovalent interactions depicted in Figure 1a are often referred to as “aromatic interactions,” since common examples of these interactions involve one or more aromatic rings. Indeed, it is customary to define many of these interactions as involving aromatic rings. However, we have shown that aromatic delocalization of the π -electrons actually hinders π -stacking and anion– π interactions.⁵⁴ For cation– π interactions,^{55–57} on the other hand, our work showed that aromatic delocalization does enhance the interaction. Regardless, the moniker “aromatic interaction” was deemed misleading because it falsely implies that these interactions are somehow dependent upon the aromaticity of the interacting ring.⁵⁴ Previously, in 2008, Grimme⁵³ questioned the uniqueness of “ π – π interactions” in small stacked aromatic systems, while, more recently, Martinez and Iverson³⁸ have questioned the utility of the term “ π -stacking interaction” in general.

Computational studies from a number of groups over the past decade have also unveiled unexpected trends in substituent effects,^{40,41,43–45,47,58} of which many have contradicted predictions from the Hunter–Sanders model.^{4,9,23–25} These pioneering computational studies have been documented in a recent review from our group.⁵⁹ In 2008, Wheeler and Houk⁶⁰ showed that substituent effects in the benzene sandwich dimer were retained even if the substituted benzene was replaced with a hydrogen atom, suggesting that π -resonance-based changes in the aryl π -electron density were not responsible for substituent effects in the benzene dimer. Previously, both Sherrill and co-workers^{43,45} and Rashkin and Waters⁶¹ had invoked direct interactions between substituents and the other ring to explain select cases of seemingly anomalous substituent effects in π -stacking and T-shaped aryl–aryl interactions. However, what Wheeler and Houk proposed⁶⁰ was far more radical: that substituent effects in π -stacking interactions were due almost entirely to these direct interactions, and π -resonance effects were unimportant. Wheeler and Houk subsequently produced similar models for edge-to-face aryl–aryl interactions,⁶² cation– π interactions,⁶³ and anion– π interactions.⁶⁴

Over the past few years, we have strived toward a more complete understanding of noncovalent interactions involving aromatic rings, with a particular focus on understanding the impact of substituents and heteroatoms on these interactions.^{36,37,54,59,60,62–69} In the process, we have developed simple and physically sound explanations of substituent effects in π -stacking,^{36,59,60,67} cation– π ,⁶³ and anion– π interactions,⁶⁴ while also uncovering deep-rooted misconceptions regarding ESPs of aromatic systems and the nature of π -acidic rings.⁶⁵ We have also examined stacking interactions in a range of more complex systems,^{70–75} including stacking interactions in model discotic systems,⁷¹ stacking interactions involving carbon nanotubes and graphene,⁷² and examples of organocatalysts in which these and other noncovalent interactions play key roles.^{21,73–75} We previously reviewed our work in this area,³⁷ so here we focus on the most recent advances.^{36,68,69,71,72} The vast majority of this work has focused on idealized noncovalent interactions, including the benzene sandwich dimer. Often, the structures of these model complexes deviate from those in real chemical and biochemical systems, sparking concern about the relevance of these gas-phase computational studies to real-world problems. However, gas-phase studies of model complexes can provide key insights into the nature of these interactions in the absence of other complicating factors. Such insights have enabled the development of physical models that aid in understanding the role of these interactions in more complex environments and in

less idealized configurations. Along these lines, we have shown³⁶ that the local nature of substituent effects in π -stacking interactions, discussed here in terms of the benzene sandwich dimer, are equally applicable to the parallel displaced configuration.

II. THEORETICAL METHODS

We have relied on a number of computational methods in order to further our understanding of noncovalent interactions involving aromatic rings. These interactions are often dominated by dispersion effects, which are problematic for many electronic structure methods. Luckily, the past decade has witnessed significant advances in efficient and effective methods for treating such noncovalent interactions, as discussed in excellent recent reviews.^{76,77} Chief among these are density functional theory (DFT) functionals that capture dispersion-like interactions, as well as efficient implementations of symmetry-adapted perturbation theory (SAPT).^{76,88–90} The latter methods can provide key insights into the underlying components of noncovalent interactions.^{41,43–48,58}

We have relied most heavily on DFT energies appended with the empirical “D2” dispersion correction of Grimme,⁷⁸ although we have also utilized the more robust D3 correction⁷⁹ in some cases. In particular, we present B97-D and B97-D3 energies, which comprise Becke’s generalized gradient approximation (GGA) functional B97⁸⁰ paired with Grimme’s D2 (B97-D) or D3 (B97-D3) dispersion corrections. When combined with the TZV(2d,2p) basis set^{81,82} and density fitting techniques, these approaches provide reliable predictions of noncovalent interactions involving aromatic rings at a very modest computational cost.^{83,84} Regardless, when studying model systems, we also present more accurate ab initio interaction energies based on coupled cluster theory. In particular, we provide estimates of counterpoise-corrected CCSD(T)/aug-cc-pVTZ interaction energies, evaluated as follows:

$$\text{CCSD(T)}/\text{aug-cc-pVTZ}$$

$$\approx \text{CCSD(T)}/\text{aug-cc-pVDZ} + \text{MP2}/\text{aug-cc-pVTZ} \\ - \text{MP2}/\text{aug-cc-pVDZ}$$

In this way, we have been able to leverage the speed of B97-D/TZV(2d,2p) predictions to examine a large number of complexes while also anchoring these results to more reliable, ab initio data for representative systems. We have also employed the M06-2X functional of Truhlar and co-workers,⁸⁵ which provides remarkably accurate predictions for a wide range of chemical systems, including nonbonded interactions. However, we note that this functional exhibits particular sensitivity to integration grids.^{86–88} Regardless, when combined with the 6-31+G(d) basis set, M06-2X provides reliable predictions of substituent effects in noncovalent interactions.^{64,67}

Often, it is desirable to obtain not only total interaction energies but also individual contributions to these interaction energies. For this purpose, we have relied on SAPT.^{77,89–91} In particular, we have employed the highly efficient, density-fitted SAPT0 code^{92,93} contained in the Psi4 software package.⁹⁴ SAPT0, used in conjunction with the jun-cc-pVDZ basis set,⁹⁵ provides reliable predictions at very modest computational cost.⁹¹ Finally, we have also relied, in some cases, on traditional tools of physical organic chemistry in the form of Hammett constants (σ_p or σ_m) and molar refractivities (MR).⁹⁶ These constants can be used, at least qualitatively, to untangle the

importance of electrostatic and dispersion effects on noncovalent interactions, respectively.

III. RESULTS AND DISCUSSION

Below, we discuss substituent effects on model π -stacking interactions, substituent and heteroatom effects on electrostatic potentials, substituent and heteroatom effects on anion– π interactions, and substituent effects in XH– π interactions. In each of these areas, detailed computational studies have provided key insights and often overturned widespread views of these interactions. Overall, the results provide a much clearer, and often simpler, view of the factors that impact the strength and orientation of noncovalent interactions involving aromatic rings.^{36,37,59}

A. Substituent Effects in π -Stacking Interactions. In 2011, we introduced³⁶ a simple way of understanding substituent effects in diverse π -stacking interactions, building on the preliminary work of Wheeler and Houk.⁶⁰ In contrast to popular, resonance-based views,^{4,9,23–25} we proposed that substituent effects in π -stacking interactions are dominated by the local, direct interactions of the substituents with the proximal vertex of the other ring (see Figure 2b).³⁶ In this view, substituent-induced changes in the aryl π -system, which undoubtedly occur, have a nearly negligible impact on the strength of π -stacking interactions and are overshadowed by these local, direct interactions. Practically, this means that substituent effects can be understood by considering only the substituent and its local environment. As long as no changes are made to this local environment, substituent effects are the same across even seemingly disparate stacked dimers.

This simple model was motivated by the observation that substituent effects in monosubstituted benzene sandwich dimers ($C_6H_5X \cdots C_6H_6$) could be reproduced, at least qualitatively, by considering the interaction of H–X with propene (C_3H_6), where the location of all conserved atoms are identical (see Figure 2c). In other words, the only components that are necessary to capture substituent effects in the benzene dimer are the substituent (capped with a hydrogen atom) and the proximal vertex of the unsubstituted ring. Initially, we proposed that these direct interactions were due primarily to the electrostatic interaction of the local dipole associated with the substituent and the local dipole associated with the C–H bond of the opposing ring. However, we recently presented⁶⁹ a more thorough physical explanation of the local, direct interaction model, as discussed below. We also note that our local, direct interaction model mirrors much earlier discussions of DNA base stacking by Gellman and co-workers.^{97,98}

The utility of the local, direct interaction model^{36,37} can be demonstrated by examining sandwich dimers of monosubstituted benzenes, $C_6H_5X \cdots C_6H_5Y$, where X and Y are any of a diverse set of substituents. Conventional views of substituent effects in π -stacking interactions^{4,9,23–25} predict a coupling between substituent effects. That is, the effect of substituents on one ring will be impacted by the nature of the substituent on the other ring. This has been observed experimentally by Hunter and co-workers,^{26,99,100} who showed that substituent effect trends are reversed, depending on whether the unsubstituted ring is electron-rich or electron-poor. On the other hand, the local direct interaction model^{36,37} predicts that, as long as the substituents are not in each other's local environment, then substituent effects should be additive. In other words, the impact of the two substituents in dimers such as those in Figure 3a should be the sum of substituent effects in the two corresponding

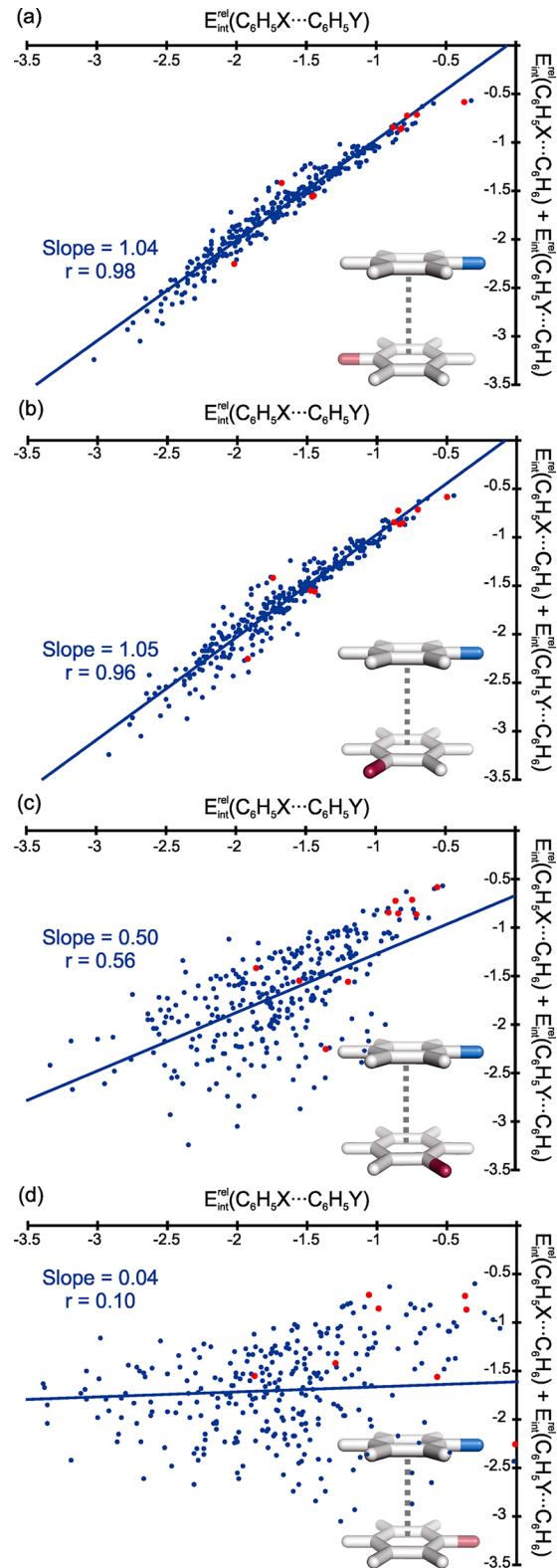


Figure 3. B97-D/TZV(2d,2p) (blue) and estimated CCSD(T)/aug-cc-pVTZ (red) interaction energies (kcal mol⁻¹), relative to the unsubstituted case, for $C_6H_5X \cdots C_6H_5Y$ sandwich dimers versus the sum of relative interaction energies for $C_6H_5X \cdots C_6H_6$ and $C_6H_5Y \cdots C_6H_6$ dimers in four orientations. Slopes of best-fit lines, along with correlation coefficients (*r*) are based on the B97-D data. Adapted from ref 36. Copyright 2011 American Chemical Society.

monosubstituted sandwich dimers. The latter trend is born out, both at the B97-D and CCSD(T) levels of theory, and interaction energies in the $C_6H_5X \cdots C_6H_5Y$ dimers depicted in Figure 3a can be predicted accurately by simply considering the substituents individually. Sherrill and co-workers⁴³ had previously demonstrated the additivity of substituent effects in stacked benzene dimers; the local, direct interaction model^{36,37} provided a simple explanation for this observation.

The correlation in Figure 3a is retained even if the relative orientation of the two rings is changed (Figure 3b), up until the two substituents enter each other's local environments (Figure 3, panels c and d). In the configuration in Figure 3d, in which the substituents are aligned, there are significant substituent–substituent interactions, which obviously cannot be captured by considering the substituents individually. The strong dependence of substituent effects on the local orientation of the two substituted rings would not occur if π -stacking interactions were mediated only by the π -electron densities of the interacting rings, which is obviously unaffected by simply changing the relative orientation of the two rings. Moreover, in the experiments that showed a coupling between substituent effects,^{18,83,84} the stacking orientation probed was similar to that in Figure 3d. Thus, it seems that these experiments were primarily measuring the direct, through-space interactions of the substituents with each other, and then attributing this to changes in the interaction of polarized aryl π -electron densities.

The local nature of substituent effects in π -stacking interactions^{36,37} has important implications for stacking interactions in larger molecular systems. In particular, because substituent effects in the benzene sandwich dimer are dominated by direct interactions of the substituent with the proximal vertex of the other ring,^{36,37} substituent effects should be different in systems where the substituent is not located above the edge of another arene. For example, we recently showed⁷² that substituent effects in π -stacking interactions between substituted benzenes and carbon nanotubes (CNTs, see Figure 4a) are dominated by dispersion interactions between the substituents and the CNT, as indicated by the strong correlation between computed interaction energies and molar refractivity constants (MR) for the substituents (see Figure 4c). Unlike the benzene dimer,^{50,60} electrostatic effects have no significant impact on substituent effects in π -stacking interactions involving CNTs, as suggested by the lack of correlation with Hammett constants (see Figure 4b). Similar results were obtained for stacking interactions involving a small model of graphene.⁷² Additionally, substituent effects are the same for endohedral and exohedral complexes of monosubstituted benzenes with CNTs, which further demonstrates the unimportance of the π -electron density in substituent effects in π -stacking interactions. If such effects were important, endohedral and exohedral complexes of substituted benzenes with CNTs would exhibit different trends due to the disparate electronic character of the interiors and exteriors of CNTs caused by the curvature of these systems.

The orientation dependence of substituent effects in π -stacking interactions also provides a powerful tool for controlling the local orientation of stacked systems.⁷¹ This is particularly important in the design of discotic liquid crystalline materials, for which charge-carrier mobilities are highly dependent on intracolumnar order¹⁰¹ and the stacking distance between aromatic cores.^{102,103} In 2012, we examined⁷¹ the interaction energies for sandwich dimers of trisubstituted benzenes as a function of the relative orientation of the two rings. Even simple substituents lead to dramatic changes in the orientation potential

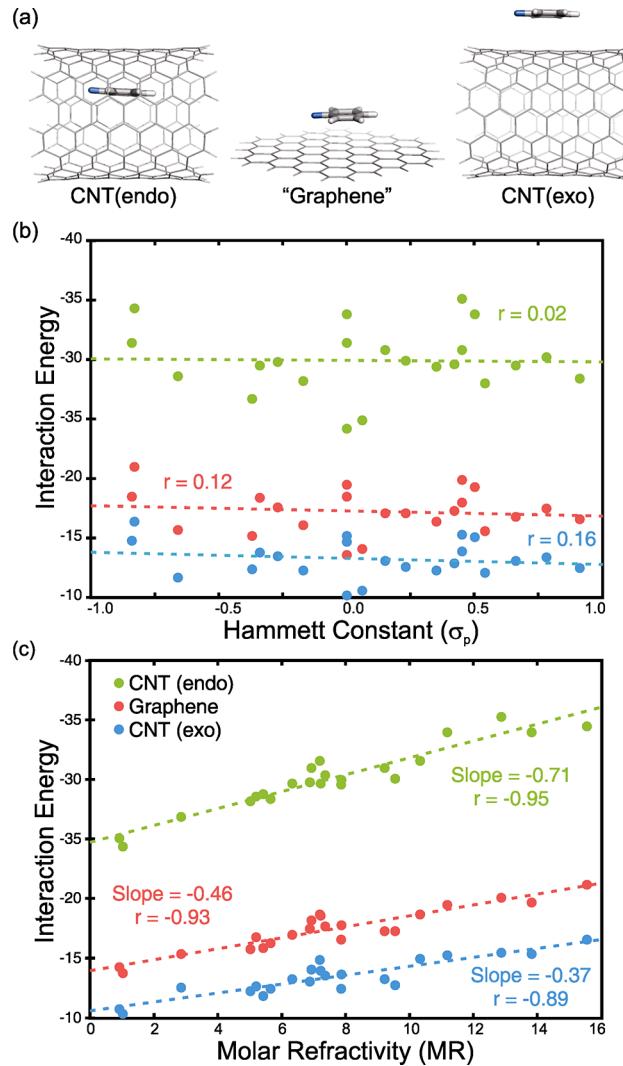


Figure 4. (a) Model complexes of monosubstituted benzene with (8,8)-CNT and a small graphene model. B97-D3/TZV(2d,2p) predicted interaction energies (kcal mol^{-1}) for substituted benzenes with CNT and graphene versus (b) Hammett constants and (c) molar refractivity constants. Panels (b and c) adapted with permission from *J. Chem. Phys.* 2013, 139, 094703. Copyright 2013 AIP Publishing LLC.

of these dimers (see Figure 5a), due to local, direct interactions of the substituents. These data provide the basis for rationally designing stacked systems that will adopt particular local orientations. This was demonstrated for the model stacked discotic systems coronene and hexabenzocoronene. For example, the interaction potential for two unsubstituted coronenes is relatively flat, with shallow minima corresponding to staggered configurations at angles of 30 and 90° (see Figure 5b, red line). However, by introducing alternating formyl ($-\text{CHO}$) and methoxy ($-\text{OCH}_3$) substituents, this potential was transformed into one with a deep minimum located at a fully eclipsed configuration (see Figure 5b, blue line). Similar transformations of the potential were achieved for substituted hexabenzocoronene.⁷¹ These results have potentially important implications for controlling the local orientation of discotic liquid crystalline systems, for which maximal rates of charge transfer are predicted for fully eclipsed configurations.¹⁰⁴

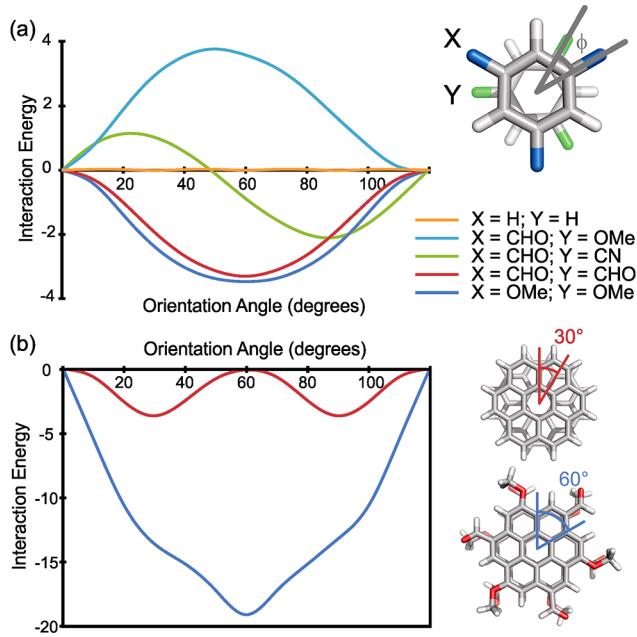


Figure 5. (a) Change in interaction energy (kcal mol^{-1}) of sandwich dimers of selected 1,3,5-trisubstituted benzenes as a function of orientation angle, ϕ ; (b) change in interaction energy (kcal mol^{-1}) of sandwich dimers of coronene (red curve) and coronenes substituted with alternating formyl and methyoxy substituents (blue curve) as a function of orientation angle. Data from ref 71.

B. Electric Fields and π -Stacking Interactions. Another key implication of the local, direct interaction model^{36,37} is the transferability of substituent effects. That is, because substituents only depend on the substituent and the proximal vertex of the other ring, the effect of a given substituent should be the same regardless of the identity of the ring to which it is attached. Initially, we demonstrated such transferability³⁶ by examining substituent effects in pyridine–benzene and pyridine–pyridine dimers, which exhibit the same substituent effects regardless of whether the substituent is on benzene or pyridine. More recently, we pushed the limits of this transferability⁶⁹ by considering monosubstituted sandwich dimers of benzene (Bz), borazine (Bn), and triazine (Tz). These three rings exhibit drastically different electronic structures and degrees of aromaticity, yet are all planar. We used SAPT0/jun-cc-pVDZ to compute interaction energies for 22 substituents on 20 monosubstituted sandwich dimers of benzene, borazine, and triazine and then examined correlations of substituent effects across these diverse stacked dimers (see Figure 6).

As predicted by the local, direct interaction model,^{36,37} we found that substituent effects were strongly correlated as long as the identity of the unsubstituted ring remained constant. For instance, interaction energies for dimers of boron-substituted borazine with benzene [$\text{Bn(B)}-\text{X}\cdots\text{Bz}$] are plotted versus substituted benzene sandwich dimers ($\text{Bz-X}\cdots\text{Bz}$) in Figure 6b. These interaction energies are strongly correlated ($r = 0.98$), and the best-fit line has a unit slope. That is, both the substituent effect trend and the strength of substituent effects are the same for these two dimers, despite the drastic differences in the character of the substituted ring. On the other hand, the effects of substituents in sandwich dimers of substituted benzene with triazine in two different orientations [with a carbon vertex aligned with the substituent, Tz(C), or with a nitrogen vertex aligned with the substituent, Tz(N)] are completely uncorrelated

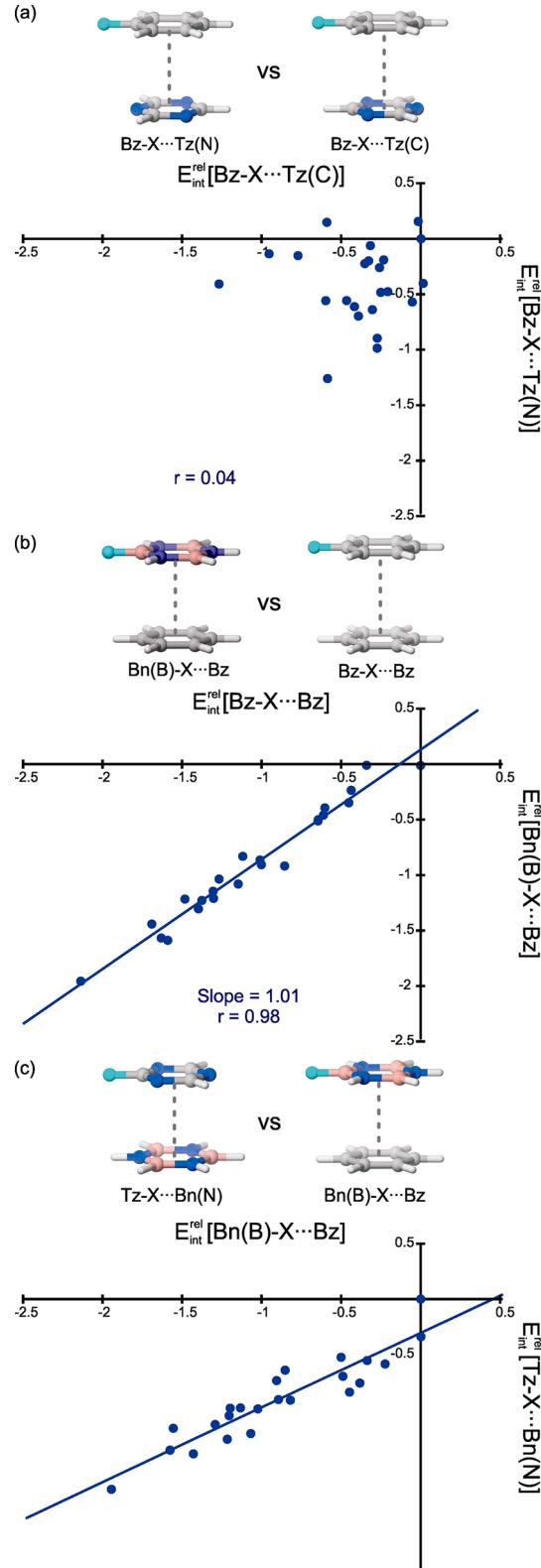


Figure 6. Comparisons of SAPT0/jun-cc-pVDZ interaction energies (kcal mol^{-1}) for selected sandwich dimers involving these rings, relative to the corresponding unsubstituted dimers. Correlation coefficients (r) and slopes of best-fit lines are also provided. Adapted from ref 69. Copyright 2013 American Chemical Society.

(Figure 6a). Such behavior is unexpected based on either the Hunter–Sanders model^{14,9,23–25} or the polar– π model of Cozzi

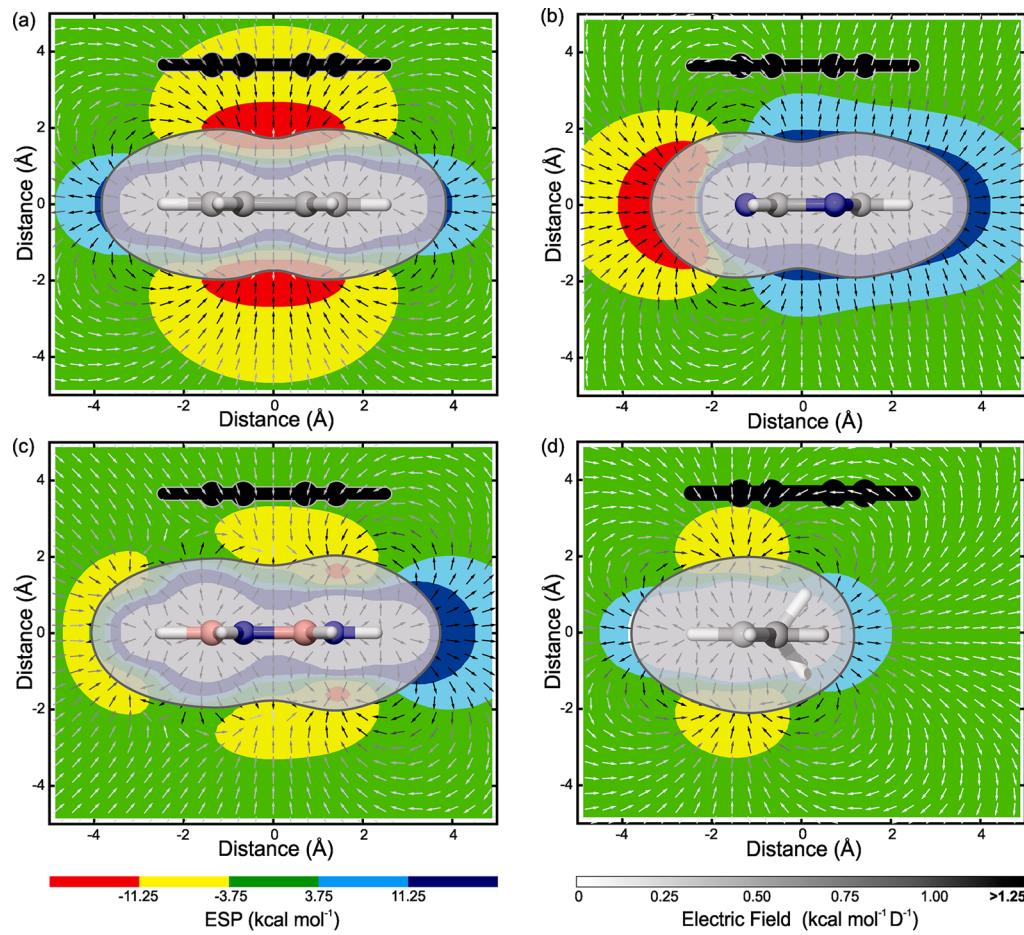


Figure 7. Electrostatic potential (solid colors, kcal mol^{-1}) and electric field (arrows, $\text{kcal mol}^{-1} \text{D}^{-1}$) in the plane perpendicular to and bisecting the molecular plane of (a) benzene, (b) triazine, (c) borazine, and (d) propene. For reference, the gray-shaded region is an electron density isosurface ($\rho = 0.001 \text{ e}/\text{bohr}^3$), and the black silhouette is of a sandwich stacked benzene at $R = 3.65 \text{ \AA}$. Panels (a–c) adapted from ref 69. Copyright 2013 American Chemical Society.

and Siegel,^{27–31} since neither the π -electron density nor quadrupole moment of triazine is affected by a simple rotation. However, this behavior is readily explained in terms of local, direct interactions.^{36,69}

Although these data supported the local, direct interaction view, they also revealed unexpected correlations among substituent effects in dimers that exhibited seemingly different local, direct interactions.^{36,37} For example, Figure 6c shows that substituent effects in the Tz–X···Bn(N) and Bn(B)–X···Bz sandwich dimers are correlated, although the slope now deviates from unity. Indeed, such correlations among substituent effects exist for all dimers in which benzene or borazine (in either orientation) is the unsubstituted ring.¹ This was not anticipated based on the original local, direct interaction model.^{36,37} Apparently, there is some inherent similarity between benzene and both vertices of borazine that leads to similar substituent effects in stacked dimers involving these rings, and the local, direct interaction model needed to be extended.

Examination of the individual components of the SAPT0 interaction energies revealed that the correlation of substituent effects in two dimers hinged on the electrostatic component of the interactions.⁶⁹ That is, if the electrostatic interactions were correlated for a pair of dimers, then the total interaction energies were correlated, whereas, if the electrostatic interactions were uncorrelated then the total interaction energies were uncorrelated. As noted above, we initially proposed that the local, direct

interactions arise primarily from electrostatic interactions of the unsubstituted ring with the local dipole associated with the substituent. This inspired us to examine the electric fields of the unsubstituted rings,⁶⁹ since the electrostatic interaction of a dipole with another molecule is simply the dot product of the dipole with the electric field at that point.

Electric fields in the plane perpendicular to and bisecting benzene, borazine, and triazine are plotted in Figure 7, along with the electrostatic potentials in these planes for reference. In these plots, the arrows indicate the direction of the electric field at that point and the color of the arrows give the strength. Overall, the electric fields of benzene and borazine are drastically different (c.f., Figure 6, panels a and c). However, the electric fields above either vertex of borazine, in the vicinity of the substituents on a stacked benzene, are similar in both direction and strength to the electric fields in the same regions above benzene. These similarities are quantified in Figure 8 (panels a and d). In 8a, we plot the dot product of the normalized electric field of benzene and borazine, providing a quantitative measure of the similarity of direction of the two electric fields at each point in space. Because the electric fields of these two molecules are parallel in the region of the substituents, both benzene and borazine will interact with the same component of the local dipole moment associated with a substituent at this position. Similarly, the strength of the electric field of borazine, relative to benzene, is plotted in Figure 8d.⁶⁹ The electric field above both

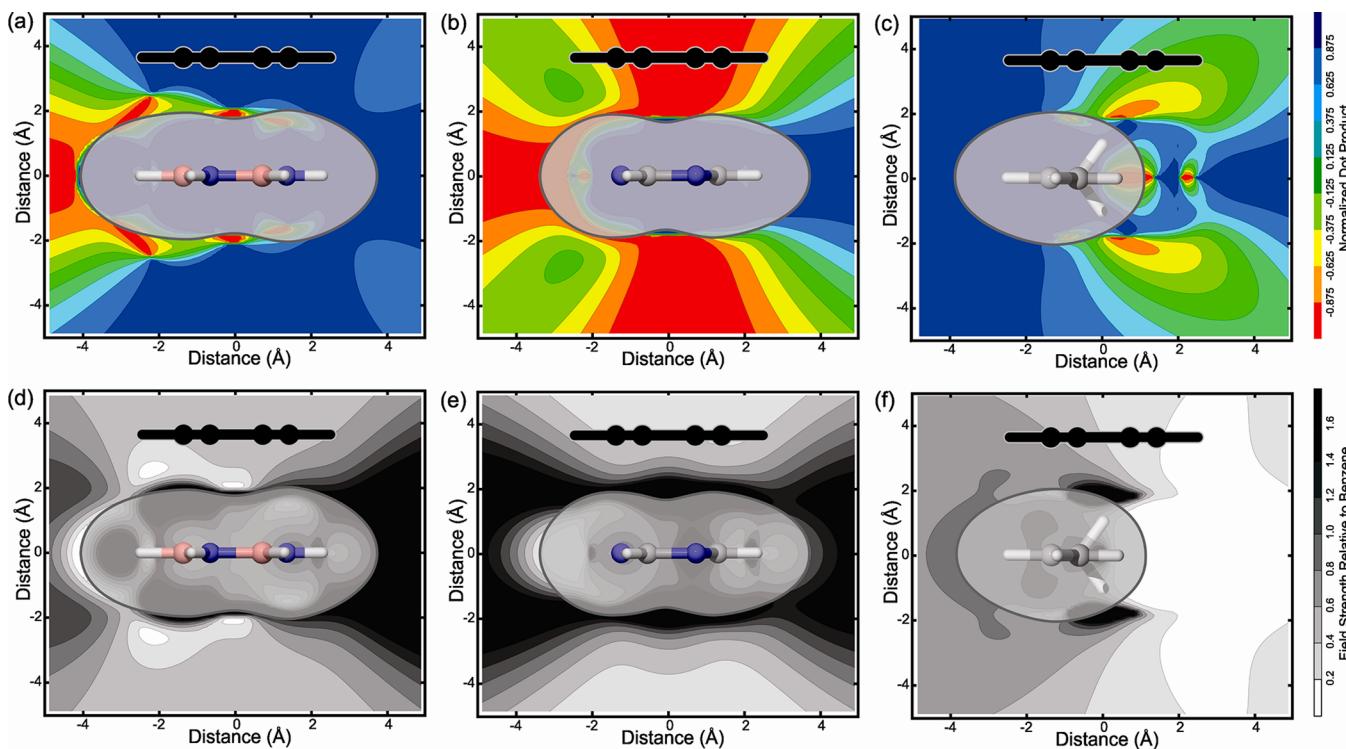


Figure 8. Contour plots of the dot product of normalized electric field vectors of benzene with those of (a) borazine, (b) triazine, and (c) propene. In these plots, blue indicates the electric field is aligned with that of benzene, while red signifies antialignment. Green indicates the electric field is orthogonal to that of benzene. Contour plots of the strength of the electric field for (d) borazine, (e) triazine, and (f) propene, relative to the electric field of benzene. For reference, in all six figures, the gray-shaded region is an electron density isosurface ($\rho = 0.001 \text{ e}/\text{bohr}^3$), and the black silhouette is of a sandwich stacked benzene at $R = 3.65 \text{ Å}$. Panels (a–b) and (d–e) are adapted from ref 69. Copyright 2013 American Chemical Society.

vertices of borazine is half the strength of the electric field above benzene. This difference in electric field strength underlies the nonunit slope of the best-fit line in Figure 6d, since the electrostatic component of the substituent effect trend is half as strong when borazine is the unsubstituted ring,⁶⁹ as compared to benzene (there are other, compensating factors that lead to a slope greater than one-half).

On the other hand, the electric fields above the vertices of triazine are almost perpendicular to the field above benzene. This explains the lack of correlation of substituent effects for sandwich dimers in which triazine and benzene are the unsubstituted rings because these two electric fields will interact with different components of the local dipole moment associated with the substituent.

Examining electric fields for the unsubstituted system in π -stacking interactions has proved valuable in understanding substituent effects in other systems. For example, the lack of significant electrostatic contributions to substituent effects in stacking interactions involving CNTs and graphene (vide supra) is readily explained by the very small electric fields in the region of the substituents above these larger systems. Similarly, we also note that the correlation in Figure 2c can be explained by comparing the electric fields of benzene and propene. In particular, the electric field above propene is almost perfectly parallel, and of similar strength, to the electric field above benzene in the region of the substituents in these complexes (see Figure 8, panels c and f). Consequently, propene is able to mimic the electrostatic interactions of benzene with the local dipole associated with the substituents, as captured by H–X.

Finally, we note that even though examining electric fields provide a more robust understanding of the local, direct

interaction model, predicting substituent effects based on computed electric fields is not always practical. For this purpose, the original local, direct interaction model (Figure 2b) still holds and provides sound qualitative predictions.^{36,37} Next, we turn to another qualitative tool for understanding noncovalent interactions, electrostatic potentials.

C. Molecular Electrostatic Potentials. ESP maps are widely used in discussions of noncovalent interactions, and much of the emphasis on π -electron density in these discussions likely stems from the misinterpretation of substituent and heteroatom effects on ESPs. As noted in the Introduction, it is common to conflate substituent- and heteroatom-induced changes in arene ESPs with changes in the aryl π -electron density. For example, the positive ESPs above aromatic systems like benzonitrile and nitrobenzene (see Figure 9a) are often attributed to π -deficiency, which, in turn, is explained by the delocalization of a formal positive charge throughout the π -system through π -resonance effects. However, in 2009, we showed⁶⁵ that π -resonance effects have a very minor impact on the ESPs of substituted aromatic systems. For example, the positive ESP above benzonitrile arises from the through-space effects of the local dipole associated with the nitrile group. Indeed, the ESPs of a broad range of substituted aromatic rings can be qualitatively, if not quantitatively, reproduced without any changes in the aryl π -system.⁶⁵ This is demonstrated in Figure 9b for toluene, benzonitrile, and nitrobenzene, where we have constructed ESPs for these systems by adding the ESP of the substituent (capped with a hydrogen atom) to the ESP of benzene. This was accomplished by computing the electrostatic potential of benzene and the hydrogen-capped substituent separately but on the same rectangular grid with the molecules positioned as they would

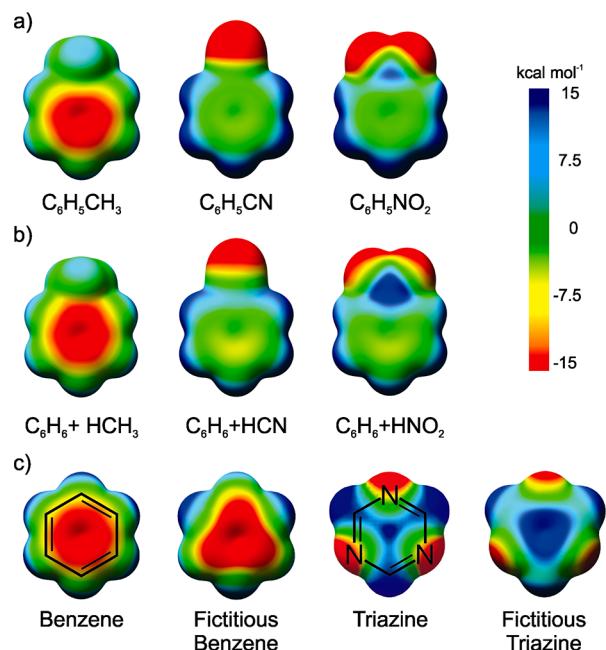


Figure 9. (a) ESPs of toluene, benzonitrile, and nitrobenzene; (b) ESPs of toluene, benzonitrile, and nitrobenzene constructed by adding the ESP of the hydrogen-capped substituent ($H-CH_3$, $H-CN$, and $H-NO_2$) to the ESP of benzene; (c) ESPs of benzene, a fictitious benzene in which the π -electron density has been replaced with that of triazine, triazine, and a fictitious triazine in which the π -electron density has been replaced with that of benzene. Data for panels (a and b) from ref 65.

be in the intact substituted benzene. The ESPs at each point on the grid were then simply added, and the total ESP plotted on the total electron density isosurface. In other words, the ESPs in Figure 9b reflect the ESP of the substituted ring if the σ - and π -electron density of the phenyl ring is identical to that of benzene. These additive ESPs are very similar to the real ESPs, despite the fact that the electron distribution of the ring is identical for all three systems.⁶⁵

Similar misconceptions abound regarding the ESP differences between *N*-heterocycles and benzene. For example, *s*-triazine is widely described as being π -electron deficient, which is explained in terms of the delocalization of positive charge throughout the π -system. The positive ESP above the ring centroid is also cited as evidence of this π -deficiency. However, the positive ESP above triazine does not arise from changes in the π -electron density. This is demonstrated in Figure 9c. First, Figure 9c shows the ESP of benzene as well as the ESP of a counterfactual benzene in which the π -electron density has been replaced with that of triazine. Although the changes in the π -electron density arising from the replacement of three C–H groups with nitrogens do impact the ESP, these effects are localized to the remaining carbon atoms. That is, simply changing the π -electron density of benzene into that of triazine does not reproduce the positive ESP above triazine. Indeed, changing the π -electron density has no significant impact on the ESP above the ring centroid. Similarly, Figure 9c also shows the ESP of triazine, as well as a fictitious triazine in which the π -electron density is that of benzene. Again, these ESPs differ, but the positive ESP above the centroid of triazine is retained even if the π -electron density is reverted to that of benzene. The positive ESP above the centroid of triazine is not a result of any changes in the π -electron density but instead arises from other effects. These other effects will be discussed in a forthcoming paper.

Overall, these results emphasize that even though ESP maps are highly useful in understanding noncovalent interactions, one cannot draw conclusions about local changes in electron density based on local changes in the ESP.^{37,65} The reason is that the ESP at a given point depends on the distribution of charge (both positive and negative) throughout the entire molecule.³⁰ More importantly, in the context of noncovalent interactions, changes in the aryl π -electron density arising from substituent and heteroatom effects do not strongly impact the ESP above the centroids of these aromatic rings, nor do they have any significant effect on noncovalent interactions involving these rings. This revelation is of particular importance when it comes to cation– π ^{55–57} and anion– π ^{64,105–112} interactions, of which the latter is discussed below.

D. Origin of Anion– π Interactions. Anion– π interactions^{105–107} are relative newcomers in the field of noncovalent interactions and are traditionally defined as attractive interactions between anions and the faces of π -acidic rings.^{2,108,109,113–118} Despite rapidly growing interest in anion– π interactions,^{19,20,110,111,119,120} there is a striking lack of rigorous explanations of their origin. Most discussions of anion– π interactions focus on the concept of π -acidity or π -electron deficiency.^{109,113,121,122} However, such discussions are rooted in the misinterpretations of ESPs that are noted above or on similar misconceptions regarding the Q_{zz} component of molecular quadrupole moments. Instead, available data suggests that neither substituents nor heteroatoms tune the strength of anion– π interactions through their impact on the aryl π -system.⁶⁴

In 2010, we showed⁶⁴ that interaction energies for model anion– π complexes of Cl^- with a broad range of substituted benzenes can be captured by simply adding the interaction of the anion with the substituent to the unfavorable interaction of the anion with benzene. In other words, the ability of a phenyl ring with electron-withdrawing substituents to bind an anion is not a result of changes in interaction of the anion with the phenyl ring itself. Instead, it is due to favorable interactions of the anion with the substituents that overwhelm the unfavorable interactions of the anion with the ring. We provided further evidence⁶⁴ for the unimportance of substituent-induced changes in the aryl π -electron density by comparing the impact of a nitrile substituent on model complexes of Cl^- with benzene and a twist-boat conformation of cyclohexane (see Figure 10, panels a and b). In particular, despite the lack of π -electrons in cyclohexane, CN-substitution results in a greater enhancement of the ability of cyclohexane to bind an anion than it does for benzene. Finally, we also demonstrated⁶⁴ that accurate ab initio interaction potentials of Cl^- with various substituted benzene rings could be reproduced by adding a simple charge–dipole interaction to the unfavorable interaction of Cl^- with benzene.

A similar, charge–dipole-based model can capture the drastically different anion-binding abilities of *N*-heterocycles. For example, in Figure 10c, we show CCSD(T)/aug-cc-pVTZ predicted interactions for model complexes of Cl^- with the faces of benzene, pyridine, pyrazine, *s*-triazine, and *s*-tetrazine as a function of the anion–arene distance. The interaction potentials for all four of the *N*-heterocycles can be reproduced almost quantitatively by simply adding the appropriate number of charge–dipole interactions to the Cl^- –benzene interaction potential. This result is consistent with the ESPs plotted in Figure 9c: differences in the π -electron density of *N*-heterocycles have little impact on the ESP above the centers of the rings and do not

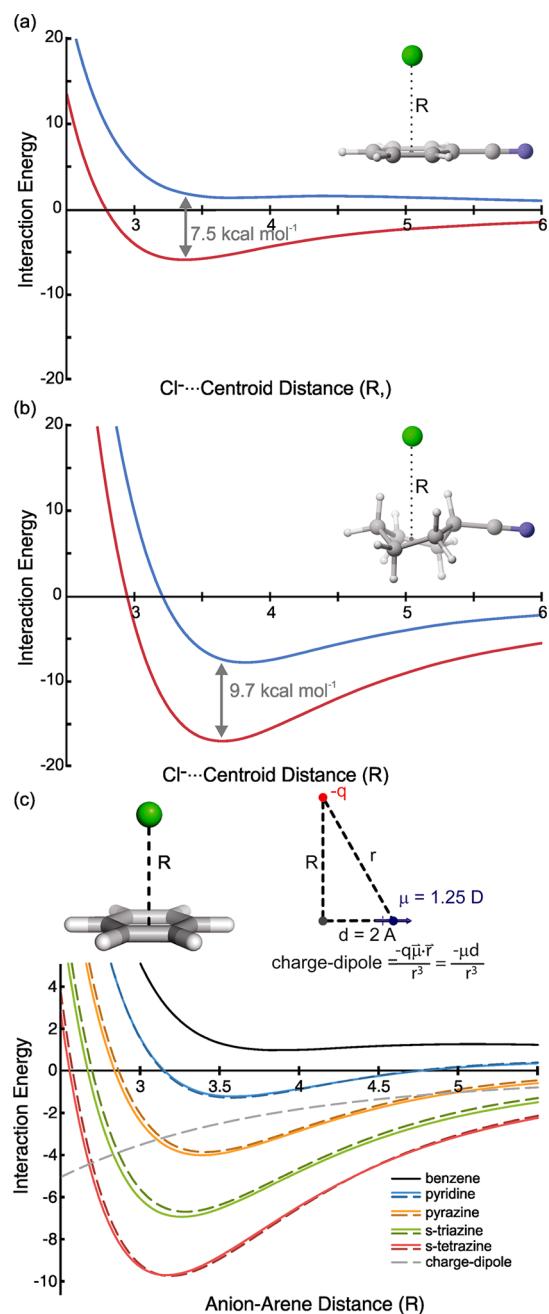


Figure 10. M06-2X/6-31+G(d) interaction energies (kcal mol⁻¹) of Cl⁻ with (a) benzene and (b) cyclohexane with (red curves) and without (blue curves) a single CN substituent, as a function of the Cl⁻...centroid distance (R , in Angstroms); (c) CCSD(T)/aug-cc-pVTZ interaction energies (kcal mol⁻¹) for model complexes of Cl⁻ with benzene, pyridine, pyrazine, s-triazine, and s-tetrazine (solid lines) versus the anion–arene distance (R , in Angstroms), as well as interaction potentials generated by adding a simple charge–dipole interaction (gray dashed line) to the interaction potential for Cl⁻ with benzene (dashed lines). Panels (a and b) adapted from ref 64. Copyright 2010 American Chemical Society.

need to be accounted for in order to capture the impact of nitrogen atoms on anion-binding.

E. Substituent Effects in XH–π Interactions. Finally, we briefly discuss our recent work on the nature of substituent effects on XH–π interactions, which can play key roles in numerous phenomena, including the tertiary structures of proteins,^{123–127} crystal packing,^{128–132} and molecular recogni-

nition.^{2,133–143} Consequently, there have been a number of computational studies of substituent effects on various XH–π interactions, including CH–π, OH–π, and NH–π interactions.^{141,142,144–147} However, these studies typically focused on a single type of XH bond, considered a limited set of substituents, and utilized different levels of theory. This prohibited a broad and systematic view of substituent effects in general XH–π interactions. In 2012, we carried out a comprehensive study of substituent effects across the full range of XH–π interactions, considering model complexes of the form XH···C₆H₅Y, where X = H₂B, H₃C, H₂N, HO, and F, and Y was any of a wide range of substituents.⁶⁸

The results provided a simple, unified physical picture of substituent effects on these interactions (see Figure 11). Overall,

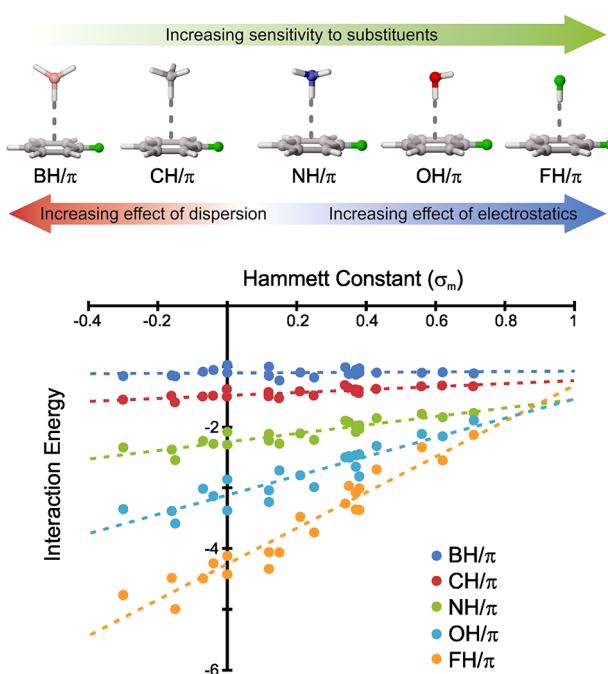


Figure 11. Model XH–π complexes as well as estimated CCSD(T)/aug-cc-pVTZ interaction energies (kcal mol⁻¹) for these model complexes with a range of substituted benzenes plotted vs Hammett constants. Adapted from ref 68. Copyright 2012 American Chemical Society.

we showed that the relative importance of electrostatic and dispersion effects varies depending on the polarity of the X–H bond. For example, for BH–π and CH–π interactions, substituent effects are rather weak, and are largely driven by dispersion effects. On the other hand, NH–π, OH–π, and FH–π interactions exhibit increasingly more pronounced substituent effects, and predicted interaction energies are correlated with Hammett σ_m -constants (see Figure 11).⁶⁸

IV. SUMMARY AND CONCLUSIONS

Noncovalent interactions have received considerable interest from physical chemists over the past decade, and these interactions underlie a myriad of chemical and biochemical phenomena. Satisfyingly, there have been dramatic advances over the past few years in our understanding of these interactions and the means by which their strength and geometry can be tuned.

Our recent work has focused on the impact of substituents and heteroatoms on many of these noncovalent interactions and has revealed deep-rooted misconceptions in the literature regarding

the origin of these effects. However, the physical picture that has emerged, in which substituent effects are dominated by local, through-space effects, points toward a very simple means of understanding these interactions. Although substituents undoubtedly alter the distribution of π -electron density within substituted aromatic rings, any impact of these changes is apparently overshadowed by local, direct interactions. Ultimately, this provides the groundwork for simple qualitative predictions of substituent effects in sundry noncovalent interactions and opens the door for rational design of supramolecular systems that exploit these interactions.

Despite this recent progress in understanding the nature of noncovalent interactions involving aromatic rings, many questions remain. The most pressing of these involves the effects of solvent, since the vast majority of computational studies of these interactions have involved gas-phase models. Moreover, the majority of computational studies of these interactions, including most of those summarized above, have involved rather artificial model systems in idealized configurations. Nonetheless, these studies of model systems have provided key insights into these noncovalent interactions, and have enabled us, along with others, to lay a firm foundation on which more complete models of π -stacking and other noncovalent interactions can be built. Ultimately, the prospects for a more complete understanding of these interactions, as well as conceptual tools to enable their rational exploitations in realistic chemical and biochemical systems, seems bright.

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Notes

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Jacob W. G. Bloom received a B.A. in Chemistry and Physics from New College of Florida in 2009 and an M.S. in Physical Chemistry from the University of Georgia in 2010. He recently completed his Ph.D. in the Wheeler Group at Texas A&M University. His Ph.D. research focused on computational studies of model noncovalent interactions, Ni-catalyzed aryl–aryl cross-coupling reactions, and conjugated polymers.

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