Understanding Substituent Effects in Noncovalent Interactions Involving Aromatic Rings

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CONSPECTUS

Noncovalent interactions involving aromatic rings such as π-stacking, cation/π, and anion/π interactions are central to many areas of modern chemistry. Decades of experimental studies have provided key insights into the impact of substituents on these interactions, leading to the development of simple intuitive models. However, gas-phase computational studies have raised some doubts about the physical underpinnings of these widespread models. In this Account we review our recent efforts to unravel the origin of substituent effects in π-stacking and ion/π interactions through computational studies of model noncovalent dimers.

First, however, we dispel the notion that so-called aromatic interactions depend on the aromaticity of the interacting rings by studying model π-stacked dimers in which the aromaticity of one of the monomers can be "switched off". Somewhat surprisingly, the results show that not only is aromaticity unnecessary for π-stacking interactions, but it actually hinders these interactions to some extent. Consequently, when thinking about π-stacking interactions, researchers should consider broader classes of planar molecules, not just aromatic systems.

Conventional models maintain that substituent effects in π-stacking interactions result from changes in the aryl π-system. This view suggests that π-stacking interactions are maximized when one ring is substituted with electron-withdrawing groups and the other with electron donors. In contrast to these prevailing models, we have shown that substituent effects in π-stacking interactions can be described in terms of direct, local interactions between the substituents and the nearby vertex of the other arene. As a result, in polysubstituted π-stacked dimers the substituents operate independently unless they are in each other's local environment. This means that in π-stacked dimers in which one arene is substituted with electron donors and the other with electron acceptors the interactions will be enhanced only to the extent provided by each substituent on its own, unless the substituents on opposing rings are in close proximity. Overall, this local, direct interaction model predicts that substituent effects in π-stacking interactions will be additive and transferable and will also depend on the relative position of substituents on opposing rings.

For cation/π and anion/π interactions, similar π-resonance-based models pervade the literature. Again, computational results indicate that substituent effects in model ion/π complexes can be described primarily in terms of direct interactions between the ion and the substituent. Changes in the aryl π-system do not significantly affect these interactions. We also present a simple electrostatic model that further demonstrates this effect and suggests that the dominant interaction for simple substituents is the interaction of the charged ion with the local dipole associated with the substituents.

Finally, we discuss substituent effects in electrostatic potentials (ESPs), which are widely used in discussions of noncovalent interactions. In the past, widespread misconceptions have confused the relationship between changes in ESPs and local changes in the electron density. We have shown that computed ESP plots of diverse substituted arenes can be reproduced without altering the aryl π-density. This is because substituent-induced changes in the ESP above the center of aryl rings result primarily from through-space effects of substituents rather than through changes in the distribution of the π-electron density.
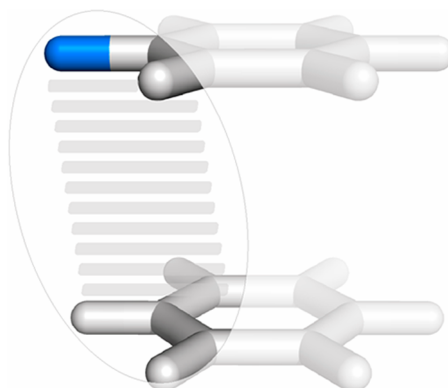
1. Introduction

Noncovalent interactions involving aromatic rings (e.g.: π-stacking, cation/π, and anion/π interactions) are central

to myriad areas of chemistry, materials science, and molecular biology.[1−4] Even though these interactions are relatively weak compared to covalent bonds, they can exert enormous
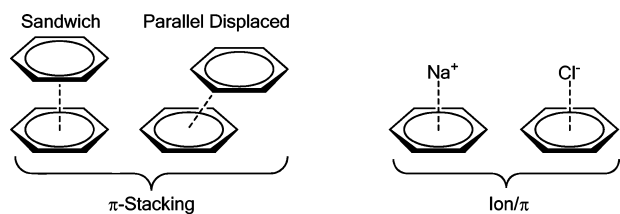
FIGURE 1. Prototypical π-stacking and ion/π interactions.

influence when occurring *en masse*. Consequently, subtle changes in the strength of these interactions, such as those induced by substituents, can have substantial impact when replicated across many such interactions. Understanding the effect of substituents on these interactions can shed significant light on many chemical and biochemical phenomena.[5-7]

Such understanding can be achieved by studying model noncovalent dimers, either through experiment or computation. Prototypical π-stacking and ion/π interactions are depicted in Figure 1. For π-stacking interactions, two model configurations of the benzene dimer are often considered: the D_{6h}-symmetric sandwich dimer and the parallel displaced dimer. The sandwich dimer is a second-order saddle point, while the minimum energy parallel displaced configuration lies about 1 kcal mol^{-1} lower in energy.[8] Regardless, the sandwich configuration is widely studied computationally and has long served as a platform for the development of qualitative models of π-stacking interactions.[4,9] We have recently shown[10] that substituent effects in the sandwich dimer configuration are strongly correlated with those in the parallel displaced arrangement. Thus, information gleaned from studies of the benzene sandwich dimer[8,10-19] should be transferable to the parallel displaced configuration. For cation/π and anion/π interactions, model systems are considered computationally in which the ion lies directly above the ring centroid. Although this configuration is often not a minimum energy configuration (particularly for anion/π interactions, for which this configuration is rarely an energy minimum),[20-22] such symmetric arrangements enable comparisons of substituent effects devoid of complications arising from differences in geometry.

For the last two decades, substituent effects in π-stacking interactions (i.e.: changes in the interaction energy for substituted systems relative to the unsubstituted dimer) have been described primarily in terms of the electrostatic model outlined by Hunter and Sanders[4,9,23-25] or the "polar/π" model espoused by Cozzi and Siegel.[26-30] In both models,[4,9,23-30] substituent effects in π-stacking interactions arise from substituent-induced changes in the aryl π-system.

For example, in the Hunter−Sanders model,[4,9,23-25] electron-withdrawing substituents are said to diminish the electron density in the π-cloud of the substituted ring, which decreases the electrostatic repulsion with the π-system of the interacting ring and enhances the π-stacking interaction. Electron-donating substituents result in weaker $\pi-\pi$ interactions through the opposite mechanism.

Substituent effects in π-stacking interactions have been quantified experimentally using everything from conformationally flexible systems and molecular torsional balances[26,28-33] to stereoselective Diels−Alder reactions[11] and supramolecular host−guest experiments.[23-25] The overwhelming majority of these experiments have supported the predictions of the Hunter−Sanders model: electron-donating substituents destabilize π-stacking interactions while electron acceptors stabilize these interactions.[4,9,23-25]

Over the past decade, advances in computational chemistry have enabled high-accuracy gas-phase studies of prototypical noncovalent interactions. The development of density functional theory (DFT) methods capable of treating dispersion-dominated noncovalent interactions has opened the floodgates to computational studies of both simple model systems as well as more complex noncovalent dimers. These studies have led to some upheaval in the literature,[10-15,17-20,34-40] as venerable intuitive models of these interactions have been subject to increased scrutiny. In this Account, we review recent computational studies aimed at understanding the nature of substituent effects in π-stacking, cation/π, and anion/π interactions.[18] In particular, we have shown that substituent effects in noncovalent interactions involving aromatic rings can be explained solely in terms of direct, through-space interactions of the substituents, with π-resonance effects playing no significant role.

2. Computational Methods for Non-Covalent Interactions

Because noncovalent interactions present particular challenges to computational chemistry, we provide a brief overview of commonly employed methods. The reader is directed toward recent reviews for more details.[8,41-43] The most reliable means of studying noncovalent interactions is through coupled cluster methods paired with large basis sets.[8,44] However, such robust approaches [*e.g.*: CCSD(T)/ AVTZ, where AVXZ signifies of aug-cc-pVXZ basis sets of Dunning and co-workers[45]] are computationally demanding and hence only applicable to medium-sized molecules. As such, an approximation can be made in which basis set effects are captured at a lower level of theory (e.g.: MP2)

and appended to CCSD(T) results computed with a smaller basis set.

Alternatively, several widely available DFT methods[46−52] are capable of describing dispersion-dominated complexes at a significantly reduced computational cost relative to that of CCSD(T).[42] Our work[10,11,18−20,34−36,53,54] has relied heavily on DFT, most notably the M05-2X and M06-2X methods of Truhlar and co-workers[49−52] and the B97-D functional of Grimme et al.[46−48] We have found that B97-D/TZV(2d,2p) provides an appealing compromise of speed and accuracy for many of these nonbonded interactions. For selected systems, DFT data are bolstered by CCSD(T) results. This has allowed us to exploit the computational efficiency of DFT to study a large number of substituted systems and to develop a broad view of these interactions while simultaneously examining selected systems at a higher level of theory.

Finally, symmetry-adapted perturbation theory (SAPT)[55] provides a robust means of predicting interaction energies for nonbonded complexes while also decomposing these energies into physically meaningful components. Such computations have provided key insights into substituent effects in many noncovalent interactions.[8,12−14,37−40]

3. What about Aromaticity?

Before delving into substituent effects, we first address the issue of aromaticity in so-called "aromatic interactions", which is a common moniker for π-stacking and other interactions.[4,56−58] Indeed, many researchers tacitly assume that aromatic monomers are required for favorable π-stacking interactions. This is based in part on the assumption that the π-cloud of aromatic systems is more polarizable, and thus expected to lead to enhanced dispersion interactions.

In 2008, Grimme[59] sought to determine whether special π−π interactions exist, or if aryl−aryl interactions are similar to analogous interactions between cycloalkanes. He showed that for small systems there was no discernible difference between aromatic and aliphatic systems. However, for systems larger than naphthalene there is the possibility of enhanced stacking interactions in the aromatic dimers compared to the analogous aliphatic systems.

In 2011, we tackled the issue of aromaticity in π-stacking interactions more directly,[53] showing that aromaticity is not required. This was accomplished in part using the model dimers depicted in Figure 2. SCS-MP2 interaction energies for sandwich dimers of benzene with an aromatic and a nonaromatic substituted naphthalene indicate that aromatic
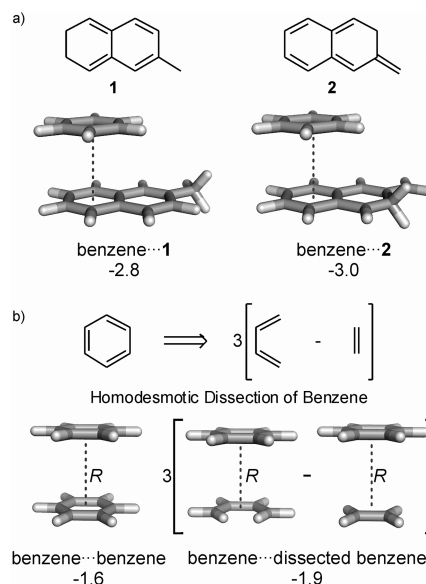
FIGURE 2. Model systems used to quantify the impact of aromatic π-delocalization on π-stacking interactions: (a) 2-methylnaphthalene (**1**, aromatic) and 2-methylene-2,3-dihydronaphthalene (**2**, nonaromatic); (b) intact benzene and nonaromatic dissected benzene model. Interaction energies are given in kcal mol^{-1} and are from ref 53.

delocalization leads to a 0.2 kcal mol^{-1} decrease in the strength of the interaction. CCSD(T)/AVTZ applied to the benzene sandwich dimer and a dimer of benzene with a nonaromatic dissected benzene similarly show that aromatic π-delocalization hinders π-stacking interactions by about 0.3 kcal mol^{-1}.

The interaction energies of the two model dimers depicted in Figure 2b are plotted in Figure 3a against the inter-ring separation. The stacking interaction is stronger with the nonaromatic system across the full range of inter-ring distances. Previously, Corminboeuf, Schleyer, and Warner[60] demonstrated that, in superphane structures, closely stacked antiaromatic rings exhibit aromatic character. However, this phenomenon occurred at close inter-ring distances (∼2 Å), and its partially covalent origin is distinct from the effects discussed here.[53]

SAPT2 computations (Figure 3b) helped uncover the origin of the enhanced π-stacking interactions of nonaromatic planar polyenes.[53] Surprisingly, dispersion interactions play essentially no role. Instead, the decrease in interaction energy upon aromatic delocalization arises primarily from enhanced exchange repulsion. At distances beyond 3.5 Å, the electrostatic component of the interaction energy also favors the interaction of benzene with the nonaromatic dissected benzene model.

In summary, we have shown[53] that aromaticity is not required for π-stacking interactions and may actually hinder

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b)
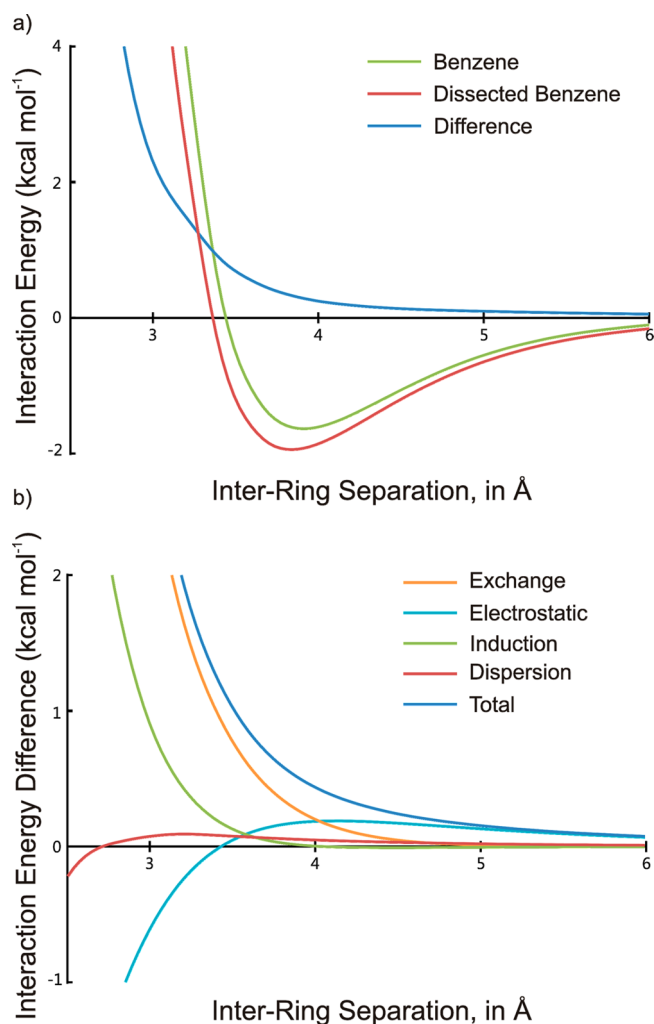
FIGURE 3. (a) CCSD(T)/AVTZ interaction energy for sandwich dimers of benzene with benzene and with the dissected benzene model versus the inter-ring separation as well the difference between these two curves. (b) SAPT2 components of the *difference* between the two stacking interactions depicted in part a, as well as the total difference in interaction energy. Data from ref 53.

these interactions. Consequently, it could prove beneficial to think more broadly about π-stacking interactions and to consider π-stacking interactions involving nonaromatic polyenes.

4. Substituent Effects in the Benzene Dimer and Beyond

A series of high-accuracy gas-phase computational studies by Kim et al.[57] and Sherrill and co-workers[8,12−15] in the early 2000s raised doubts about the simple electrostatic model championed by Hunter and Sanders.[4,9,23−25] For example, Sherrill et al. showed[15] that both electron-donating substituents and electron-withdrawing substituents stabilize the benzene sandwich dimer, while the Hunter−Sanders model[4,9,23−25]

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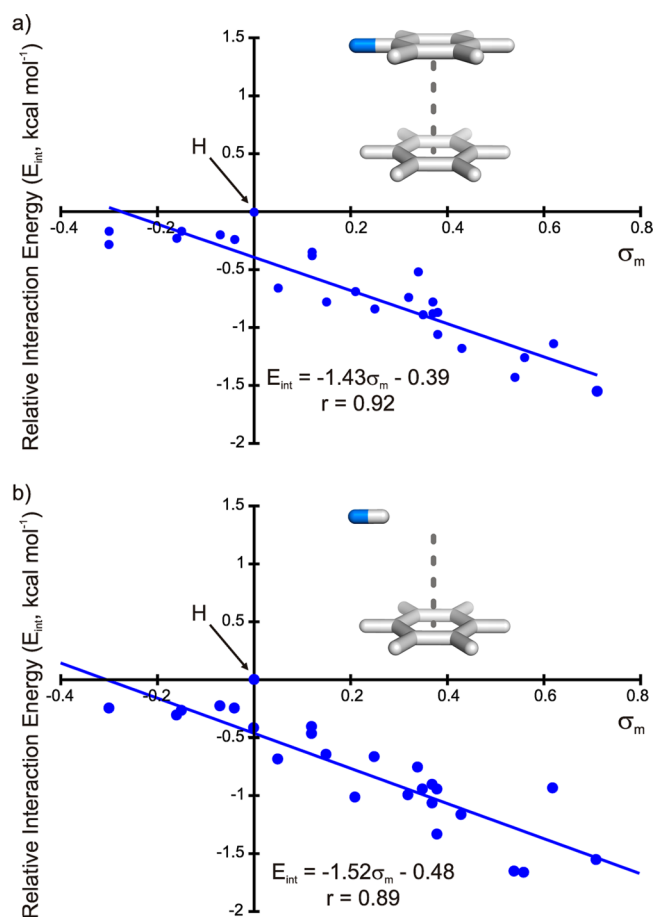
FIGURE 4. Interaction energies (relative to X = H) for (a) $C_6H_5X \cdots C_6H_6$ and (b) $HX \cdots C_6H_6$ sandwich dimers, for which X is from a set of 25 diverse substituents. Data from ref 19.

maintains that electron donors should weaken stacking interactions.

One limitation of these previous studies[8,12−15] was the consideration of a limited number of substituents. In 2008, we showed[19] that the finding of Sherrill et al.[8,12−15] that both donors and electron acceptors stabilize the benzene sandwich dimer holds for a diverse set of 25 substituents. By examining this broader range of substituents, we were able to show[19] that the unsubstituted benzene dimer was the outlier, and both electron donors and electron acceptors followed the same general trend (Figure 4a). On the basis of the correlation of computed interaction energies with Hammett σ_m constants, we proposed that the trend in substituent effects arises primarily from electrostatic interactions. The nonzero y-intercept in Figure 4a, and hence the origin of the stabilization of all substituted dimers relative to the unsubstituted case, was attributed to dispersion interactions.[19] We note that Sherrill et al.[38] subsequently showed that, for polysubstituted benzene dimers, the correlation

with σ_m observed in Figure 4a breaks down due to the increased importance of dispersion interactions.

Perhaps more importantly, in the same paper we also showed[19] that substituent effects in the benzene sandwich dimer remain unchanged if the substituted ring is replaced with a hydrogen atom, leaving all conserved atoms in place (Figure 4b). In other words, substituent effects in $C_6H_5-X\cdots C_6H_6$ dimers are strongly correlated with those in $H-X\cdots C_6H_6$ dimers at the same monomer separation (compare parts a and b of Figure 4). That replacing the aryl ring with hydrogen left the substituent effects unperturbed precludes any significant involvement of the aryl π-system in these substituent effects. Instead, substituent effects were explained solely in terms of direct interactions[19] between the substituent and the unsubstituted ring.

Since 2008, studies by Sherrill and co-workers[38,40] as well as Lewis et al.[17] and others[61,62] have provided further insight into the relative role of electrostatic and dispersion interactions in substituted benzene dimers. For example, Lewis and co-workers showed[17] that, at equilibrium separations, there is a strong linear correlation between the total interaction energy in polysubstituted benzene dimers and the electrostatic component. Sherrill et al.[40] demonstrated that while all substituents stabilize the benzene sandwich dimer at the gas-phase equilibrium geometry, at larger inter-ring separations electron donating substituents hinder the interaction, as predicted by conventional models.[4,9,23−25] The disparate behavior at small inter-ring separations was attributed to charge penetration effects.[40]

In 2011, we extended the direct-interaction view[19] of substituent effects in π-stacking interactions by recognizing that the direct interactions between the substituents and the unsubstituted ring were due to *local interactions*.[10] In other words, substituents effects do not arise from the interaction of the substituents with the other ring in its entirety, but only the nearest vertex. This led to our local, direct interaction model of substituent effects in π-stacking interactions (Figure 5), which can be used to explain substituent effects in general π-stacking interactions.[10] In this model, substituent effects arise from the interaction of the local dipole (or higher-order multipole) associated with the substituent (including the first polarized σ-bond) with the nearby local C−H dipoles of the other ring. As a result, substituent effects are insensitive to changes to the distal side of either the substituted or unsubstituted ring.

In cases where both rings bear substituents, our local, direct interaction model[10] predicts that substituents will operate independently as long as they are not in close
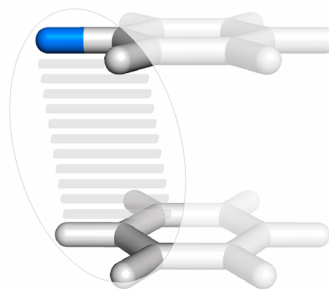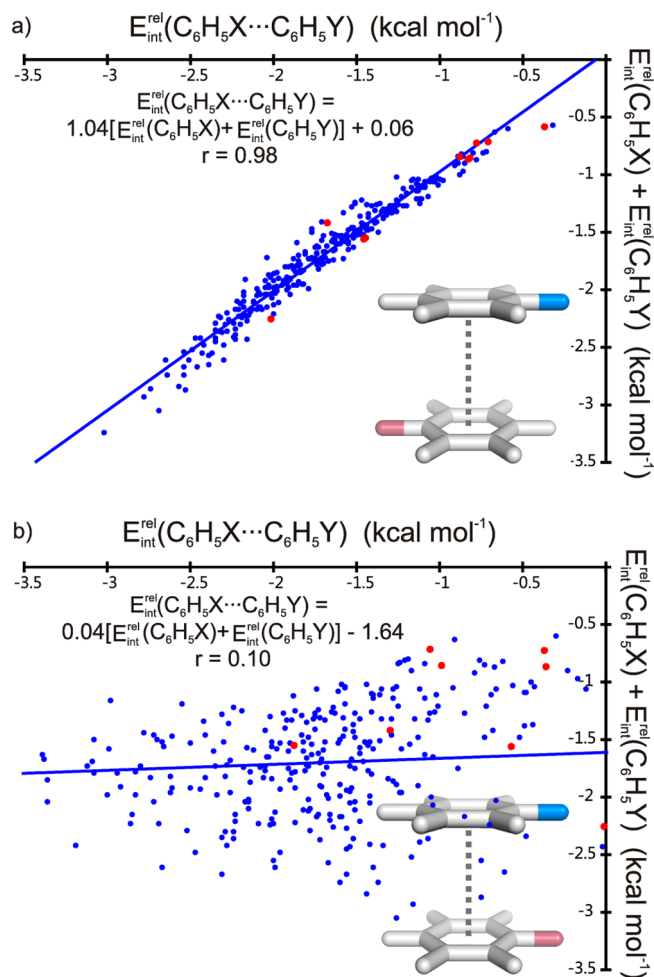

FIGURE 5. Local, direct interaction model[10] of substituent effects in π-stacking interactions. In this model, substituent effects are dominated by through-space interactions of the local dipole associated with the substituent and the proximal vertex of the other ring. As a result, changes to other parts of either ring (shaded area) have no net impact on substituent effects.

proximity. This can be seen in Figure 6a, in which relative interaction energies for 300 $C_6H_5X\cdots C_6H_5Y$ dimers are plotted against the sum of relative interaction energies for $C_6H_5X\cdots C_6H_6$ and $C_6H_6\cdots C_6H_5Y$ dimers. At both the CCSD(T) and B97-D levels of theory, there is a strong linear correlation, and interaction energies in $C_6H_5X\cdots C_6H_5Y$ dimers are captured by simply adding the effects of the individual substituents. If the two rings are oriented so that the substituents are aligned (Figure 6b), this correlation breaks down, because in this case there are direct substituent−substituent interactions that are not accounted for by considering the effects of the substituents individually.

These findings are in conflict with the Hunter-Sanders model,[4,9,23−25] which predicts a coupling of substituent effects in mixed substituted dimers. Although such coupling is supported by experimental data,[25,63,64] closer examination of these experiments shows that they involve configurations in which the two substituents are aligned, analogous to the dimers in Figure 6b. In other words, the coupling between substituent effects observed experimentally[25,63,64] is due to direct interactions between the substituents, not effects transmitted through the aryl π-system. That substituent effects in π-stacking interactions are dependent on the relative position of substituents has been demonstrated experimentally by Gung et al.[32] and Benitex and Baranger.[65]

The additivity of substituent effects in π-stacking interactions even applies in cases where chemical intuition suggests a strong coupling between substituents. For example, B97-D predicted relative interaction energies are plotted in Figure 7 as a function of the lateral displacement (R) for the interaction of benzene with benzene, *p*-nitroaniline, nitrobenzene, and aniline. Intuition suggests that the "push−pull" effect in *p*-nitroaniline will impact its interaction with
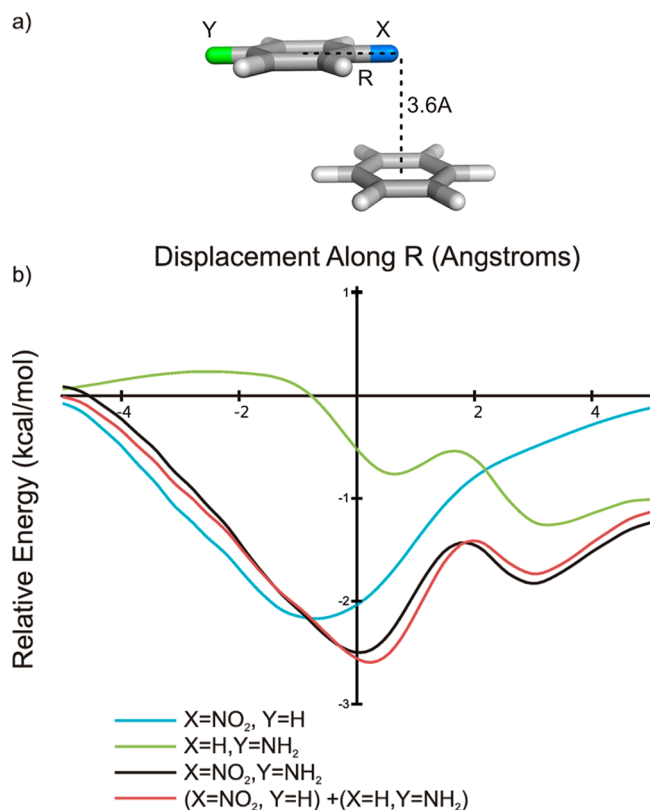
a)

$$E_{int}^{rel}(C_6H_5X\cdots C_6H_5Y)\ (kcal\ mol^{-1})$$

$$E_{int}^{rel}(C_6H_5X\cdots C_6H_5Y) =$$
$$1.04[E_{int}^{rel}(C_6H_5X)+E_{int}^{rel}(C_6H_5Y)] + 0.06$$
$$r = 0.98$$

b)

$$E_{int}^{rel}(C_6H_5X\cdots C_6H_5Y)\ (kcal\ mol^{-1})$$

$$E_{int}^{rel}(C_6H_5X\cdots C_6H_5Y) =$$
$$0.04[E_{int}^{rel}(C_6H_5X)+E_{int}^{rel}(C_6H_5Y)] - 1.64$$
$$r = 0.10$$

FIGURE 6. Comparison of interaction energies for two different sandwich dimers of $C_6H_5X\cdots C_6H_5Y$ and the sum of interaction energies for $C_6H_5X\cdots C_6H_6$ and $C_6H_6\cdots C_6H_5Y$, all relative to the unsubstituted case (X, Y = H), where X and Y are from a set of 25 substituents. B97-D/TZV(2d,2p) data are in blue; estimated CCSD(T)/AVTZ data are in red. Adapted from ref 10.

a)

b)

Displacement Along R (Angstroms)

FIGURE 7. (a) Model $Y-C_6H_4-X\cdots C_6H_6$ dimer. (b) B97-D/TZV(2d,2p) interaction energies, relative to the unsubstituted case (X, Y = H) as a function of the lateral displacement, R, for benzene with aniline, nitrobenzene, and *p*-nitroaniline. The red curve is the sum of the NO_2 and NH_2 curves, demonstrating that the substituted effects in the *p*-nitroaniline$\cdots$benzene dimer are reproduced by combining the effects of NH_2 and NO_2 separately.

benzene in stacked dimers. However, the substituent effects in the benzene$\cdots$*p*-nitroaniline dimer are well described by considering the effect of the nitro and amino substituents separately. Apparently, any effects due to the enhanced donor/acceptor effects of the NH_2/NO_2 groups in *p*-nitroaniline are overshadowed by the local, direct interactions.

One final implication of the local, direct interaction model is transferability of substituent effects. By this we mean that interactions for substituted dimers, relative to the corresponding unsubstituted case, are identical across a broad range of systems as long as the local interactions are conserved. This has been demonstrated for substituted pyridine−benzene, perfluorobenzene−benzene, and 1,2,3-trifluorobenzene−benzene dimers.[10]

In summary, although conventional views of substituent effects in π-stacking interactions, which are based solely on

π-resonance based changes in the aryl π-system, are often in agreement with experimental data, gas-phase computational studies have revealed apparent weaknesses in these models. We have shown[10,11,19,34] that substituent effects in diverse stacked dimers can be explained in terms of direct, local interactions between the substituents and the proximal vertex of the other ring. The resulting local, direct interaction model[10] readily explains why substituent effects are additive, transferable, and dependent on the relative position of the substituents.

5. Substituent Effects in Cation/π and Anion/π Interactions

Popular descriptions of substituent effects in cation/π and anion/π interactions are cast in similar language to the Hunter−Sanders model for stacking interactions.[4,9,23−25] That is, π-resonance effects are generally invoked to rationalize substituent effects in these interactions.[66−68] This reflects the widespread practice of referring to arenes

bearing electron-withdrawing substituents as "π-electron-poor" and those with electron-donors as "π-electron-rich". The former bind anions, while the latter preferentially bind cations.

The implication of these terms is that substituent effects in cation/π and anion/π interactions arise primarily from changes in the aryl π-system. We showed[20,35] that substituent effects in model cation/π and anion/π interactions are strongly correlated with the sum of interactions of the ion with the hydrogen capped substituent and unsubstituted benzene, as done previously[19,34] for the benzene dimer. In other words, substituent effects in model gas-phase ion/π interactions can be accounted for without any changes in the aryl π-system.

That substituent effects in ion/π interactions can be explained without recourse to π-resonance effects can be demonstrated another way (Figure 8). In this figure, CCSD(T) interaction potentials for Cl$^-$ and Na$^+$ above the centers of nitrile-substituted benzenes are reproduced using a simple electrostatic model. This model (dashed blue curves) is constructed by adding a classical charge–dipole interaction (solid blue curves, where the magnitude of the dipole, 3.02 D, is the computed value for HCN) to the potential for the interaction of Cl$^-$ or Na$^+$ with an unsubstituted benzene (gray curves). For ion/π interactions, these simple additive curves accurately reproduce the CCSD(T) interaction potential for the substituted system. In addition to showing that changes in the π-system are not necessary to capture substituent effects in ion/π interactions, these plots provide insight into the origin of substituent effects. Namely, substituent effects in ion/π interactions arise from interactions of the ion with the local dipole (or higher-order multipoles) associated with the substituent. In the case of anion/π interactions, anion binding occurs because these favorable charge-dipole interactions overcome repulsive interactions between the anion and the benzene ring.

6. Substituent Effects in Molecular Electrostatic Potentials

Finally, we address substituent effects in molecular electrostatic potentials (ESPs).[36] These colorful plots have proved invaluable in analyses of many noncovalent interactions. In this context, emphasis is often placed on changes in the ESP above the centers of the substituted arene, which are then touted as evidence of changes in the aryl π-system. This interpretation is due to confusion regarding the relationship between changes in the ESP and underlying changes in the local electron density. For example, it is common to conclude
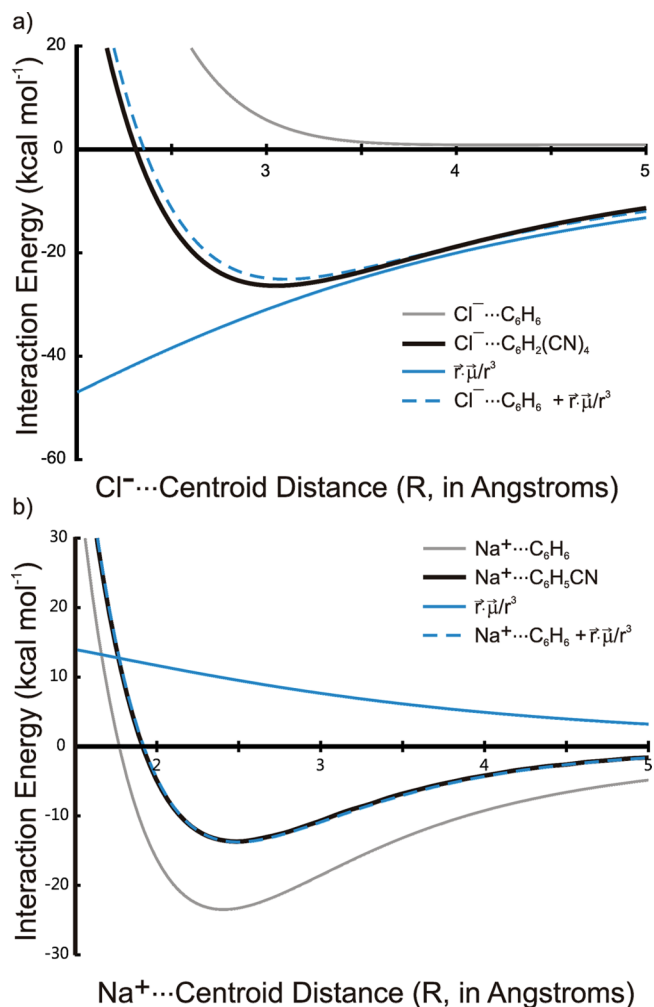
FIGURE 8. Interaction energies as a function of X$^{\pm}\cdots$centroid distance for model anion/π (a) and cation/π (b) interactions, as well as the interaction energies from a simple model (dashed curves) in which a classical charge-dipole term is added to the interaction energy for unsubstituted benzene. Data for part a are from ref 20.

that an arene has "depleted π-electron density" based on ESP plots that show a positive ESP above the ring center. We have shown[36] that substituent-induced changes in the ESP above the centers of arenes are due primarily to through-space effects of the substituents. Such changes do not necessarily reflect local changes of the π-electron distribution.

In 2009, we showed[35] that the ESP at a single point above the center of a wide range of substituted benzenes was accurately captured by adding the ESP due to a hydrogen capped substituent to the ESP of unsubstituted benzene. This was later extended[36] to ESPs mapped onto electron density isosurfaces. ESP plots for a series of substituted benzenes were constructed by adding, at each point in space, the ESP due to benzene with that due to the hydrogen-capped substituent. The resulting ESP plots (e.g.: Figure 9b) closely

resemble ESPs for the corresponding substituted benzene (Figure 9b). In other words, the diverse ESPs of substituted benzenes can be constructed by superimposing the ESP of the substituent onto the ESP of benzene. These long-range, through-space electrostatic effects apply generally, and we showed[36] that, for myriad substituted arenes, changes in the ESP are due to through-space effects of the substituents, not local changes in the π-electron density.

That through-space effects of substituents can induce such drastic changes in the ESP above the center of an aryl ring arises because of the long-range behavior of electrostatic interactions. This can be seen by examining 2D slices through the ESP, which are plotted for benzonitrile, benzene, HCN, and benzene + HCN in Figure 10. As with the ESP maps in Figure 9, the 2D ESP of C_6H_5CN is qualitatively reproduced by adding the ESP of C_6H_6 and that of HCN. The origin of the non-negative ESP above the center of the ring in C_6H_5CN is seen to arise from the large positive region in the ESP surrounding HCN. Thus, the change in the ESP above the center of benzene upon substitution by CN does not arise from depletion of the aryl π-electron density but is due to

FIGURE 9. (a) ESPs mapped onto electron density isosurfaces ($\rho = 0.005$) for toluene, ethynylbenzene, benzonitrile, and nitrobenzene. (b) "Additive ESPs" mapped onto the same electron density isosurfaces, constructed by adding the ESP of unsubstituted benzene to HCH_3, $HCCH$, HCN, and HNO_2, respectively. ESP plots from ref 36.

through-space effects of the local dipole associated with CN. These through-space effects simply overwhelm the negative ESP due to the aryl π-system.

In conclusion, although ESPs are useful visual tools for understanding noncovalent interactions, one must not equate changes in the ESP with local changes in the electron density.[36] This is vital when examining ESP plots of substituted arenes, which show a remarkable degree of variation above the ring center that is not due to changes in the π-electron density. Instead, these changes are due to long-range, through-space electrostatic effects of the substituents.

7. Summary and Prospectus

Computational studies of model noncovalent dimers have led to dramatic advances in our understanding of substituent effects in these interactions.[18] Among these findings, we have shown the following:

(1) Aromaticity is not required for so-called "aromatic interactions", and it could prove beneficial to think more broadly when designing systems expected to engage in favorable π-stacking interactions.[53]

(2) Substituent effects in π-stacking and ion/π interactions can be explained solely in terms of direct interactions with the substituents.[10,11,19,20,34−36] Our local, direct interaction model[10] provides a simple framework within which substituent effects in diverse π-stacking interactions can be explained, including many systems for which conventional views encounter difficulties.

(3) Computed electrostatic potentials, although useful in analyzing noncovalent interactions, are often misinterpreted.[36] Specifically, substituent-induced changes in the ESP above the center of aryl rings do not necessarily indicate changes in the π-electron density. Instead, such changes are due primarily to through-space effects of the substituents.[36]

A broader implication of these findings concerns the parametrization of classical molecular mechanical force fields and coarse-grained models. In particular, the local
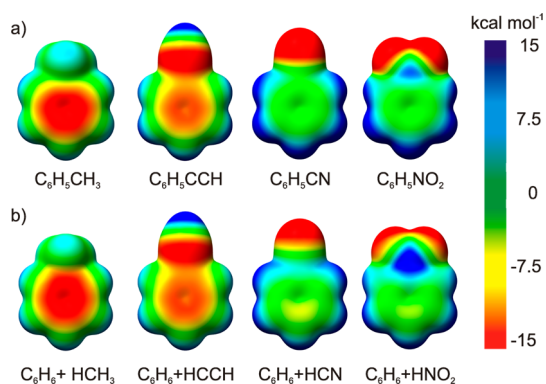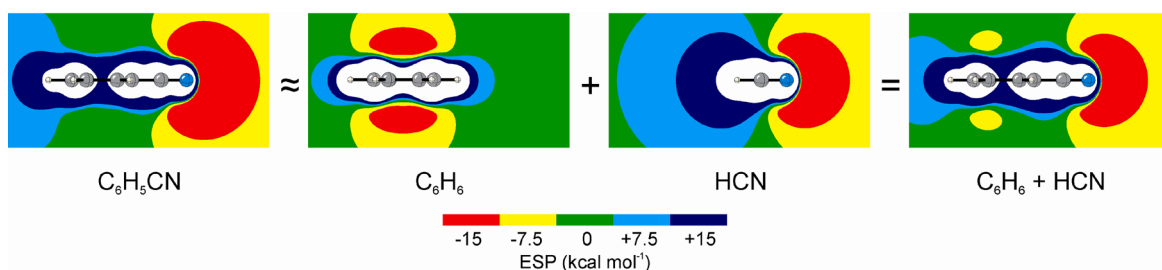
FIGURE 10. Two-dimensional "slice" (perpendicular to the molecular plane) through the ESP of cyanobenzene (left), which is well-represented by taking the sum of ESPs from benzene and HCN (rightmost figure). The middle ESP plots for benzene and HCN show that the change in the ESP above the center of cyanobenzene arises from the large positive lobe in the ESP of the nitrile substituent.

nature of substituent effects justifies the development of transferable parameters for aryl substituents and also explains why traditional MM force fields can capture substituent effects in noncovalent interactions with aromatic rings without consideration of polarization effects.

Looking ahead, there is still much that we do not yet understand regarding the nature of these noncovalent interactions or the means by which substituents and heteroatoms alter these interactions. Combining the assets of experiment with computational studies can provide a powerful means of filling these gaps. Our local, direct interaction view[10] provides a powerful tool for understanding substituent effects in these interactions. In particular, the local nature of these effects means that stacking interactions in complex systems can be understood by considering substituents individually, obfuscating the need to consider coupling among different substituents or heteroatoms. Thus, this local model[10] ultimately leads to a simpler and more digestible view of substituent effects in noncovalent interactions compared to the π-resonance-based models that pervade the literature, and will hopefully prove useful moving forward. The implications of this model (additivity, transferability, and dependence of substituent effects on the relative position of substituents) can be probed experimentally, which should provide insight into the validity of this viewpoint and ultimately provide a more sound understanding of substituent effects in noncovalent interactions involving aromatic rings.

BIOGRAPHICAL INFORMATION

Steven E. Wheeler graduated from New College of Florida in 2002 with degrees in Chemistry and Physics. He obtained his Ph.D. in 2006 under Fritz Schaefer at the University of Georgia before joining Ken Houk's group at UCLA as an NIH postdoctoral fellow. Since 2010 he has been a faculty member at Texas A&M University, where his research group uses computational chemistry to understand the nature of noncovalent interactions involving aromatic rings and to quantify their impact on problems in organocatalysis, supramolecular chemistry, and protein–DNA interactions.

FOOTNOTES

The authors declare no competing financial interest.

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