

Through-Space Effects of Substituents Dominate Molecular Electrostatic Potentials of Substituted Arenes

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Abstract: Model systems have been studied using density functional theory to assess the contributions of π -resonance and through-space effects on electrostatic potentials (ESPs) of substituted arenes. The results contradict the widespread assumption that changes in molecular ESPs reflect only local changes in the electron density. Substituent effects on the ESP above the molecular plane are commonly attributed to changes in the aryl π -system. We show that ESP changes for a collection of substituted benzenes and more complex aromatic systems can be accounted for mostly by through-space effects, with no change in the aryl π -electron density. Only when π -resonance effects are substantial do they influence changes to any extent in the ESP above the aromatic ring. Examples of substituted arenes studied here are taken from the fields of drug design, host–guest chemistry, and crystal engineering. These findings emphasize the potential pitfalls of assuming ESP changes reflect changes in the local electron density. Since ESP changes are frequently used to rationalize and predict intermolecular interactions, these findings have profound implications for our understanding of substituent effects in countless areas of chemistry and molecular biology. Specifically, in many noncovalent interactions there are significant, often neglected, through-space interactions with the substituents. Finally, the present results explain the good performance of many molecular mechanics force-fields when applied to supramolecular assembly phenomena, despite the neglect of the polarization of the aryl π -system by substituents.

I. Introduction

Molecular electrostatic potentials (ESPs) have emerged as powerful predictive and interpretive tools in disparate areas of chemistry, rational drug design, and molecular biology.^{1,2} Colorful plots of ESPs have been used to rationalize trends in organic reactivity³ and binding in host–guest complexes and noncovalent interactions (cation/ π , π – π , etc.).^{4–9} Information gleaned from ESPs is often utilized in analyses of protein–ligand and protein–protein interactions¹⁰ as well as studies of the folding of model proteins.¹¹ Quantitative ESP-based reactivity descriptors have also emerged, offering alternatives to traditional substituent constants.¹² Computed ESPs have been correlated with impact sensitivities of explosive compounds¹³ and toxicity in polychlorinated

biphenyls (PCBs).¹⁴ Moreover, ESPs can be readily computed using standard electronic structure theory packages or derived from experimental X-ray diffraction data,¹⁵ providing a simple, easily accessible tool for understanding numerous phenomena.

The ESP at a given point near a molecule is a measure of the electrostatic energy a positive unit test charge would experience at that point. Negative ESPs correspond to an attractive interaction with this test charge, while positive ESPs indicate repulsion. Nonuniform electrostatic potentials arise in molecular environments from the competing effects of the nuclear charges and the surrounding electrons. The use of ESPs to predict and rationalize reactivity trends was pioneered by Scrocco, Tomasi, and co-workers,¹⁶ who studied electrophilic attack of three-membered rings and nucleic acid bases and proton affinities of amides. Subsequently, ESP plots have been

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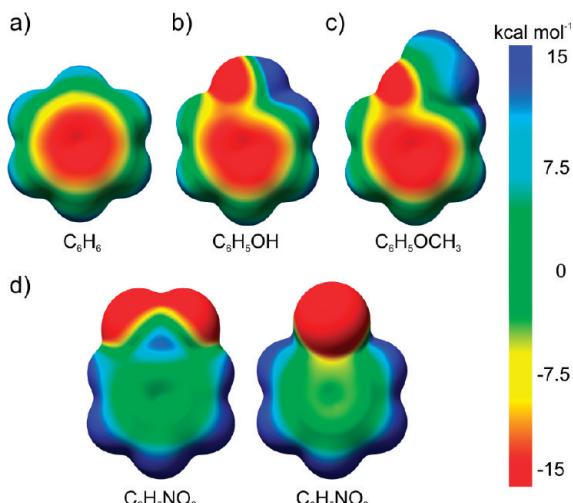


Figure 1. Plots of the electrostatic potential of (a) benzene, (b) phenol, (c) anisole, and (d) planar nitrobenzene (left) and perpendicular nitrobenzene (right) mapped onto electron density isosurfaces (0.001 e/au^3).

applied to sundry chemical systems driven, in large part, by the many reports of Politzer and Murray.^{2,3} ESP plots also enjoy wide applicability in the analysis of noncovalent interactions. They have been used in the development of conceptual models of the electrostatic component of prototypical interactions, and they have provided a simple means of approximating the interaction strength and geometry of noncovalent complexes.^{4–9} ESPs have been applied to noncovalent interactions of increasingly complex systems, culminating in studies of protein–ligand and protein–protein interactions.⁴

Unfortunately, the literature is peppered with false assumptions regarding the effect of substituents on ESPs. It is common to equate changes in the ESP in a given region with *local* changes in the electron density. For example, in a recent study of noncovalent interactions in mechanically interlocked compounds, Goddard, Stoddart, and co-workers¹⁷ used ESP plots to evaluate electron density differences of the central naphthalene core for a series of substituted systems. Indeed, when presenting ESP plots, many authors explicitly label regions of negative electrostatic potential as “electron-rich” and positive ESP regions as “electron-poor”.¹⁸ This connection between ESP values and the local electron density is also advanced in otherwise stellar textbooks on physical organic chemistry¹⁹ and in publications advocating the use of ESP plots in undergraduate education.²⁰ Politzer and Murray³ emphasized nearly two decades ago that the ESP is the “net result at a given point of the integrated effects of all of the electrons and nuclei, whereas $\rho(\mathbf{r})$ of course represents only the electronic density at that point.” While negative ESPs often do correspond to electron-rich regions, the assumption that changes in ESPs necessarily indicate local changes in the electron density is incorrect.

The gas-phase ESP at a given point, $V(\mathbf{r})$, is defined by eq 1, where Z_A and \mathbf{R}_A are the charge and position of nucleus A, respectively, and $\rho(\mathbf{r}')$ is the electron density at position \mathbf{r}' , all in atomic units:

$$V(\mathbf{r}) = \sum_{\text{nuclei}} \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} - \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' \quad (1)$$

The integral in eq 1 runs over all space. Thus, at a given point, the ESP is dependent on the electron density in all surrounding space, though this dependency dies off with distance. Despite this $1/r$ dependence, seemingly subtle changes in the electron density can have profound effects on the ESP at a given point several angstroms away. For example, a charge of 0.1 e contributes more than 10 kcal mol^{-1} to the ESP at a distance of 3 \AA .

Substituent effects on aromatic rings have been studied extensively since the pioneering work of Hammett.²¹ Generally, the effects of a substituent on an aryl ring are transmitted via numerous potential mechanisms, which are often conceptually divided into π -resonance, inductive (through- σ -bond), and field (through-space) effects.²² There have been numerous attempts to quantify these often competing effects, leading to the development of a bevy of substituent constants.²³ Among the most popular separations of π - and σ -effects come from the works of Roberts and Moreland,²⁴ Taft,²⁵ and Swain and Lupton,²⁶ who partitioned substituent constants into resonance effects (as quantified by σ_R or R) and inductive/field effects (σ_I or F). In these schemes, more negative numbers indicate stronger electron donating tendency, while more positive values correspond to stronger electron acceptors. Substituent effects arise from some combination of resonance and inductive/field effects, with the relative contribution varying with the substituent. ESP maps of substituted benzenes should similarly reflect both π -resonance and inductive/field effects.

The potentially large contribution of through-space substituent effects is mostly absent in discussions of arene ESPs in the modern literature. Many authors assume changes in arene ESPs reflect donation into or out of the aryl π -system. For example, in their extensive studies of substituent effects on the benzene dimer,^{8,9,27–29} Sherrill and co-workers utilized ESP plots to characterize the “degree of π -density” in substituted benzenes. This idea is appealing since it enables simple resonance-based explanations of trends in electrostatic potential plots. That is, the ESP above benzene substituted with an electron-withdrawing group will generally be more positive than that of benzene, rationalized based on resonance forms with a formal positive charge at the *ortho* and *para* positions. More negative ESPs above benzenes substituted with electron donors are often explained by resonance forms with a negative charge on the benzene ring.

Two subtle exceptions to such π -resonance-based explanations of ESPs are phenol and anisole. Based on Hammett substituent constants, OH and OMe are π -electron-donating substituents [$R(OCH_3) = -0.56$, $R(OH) = -0.70$],²³ so the ESPs above the aryl ring in these two systems should be more negative than in benzene, according to the simple π -resonance picture. However, the ESPs above phenol and anisole are slightly more positive than that of benzene (see Figure 1a–c). Analogously, the interactions of Na^+ with C_6H_5OH and $C_6H_5OCH_3$ are slightly weaker than the $Na^+ \cdots C_6H_6$ interaction.^{5,30,31} This seemingly counterintuitive phenomenon has been mentioned previously,^{27,30,32} most

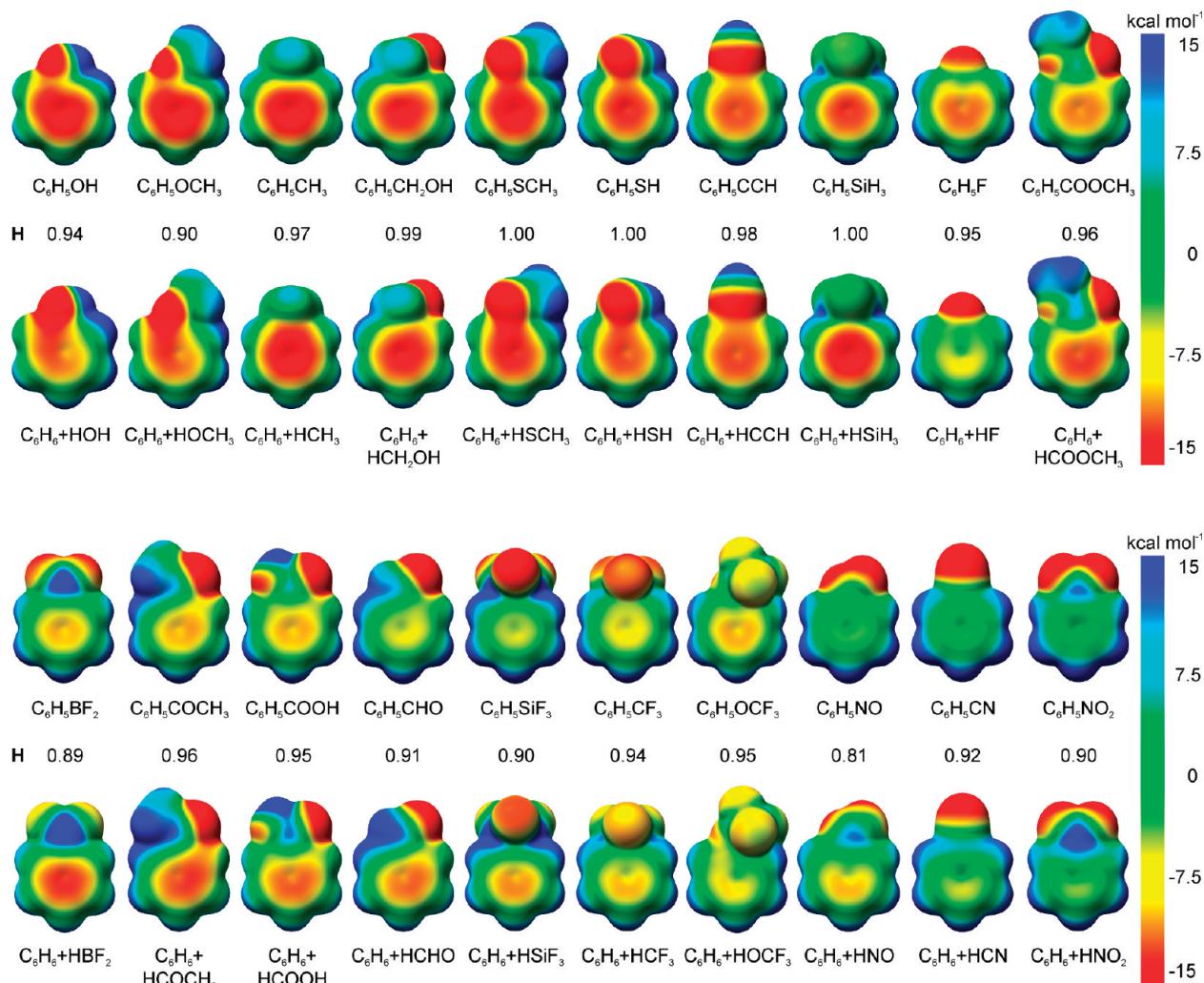


Figure 2. Plots of electrostatic potentials of monosubstituted benzenes (first and third row) and corresponding additive ESPs (second and fourth row). ESPs are mapped on electron density isosurfaces ($0.001 \text{ e}/\text{au}^3$) for the substituted benzene. The H index is computed for the ESP values on the isodensity surfaces for the true and additive ESPs.

prominently by Dougherty and co-workers,^{5,30} who noted that the strength of cation– π interactions and the ESP above the center of substituted benzenes are more strongly correlated with σ_m constants than σ_p . Hunter and co-workers⁷ also reported a strong correlation between σ_m and the ESP at the centroid of substituted aromatic rings. This σ_m dependence is contrary to the prevalent π -resonance-based explanations of ESPs of substituted arenes, since σ_m constants reflect mostly nonresonance effects. In the case of phenol and anisole, the σ -withdrawing effect on the ESP overwhelms the π -donation, as noted by Klärner and co-workers.³²

A more clear-cut example of the dominant role of inductive/field effects on ESPs was provided by Politzer and co-workers in 1987.³³ The ESP map of nitrobenzene is positive everywhere above the aryl plane, a feature which might naively be attributed to π -electron withdrawal. However, Politzer et al.³³ showed that the ESP of nitrobenzene is essentially unchanged upon a 90° rotation of the nitro group (see Figure 1d). In perpendicular nitrobenzene, there can be no π -resonance between the NO_2 and the aryl π -system, yet the ESP is still positive everywhere above the benzene plane. Clearly, in nitrobenzene, π -resonance has little net effect on the ESP; substituent effects on the ESP

must arise from inductive/field effects. This finding is consistent with the typical characterization of NO_2 as a strong inductive electron-withdrawing group but modest resonance acceptor ($F = 0.65$, $R = 0.13$).²³

Substituent effects on the electrostatic properties of aromatic systems are central to many areas of modern chemistry and molecular biology, and maps of molecular electrostatic potentials constitute a powerful and popular tool for rationalizing and predicting noncovalent interactions. Consequently, a full understanding of chemical and biochemical systems must rest on a sound understanding of the changes in ESPs induced by substituents. Previously, we demonstrated³¹ that substituent effects on the ESP at a point approximately 2.4 \AA above the center of monosubstituted benzenes arise primarily from direct through-space effects of the substituents, and π -resonance effects play a relatively minor role. We now show that, for a wide range of substituents, changes in ESP maps of substituted aromatic systems are generally dominated by through-space effects of the substituents. More importantly, the widespread, often implicit, assumption that changes in ESPs necessarily indicate local changes in electron density is shown to be unfounded and, in many cases, misleading.

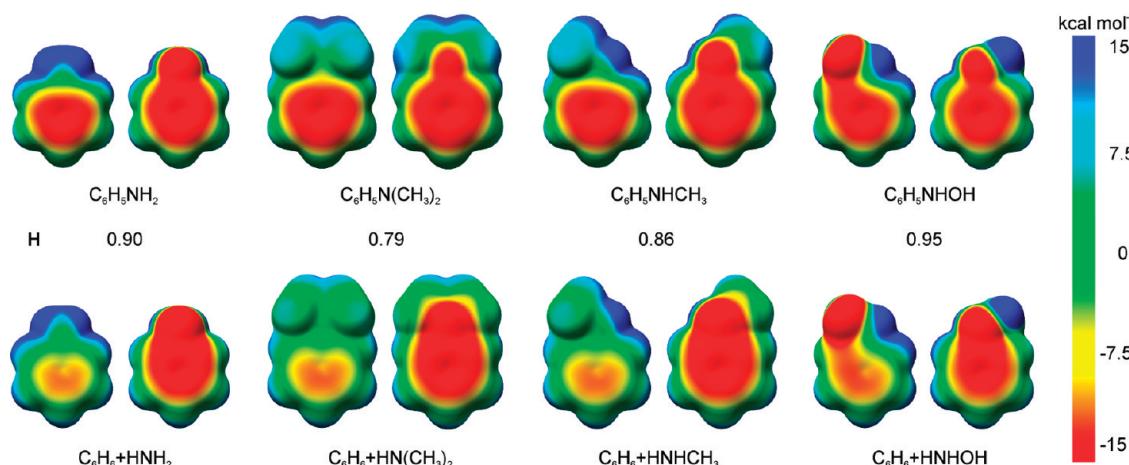


Figure 3. Front and back views of electrostatic potentials of aniline derivatives (top row) and corresponding additive ESPs (bottom row). ESPs are mapped on electron density isosurfaces ($0.001 \text{ e}/\text{au}^3$) for the substituted benzene. The H index is computed for the ESP values on the isodensity surfaces for the true and additive ESPs.

II. Theoretical Methods

The molecular electrostatic potential, $V(\mathbf{r})$, was evaluated on a rectangular grid enveloping each molecule according to eq 1 and using electron densities computed at the B3LYP/6-31G(d) level of theory³⁴ with Gaussian03.³⁵ These ESP plots are relatively insensitive to the method and basis set employed, as demonstrated for cyanobenzene in Supporting Information (see Figure S1). Graphical representations of these ESPs were generated by mapping the ESP onto a molecular surface corresponding to an isodensity contour at $\rho = 0.005$ or $0.001 \text{ e}/\text{au}^3$ using UCSF Chimera.³⁶ The wide range of systems considered necessitated the use of several different scales for plotted ESPs. The scales utilized are displayed in each figure, and within a given figure, the ESP scale is always the same to facilitate straightforward comparisons of different systems.

An additive ESP model was employed to differentiate between π -resonance and inductive/field effects, constructed as follows for monosubstituted benzenes: for each point on an identical rectangular grid, the ESP was evaluated for C_6H_6 , $\text{C}_6\text{H}_5\text{X}$, and HX , with each system positioned so that conserved atoms were placed identically. For example, for fluorobenzene, all six carbons and the five unsubstituted hydrogens have the same Cartesian coordinates in C_6H_6 as $\text{C}_6\text{H}_5\text{F}$. The fluorines in $\text{C}_6\text{H}_5\text{F}$ and HF also have identical coordinates. The positions of the substituted atoms were optimized. These constraints result in no discernible difference in ESP plots, as demonstrated in Figure S2 of the Supporting Information. The ESPs of C_6H_6 and HX were then added at each point on this grid, and the resulting additive ESP was mapped onto the electron density isosurface of $\text{C}_6\text{H}_5\text{X}$.³⁷ To provide a quantitative measure of the similarity of the additive and true ESPs, the Hodgkin index,³⁸ H , has been computed for the ESP values on the plotted isodensity surfaces. The Hodgkin index for two sets of ESP values ranges from -1.00 , for two equal but opposite sets of ESP values, to 1.00 for identical ESPs.

III. Plots of Molecular Electrostatic Potentials

A. Substituted Benzenes. Monosubstituted benzenes serve as models for more complex substituted aromatic systems, and without understanding the effect of substituents in these paradigmatic systems, there is little hope for a sound analysis of more complex substituted arenes. Standard ESP plots are provided for 20 substituted benzenes in Figure 2 (first and third rows). ESP plots for four aniline derivatives are shown in the top row of Figure 3. These ESP plots show the expected qualitative trends: electron-withdrawing substituents generally increase the ESP above the aryl ring, while donors lead to a decrease in the ESP, relative to benzene. These ESP maps reflect both π -resonance and inductive/field effects, the relative contribution of which cannot be discerned from these plots alone.

To assess the role of nonresonance effects, ESPs from an additive model for each of these species are also plotted in Figure 2 (second and fourth row) and the bottom row of Figure 3 and constructed as described in Section II. This primitive model should approximate the polarization of the $\text{C}-\text{X}$ σ -bond as well as the direct through-space effects of the substituents in the substituted benzene. More importantly, these additive ESPs reflect substituent effects on the ESP *not* due to changes in the aryl π -system, since the π -electron-density is that of unsubstituted benzene.

The similarities of the additive ESPs to the true ESPs in Figure 2 are striking. Computed Hodgkin indices³⁸ further underscore the similarity of the additive and true ESPs, with most values of H exceeding 0.95. For all substituents, the plots of the intact substituted benzenes are qualitatively similar to those derived from this simple additive model. Indeed, for several substituents, the plots are indistinguishable (see, for example, phenylmethanol, thioanisole, benzenethiol, ethynylbenzene, and phenylsilane). For these systems in particular, changes in the ESP relative to that of benzene arise entirely from through-space effects. π -resonance cannot possibly play an appreciable role, since, in the additive ESPs,

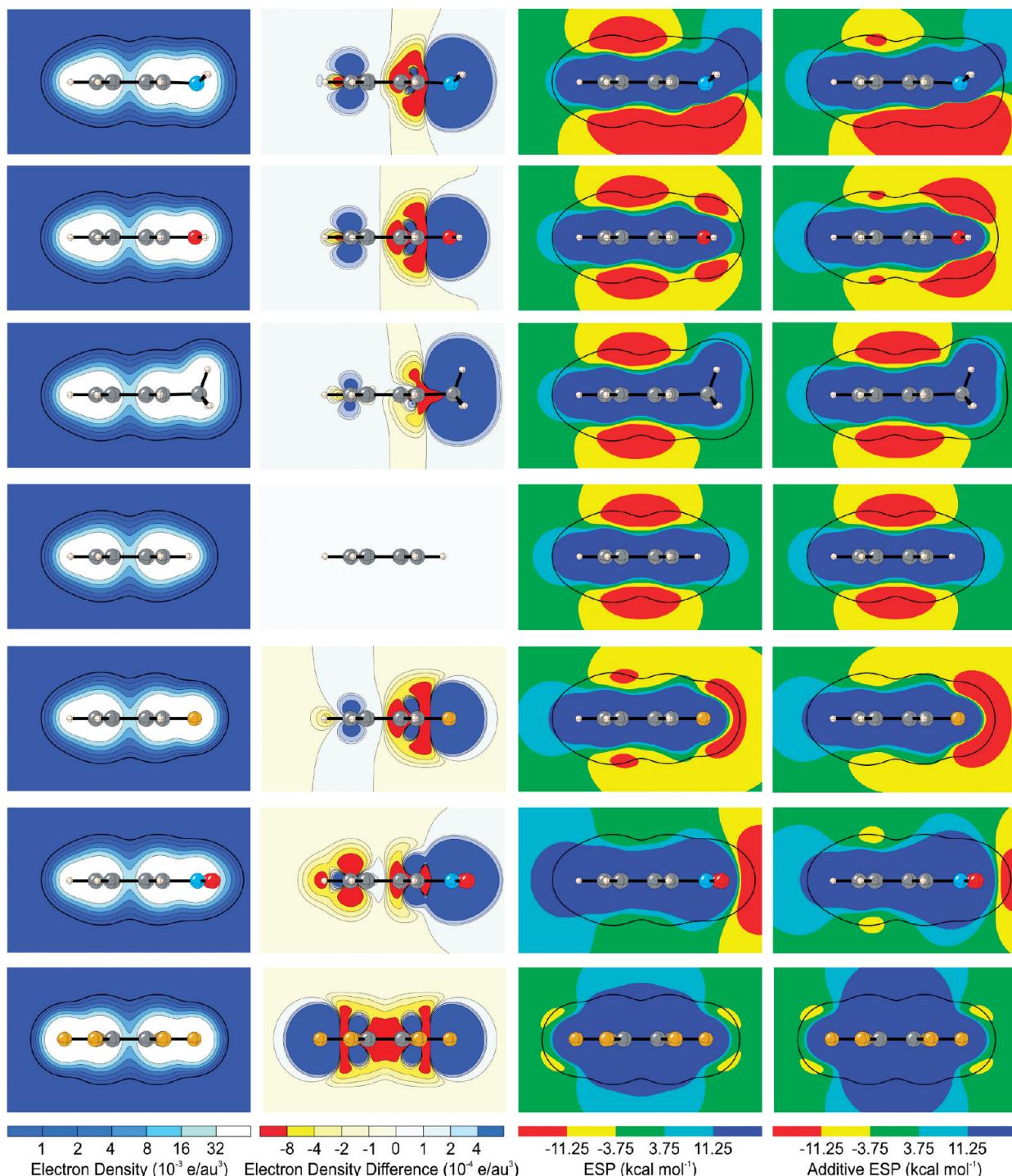


Figure 4. Contour plots of the electron density, electron density difference versus benzene [$\Delta\rho = \rho(\text{C}_6\text{H}_5\text{X}) - \rho(\text{C}_6\text{H}_6)$], electrostatic potential, and additive ESP for aniline, phenol, toluene, benzene, fluorobenzene, nitrobenzene, and hexafluorobenzene. The thick black line in the density and ESP plots denotes the electron density contour ($0.001 \text{ e}/\text{au}^3$) used to construct the isodensity surfaces in Figures 2 and 3.

the aryl π -system is identical to that of the unsubstituted benzene by construction.

There is some deviation between the additive and the true ESPs for several of the systems in Figure 2. These deviations occur primarily for strong electron-donating or -accepting substituents (OCH_3 , BF_3 , SiF_3 , NO , and NO_2), suggesting that changes in the aryl π -system influence the molecular ESPs of these substituted systems. Similar behavior was observed previously³¹ for the ESP at a single point above

the center of substituted benzenes. The observed deviations are in accord with standard resonance parameters for these substituents: for example, OH is a strong π -electron donor ($R = -0.64$), and consequently, the additive ESPs is more positive above the ring than for the true ESP. Conversely, NO is a strong π -electron-withdrawing group ($R = 0.42$), and the additive ESP is more negative than the ESP for $\text{C}_6\text{H}_5\text{NO}$. The agreement between the additive and true ESPs for the aniline derivatives (Figure 3) is generally slightly

poorer ($H = 0.78$ to 0.95) than that observed for the substituents depicted in Figure 2, in accord with the very strong π -donating character of substituted amines.

Contour plots of the ESP in a plane perpendicular to the aryl ring and passing through the *ipso* and *para* carbons are shown in Figure 4 for benzene and in five substituted benzenes (NH_2 , OH , CH_3 , F , and NO_2). These plots, employing the same color-scheme as the surface maps shown in Figures 2 and 3, offer an alternative, complementary view and enable a more complete comparison of the true ESPs with the additive ESPs. To clarify the connection between these contour plots and the ESP maps in Figures 2 and 3, the electron density contour value used to construct the isodensity surfaces is superimposed on the ESP contour plots. Also shown in Figure 4 are contour plots of the additive ESPs for these selected systems. There are small differences between the additive ESPs and the true ESPs. However, the values of the ESP in this plane are mimicked by the additive model, and no changes in the π -electron-density are necessary to recover much of the substituent effect on the ESP. Specifically, for fluorobenzene, the regions of positive and negative ESP are roughly the same between the additive and the true ESP plots. The primary difference is the very small region above the center of the ring where the ESP dips below $-11.25 \text{ kcal mol}^{-1}$ (red), which is visible in the true ESP but missing in the additive ESP (the additive ESP is $-8.9 \text{ kcal mol}^{-1}$ in this region). Similarly, for aniline, the additive ESP overestimates the ESP above the ring, as was apparent in Figure 3.

Electron density contour plots for these systems are also shown in Figure 4. The electron densities are similar, as expected, apart from the area immediately surrounding the substituent. However, π -electron densities of aryl rings do change in response to introduced substituents. This can be most readily seen in contour plots of the difference in electron density between the substituted benzenes and the benzene [i.e., $\Delta\rho = \rho(\text{C}_6\text{C}_5\text{X}) - \rho(\text{C}_6\text{H}_6)$]. Because the scale is chosen to showcase the density differences around C_{para} , the $\Delta\rho$ values immediately surrounding the substituent are far off of the scale.

The changes in the electron density surrounding C_{para} exhibit expected trends: π -donating substituents (NH_2 , OH , CH_3 , and F) show a net gain in density above and below C_{para} , while π -accepting NO_2 reduces the electron density in this region. Despite these changes in the electron density surrounding C_{para} , the density above and below the center of the ring is essentially unchanged in each of these systems. These density difference plots can be used to rationalize the differences between the additive ESP and the true ESP contour plots. In the additive model, there is no change in the aryl π -system, so the effects of the density differences above and below C_{para} will be neglected. For aniline, the overestimation of the ESP above C_{para} in the additive ESP is due to the neglect of the increase in π -electron density at the *para* carbon in the additive model. Similarly, the additive ESP of nitrobenzene slightly underestimates the ESP above C_{para} , consistent with the decrease in density in that region in the intact system that is not present in the additive model.

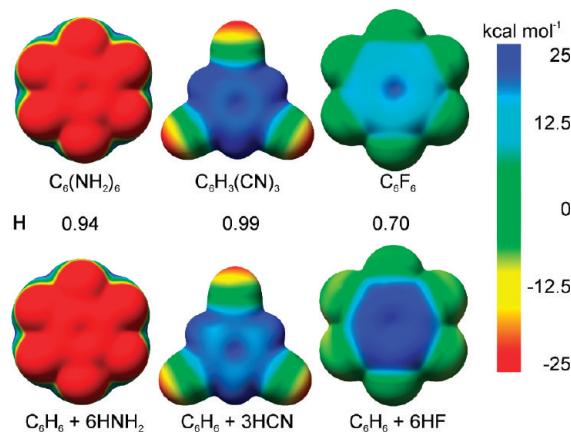


Figure 5. Plots of electrostatic potentials of polysubstituted benzenes (top) and corresponding additive ESPs (bottom). ESPs are mapped onto electron density isosurfaces (0.001 e/au^3) for the substituted benzene. The H index is computed for the ESP values on the isodensity surfaces for the true and the additive ESPs.

Since the additive ESPs are similar to the true ESP in each of these cases, it is clear that the effects of these π -electron density changes on the ESP are relatively minor. This is unsurprising, since these density changes are modest compared to the changes in the electron density surrounding the substituent. The through-space electrostatic effects of the substituents swamp the effect of π -donation and withdrawal, which, in most cases, shows up as a small perturbation of the ESP changes arising from nonresonance effects.

B. Polysubstituted Benzenes. ESPs for three polysubstituted benzenes are presented in Figure 5, along with additive ESPs. Computed Hodgkin indices again indicate a strong similarity between the true ESPs and the additive ESPs. These polysubstituted benzenes were recently studied by Ringer and Sherrill⁹ in the context of the sandwich configuration of the benzene dimer. Ringer and Sherrill argued⁹ that the ESP of the pictured rotamer of hexaaminobenzene “confirms an electron-rich π cloud”, while $\text{C}_6\text{H}_3(\text{CN})_3$ and C_6F_6 are similarly shown to have “noticeably depleted electron density in the center of the substituted rings.” The negative ESP above hexaaminobenzene and the positive ESP above tricyanobenzene and hexafluorobenzene do not necessarily arise from any change in the π -electron-density, since in the additive ESPs the aryl π -system is identical in each case. Labeling substituted aryl rings “ π -electron-rich” or “ π -electron-poor” based solely on computed ESP plots is clearly unfounded.

Hexafluorobenzene is of particular importance, since the reversed quadrupole moment of C_6F_6 , compared to C_6H_6 , is invoked to explain the strong face-to-face interaction of benzene and perfluorobenzene.^{4,39–43} Perfluorobenzene also features in discussions of anion/ π interactions⁴⁴ and in related complexes in which the π -cloud of C_6F_6 purportedly serves as an electron acceptor.⁴⁵ The reversal in electrostatics of perfluorobenzene is sometimes attributed to the withdrawal of electron density from the center of the ring by the fluorines. However, Laidig⁴⁶ showed in 1991 that the quadrupole moment of C_6F_6 arises primarily from the build-up of electron density along the periphery of the ring (i.e.,

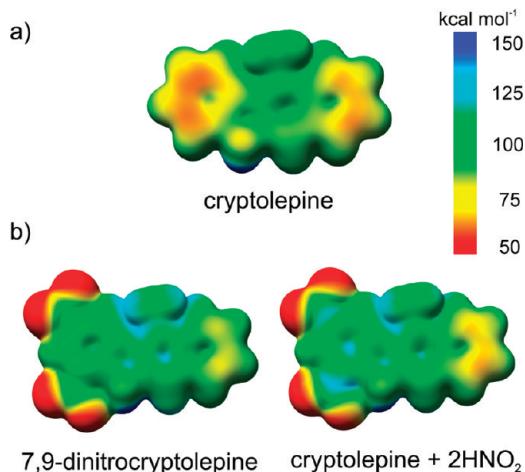


Figure 6. (a) ESP of cryptolepine; (b) ESP of 7,9-dinitrocryptolepine and additive ESP of 7,9-dinitrocryptolepine constructed by adding the ESP of cryptolepine to the ESP of two HNO_2 molecules and mapped onto the electron density isosurface of dinitrocryptolepine. Density isosurfaces correspond to $\rho = 0.005 \text{ e/au}^3$. The H index for the true and the additive ESP plots is 1.00.

on the fluorines) rather than from the drastic changes of the electron density along the C_6 symmetry axis.

Contour plots of the electron density and density difference versus benzene for C_6F_6 are shown in Figure 4, along with contour plots of the ESP and the additive ESP. There is clearly a depletion of electron density above and below the plane of the ring due to the six fluorines. However, the introduction of a large amount of density associated with the fluorines easily swamps the changes above and below the benzene plane. As seen in Figure 4, the additive ESP of perfluorobenzene closely resembles the true ESP, demonstrating that the highly positive ESP above the center of the ring arises primarily from through-space effects of the fluorines and has no effect on the aryl π -system. Thus, while the π -electron-density of C_6F_6 is depleted compared to benzene (See Figure 4), the positive ESP above the ring is not evidence of this but merely of the through-space electrostatic effects of the F substituents.

C. Substituted Cryptolepines. Cryptolepine, a cytotoxic alkaloid from the West African shrub *Cryptolepis sanguinolenta*, is of interest as a lead for the development of both antimalarial and antitumor drugs.^{47–49} Cytotoxicity of cryptolepine arises from its intercalation into DNA at nonalternating G-C sequences and inhibition of topoisomerase II.^{49,50} The origin of the antimalarial activity is less well understood, though it is thought to involve the inhibition of hemazoin formation, similar to chloroquine.⁴⁷ There are ongoing efforts to develop cryptolepine derivatives that offer comparable or exceptional antimalarial activity without the associated cytotoxicity. 7,9-dinitrocryptolepine has been shown to exhibit antimalarial activity in the absence of DNA intercalation and toxicity, though the mode of antimalarial activity might differ from that of the parent compound.^{47,51}

Electrostatic interactions are expected to be important in both the DNA intercalation and the inhibition of hemazoin formation for substituted cryptolepines.⁵² ESP plots of cryptolepine and dinitrocryptolepine are shown in Figure 6.

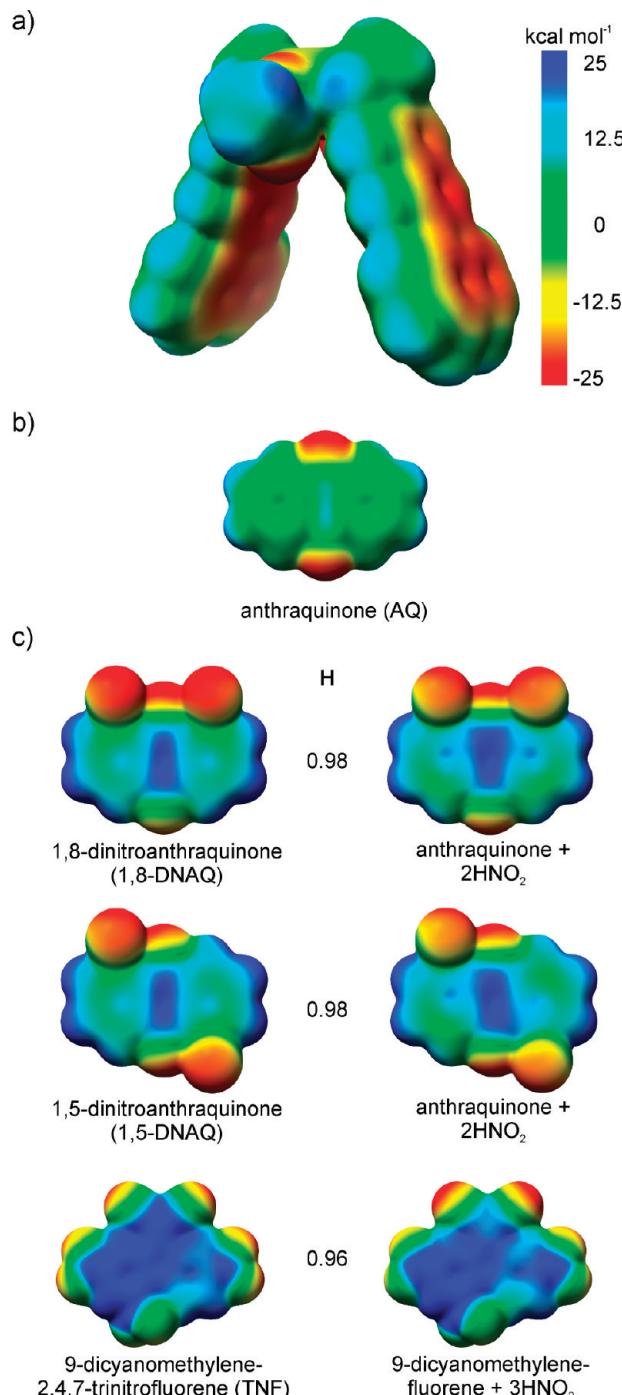
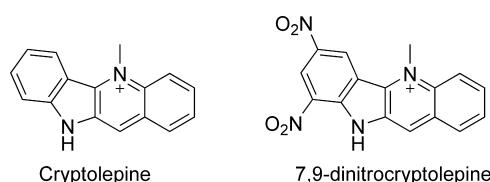
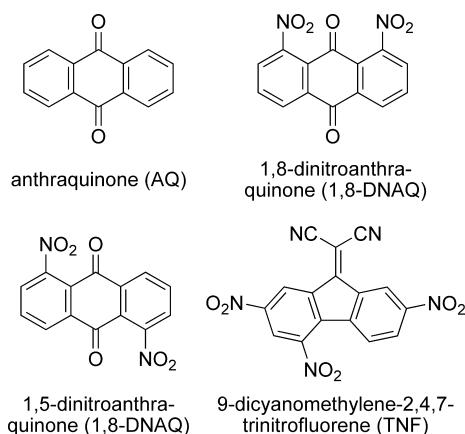


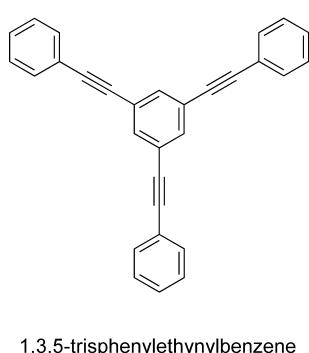
Figure 7. (a) ESPs of the molecular tweezers of Klärner and co-workers;^{54,56} (b) ESP of anthraquinone; (c) ESPs (left) and additive ESPs (right) of two dinitroanthraquinones and 9-dicyanomethylene-2,4,5-trinitrofluorene. Density isosurfaces correspond to $\rho = 0.001 \text{ e/au}^3$. The H index is computed for the ESP values on the isodensity surfaces for the true and additive ESPs.

The two nitro groups have a significant effect on the ESP, with the most pronounced changes localized on the substituted ring. An additive ESP for 7,9-dinitrocryptolepine is included in Figure 6b, constructed by adding the ESP of cryptolepine to the ESP of two appropriately placed HNO_2 moieties. Because there are only very minor differences between the true ESP and the additive model ($H = 1.00$), it is clear that the majority of the substituent effect arises from

Scheme 1**Scheme 2**

through-space effects. The π -system of cryptolepine plays a very minor role. In general, when considering ESPs of substituted analogs of candidate drugs built on aryl frameworks, the role of direct through-space effects of substituents is potentially significant and must be considered.

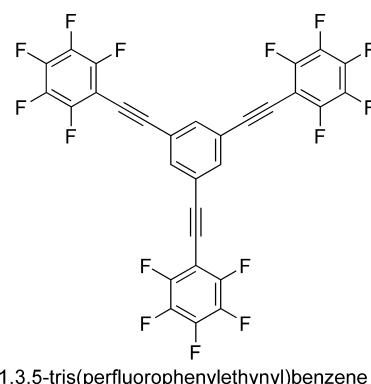
D. ESPs in Crystal Engineering and Host–Guest Chemistry. The field of supramolecular chemistry has blossomed in recent years, enabling the construction of complex molecular systems, molecular machines, and materials with novel properties through subtle control over intermolecular interactions.^{4,53} Often this control arises from substituent effects on noncovalent interactions. In this regard, plots of molecular electrostatic potentials are valuable tools. One example of host–guest systems for which ESP maps have been employed are the molecular tweezers of Klärner and co-workers.^{54–56} Klärner et al. synthesized and characterized a series of molecular tweezers based on bimethylene “hinges” separated by a benzene bridge with polycyclic aromatic “arms”.⁵⁴ These receptors are powerful binders of what were described as “electron deficient” aryl systems.⁵⁶ The preferential binding was rationalized in part based on

Scheme 3

computed ESPs of the clips and the guest molecules (see Figure 7a–b). It was noted that substituted aryl systems with more positive ESPs (e.g., 1,8-DNAQ, 1,5-DNAQ, and TNF) are bound much more strongly than analogous systems with more negative ESPs (e.g., AQ), due to the favorable electrostatic interactions with the predominantly negative ESPs of the inner walls of the tweezers in the former case. Additive ESP plots of 1,8-DNAQ, 1,5-DNAQ, and TNF are provided in Figure 7c. In each case, the additive ESP is essentially indistinguishable from the true ESPs ($H = 0.96–0.98$). These significant changes in the ESP arise almost entirely from through-space effects; π -resonance plays no discernible role.

Another example gleaned from the field of supramolecular chemistry exploits the avidity of arenes for perfluorinated arenes,^{4,39–43} originally observed by Patrick and Prosser.⁴⁰ As mentioned in Section III.B, this favorable interaction results from the opposite sign but comparable magnitude of the quadrupole moments of benzene and hexafluorobenzene.^{39,57} This strong attractive stacking interaction has led to the use of the $\text{C}_6\text{H}_6 \cdots \text{C}_6\text{F}_6$ interaction as a supramolecular synthon,⁵⁸ and this interaction has been exploited in countless systems. For example, Grubbs and co-workers⁴³ utilized perfluoroarene–arene interactions to achieve topological and stereochemical control over the photochemically driven reaction of 1,3-diynes in the condensed phase. Ponzini, Zagha, Hardcastle, and Siegel⁵⁹ later demonstrated the utility of such interactions in the generation of highly ordered crystals of 1,3,5-trisphenethynylbenzene and 1,3,5-tris(perfluorophenethynyl)benzene (Scheme 3). In both cases,^{59,43} the electrostatic complementarity of the phenyl and perfluorophenyl moieties lead to highly ordered alternating face-to-face stacks in mixed crystals, while the two components on their own formed slipped–stacked arrangements.

ESPs of trisphenethynylbenzene and the fluorinated analog are shown in Figure 8. The complementary nature of the ESPs of the aryl and perfluoroaryl functionalities is immediately apparent. However, the additive ESP of the perfluorinated system (Figure 8, far right) once again shows that the highly positive ESP above the center of perfluorinated aryl rings is reproduced without any changes in the aryl π -system ($H = 0.78$).



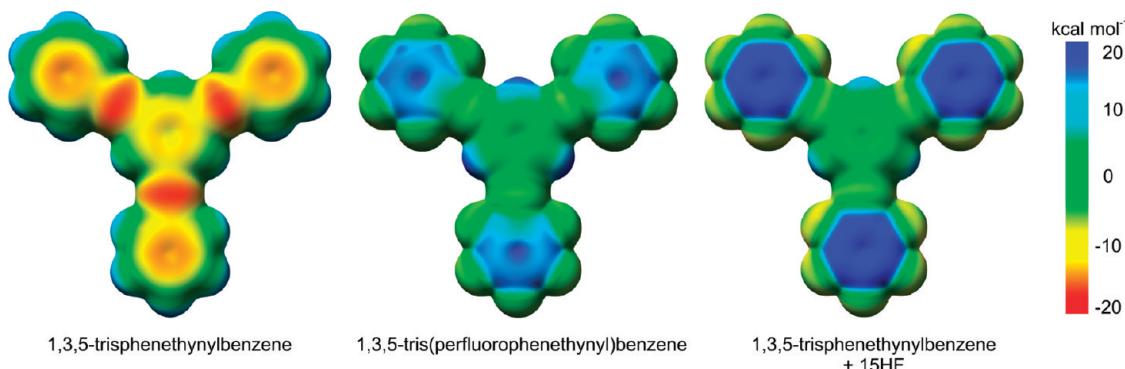


Figure 8. ESP plot of 1,3,5-trisphenethynylbenzene (left) and plot of the true (middle) and additive (right) ESP of 1,3,5-tris(perfluorophenethynyl)benzene, mapped onto electron density isosurfaces (0.001 e/au^3). The H index for the true and the additive ESP plots is 0.78.

IV. Implications for Non-Covalent Interactions with Aromatic Systems

Many qualitative models of substituent effects in noncovalent interactions with aromatic rings rest on the assumption that the dominant electrostatic effect arises from the polarization of the aryl π -system. This is most prominent in models of the benzene dimer advocated by Cozzi and Siegel⁶⁰ (the polar/ π model) and Hunter and co-workers.^{7,42,61} The crux of these primarily electrostatic models is that electron donors increase the aryl π -electron density, increasing the electrostatic repulsion with the π -system of the nonsubstituted ring, while electron acceptors enhance the benzene–benzene interaction through the opposite mechanism. While there have been numerous publications criticizing these models,^{9,27,28,62} the underlying assumption that substituents modulate the electrostatic properties above the plane of benzene via polarization of the aryl π -system has previously remained largely unaddressed.

We have recently analyzed prototypical noncovalent interactions with substituted benzenes, including the sandwich and edge-to-face configurations of the benzene dimer⁶³ and the cation– π interaction of Na^+ with $\text{C}_6\text{H}_5\text{X}$.³¹ The primary conclusions were that direct through-space interactions of the substituents were the dominant cause of substituent effects.^{31,63} The electrostatic component of these direct interactions is reflected in the current finding that variation in ESPs maps of substituted benzenes is due, in large part, to through-space effects of the substituents. Thus, all models of substituent effects in intermolecular arene interactions based on ESPs should similarly reflect the role of through-space effects. Given the prevalence of electrostatic models, there is a potential for a broad revision of our understanding of the effect of substituents in myriad systems. For example, in the perfluoroarene–arene interactions utilized in crystal engineering, the present results suggest that this strong interaction arises primarily from the direct interaction of the fluorines with the nonfluorinated ring and not from π -polarization. Similarly, in the prototypical anion– π interaction between halide anions and C_6F_6 ,⁴⁴ the favorable interaction is potentially due largely to direct through-space interactions and not from a depleted π -system, as generally assumed.⁴⁴ Indeed, Clements and Lewis⁶⁴ showed that the attractive interaction between halogenated

benzenes and F^- is due to direct interactions with the substituents.

The present work is a clarion call for the reevaluation of models of substituent effects in noncovalent interactions in which ESP arguments are central, since often it was assumed that changes in arene ESPs reflect changes in the aryl π -system. Specifically, the previously underappreciated role of direct through-space interactions of substituents must be reconsidered.

V. Summary and Conclusions

Molecular ESPs are powerful tools for the interpretation and the prediction of chemical phenomena and noncovalent interactions. However, deep-rooted misconceptions regarding the effect of substituents on the ESPs of substituted aromatic systems pervade the literature. Equating changes in ESPs with changes in the local electron density is prevalent, as exemplified by the “ π -electron-rich” and “ π -electron-poor” monikers assigned to aromatic systems, often based solely on ESP plots. While substituents do perturb the aryl π -system, the effects of these changes on the electrostatic potential surrounding aromatic systems are often swamped by the significant changes in the electron densities associated with the substituents. Several groups⁶⁵ have demonstrated that most substituents have no significant effect on the aromaticity of benzene. This resiliency of the benzene π -system shows up again in arene ESPs; for most substituents, the polarization of the aryl π -cloud is modest and does not significantly alter the ESP above the aromatic ring.

The role of through-space effects on ESPs was demonstrated here for a series of substituted benzenes and for more complex substituted arenes taken from disparate areas of research. Specifically, the change in the ESP of cryptolepine, a potent antimalarial and cytotoxic agent, induced by nitro substituents was shown to be independent of the aryl π -system. Similarly, the highly positive ESP values above the face of perfluorinated arenes, which are ubiquitous in supramolecular chemistry, can be reproduced with no alteration of the aryl π -system. Implications for our understanding of noncovalent interactions with substituted aromatic rings are profound, since substituent effects on the electrostatic component of many of these interactions arise primarily from direct interactions with the substituents.

Based on traditional, π -resonance-based models of non-covalent interactions with arenes, one would expect classical molecular mechanics force fields to perform poorly for supramolecular assembly phenomena. This is because MM force fields typically do not explicitly account for the perturbation of aryl π -systems by substituents. However, the present finding that polarization of the aryl π -system has minor affects on arene ESPs explains the often excellent performance of MM force fields for $\pi-\pi$ interactions.⁶⁶ The neglect of changes in aryl π -systems by substituents is, therefore, warranted. Treatment of only direct interactions with the substituents should suffice.

A hallmark of chemistry is the development and the widespread employment of qualitative predictive models. ESP plots constitute a powerful tool in this regard, demonstrating utility in many areas of chemistry and molecular biology. Without a sound understanding of substituent effects on ESPs, the utility of these tools is handicapped. A counterintuitive, yet striking, demonstration of the dominance of through-space effects on ESPs of substituted arenes has been provided with far-reaching implications in the understanding of noncovalent interactions in the fields of host–guest chemistry, crystal engineering, and rational drug design, among others. Perhaps most importantly, we have clearly shown that changes in ESPs do not necessarily reflect changes in the local electron density.

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Supporting Information Available: Plots comparing ESPs at different levels of theory and with and without geometry constraints. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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