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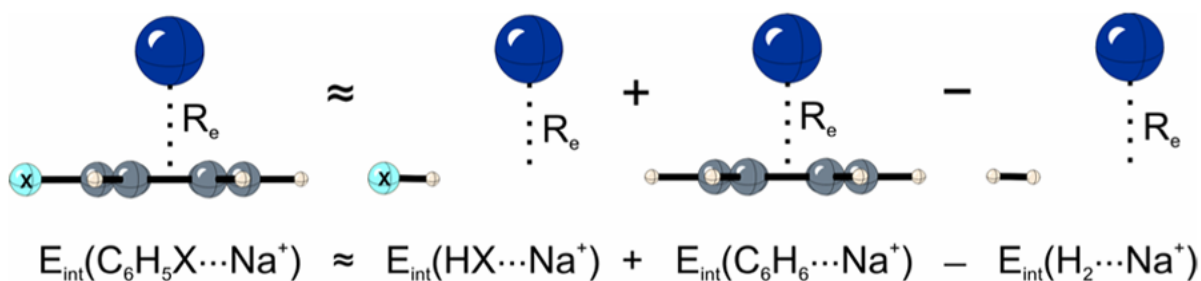
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Substituent Effects in Cation/ π Interactions and Electrostatic Potentials above the Center of Substituted Benzenes Are Due Primarily to through-Space Effects of the Substituents

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Abstract



Substituent effects in cation/ π interactions have been examined using the M05-2X DFT functional and CCSD(T) paired with triple- ζ quality basis sets. In contrast to popular, intuitive models, trends in substituent effects are accounted for primarily by direct, through-space interactions with the substituents. While there is some scatter in the data, which is attributed to π -polarization, the trend in substituents effects in cation/ π interactions is captured by an additive model in which the substituent is isolated from the aryl ring. Similarly, changes in the electrostatic potential at a point above the center of substituted benzenes arise largely from through-space effects of the substituents. π -polarization is not the dominant underlying cause.

Cation/ π interactions are ubiquitous in molecular biology, drug design, and host-guest chemistry.^{1,2} These strong non-covalent interactions, which often involve an alkali metal or tetraalkylammonium cation interacting with the face of an aromatic ring, were thrust into the limelight by Dougherty and co-workers.^{1,3–6} Substituent effects in cation/ π interactions have been exploited to characterize binding sites of nicotinic acetylcholine receptors and have provided insight into these systems in the absence of detailed structural information.⁵

While numerous factors contribute to binding,⁷ substituent effects in cation/ π interactions are usually explained using simple electrostatic models.¹ Mecozzi, West, and Dougherty⁶ demonstrated that the electrostatic potential (ESP) evaluated at a single point above the center of a substituted aryl ring predicts the strength of the cation/ π interaction; more negative ESPs indicate stronger interactions. In this context, Dougherty *et al.*^{1,6} stressed the importance of *inductive* effects over π -resonance, based on correlations with σ_m rather than σ_p . However, Hunter and co-workers and others⁸ have attributed substituent effects to the polarization of the aryl π -system. Below, we show that π -polarization models of the cation/ π interaction are flawed; substituent effects arise primarily from direct, through-space interactions with the substituents.

Interaction energies [$E_{\text{int}}(\text{C}_6\text{H}_5\text{X})$, kcal mol⁻¹] for Na⁺ above the center of 25 substituted benzenes were computed using M05-2X/6-311+G(2df,2p).⁹ The equilibrium distance (R_e) of Na⁺ above the ring centroid was found by scanning normal to the benzene plane at 0.05 Å intervals with the substituted benzene fixed at the M05-2X/6-31+G(d) optimized geometry. The mean R_e value for the 25 systems studied is 2.37 Å. CCSD(T) energies were evaluated for five substituents (H, CN, F, CH₃, and NH₂) at M05-2X geometries using the cc-pCVTZ basis set for Na and aug-cc-pVTZ otherwise. These correlated computations, denoted CCSD(T)/AVTZ henceforth, employed the standard frozen-core approximation for all atoms except Na, for which only the 1s orbital was frozen. M05-2X slightly overestimates the C₆H₅X^{...}Na⁺ binding energy relative to CCSD(T). However, this overbinding is systematic and there is a very strong linear correlation ($r = 0.9999$, see SI Figure S1) between the M05-2X and CCSD(T) data. M05-2X computations were executed with NWChem^{10,11} using a DFT quadrature grid with 70 radial and 590 angular points while Molpro¹² was used for CCSD(T). Final M05-2X and CCSD(T) energies were counterpoise corrected.

To understand the role of the aryl π -system, a ‘truncated’ model was constructed by replacing the phenyl ring in the equilibrium C₆H₅X^{...}Na⁺ geometry with a hydrogen atom. This hydrogen was placed along the C–X bond, and the H–X distance was optimized with all other internal coordinates fixed. A similar model has been used to study substituent effects in the benzene dimer.¹³

In Figure 1(a), $E_{\text{int}}(\text{C}_6\text{H}_5\text{X})$ is plotted against the sum of interaction energies for the truncated model system and benzene. To approximately account for the ‘extra’ two hydrogens, the interaction energy of H₂ with Na⁺ at the R_e distance for the corresponding C₆H₅X^{...}Na complex was subtracted from this sum to yield an additive approximation to the cation/ π binding energy [$E_{\text{int}}(\text{HX}) + E_{\text{int}}(\text{C}_6\text{H}_6) - E_{\text{int}}(\text{HH})$]. In this additive model there can clearly be no polarization of the benzene π -system, and any effect of the substituent must involve through-space interactions with the substituents. There is a good correlation ($r = 0.90$) between the interaction energies for C₆H₅X^{...}Na⁺ and this additive model, with unit slope. There are clear outliers (see Table 1); for several systems there are significant (> 3 kcal mol⁻¹) deviations between our additive model and results for the intact substituted rings. These deviations occur for strong π -electron acceptors, for which the additive model overestimates E_{int} , or strong π -donors, for which E_{int} is underestimated. In these limiting cases, donation or withdrawal from the π -system presumably plays a role. Indeed, the *differences* between interaction energies for the substituted aromatic ring and our additive model correlate with the resonance parameter R ($r = 0.88$, see SI Figure S2), supporting the involvement of π -resonance in the observed deviations. However, the overall trend in substituent effects in cation/ π interactions does not depend on the π -system of the phenyl ring, but is accounted for by through-space interactions of the substituents. Frontera *et al.*¹⁴ recently reported through-space substituent effects in complexes of paracyclophanes with Na⁺ and Li⁺ in which the substituents were on the non-complexed phenyl ring.

To further explain this non-intuitive behavior, changes in the ESP above the center of substituted benzenes were examined (see Table 1). ESPs evaluated at the position of Na in the C₆H₅X^{...}Na⁺ complexes are plotted against an additive model of ESPs in Figure 1(b). The additive ESP comprises the ESP above the hydrogen capped substituent (positioned exactly as in the C₆H₅X^{...}Na⁺ dimer) plus the ESP above benzene minus the ESP due to H₂, all evaluated at the position of sodium in C₆H₅X^{...}Na⁺.

There is a strong correlation between these two sets of ESPs ($r = 0.92$), indicating that π -polarization has no appreciable net effect on the ESPs above the center of substituted benzenes. Instead, changes in ESPs arise from through-space substituent effects. Such long-range effects are readily explained by the $1/r$ dependence of the ESP on surrounding charges. Apparently,

the aryl π -system provides a relatively constant backdrop on top of which the through-space electrostatic effects of the substituents are superimposed. As with the cation/ π interactions, there are some deviations between our additive model and the explicitly computed ESPs. These deviations again correlate with the resonance parameter R ($r = 0.92$; see SI Figure S3), indicating some involvement of π -polarization.

The electrostatic nature of substituent effects in cation/ π interactions has long been established.^{1,3,6} While the present results support Dougherty's electrostatic model, the common assumption that these electrostatic effects are a result of π -polarization is incorrect. Substituent effects in cation/ π interactions, and the related changes in the ESP above the center of substituted benzenes, do not arise mainly from polarization of the benzene π -system. Instead, these effects can be accounted for primarily by through-space effects of the substituents. In general, π -polarization appears to play only a minor role. The present findings challenge deep-rooted intuitions concerning the polarization of the aryl π -system in substituted benzenes and have broad implications due to the use of substituted aromatic amino acid analogs in the characterization of cation binding sites⁵ and the employment of ESPs of substituted aromatic rings in pharmacophore modeling. Implications of the present findings for substituent effects in general non-covalent interactions with aromatic rings will be discussed in forthcoming publications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

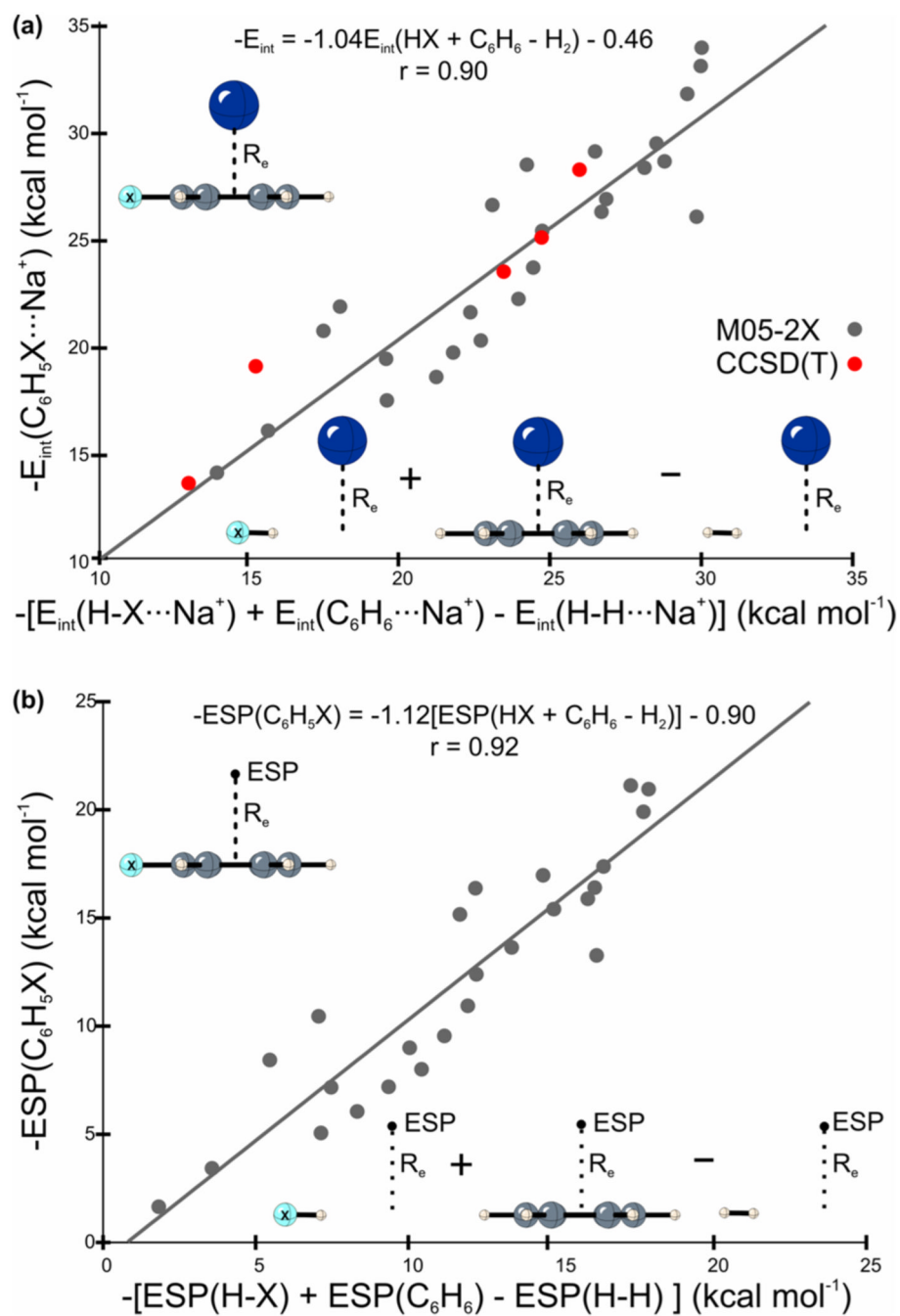
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**Figure 1.**

(a) M05-2X/6-311+G(2df,2p) (gray) and CCSD(T)/AVTZ (red) interaction energies of Na^+ with $\text{C}_6\text{H}_5\text{X}$ versus a simple additive model (kcal mol^{-1}). Least squares fit applied only to the M05-2X data; (b) M05-2X/6-311+G(2df,2p) ESPs evaluated at a single point above the center of the ring of substituted benzenes versus the ESP at that point from a simple additive model (kcal mol^{-1}). All quantities evaluated at the equilibrium $\text{C}_6\text{H}_5\text{X}\cdots\text{Na}^+$ geometries.

Table 1

M05-2X/6-311+G(2df,2p) interaction energies for Na⁺ with C₆H₅X [$E_{\text{int}}(\text{C}_6\text{H}_5\text{X})$] and the additive model [$E_{\text{int}}(\text{HX} + \text{C}_6\text{H}_6 - \text{H}_2)$], and ESPs for C₆H₅X and (HX + C₆H₆ - H₂), all in kcal mol⁻¹. All quantities evaluated at the corresponding equilibrium C₆H₅X^{...Na}⁺ distance. CCSD(T)/AVTZ interaction energies are in parentheses.

X	$E_{\text{int}}(\text{C}_6\text{H}_5\text{X})$	$E_{\text{int}}(\text{HX} + \text{C}_6\text{H}_6 - \text{H}_2)^a$	ESP(C ₆ H ₅ X)	ESP(HX + C ₆ H ₆ - H ₂) ^b
N(CH ₃) ₂	33.9	30.0	21.1	17.3
NHCH ₃	33.1	30.0	21.0	17.9
NH ₂	31.8 (28.2)	29.5 (26.0)	19.9	17.7
CH ₂ OH	29.5	28.5	17.4	16.4
NHOH	29.1	26.5	17.0	14.4
SCH ₃	28.6	28.8	15.4	14.8
OCH ₃	28.5	24.2	16.4	12.2
CH ₃	28.3 (25.0)	28.1 (24.7)	16.4	16.1
H	26.9 (23.5)	26.9 (23.5)	15.9	15.9
OH	26.6	23.1	15.2	11.7
SH	26.3	26.7	13.6	13.4
SiH ₃	26.0	29.9	13.3	16.2
CCH	25.4	24.7	12.4	12.2
CO ₂ CH ₃	23.6	24.4	10.9	12.0
COCH ₃	22.2	23.9	9.5	11.2
F	21.8 (19.0)	18.0 (15.3)	10.4	7.1
COOH	21.5	22.3	9.0	10.1
OCF ₃	20.7	17.5	8.4	5.5
BF ₂	20.2	22.7	8.0	10.4
CHO	19.7	21.8	7.2	9.4
CF ₃	19.4	19.5	7.2	7.5
SiF ₃	18.5	21.2	6.0	8.3
NO	17.4	19.6	5.0	7.1
CN	16.0 (13.5)	15.6 (13.1)	3.4	3.6
NO ₂	14.0	13.9	1.6	1.8

$$^a E_{\text{int}}(\text{HX} + \text{C}_6\text{H}_6 - \text{H}_2) = E_{\text{int}}(\text{HX}) + E_{\text{int}}(\text{C}_6\text{H}_6) - E_{\text{int}}(\text{HH})$$

$$^b \text{ESP}(\text{HX} + \text{C}_6\text{H}_6 - \text{H}_2) = \text{ESP}(\text{HX}) + \text{ESP}(\text{C}_6\text{H}_6) - \text{ESP}(\text{HH}).$$