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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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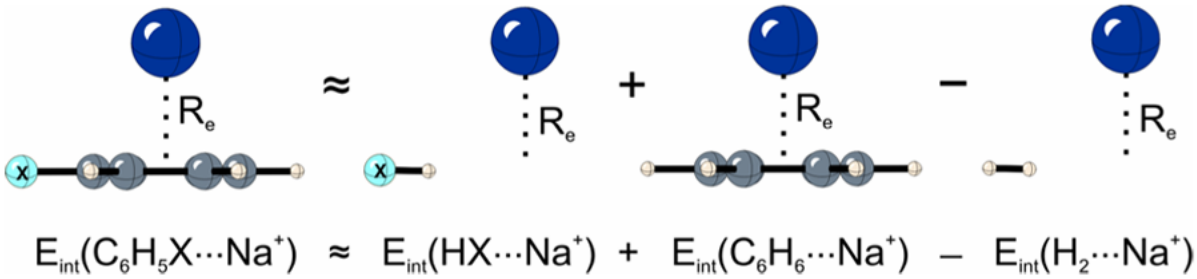
Abstract



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 Dougherty[6] 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 others[8] 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.

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Interaction energies [$E_{int}(C_6H_5X)$, 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, CH_3, and NH_2) 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 1*s* orbital was frozen. M05-2X slightly overestimates the $C_6H_5X\cdots Na^+$ 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 Molpro[12] 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 $C_6H_5X\cdots Na^+$ 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), $E_{int}(C_6H_5X)$ 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 H_2 with Na^+ at the R_e distance for the corresponding $C_6H_5X\cdots Na$ complex was subtracted from this sum to yield an additive approximation to the cation/π binding energy [$E_{int}(HX) + E_{int}(C_6H_6) - E_{int}(HH)$]. 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 $C_6H_5X\cdots Na^+$ 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 $C_6H_5X\cdots Na^+$ 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 $C_6H_5X\cdots Na^+$ dimer) plus the ESP above benzene minus the ESP due to H_2, all evaluated at the position of sodium in $C_6H_5X\cdots Na^+$.

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 sites[5] and the employment of ESPs of substituted aromatic rings in pharmacophor 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.

Acknowledgments

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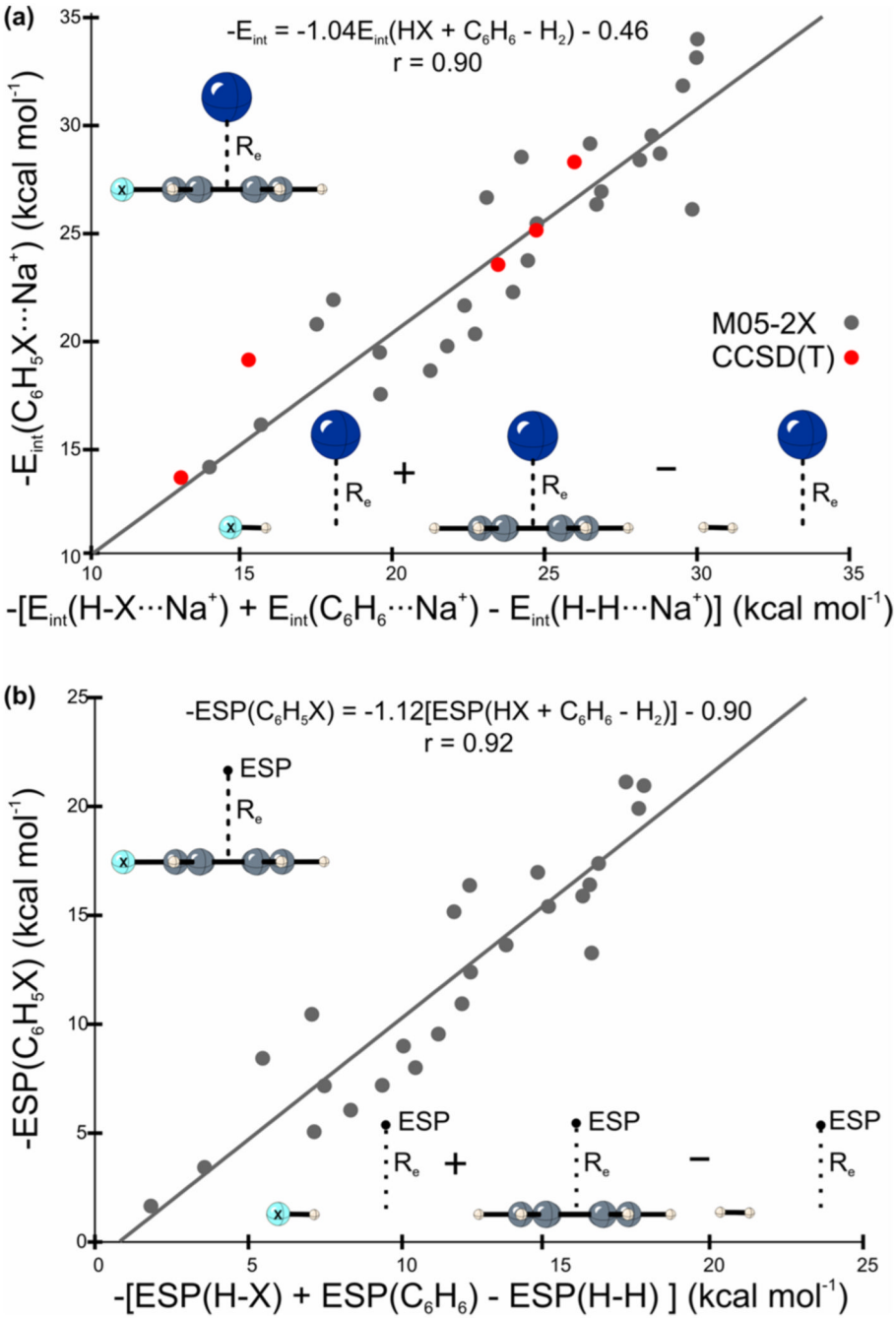

Figure 1.

(a) M05-2X/6-311+G(2df,2p) (gray) and CCSD(T)/AVTZ (red) interaction energies of Na^+ with C_6H_5X 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 $C_6H_5X^{\cdots}Na^+$ geometries.

Table 1

M05-2X/6-311+G(2df,2p) interaction energies for Na^+ with C_6H_5X [$E_{int}(C_6H_5X)$] and the additive model [$E_{int}(HX + C_6H_6 – H_2)$], and ESPs for C_6H_5X and ($HX + C_6H_6 – H_2$), all in kcal mol^{-1}. All quantities evaluated at the corresponding equilibrium $C_6H_5X^{\cdots}Na^+$ distance. CCSD(T)/AVTZ interaction energies are in parentheses.

X	$E_{int}(C_6H_5X)$	$E_{int}(HX + C_6H_6 – H_2)$[a]	$ESP(C_6H_5X)$	$ESP(HX + C_6H_6 – H_2)$[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_2OH	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_2CH_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
CF3	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] $E_{int}(HX + C_6H_6 – H_2) = E_{int}(HX) + E_{int}(C_6H_6) – E_{int}(HH)$

[b] $ESP(HX + C_6H_6 – H_2) = ESP(HX) + ESP(C_6H_6) – ESP(HH)$.