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COMMUNICATIONS

Published on Web 02/16/2009

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

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Cation/π interactions are ubiquitous in molecular biology, drug design, and host−guest chemistry.[1,2] These strong noncovalent 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 and co-workers[1,6] stressed the importance of *inductive* effects over π resonance, on the basis of 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. Here we show that π-polarization models of cation/π interactions are flawed and that substituent effects arise primarily from direct through-space interactions with the substituents.

The interaction energies [$E_{int}(C_6H_5X)$, kcal mol^{-1}] of Na$^+$ above the centers of 25 substituted benzenes were computed at the M05-2X/6-311+G(2df,2p) level.[9] The equilibrium distances (R_e) of Na$^+$ above the ring centroids were 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 was 2.37 Å. CCSD(T) energies were evaluated for five substituents (H, CN, F, CH_3, and NH_2) at the M05-2X geometries using the cc-pCVTZ basis set for Na and the aug-cc-pVTZ basis set otherwise. These correlated computations, henceforth denoted CCSD(T)/AVTZ, employed the standard frozen-core approximation for all of the atoms except Na, for which only the 1s 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 Figure S1 in the Supporting Information (SI)] 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 1a, $E_{int}(C_6H_5X)$ is plotted against the sum of the interaction energies for the truncated model system and benzene.

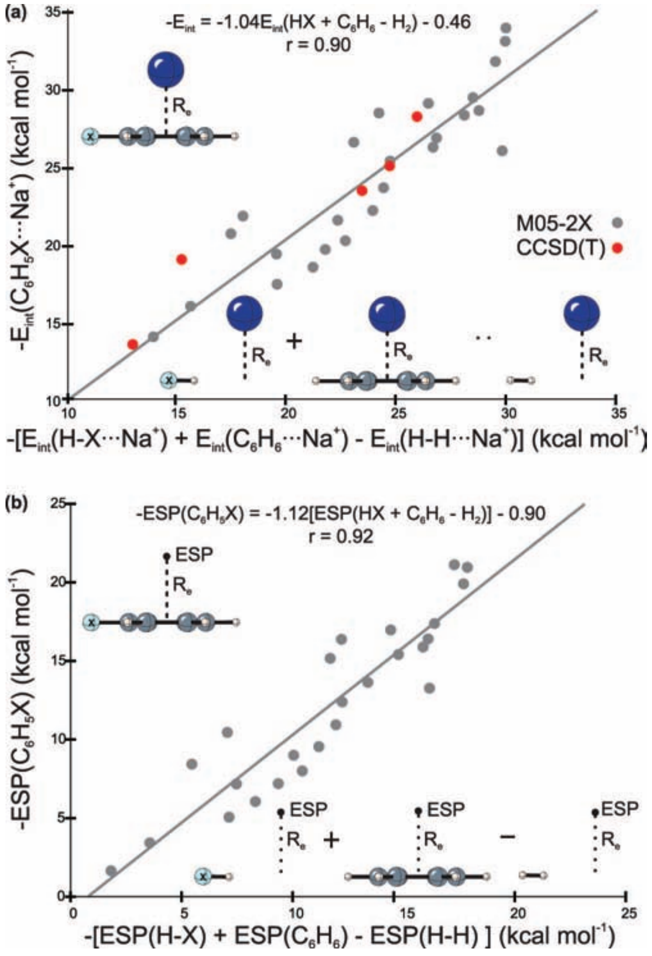

Figure 1. (a) M05-2X/6-311+G(2df,2p) (gray) and CCSD(T)/AVTZ (red) interaction energies of Na$^+$ with C_6H_5X plotted versus values from a simple additive model. The least-squares fit shown was applied only to the M05-2X data. (b) M05-2X/6-311+G(2df,2p) ESPs, each evaluated at a single point above the center of a substituted benzene ring, plotted versus the corresponding ESPs from a simple additive model. All quantities were evaluated at the equilibrium $C_6H_5X\cdots Na^+$ geometries.

To approximately account for the two "extra" hydrogens, the interaction energy of H_2 with Na$^+$ at a distance equal to R_e 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 clearly can be no polarization of the benzene π system, and any effect of the substituent must involve through-space interactions

10.1021/ja809097r CCC: $40.75 © 2009 American Chemical Society

Table 1. M05-2X/6-311+G(2df,2p) Interaction Energies of Na^+ with C_6H_5X [$E_{int}(C_6H_5X)$] and Values from the Additive Model [$E_{int}(HX + C_6H_6 - H_2)$] as well as ESPs for C_6H_5X and ($HX + C_6H_6 - H_2$) [All Values Are in kcal mol^{-1} and Were Evaluated at the Corresponding $C_6H_5X\cdots Na^+$ Equilibrium Distance; CCSD(T)/AVTZ Interaction Energies are Given 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] $ESP(HX + C_6H_6 - H_2) = ESP(HX) + ESP(C_6H_6) - ESP(HH)$.

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 the results for the intact substituted rings. These deviations occur for strong π-electron acceptors, for which the additive model overestimates E_{int}, and for 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 are correlated 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 explained 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 noncomplexed phenyl ring.

To further explain this nonintuitive behavior, changes in the ESPs above the centers 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 1b. 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 less the ESP due to H_2, all evaluated at the position of Na 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 centers 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 the 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 a substituted benzene, do not arise mainly from polarization of the benzene π system. Instead, these effects arise primarily from 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 because of the use of substituted aromatic amino acid analogues in the characterization of cation binding sites[5] and the employment of ESPs of substituted aromatic rings in pharmacophor modeling. The implications of the present findings for substituent effects in general noncovalent interactions with aromatic rings will be discussed in forthcoming publications.

Acknowledgment. This work was supported by NIH-1F32GM082114 (S.E.W.) and the NSF (CHE-0548209). S.E.W. thanks H. M. Jaeger, F. A. Evangelista, and K. M. Williams. Computer resources were provided in part by the UCLA Institute for Digital Research and Education (IDRE).

Supporting Information Available: Complete refs 10 and 12, a plot comparing CCSD(T) and M05-2X results, plots versus R of differences between additive models and $E_{int}(C_6H_5X\cdots Na^+)$ and $ESP(C_6H_5X)$, Cartesian coordinates, and electronic energies. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303–1324.

(2) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew Chem., Int. Ed* **2003**, *42*, 1210–1250. Zürcher, M.; Diederich, F. *J. Org. Chem.* **2008**, *73*, 4345–4361.

(3) Mecozzi, S.; West, A. P., Jr.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 10566–10571.

(4) Dougherty, D. A. *Science* **1996**, *271*, 163–168. Gallivan, J. P.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 9459–9464. Kumpf, R. A.; Dougherty, D. A. *Science* **1993**, *261*, 1708–1710.

(5) (a) Zhong, W.; Gallivan, J. P.; Zhang, Y.; Li, L.-C.; Lester, H. A.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 12088–12093. Dougherty, D. A. *Chem. Rev.* **2008**, *108*, 1642–1653. Dougherty, D. A. *J. Org. Chem.* **2008**, *73*, 3667–3673.

(6) Mecozzi, S.; West, A. P., Jr.; Dougherty, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 2307–2308.

(7) Kim, D.; Hu, S.; Tarakeshwar, P.; Kim, K. S. *J. Phys. Chem. A* **2003**, *107*, 1228–1238. Cubero, E.; Luque, F. J.; Orozco, M. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 5976–5980. Tsuzuki, S.; Yoshida, M.; Uchimaru, T.; Mikami, M. *J. Phys. Chem. A* **2001**, *105*, 769–773.

(8) Hunter, C. A.; Low, C. M. R.; Rotger, C.; Vinter, J. G.; Zonta, C. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4873–4876. Amunugama, R.; Rodgers, M. T. *Int. J. Mass Spectrom.* **2003**, *227*, 339–360. Suresh, C. H.; Gadre, S. R. *J. Phys. Chem. A* **2007**, *111*, 710–714.

(9) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 364–382.

(10) Bylaska, E. J.; et al. *NWChem: A Computational Chemistry Package for Parallel Computers*, version 5.1; Pacific Northwest National Laboratory: Richland, WA, 2007.

(11) Kendall, R. A.; Apra, E.; Bernholdt, D. E.; Bylaska, E. J.; Dupuis, M.; Fann, G. I.; Harrison, R. J.; Ju, J.; Nichols, J. A.; Nieplocha, J.; Straatsma, T. P.; Windus, T. L.; Wong, A. T. *Comput. Phys. Commun.* **2000**, *128*, 260–283.

(12) Werner, H.-J.; et al. *MOLPRO Quantum Chemistry Package*, version 2006.1.

(13) Wheeler, S. E.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10854–10855. Wheeler, S. E.; Houk, K. N. *Mol. Phys.* **2009**, DOI: 10.1080/00268970802537614.

(14) Frontera, A.; Quiñonero, D.; Garau, C.; Costa, A.; Ballester, P.; Deyà, P. M. *J. Phys. Chem. A* **2006**, *110*, 5144–5148.

JA809097R