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Cation−π Interactions in Simple Aromatics: Electrostatics Provide a Predictive Tool

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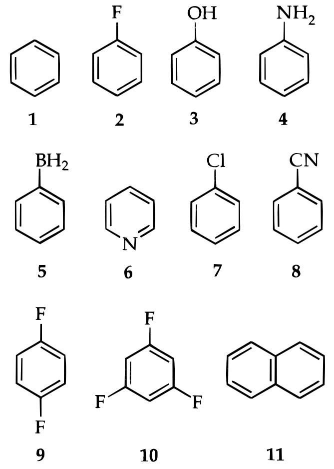
In recent years, the cation−π interaction has come to be appreciated as an important noncovalent binding force.[1] Studies in the gas phase,[2] in aqueous media using synthetic receptors,[3] and in a biological context with a number of protein systems[1,4,5] have established the broad scope and significance of this interaction. A complete, quantitative description of the cation−π interaction would involve a number of intermolecular forces, such as charge−quadrupole, charge−dipole, charge−induced dipole, charge transfer, dispersion forces, and, in some cases, a hydrophobic component. However, we have argued[1,3a,4] that, to first order, the major aspect of the cation−π interaction is electrostatic in nature, involving the interaction of the cation with the large, permanent quadrupole moment of the aromatic.[6] In the present work we describe an evaluation of the extent to which the electrostatic model can rationalize *variations* in cation binding abilities among various aromatic systems. We find that, indeed, the electrostatic model provides a quantitative understanding of the trend seen across a series of prototypical aromatic systems.

We have performed a series of *ab initio* computational studies on the binding of the sodium cation (Na^+) to the π face of structures **1**−**11** (Chart 1). We consider such complexes to provide a good model for the quantitative trends expected in the cation−π interaction. For example, we have previously shown[3b] that using NH_4^+ in place of Na^+ does not alter any trends in such data, and so these simpler model calculations are relevant to real experimental systems. Binding energies were evaluated at the 6-31G**//6-31G** level,[7] using the Gaussian 92[8] package. This level of theory is quite adequate for such a study.[9] To estimate the electrostatic contribution to binding, we replaced the Na^+ of the optimized complex with a dummy probe atom and evaluated the electrostatic potential (EP_{opt}) at that point. We also performed the same calculation using the geometry of the uncomplexed aromatic molecule and evaluating the potential 2.47 Å[10] above the center of the ring (EP_{unopt}). The latter approach interrogates the aromatic absent any distortions due to the Na^+, as is perhaps appropriate for an electrostatic model. Either approach leads to the same conclusions, and we will emphasize the EP_{opt} data here.

Chart 1



Consider first the binding energies (BE) of the prototype monosubstituted aromatics **1**−**5** (Table 1). Superficially, the trend makes sense—aniline (**4**) is better than benzene at binding Na^+, while fluorobenzene (**2**) is worse. However, phenol (**3**), which is generally considered to be an "electron-rich" π system, is no better than benzene at binding Na^+. Also, one might have expected the full π acceptor **5** to be much more deactivated than **2**, but this is not the case.

While the trend for **1**−**5** does not fit any kind of resonance-based arguments, it is in rough agreement with a Hammett analysis based on the substituent constants σ_m or σ_m^+.[11] This means that inductive effects are much more relevant than resonance effects in the binding of the sodium cation. A more satisfying rationalization of the binding data was obtained by

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(4) Kumpf, R. A.; Dougherty, D. A. *Science* **1993**, *261*, 1708−1710.

(5) Dougherty, D. A.; Stauffer, D. A. *Science* **1990**, *250*, 1558−1560.

(6) See also: (a) Luhmer, M.; Bartik, K.; Dejaegere, A.; Bovy, P.; Reisse, J. *Bull. Soc. Chim. Fr.* **1994**, *131*, 603−606. (b) Williams, J. H. *Acc. Chem. Res.* **1993**, *26*, 593−598.

(7) The initial structures for the complexes were generated by placing the sodium atom above the ring centroid. In all the complexes, the sodium position and the geometry of the aromatic molecule were then optimized, except for the case of pyridine (**6**), for which the sodium cation was fixed over the ring and the complex optimized with this constraint. We note that compounds **2**−**10** also exhibit a secondary binding site for sodium on the heteroatom, and in some cases these heteroatom complexes are more stable than the cation−π complex. Details on these heteroatom complexes will be described elsewhere.

(8) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Wong, M. W.; Foresman, J. B.; Robb, M. A.; Head-Gordon, M.; Replogle, E. S.; Comperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 92/DFT*, Revision F.4; Gaussian, Inc., Pittsburgh, PA 1993.

(9) Two lines of reasoning support this contention. First, experimental data exist for five benzene−cation complexes (Li^+, Na^+, K^+, NH_4^+, NMe_4^+). For all five, the current level of theory (or lower) provides good agreement with experiment.[2,4] For example, ΔH°_{exptl} for **1**·Na^+ is 27.1 kcal/mol, in excellent agreement with our calculations. Unfortunately, no relevant experimental data exist for **2**−**11**. Second, substantially higher levels of theory produce the same trends. In particular, MP2/6-31G**//6-31G** binding energies for Na^+ to **1**, **2**, and **4** are 29.7, 25.2, and 35.1 kcal/mol, respectively—the exact same trend as seen at the Hartree−Fock level. Also, estimates of the basis set superposition error (BSSE) were obtained by performing counterpoise calculations on the complexes of **1**−**11** with sodium cation. The absolute BSSEs were found to be small (1.4−1.8 kcal/mol), and the ΔBSSEs within the series were insignificant. In fact, including corrections for zero-point energy and BSSE almost completely compensated for the increase in binding energy seen from the MP2 correction. Given this, and since the HF value for **1**·Na^+ was closer to experiment than the MP2, we have emphasized the Hartree−Fock results.

(10) The Na^+-to-ring centroid distance for the optimized complexes ranged from 2.43 to 2.60 for the series of structures we examined. The intermediate value of 2.47 Å was chosen for calculation of EP_{unopt}.

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Table 1. Calculated[a] Binding Energies[b] (BE) and Electrostatic Contributions[b] (EP$_{opt}$ and EP$_{unopt}$) to the Binding Energies for Complexes of Compounds **1**−**11** with Na$^+$

complex	BE	EP$_{opt}$[c]	EP$_{unopt}$[d]
1·Na$^+$	−27.1	−15.6	−15.0
2·Na$^+$	−22.0	−10.5	−9.8
3·Na$^+$	−26.9	−15.8	−13.9
4·Na$^+$	−31.8	−20.7	−19.3
5·Na$^+$	−24.4	−12.1	−11.0
6·Na$^+$	−20.0[e]	−8.9	−8.4
7·Na$^+$	−21.5	−9.8	−9.3
8·Na$^+$	−15.7	−3.7	−3.3
9·Na$^+$	−16.8	−5.2	−4.6
10·Na$^+$	−12.4	−1.2	0.3
11·Na$^+$	−28.7	−14.9	−14.2

[a] 6-31G**//6-31G**. [b] In kcal/mol. [c] Electrostatic potential is calculated using the optimized geometry of the complexes. [d] Electrostatic potential is calculated using the optimized geometry of the uncomplexed aromatic molecules and setting the sodium cation at the distance of 2.47 Å from the center of the ring. [e] Not a true minimum at this level of theory. See ref 7.

simple inspection of the electrostatic potential maps[1,3b] for **1**−**5**. As such, we quantitatively evaluated the electrostatic potential at the sodium position as a measure of the electrostatic contribution to the binding energy (Table 1). A plot of EP vs BE for these simple systems (**1**−**5**) was quite provocative. The slope was roughly 1 and the intercept large—ca. 12 kcal/mol. That is, a structure with no electrostatic component was predicted to have a BE of 12 kcal/mol. For this reason, we evaluated 1,3,5-trifluorobenzene (**10**), a structure well-known to have a quadrupole moment very near zero.[6b] As shown in Table 1, the BE of **10** was roughly as expected, and the EP was close to zero.

The full results for structures **1**−**11** are given in Table 1 and Figure 1. Consideration of just the raw data of Table 1 would suggest that the electrostatic component of the cation−π interaction is highly variable: in the range of 40−60% in most systems, but near zero in some. However, Figure 1 provides a deeper insight. Plotting EP$_{opt}$ vs BE gives a slope of 1 and an intercept near 12 kcal/mol.[12] This means that across the series **1**−**11**, *essentially 100% of the variation in binding energy is reflected in the electrostatic term*. All other factors (induced dipole interaction, charge transfer, etc.) are absorbed into a *constant* term, worth ca. 12 kcal/mol in these structures.

It is surprising how well such a simple model treats such a considerable variation in BE. Of course, there are subtle deviations from the scheme. For example, naphthalene lies clearly above the correlation line. The major factors other than the electrostatic term—mainly the polarizability-related terms—should be larger for a molecule with a larger surface area, and so more significant for naphthalene. Still, this variation must be fairly small.

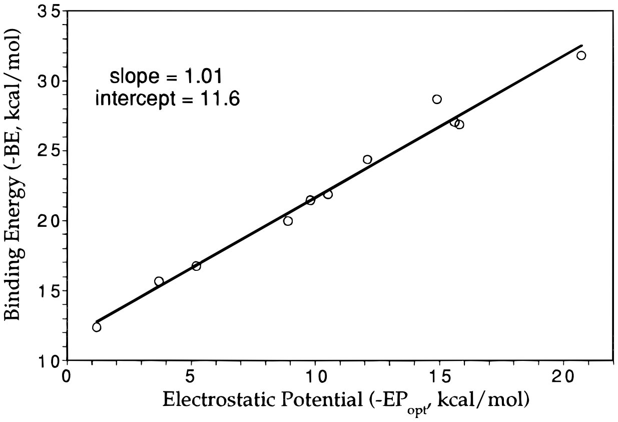

Figure 1. Correlation between binding energy and electrostatic potential for molecules **1**−**11** in their complexes with sodium cation. For this plot, the correlation coefficient is 0.991.

The current results are consistent with other analyses of the cation−π interaction. In particular, Kollmann suggested that electrostatic terms account for ca. 60% of total BE for ethylene·Li$^+$,[13] similar to our finding for benzene. A number of recent studies[2f,g,i] have described various schemes for partitioning the binding energy in complexes between aromatic molecules and ammonium cations.[14] We believe that the simple, direct evaluation of electrostatic energy employed here has advantages over component analyses of the full wave function, which are always subject to complex interpretation. It is clear that in most aromatic systems, electrostatic interactions between an ion and the quadrupole moment of an aromatic make major contributions to the cation−π interaction. Perhaps more importantly for designing or evaluating new systems, trends across a series of related structures can be completely rationalized by considering only electrostatic terms.

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Supporting Information Available: HF 6-31G** energies of compounds **1**−**11** and complexes **1**·Na$^+$−**11**·Na$^+$; plot of binding energies of compounds **1**−**4, 7, 8** vs σ_m (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(12) A plot of EP$_{unopt}$ vs BE gives a slope of 1.04 and an intercept of 12.3, with a correlation coefficient of 0.992.

(13) Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 4177−4178.

(14) (a) Note that in studies of C_6H_6−$NMe_4{}^+$ interactions,[2g,h] polarization of the $NMe_4{}^+$ group will also contribute to the binding, increasing the apparent importance of polarizability in the binding. Here, we have evaluated only the role of the aromatic in cation−π interactions by choosing a nonpolarizable cation.