J. Am. Chem. Soc. **1995,** *117,* 4177−4178

Cation−π Interactions: Nonadditive Effects Are Critical in Their Accurate Representation

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Received October 7, 1994

The cation−π interaction is of increasing interest in enzyme−ligand interactions, an example being the interaction between acetylcholine and its esterase.[1] Experiments on model systems show this interaction to be unusually strong.[2] Calculations using state of the art additive molecular mechanics[2] significantly underestimate the interaction energy of alkali cations with benzene. Rather high level quantum mechanical basis sets appear to be required to provide adequate flexibility. Such an approach is impractical for modeling more complex systems. We thus undertook calculations using nonadditive molecular mechanics.[3] Our calculations, presented below, show the importance of nonadditive effects in describing cation−π interactions.

The standard molecular mechanical methods used to study interactions in molecular systems rely on two-body additive potential functions. The interaction parameters are often calibrated to reproduce the properties of liquids (OPLS)[4] or solids.[5] These approaches inherently incorporate some average effect of "many-body" interactions but evaluate the interaction energy solely as a two-body interaction. Such models have led to accurate representations of the properties of liquid water[6,7] as well as organic liquids.[4] They also often even lead to a quite reasonable estimate of the gas phase interaction energy, provided that the polarization effects in the gas and liquid phases are similar.

For example, the interaction energy of a water dimer using the TIP3P potential is about 1 kcal/mol too exothermic[6] with the enthalpy of vaporization calibrated to reproduce experiment. For $Na^+\cdots OH_2$, the Aqvist[8] model leads to a ΔH of −22.9 kcal/mol, only slightly smaller than the experimental value (−24.0 kcal/mol),[3] with the model calibrated to reproduce the free energy of solvation of the ion in water. As pointed out by Dougherty,[2] an OPLS/Aqvist model for the interaction of Li^+ with benzene leads to an interaction energy that is significantly too small. A small percentage of the discrepancy is due to the fact that the OPLS model of benzene,[9] by being calibrated to reproduce both the liquid properties and the aqueous solvation free energy, has a quadrupole moment about 20% smaller than the experimental value. A model that uses electrostatic potential fit charges,[10] which more accurately reproduces the quadrupole moment of benzene, and leads to an enthalpy of interaction that is in improved agreement with experiment ($\Delta H = -25.3$ kcal/mol). A similar underestimate is found for the interaction of benzene with Na^+, K^+, NH_4^+, and $N(CH_3)_4^+$ (Table 1).

Recently, we developed a model for water and cation complexes,[3,11] methanol,[11] and *N*-methylacetamide[11] that includes polarization explicitly. The partial charges are those derived by restrained fitting to the quantum mechanical electrostatic potential,[10] the van der Waals parameters are the same as those determined for the additive level,[12] and the atomic polarizabilities are taken from the table of Applequist.[13] However, in the case of benzene, it is not clear which polarizability to use, even though ref 13 suggests values for sp (0.36 Å^3), sp^2 (0.616 Å^3), and sp^3 (0.87 Å^3) carbon atoms. However, the development set of molecules used by Applequist did not contain any aromatic moieties. We then examined values for the polarizability of aromatic carbons within the 0.36−0.87 Å^3 range. We determined that the "best" value is 0.36 Å^3. The results of a model using this value are presented in Table 1. As one can see, the agreement with the experimental ΔH is excellent for both NH_4^+ and $N(CH_3)_4^+$ interacting with benzene.

For the alkali cations (Li^+, Na^+, K^+) interacting with benzene, we find reasonable agreement with the experimental ΔH using the same Aqvist 6−12 parameters with the previously employed alkali polarizabilities (nonadditive model, RESP-Aqvist). When we employ the alkali parameters we have previously developed for alkali−water clusters (Dang−Lybrand)[14] and use the standard nonbonded combining rules, we find a much too short cation−benzene distance and a much too negative ΔH value (e.g., for $Li^+\cdots$benzene, $R = 1.26$ Å and $\Delta H = -59$ kcal/mol). Although one could simply abandon the combining rule and adjust the 6−12 parameter, an alternative approach is to use the "three-body exchange repulsion" term for alkali$\cdots$(C(sp^2))$_2$ interactions. Such a term was also employed in the alkali$\cdots$water[3] clusters. The calculated values with such a model are presented in parentheses in Table 1. As one can see, with either model, the agreement with the experimental ΔH is reasonable.

There are also some other subtle issues here. For example, this nonadditive molecular mechanical model, like the additive model, does not include nonbonded interactions involving atoms bonded or separated by two bonds from each other. When a cation approaches benzene, neighboring and next-neighbor carbons can polarize to give dipoles which do not "see" each other, and thus are larger than they would be if they did. Thus the use of $\alpha = 0.36$ Å^3 for the polarizability may be viewed as an "effective" polarizability within such a model. The studies of No *et al.*,[15a] Kang *et al.*,[15b] and Miller[15c] suggest larger values of α for aromatic carbons. We find that if one changes the aromatic carbon α from the 0.36 Å^3 noted above to the Applequist value for an sp^2 carbon, 0.616 Å^3, the $-\Delta H$ for $NH_4^+\cdots$benzene changes from 19.5 kcal/mol (experiment, 19.3 kcal/mol; *ab initio*, 19.1 kcal/mol) to 21.2 kcal/mol. Given the uncertainties in the calculations[16] and experiment,[17] an α in the

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Table 1. Energetics of Cation-π Interactions (energies, kcal/mol; distances, Å)

Additive Models

		OPLS/Aqvist[a]			RESP/Aqvist[b]		
complex	ΔH(exp)[c]	ΔE_0[d]	ΔH[e]	R[f]	ΔE_0[d]	ΔH[e]	R[f]
Li^+−benzene	−38.3[g]	−20.8	−19.8	1.90	−26.6 (−25.1[l])	−25.3	1.80
Na^+−benzene	−28.0[h]	−13.9	−13.3	2.42	−15.0	−14.5	2.33
K^+−benzene	−19.2[i]	−9.9	−9.4	2.85	−12.3	−11.8	2.76
NH_4^+−benzene	−19.3[j]	−11.4	−10.2	2.92	−15.0	−13.5	2.84
$N(CH_3)_4^+$−benzene	−9.4[k]	−7.3	−6.0	4.13	−8.7	−7.4	4.10
Li^+−ethylene					−14.9	−13.9	2.07

Nonadditive and Quantum Mechanical Models

		Nonadditive[m] RESP/Aqvist (Dang/Lybrand)[o]			QM[n]	
	ΔH(exp)[c]	ΔE_0[d]	ΔH[e]	R[f]	ΔE_0[d]	R[f]
Li^+−benzene	−38.3[g]	−43.6 (−45.4)	−41.5 (−38.1)	1.65 (1.70)	−43.8	1.92
Na^+−benzene	−28.0[h]	−26.6 (−30.3)	−26.0 (−28.9)	2.24 (2.14)	−29.5	2.39
K^+−benzene	−19.2[i]	−18.2 (−20.4)	−17.8 (−19.4)	2.60 (2.61)	−15.0	2.84
NH_4^+−benzene	−19.3[j]	−21.2	−19.5	2.72	−19.1	2.91
$N(CH_3)_4^+$−benzene	−9.4[k]	−11.2	−9.9	4.10	−15.4	4.23
Li^+−ethylene		−23.7 (−25.2)	−22.3 (−23.6)	1.97 (1.99)	−24.3	2.31

[a] OPLS (ref 4) model for benzene and ammonium ions with the parameters of ref 8 for the alkali cations. [b] Using the van der Waals parameters and RESP derived charges described in refs 10 and 12 for benzene and the organic ions with parameters from ref 8 for the alkali cations. [c] Experimental enthalpy of complex formation. [d] Optimized interaction energy at the energy minimum. [e] Interaction enthalpy, calculated by employing normal mode analysis (ref 23) to add the vibrational, rotational, and translational energies to ΔE_0 and then using the relation between ΔH and ΔE ($\Delta H = \Delta E_{total} + (\Delta n)RT$ ($T = 298$ K)). [f] Minimum energy distance from the "center" of the ion to the center of the benzene ring. [g] Reference 19. [h] Reference 20. [i] Reference 21. [j] Reference 16. [k] Reference 22. [l] Energy for $R = 1.90$ Å. [m] Using the model described in refs 10 and 12 for molecular mechanics. Polarizabilities for Applequist (ref 13) except for the benzene carbon (0.36 Å^3), RESP (ref 10) charges, and van der Waals parameters (ref 12). Alkali nonbonded parameters are from ref 8. Calculations performed with the Amber suite of programs (ref 23). [n] MP2/6-31G*//MP2/6-31G*; calculations performed with Gaussian92 (ref 24). [o] Values in parentheses are for the Dang/Lybrand[11,15] models employing a three-body exchange repulsion for $M^+\cdots(C(sp^2))_2$. Since the C−C distance is nearly a constant here, we have assumed $\gamma = 0$ and used the equation

$$E_{3\text{-body}} = \sum_{j}^{(\text{ion}-\text{C})_{\text{pairs}}} A\exp(-\beta R_{(\text{ion}-\text{C})_j})$$

with the parameters $A = 10^{11}$, $\beta = 5.80$ for Li^+; $A = 10^{11}$, $\beta = 5.20$ for Na^+; and $A = 10^{10}$, $\beta = 4.05$ for K^+.

range of 0.5 Å^3 is appropriate for use within a model such as ours, but this value is still significantly smaller than that suggested by No *et al.*

Also, based on the *ab initio* calculations, our nonadditive model underestimates the cation to benzene center distance in these five complexes by an average of ~0.2 Å, with the agreement slightly worse for the alkali cations than for the more delocalized N^+ cations. One could increase the van der Waals repulsions and reproduce the distances, but this would worsen the agreement with the ΔH values, although they would be significantly improved over the additive model. For example, if we adjust the three-body potential to give $R(Li^+\cdots$benzene$)$ = 1.9 Å, we get $\Delta H = -32.1$ kcal/mol.

To reproduce accurately both R and ΔH may require the inclusion of charge transfer attraction in these models, although one could imagine empirically adjusting the existing parameters in the model to achieve more quantitative accuracy. Quantum mechanical energy component analyses using the Morokuma decomposition[18] at the optimum separations find that, for $Li^+\cdots OH_2$, the electrostatic energy is quite close to the total interaction energy, whereas for $Li^+\cdots$ethylene, the electrostatic energy is only ~60% of the total energy. This is consistent with the results of the additive model (RESP-Aqvist), which leads to a $|\Delta H|$ value that is ~60% of the correct one. Both polarization and charge transfer are important in the $Li^+\cdots$ethylene interaction.

We do not understand why the *ab initio* interaction energy calculation for $N(CH_3)_4^+\cdots$benzene is in much worse agreement with experiment than those for the other *ab initio* interaction energies for the other cation−π complexes, but perhaps counterpoise corrections are more important in the case of $N(CH_3)_4^+\cdots$benzene. That this may be the case is supported by the calculations of Kim *et al.*[17] These authors carried out high-level *ab initio* calculations on NH_4^+ and TMA^+ interactions with water and benzene. They noted the importance of electrostatic, polarization, and dispersion contributions to the cation−π attraction, all of which are included in our nonadditive molecular mechanical model.

In summary, we have shown that the addition of polarizability to a molecular mechanical model allows it to model cation−π interaction energies much more accurately than two-body additive models.

Acknowledgment. P.A.K. acknowledges research support from the NSF (CHE-91-13472) and also acknowledges useful comments by Dennis Dougherty.

JA9432980

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