Binding of Organic Cations to a Cyclophane Host As Studied with Molecular Dynamics Simulations and Free Energy Calculations

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We have studied the binding of two organic cations, an iminium (IM) and a guanidinium (GU), to a cyclophane host P^{4-}-$4Na^+$, using molecular dynamics simulations and free energy calculations. A proper treatment of the long-range electrostatic forces is essential for the stability of these highly charged complexes, and a simple cutoff at 12 Å results in an artifactual dissociation of the IM−P^{4-}-$4Na^+$ complex. Since the host is highly aromatic and the guests cationic, cation−π interactions play an important role in the complex stability. In free energy calculations, using a simple additive force field, we calculate that the relative free energy of association of IM and GU binding to the host is 2.3 kcal/mol favoring IM, which is of the correct sign but 1.4 kcal/mol too small in magnitude. Differences in van der Waals interaction energies are mainly responsible for the different binding strengths, and the host adopts different shapes when accommodating IM compared to GU. To approximately estimate the contribution to the complex stability from the polarization energy, we calculated the in vacuo interaction energies in the two complexes, using a nonadditive force field, previously shown to accurately describe alkali cation−aromatic interaction energies in vacuo. Adding the contribution from the polarization energy upon forming the two complexes in this calculation to the estimate from the free energy calculation, we obtain an improved relative binding free energy (−4.0 kcal/mol), which is in close agreement with the experimental value of −3.7 kcal/mol.

Introduction

Studies of model systems and analysis of macromolecular structures have established the importance of cation−π interactions as a driving force in molecular recognition (reviewed in refs 1, 2). Dougherty et al.[3] have found a class of cyclophane hosts that bind strongly (4−9 kcal/mol) to organic cations, such as iminium, tetraethylammonium, sulfonium, and guanidinium ions. Cation−π interactions play an important role in the complex stability between the highly aromatic cyclophane and the organic cations. By comparing the binding free energy between iminium and an electroneutral derivative with identical shape, a lower limit for the cation−π interaction energy in these systems has been estimated to be as high as 2.5 kcal/mol.[3] Cation−π interactions have previously been shown[4] to be relatively inaccurately described by simple additive, effective pair potentials which are commonly used in molecular dynamics (MD) simulations. For a more accurate treatment of such interactions it was shown[4] that many-body interactions could be taken into account by including polarization energy in the force field. In this work we have studied the binding of two organic guests, an iminium (IM) and a guanidinum (GU) to the cyclophane host P^{4-}-$4Na^+$ (Figure 1). These systems are computationally challenging for two reasons. First, the complexes are highly charged and we expect a proper treatment of
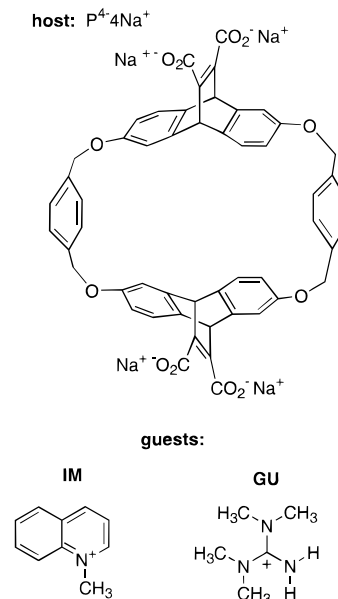

Figure 1. (Top) The cyclophane host P^{4-}-$4Na^+$. (Bottom) the two guests, an iminium (IM) an a guanidinium (GU).

long-range electrostatic interactions to be important for the stability of the complexes. We have studied the importance of these interactions for the complex stability, and it turned out that a long-range electrostatic correction method—Particle Mesh Ewald (PME)[5]—was essential in the simulations. A simple truncation of the electrostatic forces beyond 12 Å led to a

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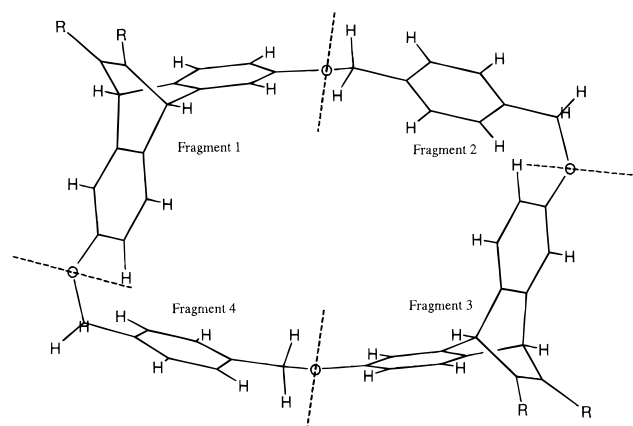‡ University of Stockholm.
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Figure 2. Logical division of the host cage in four fragments (R = COOMe or COO⁻).

dissociation of the complex, while in MD simulations using the PME method the host−guest complexes remained stable throughout the simulation. Second, since cation−π interactions are important for the complex stability, we expect a nonadditive

force field to be important for an accurate estimate of relative binding free energy of the two organic cations to the host molecule. We show that the relative binding free energy of the two guests to the host is underestimated by 1.4 kcal/mol using the thermodynamic integration (TI) free energy calculation method (reviewed in refs 6, 7), with a simple additive force field. Given the computational expense of carrying out fully nonadditive free energy calculations,[8] we estimated the difference in polarization energies in the complexes and free guests in vacuo. A correction of the free energy obtained from the TI calculation with this estimate of the contribution from the polarization free energy results in a relative binding free energy of −4.0 kcal/mol, in close agreement with the experimental value of −3.7 kcal/mol.[3]

Methods

Parametrization. The starting geometry of the neutral tetramethyl ester host P was taken from the X-ray structure.[9] Hydrogen atoms were added using the Macromodel 3.5a package,[10] and the molecular electrostatic potential (MEP) was calculated with the Gaussian 90 program at the HF/6-31G* basis
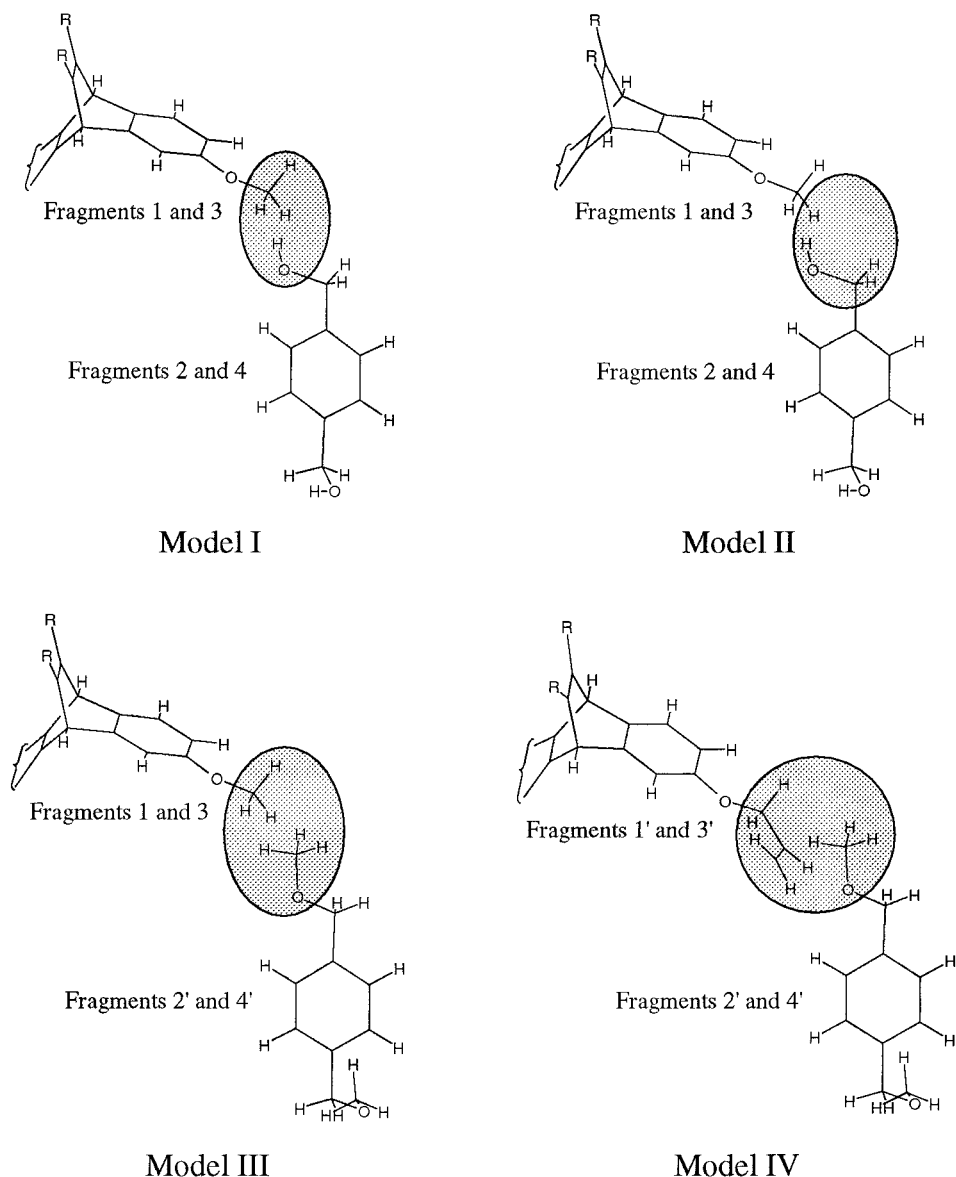

Figure 3. Models used to derive the charges of the hosts P (R = COOMe) and P^{4-} (R = COO⁻). The sum of atomic charges in the gray areas was constrained to zero during the multiple RESP caclulation.
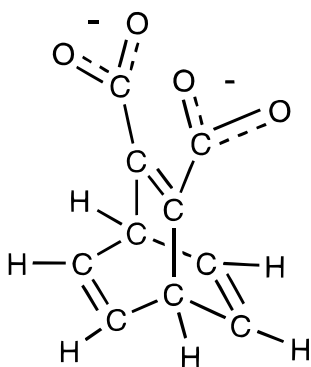
Figure 4. Molecule that was used to determine charges on the tetraanionic P^{4-}.
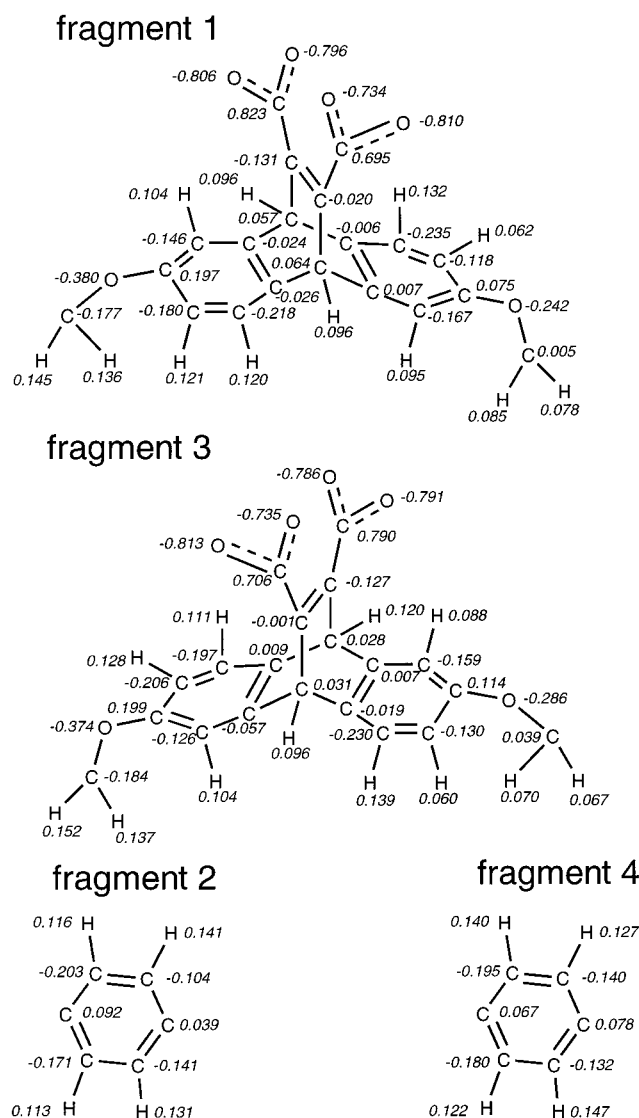

Figure 5. Partial charges of the four fragments that were used to create the host P^{4-}.

Figure 6. Partial charges of the two guests, IM and GU.

set level using the geometry of the fragments in the host molecule. Atomic charges are then obtained from these MEPs by performing a multiple-molecules RESP calculation in which the overlap regions (gray areas in Figure 3) between fragments were constrained to have a net charge of zero.

Models I and II were based on the same set of fragments and differed only by the choice of the atoms belonging to the overlap region. In model III, the fragments 2 and 4 were replaced by their dimethyl ether derivatives (fragments 2' and 4'). Model IV had the biggest overlap region, as diallyl derivatives of the fragments 1 and 3 as well as fragments 2' and 4' were used. Analysis of the RESP-fitted charges obtained for these four models has led to the conclusion that the best one was model IV, for which the average absolute error was less than 0.04 e$^-$ for the heavy atoms of the internal face of the cage.

To obtain a geometry for the tetraionic P^{4-} host, we performed a partial geometry optimization (at the HF/6-31G* level) of a simplified model (Figure 4) of the bicyclo[2.2.2]-octatriene part of the fragments 1 and 3. During the minimization, only the structure of the "maleic acid" part was allowed to vary, the position of the other atoms being fixed at the corresponding fragment geometries. The optimized dianion of the maleic acid was then pasted into the fragments 1' and 3' to replace the dimethyl ester moiety, and MEP was calculated. Atomic partial charges for the host P^{4-} (Figure 5) were derived from these MEPs using the model IV described above.

The partial charges of IM and GU (Figure 6) were derived from full 6-31G* geometry optimization followed by RESP fits to the resulting electrostatic potentials.

Setup and Equilibration. *P^{4-}-4Na$^+$−IM Complex.* We added four sodium ions close to each carboxyl group in P^{4-}. To obtain a reasonable initial configuration of the host−guest complex, IM was positioned in the host at eight slightly different positions, chosen by graphical inspection, using the program MidasPlus.[12] The eight different complexes were simulated in vacuo for 100 ps after a short minimization with the AMBER 5.0 suite of programs[13] using the Cornell et al. force field.[14] We used a time step of 2 fs and a nonbonded cutoff of 12 Å in these simulations. In four simulations, IM escaped from the host

set level. Atomic partial charges were derived from the MEP using a two-stage fitting RESP procedure.[11] The charges obtained for the complete molecule (model 0) were used as reference. The host P was then divided in four fragments (Figure 2), and four different models (Figure 3) were elaborated in order to get the best set of charges (i.e., charges based on fragment calculations versus the reference charges). For each fragment, the electrostatic potential was calculated at the HF/6-31G* basis
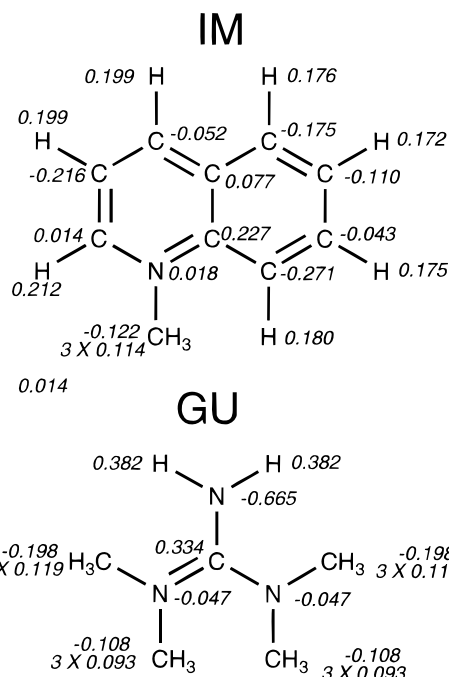
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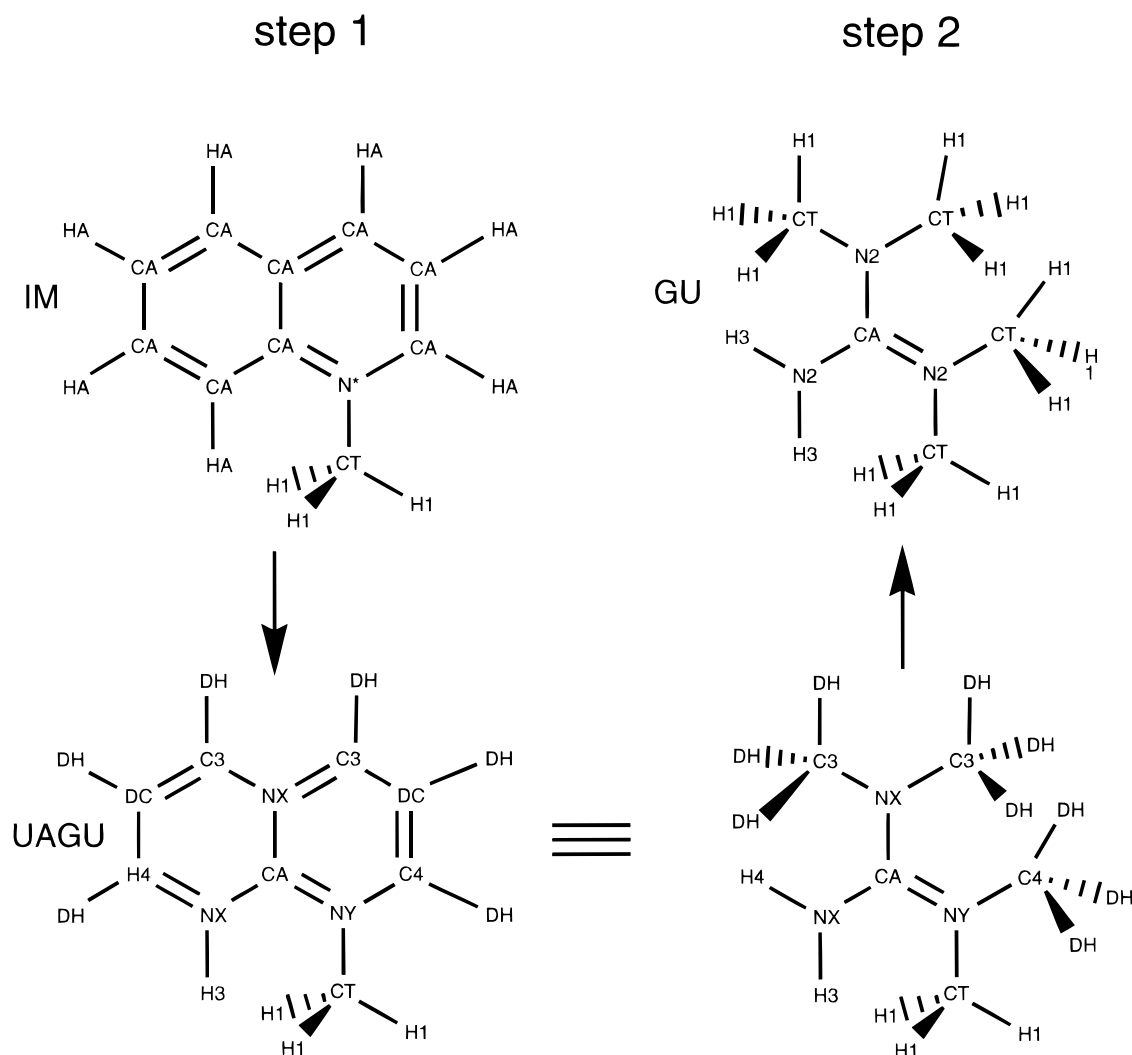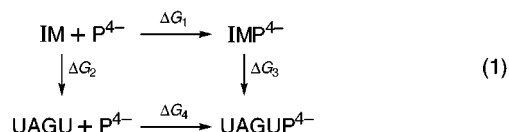
step 1

step 2

Figure 7. Two-step perturbation of IM to GU, via the intermediate UAGU, which is a united atom representation of GU.

and the remaining four simulations were simulated for another 500 ps. In two of these prolonged simulations, IM had found an identical position in the host, and we chose that configuration of the complex as the starting structure. The complex was then immersed in a box of TIP3P[15] water with approximate dimensions $47.9 \times 39.7 \times 39.0$ Å^3. To achieve electroneutrality, one chloride ion was also positioned in the vicinity of the complex. Water molecules and ions were then equilibrated for 50 ps, keeping the complex atoms rigid. Also here, we used a time step of 2 fs and a nonbonded cutoff of 12 Å, and the nonbonded list was updated every 10 time steps. We applied the SHAKE algorithm[16] to bonds containing hydrogen atoms. Periodic boundary conditions were applied, and the simulations were performed at constant pressure, allowing changes in the box dimensions. Thereafter, we released the complex and gradually heated the system for 60 ps. This was followed by two different kinds of 100 ps equilibration at 300 K. In the first equilibration, we continued with the same parameters and protocol as for the heating, whereas in the second equilibration, the long-range electrostatic forces were treated with the Particle Mesh Ewald (PME) method.[5] With these two different equilibration schemes, we showed that inclusion of long-range electrostatic forces is necessary, since the guest escaped from the host within the 100 ps equilibration of the complex without PME. When the PME technique was applied, the position of the guest was little changed compared to the starting structure.

IM. The guest IM was immersed in a box of TIP3P water with dimensions $33.4 \times 31.9 \times 31.3$ Å^3, and one chloride ion was added for electroneutrality. After a 50 ps equilibration of the waters and ion around rigid IM, we released the IM atoms and heated the system gradually for 60 ps, followed by a 100 ps equilibration at 300 K. We used the same protocol as for the equilibration of the complex, and we applied PME to the long-range electrostatic interactions.

Free Energy Calculations. The IM $\rightarrow$ GU perturbation was performed in two steps. This is because an accurate calculation of the bond potential of mean force (pmf) contribution to the free energy when changing the bond length cannot be done when the bonds are part of a closed ring system.[17] Therefore, in step 1 (see Figure 7), all bond lengths were unchanged during the simulations, and the carbon atoms on which hydrogen atoms were to be grown in the following step were perturbed into united carbon atoms (type C3 and C4, see Figure 7). The perturbation in step 1 can be represented by the following thermodynamic cycle:

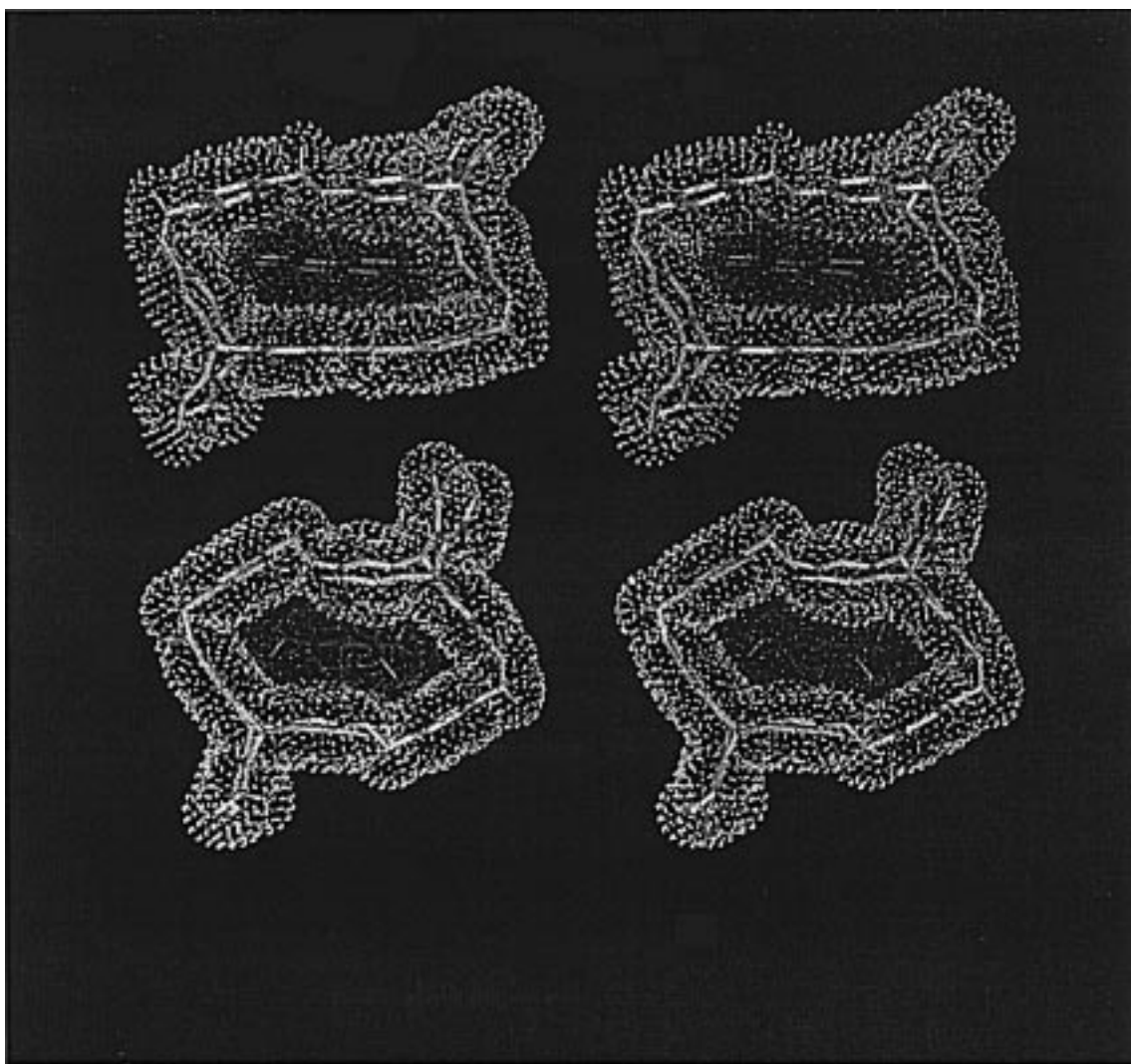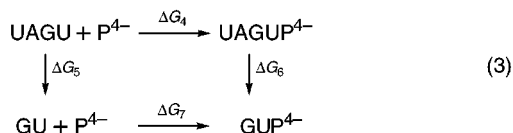$$\begin{array}{ccc} \text{IM} + \text{P}^{4-} & \xrightarrow{\Delta G_1} & \text{IMP}^{4-} \\ \downarrow{\scriptstyle \Delta G_2} & & \downarrow{\scriptstyle \Delta G_3} \\ \text{UAGU} + \text{P}^{4-} & \xrightarrow{\Delta G_4} & \text{UAGUP}^{4-} \end{array} \quad (1)$$

Figure 8. (Stereoview) (top) IM$-$P^{4-}-4Na$^+$ and (bottom) GU$-$P^{4-}-4Na$^+$. The guests IM and GU are gray shaded.

where UAGU is the intermediate structure. Since G is a state function, the following applies:

$$\Delta\Delta G_1 = \Delta G_4 - \Delta G_1 = \Delta G_3 - \Delta G_2 \quad (2)$$

In the second step, the bond lengths were perturbed into those of GU and hydrogen atoms were grown on the C3 and C4 carbons, which simultaneously were perturbed into all-atom aliphatic carbons (atom type CT, Figure 7). The following thermodynamic cycle applies for the second step:

$$
\begin{array}{ccc}
\text{UAGU} + \text{P}^{4-} & \xrightarrow{\Delta G_4} & \text{UAGUP}^{4-} \\
\downarrow{\scriptstyle \Delta G_5} & & \downarrow{\scriptstyle \Delta G_6} \\
\text{GU} + \text{P}^{4-} & \xrightarrow{\Delta G_7} & \text{GUP}^{4-}
\end{array}
\quad (3)
$$

and since G is a state function,

$$\Delta\Delta G_2 = \Delta G_7 - \Delta G_4 = \Delta G_6 - \Delta G_5 \quad (4)$$

subtracting eq 4 from eq 2 gives

$$\Delta\Delta G = \Delta\Delta G_2 - \Delta\Delta G_1 = \Delta G_7 - \Delta G_1 = \Delta G_6 - \Delta G_5 + \\ \Delta G_3 - \Delta G_2 \quad (5)$$

TABLE 1: Free Energy Calculations IM $\rightarrow$ GU via the Intermediate UAGU; Energy Values (kcal/mol) Are Averages from a Forward and a Reverse Run, and the Error Estimates Are within Parentheses[c]

(a) IM $\rightarrow$ UAGU

	ΔG_2	ΔG_3	$\Delta G_3 - \Delta G_2$
ΔG_{tot}	54.41 ± 0.25	51.75 ± 0.70	-2.66
$\Delta G_{el.stat}$	6.37 ± 0.01	7.25 ± 0.05	0.87
ΔG_{vdw}	7.86 ± 0.19	4.37 ± 0.68	-3.49
$\Delta G_{1,4vdw}$	-4.96 ± 0.01	-4.96 ± 0.01	0.00
$\Delta G_{1,4el.stat}$	39.93 ± 0.01	39.91 ± 0.01	-0.02
$\Delta G_{badh}{}^{a}$	5.21 ± 0.08	5.18 ± 0.07	-0.03

(b) UAGU $\rightarrow$ GU

	ΔG_5	ΔG_6	$\Delta G_6 - \Delta G_5$
ΔG_{tot}	37.38 ± 0.14	37.78 ± 0.26	0.40
$\Delta G_{el.stat}$	42.73 ± 0.08	42.32 ± 0.01	-0.41
ΔG_{vdw}	2.81 ± 0.03	3.46 ± 0.11	0.66
$\Delta G_{1,4vdw}$	3.87 ± 0.01	3.98 ± 0.01	0.11
$\Delta G_{1,4el.stat}$	-59.24 ± 0.01	-59.09 ± 0.01	0.15
ΔG_{badh}	51.05 ± 0.12	51.23 ± 0.04	0.18
$\Delta G_{pmf}{}^{b}$	-3.83 ± 0.02	-4.11 ± 0.11	-0.28

[a] Free energy contribution from bonds, angles and dihedrals. [b] Potential of mean force (pmf) correction to the free energy when changing the bond length. [c] $\Delta G_{solv} = \Delta G_2 + \Delta G_5 = 91.79$ (±0.28) kcal/mol. $\Delta G_{bind} = \Delta G_3 + \Delta G_6 = 89.54$ (±0.74) kcal/mol. $\Delta\Delta G = \Delta G_{bind} - \Delta G_{solv} = -2.26$ (±0.80) kcal/mol, experimental value[3] -3.7 kcal/mol.

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The four free energy quantities on the right-hand side of eq 5 were estimated with the thermodynamic integration (TI)method (reviewed in refs 6, 7). In this method, a coupling parameter λ is introduced, which varies from $\lambda = 0$ (for IM in eq 1 and UAGU in eq 3) to $\lambda = 1$ (for UAGU in eq 1 and GU in eq 3). The free energy change is then evaluated according to

$$\Delta G = \int_0^1 \left\langle \frac{\partial H(\lambda)}{\partial \lambda} \right\rangle_\lambda \, \mathrm{d}\lambda \qquad (6)$$

where $H(\lambda)$ is the potential energy of the system as a function of the coupling parameter λ and $\langle \ \rangle_\lambda$ is an ensemble average. The integral is evaluated numerically from a number of evenly spaced windows (spacing $= \Delta\lambda$) with λ values ranging from 0 to 1. $\langle \partial H(\lambda)/\partial\lambda \rangle_\lambda$ is calculated by averaging over MD trajectories run at a certain number of steps in each window. The calculations were run with the AMBER 4.1 program GIBBS, and we applied the same parameters and protocol as for the MD simulations above, with the PME method for the long-range electrostatics, except that the SHAKE algorithm was applied to all bonds. For all four ΔG's on the right-hand side of eq 5, we used a $\Delta\lambda$ of 0.01 (i.e., 101 windows for the λ-interval [0,1]), and prior to a data collection time in each window of 2 ps, the system was equilibrated for 1 ps per window. *All perturbations were run in the forward and reverse directions and the energies in Table 1 are averaged values.* When continuing the perturbations from the end points of step 1 to the starting points of step 2, which are physically identical but topologically different, we *discarded all water molecules* and resolvated UAGU (both in solution and in P^{4-}-$4Na^+$) by adding new boxes of water molecules around the molecule(s). These systems were equilibrated, using the same scheme as for IM (P^{4-}-$4Na^+$), described above.

Estimation of the Polarization Free Energies. To estimate the contribution of the polarization energy to the free energy, we minimized the guests, free and in complexes with the host P^{4-}, in a vacuum. In an initial attempt we included the four Na^+ in these calculations. However, the energies were found to be very sensitive to the exact locations of the sodium ions, introducing a lot of noise in the estimations. Since we believe it is reasonable to assume that the average locations of the ions are very similar in the two complexes, we performed the estimations without the surrounding counterions. The atomic polarizabilities were adopted from those of Appelquist et al.[18] and are also listed in ref 8.

Results and Discussion

The two-step perturbation of IM into GU, via the united atom version of GU (UAGU), results in a binding free energy difference of -2.3 ± 0.8 kcal/mol (Table 1), which is considerably less negative than the experimental value of -3.7 kcal/mol.[3] A decomposition of the free energy into various components shows that the van der Waals energy is almost solely responsible for the difference in stability. Summing over the two steps yields a $\Delta\Delta G_{\mathrm{vdw}}$ of -2.8 ± 0.7, which largely dominates the contributions to the binding stability. The van der Waals surfaces between the *p*-xylyl groups (fragments 2 and 4, see Figure 2) in P^{4-}-$4Na^+$ are less complimentary to GU than to IM, where the fit is almost perfect (Figure 8). This results in two small cavities on either side of the GU methyl groups that contact the *p*-xylyl groups of the host, which is absent in IM$-P^{4-}$-$4Na^+$. The shape of P^{4-} is also different in the two complexes (Figure 8). In GU$-P^{4-}$-$4Na^+$, the ethenoanthracene units (fragments 1 and 3 in Figure 2) have moved closer

TABLE 2: Energies (kcal/mol) from Minimizations in Vacuo Using Atomic Polarizabilities[18]

(a) IM		
energy	IM$-P^{4-}$	IM
E_{bond}	5.59	0.81
E_{angle}	17.19	0.43
E_{dihed}	19.43	0.0
E_{vdw}	-37.52	-0.39
E_{14vdw}	57.96	7.94
$E_{\mathrm{el.stat}}$	-49.51	5.63
$E_{\mathrm{14el.stat}}$	69.75	11.69
E_{polar}	-49.22	-1.59
E_{tot}	33.66	24.52

(b) GU		
energy	GU$-P^{4-}$	GU
E_{bond}	5.92	0.83
E_{angle}	20.88	2.05
E_{dihed}	22.15	5.04
E_{vdw}	-33.64	0.72
E_{14vdw}	55.01	4.73
$E_{\mathrm{el.stat}}$	-50.33	6.98
$E_{\mathrm{14el.stat}}$	57.48	-1.01
E_{polar}	-49.40	-3.49
E_{tot}	28.08	15.84

(c) $\Delta\Delta E$ [(IM$-P^{4-}$)$-$IM $-$ ((GU$-P^{4-}$)$-$GU)]	
energy	
E_{bond}	-0.32
E_{angle}	-2.07
E_{dihed}	2.32
E_{vdw}	-2.77
E_{14vdw}	-0.26
$E_{\mathrm{el.stat}}$	2.17
$E_{\mathrm{14el.stat}}$	-0.43
E_{polar}	-1.72
E_{tot}	-3.10

to the center of the cavity than in IM$-P^{4-}$-$4Na^+$, and the rectangular shape of the host is distorted.

Next, we estimated the magnitude of many-body interactions by minimizing the complexes, as well as free guests, in vacuo using atomic polarizabilities,[18] just as was done in ref 4 for modeling monovalent cation interactions with benzene. From the minimizations of the complexes and free guests in vacuo, we obtain a difference in the polarization energy to form the two complexes of -1.7 kcal/mol (Table 2). It is interesting that the polarization energy contribution to the relative interaction energy of IM is larger than that of GU. Caldwell and Kollman[4] found that, for the simple cation$-\pi$ complexes, the smallest, most localized cations had a larger net polarization interaction energy. However, IM is able to form a better and more complementary interaction with the host P^{4-} and thus able to more effectively polarize more of the inducible dipoles. Using the estimate of $\Delta\Delta E_{\mathrm{pol}}$ from Table 2 of -1.7 kcal/mol for the relative polarization energy of complex binding to the free energy yields a total of -4.0 kcal/mol, which is in significantly better agreement with the experimental result of -3.7 kcal/mol[3] than the additive $\Delta\Delta G$ only.

Conclusions

In this work we have shown that inclusion of long-range electrostatic forces in the simulations of the highly charged host$-$guest complexes is a requirement for the complex stability. This has been demonstrated before for highly charged systems such as DNA and RNA,[5] but this is also clearly of significance

for highly charged host−guest systems such as those studied here. A simple truncation of the electrostatic forces results in a dissociation of the IM−P^{4-}-4Na$^+$ complex, whereas it remained stable throughout the simulation when using the PME method to handle the long-range electrostatic forces. Second, we have calculated the relative free energy of binding two guests IM and GU to the tetraanionic cyclophane host P^{4-} and showed that it is underestimated by 1.4 kcal/mol if we use a simple additive force field in the free energy calculations. To approximate the relative polarization energies, we calculated them using energy minimizations in vacuo. Correcting the free energy obtained from the additive force field free energy calculation with this estimate of the polarization energy contribution results in a binding free energy difference between IM and GU to P^{4-}-4Na$^+$ of −4.0 kcal/mol, which is in close agreement with the experimental value of −3.7 kcal/mol.[3] Although this level of agreement is fortuitous, given the approximations involved in the calculation of polarization energies, it is encouraging that it is of the right sign and magnitude. On the basis of prior studies,[4] one would have expected that complexes involving the smaller, more localized cation would have the greater polarization energy; in fact, the opposite is found for the complexes studied here.

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