motrypsin (45 units/mL) for 5 h with no visible cleavage. The apoproteins were digested (0.75 units/mL) for 1 h at room temperature. Only the apo-L-RbDD was digested as determined by electrophoresis on a denaturing polyacrylamide gel.[11] The resistance of Fe^{3+}-L-rubredoxin to proteolysis is not surprising, in that it appears to be a very well-folded structure.[8] Even after boiling in reducing SDS–sample buffer and subsequent electrophoresis, the Fe^{3+}-bound forms of each isomer did not denature and appeared as red, comigrating bands on an SDS gel.

Initial crystallization studies of racemic RbDD (prepared by mixing equimolar amounts of the two enantiomers) have been performed. The goal is to produce crystals with one molecule in the asymmetric unit and an inversion center relating enantiomers. Although it has been suggested that there are entropic effects favoring racemate formation over spontaneous resolution,[12] Brock et al. have recently pointed out that these effects are extremely small.[1] There may be, however, enthalpic effects favoring racemate crystallization.[1] Clumps of small but apparently well-formed crystals have been obtained under a variety of conditions. CD studies of solutions produced by dissolving small clumps of crystals have revealed no significant CD, suggesting that these crystals do, indeed, contain the racemate. Using similar conditions, larger crystals suitable for diffraction studies have been grown. Characterization of these crystals by X-ray[13] and other methods is in progress.

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Enhanced View of Structure and Binding for Cyclophane–Arene Complexes through Joint Theoretical and Experimental Study

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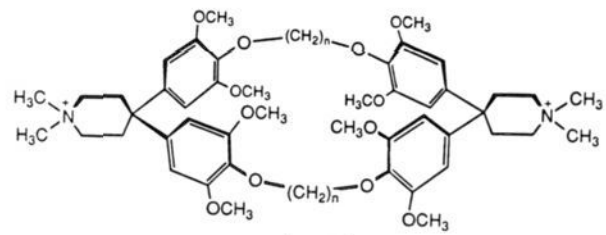
Cyclophane hosts are valuable models for exploring apolar binding in aqueous solution;[1-3] however, simple correlations with aromatic guest solubility or electron donor–acceptor indices are masked by solvophobic forces and specific substituent solvation.[2] Consequently, we have pursued theoretical means to help clarify the structures and solvation of complexes and the energetic contributions to binding.[4] We report here the first Monte Carlo simulations for cyclophane complexes, new experimental data that illustrate the predictive value of the methodology, and combined results that provide striking structural details.

Table I. Calculated and Experimental Free Energy Changes (kcal/mol)

p-xylene to	ΔG_G	ΔG_C	$\Delta\Delta G_b$ calcd[a]	$\Delta\Delta G_b$ exptl[b]
benzene	0.0	2.0	−2.0 ± 0.2	−1.5 ± 0.2[c]
p-cresol	−5.6	−5.7	0.1 ± 0.3	−0.4 ± 0.1[c]
hydroquinone	−11.4	−8.6	−2.8 ± 0.3	−2.2 ± 0.2[d]
p-dicyanobenzene	−7.7	−7.6	−0.1 ± 0.4	−0.1 ± 0.1[d]

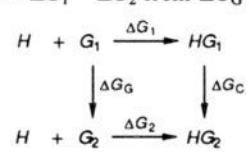
[a] At 298 K. [b] At 293 K. [c] This work. [d] Reference 2.

Figure 1. Sample configuration of host **1** with hydroquinone. Only water molecules hydrogen bonded to hydroquinone are shown.



1, $n = 3$
2, $n = 4$

An initial goal was to compute relative free energies of binding ($\Delta\Delta G_b$) for benzene derivatives with **1** in water. The BOSS program, which performs Monte Carlo statistical mechanics simulations, was enhanced to permit sampling for any bonds, bond angles, and dihedral angles.[5] The stretching and bending force constants come from the AMBER force field,[6] and the nonbonded interactions are described by the OPLS potentials.[7] All atoms are explicit except for hydrogens in CH_2 and CH_3 groups. Bond lengths were fixed except for the length of one ring-closure bond in the macrocycle. Internal coordinates in the benzene and piperidinium rings were not sampled; however, all remaining dihedral angles and the bond angles within the macrocycle were sampled. Statistical perturbation theory[8] was applied with the cycle below to compute $\Delta\Delta G_b = \Delta G_1 - \Delta G_2$ from $\Delta G_G - \Delta G_C$.[9]



Initially, *p*-xylene was energy optimized into the crystal structure

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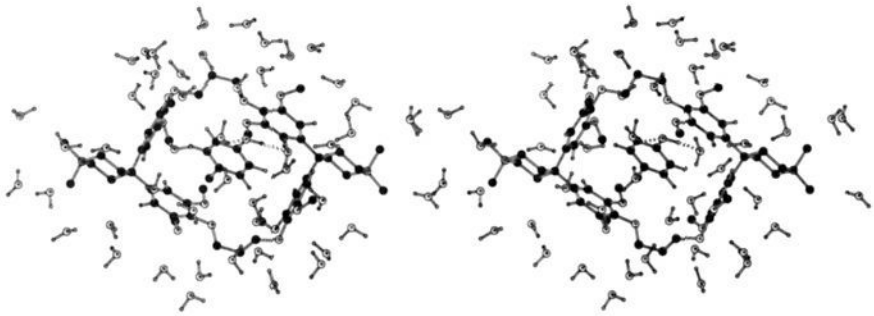

Figure 2. Stereoplot of the complex of host **1** with *p*-cresol oriented with the hydroxyl group hydrated. Water molecules within 3.5 Å of any solute atom are shown.

of **1**.[10] Included in the calculations for the complexes and isolated guests were 768 and 500 TIP4P water molecules,[11] respectively. All calculations were run at 298 K and 1 atm with ca. 10 Å energy cutoffs, periodic boundary conditions, and Metropolis sampling, as before.[4] A series of six or seven simulations was required to mutate gradually *p*-xylene to the other guests.[12] Each simulation had 1M to 4M configurations of equilibration, followed by 2M to 4M configurations of averaging. Solute variations were attempted every 20–25 configurations with changes in a random subset of internal coordinates.[13]

p-Xylene was first perturbed to hydroquinone. The calculated preference for binding *p*-xylene was 2.8 ± 0.3 kcal/mol, in good accord with the previous experimental result of 2.2 ± 0.2 kcal/mol (Table I).[2] On the basis of a notably exothermic ΔH_b and negative $T\Delta S_b$, it was proposed that an intracomplex hydrogen bond occurred between ether oxygens of host **2** and a hydroxyl group of hydroquinone.[3] This was confirmed in the calculations for **1**; the hydrogen bond primarily involves one of the ether oxygens in the macrocycle and requires that the phenolic hydrogen rotate 40–50° out of plane. This OH group is too buried to be hydrated, while the other hydroxyl has two hydrogen bonds with water molecules (Figure 1). Good accord was also obtained between theory and experiment for *p*-dicyanobenzene (Table I).

Subsequent perturbations to benzene predicted a 2.0 ± 0.2 kcal/mol preference for binding *p*-xylene. **1** was then prepared, and its binding constant with benzene was measured by ^{1}H NMR titrations in D_2O, as before.[2] The resultant ΔG_b of −2.69 ± 0.20 kcal/mol at 293 K implies weaker binding for benzene than *p*-xylene[2] by 1.5 ± 0.2 kcal/mol. The results for *p*-cresol proved particularly interesting. On the basis of the observed ΔH_b and $T\Delta S_b$ for **2** with *p*-cresol, it was also expected than an intracomplex hydrogen bond existed.[3] With evolution into this geometry, the computed $\Delta\Delta G_b$ was −2.8 ± 0.3 kcal/mol, favoring *p*-xylene. The NMR experiment was then performed; ΔG_b is −3.81 ± 0.10 kcal/mol, which gives $\Delta\Delta G_b$ = −0.4 ± 0.1 kcal/mol. The discrepancy prompted running the simulation with evolution into the geometry with the hydroxyl group hydrated (Figure 2), which yielded a $\Delta\Delta G_b$ of 0.1 ± 0.3 kcal/mol. Thus, the calculations make a clear choice for this orientation. Confirmation comes from the pattern of upfield induced ^{1}H NMR chemical shifts at saturation binding ($\Delta\delta_{sat}$) in *p*-cresol complexed to **1**, 1.29 ppm for the methyl group protons and 1.09 and 2.96 ppm for the protons ortho to the hydroxyl and methyl groups.

These observations cause us to reinterpret the origin of the anomalously exothermic ΔH_b and negative $T\Delta S_b$ for *p*-cresol and hydroquinone binding to **2**. Images as in Figure 2 suggest that the hydrated hydroxyl group of these guests helps nucleate an extended hydrogen-bonded network on the surface of the complex that yields enhanced hydration of the host's proximal ether groups and a lower ΔH_b. The participating water molecules are highly ordered to fit into the network and the host's crevices. A nonhydroxylic guest such as *p*-xylene also protrudes on one side of the host; the methyl group inhibits full formation of the network and leads to a less favorable ΔH_b, but more favorable $T\Delta S_b$.

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Supplementary Material Available: The OPLS parameters for the solutes and plots of the free energy changes for the mutations (7 pages). Ordering information is given on any current masthead page.

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Use of Cholestanylindene-Derived Nonbridged Group 4 Bent Metallocene/Methylalumoxane Catalysts for Stereoselective Propene Polymerization

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Brintzinger's C_2-symmetric group 4 *ansa*-metallocenes and related compounds[1] have brought remarkable progress to the use of homogeneous Sinn/Kaminsky type bent metallocene/alumoxane-derived Ziegler catalysts for stereoselective α-olefin polymerization.[2-4] An a priori assessment of nonbridged planarly

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