

Monte Carlo Investigations of Selective Anion Complexation by a Bis(phenylurea) *p*-*tert*-Butylcalix[4]arene

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Abstract: Monte Carlo statistical mechanics simulations have been employed to elucidate the complexation of halide ions in chloroform by the bis(phenylurea) *p*-*tert*-butylcalix[4]arene of Scheerder et al. The calculations employed OPLS potential functions including new parameters for iodide ion. Gas-phase optimizations for the host–guest systems, as well as for halide–water and halide–urea complexes, were performed to characterize the structures of the complexes and to quantify the intrinsic binding affinities. The computations reveal that the gas-phase optimized structures of the complexes are largely maintained in chloroform solution, though there is a ca. 20 kcal/mol reorganization penalty for the host to achieve the binding geometry. Statistical perturbation theory was used to compute the relative free energies of binding for the halide ions with the calixarene in chloroform. The observed affinity order, $\text{Cl}^- > \text{Br}^- > \text{I}^-$, was quantitatively well reproduced; however, in contrast to the experimental report of no complexation for F^- , the simulations find that F^- should bind with by far the greatest affinity among the halides. The possibility that interference by water in the experiments led to the observed lack of fluoride binding was explored through simulations of the halides with water molecules in chloroform. The results indicate that complexation of F^- by two water molecules would be sufficient to overcome complexation by the bis-urea host.

Introduction

Molecular recognition is central to many areas of chemistry and biochemistry, including catalysis, cell adhesion, signal transduction, and enzyme inhibition.¹ Synthetic hosts and guests have been developed to mimic such activities and to elucidate the underlying intermolecular interactions. The accurate prediction of associated binding affinities is an important goal; however, it requires careful consideration not only of the interactions between the binding partners but also of the solvation of the host, guest, and complex.² We have turned to computer simulations with full atomic detail to probe quantitatively molecular recognition in solution for both prototypical systems and specific applications.³ This permits comparison of experimental and predicted binding affinities as well as provides details on structure and energy components.

Though early work in the molecular recognition field centered on selective hosts for cations, interest in anion complexation has been increasing.¹ Anion binding is generally achieved in aprotic solvents with receptors incorporating ammonium, guanidinium, or Lewis-acid fragments. This study was stimulated

by the novel work of Scheerder et al. on the use of urea-derivatized *p*-*tert*-butylcalix[4]arenes as neutral hosts for anion binding.⁴ They observed the strongest binding for halide ions with the bis(phenylurea) derivative shown in Figure 1. This host is unusual in that it binds anions solely through hydrogen bonding rather than ion pairing. The host facilitates the transport of anions into nonpolar media and was developed as part of a broader program on ion transport through membranes. The work is of interest not only because of the unique qualities of the host but also because it illustrates the importance of environmental details in binding studies. Although the observed order of binding affinities was determined to be $\text{Cl}^- > \text{Br}^- > \text{I}^-$, it was reported that “none of the urea derivatives show complexation with F^- ”.⁴ Given that the observed binding affinity decreases with increasing ionic size, it could have been expected that fluoride ion would show the greatest affinity. This study explores the structures and complexation energetics of the halide ions with the host, water, and urea. The anomalous observations for fluoride ion binding are attributed to the inadvertent addition of water with the hygroscopic fluoride salt or the chloroform solvent.

Computational Details

Force Field. The inter- and intramolecular interactions were described by the OPLS force field, which treats the energy of a system as a sum of harmonic terms for bond stretching and angle bending, a Fourier series for each torsional angle, and Coulomb and Lennard-Jones terms for atoms separated by three or more bonds (eqs 1–4).⁵ The latter “nonbonded” terms are scaled by a factor of 0.5 for the 1,4-

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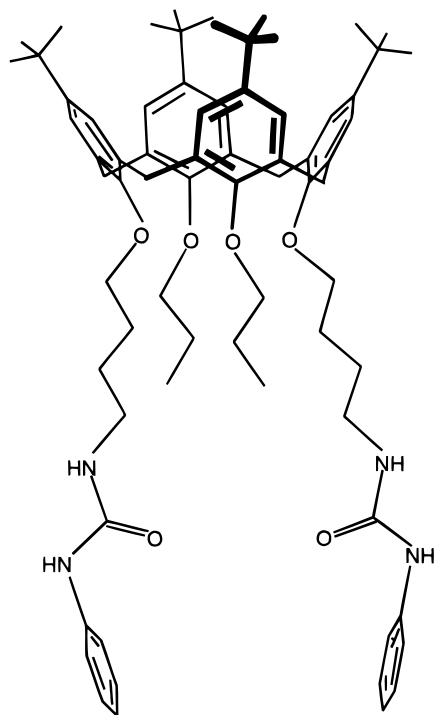


Figure 1. Molecular structure of the bis(phenylurea) *p*-*tert*-butylcalix[4]arene.

intramolecular interactions and are unscaled for longer-range intramolecular and all intermolecular interactions.^{5b}

$$E_{\text{bond}} = \sum_i k_{b,i} (r_i - r_{0,i})^2 \quad (1)$$

$$E_{\text{bend}} = \sum_i k_{\theta,i} (\vartheta_i - \vartheta_{0,i})^2 \quad (2)$$

$$E_{\text{torsion}} = \sum_i [V_{1,i}(1 + \cos \varphi_i)/2 + V_{2,i}(1 - \cos 2\varphi_i)/2 + V_{3,i}(1 + \cos 3\varphi_i)/2] \quad (3)$$

$$E_{\text{nb}} = \sum_i \sum_{j>i} \{q_i q_j e^2 / r_{ij} + 4\epsilon_{ij}[(\sigma_{ij}/r_{ij})^{12} - (\sigma_{ij}/r_{ij})^6]\} \quad (4)$$

A combination of all-atom and united-atom representations was used for the calixarene host. Specifically, the *tert*-butyl groups on the upper rim of the host and the CH_n groups in the "tails" along the lower rim were represented with the united-atom model; all other atoms were explicit. No bonds were flexible with the exception of a ring-closure bond for the macrocycle, and all aromatic moieties were constrained to be rigid; all other bond and dihedral angles were flexible. The Lennard-Jones parameters were drawn from the OPLS models of 12-site benzene,⁶ united- and all-atom alkanes,⁷ ethers,⁸ and urea.⁹ The charges for most atoms were taken from the same sources; however, the partial charges for the phenylurea fragments were obtained from fitting to an ab initio electrostatic potential surface for methylphenylurea at the B3LYP/6-31G*/6-31G* level. Such EPS charges have been

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Table 1. Nonbonded Parameters for the Calixarene and the Halides

OPLS type ^a	AMBER type	<i>q</i> (e)	σ (Å)	ϵ (kcal/mol)
1	CA	-0.115	3.550	0.070
2	CA	0.135	3.550	0.070
3	CT	0.110	3.500	0.066
4	HA	0.115	2.420	0.030
5	CT	0.115	3.800	0.050
6	HC	0.060	2.500	0.030
7	C3	0.000	3.960	0.145
8	OS	-0.385	3.000	0.170
9	C2	0.250	3.800	0.118
10	C2	0.000	3.905	0.118
11	C2	0.000	3.905	0.118
11 ^b	C3	0.000	3.905	0.175
12	C2	0.155	3.800	0.118
13	N	-0.534	3.250	0.170
14	H	0.350	0.000	0.000
15	C	0.691	3.750	0.105
16	O	-0.493	2.960	0.210
17	N	-0.661	3.250	0.170
18	H	0.320	0.000	0.000
19	CA	0.453	3.550	0.070
20	CA	-0.310	3.550	0.070
21	CA	-0.106	3.550	0.070
22	CA	-0.129	3.550	0.070
23	HA	0.159	2.420	0.030
24	HA	0.135	2.420	0.030
25	HA	0.092	2.420	0.030
	F ⁻	-1.000	2.73295	0.72000
	Cl ⁻	-1.000	4.41724	0.11779
	Br ⁻	-1.000	4.62376	0.09000
	I ⁻	-1.000	5.40000	0.07000

^a See Figure 2 for numbering. ^b For a propyl group.

Table 2. Angle Bending Parameters for the Calixarene Host

OPLS type ^a	AMBER type	θ_0 (deg)	<i>k</i> (kcal mol ⁻¹ rad ⁻²)
6-3-6	HC-CT-HC	107.80	33.00
2-1-3	CA-CA-CT	120.00	70.00
1-3-1	CA-CT-CA	109.50	40.00
1-3-6	CA-CT-HC	109.50	35.00
2-8-9	CA-OS-C2	113.00	46.50
8-9-10	OS-C2-C2	109.50	80.00
9-10-11	C2-C2-C2	112.40	63.00
10-11-12	C2-C2-C2	112.40	63.00
11-12-13	C2-C2-N	111.20	80.00
12-13-15	C2-N-C	121.90	50.00
13-15-17	N-C-N	114.20	70.00
15-17-19	C-N-CA	123.20	50.00
17-19-20	N-CA-CA	120.00	70.00
18-17-19	H-N-CA	119.80	35.00
16-15-17	O-C-N	122.90	80.00
14-13-15	H-N-C	119.80	35.00
14-13-12	H-N-C2	118.40	38.00

^a See Figure 2 for numbering.

demonstrated to be a viable choice for reproducing experimental free energies of solvation¹⁰ and have also performed well in previous binding studies.³ The complete set of nonbonded parameters is given in Table 1. The angle bending parameters are listed in Table 2 and come primarily from the AMBER force fields.¹¹

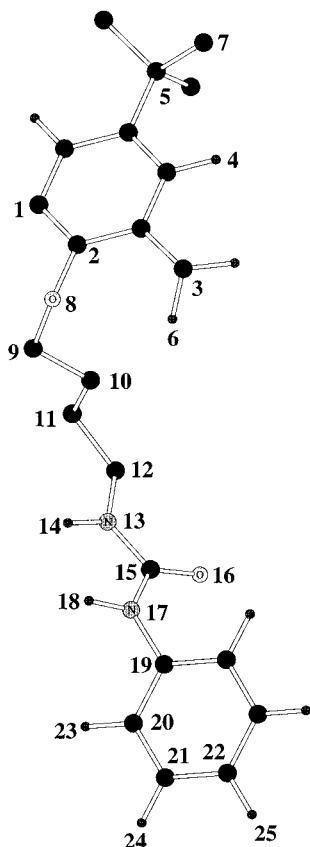
The torsional parameters for the host were taken mostly from the OPLS all-atom force field.^{5b} However, several of the torsional types had not previously been parametrized or were unavailable because the atoms involved a mix of all- and united-atom types. The missing

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Table 3. Fourier Coefficients for the Dihedral Angles in the Calixarene Host

OPLS type ^a	AMBER type	V ₁ (kcal/mol)	V ₂ (kcal/mol)	V ₃ (kcal/mol)
9-8-2-1	C2-OS-CA-CA	0.000	3.980	0.000
10-9-8-2	C2-C2-OS-CA	-5.540	2.798	1.570
11-10-9-8	C2-C2-C2-OS	-2.264	1.186	2.710
12-11-10-9	C2-C2-C2-C2	-3.804	1.782	2.793
13-12-11-10	N-C2-C2-C2	-2.740	1.219	3.833
15-13-12-11	C-N-C2-C2	-2.874	0.393	0.452
17-15-13-14	N-C-N-H	0.000	9.769	0.000
19-17-15-13	CA-N-C-N	3.701	12.157	0.000
20-19-17-15	CA-CA-N-C	0.000	1.000	0.000

^a See Figure 2 for numbering.**Figure 2.** Fragment of the calixarene with numbering corresponding to atom types in Tables 1–3.

parameters were derived by fitting to torsional profiles from calculations with the MM3 force field in MacroModel.¹² Briefly, the torsional profile obtained from the nonbonded and angle bending terms associated with rotation about a given bond (eqs 2 and 4) was subtracted from the MM3 profile and the difference fitted to the Fourier series in eq 3. The sum of the nonbonded, angle bending, and Fourier terms then reproduces the MM3 profile. Table 3 contains a complete listing of all the torsional parameters used for the calixarene host. Any torsions not explicitly mentioned in Table 3 were specified as zero. A fragment of the host with the numbering used in Tables 1–3 is shown in Figure 2.

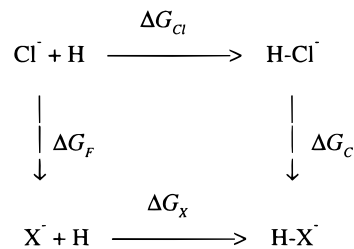
Previously reported nonbonded parameters were adopted for the fluoride, chloride, and bromide ions.^{13a,b} Since parameters were not available for iodide ion, they were developed ($q = -1 e$, $\sigma = 5.400 \text{ \AA}$, and $\epsilon = 0.070 \text{ kcal/mol}$) by fitting to ab initio 6-311++G*(ECP) results

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for the optimal complex of I⁻ and a water molecule and by reproducing in Monte Carlo simulations the experimentally observed difference in free energies of hydration for chloride and iodide ion.^{13c} All simulations of solvated systems were performed in OPLS chloroform,^{14a} and TIP4P was the water model in all cases.^{14b}

Monte Carlo (MC) Simulations. Relative binding energies ($\Delta\Delta G_b$) for bromide, iodide, and fluoride ions versus chloride ion with the calixarene host in chloroform were computed via the thermodynamic cycle shown below.



$$\Delta\Delta G_b = \Delta G_X - \Delta G_{Cl} = \Delta G_C - \Delta G_F$$

The experimentally measured relative free energy of binding, $\Delta G_X - \Delta G_{Cl}$, is equal to the computed $\Delta G_C - \Delta G_F$, which comes from the nonphysical “mutations” of one ion to another, both free (ΔG_F) and complexed to the host in solution (ΔG_C). These free energy changes were calculated with Monte Carlo simulations employing free energy perturbation (FEP) theory via the Zwanzig equation (eq 5):¹⁵

$$\Delta G(A \rightarrow B) = -k_B T \ln \langle \exp[-(E_B - E_A)/k_B T] \rangle_A \quad (5)$$

where A and B denote reference and perturbed states, respectively, and $\langle \rangle_A$ means that the Monte Carlo sampling is carried out for the reference state. In practice, each mutation is divided into a series of smaller steps and any parameters which change during the course of the mutation are linearly scaled between the reference and perturbed states by means of a coupling parameter, λ , which varies from 0 to 1. In this case, each conversion of one ion to another was performed in five steps with double-wide sampling using a $\Delta\lambda$ of 0.1. This methodology and the utility of its application to many similar problems are well documented.^{2,3} The same approach was used in the earliest FEP study of a host-guest system, which addressed halide ion binding by a spherand.¹⁶ Subsequently, FEP results for calixarene-cation complexes have been reported in several recent papers, particularly by Wipff and co-workers.¹⁷ However, there do not appear to be previous FEP studies of anion binding by calixarenes.

Additional MC/FEP calculations were performed here to investigate the possibility that the lack of experimentally observed fluoride binding by the host was due to preferential binding of fluoride ion by water molecules in the chloroform solvent. Completely analogous mutations of chloride ion to fluoride ion were performed with one and two TIP4P water molecules acting as the “host”. MC/FEP calculations were also carried out in which fluoride ion was annihilated in the presence of the host or one or two water molecules in chloroform, which allows comparison of absolute free energies of binding.¹⁸ The fluoride was first converted to a helium atom ($q = 0$, $\sigma = 2.556 \text{ \AA}$, and $\epsilon = 0.020 \text{ kcal/mol}$) and then to a null particle ($q = \sigma = \epsilon = 0$). Ten FEP windows were used for these calculations with a $\Delta\lambda$ of 0.05. A

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Table 4. Results of Gas-Phase Optimizations for Calixarene–Ion Complexes^a

ion	ΔE	ΔE_{deform}	ΔE_{inter}	av H-bond distance (Å)
F ⁻	-58.90	25.01	-83.91	1.77
Cl ⁻	-30.45	20.83	-51.28	2.37
Br ⁻	-28.21	21.07	-49.29	2.42
I ⁻	-20.21	21.28	-41.49	2.71

^a All energies are in kilocalories per mole. $E_{\text{host}} = -68.54$ kcal/mol. ΔE is the net interaction energy, which consists of the intermolecular term, ΔE_{inter} , and the penalty for deformation of the host, ΔE_{deform} .

harmonic restraint with a force constant of $5.0 \text{ kcal mol}^{-1} \text{ \AA}^{-2}$ was applied to the disappearing particle to keep it in the vicinity of the binding site.¹⁸ Specifically, the restraint connected the disappearing particle to a point midway between the carbonyl carbons of the urea moieties of the calixarene or to a water oxygen. All computations were performed with the BOSS program.¹⁹

Initially, the host and host–ion complexes were energy-minimized during a conformational search. The lowest-energy structure for the chloride ion complex provided a starting geometry for the bound MC simulations. For reference, optimizations were also carried out for each halide ion with two OPLS urea molecules and with one and two TIP4P water molecules.

The MC simulations were performed for the ion–calixarene complexes in a ca. $39 \times 46 \times 48 \text{ \AA}$ box containing 626 chloroform molecules, which was subject to periodic boundary conditions and preferential sampling. An attempt to move the solute was made every 150 configurations, including variation of a random subset of internal coordinates. The solute–solute and solute–solvent interactions were truncated at 12 Å and quadratically feathered to zero over the last 0.5 Å. The cutoff procedure for the solute–solvent interactions was based on the distances between the chloroform carbon and a set of well-distributed atoms of the host or the ion. If any of the distances was within the cutoff, the solute–solvent interaction was included. The unbound mutations were performed in a cubic box of 127 chloroform molecules, ca. 26 Å on a side, subject to the same conditions as above. All MC windows with the calixarene involved 1.5×10^6 configurations of equilibration and 6×10^6 configurations of averaging, while each window for the unbound ions covered 1.5×10^6 and 2×10^6 configurations of equilibration and averaging, respectively. The mutations of an ion bound to one or two TIP4P water molecules as a host in chloroform were performed in a cubic box of 265 chloroform molecules. In this case, each FEP window covered $1\text{--}2 \times 10^6$ configurations of equilibration and $2\text{--}4 \times 10^6$ configurations of averaging. Ranges of motions for both solvent and solute molecules were adjusted to give acceptance ratios of ca. 40% for new configurations. This limited the ranges for the variations in dihedral angles for the calixarene host to $1\text{--}5^\circ$. The solvent molecules were treated as rigid bodies; i.e., they only experienced translational and rotational sampling. All MC simulations were performed in the isothermal isobaric (NPT) ensemble at 25 °C and 1 atm.

Results and Discussion

Gas-Phase Structures and Energetics. The energetic results of the gas-phase optimizations for the host alone and for its complexes with the four halide ions are presented in Table 4. The corresponding structures of the host and of the complexes with chloride and fluoride ions are shown in Figures 3 and 4. Not surprisingly, the two urea moieties of the isolated host form intramolecular hydrogen bonds (Figure 3). One carbonyl oxygen acts as the acceptor for hydrogen bonds with both NH hydrogens of the other urea group. The longer hydrogen bond (2.289 Å) is with the NH attached to the phenyl substituent, while the NH more proximal to the calixarene core forms the

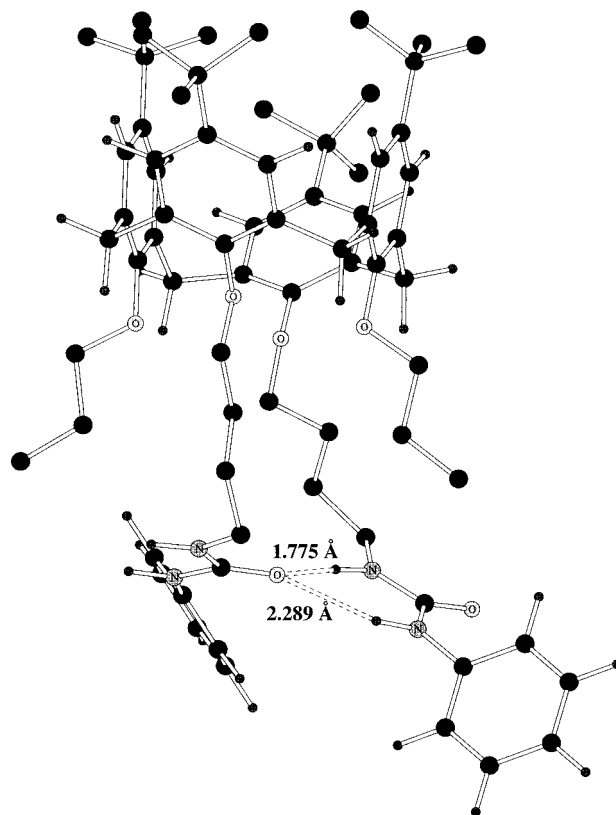


Figure 3. Lowest-energy structure from optimizations of the calixarene with the OPLS force field.

shorter one (1.775 Å). The conformation also draws the latter hydrogen near the face of the phenyl ring of the other side chain. This optimized gas-phase structure agrees well with the experimental picture for the host in chloroform solution. Hydrogen bonding of the urea groups is indicated by NMR, and a 0.45 ppm upfield shift is found for the proximal NH proton, which was attributed to shielding by the opposing phenyl ring.⁴ The hydrogen bonding enforces the cone conformation for the polyurea-derivatized calix[4]arenes.⁴ Of course, the intramolecular hydrogen bonding is not a desirable feature for these molecules as hosts since it must be disrupted to allow complexation with anions. In fact, the poorer anion binding ability of tetrakis-urea versus the bis-urea derivatives of the calix[4]arene was attributed to enhanced intramolecular hydrogen bonding in the former hosts.⁴

The structures of the optimized calixarene–halide complexes are similar for chloride, bromide, and iodide; however, the fluoride–calixarene complex reflects the smaller radius for this ion (Figure 4). In all cases, the urea moieties are canted to provide a distorted tetrahedral geometry about the halide ion. For the fluoride complex, the urea groups and side chains are closer together. The average F–HN hydrogen-bond length is 1.77 Å versus ion–HN distances of 2.4–2.7 Å for the other halides (Table 4). The net interaction energies (host + ion → complex) using the lowest-energy structures are -58.9, -30.5, -28.2, and -20.2 kcal/mol for F⁻, Cl⁻, Br⁻, and I⁻, respectively. There is a substantial penalty, 21–25 kcal/mol, for distorting the host to the binding geometry arising from the loss of the intramolecular hydrogen bonding. This is offset by the ion–host hydrogen bonding, which is favorable by -41 to -84 kcal/mol. The very attractive intrinsic interaction of fluoride ion with the calixarene suggests that F⁻ should bind readily to the host in a relatively nonpolar solvent like chloroform. At

(19) Jorgensen, W. L. *BOSS*, version 3.8, Yale University: New Haven, CT, 1997.

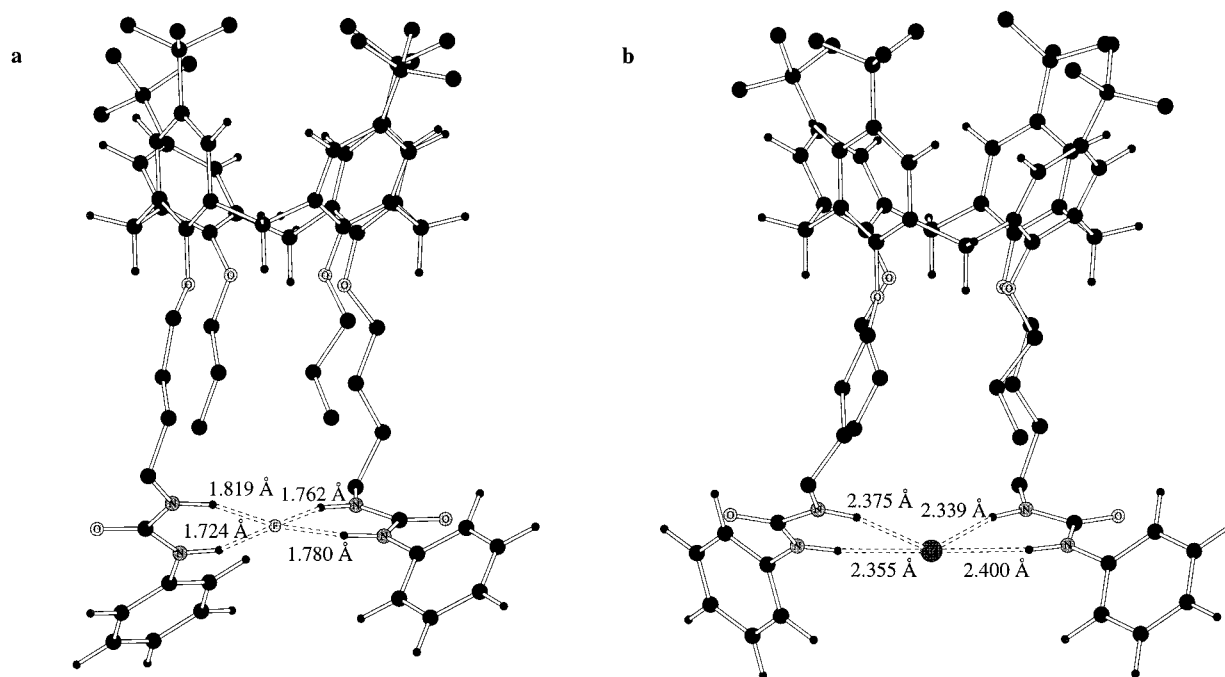


Figure 4. Lowest-energy structures for the calixarene host bound to (a) fluoride ion and (b) chloride ion in the gas phase.

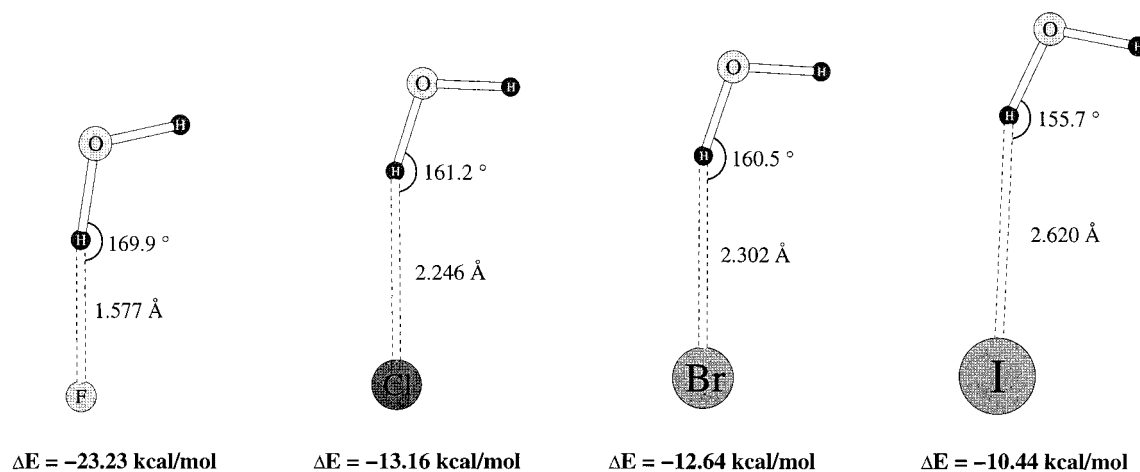


Figure 5. Lowest-energy structures for the halide ions bound to one TIP4P water molecule.

this point, there is certainly nothing in the optimized structures or interaction energies that indicates a potential problem in forming the fluoride complex.

For comparison with these interaction energies, the results of gas-phase optimizations of the halide ions with one and two water molecules and with two urea molecules are shown in Figures 5–7. The reported interaction energies are for formation of the complexes from the separated components. In the latter cases, if one wanted to compare them with the dimerized solvent molecules, the optimal interaction energy for the linear TIP4P water dimer is -6.23 kcal/mol and for the cyclic OPLS urea dimer -12.52 kcal/mol .^{9,14b} The computed optimal interaction energies for the ions with a single TIP4P water molecule are -23.2 , -13.2 , -12.6 , and -10.4 kcal/mol for F^- , Cl^- , Br^- , and I^- , respectively (Figure 5). These values are essentially identical to the corresponding enthalpy changes from the mass spectrometry measurements of Kebarle and co-workers, namely, -23.3 , -13.1 , -12.6 , and -10.2 kcal/mol , respectively.²⁰ Proper comparison requires conversion of the computed interac-

tion energies to enthalpies at 298 K, which adds ca. 0.5 kcal/mol to the computed energies.^{21,22} The potential functions have been parametrized to provide this accord and are known to describe well the energetics of small ion–water clusters.^{22,23}

The results in Figure 6 for the complexes with two water molecules show interaction energies a little less than twice the values for the monohydrates owing to the repulsion between the water molecules in the complexes. The computed results of -45.6 , -25.9 , -24.8 , and -20.6 kcal/mol for F^- , Cl^- , Br^- , and I^- , respectively, are again similar to Kebarle's experimental enthalpies²⁰ of -39.9 , -25.8 , -24.9 , and -20.0 kcal/mol , respectively. In this case, the energy to enthalpy correction for the chloride complex is still ca. 0.5 kcal/mol .²² Though the predicted value for fluoride appears to be too attractive, it is notable that ab initio calculations at the MP3/6-31+G(d) level give interaction energies of -48.6 and -28.1 kcal/mol for

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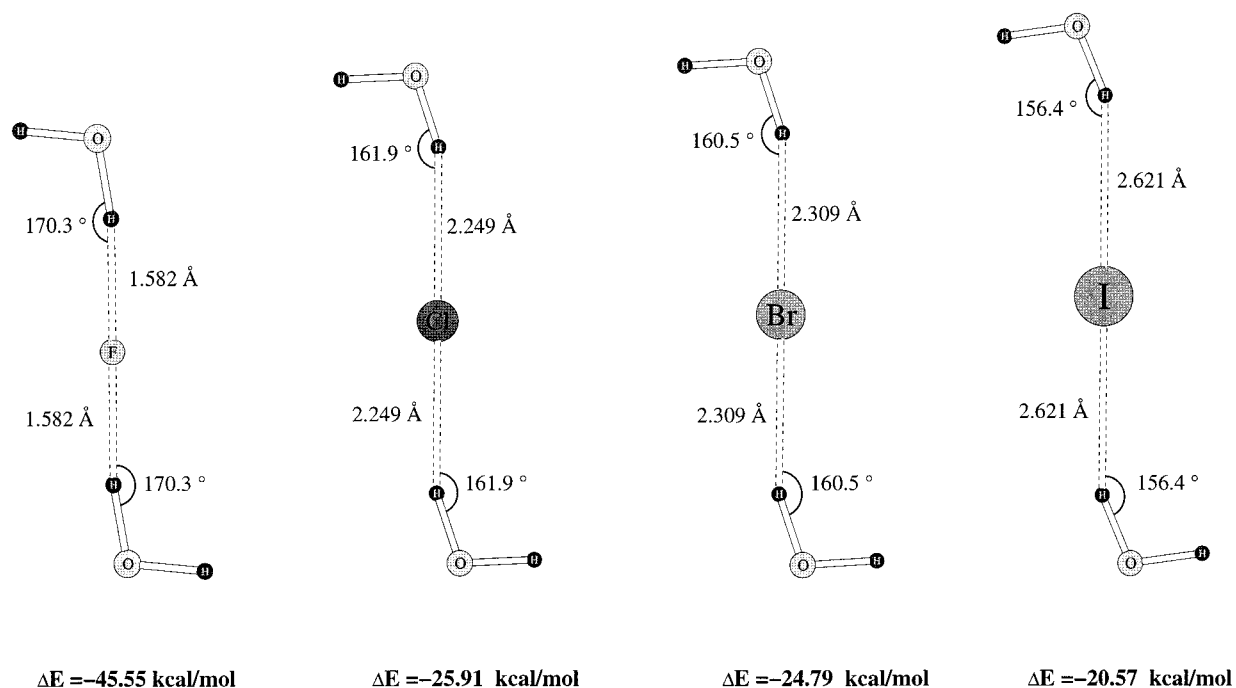


Figure 6. Lowest-energy structures for the halide ions bound to two TIP4P water molecules.

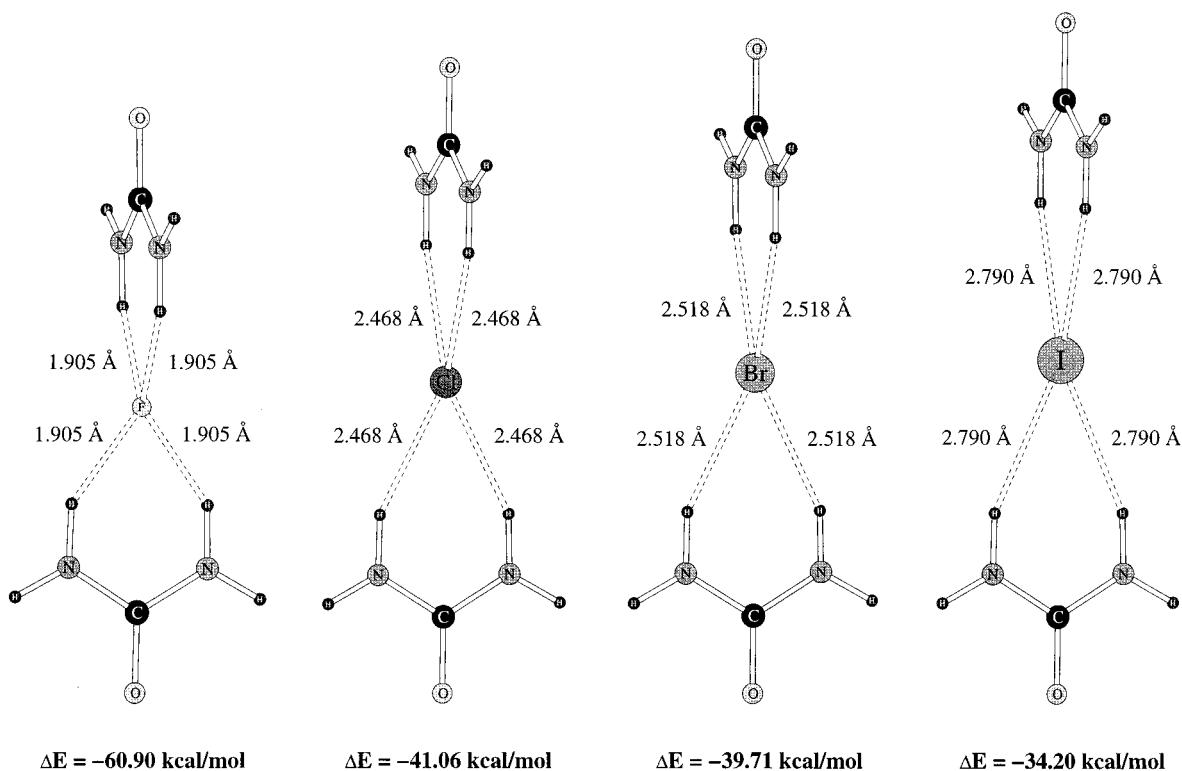


Figure 7. Lowest-energy structures for the halide ions bound to two OPLS urea molecules.

$F^-(H_2O)_2$ and $Cl^-(H_2O)_2$, respectively.²³ In any event, these computed results mirror the large step between fluoride and chloride affinities and the small difference between chloride and bromide, which are apparent in the experimental hydration enthalpies.

The optimized interaction energies for one OPLS urea molecule with the halide ions are -31.53 , -21.20 , -20.51 , and -17.63 kcal/mol for F^- , Cl^- , Br^- , and I^- , respectively. Related experimental data do not appear to be available. The ions are on the dipole axis and form two hydrogen bonds with urea as in the structures with two urea molecules in Figure 7. The

orthogonal relationship between the urea molecules minimizes their repulsion and provides distorted tetrahedral coordination for the ions. The interaction energies with two ureas are about 50% more attractive than those with two water molecules, which can be attributed to the doubling of the number of hydrogen bonds as well as to the dipole moment of 4.87 D for OPLS urea versus 2.18 D for TIP4P water. Furthermore, when the intermolecular energy terms in Table 4 and the results in Figure 7 are compared, it is apparent that the interactions between the ions and the bis-urea calix[4]arene are at least as those favorable as for the ions with two unconstrained urea molecules; i.e., there

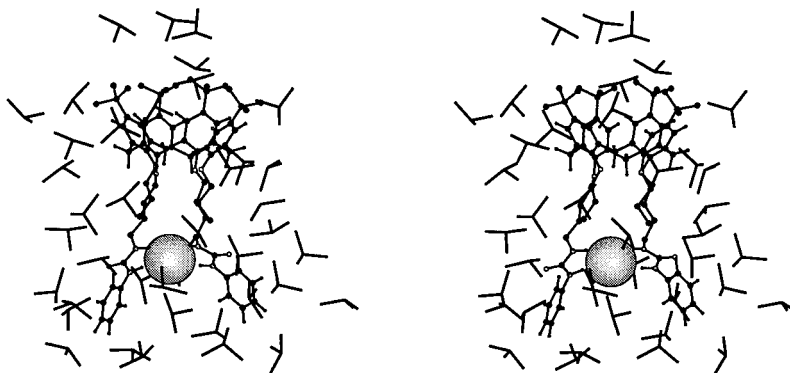


Figure 8. Stereoplot of the last configuration from a Monte Carlo simulation of the complex of the calixarene and chloride ion in chloroform. Only chloroform molecules with an atom within 4 Å of the complex are illustrated.

Table 5. Computed Free Energy Changes for the Halide Ions and Calixarene in Chloroform^a

	ΔG_F (kcal/mol)	ΔG_C (kcal/mol)	$\Delta\Delta G_b$ (calc) (kcal/mol)	$\Delta\Delta G_b$ (expt) (kcal/mol) ^b
I ⁻	6.52 ± 0.06	8.62 ± 0.08	2.10 ± 0.10	1.46
Br ⁻	1.50 ± 0.01	1.88 ± 0.01	0.33 ± 0.01	0.60
F ⁻	-16.07 ± 0.13	-26.44 ± 0.20	-10.37 ± 0.24	N/A

^a Statistical uncertainties are $\pm 1\sigma$ as obtained from the batch means procedure. ^b Reference 4.

are no geometrical restrictions provided by the calixarene framework that diminish the electrostatic interactions between the host and the ions.

Relative Free Energies of Binding in Chloroform. Structurally, the complexes in chloroform remained close to the gas-phase optimized geometries. This is not surprising in view of the limited flexibility of calix[4]arenes that form hydrogen bonds on one rim²⁴ and given the strength of the interactions with the anions (Table 4). The stereoplot in Figure 8 of the last MC configuration at the chloride end of one of the FEP calculations is illustrative. It also shows no penetration by chloroform molecules into the binding site or into the cone formed by the four benzene rings. There is one chloroform molecule positioned between the phenyl rings on the urea groups. Its carbon is 3.90 Å from the chloride ion, while no other chloroform carbon is closer than 5 Å from the ion.

The free energetic results of the perturbations of chloride to the other halides alone in chloroform and bound to the calixarene in chloroform are presented in Table 5 along with the experimental data. It can be seen that the solvation and thermal averaging greatly diminish the intrinsic gas-phase differences from Table 4. Thus, chloride ion is computed to have a more exoergic free energy of binding than bromide and iodide by 0.33 and 2.10 kcal/mol, respectively, while the interaction energy differences are 2.2 and 10.2 kcal/mol, respectively (Table 4). The computations do very well at quantitatively reproducing the experimental differences in free energies of binding: 0.60 kcal/mol for chloride to bromide and 1.46 kcal/mol for chloride to iodide.⁴ However, as expected from the gas-phase optimizations, the prediction is that the calixarene's affinity for fluoride ion in chloroform is much (10.4 ± 0.2 kcal/mol) greater than that for chloride ion.

The question, then, is why fluoride binding was not observed experimentally.⁴ It should immediately be noted that the calculations did not include the tetrabutylammonium counterion

of the halide salts from the experiments. So, one possibility is that tetrabutylammonium fluoride remains ion-paired in chloroform. Another possibility is that some water has been inadvertently introduced in the experiments either in the chloroform solvent or with the salts. Difficulties in obtaining anhydrous fluoride salts are known.²⁵ In fact, attempts to obtain anhydrous tetrabutylammonium fluoride typically lead to decomposition, including production of hydrated fluoride ion and bifluoride ion.^{25a} Naturally, the added water could compete with the host for binding the anions. This possibility was investigated through the additional FEP calculations, which were particularly aimed at attempting to establish how many water molecules would be needed to eliminate binding to the host.

Chloride ion was first perturbed to fluoride ion in the presence of one and two TIP4P water molecules in chloroform. The results of these simulations are presented in Table 6, along with a recapitulation of the uncomplexed chloride to fluoride results from Table 5. The ions remained bound to the water molecules throughout the MC simulations. The free energy changes for the chloride to fluoride perturbation are -26.4 kcal/mol when bound to the calixarene in chloroform, -22.4 kcal/mol when bound to one water molecule in chloroform, and -28.1 kcal/mol when bound to two water molecules in chloroform. Of course, these values are all more negative than that for the chloride to fluoride perturbation in anhydrous chloroform, -16.1 kcal/mol. The results state that the selectivity for binding fluoride ion over chloride ion is in the following order: two water molecules > the calixarene host > one water molecule. Though this does not guarantee that fluoride would prefer binding to two water molecules rather than to the host, the pattern suggests this and is not out of the range of the reference interaction energies in Table 4 and Figure 6.

Absolute Free Energies of Binding in Chloroform. However, the absolute preference was established in the subsequent FEP calculations in which fluoride ion was annihilated when bound to the calixarene and to one and two water molecules in chloroform. The computed free energy changes are 69.0 ± 0.3, 60.6 ± 0.4, and 70.4 ± 0.4 kcal/mol, respectively. Therefore, fluoride is predicted to bind more strongly to two water molecules than to the host by 1.4 ± 0.5 kcal/mol. Furthermore, annihilation of unrestrained fluoride ion alone in chloroform yielded a free energy change, $-\Delta G_{sol}$, of 45.4 ± 0.3 kcal/mol, and the correction for the harmonic restraint is 4.64 kcal/mol with 1 mol/L standard states.¹⁸ Combination via the thermodynamic cycle below

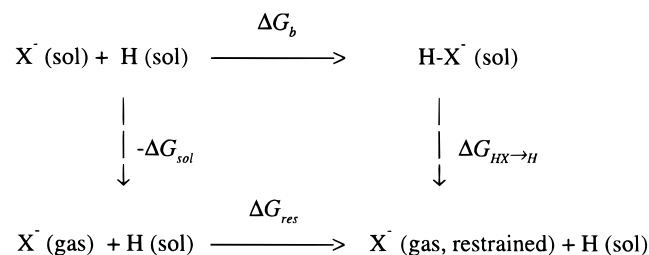
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Table 6. Computed Free Energy Changes for Perturbations of Chloride Ion to Fluoride Ion in Chloroform^a

	unbound (kcal/mol)	bound to host (kcal/mol)	with one H ₂ O (kcal/mol)	with two H ₂ O (kcal/mol)
ΔG	-16.07 ± 0.13	-26.44 ± 0.20	-22.37 ± 0.10	-28.10 ± 0.09
$\Delta\Delta G_b$		-10.37 ± 0.24	-6.30 ± 0.17	-12.03 ± 0.16

^a Statistical uncertainties are $\pm 1\sigma$ as obtained from the batch means procedure.



$$\Delta G_b = \Delta G_{\text{res}} - \Delta G_{\text{sol}} - \Delta G_{HX \rightarrow H}$$

then yields absolute free energies of binding, ΔG_b , for fluoride ion with the calixarene, one water molecule, and two water molecules in chloroform of -19.0 ± 0.4 , -10.6 ± 0.5 , and -20.4 ± 0.5 kcal/mol, respectively.²⁶

Consideration of the results from the Cl⁻ to F⁻ perturbations in Table 5 then provides a predicted ΔG_b of -8.6 ± 0.5 kcal/mol for chloride ion with the calixarene, while the experimental value is -5.3 ± 0.1 kcal/mol.⁴ It is suspected that the more attractive prediction stems about equally from (1) overestimation of the fluoride affinity owing to the neglect of specific polarization effects^{13a} and (2) incomplete sampling for the annihilations. At the completion of the MC simulations, the calixarene did not end up with an internal hydrogen bond between the urea groups, as expected from Figure 3 and the discussion above. If, however, the incipient ion were grown into such a starting structure, the free energetics would be less favorable than those obtained here. The annihilations are also subject to greater quantitative uncertainties owing to choices made in the selection of the restraints.^{18,27} The sampling is expected to be fully adequate for the annihilations in the presence of the one or two water molecules. Thus, the results firmly support the notion that complexation of fluoride ion by two water molecules would be enough to overcome complexation by the calixarene host. Of course, one could further consider possible binding of the hydrated ion by the host. However, the key point is that it would take little water to distort seriously the binding measurements.²⁸

It may also be noted that in the simulations with two water

molecules in chloroform, when the ion is removed, the two water molecules become hydrogen bonded. In addition, when a MC simulation is executed starting with the water dimer in a box with 265 chloroform molecules at 25 °C and 1 atm, the water molecules remain dimerized for a run of 1×10^7 configurations and the average water–water interaction energy is -4.5 kcal/mol versus -6.2 kcal/mol for the optimal TIP4P dimer. This behavior is consistent with the measured equilibrium constant, 4 M^{-1} , that has recently been reported for formation of the water dimer in chloroform.²⁹

Conclusions

The interactions between halide ions and the bis(phenylurea) *p*-*tert*-butylcalix[4]arene of Scheerder et al. have been characterized through gas-phase energy minimizations and Monte Carlo simulations in solution using OPLS potential functions. This necessitated potential function development, including that for iodide ion that may be used in further studies. Excellent agreement with experiment was obtained for the relative free energies of binding of chloride, bromide, and iodide ions with the calixarene in chloroform. The computations also indicate that the gas-phase optimized structures of the complexes are largely maintained in solution, though there is a ca. 20 kcal/mol reorganization penalty for the host to achieve the binding geometry. However, in contrast to the experimental results, the calculations found that fluoride ion should bind to the calixarene with by far the greatest affinity. The difficulty in obtaining anhydrous tetraalkylammonium fluoride salts was suggested as the source of the discrepancy. This notion was also pursued through additional FEP calculations with the conclusion that only two water molecules would be needed per fluoride ion to eliminate binding to the calixarene. The results emphasize the importance of environmental details in the outcome of binding measurements. The success of the MC/FEP calculations also further illustrates the utility of computational models, which employ explicit solvation, thermal averaging, and well-developed force fields, for the atomic-level characterization of host–guest chemistry.

Acknowledgment. Gratitude is expressed to the National Science Foundation and NATO for support of this work.

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(26) For comparison with experimental data for $-\Delta G_{\text{sol}}$, a Born correction of 11.0 kcal/mol is needed for an ion with a 12 Å radius (the cutoff) in a medium with a dielectric constant of 4.8 (chloroform). The same correction is needed for $\Delta G_{HX \rightarrow H}$, and the two Born corrections cancel in the cycle.

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