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Binding Free Energy and Extraction Selectivity Calculations of Anisole and Phenanthroline Spherands

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We report free energy perturbation (FEP) molecular dynamics (MD) simulations of the relative binding free energies of three spherands and alkali metal ions (Li^+, Na^+, K^+). The calculated free energies all favor Na^+ binding and are in reasonable agreement with experiment for two of the hosts but not the third. The third host, a mixed anisole−phenanthroline−spherand, was calculated to be significantly selective for binding Na^+ over K^+ and Li^+, whereas experiments suggest little or no selectivity between K^+, Na^+, and Li^+. Our attempts to improve the calculations by using different charge fitting schemes and by simulating the experimental conditions (addition of picrate$^-$ anion, simulations in chloroform) did not resolve the discrepancy. The fact that our simulations work in two cases but not the third (the third spherand contains subunits present in the two other spherands) suggests that there may be significant differences in the nature of the host−guest complexes in the third case.

Introduction

One of the distinctive features of alkali metal cation binding molecules such as spherands is their ion selectivity, which involves a competition between the ability of solvent and the ionophore to bind the ion. Almost always the intrinsic (negative) free energy of interaction of an ionophore follows the same order as the solvation free energy: for the alkali metal cations, $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$. However, the ion binding preference ($\Delta\Delta G_{bind}$) is determined by the difference between the relative free energy of interaction of the ion with the ionophore ($\Delta\Delta G_{interact}$) and the relative solvation free energy of the ion ($\Delta\Delta G_{solv}$). Thus, 18-crown-6 binds K^+ better than the smaller Na^+ and the larger Rb^+.

Given this tendency for significant ion selectivity, it is surprising that phenanthroline spherand **1** (see Figure 1) binds Li^+, Na^+, and K^+ with very nearly the same free energy of binding, with Na^+ binding only 0.1 kcal/mol less than Li^+ and K^+ binding 0.7 kcal/mol less.[1] In contrast, ionophores **2** and **3** have been found to have a Na^+ selectivity, with **2** preferring Na^+ over Li^+ by a very significant amount and **3** preferring Na^+ over Li^+ by a small amount and Na^+ over K^+ by a modest amount. To be able to reproduce the different selectivities of ionophores **1**−**3** is a challenge for free energy calculations. The calculations are able to reasonably reproduce the ion selectivity of **2** and **3**, but in contrast to experiment, **1** is calculated to bind Na^+ surprisingly more strongly than K^+ or Li^+.

We have considered different charge models, including counterions in the simulation and considered ion competition in chloroform rather than water in calculating the ion selectivity of **1** and none of these resolved the discrepancy between simulation and experiment.

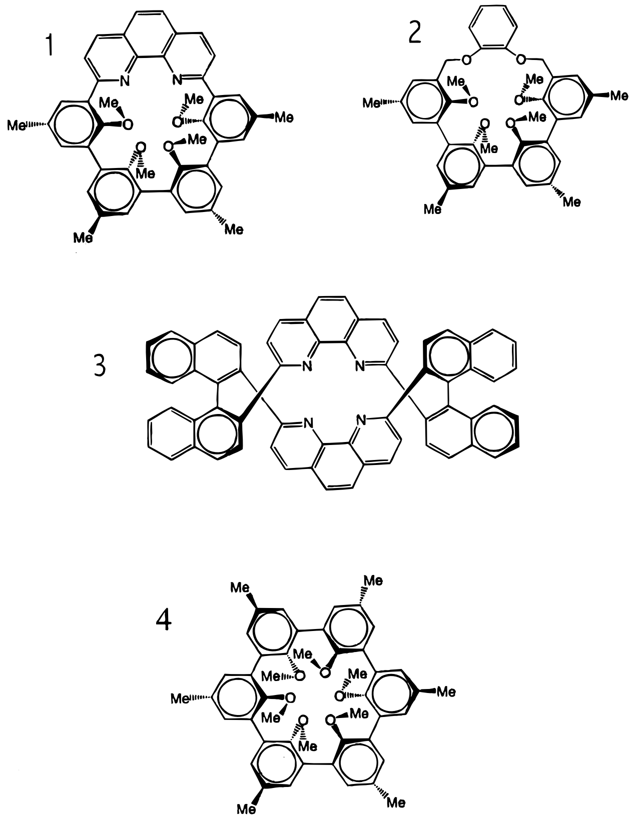

Figure 1. Chemical structures of spherands **1**−**4**.

Computer Simulation

All calculations were performed using the AMBER 4.1[2] package of programs. NPT periodic boundary conditions MD simulations were carried out in either a TIP3P water box or in a box of rigid chloroform.[3] The TIP3P water box conditions were the same as used in previous papers,[4,5] the cutoff was set

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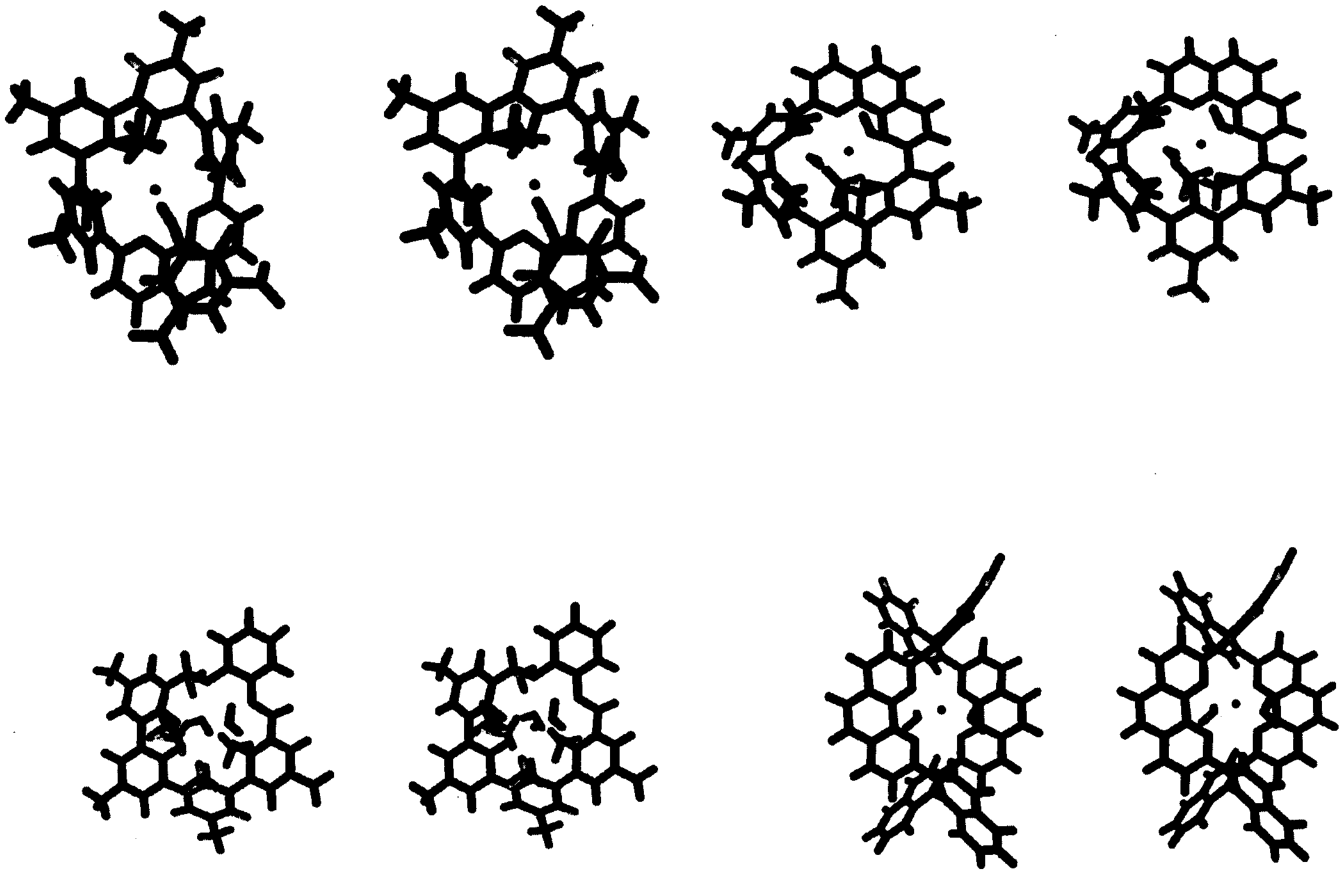

Figure 2. Stereopictures of host−guest complexes with nearest waters taken from simulations using Midas.[15] Coming from left to right, top to bottom: structure **1** with attached picrate$^-$ anion in chloroform, structure **1** in water, structure **2** in water, and structure **3** in water.

to 8 Å, and a time step of 1.5 fs was used. The size of the chloroform box was 30 × 30 × 30 Å^3, the pressure was 1 atm, and the temperature was 300 K, a 12 Å cutoff was used. The total length of the simulations in chloroform was 120 ps. All bonds were constrained using SHAKE, and the time step of 2 fs was used. The compressibility of the system was set to 108.6×10^{-6} bar^{-1} for chloroform, and a modified version of AMBER including cutoff correction[6] was used. After 20 ps of equilibration the FEP transformation started. The FEP calculation consisted of 50 windows and each window was 1000 steps long, 500 steps of equilibration and 500 steps of sampling. Simulations typically involved 630 molecules of chloroform. The water box typically contained about 1000 water molecules.

The AMBER "Parm94" force field[7] was used for most of the interactions involved. For the anisole units, additional force field parameters were taken from Sun et al.[4] For the calculations of picrate anion additional parameters (originally designed for nitrobenzene) were taken from Meng[8] and the torsional barrier for the nitro group rotation was fitted to reproduce the ab initio value obtained from MP2/6-31G* single point calculation of nitrobenzene with a parallel and perpendicular nitro group (6.1 kcal/mol). The other degrees of freedom were optimized with HF/6-31G*. Gaussian 94[9] was used for all ab initio calculations.

The host−guest interaction functions were given by van der Waals and electrostatic terms. Standard AMBER 12-6 van der Waals parameters[7] were used. A charge of $+1.0e^-$ was used for the guest atom. The atomic charges on all particles of the host subsystem were calculated using the common ESP[10] and RESP[11] procedures. The ESP + weight and RESP charges for anisole unit were taken from Sun et al.[4] RESP charges for naphthalene, phenanthroline, dimethoxybenzene, and picrate$^-$ anion were calculated at HF/6-31G* level.

A polarizable model for simulations in vacuo was also prepared. RESP and ESP charges scaled by a factor of 0.88 were used on the phenanthroline and anisole parts, respectively. The necessity of scaling the charges arises from the fact that ab initio Hartree−Fock calculations enhance molecular dipole moments. The scaling factor of around 0.9 has been suggested by Caldwell and Kollman.[12] No three-body exchange repulsion terms were used. The atomic polarizabilities were taken from the work of Applequist.[13] A polarizability of 1.003 Å^3 was used for the K$^+$ atom.

Moil-View[14] and Midas[15] were used for molecular display.

Results

Relative binding free energies of spherands (hosts H_i) and cations Li$^+$, Na$^+$, K$^+$ (guests G_i) were calculated in water and chloroform. In the present paper we report the binding free energies for spherand hosts **1**−**3** (see Figure 1), which were examined experimentally by Cram.[1,16] Stereopictures of the hosts and guests and nearest water molecules taken from the simulations are shown in Figure 2.

The host−guest binding free energies are commonly calculated using FEP in water. The experimental conditions,[1,17] are, however, quite complex and it is not clear whether for some of the hosts it would not be more accurate to use organic solvents or even water/organic interface calculations. In the experiment the host solvated in the organic solvent extracts the cation from the water/organic interface. The extraction selectivity is evaluated from the concentration of the cation in the organic phase without the host. The cation is present in the form of a picrate salt and the concentration measurements are based on picrate$^-$ anion absorption. Free energies are calculated from measured

SCHEME 1: Thermodynamic Cycle for Calculation of Host (H_i)−Guest (G_i) Binding Free Energies[a]

$$\begin{tikzcd}
G_1 + H_i \arrow[r, "\Delta G_{3,sol}"] \arrow[d, "\Delta G_{c1,sol}"'] & G_2 + H_i \arrow[d, "\Delta G_{c2,sol}"] \\
G_1\text{-}H_i \arrow[r, "\Delta G_{4,sol}"'] & G_2\text{-}H_i
\end{tikzcd}$$

[a] Subscript c stands for complexation; sol stands for solvent, i.e., water or chloroform.

SCHEME 2: Extraction Selectivity Calculation Thermodynamic Cycle[a]

$$\begin{tikzcd}
G_{1,wat} + H_{i,chl} \arrow[r, "\Delta G_{3,wat}"] \arrow[d, "\Delta G_{ex1}"'] & G_{2,wat} + H_{i,chl} \arrow[d, "\Delta G_{ex2}"] \\
(G_1\text{-}H_i)_{chl} \arrow[r, "\Delta G_{4,chl}"'] & (G_2\text{-}H_i)_{chl}
\end{tikzcd}$$

[a] Subscript wat stands for water, chl for chloroform, and exj for extraction of guest *i* from water to chloroform by host *i*.

concentrations. In this paper we have applied the common "water" methodology and then we have tried to improve our results for host **1** by using more complex solvent models. A similar approach was recently used by Varnek and Wipff[18] to calculate the relative binding free energies and extraction coefficients of a calix [4]-bis-crown-6 host. We used Varnek and Wipff's notation[18] of the calculated free energies in our paper. The thermodynamic cycle used is shown in Scheme 1. Experimentally measured binding free energies for guests **1** and **2** are labeled $\Delta G_{c\mathbf{1},sol}$ and $\Delta G_{c\mathbf{2},sol}$, respectively. The relative binding free energies were calculated as $\Delta G_{\mathbf{4},sol}$ - $\Delta G_{\mathbf{3},sol}$.

$$\Delta\Delta G_{c,sol} = \Delta G_{c\mathbf{2},sol} - \Delta G_{c\mathbf{1},sol} = \Delta G_{\mathbf{4},sol} - \Delta G_{\mathbf{3},sol} \quad (1)$$

Similar cycles were used to calculate the extraction selectivity $\Delta\Delta G_{ex} = \Delta G_{ex\mathbf{2}} - \Delta G_{ex\mathbf{1}} = \Delta G_{\mathbf{4},chl} - \Delta G_{\mathbf{3},wat}$ of guest **2** relative to guest **1** by host H from water to chloroform (Scheme 2). In this case we assume the possibility that in experiment the host may stay in the organic phase, while the cation stays in water and may eventually penetrate through the interface to the organic phase and complex with the host. This process may happen with or without the counterion, which is in this case the anion picrate$^-$. It is still unclear whether the host takes some water into the organic phase, how the cation penetrates the interface (possibly with the help of the organic counterion), etc. These questions are not the main subject of this paper and were to some extent addressed by Varnek and Wippf[18] using simulations on the actual interface. In the case of the host calix [4]-bis-crown-6 they found that the host stays close to the interface during the simulation. They also showed that the most relevant (with respect to the experimental numbers) free energies calculated are the relative free energy of complexation in water $\Delta\Delta G_{c,wat}$ and the extraction selectivity $\Delta\Delta G_{ex}$. These findings may, however, depend on the character of the host. In the case of host **3** the same behavior was observed. For hosts with a covered cavity (e.g., **1**) the $\Delta\Delta G_{c,wat}$ and $\Delta\Delta G_{ex}$ are close to each other. The least relevant is the complexation free energy in chloroform $\Delta\Delta G_{c,chl}$. This is probably because the calculated solvation free energy differences of ions in chloroform ($\Delta G_{\mathbf{3},chl}$) are not relevant to the actual extraction process, even in the presence of picrate$^-$ anion. In reality, the cations are almost certainly interacting with some waters even in the organic phase. Therefore, $\Delta G_{\mathbf{3},chl}$ may be better represented by $\Delta G_{\mathbf{3},wat}$. (Note that Varnek and Wipff[18] used opposite signs ($-\Delta\Delta G_{c,sol}$, $-\Delta\Delta G_{ex}$) to those used here.)

TABLE 1: $\Delta G_{\mathbf{3},sol}$ and Calculated Errors (kcal/mol) in Water and Chloroform

ions (G_i)	$\Delta G_{\mathbf{3},wat}$	δ[a]	$\Delta G_{\mathbf{3},chl}$	δ[a]	exptl$_{wat}$[b]
$Na^+ \rightarrow K^+$	17.15	0.05	4.52	0.13	17.6
$Na^+ \rightarrow Li^+$	−25.33	0.11	−5.30	0.21	−23.9
PIC[c] $Na^+ \rightarrow K^+$	17.88	0.14	11.33	0.31	17.6
PIC[c] $Na^+ \rightarrow Li^+$	−25.77	0.27	−16.79	0.34	−23.9

[a] Standard deviation. [b] Reference 19. [c] Simulations performed in the presence of picrate$^-$.

TABLE 2: Average Distances (Å) of the Guests from the Nearest Host Nitrogen and Oxygen Atoms

	host			
	1[a]		**2**	**3**
atom	N	O	O	N
Li^+	2.2	2.1	2.1	2.3
Na^+	2.6	2.4	2.4	2.4
K^+	2.7	2.6	2.7	2.7

[a] ESP + weight charges on anisole units, RESP charges on phenanthroline, no picrate$^-$ present.

The calculated FEP results for $\Delta G_{\mathbf{3},wat}$ and $\Delta G_{\mathbf{3},chl}$ with or without picrate$^-$ counterion and respective experimental solvation free energies[19] are shown in Table 1. Double-wide sampling in both directions was used. The free energy was estimated as an average of all the four numbers and the error of the method δ was calculated as the standard deviation. The highest error was encountered in the case of chloroform simulations in the presence of the picrate$^-$. It is caused by slower convergence of the chloroform simulations and by the nonrigidity and mobility of the picrate$^-$−cation$^+$ complexes. Average distances of the guests from the nearest host oxygen and nitrogen atoms are shown in Table 2.

Calculated free energies, $\Delta G_{\mathbf{4},wat}$ and $\Delta G_{\mathbf{4},chl}$, and relative free energies, $\Delta\Delta G_{c,wat}$ and $\Delta\Delta G_{c,chl}$, and $\Delta\Delta G_{ex}$, are presented in Table 3. Free energies for host **4** were calculated by Sun et al.[4] and are shown for illustration only. The simulations with picrate$^-$ in chloroform were again the least accurate. High error was also observed in the case of host **3**, because of its flexibility.

Discussion

The structure originally investigated (**1**) is a hybrid between hosts **3** and **2**. After finding out that there is a considerable difference between the experimental numbers and our calculations, we tried to find the reason for this difference. To elucidate possible errors, we calculated the relative binding free energies for spherands **2** and **3**. The data for **4** were already available.[4] For structures **2**−**4** the calculated relative free energies are in reasonable agreement with experiment. In this light it is especially surprising that we were not able to reproduce the experimental data for spherand **1**, because we succeeded in calculation of the relative binding free energies of spherands **2**−**4**.

It is not surprising that structure **3** is not highly selective, because it is more flexible than the other structures. It is also open so that the solvent molecules can approach the cation and interact with it. Since the nature of chloroform cation interaction

TABLE 3: Calculated $\Delta G_{4,\mathrm{sol}}$, Complexation Free Energies $\Delta\Delta G_{\mathrm{c,sol}}$, and Extraction Selectivities $\Delta\Delta G_{\mathrm{ex}}$ and Their Standard Deviations δ

H_i[a]	charge model[b]	O/N[c]	guests (G_i)	$\Delta G_{\mathbf{4},\mathrm{wat}}$ δ	$\Delta G_{\mathbf{4},\mathrm{chl}}$ δ	$\Delta\Delta G_{\mathrm{c,wat}}$ δ	$\Delta\Delta G_{\mathrm{c,chl}}$ δ	$\Delta\Delta G_{\mathrm{ex}}$ δ	exp[d]
4[e]	ESP[f]	−0.497	$Na^+ \rightarrow K^+$			17.6			>13.2
		−				0.15			
			$Na^+ \rightarrow Li^+$			−2.7			<−3.8
						0.22			
1	ESP	−0.497	$Na^+ \rightarrow K^+$	24.31	26.73	7.16	22.21	9.58	0.7
	RESP[g]	−0.548		0.34	0.26	0.39	0.39	0.31	
			$Na^+ \rightarrow Li^+$	−19.73	−17.17	5.60	11.87	8.16	−0.1
				0.10	0.22	0.21	0.43	0.33	
1	RESP	−0.440	$Na^+ \rightarrow K^+$	25.08		7.93			0.7
		−0.548		0.25		0.40			
			$Na^+ \rightarrow Li^+$	−19.57		5.76			−0.1
				0.14		0.25			
1	RESP[h]	−0.440	$Na^+ \rightarrow K^+$	23.43		6.28			0.7
	scaled	−0.329		0.71		0.76			
			$Na^+ \rightarrow Li^+$	−19.45		5.88			−0.1
				0.01		0.12			
1	ESP	−0.497	$Na^+ \rightarrow K^+$	25.06		7.91			0.7
		−0.715		0.42		0.53			
			$Na^+ \rightarrow Li^+$	−20.22		5.11			−0.1
				0.12		0.23			
1 PIC[i]	ESP	−0.497	$Na^+ \rightarrow K^+$		25.40		14.07	7.52	0.7
	RESP[g]	−0.548			1.65		1.96	1.79	
			$Na^+ \rightarrow Li^+$		−19.66		−2.87	6.11	−0.1
					0.24		0.58	0.51	
1 PIC WAT[j]	ESP	−0.497	$Na^+ \rightarrow K^+$		24.51			6.63	0.7
	RESP[g]	−0.548			1.10			1.24	
			$Na^+ \rightarrow Li^+$		−19.19			6.58	−0.1
					0.10			0.37	
2	ESP	−0.497	$Na^+ \rightarrow K^+$	22.74		4.59			2.1
	RESP[g]	−		0.88		0.93			
		−0.329[k]							
			$Na^+ \rightarrow Li^+$	−19.08		6.25			6.0
				0.29		0.40			
3	RESP	−	$Na^+ \rightarrow K^+$	18.98	15.40	1.83	10.88	−1.75	1.1
		−0.548		1.30	0.16	1.35	0.29	0.21	
			$Na^+ \rightarrow Li^+$	−24.70	−17.13	0.63	−11.83	8.20	0.1
				0.05	0.31	0.16	0.52	0.42	

[a] See the text and Figure 1 for explanation of host numbers. [b] Charge model used for anisole units and for other parts of the molecule. Default charge model is ESP + weight taken from Sun et al.[4] on all anisole units and RESP on dimethoxybenzene, naphthalene, and phenanthroline units. [c] Charge on anisole oxygen and phenanthroline nitrogens. [d] Experimental binding free energies from Cram et al.[1,16] [e] Results of Sun et al.[4] [f] ESP + weight charges of Sun et al.[4] [g] ESP + weight charges on anisole units, RESP charges on phenanthroline. [h] RESP charges on anisole units and scaled RESP charges on phenanthroline (see text). [i] Picrate$^-$ counterion included. [j] Picrate$^-$ counterion and water molecule included. [k] Charge on dimethoxybenzene oxygens.

is quite different from the water−cation interaction, the free energies $\Delta G_{i,\mathrm{sol}}$ ($i = \mathbf{3}, \mathbf{4}$) are solvent dependent. This fact results in a difference between $\Delta\Delta G_{\mathrm{c,wat}}$ and $\Delta\Delta G_{\mathrm{ex}}$.

On the contrary, in the case of structure **1** the cation is almost covered by the methoxy groups. Solvent molecules cannot get too close to the cation. Even though the phenanthroline part of the cavity is more open than the anisole part, we know from the trajectory analysis that the solvent cannot get too close to the cation. The phenanthroline nitrogens are sufficiently repulsive for water oxygens to avoid cation water interaction. Therefore, it seems not surprising that $\Delta G_{\mathbf{4},\mathrm{org}} \approx \Delta G_{\mathbf{4},\mathrm{wat}}$ and $\Delta\Delta G_{\mathrm{ex}}$ and $\Delta\Delta G_{\mathrm{c,wat}}$ do not differ significantly for molecule **1**. On the basis of these findings we assume that no other solvent or interface model can change our data. Also the introduction of the picrate anion into the simulation did not change the numbers. The picrate anion is located parallel to the phenanthroline unit (see Figure 2). The cation−picrate interaction does not affect the calculated free energies significantly. The cations stick at the phenanthroline part of the cavity because the nitrogens are more negatively charged than the oxygens. Several different charge models were examined for host **1**. Surprisingly, the calculated free energies were almost independent of the charges. A strong dependence on charges was, however, observed for host **4** by Sun et al.[4] In the case of host **1** the cation stays close to the phenanthroline nitrogens in all RESP and ESP models. We also tried to move the cation toward the oxygens by decreasing the nitrogen charges. In our scaled charges model (row 4 of Table 3) we used RESP charges on both the anisole and phenanthroline units, but the charges on phenanthroline were scaled by 0.6. None of the charge models examined (row 2−5 of Table 3) led to any significant improvement. Further, our multiple attempts to put a water molecule into the cavity together with the cation were not successful. We restrained one water molecule to stay in the cavity. The system was then subjected to a 40 ps long equilibration. After the restraint was released, either the water or the cation moved out of the cavity. We also tried to make spherand **1** more flexible by decreasing the torsional barriers between the anisole units. We hoped this might have enabled a solvent molecule to fit into the cavity. Still, we did not get any closer to the experimental free energy. Another possible explanation of the measured free energies is a different conformation of **1**. Table 4 shows calculated $\Delta\Delta G_{\mathrm{c,wat}}$ for different conformers of **1**. UDUD (U and D denotes the up and down conformation of the anisole units) is expected to be the most stable conformer and thus has been used up to now. Conformers UDDU and UUDD

TABLE 4: Calculated $\Delta G_{4,\mathrm{wat}}$, Complexation Free Energies $\Delta\Delta G_{\mathrm{c,wat}}$, and Standard Deviations δ for Different Conformers of 1

conformation[a]	E(AMBER),[b] kcal/mol	guests (G_i)	$\Delta G_{4,\mathrm{wat}}$ δ	$\Delta\Delta G_{\mathrm{c,wat}}$ δ	exp[c]
UDUD	0.0	$Na^+ \rightarrow K^+$	24.31	7.16	0.7
			0.34	0.39	
		$Na^+ \rightarrow Li^+$	−19.73	5.60	−0.1
			0.10	0.21	
UDDU	10.4	$Na^+ \rightarrow K^+$	20.02	2.87	0.7
			0.09	0.14	
		$Na^+ \rightarrow Li^+$	−19.62	5.71	−0.1
			0.04	0.15	
UUDD	21.4	$Na^+ \rightarrow K^+$	19.70	2.55	0.7
			0.23	0.28	
		$Na^+ \rightarrow Li^+$	−23.55	1.78	−0.1
			1.00	1.11	

[a] Conformation of the anisole units of spherand 1 described in terms of anisole orientation relative to phenanthroline. U stands for up, D stands for down. UDUD means the most stable up−down−up−down conformation. This conformer was used for all calculations reported in Table 3. [b] AMBER energy in vacuo after equilibration and minimization relative to conformer UDUD. In all cases ESP + weight charges were used on anisole units and RESP charges of Sun et al.[4] were used on the phenanthroline unit. [c] Experimental binding free energies from Cram et al.[1,16]

TABLE 5: Absolute Free Energy of Binding for Host 1−Li$^+$ Complex in Water

simulation	ΔG, kcal/mol	δ,[a] kcal/mol
$Li^+ \rightarrow 0$ in water	109.8	0.7
$Li^+ \rightarrow 0$ in host	114.1	0.9

[a] Standard deviation.

are local minima in vacuo. Calculated free energies using the UUDD structure are closer to experiment than those found using UDUD. But, on the basis of the molecular mechanical model we have used, the UDDU and UUDD isomers are less favorable than UDUD by 10 and 20 kcal/mol, respectively, in vacuo. Although we do not know their relative stability in water, they are not likely to be stable. Also, spontaneous racemization of all the spherands but the one substituted with *n*-butoxy groups was reported by Cram.[1] The structure of **1** was only studied experimentally by ^{1}H NMR spectra,[1] indicating C_2 symmetry and the UDUD conformation.

We have calculated the absolute free energy of **1** binding Li$^+$ using the double annihilation free energy method[20] (cf. Table 5). A cutoff of 8 Å was used with no Born correction to the absolute free energy, as it would cancel in this simple case. In the first simulation we disappeared (annihilated) the guest (Li$^+$) bound to the host **1** and calculated the free energy of bringing Li$^+$ to the host from vacuum ($\Delta G_{\mathrm{bound}}$). Then we did the same for Li$^+$ solvated in water (ΔG_{solv}). The absolute free energy of binding is then $\Delta G_{\mathrm{bind}} = \Delta G_{\mathrm{bound}} - \Delta G_{\mathrm{solv}}$. The calculated free energy $\Delta G_{\mathrm{bind}} = 4.3 \pm 1.0$ kcal/mol is not in very good agreement with the experimental 15.8 kcal/mol. Using the relative binding free energy of Li$^+$ and Na$^+$ of 5.6 kcal/mol, the absolute binding free energy of Na$^+$ is $4.3 + 5.6 = 9.9$ kcal/mol, compared to 15.7 kcal/mol measured.

To approximately estimate the role of polarization energy for host **1**, energy minimizations in vacuo were also performed and interaction energies were calculated. Three models additive, nonadditive (polarizable) with original charges, and nonadditive with charges scaled by a factor of 0.88 were taken into account. The resulting interaction energies are presented in Table 6. The inclusion of polarization energy (without charge scaling) stabilizes the host **1**−Li$^+$ complex by 4.9 kcal/mol relative to the Na$^+$ complex, compared to the additive model. There is a slight increase of 1.3 kcal/mol in the stability of the Na$^+$ relative to the K$^+$ complex, compared to the additive model. The polarization energy contribution can thus help to explain part of the discrepancy between our simulation and the experiment. With polarization, the free energy difference $\Delta\Delta G_{\mathrm{c,wat}}$ for the $Na^+ \rightarrow Li^+$ perturbation is expected to move from 5.6 to 0.7 kcal/mol, getting closer to the experimental result of −0.1 kcal/mol, but the free energy difference for the $Na^+ \rightarrow K^+$ perturbation would move from 7.2 to 8.5 kcal/mol, moving it further from the experimental result.

TABLE 6: Additive and Nonadditive Interaction Energies for Host 1 in Vacuo

alkali metal ion	E(AMBER),[a] kcal/mol	E(AMBER),[b] kcal/mol	E(AMBER),[c] kcal/mol
no ion[d]	−14.0	−34.5	−9.8
Li^{+} [e]	−112.5	−121.3	−109.5
Na^{+} [e]	−95.2	−99.1	−88.4
K^{+} [e]	−68.1	−70.7	−61.1

[a] Additive force field. [b] Nonadditive force field with same charges as footnote *a*. [c] Nonadditive force field with charges scaled by 0.88. [d] Total AMBER energy of host **1** without any ion. [e] Interaction energy calculated as total AMBER energy of the complex − total AMBER energy of the bare host (first row of the table).

Host **2** seems to be the most similar to structure to **1**. Indeed, it selectively binds sodium with roughly the same calculated free energies as **1**. The cavity of structure **2** is of about the same size as that of molecule **1**, and the −O− bonds make it more flexible. The cation sticks more to the anisole part of the cavity than to the dimethoxybenzene part. This explains the small difference in the calculated free energies for **1** and **2**. Surprisingly, the experimental data are in qualitative agreement with our calculations for spherand **2**.

Considering these findings, it seems unlikely that any reasonable charge model can change the calculated free energies for host **1** enough to reproduce the experiment. The simulations used worked well for all the other hosts. It opens a possibility that there may be something else involved in the binding free energy measurement of host **1**.

Another result of our simulations is the finding that the calculation of $\Delta\Delta G_{\mathrm{c,wat}}$ is more appropriate than $\Delta\Delta G_{\mathrm{c,chl}}$ or $\Delta\Delta G_{\mathrm{ex}}$, even though $\Delta\Delta G_{\mathrm{ex}}$ may seem closer to the experimental conditions, suggesting that the guest actually grabs some water to the organic phase or the process is happening on the interface. This is in agreement with the findings of Varnek and Wipff.[18] This result is, however, host dependent. For host **1** there is not much difference between $\Delta\Delta G_{\mathrm{c,wat}}$ and $\Delta\Delta G_{\mathrm{ex}}$, while there is considerable difference for host **3**.

Conclusions

Our conclusions are as follows: (i) Relative free energies of binding calculated in water are in better agreement with experiment than those calculated in chloroform and even extraction selectivities $\Delta\Delta G_{\mathrm{ex}}$ for the hosts investigated. (ii) The relative free energies of binding calculated in water, $\Delta\Delta G_{\mathrm{c,wat}}$, are in qualitative agreement with experimental results for all hosts except **1**. (iii) The discrepancy between the experiment and our simulation for host **1** could partly be ascribed to the polarization term.

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