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Alkali Cation Extraction by 18-Crown-6 and Its Derivatives: A Free Energy Perturbation Study

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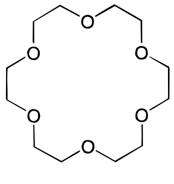
Abstract: Alkali cation extraction by 18-crown-6 derivatives (Li, G.; Still, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 3804−3805) has been studied by means of free energy perturbation (FEP) methods. The FEP simulations of the cation extraction in homogeneous solutions such as in aqueous solution or in chloroform did not yield consistent results with the corresponding experimental data. Thus, a mixed solvent system is proposed to play an important role in determining the extraction properties of the ionophores in the study. The FEP simulations in such a model system suggest that the cation extraction process occurs in organic solvent mixed with water molecules. The involvement of water in the process is determined by two factors: (1) the ability of an ionophore to form a hydrogen bond with water near its binding pocket and (2) the conformational rigidity of the host. Our calculations suggest that remote substitution can enhance the extraction property of a conformational rigid ionophore by attracting water near its binding core via a hydrogen bond network.

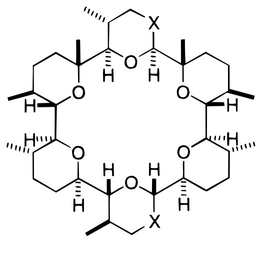
I. Introduction

The chemistry of host−guest complexes has become one of the most active fields of science.[1−4] Its direct application is in the design of chemical sensors and molecular switches. Since host−guest interactions are essentially noncovalent in nature, and their sizes are relatively smaller than many biological systems, host−guest systems serve as good models for theoretical study. One can use such systems to test and validate force field models, to understand host−guest interaction at the molecular level and, furthermore, to carry on rational design of host molecules.

Many computer simulation methods have been applied to study host−guest complexes, in particular, to understand and to predict binding selectivity of a host for different guests. Among them are linear free energy correlation methods,[5] quantum mechanical calculations,[6,7] molecular dynamics (MD), and Monte Carlo (MC) simulations. Since the host−guest complexation process occurs in liquid solution, MD and MC simulations with explicit solvent models are popular approaches in this respect. Molecular dynamics (MD) including free energy perturbation (FEP) methods have been carried out on alkali cation complexes of crown ethers,[8,9] cryptands,[10] cavitands,[11,12] and calixarenes.[13−15] Most of the MD and FEP studies discussed host−guest complexation in pure homogeneous solvents such as in water, methanol, or chloroform. Recently, Varnek and Wipff addressed extraction selectivity of alkali cation by calix-4-bis-crown-6 in pure water and chloroform and at a water/chloroform interface.[16] On the basis of molecular dynamics simulations, they observed that the host−guest complexes were "adsorbed" at the water/chloroform interface like surfactants, instead of diffusing spontaneously to the organic phase. This study indicated that a heterogeneous environment, i.e., mixed solvent, may play a role in determining extraction selectivity of hosts.



18C6



1 (X=O) **2** (X=S)

The object of this paper is to study cation extraction selectivity of Li and Still's 18-crown-6 derivatives by means of free energy perturbation methods. In 1993, Li and Still reported the synthesis of new derivatives of 18-crown-6,[17] denoted as **1** and **2**. The derivatives have 18-crown-6 (18C6) as this core in approximate D_{3d} symmetry. The six exocyclic rings are

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(1) Cram, D. J. *Science* **1988**, *240*, 760−767.

(2) Cram, D. *Angew. Chem. Eng. Ed.* **1986**, *25*, 1039−1134.

(3) Diamond, D.; McKervey, M. A. *Chem. Soc. Rev.* **1996**, *25*, 15−24.

(4) Diederich, F. *Angew. Chem. Eng. Ed.* **1987**, *27*, 89−112.

(5) Schneider, H.-J. *Chem. Soc. Rev.* **1994**, *23*, 227−234.

(6) Glendening, E. D.; Feller, D.; Thompson, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 10657−10669.

(7) Feller, D.; Apra, E.; Nichols, J. A.; Bernholdt, D. E. *J. Chem. Phys.* **1996**, *105*, 1940−1950.

(8) Eerden, J. v.; Harkema, S.; Feil, D. *J. Phys. Chem.* **1988**, *92*, 5076.

(9) Dang, L.; Kollman, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 5716−5720.

(10) Auffinger, P.; Wipff, G. *J. Am. Chem. Soc.* **1991**, *113*, 5976−5988.

(11) Thomas, B. E.; Kollman, P. A. *J. Am. Chem. Soc.* **1994**, *116*, 3449−3452.

(12) Bayly, C. I.; Kollman, P. A. *J. Am. Chem. Soc.* **1994**, *116*, 697−703.

(13) Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; Hummel, G. J. v.; Ugozoli, F.; Andreetti, G. *J. Am. Chem. Soc.* **1990**, *112*, 4165.

(14) Miyamoto, S.; Kollman, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 3668−3674.

(15) Guilbaud, P.; Varnek, A.; Wipff, G. *J. Am. Chem. Soc.* **1993**, *115*, 8298.

(16) Varnek, A.; Wipff, G. *J. Comp. Chem.* **1996**, *17*, 1520−1531.

(17) Li, G.; Still, C. *J. Am. Chem. Soc.* **1993**, *115*, 3805.

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Table 1. Alkali Metal Picrate Binding Energy (kcal/mol) by 18-Crown-6 and Its Derivatives[17]

host	$\Delta G(\mathrm{Na}^+)$	$\Delta G(\mathrm{K}^+)$	$\Delta\Delta G = \Delta G(\mathrm{K}^+) - \Delta G(\mathrm{Na}^+)$
18-crown-6	−8.7	−11.4	−2.7
1	−12.7	−11.9	+0.8
2	−10.2	−10.9	−0.7

constrained to take chair conformations by the external methyl substitution. Two of these rings contain a heteroatom, X (=O or S), peripheral to the core. Although the sizes and shapes of their binding cores are similar to that of 18C6, the derivatives exhibit distinct cation binding patterns. Standard picrate extraction experiment reveals that **1** binds Na^+ tighter than K^+ by 0.8 kcal/mol as listed in Table 1, whereas **2** favors K^+ over Na^+ by about 0.7 kcal/mol and shares the same binding pattern as 18C6, which binds K^+ tighter than Na^+ by 2.7 kcal/mol.[17] The different binding patterns cannot be simply rationalized by empirical rules such as sizes or rigidity of the binding cores. A detailed computer simulation is needed to interpret the experimental data.

From a computer simulation point of view, this series of compounds is also an ideal system for theoretical study. Their rigid conformations allow us to concentrate only on the quality of the force fields and hypotheses related to the extraction process, rather than on conformational sampling that is often a main source of errors in computer simulations. The relative small size of the system enables us to apply high-level ab initio quantum mechanical calculation to assess the force fields used in MD and FEP simulations.

The rest of the paper is organized as following. After introducing theoretical methods and computational details used in this work, we explore the effect of force field on cation complexation with 18C6 and its derivatives. We then validate our force field based on ab initio quantum mechanical calculations and establish that an additive AMBER force field is adequate to describe the complexation processes of interest. Following a discussion of calculated relative binding free energies of the systems in homogeneous solvents including pure water and pure chloroform, we discuss the calculated extraction free energies and investigate the effect of mixed solvent on the extraction processes. Finally, we propose a mixed solvent model to interpret the experimental results.

II. Methods and Computational Details

All simulations presented in this paper were carried out with the molecular simulation package Amber4.1.[18] The pairwise potential energy function of the Amber force field has the form

$$U_{\mathrm{pair}} = \sum_{\mathrm{bonds}} k_r (r - r_{\mathrm{eq}})^2 + \sum_{\substack{\mathrm{bond}\\ \mathrm{angles}}} k_\theta (\theta - \theta_{\mathrm{eq}})^2 + \sum_{\mathrm{torsions}} \frac{V_n}{2}[1 + \cos(n\varphi - \varphi_0)] + \sum_{i<j} \epsilon_{ij}\left[\left(\frac{R_{ij}^*}{r_{ij}}\right)^{12} - \left(\frac{R_{ij}^*}{r_{ij}}\right)^{6}\right] + \sum_{i<j} \frac{q_i q_j}{r_{ij}} \quad (1)$$

where k_r, $k\theta$, V_n, and φ_0 are empirical parameters relating to bond, bond angle, and torsion angle, ϵ_{ij} and R_{ij}^* are van der Waals parameters, and q_i are atomic charges. The atomic charges (q_i) used in this work were derived from the electrostatic potentials calculated at the HF/6-31G* level with AM1 optimized geometry.

Scheme 1. General Thermodynamic Cycle for Cation Binding by Ionophore

$$\begin{tikzcd}
\mathrm{H} + \mathrm{M}_1^+ \arrow[r, "\Delta G_1"] \arrow[d, "\Delta G_3"'] & \mathrm{H}\bullet\mathrm{M}_1^+ \arrow[d, "\Delta G_4"] \\
\mathrm{H} + \mathrm{M}_2^+ \arrow[r, "\Delta G_2"] & \mathrm{H}\bullet\mathrm{M}_2^+
\end{tikzcd}$$

For a nonadditive force field, the potential energy function is of the form

$$E_{\mathrm{tot}} = U_{\mathrm{pair}} + U_{\mathrm{pol}} + U_{3-\mathrm{body}} \quad (2)$$

where U_{pair} is the pairwise potential energy function having the same format as eq 1. The polarization energy function is

$$U_{\mathrm{pol}} = -\frac{1}{2}\sum_i \vec{\mu}_i \cdot \vec{E}_i^0 \quad (3)$$

with

$$\vec{\mu}_i = \alpha_i \vec{E}_i, \quad \vec{E}_i = \vec{E}_i^0 + \sum_{j\neq i\mathrm{bu>}} T_{ij}\vec{\mu}_i, \quad \vec{E}_i^0 = \sum_{j\neq i} \frac{q}{r_{ij}^2}\vec{r}_{ij} \quad (4)$$

and

$$T_{ij} = \frac{1}{r_{ij}^3}\left(\frac{3\vec{r}_{ij} \otimes \vec{r}_{ij}}{r_{ij}^2} - 1\right) \quad (5)$$

where α_i is the polarizability of atom i, $\vec{r}_{ij}$ is the distance vector between atom pairs i and j, q_i are atomic charges and $\otimes$ is tensor product. The three-body exchange repulsion energy is

$$U_{3-\mathrm{body}} = A \exp(-\beta r_{12}) \exp(-\beta r_{13}) \exp(-\beta r_{23}) \quad (6)$$

where A is a prefactor and β is an empirical parameter.

The free energy change between states A and B was estimated by means of the free energy perturbation method. By defining λ as a coupling parameter to link states A and B, such that $H(\lambda{=}0) = H(\mathrm{A})$ and $H(\lambda{=}1) = H(\mathrm{B})$, where $H(\mathrm{A})$ and $H(\mathrm{B})$ are the Hamiltonian of states A and B, respectively, the free energy difference between the intermediate states λ and $\lambda+\Delta\lambda$ is

$$\Delta G_\lambda = -RT \ln \left\langle \exp\left(-\frac{H(\lambda + \Delta\lambda) - H(\lambda)}{RT}\right)\right\rangle_\lambda \quad (7)$$

where R is the gas constant, T is absolute temperature, and $\langle\,\rangle_\lambda$ is denoted as the ensemble average at the intermediate state λ. The total free energy change from state A to B is thus,

$$\Delta G = \sum_{\lambda=0}^{1} \Delta G_\lambda \quad (8)$$

Using the thermodynamic cycle as shown in Scheme 1, the relative binding free energy of a host (H) with metal cations M_1^+ and M_2^+ can be defined as:

$$\Delta\Delta G = \Delta G_2 - \Delta G_1 = \Delta G_4 - \Delta G_3 \quad (9)$$

where ΔG_1 and ΔG_2 are absolute free energies for binding M_1^+ and M_2^+ by the host. ΔG_1 and ΔG_2 can be obtained from experimental measurements. ΔG_3 and ΔG_4 are free energy changes for cation solvation and host−cation complexation, respectively. These two components can be calculated by means of the free energy perturbation method. One often uses the calculated $\Delta G_4 - \Delta G_3$ values to compare with the experimentally observed $\Delta G_2 - \Delta G_1$ values to validate a theoretical model, or to predict relative binding free energies of a set of host−guest complexes if their experimental data are not available.

All FEP simulations in this work were carried out in the NPT ensemble at 300 K and 1 atm. The explicit solvent models including

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(18) Pearlman, D. A.; Case, D. A.; Caldwell, J. W.; Ross, W. S.; Cheatham, T. E., III; Ferguson, D. M.; Seibel, G. L.; Singh, U. C.; Weiner, P.; Kollman, P. A. Amber 4.1; University of California, San Francisco, 1995.

Table 2. Force Field Parameters for Chloroform[20][a]

bonds	k_b (kcal mol^{-1} Å^{-2})	r_0 (Å)
C−Cl	232.4	1.758
C−H[b]	340.0	1.100
angles	**k_θ (kcal mol^{-1} rad^{-2})**	**θ_0 (deg)**
Cl-C−Cl	77.7	111.3
Cl-C−H	38.1	107.7
nonbonded parameters	**R^* (Å)**	**ϵ (kcal mol^{-1})**
Cl	1.9480	0.2650
C[b]	1.9080	0.1094
H[b]	1.1870	0.0157
atomic charges[c]		
C	**Cl**	**H**
−0.278	0.010	0.248

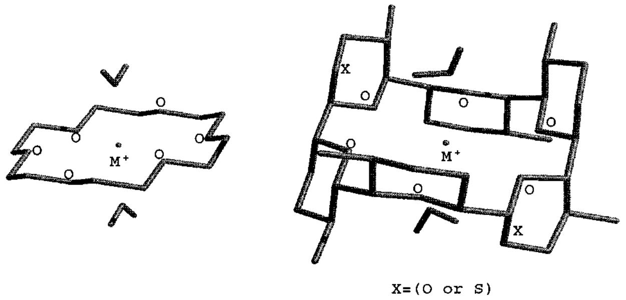
[a] C: sp^3 carbon, Cl: chlorine and H: hydrogen. The atom type is CT for carbon and H3 for hydrogen. [b] The nonbonded parameters for carbon and hydrogen are from the AMBER4.1 force field. [c] Based on RESP atomic charges.

TIP3P water[19] and flexible chloroform were used. The flexible chloroform model was based on Fox and Kollman's work.[20] The force field parameters and atomic charges of the chloroform model are listed in Table 2. The periodic boundary conditions were applied with rectangular box sizes of 34 × 40 × 40 Å^3 for water and 42 × 48 × 48 Å^3 for chloroform. The SHAKE procedure was employed to constrain all solute bonds involving at least one hydrogen atom. The time step of the simulations is 1 fs, with a nonbonded interaction cutoff of 10 Å for water and 14 Å for chloroform. The nonbonded pairs were updated every 25 steps. Each perturbation calculation consisted of 50 windows, with 1500 steps each for equilibration and data collection runs at each window. All FEP calculations were performed with forward and backward runs. A 50 ps equilibration was carried out prior to each direction of the FEP runs.

The starting structures of the simulations for 18-crown-6 derivatives, **1** and **2**, were based on the crystal structure of **1** complexed with NaSCN, which was provided by Prof. Still.[17]

III. The Effect of Force Field on Cation Binding Selectivity

The quality of a computer simulation depends on two factors: accuracy of the force field that describes intra- and intermolecular interactions, and an adequate sampling of conformational and configuration space of the system. Li and Still's work[17] indicated that the 18-crown-6 derivatives, **1** and **2**, are very rigid at their experimentally observed structure; thus, sampling becomes a less important issue in this study. In this respect, this series of compounds provide a good test set for the force field. Recent developments in force field[21−23] studies such as new charge fitting schemes and nonadditive force fields enable us to investigate the effect of force fields on host−guest binding in great detail. The questions we like to address here are the effects of atomic charges, atomic polarization, alkali cation van der Waals parameters, and some dihedral angle parameters of the host molecules (i.e., ionophores) on the binding properties.



(a) (b)

Figure 1. A two-water model complex for 18C8 and its derivatives. The 18-Crown-6 and alkali cation complex with two waters in a vacuum and the 18-crown-6 derivative and alkali cation complex with two waters in a vacuum.

To control the source of errors in our investigation, a simple model system has been introduced in Figure 1. This model system has two water molecules situated above and below the plane of the binding cores to mimic aqueous solution. Since the free energy change from Na$^+$ to K$^+$, i.e., the relative solvation free energy in aqueous solution, is constant, it is the free energy change in host−guest (cation) complexes that contributes to distinct cation binding patterns of the system. Hence we concentrated only on free energy changes in these complexes. This energy change is referred to as relative free energy of complexation hereafter. Also, because the guests are alkali cations, we refer to the hosts of interest as ionophores.

The Effect of Atomic Charges on Cation Binding Properties of 18-Crown-6 and Its Derivatives. Since the alkali cations in the study have one positive charge and the binding cores of the hosts consist of six oxygen atoms with large partial negative charges, electrostatic interactions are expected to play an important role in determining the cation-binding ability of the system. We therefore investigated the charge effect first.

There are several ways to obtain atomic charges. The ESP charges are derived from fitting the electrostatic potential of a molecule around its van der Waals surface.[24] This potential is determined by ab initio quantum mechanical calculations at the HF/6-31G* level. The recently proposed RESP scheme[21] employs a restraint function in fitting charges to the electrostatic potential to reduce artifacts for buried atoms. These buried atoms are often poorly determined in a standard ESP fitting protocol. Most recently, Sun and Kollman[25] have utilized a weighted charge-fitting scheme in their work on alkali cation complexation with spherands. They argued that with a large ionophore and a small ion, fitting a small region of space in the binding site of an ionophore would be more important than doing well elsewhere. In this study, we used ESP and RESP charges.[25] We also derived a set of charges using a weighting factor of 5 for all points of electrostatic potential, which are within 5 Å of the oxygen atoms in the binding core. This protocol (weighting factor of 5 and within 5 Å of the oxygen atoms) was based on Sun and Kollman's work on spherands.[25] In addition, there are two ways to calculate the electrostatic potential. The first approach is to break a molecule into several fragments, then calculate the electrostatic potential for each unique fragment and derive atomic charges for it. The second approach is to calculate the electrostatic potential of the whole molecule. The first approach is practical for many large molecules, but the resulting charges may be less accurate than

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(19) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, *79*, 926−935.

(20) Fox, T.; Kollman, P. A. *J. Phys. Chem.* **1998**, in press.

(21) Bayly, C. I.; Kollman, P. A. *J. Phys. Chem.* **1993**, *97*, 10269−10280.

(22) Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Kollman, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 9620−9631.

(23) Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 4177.

(24) Singh, U. C.; Kollman, P. A. *J. Comp. Chem.* **1984**, *5*, 129−144.

(25) Sun, Y.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *99*, 10081−10085.

Table 3. Atomic Charges Derived from Different Charge Fitting Schemes

	RESP			ESP		
	frag[a]	whole[b]	weighted frag[c]	frag[a]	whole[b]	weighted frag[c]
18-crown-6						
O_4	−0.430	−0.265	−0.485	−0.478	−0.280	−0.478
1						
O_{17}	−0.428	−0.319	−0.518	−0.505	−0.477	−0.523
O_{29}	−0.450	−0.356	−0.552	−0.554	−0.438	−0.559
O_{32}	−0.450	−0.240	−0.551	−0.543	−0.320	−0.555
O_{49}	−0.428	−0.288	−0.518	−0.505	−0.393	−0.523
2						
O_{17}	−0.428	−0.302	−0.518	−0.505	−0.477	−0.523
S_{29}	−0.320	−0.250	−0.326	−0.326	−0.263	−0.304
O_{32}	−0.405	−0.261	−0.470	−0.461	−0.248	−0.473
O_{49}	−0.42	−0.258	−0.518	−0.505	−0.400	−0.523

[a] Charges were calculated on the basis of fragment approach. [b] Charges were calculated from whole molecule approach. [c] Charges were fitted by using a weighting factor for electrostatic points near oxygen and were based on fragment approach. See text for details.

Table 4. Atomic Charge Effect on Free Energy Changes (ΔG in kcal/mol) As Calculated for the Model System[a]

	$\Delta G(Na^+ \rightarrow K^+)$		
charge scheme	18C6	**1**	**2**
RESP frag	14.36 ± 0.09	14.69 ± 0.26	15.08 ± 0.02
RESP whole	14.33 ± 0.03	14.93 ± 0.11	15.36 ± 0.10
ESP whole	14.30 ± 0.10	14.85 ± 0.10	15.61 ± 0.07
ESP weighted frag	14.62 ± 0.28	14.58 ± 0.27	14.83 ± 0.17

[a] The free energy errors were estimated by the difference in the free energies calculated from the forward and backward runs. The same definition is applied in the rest of related tables.

Table 5. The Additive and Nonadditive Force Field Effects on Relative Binding Free Energy (kcal/mol) for Model System[a]

	$\Delta G(Na^+ \rightarrow K^+)$		
force field	18C6	**1**	**2**
AMBER[b]	14.33 ± 0.03	14.93 ± 0.11	15.36 ± 0.10
AMBER/POL[c]	16.13 ± 0.16	15.85 ± 0.30	15.90 ± 0.23
AMBER/POL[d]	16.28 ± 0.36	16.09 ± 0.29	16.04 ± 0.00

[a] Using whole molecule based RESP charges (q_{RESP}); [b]additive force field; [c]nonadditive force field with q=0.88 q_{RESP}; and [d]nonadditive force field with q=1.0 q_{RESP}.

those derived from whole molecule based calculations. We investigated both approaches in this study.

Table 3 lists atomic charges at oxygen and sulfur atoms derived from various schemes. In general we observe that charges derived from fragment based calculations tend to have larger values than those derived from whole molecule calculations. This is probably due to the "screening effect" by neighboring oxygens in the whole molecule based approach. Comparing RESP charges with ESP charges, RESP charges seem to have smaller values than ESP charges, which can be attributed to the restraints used in the RESP fitting. Also, we note that RESP or ESP charges derived from a weighted fitting scheme are in general larger than those derived from standard protocol. This is due to the fact that we emphasize the negative electrostatic potentials near oxygen by using a weighting factor of 5 during the charge fitting procedure.

The calculated free energy changes of complexation for the model complex system are tabulated in Table 4. Overall, charges derived from various schemes lead to only minor changes in relative free energies of complexation. For simplicity, we only list the results calculated from four charge schemes. The maximum differences in relative free energies (from Na^+ to K^+) due to charges are 0.32, 0.35, and 0.78 kcal/mol for 18C6•M^+, **1**•M^+, and **2**•M^+, respectively. Therefore, we used whole molecule based RESP charges in the rest of our discussions.

The Effect of Nonadditive Force Field on Relative Free Energy of Complexation. Considering that the relative solvation free energy from Na^+ to K^+ in aqueous solution is about 17.8 kcal/mol, the FEP results for the model systems (Table 4) indicate that all three hosts bind K^+ tighter than Na^+ by more than 2 kcal/mol ($\Delta\Delta G_{bind} = \Delta G_4 - 17.8$). This is in contrast with the experimental observation as shown in Table 1, in which **1** has binding selectivity over Na^+.

The cause of the discrepancy was first thought as due to an inaccurate treatment of electrostatic interactions in the system. Regarding the strong electrostatic interaction between ionophores and cations, polarization may play a role in the complexation process. To test this hypothesis, we carried out free energy perturbation calculations using a nonadditive force field. The protocol of the nonadditive force field is based on Caldwell and Kollman's work,[23,26] except that the three-body interaction terms were not included in the calculations, because the three-body interaction parameter had not been derived for the O−K^+ pair. The charges used in the calculations are scaled RESP charges as used in the additive force field calculations. The scaling factors are either 0.88 or 1.00. The use of a scaling factor of 0.88 was based on Caldwell and Kollman's work on polarizable liquid simulation of water, methanol, and *N*-methylacetamide.[26]

As illustrated in Table 5, the nonadditive force field that includes atomic polarization does not lead to any improvement in the binding properties with respect to experimental results. **1** has almost the same binding preference for K^+ over Na^+ as 18C6 and **2**, though the values of relative free energies in all three complexes are shifted up by about 0.4−1.95 kcal/mol relative to the additive force field results. Note that the three-body repulsion terms were not included in the calculations. As this term occurs to all three complexes in the same fashion, it is likely that their relative binding patterns would not be affected even if the three-body terms were included in the calculations.

The Effects of Cation van der Waals Parameters on Complexation. Note that we have investigated the electrostatic part of the force field; we now turn to the effect of alkali cation van der Waals (VW) parameters on binding. The motivation behind this is to see if we can find a set of VW parameters for the cations of interest to reproduce the experimentally observed binding pattern for this series of ionophores. The calculations discussed in the preceding sections used Aqvist's parameters.[27] An alternative set is those developed by Dang,[28] as listed in Table 6. In all, the relative free energy of complexation does not seem to be sensitive to VW parameters of the cations (Table 6). Both Aqvist and Dang's parameters give rise to similar relative free energies, although Dang's VW parameters correspond to slightly smaller energies than Aqvist's parameters if we examine Table 6 in detail. We have investigated several other sets of VW parameters and observed the same behavior as in Table 6. We, therefore, concluded that Aqvist's VW parameters for alkali cations were not a source of the errors in the calculations.

The Effect of the Dihedral Angle Parameter on the Cation Binding Pattern. The remaining parameters to be explored

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(26) Caldwell, J. W.; Kollman, P. A. *J. Phys. Chem.* **1995**, *99*, 6208−6219.

(27) Åqvist, J. *J. Phys. Chem.* **1990**, *94*, 8021−8024.

(28) Dang, L. *J. Am. Chem. Soc.* **1995**, *117*, 6954−6960.

Table 6. The Effect of van der Waals Parameters of Alkali Metal Ions on Relative Free Energy (kcal/mol) Changes for Model System[a]

	$\Delta G(\mathrm{Na}^+ \rightarrow \mathrm{K}^+)$		
	18C6	**1**	**2**
Åqvist's VW parameters (Na^+ 1.868/0.00277 and K^+ 2.658/0.000328)[b]			
	14.33 ± 0.03	14.93 ± 0.11	15.36 ± 0.10
Dang's VW parameters (Na^+ 1.45/0.1 and K^+ 1.87/0.1)[b]			
18-crown-6	13.84 ± 0.23	13.67 ± 0.12	14.18 ± 0.05

[a] Using whole molecule based RESP charges. [b] The number in parentheses is R^*/ϵ ((Z)/(kcal/mol)).

are related to dihedral angles O−C−O−C and O−C−S−C. Howard et al's work on 1,3-dioxanes demonstrated that the dihedral angle parameter, $V_{\mathrm{O-C-O-C}}$, plays an important role in determining the conformational energies of 1,3-dioxanes.[29] A well-designed $V_{\mathrm{O-C-O-C}}$ in the molecular mechanical force field can reproduce the conformational energy landscape generated by high-level ab initio calculations such as MP2/6-31G**. We have done experiments using various $V_{\mathrm{O-C-O-C}}$ or $V_{\mathrm{O-C-S-C}}$ parameters to calculate relative free energies of complexation and found that the free energies are not sensitive to these parameters either (results not shown). This is because here we discuss relative free energy, not absolute free energy. The errors in $V_{\mathrm{O-C-O-C}}$ or $V_{\mathrm{O-C-S-C}}$ might be canceled out in the free energy difference.

IV. Comparison of the Molecular Mechanical Force Field Results with the Hartree−Fock (HF)/DZVP Results

After extensively testing the force field, a question naturally arises: How good is the AMBER force field in describing alkali cation complexation with 18C6 and its derivatives? An unambiguous assessment of the force field is obviously needed. In this section we compare the force field results with the experimental data or results from ab initio quantum mechanical calculations.

As seen in Table 7, for free 18C6 and its derivatives, the optimized geometry calculated from the force field agrees well with the RHF/6-31+G* optimized results. In 18C6, for example, the average distances between the transannular oxygen are 5.796 Å in AMBER (additive force field), 5.764 Å in AMBER/POL (additive force field + polarization), and 5.802 Å in the HF/6-31+G* calculations. In **1**, the average transannular O−O distances are 5.744 Å in AMBER, 5.718 Å in AMBER/POL, and 5.680 Å in RHF/6-31+G*. Inclusion of atomic polarization in the force field results in slightly better agreement with the ab initio results in the O−O distance of **1**. If the average transannular O−O distance is used as a measure of the size of a cavity, both ab initio and force field calculations indicated that the cavity size is decreased from 18C6 to **1**. The decrease of the cavity size is more pronounced in the ab initio results than those in force field calculations (0.12 Å vs 0.05 Å).

In the 18C6•Na^+ complex with C_1 symmetry, an average Na^+−O distance of 2.548 Å was found experimentally, while for a D_{3d}-like structure, the additive AMBER predicted an average distance of 2.802 Å. In **1**•Na^+, the additive AMBER results agree well with the corresponding experimental data in this respect. The polarization (AMBER/POL) seems to overestimate the charge redistribution and lead to bound host structures being distorted, as evidenced by the larger deviations in the minimum or maximum Na^+−O distances between the AMBER/POL and experimental results.

The X-ray crystal structure of **1**•NaSCN shows the presence of two cap waters that simultaneously interact with Na^+ and form a hydrogen bond with exocyclic oxygen on the rings. The $\mathrm{Na}^+-\mathrm{O}_{\mathrm{wat}}$ distances are 2.349 Å in AMBER, 2.337 Å in AMBER/POL, and 2.286 Å in experiment. The distance between the exocyclic oxygen of **1** and the oxygen of cap water is 2.805 Å in AMBER, 2.780 Å in AMBER/POL, and 2.999 Å in experiment. Relative to the experimental results, the additive force field underestimates the distance between the exocyclic oxygen and the oxygen of the water. Polarization leads to further underestimation of the distance.

The other important aspect of validation is to compare energetics. At the HF/DZVP (double-ξ basis set function augmented with valence shell polarization functions) level,[30] **1**•M^+•$2\mathrm{H_2O}$ complexes require more than 780 basis set functions in the calculations. The cap waters and alkali cation make the SCF convergence extremely slow due to the nature of their noncovalent interactions with the ionophores. Consequently, full geometry optimization for the complexes is prohibitively expensive at this level. On the other hand, AM1 optimizations for the complexes were not as reliable as we hoped. We thus carried out the ab initio calculations using the geometry minimized by the AMBER additive force field. As we can see from Table 8, the relative energy differences between **1**•M^+•$2\mathrm{H_2O}$ and 18C6•M^+•$2\mathrm{H_2O}$ complexes are −0.71 kcal/mol in AMBER, −1.83 kcal/mol in AMBER/POL, and −0.29 kcal/mol in the HF/DZVP calculations. Both force field models predict the same direction in relative energy change as the HF/DZVP method. In any case, all three models suggest that **1** has a stronger interaction with K^+ relative to Na^+ than 18C6. Thus, the discrepancy between experiment and calculations noted below for pure aqueous solvent (18C6 and **1** are calculated to bind K^+ more tightly, but experimentally 18C6 binds K^+ and **1** binds Na^+ more tightly) cannot be explained by defects in the interaction model. We should point out that this QM model is not the "last word", as it was based on single point calculation instead of fully geometry optimization at the ab initio level. The relatively small size of the basis set and the lack of electron correlation in the calculations give room for improvement. However, since we are interested only in the energy difference, improvements in ab initio calculations might be expected to lead to similar results.

Nevertheless, after comparing both geometrical and energetic results calculated by the force fields with the experimental and quantum mechanical calculation results, we conclude that the additive force field model is adequate to describe energetics of cation complexation with 18C6 and its derivatives. The overall good agreement between the AMBER additive force field and quantum mechanical calculations gave us confidence to explore issues related to cation extraction selectivity of these ionophores. The rest of the discussion in the paper is based on the AMBER additive force field calculations.

V. Cation Binding Free Energy in Homogeneous Solvents

The relative binding free energies in pure solvents for alkali cations and their complexes with 18C6 and its derivatives are listed in Table 9. Note that in the simulation of complexes in chloroform, we have included a counterion, Cl^-, to mimic the picrate anion. A counterion is necessary for the simulations in an organic solvent, because ions are poorly solvated in the

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(29) Howard, A. E.; Cieplak, P.; Kollman, P. A. *J. Comp. Chem.* **1995**, *16*, 243−261.

(30) Godbout, N.; Salahub, D. R.; Andzelm, J.; Wimmer, E. *Can. J. Chem.* **1992**, *70*, 560−571.

Table 7. Summary of Optimized Geometrical Parameters (Å) for Free 18C6, Its Derivatives and their Complexes with Alkali Cations[a]

	r(M^+-O)								
	18C6			**1**			**2**		
	min	av	max	min	av	max	min	av	max
free host									
AMBER[b]	2.898	2.898	2.898	2.866	2.872	2.875	2.854	2.860	2.872
AMBER/POL[c]	2.882	2.882	2.882	2.854	2.859	2.862	2.843	2.848	2.859
RHF/6-31+G* [d]	2.901	2.901	2.901	2.836	2.840	2.849			
$H{\bullet}Na^+{\bullet}2H_2O$									
AMBER[e]	2.775	2.802	2.855	2.657	2.789	2.920	2.647	2.791	2.958
AMBER/POL[e]	2.390	2.877	3.511	2.518	2.818	3.131	2.532	2.806	2.859
expt.[f]	2.452	2.548	2.623	2.723	2.763	2.836			
$H{\bullet}K^+{\bullet}2H_2O$									
AMBER	2.840	2.847	2.859	2.813	2.827	2.837	2.807	2.828	2.857
AMBER/POL	2.837	2.845	2.860	2.819	2.835	2.848	2.810	2.828	2.863

[a] Using whole molecule base RESP charges for AMBER and $q = 0.88q_{\mathrm{RESP}}$ for AMBER/POL. [b] Additive force field. [c] Nonadditive force field without three-body repulsion terms. [d] Reference 6. [e] Using D_{3d} symmetry for 18C6. [f] For 18C6, ref 6, and for **1**, results from Li and Still's work.[17]

Table 8. Minimized Energy Differences (kcal/mol), $\Delta E(\mathrm{H}) = ((E(\mathrm{H}{\bullet}\,\mathrm{K}^+{\bullet}2\mathrm{H_2O}) - E(\mathrm{K}^+)) - (E(\mathrm{H}{\bullet}\mathrm{Na}^+{\bullet}2\mathrm{H_2O}) - E(\mathrm{Na}^+)))$, for 18-Crown-6 and **1**

	ΔE(18C6)	ΔE(**1**)	ΔE(**1**) − ΔE(18C6)
AMBER[a]	15.95	15.24	−0.71
AMBER/POL[b]	17.56	15.73	−1.83
HF/DZVP	22.16	21.87	−0.29

[a] Additive force field using whole molecule based RESP charges. [b] Nonadditive force field without three-body repulsion terms. The charges are $0.88q_{\mathrm{RESP}}$.

Table 9. Calculated Free Energy Change (kcal/mol) of Alkali Cation Complex with 18-Crown-6 and Its Derivatives[a]

system	$\Delta G(\mathrm{Na}^+ \rightarrow \mathrm{K}^+)$	$\Delta\Delta G_{\mathrm{calc}}$[b]
in pure aqueous solution		
$(\mathrm{18C6{\bullet}M^+})_{\mathrm{aq}}$	16.00 ± 0.42	−1.86
$(\mathbf{1}{\bullet}\mathrm{M^+})_{\mathrm{aq}}$	16.10 ± 0.21	−1.76
$(\mathbf{2}{\bullet}\mathrm{M^+})_{\mathrm{aq}}$	16.36 ± 0.06	−1.50
$(\mathrm{M^+})_{\mathrm{aq}}$	17.86 ± 0.63	
in pure chloroform		
$(\mathrm{18C6{\bullet}M^+Cl^-})_{\mathrm{chl}}$	13.58 ± 0.32	3.12
$(\mathbf{1}{\bullet}\mathrm{M^+Cl^-})_{\mathrm{chl}}$	12.70 ± 0.17	2.24
$(\mathbf{2}{\bullet}\mathrm{M^+Cl^-})_{\mathrm{ch}}$	12.55 ± 0.27	2.09
$(\mathrm{M^+Cl^-})_{\mathrm{chl}}$	10.46 ± 0.12	
in model mixed solvent		
$(\mathrm{H_2O\,{\bullet}18C6{\bullet}M^+{\bullet}Cl^-})_{\mathrm{chl}}$	15.42 ± 0.09	15.94
$(\mathrm{H_2O}{\bullet}\mathbf{1}{\bullet}\mathrm{M^+{\bullet}Cl^-})_{\mathrm{chl}}$	16.61 ± 0.09	
$(\mathrm{H_2O}{\bullet}\mathbf{2}{\bullet}\mathrm{M^+{\bullet}Cl^-})_{\mathrm{chl}}$	17.01 ± 0.21	
$(\mathrm{2H_2O{\bullet}18C6{\bullet}M^+{\bullet}Cl^-})_{\mathrm{chl}}$	15.45 ± 0.19	
$(\mathrm{2H_2O}{\bullet}\mathbf{1}{\bullet}\mathrm{M^+{\bullet}Cl^-})_{\mathrm{chl}}$	15.94 ± 0.01	
$(\mathrm{2H_2O}{\bullet}\mathbf{2}{\bullet}\mathrm{M^+{\bullet}Cl^-})_{\mathrm{chl}}$	17.08 ± 0.58	
$(\mathrm{4H_2O{\bullet}M^+{\bullet}Cl^-})_{\mathrm{chl}}$	15.81 ± 0.30	
$(\mathrm{6H_2O{\bullet}M^+{\bullet}Cl^-})_{\mathrm{chl}}$	16.41 ± 0.14	
$(\mathrm{14H_2O{\bullet}M^+{\bullet}Cl^-})_{\mathrm{chl}}$	16.26 ± 0.28	
$(\mathrm{24H_2O\,{\bullet}M^+{\bullet}Cl^-})_{\mathrm{chl}}$	16.41 ± 0.16	

[a] Using whole molecule based RESP charges. [b] Relative binding energy in pure solvent.

solvent. The low dielectric constant of the organic solvent leads to strong ion-pair electrostatic interactions so that the ions tend to stay close to each other. On the other hand, the ions are separated far away and solvated well in water due to the fact that water has a high dielectric constant and hydrogen bond network. Consequently, discussing only cations in aqueous solution is a good approximation.

According to eq 9, the relative binding free energy can be calculated on the basis of free energy changes of alkali cations and their complexes with 18C6 derivatives. The relative binding free energies from Na^+ to K^+ in aqueous solution are −1.86 kcal/mol for 18C6, −1.76 kcal/mol for **1**, and −1.50 kcal/mol for **2**, respectively. In pure chloroform, the relative binding energies are 3.12 kcal/mol for 18C6, 2.24 kcal/mol for **1**, and 2.09 kcal/mol for **2**, respectively. Note that the signs of relative binding free energies are reversed in going from aqueous solution to chloroform. That is, 18C6 and its derivatives bind K^+ more tightly than Na^+ in aqueous solution, whereas they all favor Na^+ in chloroform. Similar behavior has also been observed in the study of alkali cation complexes of calix-4-bis-crown-6 from water to chloroform.[16] So solvent plays an important role in relative binding free energies. In any case, the calculated relative binding free energies in these two pure solvents are not consistent with the experimental picrate extraction results, in which **1** selects Na^+, but 18C6 and **2** favor K^+. We should point out that the 150 ps FEP simulation for the 18C6 system may not be long enough due to the conformational flexibility of the host.[9] Additional FEP simulations with a length of 300 ps for both forward and backward simulations were carried out. The relative free energies with the 150 and 300 ps simulations are nearly the same (16.00), and we therefore use the 150 ps results in the following discussions.

Recently, in a careful QM/MM study in aqueous solution, Thompson estimated an average binding energy of −14.8 kcal/mol per bound water molecule in **1**.[31] This is compared to the value of −12.3 kcal/mol for water bound to 18C6. This observation leads him to rationalize the tighter binding of water to **1** than to 18C6 as the reason **1** has the extraction selectivity over Na^+ in aqueous solution. Our FEP results in aqueous solution do not support such a rationale. This is because in aqueous solution, there are always bound water to ionophores, no matter whether they can form hydrogen bonds with the hosts or not. So the sign of the *relative binding energy* in **1** is not likely to be altered due to the extra hydrogen bonded cap water. Below, however, we show that Thompson's observation may well be relevant in analyses of binding free energy in chloroform solvent.

VI. Extraction free energy of 18C6 and its derivatives

Although the picrate extraction experiment has existed for many decades, how to carry out theoretical calculations on the extraction free energy is still an issue of debate. In this section we discuss thermodynamic states related to the extraction process.

So far there have been three hypotheses about the cation extraction from aqueous solution to the organic phase. In the

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(31) Thompson, M. A. *Int. J. Quantum Chem.* **1996**, *60*, 1133−1141.

Scheme 2. Thermodynamic Cycle for the Host-Partition Model

$$\begin{tikzcd}
(H)_{wat} + (M_1^+)_{wat} \arrow[r, "\Delta G_1"] \arrow[d, "\Delta G_{3,wat}"'] & (H{\bullet}M_1^+{\bullet}A^-)_{chl} \arrow[d, "\Delta G_{4,chl}"] \\
(H)_{wat} + (M_2^+)_{wat} \arrow[r, "\Delta G_2"] & (H{\bullet}M_2^+{\bullet}A^-)_{chl}
\end{tikzcd}$$

Scheme 3. Thermodynamic Cycle for the Ion-Partition Model

$$\begin{tikzcd}
(H)_{chl} + (M_1^+{\bullet}A^-)_{chl} \arrow[r, "\Delta G_1"] \arrow[d, "\Delta G_{3,chl}"'] & (H{\bullet}M_1^+{\bullet}A^-)_{chl} \arrow[d, "\Delta G_{4,chl}"] \\
(H)_{chl} + (M_2^+{\bullet}A^-)_{chl} \arrow[r, "\Delta G_2"] & (H{\bullet}M_2^+{\bullet}A^-)_{chl}
\end{tikzcd}$$

first hypothesis, known as the host partition model, the host is assumed to diffuse from an organic phase to water, where it then binds with cations (or other guests) and moves back to the original organic phase. The thermodynamic cycle corresponding to this hypothesis is shown in Scheme 2.

The relative extraction free energy is thus defined as:

$$\Delta\Delta G^{\mathrm{II}}{}_{\mathrm{extract}} = \Delta G_{4,\mathrm{chl}} - \Delta G_{3,\mathrm{wat}} \qquad (10)$$

The second hypothesis proposes that equilibrium of ions between aqueous and organic solvent is reached first, next an ion pair is formed in the organic solvent, then a complex between the host and the metal ion in the solvent is formed. This hypothesis is called the guest partition model. The thermodynamic cycle related to this assumption is drawn in Scheme 3.

Consequently, the relative extraction free energy can be expressed in the form of

$$\Delta\Delta G^{\mathrm{III}}{}_{\mathrm{extract}} = \Delta G_{4,\mathrm{chl}} - \Delta G_{3,\mathrm{chl}} \qquad (11)$$

In fact, Scheme 3 corresponds to the binding energy in chloroform and is consistent with the experimental determination of association constants (K_a) between host and metal picrates.

Experimentalists often use the following equations to determine ΔG_1 or ΔG_2.[32,33]

$$(\mathrm{H})_{\mathrm{chl}} + (\mathrm{M_1}^{+}{\bullet}\mathrm{A}^{-})_{\mathrm{chl}} \overset{K_a}{\rightleftharpoons} (\mathrm{H}{\bullet}\mathrm{M_1}^{+}{\bullet}\mathrm{A}^{-})_{\mathrm{chl}}$$

$$(\mathrm{M_1}^{+})_{\mathrm{H_2O}} + (\mathrm{A}^{-})_{\mathrm{H_2O}} + (\mathrm{H})_{\mathrm{hcl}} \overset{K_c}{\rightleftharpoons} (\mathrm{H}{\bullet}\mathrm{M_1}^{+}{\bullet}\mathrm{A}^{-})_{\mathrm{chl}}$$

$$(\mathrm{M_1}^{+})_{\mathrm{H_2O}} + (\mathrm{A}^{-})_{\mathrm{H_2O}} \overset{K_d}{\rightleftharpoons} (\mathrm{M_1}^{+}{\bullet}\mathrm{A}^{-})_{\mathrm{chl}}$$

$$\Delta 15G = -RT \ln K_a = -RT \ln(K_c/K_d) \qquad (12)$$

Finally, the third hypothesis, known as the adsorption−desorption model, assumes the adsorption of host, guest, and necessary counterions at the interface, where the host−guest complex forms and then diffuses to organic solvent. There is no experimental data clearly discriminating among these hypotheses. We begin with examining the first two hypotheses.

Scheme 4. Thermodynamic Cycle for Cation Binding by Ionophore in Mixed Solvent

$$\begin{tikzcd}
(H)_{chl} + (M_1^+{\bullet}A^-\ mH_2O)_{chl} \arrow[r, "\Delta G_1"] \arrow[d, "\Delta G_{3,chl}"'] & (H{\bullet}M_1^+{\bullet}A^-{\bullet}nH_2O)_{chl} \arrow[d, "\Delta G_{4,chl}"] \\
(H)_{chl} + (M_2^+{\bullet}A^-\ mH_2O)_{chl} \arrow[r, "\Delta G_2"] & (H{\bullet}M_2^+{\bullet}A^-{\bullet}nH_2O)_{chl}
\end{tikzcd}$$

According to eq 10, the calculated extraction free energies related to Scheme 2 are −4.28 kcal/mol for 18C6, −5.16 kcal/mol for **1**, and −5.31 kcal/mol for **2**, respectively. The extraction free energies corresponding to Scheme 3 are the previously discussed binding energies in chloroform, which are +3.12, +2.24, and +2.09 kcal/mol for the hosts in the same order. The extraction free energies calculated from these two schemes are not in agreement with the experimental values, which are −2.7, 0.8, and −0.7 kcal/mol for the hosts 18C6, **1**, and **2**, respectively. The disagreements are not only in absolute values of the relative free energies but also in rank order.

How can we discriminate **1** from 18C6 and **2** in the extraction free energy? As we have discussed in the preceding sections, since the sizes and shapes of the cavities in these three ionophores are very similar to each other, a simple lock and key model does not work. Our free energy perturbation calculations predict that all three hosts have similar cation extraction energies in either schemes 2 or 3, i.e., in a homogeneous solvent environment. Therefore, a natural step for us is to next investigate the mixed solvent effect on their binding properties. Scheme 4 is thus designed to discuss the corresponding thermodynamic cycle.

Since an elaborate free energy perturbation simulation on mixed solvent requires a very long equilibration and production run, an alternative approach is to design a simplified mixed solvent model to capture the basic features of the system. Two model systems are discussed here. The first one is an $H{\bullet}M^+{\bullet}A^-$ complex interacting with one water in chloroform solvent, denoted as the one-water complex model (Figure 2a). The second one consists of two waters situated on the two side of the binding core surface of a complex (Figure 2b), hereafter referred to as the two-water complex model. The free energy perturbation simulations were carried out in similar conditions as that in pure chloroform. The one-water and two-water complexes were first optimized in a vacuum, then they were solvated in a chloroform box with a volume of about 42 × 48 × 48 Å^3. FEP calculations were carried out forward and backward, each in 50 windows. Each window consists of a 1500 step equilibration and the same number of production run steps. Table 9 lists the calculated free energy changes for these two model systems.

Consider the relative free energy of complexation in chloroform first. In the one-water complex system, the change of free energy from Na$^+$ to K$^+$ is 15.42 kcal/mol for 18C6, 16.61 kcal/mol for **1**, and 17.01 kcal/mol for **2**, respectively. Relative to the FEP results in the one-water system, the relative free energies of complexation in the two-water complex model remain almost the same for 18C6 and **2**, but are reduced by more than 0.7 kcal/mol for **1**. This is because in **1**, there are two exocyclic oxygen atoms available to form hydrogen bonds with the two cap waters. The capped water prevents the anion from being close to the cation. Since the cation−water interaction is not as strong as the cation−anion interaction, the relative free energy of the complexation is smaller in the two-water complex model than the free energy in the one-water model for host **1**. On the other hands, there are no or weak

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(32) Moore, S. S.; Tarnowski, T. L.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6398.

(33) Koenig, K. E.; Lein, G. M.; Stuckler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553−3566.

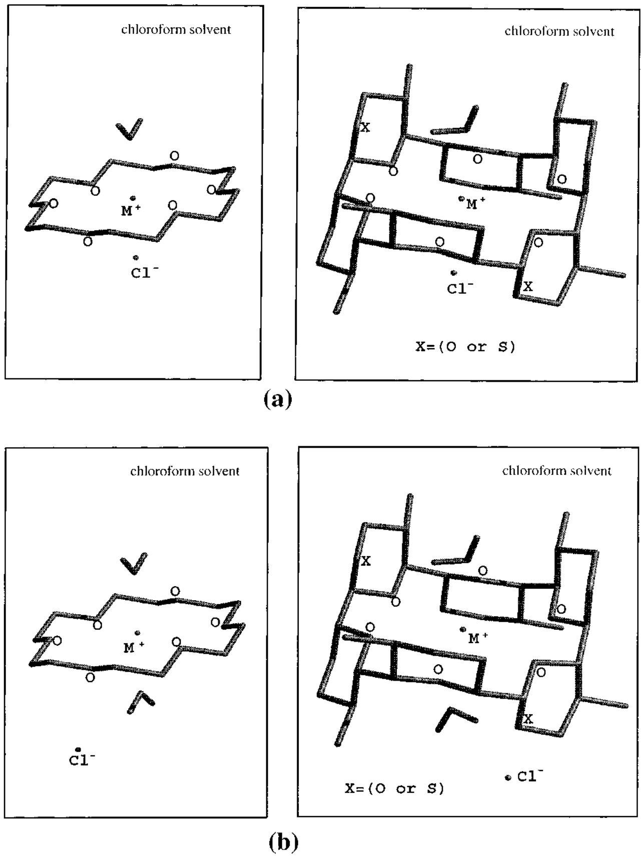


Figure 2. A mixed solvent model system for 18C6 and its derivatives. Host•M^+•Cl^- complex with one water in chloroform solvent and H•M^+ complex with two waters and one Cl^- in chloroform solvent.

hydrogen bonds between host and the two waters in the 18C6 or **2** complexes. Strong electrostatic interaction between cation and anion pulls one cap water away so that the anion can stay close to the cation. Consequently, the ions in the two-water complexes share nearly the same first-shell interaction as those in one water complexes for 18C6 or **2**. Therefore, the free energies of complexation are nearly the same for 18C6 and **2** in these two model complex systems.

In view of the free energies of complexation in pure chloroform and mixed solvent with one water or two waters in chloroform, there is only one way we have found that can discriminate the complexation free energies among these hosts, and that is to assume that the three hosts are in different environments during their extraction processes. In detail, we propose that the complexation of 18C6 with alkali cation occurs in pure chloroform solvent; the cation binding by **1** in chloroform, however, involves one cap water bound to its exocyclic oxygen in chloroform solvent. This cap water enhances both Na^+ and K^+ binding by **1**. As Na^+ binds water tighter than K^+, the relative free energy of complexation is increased in the set. Note that this assumption is consistent with Thompson's finding[31] that water interacts more strongly with **1** than 18-crown-6. For **2**, on the other hand, we make an assumption that only a "partial" water takes part in the binding processes due to the weak hydrogen bond between exocyclic sulfur and water in chloroform. A very crude estimation of the hydrogen bond strength could be made on the basis of charge ratio of the exocyclic oxygen in **1** over sulfur in **2**. Considering the charges derived from different schemes in Table 3, we observe that the ratio of charges at O_{29} of **1** and S_{29} of **2** ranges from 0.54 to 0.71. If we take 0.6 as an approximate ratio of charges at O_{29} in **1** over S_{29} in **2**, thus, based on data in Table 9, the relative complexation free energy of **2** can be estimated as 15.23 (kcal/mol) (= 0.6 × (17.01 − 12.55) + 12.55). Following this discussion, the relative free energies of cation complexation (from Na^+ to K^+) are 13.58, 16.61, and 15.23 kcal/mol by the three hosts 18C6, **1**, and **2**, respectively, as listed in Table 10.

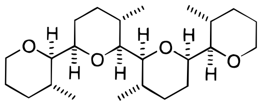
Table 10. Proposed Cation Complexation Process by 18C6 and Its Derivatives

$\Delta G_4{}^a$	$\Delta G_3{}^b$	$\Delta G_3{}^c$	$\Delta\Delta G^d$	$\Delta\Delta G^e$	$\Delta\Delta G_{\mathrm{expt}}$
$(18C6)_{chl} + (mH_2O{\bullet}M_1{}^+{\bullet}Cl^-)_{chl} \rightleftharpoons (18C6{\bullet}M_1{}^+{\bullet}Cl^-)_{chl} + mH_2O$					
13.6	15.8	16.4	−2.2	−2.8	−2.7
$(\mathbf{1})_{chl} + (mH_2O{\bullet}M_1{}^+{\bullet}Cl^-)_{chl} + H_2O \rightleftharpoons (H_2O{\bullet}\mathbf{1}{\bullet}M_1{}^+{\bullet}Cl^-)_{chl} + mH_2O$					
16.6	15.8	16.4	0.8	0.2	0.8
$(\mathbf{2})_{chl} + (mH_2O{\bullet}M_1{}^+{\bullet}Cl^-)_{chl} + 0.6H_2O \rightleftharpoons (0.6H_2O{\bullet}\mathbf{2}{\bullet}M_1{}^+{\bullet}Cl^-)_{chl} + mH_2O$					
15.2	15.8	16.4	−0.6	−1.2	−0.7

[a] Calculated relative complexation free energy from Na+ to K+. [b] Calculated relative solvation energy from Na^+ to K^+ for a reference state with 4 waters. [c] Calculated relative solvation energy for a reference state with 24 waters. [d] Calculated relative binding energies using the 4 water reference state. [e] Calculated relative binding energies using the 24r water reference state.

To calculate extraction free energy according to Scheme 4, we need to define a reference state to calculate desolvation energy of alkali ions in chloroform. It is accepted that the organic phase is not pure and is often saturated with water. Unfortunately, it is difficult to determine experimentally how many water molecules surround an ion pair in chloroform. On the basis of the sizes of the ions in the study and the number of the first shell water molecules surrounding the ions, we estimated that the number of waters around the ion pair is in the range of 4 to 24. The FEP results for the ion pairs with various numbers of waters in chloroform are listed in Table 9. If we assume a reference state with four waters surrounding the ion pair, the relative free energies of extraction in chloroform are −2.2 kcal/mol for 18C6, +0.8 for **1**, and −0.6 kcal/mol for **2**, respectively, as listed in Table 10. Even if we assume a reference state with 24 waters surrounding the ion pair, the resulting relative free energies of extraction are still qualitatively in agreement with the experimental observation. The free energies of extraction are −2.8, 0.2, and −1.2 kcal/mol for the three hosts, respectively.

Note that in our calculations we used Cl^- to mimic the picrate anion. The experimental use of picrate instead of Cl^- is to simply increase the solubility of the cations in organic solvents. We are assuming that the mixed solvent hypothesis would still be valid for the cation complexation by **1** and **2** even if we use picrate anion in the calculations. This is because the sizes and cavities of the hosts should not strongly depend on the anions used in the simulations. The similar sizes in the cavity should lead to similar extraction free energies for the three hosts in homogeneous solvents. This is also clearly evidenced from Table 4 as well, in which we carried out the simulations using a model system consisting of host−cation complexes with two waters in a vacuum. This model system is similar to the system with host-cation complexes plus two waters in a nonpolar solvent such as chloroform because of the low dielectric constant of chloroform. The observed same relative binding free energy patterns for both the model system (Table 4) and the system with host-cation complexes plus Cl^- anion and two waters in chloroform (Table 8) suggest that any simulations using picrate anion will lead to similar results as with the Cl^- anion, because the strength of interaction of picrate anion with its environment is less than that of Cl^-. We find similar results without anion and with Cl^-; thus, simulations with picrate would be expected to lead to results between these two extremes. So it is the different environment, not the anion, that discriminates **1** from 18C6 and **2** in the cation complexation process.



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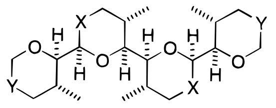

4 ($X=O$, $Y=CH_2$) **5** ($X=S$, $Y=CH_2$)
6 ($X=CH_2$, $Y=O$) **7** ($X=CH_2$, $Y=S$)

Li and Still pointed out that the remarkable sodium-binding properties of **1** are not so apparent in other acetal-containing ionophores.[17] In comparison to podand **3,** for example, podand acetals **4** and **5** are ∼2-fold less ionophoric for Na^+ and K^+ while podand acetals **6** and **7** are equally ionophoric with **3** for K^+ and only ∼2-fold more ionophoric than **3** for Na^+. The unique sodium-binding properties of **1** may be attributed to the macrocyclic effect. The rigidity of the macrocyclic cavity and its six substituent six-member rings in **1** provide a stable environment for water to simultaneous interact with ions and form a hydrogen bond with the exocyclic oxygen. In acyclic podand acetals, however, the conformational flexibility causes the strength of the hydrogen bond of a bound water to be diminished. Consequently, the cation binding properties of podand acetals could be quite different from those of **1**. One experiment can be suggested to test the mixed solvent hypothesis. If we replace one exocyclic oxygen in **1** with sulfur, the alkali cation association constants would be predicted to be nearly the same as **1** based on the one-water complex model. It will be interesting to examine this prediction experimentally.

VII. Conclusions

Computer simulations have been carried out for 18-crown-6 and its derivatives complexed by alkali cations. Extensive investigation of the force field indicated that the cation binding properties are not sensitive to atomic charges, polarization, van der Waals parameters of the alkali cations, and some dihedral angle parameters of ionophores. The additive AMBER force field model is adequate to discuss the complexation of alkali cation with 18C6 derivatives.

The binding free energy of these ionophores with alkali cations has been investigated by means of free energy perturbation calculations. The relative binding energies or extraction free energies calculated in homogeneous media (water or chloroform) disagree with the experimental picrate extraction results for **1** and **2**. Therefore, the hypothesis that the extraction process occurs in homogeneous solvent environment appears not to be valid. Mixed solvent is very likely to play an important role in determining the distinct binding properties among ionophores **1** and **2**.

To interpret experimental results, we propose that the cation complexation occurs in different environments with ionophores 18C6, **1**, and **2**. For 18C6, the complexation process occurs in pure chloroform solvent. For **1**, however, the binding process associates with one cap water in the solvent. This cap water forms a hydrogen bond with **1** during the complexation. For **2**, on the other hand, we propose that only partial water occupancy (∼0.6) is involved in the binding of cations in chloroform. It is the cap water in **1** that enhances the ability of **1** to bind Na^+ more tightly than K^+. The remote substituent on the 18-crown-6 derivatives can alter the binding affinity through such bridge waters, which bind to the ionophores through hydrogen bonds. To further interpret the experimental results, we suggest that the reference state for alkali cations consists of an ion pair (cation−anion) surrounded by a limited number (∼10) of waters in chloroform.

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