Mechanism and Thermodynamics of Ion Selectivity in Aqueous Solutions of 18-Crown-6 Ether: A Molecular Dynamics Study

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Received January 30, 1995[®]

Abstract: We have performed extensive classical molecular dynamics simulations to examine the mechanism and thermodynamics for ion selectivity of 18-crown-6 ether in aqueous solutions. We have computed the free energy profiles or potentials of mean force and the corresponding binding free energies for M^+:18-crown-6 ($M^+ = K^+$, Na^+, Rb^+, Cs^+) complexation in water. The long-range interactions are computed via the Ewald summation method, and counterion effects are considered. To the best of our knowledge, the present work is the first to employ the potential of mean force approach to the evaluation of crown ether selectivity in an aqueous solution. The resultant potentials of mean force indicate that minima free energy surfaces for K^+ and Na^+ are located at the crown ether center-of-mass. A well-defined second minimum is also observed in the potential of mean force of the Na^+:18-crown-6 complex in water. It appears that K^+ is selected over Na^+ because of the greater free energy penalty associated with displacing water molecules from Na^+ as it approaches the crown ether. This leads to a substantial increase in the activation free energy and a decrease in the corresponding binding free energy for Na^+:18-crown-6 complexation as compared to K^+:18-crown-6. The selection of K^+ over Rb^+ and Cs^+ is due to the size of the cation relative to that of the crown ether cavity. Although the calculated binding free energies underestimate the experimental measurements, they correctly reproduce the experimental sequence trends $K^+ > Rb^+ > Cs^+ > Na^+$. The present work not only reproduces the experimental observations but also provides a detailed physical description of the mechanism for ion selectivity in macrocyclic crown ethers.

I. Introduction

Since the discovery of crown ethers in 1967 by Pedersen at Du Pont,[1] the field of molecular recognition has received a considerable amount of interest.[2] It is well-known that solvation plays a major role in ion selectivity processes by influencing the stability and nature of host–guest complexes. Crown ethers have been proposed as separation agents for removing metal (i.e., Cs^+ and Sr^{2+}) from mixed nuclear and chemical wastes.[3] Computer simulation approaches have been used extensively to investigate the selectivity processes in aqueous solution. The most noticeable and widely used simulation approach is the thermodynamic cycle method.[4] This method has been used to study the relative free energies of complexation of Cl^- and Br^- by a macrotricylic receptor,[5] free energies of complexation of cations by 18-crown-6 in water,[6] molecular recognition of 18-crown-6 in methanol,[7] molecular dynamics mapping of the process of decomplexation of Cl^- from SC24,[8] the selectivity of K^+ by the naturally occurring antibiotic ionophore nonactin and valinomycine,[9] as well as other works by Wipff, Kollman, and co-workers on a variety of crown ethers and their substitutions.[10,11]

We have performed classical molecular dynamics simulations to examine the mechanisms and thermodynamics for ion selectivity in aqueous solutions of crown ethers. 18-Crown-6 is one of the most extensively studied crown systems and the abundance of experimental data for these systems provides a good prototype to verify our approach.[12] To the best of our knowledge, the present work is the first to employ the potential of mean force (pmf) approach to the evaluation of ion selectivity by crown ethers in aqueous solutions. Our work is distinguished from earlier contributions by the methodology (free energies of complexation are computed as a function of the ion–crown separation) and to the extent in which we have exploited the free energy perturbation approach. To our knowledge, the most important values of this work are the following: (1) the computed pmfs allow us to examine the solvent effects on the free energy minima positions of the complexes so that they can be related directly to the X-ray data, (2) the binding free energies can be readily computed by integrating over the pmfs, and (3) the role of solvent effects along the reaction coordinate (i.e., contact or solvent-separated pairs, conformations of the crown ether as a function of the ion–crown separation) can be examined.

It will be shown in detail in this paper that the selectivities of the crown ether depend both on the size of the cations relative to the cavity of the crown ether and on the delicate balance between the cation–crown and the cation–solvent interaction. The free energy profiles or pmfs for M^+:18-crown-6 ($M^+ = K^+$, Na^+, Rb^+, Cs^+) complexation are computed via the

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[®] Abstract published in *Advance ACS Abstracts,* June 15, 1995.

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thermodynamic perturbation method.[13] The long-range interactions are computed via the Ewald summation method,[14] and counterion effects are considered. All of the calculations described in this paper use the extended simple point charge (SPC/E) nonpolarizable water model of Berendsen and co-workers.[15] The ion−water, ion−crown, and water−crown potential parameters are appropriately developed for use in solution simulations. Future work will include nonadditive effects such as the polarization energy[16] and simulations of substituted crown ethers with a variety of functional groups.

The preliminary results have been published recently;[17] here we report a full investigation. The outline of the paper is as follows. Details of the simulation models and methods are summarized in Section II. Properties of the potential models, the structural and thermodynamic properties of the ionic solutions as well as the free energy profiles are presented and discussed in Section III, and the conclusions are summarized in Section IV.

II. Simulation Details

A. Potential Models. We use the extended simple point charge (SPC/E) nonpolarizable water model of Berendsen and co-workers to describe the water−water interactions.[15] The potential is a sum of Lennard-Jones and Coulomb interactions

$$U_{\mathrm{water}} = \sum_i \sum_j \left\{ 4\epsilon \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{r_{ij}} \right\} \qquad (1)$$

This model is a rigid, three-point charge model that accurately predicts the thermodynamic and structural properties of liquid water.

The potential function describing the intramolecular interactions of the crown ether has the following form:

$$U_{\mathrm{crown}} = \sum_{\mathrm{bonds}} \frac{K_r}{2}(r - r_{\mathrm{eq}})^2 + \sum_{\mathrm{angles}} \frac{K_\theta}{2}(\theta - \theta_{\mathrm{eq}})^2 + \sum_{\mathrm{dihedrals}} \frac{V_n}{2}[1 + \cos(n\phi + \gamma)] + \sum_i \sum_j \left\{ 4\epsilon \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{r_{ij}} \right\} \qquad (2)$$

Here, K_r and K_θ are the bond stretch and bond angle force constants and V_n, n, ϕ, and γ are the torsional barrier, the periodicity, the dihedral angle, and the phase angle, respectively. The last term of eq 2 represents the nonbonded interactions within the crown ether. The atomic partial charges and the intramolecular force constants are taken from the work by Howard et al.,[18] the Lennard-Jones parameters for the carbon and hydrogen atoms are taken from Sun et al.,[10] and the Lennard-Jones parameters for the oxygen atoms are identical to the oxygen parameters of the SPC/E nonpolarizable water model. The ion−water and crown−water interactions have the same functional form as that in eq 1. The potential parameters and their corresponding properties will be discussed in Section III.

B. Computational Methodology. The calculations employed the thermodynamic perturbation theory[13] and the molecular dynamics simulation technique to determine the potential of mean force or free energy profile for the association of the cation to crown ether in water and the corresponding absolute Helmholtz or Gibbs binding free energy. The reaction coordinate, r, is defined as the distance between the cation and the crown−ether center of mass. This approach has been described in detailed elsewhere;[17] here we present only the pertinent equations:

$$A(r \pm \delta r) - A(r) = -kT \ln\langle \exp(-\beta(U(r \pm \delta r) - U(r))) \rangle_r \qquad (3)$$

in which the Helmholtz free energy difference between a reference system, r, and a perturbed system, $r \pm \delta r$, is given as an ensemble average of a function of the potential energy difference between two systems. With $\beta = 1/kT$, k is the Boltzmann's constant and T is the temperature of the system. Here, $\langle ... \rangle_r$ indicates the average is calculated corresponding to $U(r)$, the potential energy describing the reference state r. $U(r \pm \delta r)$ is the potential energy of the system when the reaction coordinate is perturbed from r to $r \pm \delta r$. By performing a series of such calculations along the reaction coordinate, the resulting accumulated free energy changes yield the potential of mean force, $W(r)$. Subsequently, the pmf is used to estimate the ion−crown association constant and the corresponding binding free energy via the following expressions:

$$K_{\mathrm{a}} = N \int_0^C 4\pi r^2 \exp(-W(r)/kT)\, \mathrm{d}r \qquad (4)$$

in which $W(r)$ is the cation−crown potential of mean force, r is the distance between the cation and the crown ether center of mass, C is the geometric limit for association, which is usually defined as the distance corresponding to the top of the first barrier height of the pmf, and N is Avogadro's number.

In practice, the potential of mean force or free energy profile, $W(r)$ for the association of the cation to the crown ether in water with full periodic boundary conditions, is weakly dependent on the ensemble (i.e., canonical ensemble (N, V, T) or isothermal−isobaric ensemble (N, T, p)) from which the free energy difference (i.e, Helmholtz or Gibbs) was calculated. We denote $W(r) \cong W^{\mathrm{A}}(r) \cong W^{\mathrm{G}}(r)$ and similarly $K_{\mathrm{a}} \cong K_{\mathrm{a}}^{\mathrm{A}} \cong K_{\mathrm{a}}^{\mathrm{G}}$. We can express the Gibbs or Helmholtz binding free energy in terms of the cation−crown ether association constant, K_{a}, as follows:

$$\Delta G \cong \Delta A = -kT \ln K_{\mathrm{a}} \qquad (5)$$

The simulations are carried out in a periodic cube with lengths of 18.656 Å containing 198 water molecules, a single 18-crown-6 ether molecule, a cation, and a $\mathrm{Cl^-}$ ion. During the dynamic simulations, the reaction coordinate, r, is maintained by removing the translational velocity and translational force of the crown ether center of mass as well as the velocity and the force on the cation. The Ewald summation technique is used to evaluate the long-range interactions.[14] For each calculation, a total of 15 simulations are performed. All simulations are carried under the canonical ensemble at 300 K. A typical pmf calculation consists of a 10-ps equilibration period followed by 80 ps of data collection for each $\mathrm{M^+}$:18-crown-6 ether ($\mathrm{M^+} = \mathrm{Cs^+}$, $\mathrm{Rb^+}$, and $\mathrm{K^+}$) center of mass separation using a timestep of 2 fs. For the $\mathrm{Na^+}$:18-crown-6 complex, due to significant fluctuation in the conformations, the dynamics simulations carried out consisted of a 20-ps equilibration period followed by 100 ps of data collection. The SHAKE procedure[20] is adopted to constrain all the bond lengths to their equilibrium values and a constant temperature algorithm[20] is used to keep the temperature at 300 K.

The crown ether molecule is allowed to rotate freely throughout the simulations. The initial gas-phase coordinates with D_{3d} conformations for the $\mathrm{M^+}$:18-crown-6 complexes ($\mathrm{M^+} = \mathrm{Cs^+}$, $\mathrm{Rb^+}$, and $\mathrm{K^+}$) and with the C_1 conformation for the $\mathrm{Na^+}$:18-crown-6 complex are taken from the X-ray structure.[21] The initial position of the counterion $\mathrm{Cl^-}$ is placed nearly in contact with the cation via the low-temperature (near 0 K)

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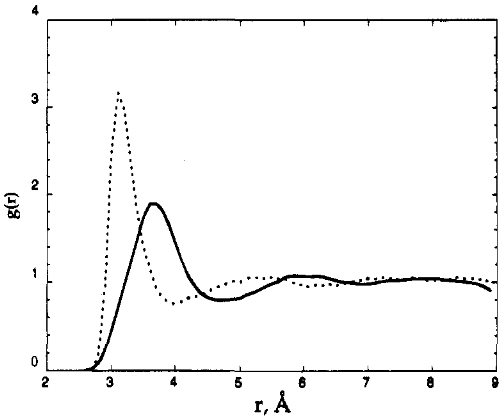

Figure 1. Calculated radial distribution functions for Cs−H (dashed line) and Cs−O (solid line) near 300 K.

molecular dynamics simulations. The pmf was calculated using a set of molecular dynamics programs developed in our laboratory. A typical pmf calculation with full Ewald summation required about 2 months of CPU time on the IBM/550 workstation. The entire project took about 1 year.

III. Results and Discussion

A. Properties of Potential Models. We begin this section by discussing the development of the ion parameters. We parametrized the ion−water potential to reproduce the experimental solvation enthalpy and selected structural properties (i.e., the coordination number and the radial distribution functions, rdf) for a single ion in an aqueous solution. In this study, we use the initial Cs^+ ion Lennard-Jones parameters from our recent work.[17] The optimum ion potential parameters were obtained by carrying out a series of molecular dynamics simulations. The system consists of one ion and 215 water molecules. A typical molecular dynamics simulation consists of a 20-ps equilibration period followed by 100 ps of data collection for each ionic solution. The simulation is carried out at constant pressure and temperature of 1 atm and 300 K, respectively. The ion Lennard-Jones parameters are adjusted until the simulation results match the corresponding experimental measurements. The solvation enthaly, ΔH_{sol}, is computed by subtracting the total potential energy of the dilute ionic solution from that of pure water. The long-range interactions are truncated using a molecule−molecule based cutoff distance of 9 Å, because the Ewald summation[14] is not applicable to this non-neutral system. The Born correction is applied to the calculation of ΔH_{sol}.[22] The error bar for the ΔH_{sol} is estimated by taking the difference of the computed ΔH_{sol} from the first half and the last half of the total trajectory.

Figure 1 contains the radial distribution functions, $g(r)$, for the Cs^+ ion in water. The peak positions of g_{Cs-O} and g_{Cs-H} are similar to the results from molecular dynamics simulations reported in literature. The first minimum of the g_{Cs-O} is rather shallow and close to 1, which suggests that the water molecules in the first hydration shell are loosely held by the cesium ion and a significant exchange of water molecules of different shells. The optimum potential parameters for the K^+, Rb^+, and Na^+ ions in water are derived in the same way as was done for the Cs^+−water potential and given in Table 1. Table 2 summarizes the solvation enthalpies, the hydration numbers of the solvated Cs^+, K^+, Rb^+, and Na^+ ions, and other characteristics of the $g(r)$s that result from both this and the experimental works. The g_{Cs-O}, g_{Rb-O}, and g_{K-O} shown in Figure 2 have similar characteristics (i.e., no second shell) with the peak heights gradually decreasing as the ion size becomes larger.

Table 1. Potential Parameters for Models of Waters, Crown Ether, and Ions: Lennard-Jones Parameters (σ and ϵ) and Charges q

atom type	σ (Å)	ϵ (kcal/mol)	q
OW[a]	3.169	0.1553	−0.8476
HW[a]	0.000	0.0000	+0.4238
Na^+	2.584	0.1000	+1.0000
K^+	3.332	0.1000	+1.0000
Rb^+	3.528	0.1000	+1.0000
Cs^+	3.884	0.1000	+1.0000
Cl^-	4.401[b]	0.1000[b]	−1.0000[b]
HT	2.650[c]	0.0157[c]	−0.0207[d]
CT	3.400[c]	0.1094[c]	+0.2442[d]
OT	3.169[a]	0.1553[a]	−0.4057[d]

[a] Reference 15. [b] Reference 16. [c] Reference 19. [d] The bond, angle, and dihedral potential parameters and partial charges for the crown ether were taken from ref 18.

Table 2. Structure and Thermodynamic Properties of Cations in Water at 300 K

	r_{M^+-O} (Å)		coord no.		ΔH_{sol} (kcal/mol)	
M^+	MD	exp[a]	MD	exp[a]	MD[b]	exp[c]
Na^+	2.4	2.3−2.4	6.0	5.0−6.0	−107 ± 5	−106
K^+	2.8	2.7−2.8	7.4	6.0−8.0	−85 ± 4	−86
Rb^+	2.9	2.9−3.0	8.4	8.0−9.0	−81 ± 4	−82
Cs^+	3.1	2.95−3.15	8.5	8.0−9.0	−77 ± 4	−76

[a] Magini, M. In *Ions and Molecules in Solution*; Tanaka, N., Ohtaki, H., Tamamushi, R., Eds.; Elsevier: Amsterdam, 1983; p 97. [b] The solvation enthalpy, ΔH_{sol}, is computed by subtracting the total potential energy of the dilute ionic solution from that of pure water. The error bar for the ΔH_{sol} is estimated by taking the difference of the computed ΔH_{sol} from the first half and the last half of the total trajectory. [c] Friedman, H. L.; Krischnan, C. V. *Water: A Comprehensive Treatise*; Franks, F., Ed.; Plenum: New York, 1973; Vol. 6, p 1.

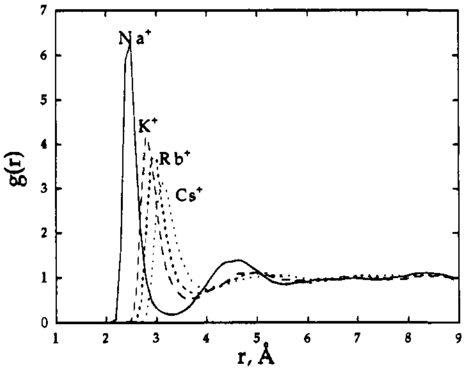

Figure 2. Calculated radial distribution functions g_{M-O} ($M^+ = Na^+$, K^+, Rb^+, Cs^+) near 300 K.

The g_{Na-O}, on the other hand, is significantly different from the rest. In addition to a sharp first peak near 2.45 Å, it exhibits a well-defined second shell, which is indicative of the degree of ordering of water molecules around the Na^+ ion. The Cl^- ion potential parameters are derived to match the nonadditive model, which has been refined to fit many properties of experimental measurements.[23]

Using these optimized ion parameters, we compute the interaction energies and minima positions of the cation−crown complexes. The atomic partial charges of the crown ether are derived from a 6-31G* calculation by Howard et al.[18] Figure 3 illustrates the gas-phase potential energy of the Cs^+:18-crown-6 complex as a function of the ion−crown center of mass

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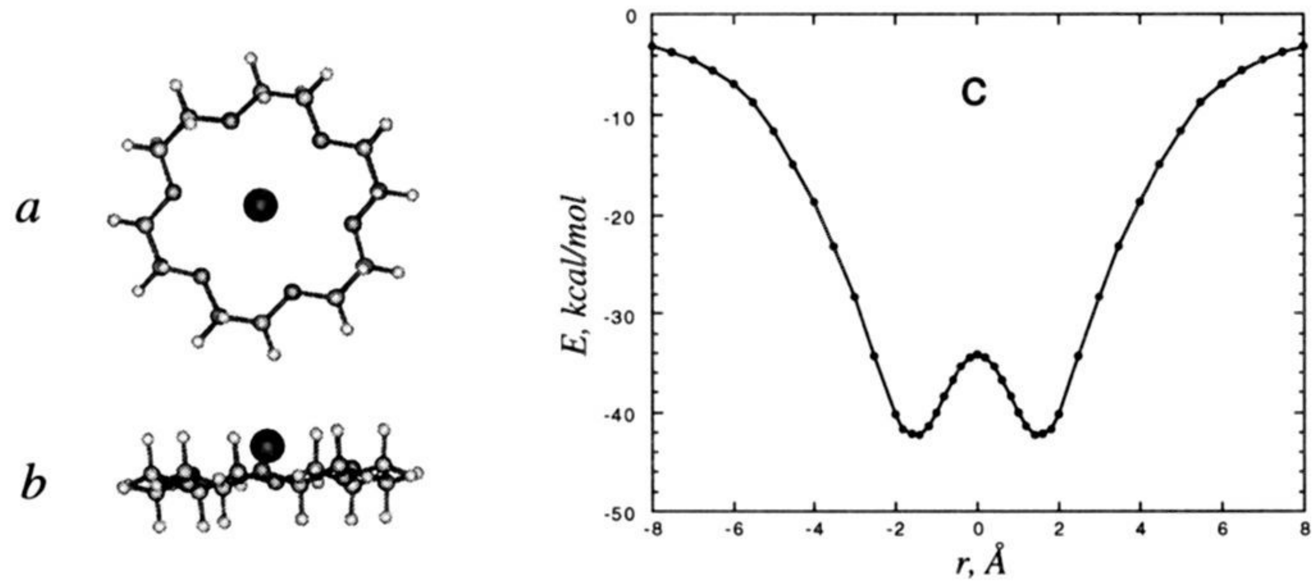

Figure 3. Gas-phase minimum energy configuration of the Cs^+:18-crown-6 complex: (a) top view, (b) side view. (c) The gas-phase intermolecular potential for a Cs^+:18-crown-6 complex as a function of the ion−crown center of mass separation. $r = 0$ Å corresponds to the crown ether center of mass.

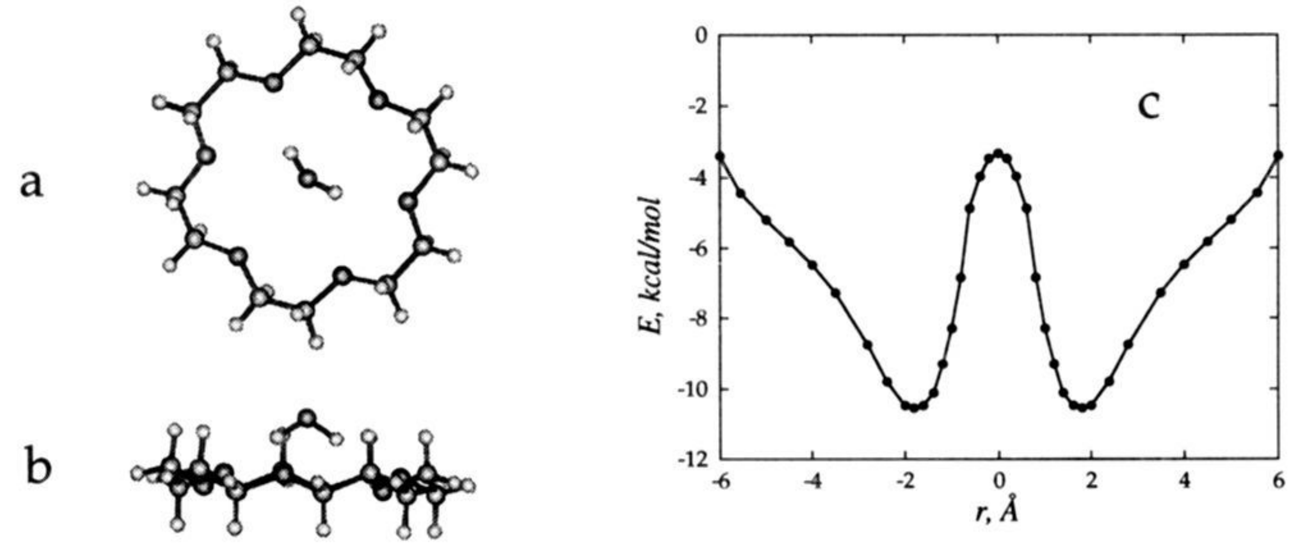

Figure 4. Gas-phase minimum energy configuration of the H_2O:18-crown-6 complex: (a) top view, (b) side view. (c) The gas-phase intermolecular potential for a H_2O:18-crown-6 complex as a function of the water−crown center of mass separation. $r = 0$ Å corresponds to the crown ether center of mass.

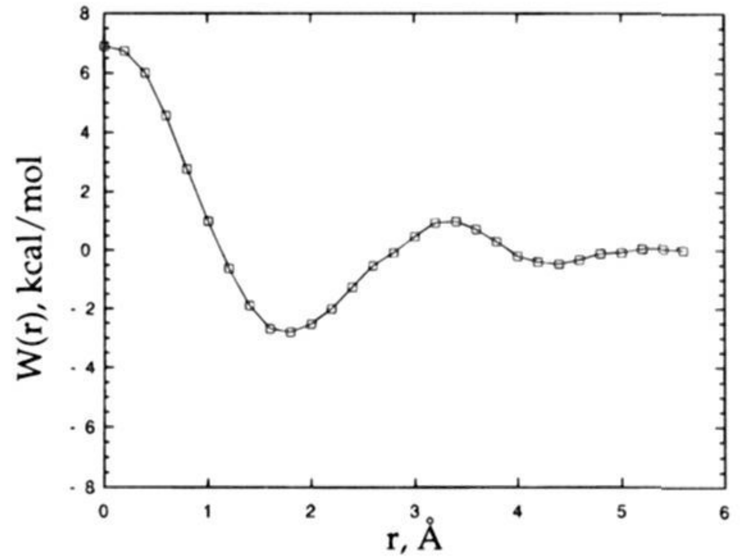

Figure 5. The pmf for the association of the Cs^+ to 18-crown-6 ether in water near 300 K. $r = 0$ Å corresponds to the crown ether center of mass.

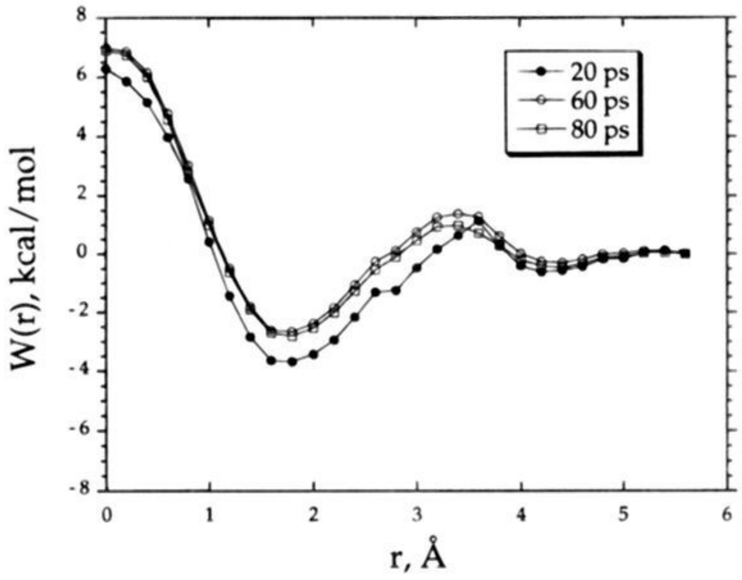

Figure 6. The pmf for the association of the Cs^+ to 18-crown-6 ether in water near 300 K as a function of the accumulation time. $r = 0$ corresponds to the crown ether center of mass.

distance. Upon examining this figure, we find that the Cs^+ ion is displaced about 1.5 Å from the center of mass of the crown ether with a minimum interaction energy of −42 kcal/mol. The minimum energy configuration as the Cs^+ ion approaches the crown ether molecule in the gas phase is also shown in Figure 3. The calculations are extended to other cation−crown ether interactions. In all cases, we find that the minima positions and the conformations agree well with the X-ray measurements. The gas-phase cation−crown interaction energies follow the correct sequence $Na^+ > K^+ > Rb^+ > Cs^+$, as would be expected from the relative size of the ions. They, however, underestimate recent quantum chemical calculations.[24] This deficiency can be overcome by including many-body interactions in these molecular systems. Research in this direction is currently in progress.

We compute the interactions between a water molecule and an 18-crown-6 as a function of oxygen−crown separations. The results are shown in Figure 4. The gas-phase minimum energy configuration of a water:18-crown-6 complex indicates that the

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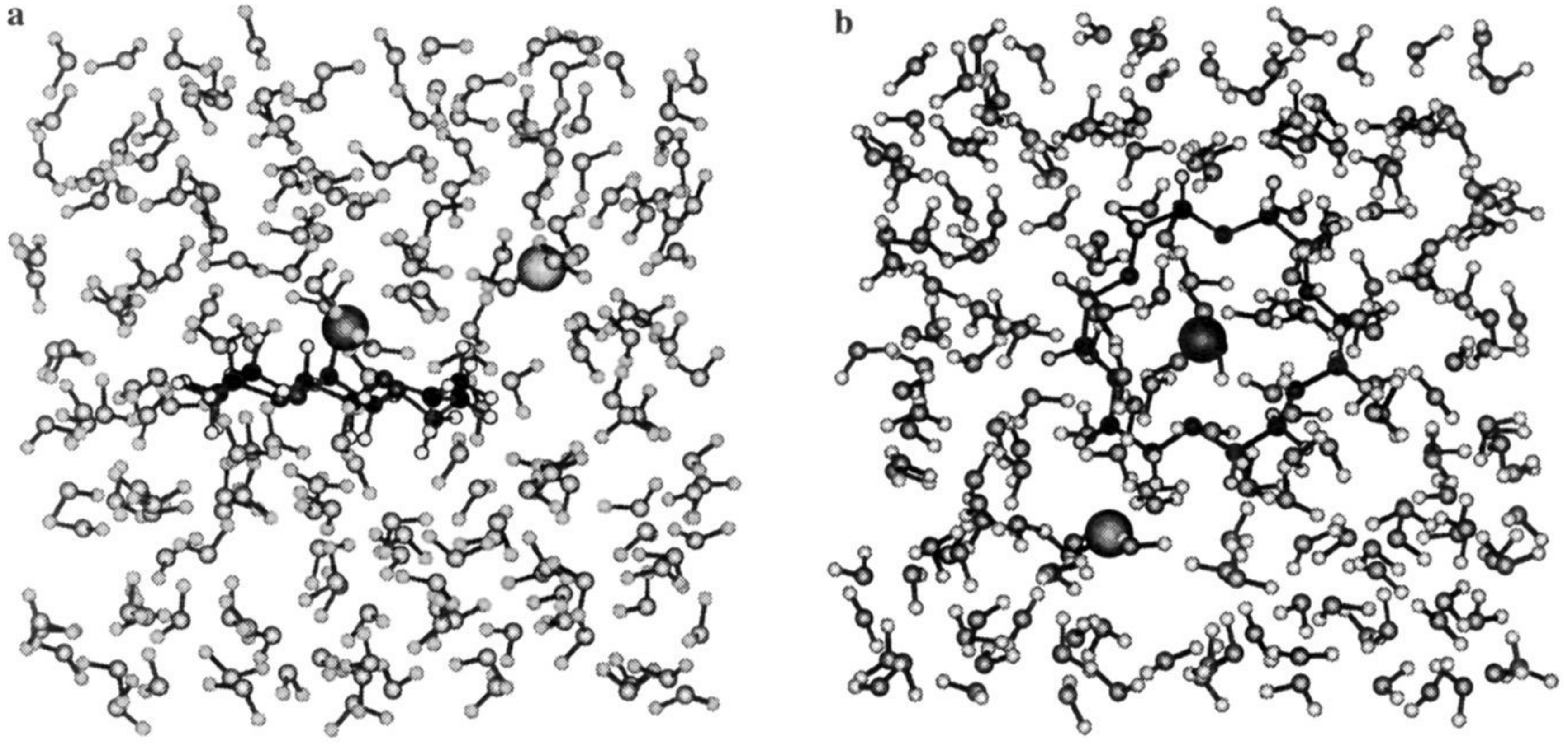

Figure 7. A snapshot of the complex Cs^+:18-crown-6:Cl^- in water: (a) side view and (b) top view. The Cs^+ ion is displaced 1.8 Å away from the crown ether center of mass.

water molecule sits above the ring and makes two hydrogen bonds to nonadjacent oxygens with a total interaction energy of ca. 10 kcal/mol as presented in Figure 4. From these results, we conclude that our model provides a reasonable description of the energetic and structural properties of the solvated ions, ion−crown interactions, and water−crown interactions and that it is appropriate to use this model in the subsequent study of the selectivity of crown ethers in aqueous solutions.

B. Free Energy Profiles. The main thrust of this paper is on the ion−crown ether free energy profile and the corresponding binding free energy. We begin the discussion with details of the free energy profile for the interaction of the Cs^+ ion with the crown ether in water, the convergence of the free energy calculations, and the role of counterion. We then compare the Cs^+ ion results with the corresponding results obtained for other ions, K^+, Rb^+, and Na^+. The calculated pmf for the Cs^+ ion interacting with the crown ether is shown in Figure 5. The numerical value of the pmf is set to zero at a separation of 5.8 Å. We feel this is a reasonable approximation, because the free energy changes beyond this point are essentially zero (i.e., less than 0.05 kcal/mol) and the pmf curve is very flat from 5.0 to 5.8 Å. The pmf data resulting from these simulations indicate that a broad minimum occurs near 1.8 Å with a dissociation barrier height of 3 kcal/mol, and a shallow minimum occurs around 4.5 Å. This small barrier height is indicative of a weakly bound Cs^+ ion to 18-crown-6 ether in water. The first minimum near 1.8 Å is somewhat larger than the corresponding gas-phase result and is probably due, in part, to the competition between the water−cation and the cation−18-crown-6 ether interactions or maybe due to the deficiency in ion potential parameters. We examine the convergence of our free energy calculations by displaying in Figure 6 the computed pmfs as a function of the accumulation time. It is clear that the simulations with 60−80 ps of averaging for each ion−crown separation appear to converge. The results of the 80 ps simulation are used throughout this discussion.

The binding free energy of -0.5 ± 0.2 kcal/mol, obtained by integrating the pmf $W(r)$ derived here up to the top of the barrier height, is in reasonable agreement with values ranging from -0.8 to -1.0 kcal/mol reported recently by Bonas et al. from mass spectrometry measurements on the same system.[25] The error was estimated by taking the difference of the computed binding free energy from the first half and the last half of the total trajectory. The binding free energy is likely to be less negative when using an angular dependent pmf, $W(r,\theta)$, as discussed previously.[17] This deficiency can be overcome by improving the Cs^+:18-crown-6 interaction potential and/or taking into account the nonadditive effects in these molecular complex systems.

During the dynamics simulation, we examined the conformation of the crown ether as a function of the cation−crown ether separation and found it retains its D_{3d} conformation with small fluctuations. This finding agrees with the complex observed in the solid state[21] or simulated in vacuo.[26] We have also monitored the Cs^+...Cl^- distances and found, with the exception of a short period of 50 ps, that the counterion is far enough from the complex to be relatively unimportant. Figure 7 depicts a snapshot of the Cs^+:18-crown-6:Cl^- complex in water at the first minimum of the potential of mean force. It is clear that the conformation of the crown ether is D_{3d} and the counterion Cl^- appears to be far away from the complex.

Figure 8 presents a comparison between the free energy profiles of association of the Cs^+, Rb^+, and K^+ ions to the crown ether molecule in water, respectively. While the pmfs appear to be similar at large cation−crown ether separations (i.e., $r >$ 3.0 Å), at short-range separations, they are significantly different. Figure 8 clearly indicates that, as the ions size decreases from that of Cs^+ to that of K^+, it is accompanied by a shift in the minima free energy surface toward the center of mass of the crown ether. This trend agrees with the observations reported from the X-ray crystallography data.[21] Moreover, the K^+:18-crown-6 pmf shows that the potassium ion fits well into the cavity of the crown ether. Subsequently, its dissociation energy is significantly larger than that found for the other complexes. This is an indication that the K^+ ion is strongly bound to the crown ether in water. During the dynamics simulations, the conformations of the crown ether molecule in the K^+:18-

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(26) Wipff, G.; Weiner, P.; Kollman, P. A. *J. Am. Chem. Soc.* **1982**, *100*, 3249.

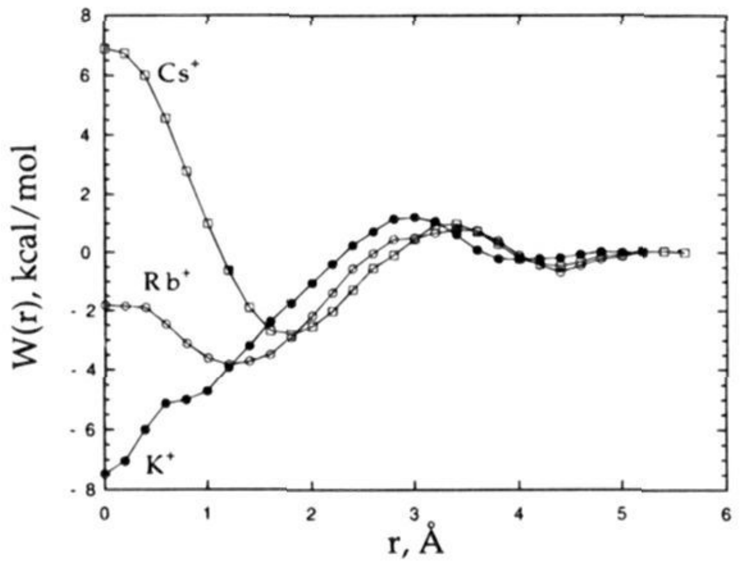

Figure 8. The pmf for the association of the M^+:18-crown-6 ($M^+ = K^+, Rb^+, Cs^+$) in water near 300 K. $r = 0$ Å corresponds to the crown ether center of mass.

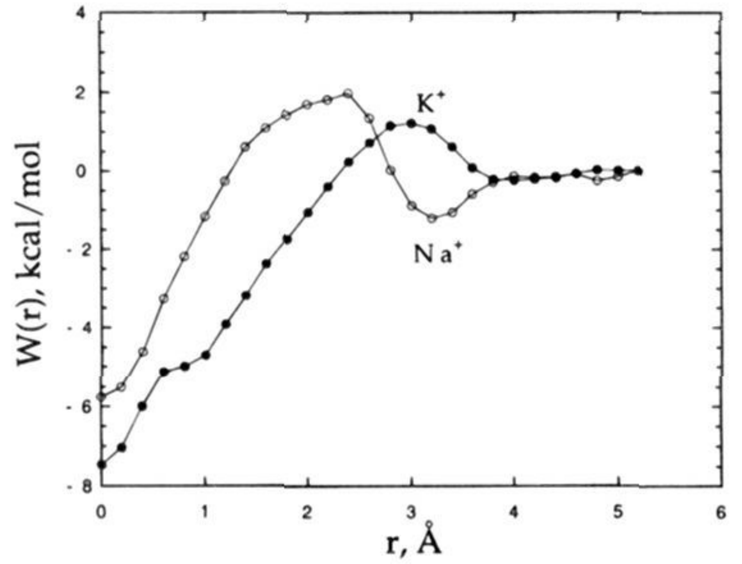

Figure 9. The pmf for the association of the M^+:18-crown-6 ($M^+ = Na^+, K^+$) in water near 300 K. $r = 0$ Å corresponds to the crown ether center of mass.

crown-6 and Rb^+:18-crown-6 complexes are monitored and found to retain their initial D_{3d} conformations. Thus, it seems that the selectivity of the K^+ over Cs^+ and Rb^+ by the crown ether in water is primarily due to the size effects.

The selectivity of K^+ over Na^+ by the crown ether in water is more complicated and involves the competition between the cation–crown and cation–water interactions. As shown in Figure 9, the resultant pmfs indicate that minima free-energy surfaces for association of the K^+ and Na^+ ions to crown ether in water are located at the crown ether center-of-mass, which are in accord with the X-ray data.[21] While the dissociation free energies of both complexes in water are very similar, the pmf of the Na^+:18-crown-6 complex exhibits a well-defined second minimum around 3.0 Å with an association barrier height of about 3.5 kcal/mol. This is significantly larger than the corresponding result for the K^+:18-crown-6 pmf and is mainly due to the larger Na^+ solvation energy, i.e., a greater free energy is required to displace water molecules from Na^+, as it approaches the crown ether center of mass. Figure 10 depicts a snapshot of the Na^+:18-crown-6 in water at the minimum free energy surface. It is clear that the crown ether retains its C_1 conformation, although it seems to flatten out due to the solvent effects. We address the selectivity issue of the crown ether in solution by computing the binding free energies for the entire sequence. We find the calculated binding free energies underestimate the experimental measurements; however, they follow the correct sequence $K^+ > Rb^+ > Cs^+ > Na^+$ as summarized in Figure 11.

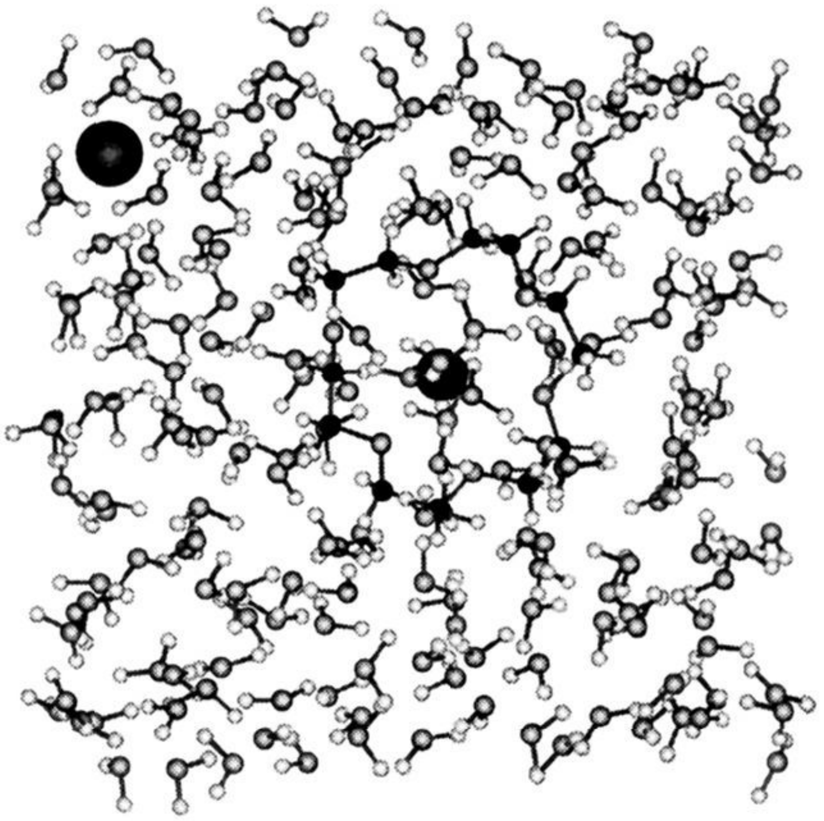

Figure 10. A snapshot of the complex Na^+:18-crown-6:Cl^- in water. The Na^+ ion is at the crown ether center of mass.

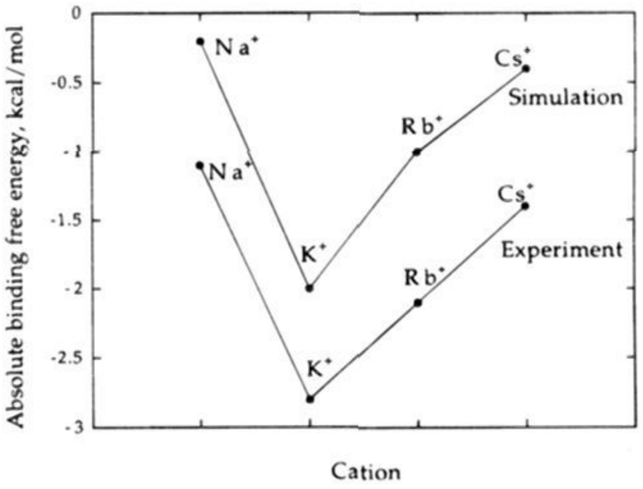

Figure 11. A comparison between molecular dynamics simulations and experimental measurements of absolute binding free energies for the cation–crown ether interactions in water.

IV. Conclusions

We have computed the free energy profiles or potential of mean force and the corresponding binding free energies for M^+:18-crown-6 ($M^+ = K^+, Na^+, Rb^+, Cs^+$) complexation in water via classical molecular dynamics methods and molecular mechanic potential models. The simulations use the Ewald summation method to evaluate the long-range interactions. The effects of the counterion are also considered. To the best of our knowledge, this work is the first to employ the potential of mean force approach to the evaluation of the crown ether selectivity in aqueous solutions.

The resultant potentials of mean force indicate that minima free energy surfaces for the K^+ and Na^+ ions are located at the crown ether center of mass, similar to the results reported from the X-ray crystallography data.[20] In addition a well-defined second minimum is observed in the potential of mean force of the Na^+:18-crown-6 complex in water. This is an indication that unlike K^+, Rb^+, and Cs^+, the Na^+ prefers to be solvated rather than desolvated. It seems that the K^+ is selected over Na^+ because of the greater free energy required to displace water molecules from Na^+ as it approaches the crown ether center of mass. The calculated pmfs clearly indicate that the selection of K^+ over Rb^+ and Cs^+ in water is primarily due to the size of the cation relative to that of the crown–ether cavity. We find the calculated binding free energies compare reasonably with experimental measurements and they follow the correct sequence $K^+ > Rb^+ > Cs^+ > Na^+$.

These results have demonstrated that the computer simulation techniques in conjunction with the potential of mean force approach can be successfully applied to a variety of chemical and physical problems. Our work is not only able to reproduce the experimental observations. It also provides a detailed physical description of the mechanism for ion selectivity in macrocylic crown ethers in aqueous solutions. However, a quantitative agreement with experimental measurements would required more advanced potential models than those employed in the present study, i.e., nonadditive polarization potentials.[16] Simulations of divalent cation−crown molecule interactions and substituted crown ether with a variety of functional groups in aqueous solution are currently in progress.

Acknowledgment. This work was performed under the auspices of the Division of Chemical Sciences, Office of Basic Energy Sciences, U.S. Department of Energy under Contract DE-AC06-76RLO 1830 with Battelle Memorial Institute, which operates the Pacific Northwest Laboratory, a multiprogram national laboratory. Computer resources were provided by the Division of Chemical Sciences and by the Scientific Computing Staff, Office of Energy Research, at the National Energy Research Supercomputer Center (Livermore, CA). I thank Professor Peter A. Kollman at the University of California, San Francisco for his contribution to the early stage of this work and Dr. Ramona Taylor at PNL for critically reading the manuscript.

JA9503037