

Selectivity of 12-Crown-4 to Cations in CH₃OH: A Monte Carlo Simulation Study

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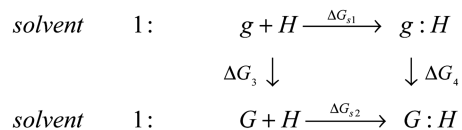
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Crown ethers¹ display the ability to selectively bind specific metals cations in the presence of complex aqueous mixtures of chemically similar ions. For example, 15-crown-5 binds Na⁺ and 18-crown-6 binds K⁺ selectively, although the configuration of crown depends on the solvents used. That ability is thought to be dependent on the size of the crown cavity, a balance between cation-ether and cation-water interactions, the polarity of solvent² and the nature of the electron donor atoms in the ring. These characteristics have been used in the design of novel materials for such processes as isotope separations,^{3,4} ion transport through membrane,⁵ and transport of therapeutic doses of radiations to tumor sites.⁶ Theoretical calculations based on molecular mechanics (MM) and molecular orbital (MO) theories give structures in a vacuum, however, those results cannot be directly compared with those of experiments. In the host-guest interaction, factors in the selective extraction of any host species include the relative free energy of desolvation of the guest molecules and the free energy of organizing the host into a suitable conformation having remote substitution for binding.⁷ Because of the large number of particles forming these systems and the variety of different interactions established, molecular dynamics (MD) and Monte Carlo (MC) statistical mechanics computer simulations are well-suited theoretical tools for understanding and predicting the physicochemical properties of those solutions at the microscopic level.⁸ Several statistical mechanical procedures have evolved for computing free energy differences.⁹⁻¹¹ It is known that solvent effects often play an important role in determining equilibrium constants, transition states and rates of reactions, π -facial selectivity, conformations, and other quantities of chemical, chemical physics and biochemical interest.¹² Therefore, computational chemists have focused their interests on the crown ethers as those molecules are the simplest that show enzyme-like specificity. However, few molecular dynamics (MD) and Monte Carlo (MC) statistical mechanics computer simulation studies of both the selectivity of 12-crown-4 (1,4,7,10-tetraoxacyclododecane) to univalent cations and $\Delta \log K_s$, are available. This prompted us to study the selectivity of 12-crown-4 to univalent cations and $\Delta \log K_s$ using Monte Carlo simulations of statistical perturbation theory (SPT) in CH₃OH.¹³ Experimental studies of the selectivity of 12-crown-4 to univalent cations in methanol and *ab initio* studies of 12-crown-4 with univalent cations have been reported.¹⁴ In this note, we present the first calculation to computing on the selectivity of 12-crown-4 to

entire series of univalent cations and $\Delta \log K_s$ of 12-crown-4 to entire series of univalent cations in CH₃OH using a Monte Carlo simulation of SPT.¹⁵ We found 12-crown-4/cation complexes with the 12-crown-4 of almost C_s symmetry never found in any crystal structure of the cation complexes of 12-crown-4. Those are the reasons why this study is communicated as note.

The calculated relative binding Gibbs free energies (selectivity index) of 12-crown-4 complexes and the published data of the relative free energies^{14(a)} and $D \log K_s$ ¹⁶ (the difference of stability constant of binding) obtained using by (1) shown in Scheme 1, are listed in Table 1. We have noticed that 12-crown-4 binds K⁺ more tightly than the other cation in CH₃OH, *i.e.*, the selectivity of 12-crown-4 to K⁺ is more favorable than to other cations in CH₃OH. A similar trend has been observed in the study of alkali cation complexes of 18-crown-6 and its derivatives in CCl₄ solutions⁷ and in the study of alkali cation complexes of 18-crown-6 in diverse solutions.^{13(a),(b)} Binding selectivity is often associated with the ionic radius of the cation and the size of the crown ether cavity that it will occupy. The larger mismatch is existed between the ionic radius of the cation and the size of the crown ether cavity, the smaller chance that the cation binds favorably to the crown ether cavity. 12-crown-4 has distances between diagonal oxygen atoms of 4.0 Å and selectively binds K⁺ over the other cations in CH₃OH where the cationic radius of K⁺ is 1.38 and the others are 0.74, 1.02, 1.49, and 1.7 Å, respectively.^{13(b)} Selectivity is apparently the result of a delicate balance of the forces that the cation experiences as the crown ether and solvent molecules compete for the cation in solution. In this study, the cations



$$\Delta \log K_s = \log K_{s2} - \log K_{s1} = (\Delta G_{s2} - \Delta G_{s1}) / 2.3RT \quad (1)$$

$$\Delta \Delta G = \Delta G_{s2} - \Delta G_{s1} = \Delta G_4 - \Delta G_3$$

$$H = 12\text{-crown-4}, g = M^+ \text{ and } G = M^+$$

$$M^+: \text{Li}^+, \text{Na}^+, \text{K}^+, \text{Cs}^+, \text{Rb}^+$$

Scheme 1. Thermodynamic Cycle Perturbation Theory.

Table 1. Relative Binding Gibbs Free energies ($\Delta\Delta G$, kcal/mol) and Differences in the Stability Constant of Binding ($\Delta\log K_s$) in CH_3OH

System	$\Delta\Delta G$ of binding		$\Delta\log K_s$	
	Cal.	Exp. ^a	Cal.	Exp. ^a
$\text{Na}^+ \rightarrow \text{Li}^+$	-3.81	-1.92 ~ -3.12	-2.79	-1.41 ~ -2.29
$\text{K}^+ \rightarrow \text{Na}^+$	-0.18	-0.16 ~ -0.23	-0.13	-0.12 ~ -0.17
$\text{Rb}^+ \rightarrow \text{K}^+$	0.25	-	0.18	-
$\text{Cs}^+ \rightarrow \text{Rb}^+$	-0.28	-	-0.21	-

^aRef. 14a.

have one positive charge and the binding cores of the hosts consist of four oxygen atoms with large partial negative charges. Electrostatic interactions are also expected to play an important role in the determining the cation-binding ability of 12-crown-4 systems as noted in ref. 14(b). We address the selectivity of 12-crown-4 to cations in CH_3OH solution by computing the relative binding free energies of 12-crown-4 complexes for an entire series of univalent cations. Comparing the relative binding free energies of 12-crown-4 complexes, in CH_3OH in this study with those in ref. 14(a), those of 12-crown-4/ Na^+ to Li^+ complexes and 12-crown-4/ K^+ to Na^+ complexes in CH_3OH of this study are -3.81 and -0.18 kcal/mol, those of CH_3OH in ref. 14(a) are -1.92 ~ -3.12 and -0.16 ~ -0.23, respectively. In contrast to them, those of 12-crown-4/ Rb^+ to K^+ complexes and 12-crown-4/ Cs^+ to Rb^+ complexes are expected to be reliable. From those data, the calculated binding free energy of 12-crown-4/ Na^+ to Li^+ complexes in CH_3OH solutions are found to be a little underestimated compared with the experimental data. However, the selectivity of 12-crown-4 to cations followed the sequence as $\text{Cs}^+ > \text{K}^+ > \text{Rb}^+ > \text{Na}^+ > \text{Li}^+$ *i.e.*, the selectivity of 12-crown-4 to Cs^+ is more favorable than to other cations in CH_3OH .

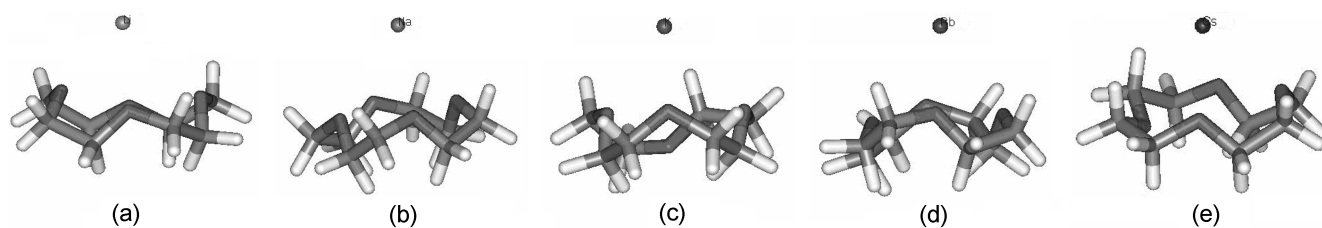
The calculated differences in stability constant ($\Delta\log K_s$) of binding of cations to 12-crown-4 can be on the basis of relative binding Gibbs free energies. The signs of differences in stability constant ($\Delta\log K_s$) of binding of univalent cations to 12-crown-4 are negative except for 12-crown-4/ Rb^+ to K^+ complexes. A negative sign of $\Delta\log K_s$ implies that 12-crown-4 binds larger cations more tightly than smaller ones but positive sign implies that 12-crown-4 binds smaller cations more tightly than larger ones. Comparing $\Delta\log K_s$ of 12-crown-4 complexes, in CH_3OH in this study with those in ref. 14(a), those of 12-crown-4/ Na^+ to Li^+ complexes and 12-crown-4/ K^+ to Na^+ complexes in CH_3OH of this study

are -2.79 and -0.13, those of CH_3OH in ref. 14(a) are -1.41 ~ -2.29 and -0.12 ~ -0.17, respectively. In contrast to them, those of 12-crown-4/ Rb^+ to K^+ complexes and 12-crown-4/ Cs^+ to Rb^+ complexes are also expected to be reliable. It is necessary to note that the sign and magnitude of the calculated $\Delta\log K_s$ closely parallel the relative binding Gibbs free energies

When 12-crown-4 is in uncomplexed, 12-crown-4 has minimum-energy geometry with S_4 symmetry that is quite different from C_4 geometry of ligand when it is complexed. A critical difference in these two geometries is orientation of the oxygen atoms in the ring. The S_4 symmetry has two oxygen atoms pointing to one side of the ring and two pointing to the other side, such that the oxygen dipoles interact weakly with one another. In the C_4 symmetry, all of oxygen atoms point to one side of the ring, such that an alkali cation can interact strongly with all four oxygen atoms.

The stereo-plots of the configurations of 12-crown-4/ M^+ (here, M^+ : Li^+ , Na^+ , K^+ , Rb^+ , and Cs^+) complexes without solvent molecules for clarity are given in Figure 1. From those configurations, all cations are displaced away from the 12-crown-4 center of mass plane. The 12-crown-4 of among 12-crown-4/ Li^+ ion complex, 12-crown-4/ Na^+ ion complex and the 12-crown-4/ Rb^+ ion complex in CH_3OH solutions has almost the C_4 symmetric conformation with each of its oxygen centers directed outward from the ether backbone as shown in Figure 1(a), (b), and (d). The crystal structure of many cation complexes of 12-crown-4 shows C_4 symmetry.¹⁴ Kim *et al.*^{14(b)} reported *ab initio* structure of the Li^+ ion complexes of 12-crown-4 under C_4 symmetry. They also found that 12-crown-4 of S_4 symmetry and Li^+ ion complexes of 12-crown-4 of C_4 symmetry are the most stable conformers. Feller *et al.*^{14(c)} also reported *ab initio* structures of the cation complexes of 12-crown-4 under C_4 symmetry. They^{14(c)} also found that Cs^+ ion is displaced far away from the crown ether center of mass plane more than other cations are. From the xyz coordinate obtained by our simulations, we also noted that Cs^+ ion is displaced away from the crown ether center of mass plane more than other cations are. For clarity, the data are not listed.

However, the 12-crown-4 of both 12-crown-4/ K^+ ion complex and the 12-crown-4/ Cs^+ ion complex in CH_3OH solutions shown in Figure 1(c), (e) has the C_s conformation¹⁷ with three oxygen pointing to one side of the ring and one pointing to the other side. Those 12-crown-4/cation complexes with the 12-crown-4 of the C_s conformation with

**Figure 1.** Side-view stereo plots of the 12-crown-4/cation complexes without solvent molecules for clarity; (a) 12-crown-4/ Li^+ (b) 12-crown-4/ Na^+ (c) 12-crown-4/ K^+ (d) 12-crown-4/ Rb^+ (e) 12-crown-4/ Cs^+

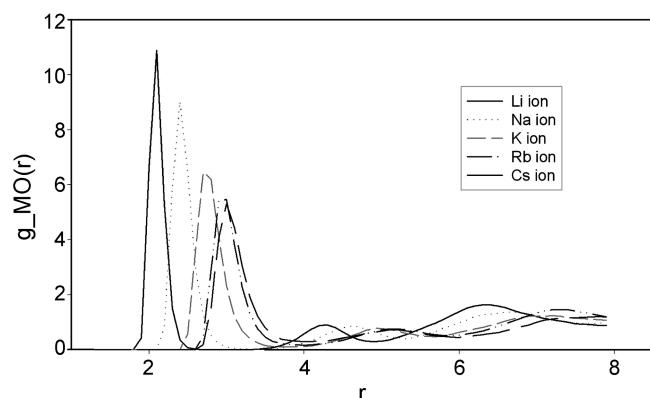


Figure 2. Radial distribution function $g_{MO}(r)$ of 12-crown-4/ M^+ ions in CH_3OH . Distances are in angstroms.

three oxygen pointing to top of the ring and one oxygen pointing to the other side have been never found in any crystal or *ab initio* structure of the cation complexes of 12-crown-4. From our results, we found that 12-crown-4/cation complexes with the 12-crown-4 of the C_s conformation with three oxygen pointing to top of the ring and one oxygen pointing to the other side are more stable in CH_3OH solutions than 12-crown-4/cation complexes under C_4 symmetry.

Both the calculated and the experimental results are sensitive to the definition of coordination number. A wide range of experimental hydration numbers is available from mobility measurements. Those values correspond to the number of solvent molecules that have undergone some constant critical change due to the complex, a change that is susceptible to measurement by a particular experimental technique. Such hydration numbers are often quite different from coordination numbers based on a structural definition, like those from diffraction experiments. Mezei and Beveridge obtained their values by integrating the ion-center of mass of water radial distribution function(RDF)'s up to the minimum of the first peaks.¹⁸ These values will not be significantly different if they are based on ion-oxygen RDF's. This is a straightforward definition and this has been adopted for all the calculated value for 12-crown-4/ M^+ ions.

The RDF of 12-crown-4/ M^+ ions complexes in CH_3OH is plotted in Figure 2. As shown in Figure 2, the first maximum sites of the 12-crown-4/ M^+ ions complex CH_3OH follows 12-crown-4/ Li^+ < 12-crown-4/ Na^+ < 12-crown-4/ K^+ < 12-crown-4/ Rb^+ < 12-crown-4/ Cs^+ . The heights of the first peak of the $g_{MO}(r)$ are changed from 12-crown-4/ Li^+ ion complex to the 12-crown-4/ Cs^+ ion complex. That may be attributed to interaction changes among 12-crown-4/ M^+ ion complex molecules and solvent molecule *i.e.* the coordination number (CN) changes of solvent molecules in the first coordination shell from 12-crown-4/ Li^+ ion complex to the 12-crown-4/ Cs^+ ion complex. In Figure 2, the second peaks are located between 6 and 8 Å in CH_3OH . As shown in Figure 2, the second peak of 12-crown-4/ Li^+ ion complex has the bigger peak intensity than the other, which indicates that 12-crown-4/ Li^+ ion complex in CH_3OH has the clear

second solvation shell. Those could be explained by the fact that the relatively stronger complex molecule-solvent molecule interactions exist in 12-crown-4/ Li^+ ion complex. In RDF, the $g_{MO}(r)$ s of 12-crown-4/ Li^+ ion complex drop to zero between the first peak and the broad second one, which indicates the absence of solvent exchange between the first and second shell in simulations. From our results, we have noted that the degree of the complex-solvents interactions is dependent on the electron pair donor properties of the solvent and the differences in solvation.¹⁹

Computational (or Experimental) Section

Monte Carlo simulations of SPT were carried out in the isothermal-isobaric ensemble at 25 and 1 atm. The model systems typically consisted of the ion and 12-crown-4 plus 250 solvent molecules in a cubic cell with periodic boundary conditions.¹³ In order to study the equilibrium thermodynamics of binding, we have used Monte Carlo simulations with the thermodynamic cycle-perturbation theory^{10(a)} shown in scheme 1 and doublewise sampling. The OPLS (optimized potential for liquid simulation) potential parameters are used for solvent and those are based on a united-atom model. The 12-crown-4 is represented with the OPLS-AA force field in this study.¹⁵ In all the calculations, the bond lengths, bond angles and dihedral angles have been varied in energy minimization step of 12-crown-4-ion complex molecule and in simulations. The intermolecular interactions were spherically truncated at 10 Å, depending on box-sizes of solvent and the reaction field method was used for long-range interactions. The cutoff correction to the solvent-solvent energy for non-aqueous solvents is applied to only Lennard-Jones potential functions.

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