

Selectivity of 18-Crown-6 between Cs⁺ and Rb⁺ Ion: Solvent Effect by a Monte Carlo Simulation Study

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We have investigated the solvent effects on $\Delta \log K_s$ (the difference of stability constant of binding) and the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6, that is, the selectivity of Cs⁺ and Rb⁺ ions to 18-crown-6 using a Monte Carlo simulation of statistical perturbation theory (SPT) in diverse solvents. Comparing the stability constant ($\Delta \log K_s$) of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 in H₂O (TIP3P) and CH₃OH in this study with those in the experimental works, those of H₂O (TIP3P) and CH₃OH in this study are 0.80 and 1.57 and those of H₂O and CH₃OH in the experimental works are 0.57 and 0.61–1.24, respectively. There is a good agreement among the studies. We have reported here the quantitative solvent–polarity relationships (QSPR) studied on the solvent effects the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6. From the calculated coefficients of QSPR, we have noted that DN dominates the differences in relative solvation Gibbs free energies of Cs⁺ and Rb⁺ ions but Aj dominates the differences in the stability constant ($\Delta \log K_s$) as well as the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6. Also, Born's function of the solvents, the polarities of the solvents, and the differences in solvation dominate the differences in the stability constant ($\Delta \log K_s$) as well as the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6.

1. Introduction

To comprehend such phenomena as binding and rate selectivity in metalloenzymes, ion-binding proteins, ion channels, and ion-selective macrocycles systems, it is necessary to be able to model the relevant host–guest interaction on a microscopic level. The study of molecular recognition for host–guest interactions^{1–4} has received an increasing interest, since the discovery of crown ethers by Pedersen at DuPont.⁵ In addition to the host–guest interaction, factors in the extraction selectivity 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 with remote substitution for binding.⁶ Complexing agents such as crown ethers display a wide range of binding specificities and the association properties of crown ethers with alkaline cations have been mainly described in terms of similarities between cation size and the size of the inner hole of the crown ether.² Interaction between cations (guests) and crown ethers (hosts) in solution are widespread and the ability of the crown ether to select one cation over the other in solution is important in environmental research. Especially, crown ethers have been proposed as separation agents for removing metal (i.e., Cs⁺ and Sr²⁺) from mixed nuclear and chemical wastes.^{7a} Another practical application of the crown ethers is for treatment of cancerous tissue.^{7b} Monoclonal antibodies can be designed to transport therapeutic doses of radioactivity to the tumor site. By directly attacking the site, this treatment spares normal tissue that is destroyed in conventional radiation therapy. The present study is far away from those actual applications; it gives useful information of the selectivity for crown ethers to ions.

Solvation plays a major role in ion selectivity processes by influencing the stability and nature of host–guest complexes. Because of the large number of particles forming these systems and the variety of different interactions established, molecular dynamics (MD) and Monte Carlo statistical mechanics (MC) computer simulations represent particularly adequate theoretical tools for understanding and predicting the physicochemical properties of those solutions at the microscopical level.^{8–10} To address those challenges and the phenomena themselves, we need the information of selectivity of 18-crown-6 for alkali metal cations in solution. These could be obtained from the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane) in solution.

Several statistical mechanical procedures have evolved for computing free-energy differences. Two particularly promising approaches are umbrella sampling^{11–15} and a perturbation procedure^{16,17} in which one ion is mutated into the other. Especially the ability to accurately calculate solvation free energies of molecules using the perturbation procedure is one of the important and recent developments in computational chemistry.¹⁸

Solvent effects often play an important role in determining equilibrium constants, transition states, and rates of reactions, π -facial selectivity,¹⁹ conformations, and the other quantities of chemical, chemical physics, and biochemical interest. However, few studies of solvent effects on both the relative free energies of binding of ions to 18-crown-6 and $\Delta \log K_s$ are available.

In this study, we have investigated the solvent effect on the relative stability constant of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 and the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6, using Monte Carlo simulation of statistical perturbation theory (SPT). H₂O (TIP3P, TIP4P models), CHCl₃, CH₃CN, THF, CH₃OH, CCl₄, MeCl₂, MEOME,

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and C₃H₈ are selected as solvents.²⁰ Experimental studies of the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 in water and methanol have been reported. The study to calculate $\Delta \log K_s$, as well as the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 in diverse solvents, is not available.

We present the first calculation to computing solvent effects on the differences in $\log K_s$ (stability constant) as well the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 using Monte Carlo simulation of statistical perturbation theory (SPT) in this study. We have first reported here the quantitative solvent–polarity relationships (QSPR) studied on the solvent effects on the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6. This study provides additional interests of the solvent effect on equilibrium constants, transition states, rates of the organic reaction,²¹ and the other quantities of chemical, biochemical, and chemical physics interest.

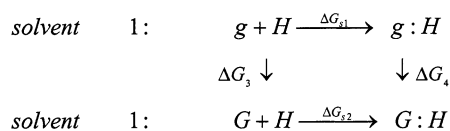
The paper is organized as follows. In section 2, we describe the computational details, that is, Monte Carlo simulations and potential functions that were used. Section 3 presents the results and discussion, that is, relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 and relative binding Gibbs free energies of Cs⁺ and Rb⁺ ions to 18-crown-6, relative stability constants of Cs⁺ and Rb⁺ ions to 18-crown-6, the quantitative solvent–polarity relationships (QSPR) studied on the solvent effects, the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6, and the structural properties and radial distribution function of Cs⁺ and Rb⁺ ions in 18-crown-6 complex to solvents obtained by simulations. The conclusion is summarized in section 4.

2. Computational Details

2.1. Monte Carlo Simulations. The procedure used here is similar to that employed to study in refs 22a, 23, 24, 25, and 27. Monte Carlo simulations were carried out in the isothermal–isobaric ensemble at 25 °C and 1 atm for systems typically consisting of the ion and 18-crown-6 plus 255 solvent molecules in a cubic cell with periodic boundary conditions. First, the Monte Carlo simulations are described, including a summary of the method for computing the relative free-energy changes and a brief discussion of the potential functions is given. The free-energy changes were obtained via a series of five separate simulations with SPT in forward and backward directions.^{18,22a–27}

To study the equilibrium thermodynamics of binding, we have used Monte Carlo simulations with the thermodynamic cycle–perturbation theory and doublewide sampling.^{22a–27}

In the notation of this method, the relative free energy of binding between guest G and g to the host H can be expressed as $\Delta \Delta G = \Delta G_{s2} - \Delta G_{s1} = \Delta G_4 - \Delta G_3$



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

$$\Delta G_{s2} = -2.3RT \log K_{s2} \quad (2)$$

Here, ΔG_s is free energies of binding of guest to host and any thermodynamic state function and $\log K_s$ is stability constant of guest to host.

From the cycle, eq 3 is obtained which yields eq 4.

The last expression associates the difference in $\log K_s$'s with the difference in the relative free energies of binding of Cs⁺ and Rb⁺ ion to 18-crown-6²⁸ in one solvent.

$$\Delta G_{s2} - \Delta G_{s1} = \Delta G_4 - \Delta G_3 \quad (3)$$

$$\Delta \log K_s = \log K_{s2} - \log K_{s1} = (\Delta G_{s2} - \Delta G_{s1})/2.3RT \quad (4)$$

In this study, the substitutions are H = 18-crown-6, g = Rb⁺, and G = Cs⁺. ΔG_{s1} and ΔG_{s2} are available from Monte Carlo simulation in which guest is binding to host in the solvents.

Simulations were run for a coupling parameter, λ_i , which was used to smoothly transform Cs⁺ with 18-crown-6 ($\lambda = 0$) to Rb⁺ with 18-crown-6 ($\lambda = 1$). In this context, it is convenient to define a coupling parameter λ that allows the smooth conversion of system 0 to 1. Simulations were run for $\lambda_i = 0.0, 0.2, 0.4, 0.6, 0.8$, and 1.0. Then, for many possible features ζ of the systems including geometrical and potential function parameters, eq 5 can be used to represent the mutation of system 0 to 1 as λ goes from 0 to 1:^{22a–25}

$$\zeta(\lambda) = \zeta_0 + \lambda(\zeta_1 - \zeta_0) \quad (5)$$

In this study, each simulation entailed an equilibration period for 4×10^6 configurations starting from equilibrated boxes of solvent, followed by averaging for 2×10^7 configurations. Little drift in the averages was found during the last 1×10^7 configuration.^{22a–25} Metropolis and preferential sampling methods were employed in simulations, and the ranges for attempted translations and rotations of the solute and solvent molecules were adjusted to give a ca. 45% acceptance rate for new configurations.^{22a–25}

2.2. Potential Functions. The pair potential energy function of the OPLS force field is of the following form:²⁰

$$E_{\text{total}} = \sum_{\text{bonds}} K_r(r - r_0)^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_0)^2 + \sum_{\text{torsions}} \frac{V_n}{2} [1 \pm \cos(n\phi - \gamma)] + \sum_{\text{non-bonded}} \left[\frac{A_{ij}}{r_{ij}^{12}} - \frac{C_{ij}}{r_{ij}^6} + \frac{q_i q_j}{\epsilon r_{ij}} \right] f_{ij} \quad (6)$$

$$f_{ij} = 0.5 \text{ if } i, j \text{ are } 1, 4; \text{ otherwise, } f_{ij} = 1.0$$

where K_r , K_θ , V_n , and ϕ are empirical parameters related to bond length, bond angle, and torsion angle, respectively. The ion and molecules are represented by interaction sites located on nuclei that have associated charge, q_i and Lennard-Jones parameter σ_i and ϵ_i . One of the standard rules is used such that $A_{ij} = (A_{ii}A_{jj})^{1/2}$ and $C_{ij} = (C_{ii}C_{jj})^{1/2}$. Furthermore, the A and C parameters may be expressed as $A_{ii} = 4\epsilon_i\sigma_i^{12}$ and $C_{ii} = 4\epsilon_i\sigma_i^6$ where σ and ϵ are the Lennard-Jones radius and energy terms and i and j indices span all of the 18-crown-6, solvents, and water sites. In ref 29, Jorgensen noted that the equation has been dominant with two-body potential functions that are parametrized to take the higher-order interaction and polarization effect into account. In ref 6, Kollman et al. also concluded that the additive force field model is adequate to describe energetics of cation complexation with 18-crown-6.

The OPLS (optimized potential for liquid simulation) potential parameters are used for solvents and those are based on a united-atom model^{22a,20} but the TIP4P and TIP3P models have been used for water.²⁰ The 18-crown-6 is represented with the OPLS all-atom (AA) force field.²⁰ The charges and Lennard-Jones parameters have been selected to yield correct thermodynamic and structural results of pure liquids.²⁰ The results were obtained

TABLE 1: Relative Solvation Gibbs Free Energies (kcal/mol) and the Relative Binding Gibbs Free Energies (kcal/mol) in Several Solvents and Born's Function of Bulk Solvents

solvent	ΔG			
	ΔG (Cs ⁺ → Rb ⁺) ^c	(18-crown-6/Cs ⁺ → 18-crown-6/Rb ⁺)	$\Delta\Delta G$ of binding	1 - 1/ ϵ
H ₂ O (TIP3P)	-8.24	-9.33 ± 0.40	1.09	0.987
H ₂ O (TIP4P)	-7.52	-8.95 ± 0.33	1.43	0.987
H ₂ O (rigid SPC) ^a	-7.8 ± 1.6			0.987
H ₂ O exp ^b	-7.7			0.987
CH ₃ CN	-7.65	-9.43 ± 0.39	1.78	0.973
CH ₃ OH	-8.77	-10.92 ± 0.56	2.15	0.963
CH ₃ OH exp ^b			0.84-1.68	0.963
MeCl ₂	-4.19	-10.07 ± 0.21	5.88	0.888
THF	-7.80	-10.71 ± 0.24	2.91	0.868
MEOME	-7.49	-11.07 ± 0.28	3.58	0.801
CHCl ₃	-1.75	-10.36 ± 0.20	8.61	0.792
CCl ₄	-1.03	-10.38 ± 0.20	9.35	0.552
C ₃ H ₈	-0.48	-9.82 ± 0.20	9.34	0.138

^a Reference 38. ^b Reference 30. ^c Reference 24.

from Monte Carlo simulations using well-established procedures.²²⁻²⁷

In all the calculations, the bond lengths, bond angles, and dihedral angles have been varied in minimization step and in simulations so that the statistical uncertainties for the computed values are in ($\pm 1\sigma$) fluctuations. The intermolecular interactions were spherically truncated at 8.5, 10, and 12.0 Å, depending on box sizes of solvents.^{22,23}

The cutoff correction to the solvent-solvent energy for nonaqueous solvents is applied to only Lennard-Jones potential functions.²⁰

3. Results and Discussion

3.1. Relative Free Energies of Binding. To study the solvent effect on differences in stability constant ($\Delta \log K_s$) as well as the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6, we have computed those in the two water models and in the other solvents.

The calculated relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 along with the experimental works are listed in Table 1. The reported statistical uncertainties for the computed values are ($\pm 1\sigma$) fluctuations and were obtained from separate averages over 4×10^6 to 20×10^6 configurations. The computed ordering relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 in several solvents is H₂O(TIP4P) > H₂O(TIP3P) > CH₃CN > C₃H₈ > MeCl₂ > CHCl₃ > CCl₄ > THF > CH₃OH > MEOME. This comes about by the change in relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 being more favorable in MEOME than in the polar and less polar or nonpolar solvents. In this study, we have noted that the intermolecular interactions were dependent on box sizes of solvents and the potential cutoff, but the results truncated at 8.5, 10, and 12.0 Å, dependent on box sizes of solvents, are only listed in Table 1 for clarity.

Comparing relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 in H₂O (TIP3P) in this study with that in ref 30, that of H₂O (TIP3P) in this study is -9.33 ± 0.40 kcal/mol and the experimental work in water³⁰ obtained by calorimeter methods is -8.48 kcal/mol. There is good agreement between the studies if we consider both methods used the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 and standard deviations. In contrast to them, the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 in the other solvents is expected to be reliable. The relative free energy of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 in H₂O

(TIP3P) is smaller than that of H₂O (TIP4P). This difference of solvation could be explained by the difference of polarity between water models.

3.2. Relative Binding Gibbs Free Energies. The relative binding Gibbs free energies of 18-crown-6 complexes can be calculated using ΔG_{s1} and ΔG_{s2} in eq 3, and the published data of the relative free energies³⁰ are also listed in Table 1. The ordering of the relative binding Gibbs free energies in several solvents is CCl₄ > C₃H₈ > CHCl₃ > MeCl₂ > MEOME > THF > CH₃OH > CH₃CN > H₂O(TIP4P) > H₂O(TIP3P). This comes about by the change in relative binding Gibbs free energies being more favorable in H₂O (TIP3P) than in the polar and less polar or nonpolar solvents. That is, 18-crown-6 binds Rb⁺ more tightly than Cs⁺ in all solutions, that is, the selectivity of 18-crown-6 to Rb⁺ is more favorable than to Cs⁺ in all solvents. A similar trend has been observed in the study of alkali cation complexes of 18-crown-6 and its derivatives in CCl₄ solutions⁶ and in the study of alkali cation complexes of 18-crown-6 in diverse solutions.^{22a} 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 the mismatch between the ionic radius of the cation and the size of the crown ether cavity, the less that the cation binds favorably. 18-crown-6 has a cavity radius ranging between 1.3 and 1.6 Å, and selectively binds Rb⁺ over Cs⁺ in all solvents where the cationic radii are 1.49 and 1.7 Å, respectively.^{22b} Alkali and alkaline earth metal ion complexes of 18-crown-6 are enthalpy stabilized and entropy destabilized; the opposite is true of and the stability decreases along the series of lanthanide complexes is enthalpic in origin for cations up to Nd³⁺ in CH₃OH. This fact reflects the delicate balance among ligand (18-crown-6)-cation binding, solvation, and ligand conformation that exists in complex systems. The complexes with the higher atomic number are generally more stable than those of the lower atomic number. Selectivity is apparently the result of 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 have one positive charge and the binding cores of the hosts consist of six oxygen atoms with large partial negative charges; electrostatic interactions are also expected to play an important role in determining the cation-binding ability of 18-crown-6 system.^{23,25}

Comparing relative binding Gibbs free energies in H₂O (TIP3P) and CH₃OH in this study with those in ref 30, those of H₂O (TIP3P) and CH₃OH in this study are 1.09 and 2.15 kcal/mol and that of the experimental work in water and CH₃OH³⁰ obtained by using calorimeter, conductance, and ISE methods are 0.78 kcal/mol and 0.84-1.68 kcal/mol, respectively. In contrast to them, the relative binding Gibbs free energies in the other solvents are expected to be reliable.

We address the selectivity of 18-crown-6 in aqueous solution by computing the relative binding free energies of 18-crown-6 complexes for an entire series of monocations from the results obtained by the present work and our published data.^{22a,23} We have found that the calculated binding free energies of 18-crown-6 complexes in aqueous solutions slightly overestimate the experimental data; however, they followed the correct sequence, K⁺ > Rb⁺ > Cs⁺ > Na⁺ as given in Figure 1, that is, our assumed binding free energies of 18-crown-6 complexes in aqueous solutions closely parallel the binding Gibbs free energies of the experimental. There is good agreement between the studies if we consider both methods and potential parameter used to obtain the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 in simulation and standard deviations.

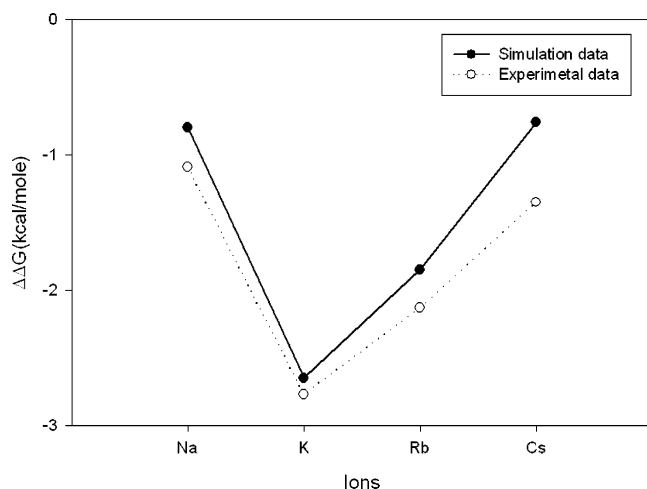


Figure 1. Plot of comparison between the free energies binding of Monte Carlo simulations and experiment data of the free energies of the cation–18-crown-6 interactions in water.

TABLE 2: Differences in the Stability Constant of Cs⁺ and Rb⁺ Ion to 18-Crown-6

solvent	log K_{s2} – log K_{s1}
H ₂ O (TIP3P)	0.80
H ₂ O (TIP4P)	1.05
exp (water) ^a	0.76
CH ₃ CN	1.31
CH ₃ OH	1.57
exp (CH ₃ OH) ^a	0.61–1.24
MeCl ₂	4.32
THF	2.14
MEOME	2.63
CHCl ₃	6.32
CCl ₄	6.87
C ₃ H ₈	6.86

^a Reference 30.

We have first reported here the quantitative solvent–polarity relationships (QSPR) studied for the solvent effects on the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6. Using the following eq 7, we calculated the coefficient of QSPR studied on the solvent effects on the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 using multiparameters regression method.³¹

$$\Delta\Delta G(\Delta G) = m_1 \epsilon + m_2 E_T + m_3 \beta + m_4 \alpha + m_5 \pi^* + m_6 DN + m_7 A_j + m_8 B_j \quad (7)$$

Where ϵ is dielectric constants and E_T is solvent polarity. β , α , and π^* are Kamlet–Taft's solvatochromic parameters. DN is donor number of solvent. A_j is solvent acidity and B_j is solvent basicity.³¹ All of the solvent polarities have been collected from the literature³¹ and are listed in Table 4. The calculated coefficients of QSPR are listed in Table 5. From the coefficients of QSPR data, we have noted that DN and π^* dominate the differences in relative solvation Gibbs free energies of Cs⁺ and Rb⁺ ions but A_j and E_T dominate the differences in the stability constant ($\Delta\log K_s$) as well as the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6.

3.3. Relative Stability Constants. According to eq 4, the differences in stability constant ($\Delta\log K_s$) of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 can be calculated on the basis of relative binding Gibbs free energies. The differences in stability constant ($\Delta\log K_s$) of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 are listed in Table 2. The signs of differences in stability constant ($\Delta\log K_s$) of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 are positive in all solutions. A sign of $\Delta\log K_s$

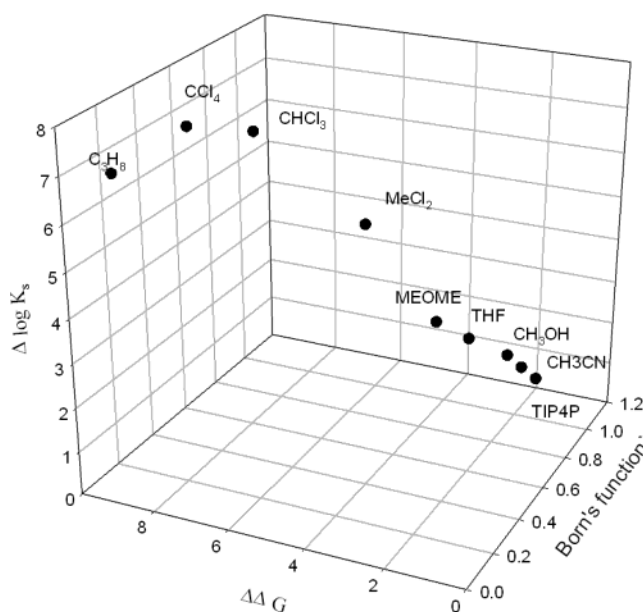


Figure 2. Plot of relative binding Gibbs free energies ($\Delta\Delta G$) of Cs⁺ and Rb⁺ ion to 18-crown-6 and the difference of stability constant ($\Delta\log K_s$) of binding of Cs⁺ and Rb⁺ ion to 18-crown-6 vs Born's function of the solvent at 298 K and 1 atm.

implies that 18-crown-6 binds Rb⁺ more tightly than Cs⁺ in all solutions. The relative binding Gibbs free energies of Cs⁺ and Rb⁺ ions to 18-crown-6 and the differences in stability constant ($\Delta\log K_s$) of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 versus Born's [i.e., $(1 - 1/\epsilon)$, where ϵ is dielectric constant of bulk solvent] function of the solvents are plotted in Figure 2.

As shown in Figure 2, relative binding Gibbs free energies of Cs⁺ and Rb⁺ ions to 18-crown-6 and the differences in stability constant ($\Delta\log K_s$) of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 versus Born's function of the solvent decreased with increasing Born's function of solvents except THF and MEOME. This trend of relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 and relative binding Gibbs free energies could be explained by the differences in solvation. Especially, the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 in THF and MEOME could be explained by the fact that the relatively strong complex–solvent interactions exist in THF and MEOME solutions even though Born's function of THF and MEOME is small in value. The relatively strong complex–solvent interactions in THF and MEOME solutions are due to the electron pair donor properties of the solvents to ion, that is, donor number (DN) of THF and MEOME established by Gutmann.³¹

Comparing the stability constant ($\Delta\log K_s$) of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 in H₂O (TIP3P) and CH₃OH in this study with those in ref 30, those of H₂O (TIP3P) and CH₃OH in this study are 0.80 and 1.57 and those of H₂O and CH₃OH in ref 30 obtained by using calorimeter, conductance, and ISE methods are 0.57 and 0.61–1.24, respectively. In contrast to them, the stability constant ($\Delta\log K_s$) of binding of Cs⁺ and Rb⁺ ion to 18-crown-6 in the other solvents is also expected to be reliable. The sign and magnitude of the calculated $\Delta\log K_s$ closely parallel the relative binding Gibbs free energies.

3.4. Structural Properties and Radial Distribution Function (RDF). The solvent–ion structure can be characterized through radial distribution functions (RDFs), $g_{ai}(r)$, which give the probability of finding an atom of type i a distance r from an atom of type a . The positions of the first maximum of the ion in the 18-crown-6-ion complexes (O, C, Cl, and CH₂) in

TABLE 3: Structural Properties of 18-Crown-6/Cs⁺ and 18-Crown-6/Rb⁺ Ion Complex in Several Solvents

solvent	18-crown-6/Cs ⁺ ion		18-crown-6/Rb ⁺ ion	
	R_{i-o} (Å)	CN ^a	R_{i-o} (Å)	CN
H ₂ O (TIP3P)	3.1	3.4	2.9	2.8
H ₂ O (TIP4P)	3.1	3.0	2.9	2.6
CH ₃ OH	3.1	2.2	2.8	2.0
THF	3.1	2.7	2.9	2.3
MeOMe	3.1	2.5	2.9	2.0

solvent	18-crown-6/Cs ⁺ ion		18-crown-6/Rb ⁺ ion	
	R_{i-c} (Å)	CN	R_{i-c} (Å)	CN
CH ₃ CN	4.1	3.6	4.0	2.9

solvent	18-crown-6/Cs ⁺ ion		18-crown-6/Rb ⁺ ion	
	R_{i-CH} (Å)	CN	R_{i-CH} (Å)	CN
CHCl ₃	5.1	2.7	5.0	2.2

solvent	18-crown-6/Cs ⁺ ion		18-crown-6/Rb ⁺ ion	
	R_{i-Cl} (Å)	CN	R_{i-Cl} (Å)	CN
CCl ₄	4.6	0.9	3.8	

solvent	18-crown-6/Cs ⁺ ion		18-crown-6/Rb ⁺ ion	
	R_{i-CH_2} (Å)	CN	R_{i-CH_2} (Å)	CN
CH ₂ Cl ₂	5.0	4.1	4.9	2.8
C ₃ H ₈	5.3	1.8	4.8	1.5

^a Coordination number.**TABLE 4: Empirical Parameter of Solvent Polarity^a**

	ϵ	E_T	β	α	π^*	DN	Aj	Bj
H ₂ O(TIP4P)	78.3	1	0.18	1.17	1.09	33	1	1
CH ₃ CN	36.6	0.46	0.31	0.19	0.75	14.1	0.37	0.86
CH ₃ OH	32.7	0.762	0.62	0.93	0.6	30	0.75	0.5
THF	7.6	0.207	0.55	0	0.58	20	0.17	0.67
CHCl ₃	4.8	0.259	0	0.4	0.58	4	0.42	0.73
CCl ₄	2.2	0.052	0	0	0.28	0	0.09	0.34

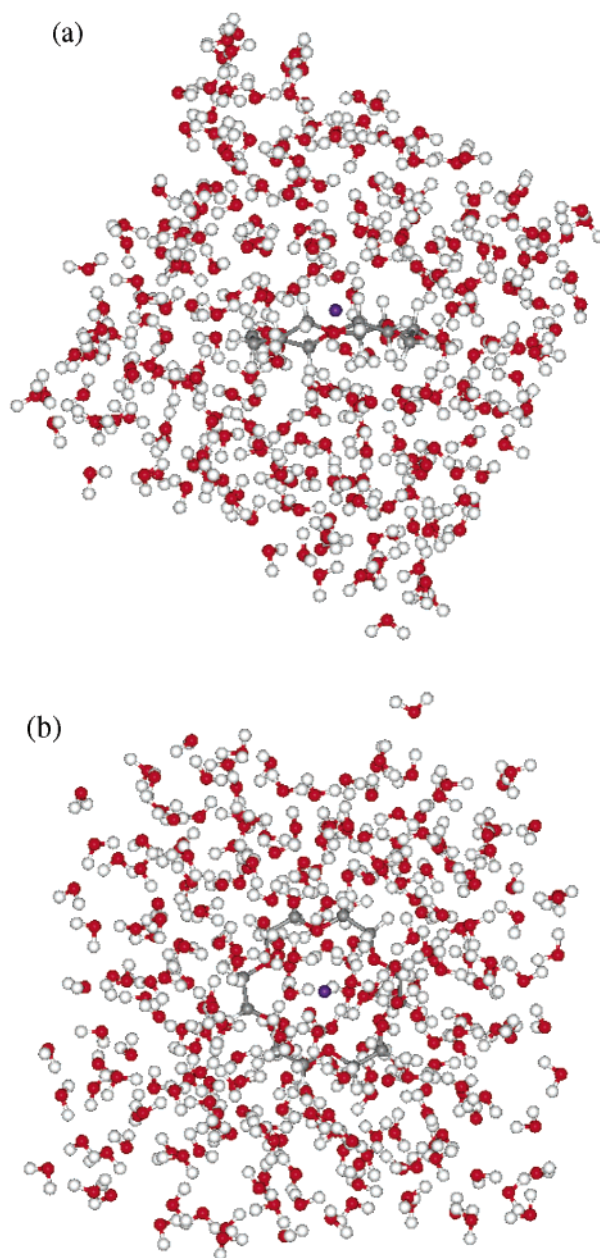
^a Reference 31.

the solvents obtained from RDFs are listed in Table 3. They decrease when the 18-crown-6/Cs⁺ ion complex transforms to the 18-crown-6/Rb⁺ ion complex in all solvents. The coordination numbers (CN) of solvent molecules in the first coordination shell of 18-crown-6/Cs⁺ ion and 18-crown-6/Rb⁺ ion complexes evaluated by integrating ion (O, C, Cl, and CH₂) solvent RDFs to their first minimum are also listed in Table 3. The number of solvent molecules in the first coordination shell around the ion for all solvents decreases when 18-crown-6/Cs⁺ ion complex transforms to the 18-crown-6/Rb⁺ ion complex. Those trends could be explained by the strengthened solvent–complex interactions when 18-crown-6/Cs⁺ ion complex transforms to the 18-crown-6/Rb⁺ ion complex. We could not compare the computed data of this study with the published work because there were no studies for structural properties when 18-crown-6/Cs⁺ ion complex transforms to the 18-crown-6/Rb⁺ ion complex in the diverse solvents.

Uncomplexed 18-crown-6 in gas phase has two conformations, those of apparent lowest energy (C_i) and highest symmetry (D_{3d}). The C_i form has four of six oxygens directed inward from the ether backbone with the other two directed outward. This

TABLE 5: Coefficients of QSPR (Quantitative Solvent–Polarity Relationships) of $\Delta\Delta G$ (ΔG) = $m_1 \epsilon + m_2 E_T + m_3 \beta + m_4 \alpha + m_5 \pi^* + m_6 DN + m_7 Aj + m_8 Bj$

	m_1	m_2	m_3	m_4	m_5	m_6	m_7	m_8
ion	−4.216	0.909	0.430	−2.461	−16.435	−30.700	33.976	−0.314
complex	−7.031	3.898	0.251	2.007	−9.235	−20.617	16.495	−0.235

**Figure 3.** Stereoplots of the 18-crown-6/Cs⁺ ion complex in water: (a) side view and (b) top view. The Cs⁺ ion is displaced away from the 18-crown-6 center of mass plane.

conformation is observed in X-ray analysis of crystalline 18-crown-6³² and is the most frequently sampled conformation in both gas-phase simulation^{4a} and simulations of 18-crown-6 in polar solvent.^{2b} The D_{3d} structure with each of its oxygen centers directed inward from the ether backbone forms a nucleophilic cavity for interaction with guest molecules or ions. Proton and carbon 13 NMR³³ and condensed phase simulations suggested that the D_{3d} conformation is the dominant one in a polar solvent.^{2a}

Stereoplots of the configurations of 18-crown-6/Cs⁺ ion complex and the 18-crown-6/Rb⁺ ion complex are given in Figures 3 and 4. From those configurations, Cs⁺ ion is displaced

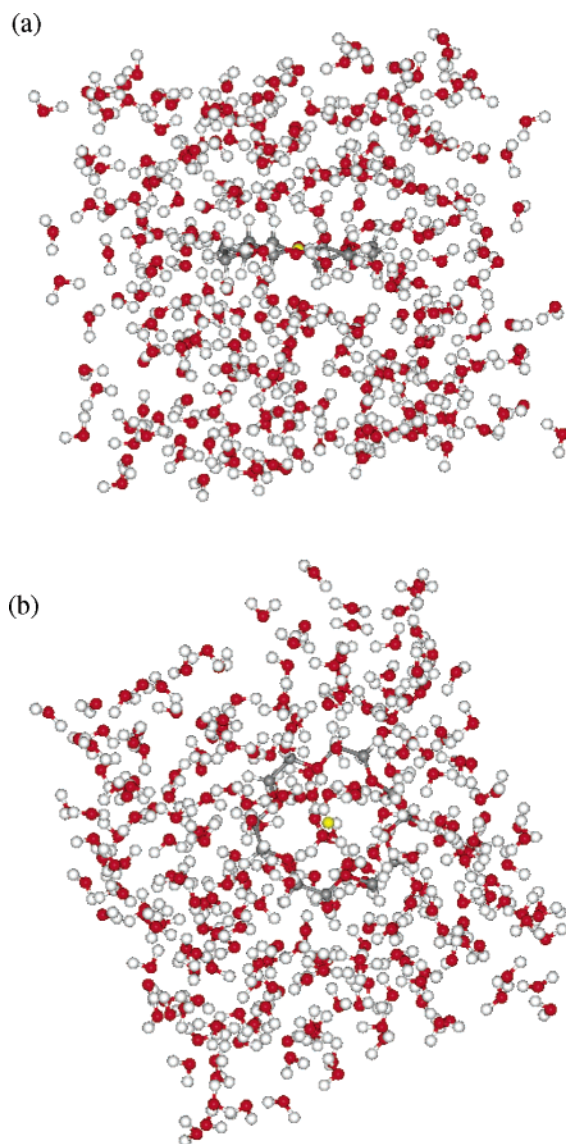


Figure 4. Stereoplots of the 18-crown-6/Rb⁺ ion complex in water: (a) side view and (b) top view.

away from the crown ether center of mass planes, Rb⁺ ion is not. However, the 18-crown-6 of both 18-crown-6/Cs⁺ ion complex and the 18-crown-6/Rb⁺ ion complex in solutions has the D_{3d} conformation with each of its oxygen centers directed inward from the ether backbone. Feller also found that the 18-crown-6 of both 18-crown-6/Cs⁺ ion complex and the 18-crown-6/Rb⁺ ion complex has the D_{3d} conformation and this conformation is the most stable compared to the other symmetric conformations.^{4c} From the xyz coordinate about both ions obtained by our simulations, we noted that Cs⁺ ion is displaced about par away from the crown ether center of mass plane more than Rb⁺ ion is. For clarity, the data are not listed. Dang also noted that Cs⁺ ion is displaced 1.8 Å away from the crown ether center of mass.^{3b}

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.^{34,35} Those values correspond to the number of solvent molecules that have undergone some constant critical change because of the complex, a change that is susceptible to measurement by a particular experimental technique. Such hydration numbers are often quite different from coordination

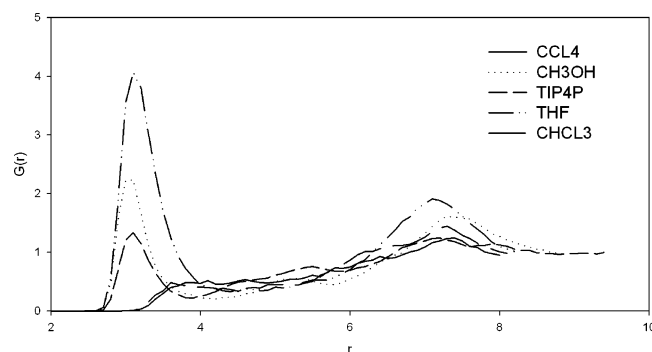


Figure 5. Radial distribution function, $g(r)$, of 18-crown-6/Cs⁺ ion complex in selected solvents. Distances are in angstroms throughout.

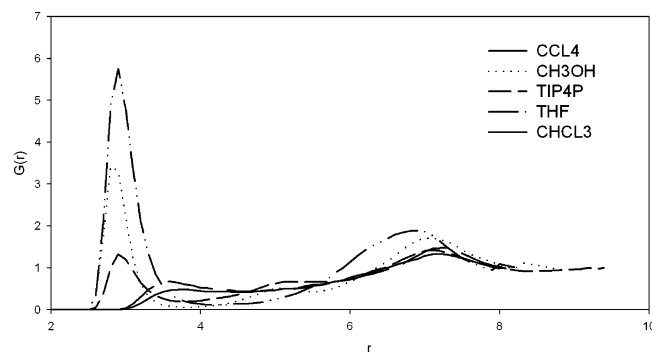


Figure 6. Radial distribution function of 18-crown-6/Rb⁺ ion complex in selected solvents.

numbers based on a structural definition, like those from diffraction experiments.³⁶

Mezei and Beveridge obtained their values by integrating the ion center of mass of water RDFs up to the minimum of the first peaks.³⁷ These values will not be significantly different if they are based on ion oxygen RDFs. This is a straightforward definition and this has been adopted for all the calculated values for 18-crown-6/Cs⁺ ion and 18-crown-6/Rb⁺ ion complexes.

The RDFs of 18-crown-6/Cs⁺ ion and 18-crown-6/Rb⁺ ion complexes in selected solvents for clarity are plotted in Figure 5 to Figure 6. As shown in Figure 5, the ordering of smaller r -values, the positions of the first maximum of the 18-crown-6/Cs⁺ ion complex (O, Cl) in the solvents is CH₃OH < THF < H₂O (TIP3P) < CHCl₃ < CCl₄. However, the ordering of smaller r -values, the positions of the first maximum of the 18-crown-6/Rb⁺ ion complex (O, Cl) in the solvents is CH₃OH = THF < H₂O (TIP3P) < CHCl₃ < CCl₄ shown in Figure 6 and the $g(r)$ intensity of the first peak is changed as 18-crown-6/Cs⁺ ion complex transforms to the 18-crown-6/Rb⁺ ion complex. That is due to interaction changes between the 18-crown-6/Cs⁺ ion or 18-crown-6/Rb⁺ ion complex molecule and solvent molecule, that is, the coordination number (CN) changes of solvent molecules in the first coordination shell of 18-crown-6/Cs⁺ ion and 18-crown-6/Rb⁺ ion complexes.

In Figures 5 and 6, the second peaks are located between 6 and 8 Å in THF, CH₃OH, and H₂O (TIP3P) solutions. In Figure 5, the second peaks of THF and CH₃OH have the bigger peak intensities than the other, which indicate that 18-crown-6/Cs⁺ ion complex in THF and CH₃OH have the clear second solvation shell. This could be explained by the fact that the relatively stronger complex molecule–solvent interactions exist in THF and CH₃OH solutions than in the others. The strong complex molecule–solvent interaction in THF and CH₃OH solutions is also due to the electron pair donor properties of the solvent molecule to ion in complex, that is, donor number (DN).³¹

In Figure 6, the second peak of THF has also the bigger peak intensities than the others, which indicate that 18-crown-6/Rb⁺ ion complex in THF has the clear second solvation shell. This could also be explained by the fact that relatively stronger complex molecule–solvent interactions exist in THF solutions than in the others. From our results, we have noted that the degree of the complex–solvent interactions is dependent on the Born's function of the solvents, the electron pair donor properties of the solvent, and the differences in solvation.

4. Conclusion

To study the solvent effect on differences in stability constant ($\Delta\log K_s$) as well as the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6, we have compared differences in stability constant ($\Delta\log K_s$) as well as the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6 in this study with those of the experimental works. There is a good agreement between the studies. From this study, we have noted that Born's function of the solvents, the electron pair donor properties of the solvent, and the differences in solvation dominate the differences in the stability constant ($\Delta\log K_s$) as well as the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6. We have reported here the QSPR studied on the solvent effects on the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6. From the calculated coefficients of QSPR, we have noted that DN dominates the differences in relative solvation Gibbs free energies of Cs⁺ and Rb⁺ ions but Aj dominates the differences in the stability constant ($\Delta\log K_s$) as well as the relative free energies of binding of Cs⁺ and Rb⁺ ions to 18-crown-6. The results in this study obtained by the Monte Carlo simulation of SPT appear promising in providing estimates of the solvent effects on stability constant of trivalent-cations binding to hosts (ionophores) among polar solvents and the less polar or nonpolar solvents. This study also provides additional information of the solvent effect on cation– π interaction, equilibrium constants, transition states, rates of the organic reaction, π -facial selectivity, conformations, and the other quantities of chemical and biochemical interest.

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