

## QFPR Analysis for Selectivity of between Na<sup>+</sup> and Li<sup>+</sup> Ions to 12-Crown-4: by a Monte Carlo Simulation Study

Hag-Sung Kim

Department of Environmental & Chemical Industry, Ulsan College, Ulsan 680-749, Korea. E-mail: hskim@uc.ac.kr  
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We investigated the solvent effects on the relative free energies of binding of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4 and  $\Delta\log K_s$  (the difference of stability constant of binding) by a Monte Carlo simulation of statistical perturbation theory (SPT) in several solvents. Comparing the relative free energies of binding of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4, in CH<sub>3</sub>OH of this study with experimental works, there is a good agreement among the studies. We have reported the quantitative free energy polarity (of solvent) relationships (QFPR) of the relationship between the relative free energies and solvent polarity studied on the solvent effects on the relative free energies of binding of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4.

**Key Words:** Stability constant, Quantitative free energy polarity (of solvent) relationships (QFPR), Monte Carlo simulation, Perturbation theory

### Introduction

Complexing agents like crown ethers<sup>1-2</sup> 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. For example, 15-crown-5 binds Na<sup>+</sup> and 18-crown-6 binds K<sup>+</sup> 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 solvent<sup>2</sup> 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,<sup>3-4</sup> ion transport through membrane,<sup>5</sup> and transport of therapeutic doses of radiations to tumor sites.<sup>6</sup> The selectivity of 12-crown-4 (1,4,7,10-tetraoxacyclododecane) mainly depends on the way in which 4 oxygen atoms are arranged to interact with guest molecule.

In addition to the host-guest interaction, factors in the extraction selectively 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.<sup>7</sup>

Due to the large number of particles forming these systems and to the variety of different interactions established, computer simulations represent a particularly adequate theoretical tool for understanding and predicting the physicochemical properties of those solutions at the microscopical level.<sup>8-10</sup> Interaction between cations and crown ethers 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.<sup>11</sup> To address those challenges and phenomena themselves, we need the information of selectivity of 12-crown-4 for alkali metal cations in solution.

Several statistical mechanical procedures have evolved for computing free energy differences. Two promising approaches

are umbrella sampling<sup>12-16</sup> and a perturbation procedure<sup>17-18</sup> 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.<sup>19</sup>

It is known that solvent effects often play an important role in determining equilibrium constants, transition states and rates of reactions,  $\pi$ -facial selectivity,<sup>20</sup> conformations, and the other quantities of chemical, chemical physics and biochemical interest.

However, few molecular dynamics (MD) and Monte Carlo (MC) statistical mechanics computer simulation studies of both the selectivity of 12-crown-4 to univalent cations and  $\Delta\log K_s$ , are available. This prompted me 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 diverse solvents.<sup>21</sup>

In this study, the solvent effect on the relative stability constant of binding of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4 have been investigated by using Monte Carlo simulations of statistical perturbation theory (SPT). H<sub>2</sub>O (TIP3P), H<sub>2</sub>O (TIP4P), CHCl<sub>3</sub>, CH<sub>3</sub>CN, THF, CH<sub>3</sub>OH, CCl<sub>4</sub>, MeCl<sub>2</sub>, MEOME, and C<sub>3</sub>H<sub>8</sub> are selected as solvents.<sup>22</sup> Experimental studies of the relative free energies of binding of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4 in methanol have been reported.<sup>23</sup> The fundamental and theoretical approach to compute solvent effects on differences of  $\log K_s$  (stability constant) as well the relative free energies of binding of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4 is, for the first time, explored based on fluid simulations at the atomic level for those by Monte Carlo simulation of statistical perturbation theory (SPT) in this study. I have reported here the quantitative free energy polarity relationships (QFPR) studied on the solvent effects on the relative free energies of binding of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4. This study provides additional interests of the solvent effect on equilibrium constants, transition states, rates of the organic reaction,<sup>24</sup> and the other quantities of chemical, biochemical interest and chemical-physics.

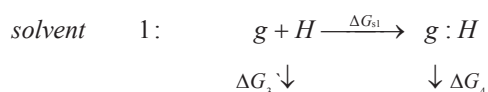
### Computational Details

The procedure used is similar to that employed to study in Refs. 21, 25-26. The modeled systems are consisted of the ion and 12-crown-4 plus 250 solvent molecules in a cubic cell with periodic boundary conditions. The Monte Carlo simulations are firstly described, including a summary of the method for computing the relative free energy changes and a brief discussion of the potential functions is given.

**Monte Carlo simulations.** 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 12-crown-4 plus 250 solvent molecules in a cubic cell with periodic boundary conditions. The free energy changes were obtained via a series of 5 separate simulations with SPT.<sup>25,26</sup>

In order to study the equilibrium thermodynamics of binding, we have used Monte Carlo simulations with the thermodynamic cycle-perturbation theory and doublewide sampling.<sup>25,26</sup>

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,  $\Delta G_s$  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.

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

$$\Delta \log K_2 = \log K_{s2} - \log K_{s1} = (\Delta G_{s2} - \Delta G_{s1}) / 2.3RT \quad (4)$$

The last expression associates the difference in  $\log K_s$ 's with the difference in the relative free energies of binding of  $\text{Na}^+$  and  $\text{Li}^+$  ions to 12-crown-4<sup>27</sup> in the two solvents.

In this study, the substitutions are H = 12-crown-4, g =  $\text{Li}^+$  and G =  $\text{Na}^+$ .  $\Delta G_3$  and  $\Delta G_4$  are available from Monte Carlo simulations in which guest are binding to host in the solvents.

Each simulation entailed an equilibration period for  $4 \times 10^6$  configurations starting from equilibrated boxes of solvent, followed by averaging for  $2 \times 10^7$  configurations. Little drift in the averages was found during the last  $1 \times 10^7$  configuration.<sup>25,26</sup> Other details are that Metropolis and preferential sampling were employed, 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.<sup>25,26</sup>

**Potential functions.** The pair potential energy function of the OPLS force field is of the following form.<sup>22</sup>

$$E_{total} = \sum_{bonds} K_r (r - r_0)^2 + \sum_{angles} K_\theta (\theta - \theta_0)^2 + \sum_{torsions} \frac{V_n}{2} [1 \pm \cos(n\phi - \gamma)] + \sum_{non-bonded} \left[ \frac{A_{ij}}{r_{ij}^{12}} - \frac{C_{ij}}{r_{ij}^6} + \frac{q_i q_j}{\epsilon r_{ij}} \right] f_{ij} \quad (5)$$

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

Where  $K_r$ ,  $K_\theta$ ,  $V_n$ , and  $\phi$  are the empirical parameters related to bond, bond angle and torsion angle. The ion and molecules are represented by interaction sites located on nuclei that have associated charge,  $q_i$  and Lennard-Jones parameter  $\sigma_i$  and  $\epsilon_i$ . 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  $A_{ij} = 4\epsilon_i\sigma_i^{12}$  and  $C_{ij} = 4\epsilon_i\sigma_i^6$  where  $\sigma$  and  $\epsilon$  are the Lennard-Jones radius and energy terms and i and j indices span all of the 12-crown-4, solvents and water sites. In Ref. 28, we noted that the equation has been dominant with two-body potential functions that are parameterized to take the higher-order interaction and polarization effect into account. In Ref. 7, 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<sup>22,25-26</sup> but the TIP3P and TIP4P models have been used for water.<sup>25-26</sup> The 12-crown-4 is represented with the OPLS-AA force field.<sup>22,25-26</sup>

The charges and Lennard-Jones parameters have been selected to yield correct thermodynamic and structural results of pure liquids.<sup>22,25-26</sup> The results were obtained from Monte Carlo simulations using well-established procedures.<sup>22,29-30</sup> In all the calculations, the bond lengths, bond angles and dihedral angles have been varied in simulations. The intermolecular interactions were spherically truncated at 8.5, 10, 12.0 Å, depending on box-sizes of solvents.<sup>22,25-26</sup> The cutoff correction to the solvent-solvent energy for non-aqueous solvents is applied to only Lennard-Jones potential functions.<sup>22,25-26</sup>

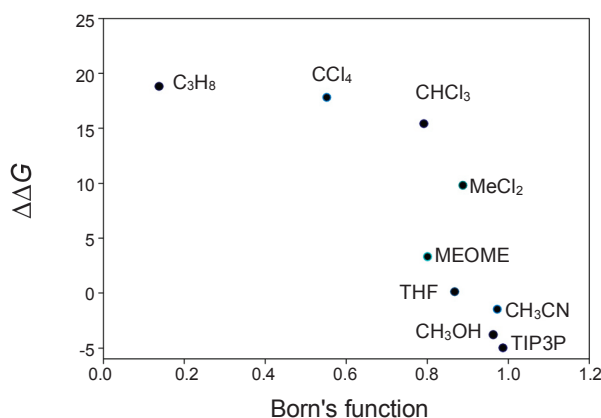
### Results and Discussion

**Different free energies of the solvated complexes ( $\Delta G_4$ ).** We have computed the differences in stability constant ( $\Delta \log K_s$ ) as well as  $\Delta G_4$  of binding of  $\text{Na}^+$  and  $\text{Li}^+$  ions to 12-crown-4 in water and in several organic solvents.

The calculated  $\Delta G_4$  of 12-crown-4/ $\text{Na}^+$  and  $\text{Li}^+$  ions complexes are listed in Table 1. The computed ordering of the  $\Delta G_4$  of 12-crown-4/ $\text{Na}^+$  and  $\text{Li}^+$  ions complexes in several solvents is  $\text{CHCl}_3 > \text{MeCl}_2 > \text{CCl}_4 > \text{C}_3\text{H}_8 > \text{CH}_3\text{CN} > \text{THF} > \text{H}_2\text{O}$

**Table 1.** The differences solvation Gibbs free energies,  $\Delta G$  (kcal/mol) and the relative binding Gibbs free energies,  $\Delta\Delta G$  (kcal/mol) in several solvents and Born's function of bulk solvents

Solvent	$-\Delta G_3^a$	$-\Delta G_4$	$\Delta\Delta G (= \Delta G_4 - \Delta G_3)$	$1-1/\epsilon$
H <sub>2</sub> O (TIP3P)	$-27.6 \pm 0.72$	$-22.6 \pm 0.38$	-5.0	0.987
H <sub>2</sub> O (TIP4P)	$-25.0 \pm 0.41$	$-20.5 \pm 0.19$	-4.5	0.987
H <sub>2</sub> O (rigidSPC) <sup>d</sup>	$-23.7 \pm 1.1$	-	-	0.987
Exp. <sup>b</sup>	-23.9	-	-	0.987
CH <sub>3</sub> CN	$-21.2 \pm 0.18$	$-19.6 \pm 0.49$	-1.5	0.973
CH <sub>3</sub> OH	$-25.5 \pm 0.67$	$-21.7 \pm 0.31$	-3.81	0.963
Exp. <sup>c</sup>	-	-	-2.03 ~ -3.1	0.963
MeCl <sub>2</sub>	$-9.40 \pm 0.17$	$-19.2 \pm 0.22$	9.8	0.888
THF	$-19.6 \pm 0.52$	$-19.7 \pm 0.54$	0.1	0.868
MEOME	$-17.8 \pm 0.54$	$-21.1 \pm 0.37$	3.3	0.801
CHCl <sub>3</sub>	$-3.83 \pm 0.10$	$-19.2 \pm 0.22$	15.4	0.792
CCl <sub>4</sub>	$-1.64 \pm 0.09$	$-19.4 \pm 0.24$	17.8	0.552
C <sub>3</sub> H <sub>8</sub>	$-0.68 \pm 0.04$	$-19.5 \pm 0.16$	18.8	0.138

<sup>a</sup>Ref. [26] <sup>b</sup>Ref. [7] <sup>c</sup>Ref. [23]**Figure 1.** Plot of relative binding Gibbs free energies ( $\Delta\Delta G$ ) of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4 vs. Born's function of the solvents at 298K and 1 atm.

(TIP4P) > MEOME > CH<sub>3</sub>OH > H<sub>2</sub>O (TIP3P). This comes about by the change in  $\Delta G_4$  of 12-crown-4/Na<sup>+</sup> and Li<sup>+</sup> ions complexes being more favorable in H<sub>2</sub>O (TIP3P) than in the polar and less polar or non-polar solvents within used solvents. The computed  $\Delta G_4$  of solvation for ions in CHCl<sub>3</sub> or MeCl<sub>2</sub> is small. Clearly, the replacement of the stronger complex-solvent interactions with the weaker complex-dipole interactions is responsible for the decreasing effect.<sup>25-26</sup>

We couldn't compare  $\Delta G_4$  of 12-crown-4/Na<sup>+</sup> and Li<sup>+</sup> ions complexes of this study with those of the experimental because there was no the experimental data.

**Relative binding Gibbs free energies ( $\Delta\Delta G$ ).** The  $\Delta\Delta G$  calculated using Eq.3 and the experimental data of  $\Delta\Delta G$ <sup>23</sup> are also listed in Table 1. The ordering of the  $\Delta\Delta G$  in diverse solvents is C<sub>3</sub>H<sub>8</sub> > CCl<sub>4</sub> > CHCl<sub>3</sub> > MeCl<sub>2</sub> > MEOME > THF > CH<sub>3</sub>CN > CH<sub>3</sub>OH > H<sub>2</sub>O (TIP4P) > H<sub>2</sub>O (TIP3P). This comes about by the change in  $\Delta\Delta G$  being more favorable in H<sub>2</sub>O (TIP3P) than in the polar and less polar or non-polar solvents within used solvents. The  $\Delta\Delta G$  of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4 and the  $\Delta\Delta G$  versus Born's function of the solvents are plotted

**Table 2.** Differences of stability constant of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4

Solvent	$\log K_{s2} - \log K_{s1}$
H <sub>2</sub> O (TIP3P)	-3.67
CH <sub>3</sub> CN	-1.10
CH <sub>3</sub> OH	-2.79
Exp.(CH <sub>3</sub> OH) <sup>a</sup>	-1.49 ~ -2.29
MeCl <sub>2</sub>	7.20
THF	0.07
MEOME	2.42
CHCl <sub>3</sub>	11.31
CCl <sub>4</sub>	13.07
C <sub>3</sub> H <sub>8</sub>	13.80

<sup>a</sup>Ref. [23]

in Figure 1. Note that the signs of  $\Delta\Delta G$  are reversed in going from H<sub>2</sub>O (TIP3P), H<sub>2</sub>O (TIP4P), CH<sub>3</sub>OH and CH<sub>3</sub>CN solutions to THF, MEOME, MeCl<sub>2</sub>, CHCl<sub>3</sub>, C<sub>3</sub>H<sub>8</sub> and CCl<sub>4</sub> solutions. That is, 12-crown-4 binds Li<sup>+</sup> more tightly than Na<sup>+</sup> in H<sub>2</sub>O (TIP3P), H<sub>2</sub>O (TIP4P), CH<sub>3</sub>OH and CH<sub>3</sub>CN solutions, whereas 12-crown-4 favors Na<sup>+</sup> in the other solutions. Similar trend has been observed in the study of alkali cation complexes of 18-crown-6 and its derivatives in H<sub>2</sub>O (TIP3P) and CCl<sub>4</sub> solutions.<sup>21,25-26</sup> 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 exists in between the ionic radius of the cation and the size of the crown ether cavity, the less that the cation binds favorably. Alkali and alkaline earth metal ion complexes of 18-crown-6 are enthalpy stabilized and entropy destabilized, the opposite is true for lanthanide complexes and the stability decrease along the series of lanthanide complexes is enthalpy stabilized in origin for lanthanide cations up to Nd<sup>3+</sup> in CH<sub>3</sub>OH. Those facts reflect the delicate balance among ligand (12-crown-4)–cation binding, solvation and ligand conformation that exists in complex systems. Selectivity is appa-

**Table 3.** Structural properties of 12-crown-4/Na<sup>+</sup> and 12-crown-4/Li<sup>+</sup> ion complex in diverse solvents

Solvent	12-crown-4/Na <sup>+</sup> ion		12-crown-4/Li <sup>+</sup> ion	
	R <sub>i-o</sub> (Å)	CN (Coordination Number)	R <sub>i-o</sub> (Å)	CN
H <sub>2</sub> O (TIP3P)	2.4	3.1	2.1	2.7
CH <sub>3</sub> OH	2.4	3.4	2.1	2.9
THF	2.5	3.6	2.1	3.1
MeOMe	2.5	3.8	2.1	3.2
	R <sub>i-N</sub> (Å)	CN	R <sub>i-N</sub> (Å)	CN
CH <sub>3</sub> CN	3.5	4.2	3.3	3.9
	(R <sub>i-CH</sub> ) (Å)	CN	(R <sub>i-CH</sub> ) (Å)	CN
CHCl <sub>3</sub>	4.7	5.5	4.3	4.3
	(R <sub>i-Cl</sub> ) (Å)	CN	(R <sub>i-Cl</sub> ) (Å)	CN
CCl <sub>4</sub>	3.2	4.2	6.5	-
	R <sub>i-CH<sub>2</sub></sub> (Å)	CN	R <sub>i-CH<sub>2</sub></sub> (Å)	CN
CH <sub>2</sub> Cl <sub>2</sub>	4.5	5.3	2.5	5.0
C <sub>3</sub> H <sub>8</sub>	7.0	-	6.9	-

rently 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 used cations have one positive charge and the binding cores of the hosts consist of four oxygen atoms with large partial negative charges, the electrostatic interactions are expected to play an important role in the determining the cation-binding ability of 12-crown-4 system.<sup>21,25-26</sup>

$\Delta\Delta G$ , in CH<sub>3</sub>OH calculated in this study as -3.81 kcal/mole agrees well with experimental results of -2.03 ~ -3.10 kcal/mol obtained by using Calorimeter, Conductance and ISE methods<sup>23</sup> in CH<sub>3</sub>OH. Based on those results,  $\Delta\Delta G$  of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4 in the other solvents are expected to be reliable

We have reported here a new quantitative free energy polarity (of solvent) relationships (QFPR) of the relationship between

the relative free energies and solvent polarity studied for the solvent effects on the relative free energies of binding of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4. Using the following Eq. 7, we calculated the coefficient of QFPR studied on the solvent effects on the relative free energies of binding of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4 using multi-parameters regression method.<sup>26(e)</sup>

$$\Delta\Delta G (\Delta G) = mL \varepsilon + m2 E_T + m3 \beta + m4 \alpha + m5 \pi^* + m6 DN + m7 A_j + m8 B_j \quad (7)$$

Where,  $\varepsilon$  is dielectric constant, and  $E_T$  is solvent polarity.  $\beta$ ,  $\alpha$  and  $\pi^*$  (scale of solvent dipolarity/polarizability) are Kamlet-Taft's solvatochromic parameters. DN is donor number of solvent.  $A_j$  is solvent acidity and  $B_j$  is solvent basicity.<sup>31</sup> All solvent polarities have been collected from the literature<sup>31</sup> and listed in Table 4. The calculated coefficients of QFPR are listed in Table 5. From the coefficients of QFPR data, we have noted that  $\beta$  (solvent HBA basicities of Kamlet-Taft's solvatochromic parameters) dominates the differences in relative solvation Gibbs free energies of Na<sup>+</sup> and Li<sup>+</sup> ions and  $\beta$  dominates the negative values in differences in the stability constant ( $\Delta\log K_s$ ) as well as the relative free energies of binding of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4 and  $\alpha$  (solvent HBD acidities of Kamlet-Taft's solvatochromic parameters) dominates the positive values in differences in the stability constant ( $\Delta\log K_s$ ) as well as the relative free energies of binding of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4.

**Relative stability constants.** According to Eq. 4, the differences in stability constant ( $\Delta\log K_s$ ) of binding of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4 can be calculated by based on relative binding Gibbs free energies. The signs of stability constant ( $\Delta\log K_s$ ) of binding of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4 are also reversed in going from H<sub>2</sub>O (TIP3P), CH<sub>3</sub>OH and CH<sub>3</sub>CN solutions to THF, MEOME, MeCl<sub>2</sub>, CHCl<sub>3</sub>, C<sub>3</sub>H<sub>8</sub> and CCl<sub>4</sub> solutions. A sign reversed of  $\Delta\log K_s$  implies that 12-crown-4 binds Li<sup>+</sup> more tightly than Na<sup>+</sup> in H<sub>2</sub>O (TIP3P), CH<sub>3</sub>OH and CH<sub>3</sub>CN solu-

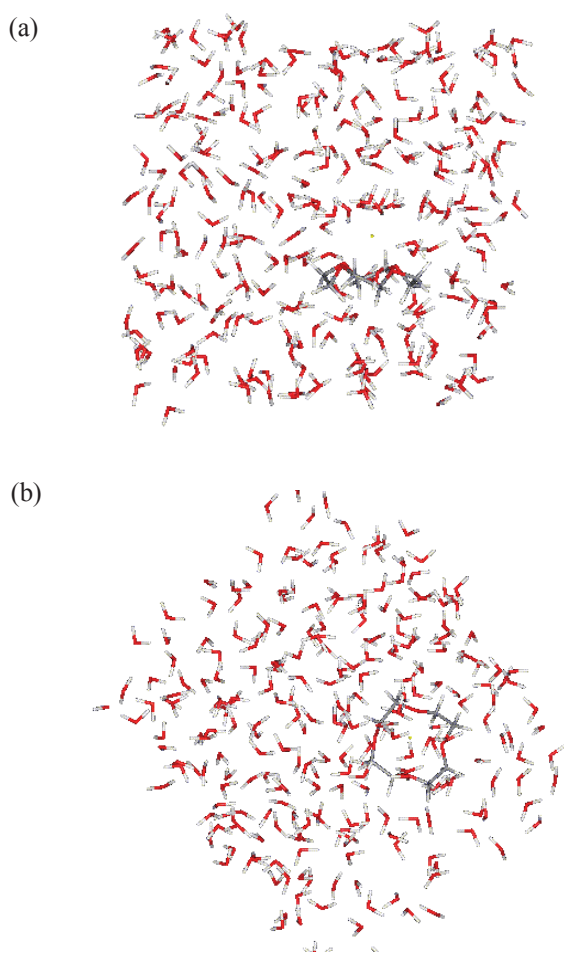
**Table 4.** Empirical parameters of solvent polarity<sup>a</sup>

	$\varepsilon$	$E_T$	$\beta$	$\alpha$	$\pi^*$	DN	$A_j$	$B_j$
H <sub>2</sub> O	78.3	1	0.18	1.17	1.09	33	1	1
CH <sub>3</sub> CN	36.6	0.46	0.31	0.19	0.75	14.1	0.37	0.86
CH <sub>3</sub> 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 <sub>3</sub>	4.8	0.259	0	0.4	0.58	4	0.42	0.73
CCl <sub>4</sub>	2.2	0.052	0	0	0.28	0	0.09	0.34

<sup>a</sup>Ref. [31]

**Table 5.** Coefficients of QFPR of  $\Delta\Delta G = m1 \varepsilon + m2 E_T + m3 \beta + m4 \alpha + m5 \pi^* + m6 DN + m7 A_j + m8 B_j$ 

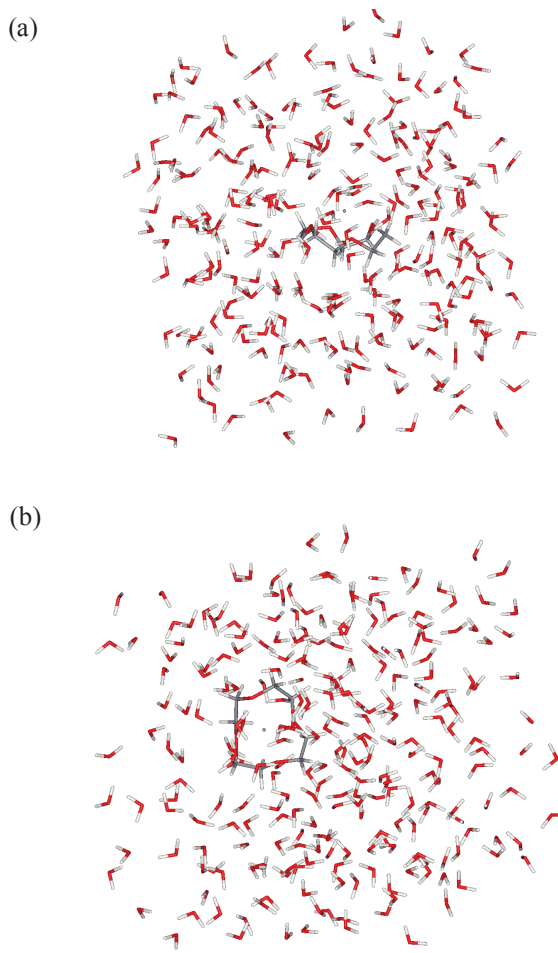
	m1	m2	m3	m4	m5	m6	m7	m8
ion	-0.26	0	-32.96	0.11	0	0.17	0	-5.80
complex	-0.24	0	-28.76	1.97	0	0.10	0	-7.56



**Figure 2.** Stereo-plots of the 12-crown-4/ $\text{Na}^+$  ion complex in water; (a) side view and (b) top view.

tions, whereas 12-crown-4 favor  $\text{Na}^+$  in THF, MEOME,  $\text{MeCl}_2$ ,  $\text{CHCl}_3$ ,  $\text{C}_3\text{H}_8$  and  $\text{CCl}_4$  solutions. The stability constant ( $\Delta \log K_s$ ) of binding of  $\text{Na}^+$  and  $\text{Li}^+$  ions to 12-crown-4, in  $\text{CH}_3\text{OH}$  calculated in this study as  $-2.79$  agrees well with experimental results of  $-1.49 \sim -2.29$  in  $\text{CH}_3\text{OH}$ <sup>23</sup> obtained by using Calorimeter, Conductance and ISE methods. Based on those results, the stability constants ( $\Delta \log K_s$ ) of binding of  $\text{Na}^+$  and  $\text{Li}^+$  ions to 12-crown-4 in the other solvents are also expected to be reliable.

As shown in Figure 1, the different free energies of binding of  $\text{Na}^+$  and  $\text{Li}^+$  ions to 12-crown-4 and relative binding Gibbs free energies vs. Born's function of the solvent decreased with increasing Born's function of solvents except  $\text{CH}_3\text{OH}$ , THF and MEOME. This trend of relative free energies of binding of  $\text{Na}^+$  and  $\text{Li}^+$  ions to 12-crown-4 and relative binding Gibbs free energies could be explained by the differences in solvation. Especially, the relative free energies of binding of  $\text{Na}^+$  and  $\text{Li}^+$  ions to 12-crown-4 in  $\text{CH}_3\text{OH}$ , THF and MEOME could be explained by the fact that strong complex-solvent interactions exist in  $\text{CH}_3\text{OH}$ , THF and MEOME solutions even though Born's functions of  $\text{CH}_3\text{OH}$ , THF and MEOME are small in value. The strong complex-solvent interactions in  $\text{CH}_3\text{OH}$ , THF and MEOME solutions are due to the electron pair donor properties of the solvents to ion, i.e., Donor number (DN) of  $\text{CH}_3\text{OH}$ ,

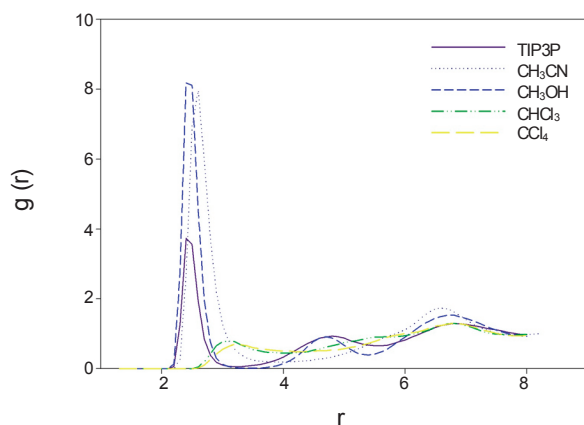


**Figure 3.** Stereo-plots of the 12-crown-4/ $\text{Li}^+$  ion complex in water; (a) side view and (b) top view.

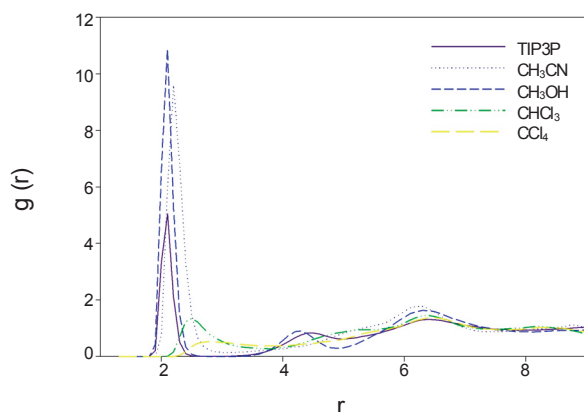
THF and MEOME established by Gutmann.<sup>31</sup>

#### 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  $i$  at a distance  $r$  from an atom of type  $a$ . The positions of the first maximum of  $\text{Na}^+$  and  $\text{Li}^+$  ions in the 12-crown-4-ion complexes ( $-\text{O}$ ,  $\text{N}$ ,  $\text{Cl}$ ,  $\text{CH}$  and  $\text{CH}_2$ ) in the solvents obtained from RDF's are listed in Table 3. They decrease when the 12-crown-4/ $\text{Na}^+$  ion complex transforms to the 12-crown-4/ $\text{Li}^+$  ion complex in all solvents except  $\text{CCl}_4$ . The coordination numbers (CN) of solvent molecules in the first coordination shell of 12-crown-4/ $\text{Na}^+$  ion and 12-crown-4/ $\text{Li}^+$  ion complexes evaluated by integrating ion-( $\text{O}$ ,  $\text{C}$ ,  $\text{Cl}$  and  $\text{CH}_2$ ) solvent RDF's to their first minimum are also listed in Table 3. The number of solvent molecules in the first coordination shell around the ion decreases when 12-crown-4/ $\text{Na}^+$  ion complex transforms to the 12-crown-4/ $\text{Li}^+$  ion complex for all solvents. Those trends could be explained by the strengthened solvent-complex interactions when 12-crown-4/ $\text{Na}^+$  ion complex transforms to the 12-crown-4/ $\text{Li}^+$  ion complex. We couldn't compare the data of this study with the published works because there have been no studies for structural properties when 12-crown-4/ $\text{Na}^+$  ion complex transforms to the 12-crown-4/ $\text{Li}^+$



**Figure 4.** Radial distribution function,  $g(r)$ , of 12-crown-4/ $\text{Na}^+$  ion complex in selected solvents. Distances are in angstroms throughout.



**Figure 5.** Radial distribution function of 12-crown-4/ $\text{Li}^+$  ion complex in selected solvents.

ion complex in the diverse solvents.

Uncomplexed 12-crown-4 in gas phase has five conformations, that of apparent high energy (C1), Ci, C4, Cs and highest symmetry (S4). The C4 form has all of oxygen atoms point to one side of the ring. The S4 conformation has two oxygen atoms pointing to one side of the ring and two pointing to the other side of the ring. The Ci conformation is observed in X-ray analysis of crystalline 12-crown-4 at  $-150\text{ }^\circ\text{C}$ .<sup>32</sup> Since S4 conformation is not as planar as the experimentally known Ci, or C4 conformations, because this conformation is not observed experimentally due to the crystal packing forces.

Stereo-plots of the configurations of 12-crown-4/ $\text{Na}^+$  ion and 12-crown-4/ $\text{Li}^+$  complex in TIP3P water are given in Figure 2-3. The 12-crown-4 of both 12-crown-4 ion complexes in solutions has all of oxygen atoms point to one side of the ring as C4 form.

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.<sup>33-34</sup> 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.<sup>35</sup>

Mezei and Beveridge obtained their values by integrating the ion-center of mass of water rdfs up to the minimum of the first peaks.<sup>36</sup> 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 value for 12-crown-4/ $\text{Na}^+$  ion and 12-crown-4/ $\text{Li}^+$  ion complexes.

The rdfs of 12-crown-4/ $\text{Na}^+$  ion and 12-crown-4/ $\text{Li}^+$  ion complexes in selected solvents for clarity are plotted in Figure 4 to Figure 5. As shown in Figure 4 and Figure 5, the positions of the first maximum of the 12-crown-4/ $\text{Na}^+$  ion complex and the 12-crown-4/ $\text{Li}^+$  ion complex ( $\text{O}$ ,  $\text{N}$ ,  $\text{Cl}$ ) in the various solvents follow the ordering  $\text{H}_2\text{O}$  (TIP3P) =  $\text{CH}_3\text{OH}$  <  $\text{CH}_3\text{CN}$  <  $\text{CHCl}_3$  <  $\text{CCl}_4$ . But the height of the first peak of  $g(r)$  are changed as 12-crown-4/ $\text{Na}^+$  ion complex transforms to the 12-crown-4/ $\text{Li}^+$  ion complex. That is due to interaction changes between the 12-crown-4/ $\text{Na}^+$  ion or 12-crown-4/ $\text{Li}^+$  ion complex molecule and solvent molecule i.e. the coordination number (CN) changes of solvent molecules in the first coordination shell of 12-crown-4/ $\text{Na}^+$  ion and 12-crown-4/ $\text{Li}^+$  ion complexes.

In Figure 4 and Figure 5, the second peaks are located between 4 and 8 Å in TIP3P,  $\text{CH}_3\text{OH}$  and  $\text{CH}_3\text{CN}$  solutions. In Figure 4, the second peak of  $\text{CH}_3\text{CN}$  has the larger peak intensities than the other, which indicate that 12-crown-4/ $\text{Na}^+$  ion complex in  $\text{CH}_3\text{CN}$  has the clear second solvation shell. Those could be explained by the fact that the relatively stronger complex molecule-solvent molecule interactions exist in  $\text{CH}_3\text{CN}$  solution than in the others. The strong complex molecule-solvent molecule interaction in  $\text{CH}_3\text{CN}$  solution is also due to the electron pair donor properties of the solvent molecule to ion in complex.<sup>31</sup>

In Figure 5, the second peak of  $\text{CH}_3\text{CN}$  has also the bigger peak intensities than the others, which indicate that 12-crown-4/ $\text{Li}^+$  ion complex in  $\text{CH}_3\text{CN}$  has the second solvation shell. Those could also be explained by the fact that the relatively stronger complex molecule-solvent molecule interactions exist in  $\text{CH}_3\text{CN}$  solutions than in the others. From those of our results, we have noted that the degree of the complex-solvents interactions is dependent on the Born's function of the solvents, the electron pair donor properties of the solvent and the differences in solvation.

## Conclusion

We have studied differences in stability constant ( $\Delta\log K_s$ ) as well as  $\Delta\Delta G$  of  $\text{Na}^+$  and  $\text{Li}^+$  ions to 12-crown-4 and have compared those in this study with those of the published works. There is good agreement among the studies if we consider both methods used to obtain the stability constant ( $\Delta\log K_s$ ) of binding of  $\text{Na}^+$  and  $\text{Li}^+$  ions to 12-crown-4 and standard deviations. From this study, we have noted that Born's function of the solvents and the differences in solvation dominate the differences in the stability constant ( $\Delta\log K_s$ ) as well as  $\Delta\Delta G$  of  $\text{Na}^+$  and  $\text{Li}^+$  ions to 12-crown-4. We have reported the QFPR studied on the solvent effects on  $\Delta\Delta G$  of  $\text{Na}^+$  and  $\text{Li}^+$  ions to 12-crown-4. From the calculated coefficients of QFPR, we noted that  $\beta$  dominates  $\Delta G_4$  of  $\text{Na}^+$  and  $\text{Li}^+$  ions and also domi-

nates the negative values in differences in the stability constant ( $\Delta \log K_s$ ) as well as  $\Delta \Delta G$  of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4 and  $\alpha$  dominates the positive values in differences in the stability constant ( $\Delta \log K_s$ ) as well as  $\Delta \Delta G$  of Na<sup>+</sup> and Li<sup>+</sup> ions to 12-crown-4.

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 ions binding to ionophores among polar solvents and the less polar or non-polar solvents.

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