# Selectivity of between K$^+$ and Na$^+$ Ions to 12-Crown-4: QSPR Analysis by a Monte Carlo Simulation Study

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The solvent effects on the relative free energies of binding of K$^+$ and Na$^-$ ions to 12-crown-4 and $\Delta\log K_s$ (the difference of stability constant of binding) have been investigated by a Monte Carlo simulation of statistical perturbation theory (SPT) in several solvents. Comparing the relative free energies of binding of K$^-$ and Na$^-$ ions to 12-crown-4, in CH$_3$OH of this study with experimental works, 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 K$^+$ and Na$^+$ ions to 12-crown-4. We noted that DN(donor number) dominates the differences in relative solvation Gibbs free energies of K$^-$ and Na$^+$ ions and DN dominates the negative values in differences in the stability constant ($\Delta\log K_s$) as well as the relative free energies of binding of K$^+$ and Na$^-$ ions to 12-crown-4 and $\pi^*$ (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 K$^+$ and Na$^-$ ions to 12-crown-4.

**Key Words :** Stability constant, Quantitative solvent-polarity relationships (QSPR). Monte Carlo simulation

## Introduction

Crown ethers[1,2] have displayed 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 solvent[2] 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] 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.[7]

Understanding the phenomenon related to the solvation of cation-ionophores has been an important quest in chemical physics, and of course in many related fields where this phenomenon has a relevant role. 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.[8-10] 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.[11] To address those challenges and the phenomena themselves, we need the information of selectivity of 12-crown-4 for alkali metal cations in solution. These could be obtained from the relative free energies of 12-crown-4 complexation with metal cation mutation in solution.

Several statistical mechanical procedures have evolved for computing free energy differences. Two particularly promising approaches are umbrella sampling[12-16] and a perturbation procedure[17,18] 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.[19]

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

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 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 diverse solvents.[21]

In this study, we have investigated the solvent effect on the relative stability constant of binding of K$^+$ and Na$^-$ ions to 12-crown-4, using Monte Carlo simulations of statistical perturbation theory (SPT). H$_2$O (TIP3P), CHCl$_3$, CH$_3$CN, THF, CH$_3$OH, CCl$_4$, MeCl$_2$, MEOME, and C$_3$H$_8$ are select-

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ed as solvents.[22] Experimental studies of the relative free energies of binding of K$^+$ and Na$^-$ ions to 12-crown-4 in methanol have been reported.[23] But the study to calculating $\Delta\log K_s$, as well as the relative free ene rgies of binding of K$^-$ and Na$^+$ ions to 12-crown-4 in diverse solvents is not available. The fundamental and theoretical approach to computing solvent effects on differences of log $K$s (stability constant) as well the relative free energies of binding of K$^+$ and Na$^-$ 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. We have reported here the quantitative solvent-polarity relationships (QSPR) studied on the solvent effects on the relative free energies of binding of K$^+$ and Na$^+$ ions to 12-crown-4. This study provides additional interests of the solvent effect on equilibrium constants, transition states, rates of the organic reaction,[24] and the other quantities of chemical, biochemical interest and chemical-physics.
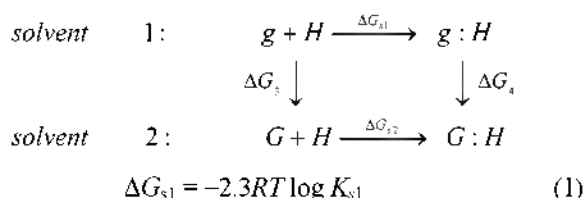
## Computational Details

The procedure used here is similar to that employed to study in Refs. 21, 25-26. The modeled systems consisted of the ion and 12-crown-4 plus 250 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.

**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.[25,26]

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

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

$$\text{solvent} \quad 1: \quad g + H \xrightarrow{\Delta G_{s1}} g:H$$
$$\Delta G_3 \downarrow \qquad\qquad \downarrow \Delta G_4$$
$$\text{solvent} \quad 2: \quad G + H \xrightarrow{\Delta G_{s2}} G:H$$

$$\Delta G_{s1} = -2.3RT \log K_{s1} \tag{1}$$

$$\Delta G_{s2} = -2.3RT \log K_{s2} \tag{2}$$

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).

$$\Delta G_{s2} - \Delta G_{s1} = \Delta G_4 - \Delta G_3. \tag{3}$$

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

The last expression associates the difference in log $K_s$'s with the difference in the relative free energies of binding of K$^+$ and Na$^+$ ions to 12-crown-4[27] in the two solvents.

In this study, the substitutions are H = 12-crown-4, g = Na$^-$ and G = K$^+$. $\Delta G_3$ 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 × 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.[25,26] 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.[25,26]

**Potential Functions.** The pair potential energy function of the OPLS force field is of the following form[22]:

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

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

Where $K_r$, $K_\theta$, $V_n$, and $\varphi$ 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 $\varepsilon_i$. 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 $A_{ii} = 4\varepsilon_i\sigma_i^{12}$ and $C_{ii} = 4\varepsilon_i\sigma_i^6$ where $\sigma$ and $\varepsilon$ 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 comlexation with 18-crwon-6.

The OPLS (optimized potential for liquid simulation) potential parameters are used for solvents and those are based on a united-atom model[22,25,26] but the TIP3P model has been used for water.[25,26] The 12-crown-4 is represented with the OPLS-AA force field.[22,25,26]

The charges and Lennard-Jones parameters have been selected to yield correct thermodynamic and structural results of pure liquids.[22,25,26] The results were obtained from Monte Carlo simulations using well-established procedures.[22,29,30] 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.[22,25,26] The cutoff correction to the solvent-solvent energy for non-

aqueous solvents is applied to only Lennard-Jones potential functions.[22,25,26]

## Results and Discussion

**Different free energies of the solvated complexes.** To study the solvent effect on differences in stability constant ($\Delta\log K_s$) as well as the different free energies of binding of $K^-$ and $Na^-$ ions to 12-crown-4. we have computed those in water and in organic solvents.

The calculated different free energies of 12-crown-4/$K^+$ and $Na^-$ ions complexes are listed in Table 1. The reported statistical uncertainties for the computed values are ($\pm$ 1s) fluctuations and were obtained from separate averages over $4 \times 10^6$ to $20 \times 10^6$ configurations. The computed ordering different free energies of 12-crown-4/$K^-$ and $Na^-$ ions complexes in diverse solvents is $CCl_4 > C_3H_8 > CHCl_3 > MeCl_2 > MEOME > THF > CH_3CN > CH_3OH > H_2O$ (TIP3P). This comes about by the change in different free energies of 12-crown-4/$K^+$ and $Na^+$ ions complexes being more favorable in $H_2O$ (TIP3P) than in the polar and less polar or non-polar solvents. The computed difference in free energies of solvation for ions in $CCl_4$ is small. Clearly, the replacement of the stronger complex-solvent interactions with the weaker complex-dipole interactions is responsible for the decreasing effect.[25,26]

We couldn't compare the different free energies of 12-crown-4/$K^-$ and $Na^+$ ions complexes of this study with the different free energies of 12-crown-4/$K^-$ and $Na^-$ ions complexes free energy of $K^-$ and $Na^+$ ions to 12-crown-4.

**Relative binding Gibbs free energies.** The relative binding Gibbs free energies calculated using Eq. (3) and the experimental data of the relative free energies[23] are also listed in Table 1. The ordering of the relative binding Gibbs free energies in diverse solvents is $CCl_4 > C_3H_8 > CHCl_3 > MeCl_2 > MEOME > THF > CH_3CN > CH_3OH > H_2O$ (TIP3P). This comes about by the change in relative binding Gibbs free energies being more favorable in $H_2O$ (TIP3P)

than in the polar and less polar or non-polar solvents. The relative free energies of binding of $K^-$ and $Na^-$ ions to 12-crown-4 and the relative binding Gibbs free energies versus Born's function of the solvents are plotted in Figure 1. Note that the signs of the relative binding Gibbs free energies are reversed in going from $H_2O$ (TIP3P). $CH_3OH$. solutions to $CH_3CN$, THF, MEOME, $MeCl_2$, $CHCl_3$. $C_3H_8$ and $CCl_4$ solutions. That is. 12-crown-4 binds $K^-$ more tightly than $Na^-$ in $H_2O$ (TIP3P). $CH_3OH$. solutions. whereas 12-crown-4 favors $Na^+$ in the other solutions. Similar trend has been observed in the study of alkali cation complexes of 18-crown-6 and its derivatives in $H_2O$ (TIP3P) and $CCl_4$ solutions.[21,25,26] 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 lager mismatch 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
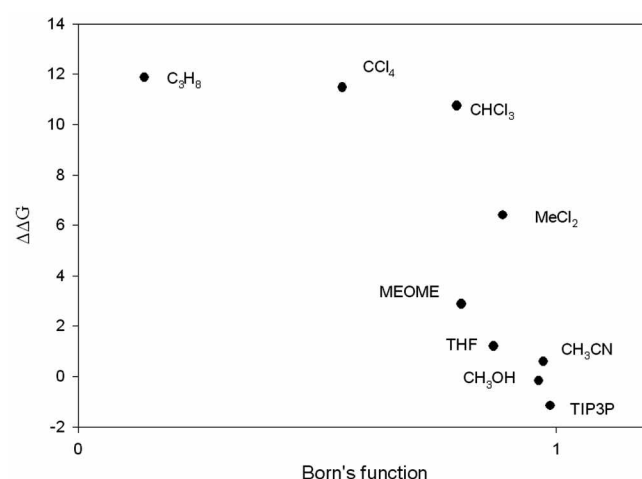


**Figure 1.** Plot of relative binding Gibbs free energies ($\Delta\Delta G$) of $K^-$ and $Na^-$ ions to 12-crown-4 *vs.* Born's function of the solvent at 298 K and 1 atm.

**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 | $\Delta G$ ($K^- \to Na^+$)[e] | $\Delta G$ (12-Crown-/$K^+ \to$ 12-Crown-4/$Na^-$) | $\Delta\Delta G$ of binding | $1 - 1/\varepsilon$ |
|---|---|---|---|---|
| $H_2O$(TIP3P) | $-18.67 \pm 0.31$ | $-17.51 \pm 0.17$ | $-1.16$ | 0.987 |
| $H_2O$(SPC)[a] | $-21.65$ | – | – | 0.987 |
| $H_2O$(TIP3P)[b] | $-17.86 \pm 0.63$ | – | – | 0.987 |
| Exp. (water)[c] | $-17.6$ | – | – | 0.987 |
| $CH_3CN$ | $-14.99 \pm 0.28$ | $-15.59 \pm 0.17$ | 0.6 | 0.973 |
| $CH_3OH$ | $-18.08 \pm 0.28$ | $-17.90 \pm 0.31$ | $-0.18$ | 0.963 |
| Exp. ($CH_3OH$)[d] | $-17.3$ | – | $-0.16 \sim -0.23$[c] | 0.963 |
| $MeCl_2$ | $-7.59 \pm 0.09$ | $-13.99 \pm 0.10$ | 6.4 | 0.888 |
| THF | $-15.38 \pm 0.33$ | $-16.58 \pm 0.20$ | 1.2 | 0.868 |
| MEOME | $-13.51 \pm 0.13$ | $-16.39 \pm 0.17$ | 2.88 | 0.801 |
| $CHCl_3$ | $-2.98 \pm 0.08$ | $-13.73 \pm 0.11$ | 10.75 | 0.792 |
| $CCl_4$ | $-1.66 \pm 0.09$ | $-13.15 \pm 0.15$ | 11.49 | 0.552 |
| $C_3H_8$ | $-0.78 \pm 0.05$ | $-12.65 \pm 0.07$ | 11.87 | 0.138 |

[a]Ref. [37]. [b]Ref. [7]. [c]Ref. [23]. [d]Ref. [38]. [e]Ref. [26]

**Table 2.** Differences of stability constant of $K^+$ and $Na^-$ ions to 12-crown-4

| Solvent | $\log K_{s2} - \log K_{s1}$ |
|---|---|
| $H_2O$(TIP3P) | −1.69 |
| $CH_3CN$ | 0.88 |
| $CH_3OH$ | −0.13 |
| Exp. $(CH_3OH)^a$ | −0.12 ~ −0.17 |
| $MeCl_2$ | 9.33 |
| THF | 1.75 |
| MEOME | 4.20 |
| $CHCl_3$ | 15.68 |
| $CCl_4$ | 16.76 |
| $C_3H_8$ | 17.32 |

$^a$Ref. [23]

**Table 3.** Structural properties of 12-crown-4/$K^-$ and 12-crown-4/$Na^+$ ion complex in diverse solvents

| Solvent | 12-crown-4/$K^-$ion | | 12-crown-4/$Na^-$ion | |
|---|---|---|---|---|
| | $R_{j\text{-}o}$ (Å) | CN (Coordination Number) | $R_{j\text{-}o}$ (Å) | CN |
| $H_2O$(TIP3P) | 2.7 | 3.6 | 2.4 | 3.1 |
| $CH_3OH$ | 2.7 | 3.6 | 2.4 | 3.0 |
| THF | 2.8 | 3.7 | 2.5 | 3.1 |
| MeOMe | 2.8 | 3.7 | 2.5 | 3.0 |
| | $R_{j\text{-}N}$(Å) | CN | $R_{j\text{-}N}$(Å) | CN |
| $CH_3CN$ | 2.8 | 4.1 | 2.6 | 3.5 |
| | $(R_{j\text{-}CH})$ (Å) | CN | $(R_{j\text{-}CH})$ (Å) | CN |
| $CHCl_3$ | 4.9 | 4.5 | 4.6 | 3.1 |
| | $(R_{j\text{-}Cl})$ (Å) | CN | $(R_{j\text{-}Cl})$ (Å) | CN |
| $CCl_4$ | 3.9 | 0.6 | 3.2 | − |
| | $R_{j\text{-}CH2}$ (Å) | CN | $R_{j\text{-}CH2}$(Å) | CN |
| $CH_2Cl_2$ | 4.8 | 4.3 | 4.5 | 3.7 |
| $C_3H_8$ | 7.5 | − | 7.3 | − |

true for lanthanide complexes and the stability decreases along the series of lanthanide complexes is enthalpy stabilized in origin for lanthanide cations up to $Nd^{3-}$ in $CH_3OH$. Those facts reflect the delicate balance among ligand (12-crown-4)-cation binding, solvation and ligand conformation that exits 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 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.[21,25,26]

The relative binding Gibbs free energies, in $CH_3OH$ calculated in this study as −0.18 kcal/mole agrees well with



(a)

(b)
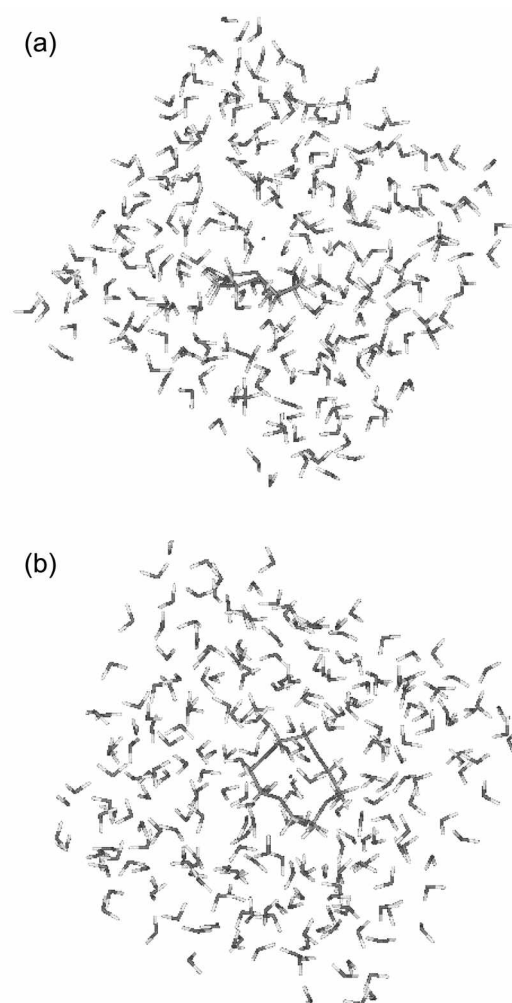
**Figure 2.** Stereoplots of the 12-crown-4/$K^-$ ion complex in water; (a) side view and (b) top view.

experimental results of −0.16 ~ −0.23 kcal/mol obtained by using Calorimeter, Conductance and ISE methods[23] in $CH_3OH$. Based on those results, the relative binding Gibbs free energies of $K^-$ and $Na^+$ ions to 12-crown-4 in the other diverse solvents is expected to be reliable

We have reported here a new quantitative solvent-polarity relationships (QSPR) studied for the solvent effects on the relative free energies of binding of $K^-$ and $Na^-$ ions to 12-crown-4. Using the following eq. (7), we calculated the coefficient of QSPR studied on the solvent effects on the relative free energies of binding of $K^-$ and $Na^-$ ions to 12-crown-4 using multi-parameters regression method.[42]

$$\Delta\Delta G \,(\Delta G) = m1\ \varepsilon + m2\ E_T + m3\ \beta + m4\ \alpha + m5\ \pi^* + m6\ DN + m7\ Aj + m8\ Bj. \tag{7}$$

Where, $\varepsilon$ is dielectric constants, and $E_T$ is solvent polarity, $\beta$, $\alpha$ and $\pi^*$ are Kamlet-Taft's solvatochromic parameters. DN is donor number of solvent, Aj is solvent acity and Bj is solvent basity.[42] All of solvent polarities have been collected from the literature[31] and listed in Table 4. The calculated the coefficients of QSPR are listed in Table 5. From the coefficients of QSPR data, we have noted that DN dominates the

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differences in relative solvation Gibbs free energies of $K^+$ and $Na^-$ ions and DN dominates the negative values in differences in the stability constant ($\Delta$log $K_s$) as well as the relative free energies of binding of $K^+$ and $Na^-$ ions to 12-crown-4 and $\pi^*$ dominates the positive values in differences in the stability constant ($\Delta$log $K_s$) as well as the relative free energies of binding of $K^-$ and $Na^+$ ions to 12-crown-4.

**Relative stability constants.** According to Eq. (4), the differences in stability constant ($\Delta$log $K_s$) of binding of $K^+$ and $Na^+$ ions to 12-crown-4 can be calculated by based on relative binding Gibbs free energies. The signs of in stability constant ($\Delta$log $K_s$) of binding of $K^-$ and $Na^-$ ions to 12-crown-4 are also reversed in going from $H_2O$ (TIP3P). $CH_3OH$. solutions to $CH_3CN$, THF, MEOME. $MeCl_2$. $CHCl_3$, $C_3H_8$ and $CCl_4$ solutions. A signs reversed of $\Delta$log $K_s$ implies that 12-crown-4 binds $K^+$ more tightly than $Na^-$ in $H_2O$ (TIP3P), $CH_3OH$ solutions. whereas 12-crown-4 favor $Na^+$ in $CH_3CN$. THF, MEOME, $MeCl_2$. $CHCl_3$, $C_3H_8$ and $CCl_4$ solutions. The stability constant ($\Delta$log $K_s$) of binding of $K^-$ and $Na^+$ ions to 12-crown-4, in $CH_3OH$ calculated in this study as $-0.13$ kcal/mole agrees well with experimental results of $0.12 \sim -0.17$ in $CH_3OH^{23}$ obtained by using Calorimeter, Conductance and ISE methods. Based on those results. the stability constant ($\Delta$log $K_s$) of binding of $K^+$ and $Na^+$ ions to 12-crown-4 in the other diverse solvents is also expected to be reliable

As shown in Figure 1, the different free energies of binding of $K^-$ and $Na^-$ 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 $CH_3OH$. THF and MEOME. This trend of relative free energies of binding of $K^-$ and $Na^+$ 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 $K^+$ and $Na^-$ ions to 12-crown-4 in $CH_3OH$. THF and MEOME could be explained by the fact that strong complex-solvent interactions exist in $CH_3OH$. THF and MEOME solutions even though Born's functions of $CH_3OH$, THF and MEOME are small in value. The strong complex-solvent interactions in $CH_3OH$. THF and MEOME solutions are due to the electron pair donor properties of the solvents to ion. *i.e.*. Donor number (DN) of $CH_3OH$. THF and MEOME established by Gutmann.[31]

**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 12-crown-4 -ion complexes-(O. N. Cl. CH and $CH_2$) in the solvents obtained from RDF's are listed in Table 3. They decrease when the 12-crown-4/$K^-$ ion complex transforms to the 12-crown-4/$Na^-$ ion complex in all solvents. The coordination numbers (CN) of solvent molecules in the first coordination shell of 12-crown-4/$K^+$ ion and 12-crown-4/$Na^-$ ion complexes evaluated by integrating ion-(O. C. Cl and $CH_2$) solvent RDF's to their first minimum are also listed in Table 3. The number of solvent molecules in

**Table 4.** Empirical parameter of solvents polarity [a]

| | $\varepsilon$ | $E_T$ | $\beta$ | $\alpha$ | $\pi^*$ | DN | Aj | Bj |
|---|---|---|---|---|---|---|---|---|
| $H_2O$(TIP4P) | 78.3 | 1 | 0.18 | 1.17 | 1.09 | 33 | 1 | 1 |
| $CH_3CN$ | 36.6 | 0.46 | 0.31 | 0.19 | 0.75 | 14.1 | 0.37 | 0.86 |
| $CH_3OH$ | 32.7 | 0.762 | 0.62 | 0.93 | 0.6 | 30 | 0.75 | 0.5 |
| THF | 7.6 | 0.207 | 0.55 | – | 0.58 | 20 | 0.17 | 0.67 |
| $CHCl_3$ | 4.8 | 0.259 | – | 0.4 | 0.58 | 4 | 0.42 | 0.73 |
| $CCl_4$ | 2.2 | 0.052 | – | 0 | 0.28 | – | 0.09 | 0.34 |

Reference 31.

**Table 5.** Coefficients of QSPR (quantitative solvent-polarity relationships) of $\Delta\Delta G$ = m1 $\varepsilon$ + m2 $E_T$ + m3 $\beta$ + m4 $\alpha$ + m5 $\pi^*$ + m6 DN + m7 Aj + m8 Bj

| | m1 | m2 | m3 | m4 | m5 | m6 | m7 | m8 |
|---|---|---|---|---|---|---|---|---|
| ion | –4.04 | 0 | –0.11 | 0 | 2.63 | –17.24 | 0 | –0.14 |
| complex | –3.76 | 0 | –0.01 | 0 | 2.77 | –14.89 | 0 | –0.14 |

the first coordination shell around the ion decreases when 12-crown-4/$K^-$ ion complex transforms to the 12-crown-4/$Na^-$ ion complex for all solvents. Those trends could be explained by the strengthened solvent-complex interactions when 12-crown-4/$K^+$ ion complex transforms to the 12-crown-4/$Na^+$ 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/$K^-$ ion complex transforms to the 12-crown-4/$Na^+$ 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. Ci, conformation is observed in X-ray analysis of crystalline 12-crown-4 at $-150$ °C.[32] 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/$K^-$ ion and 12-crown-4/$Na^+$ complex in TIP3P water are given in Figure 3-4. 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 $C_4$ 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.[33,34] 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.[35]

Mezei and Beveridge obtained their values by integrating the ion-center of mass of water rdf's up to the minimum of
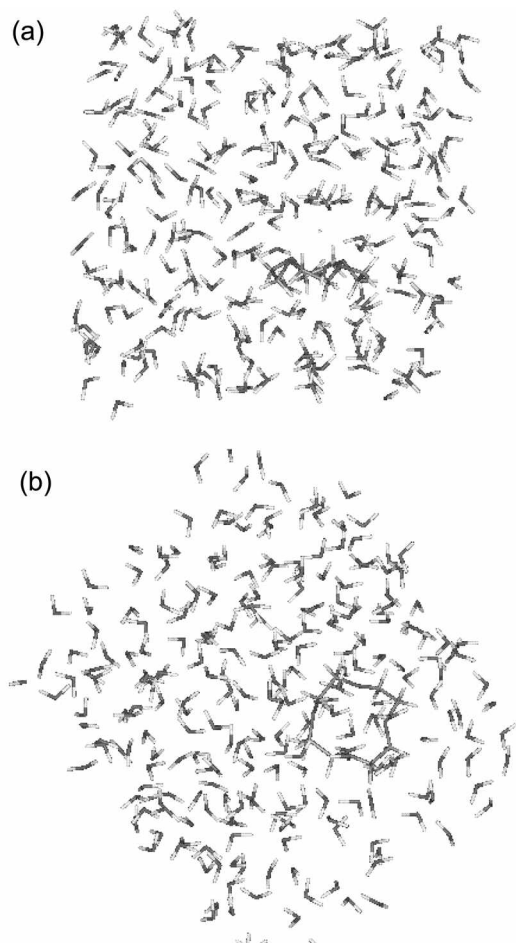
(a)



(b)



**Figure 3**. Stereoplots of the 12-crown-4/Na⁺ ion complex in water; (a) side view and (b) top view.

the first peaks.[36] 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/K⁺ ion and 12-crown-4/Na⁺ ion complexes.

The rdfs of 12-crown-4/K⁺ ion and 12-crown-4/Na⁻ 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/K⁻ ion complex and the 12-crown-4/Na⁺ ion complex -(O, N, Cl ) in the various solvents follow the ordering $H_2O$ (TIP4P) = $CH_3OH$ < MEOME = $CH_3CN$ < $CCl_4$ < $CHCl_3$. But the height of the first peak of g(r) are changed as 12-crown-4/K⁺ ion ion complex transforms to the 12-crown-4/Na⁺ ion complex. That is due to interaction changes between the 12-crown-4/K⁻ ion or 12-crown-4/Na⁺ 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/K⁻ ion and 12-crown-4/Na⁻ ion complexes.

In Figure 4 and Figure 5, the second peaks are located between 4 and 8 Å in MEOME, $CH_3OH$ and $CH_3CN$ solutions. In Figure 4, the second peaks of MEOME and $CH_3CN$ have the larger peak intensities than the other, which indicate that 12-crown-4/K⁺ ion complexes in MEOME and
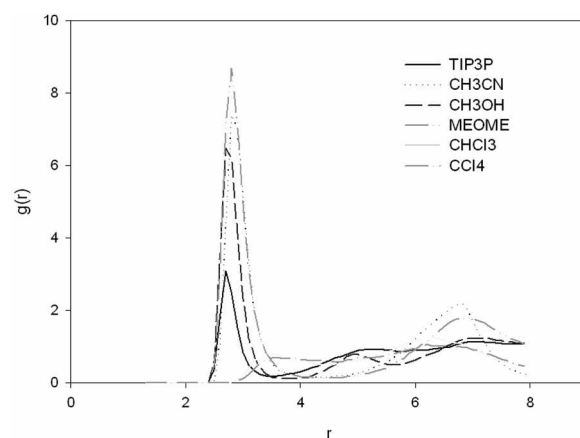


**Figure 4**. Radial distribution function, g(r), of 12-crown-4/K⁻ ion complex in selected solvents. Distances are in angstroms throughout.
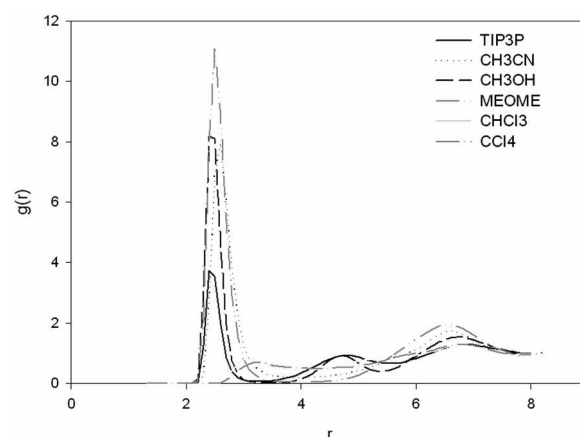


**Figure 5**. Radial distribution function of 12-crown-4/Na⁻ ion complex in selected solvents.

$CH_3CN$ have the clear second solvation shell. Those could be explained by the fact that the relatively stronger complex molecule-solvent molecule interactions exist in MEOME and $CH_3CN$ solutions than in the others. The strong complex molecule-solvent molecule interaction in MEOME and $CH_3CN$ solutions is also due to the electron pair donor properties of the solvent molecule to ion in complex. *i.e.*, Donor number (DN).[31]

In Figure 5, the second peak of MEOME has also the bigger peak intensities than the others. which indicate that 12-crown-4/Na⁺ ion complex in MEOME has the clear second solvation shell. Those could also be explained by the fact that the relatively stronger complex molecule-solvent molecule interactions exist in MEOME 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 compared differences in stability constant (Δlog $K_s$) as well as the relative free energies of binding of K⁻ and

$Na^+$ ions to 12-crown-4 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 $K^+$ and $Na^+$ 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 the relative free energies of binding of $K^-$ and $Na^-$ ions to 12-crown-4. We have reported here the QSPR studied on the solvent effects on the relative free energies of binding of $K^-$ and $Na^-$ ions to 12-crown-4. From the calculated coefficients of QSPR, we have noted that DN (donor number) dominates the differences in relative solvation Gibbs free energies of $K^+$ and $Na^+$ ions and DN dominates the negative values in differences in the stability constant ($\Delta \log K_s$) as well as the relative free energies of binding of $K^+$ and $Na^+$ ions to 12-crown-4 and $\pi^*$ (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 $K^-$ and $Na^+$ 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.

## References

1. Michaux, G.; Reisse, J. *J. Am. Chem. Soc.* **1982**, *104*, 6895.
2. (a) Perdersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495. 7017. (b) Perdersen. C. J. *Science* **1988**, *241*, 536.
3. Chiarizia, R.; Horwitz, E. P.; Dierz, M. L. *Solvent Extraction and Ion Exchange* **1992**, *10*, 313, 337.
4. Frazier, R.; Wai, C. M. *Talanta* **1992**, *39*, 211.
5. Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 123.
6. Kozak, R. W.; Waldmann, T. A.; Atcher, R. W.; Gansow, O. A. *Trends Biotechnol* **1985**, *4*, 359.
7. Wang, J.; Kollman, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 11106.
8. Florian, J.; Warshel, A. *J. Phys. Chem. B* **1999**, *103*, 10282.
9. Allen. M. P.; Tidelsley, D. J. *Computer Simulation of Liquids*; Oxford University Press: Oxford, 1987.
10. Simkin. B. Y.; Sheikhet, I. I. *Quantum Chemical and Statistical Theory of Solution: A Comprehensive Approach*; Ellis Horwood: London, 1995.
11. Schulz, W. W.; Bray, L. A. *Sep. Sci. Technol.* **1987**, *22*, 191.
12. Valleau, J. P.; Torrie. G. M. In *Statistical Mechanics*, Part A.; Berne, B. J., Ed.; Plenum: New York, 1977; p 169.
13. Jorgensen. W. L. *J. Phys. Chem.* **1983**, *87*, 5304.
14. Rebertus, D. W.; Berne, B. J.; Chandler. D. *J. Chem. Phys.* **1979**, *70*, 3395.
15. Mezei. M.; Mehrotra, P. K.; Beveridge, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 2239.
16. Chandrasekhar. J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 2974.
17. Bayly, C. I.; Kollman, P. A. *J. Am. Chem. Soc.* **1994**, *16*, 697.
18. Tembe, B. L.; McCammon. J. A. *Comput. Chem.* **1984**, *8*, 281.
19. Kollman. P. A. *Chem. Rev.* **1993**, *93*, 2395.
20. Kim. K. S.; Tarakeshwar. P.; Lee. J. Y. *Chem. Rev.* **2000**, *100*, 4145.
21. (a) Kim, H. S. *J. Phys. Chem. B* **2002**, *106*, 11579. (b) Kim, H. S. *Chem. Phys. Lett.* **2001**, *346*, 135. (c) Kim. H. S. *Phys. Chem. Chem. Phys.* **2000**, *2*, 1919. (d) Kim, H. S. *Bull. Kor. Chem. Soc.* **2003**, *23*, 751.
22. Jorgensen. W. L. *BOSS.* Version 4.5; Yale University: New Haven. CT. 2003.
23. Izatt, R. M.; Bradshow. J. S.; Nielsen, S. A.; Lamb. J. D.; Christensen, J. J. *Chem. Rev.* **1985**, *85*, 271.
24. (a) Hawkins. G. D.; Liotard. D. A.; Cramer. C. J.; Truhlar, D. G. *J. Org. Chem.* **1998**, *63*, 4305. (b) Lee, I.; Kim. C. K.; Han. I. S.; Lee. H. W.; Kim. W. K.; Kim. Y. B. *J. Phys. Chem. B* **1999**, *103*, 7302.
25. (a) Kim. H. S. *Chem. Phys.* **2003**, *287*, 253. (b) Kim. H. S. *J. Phys. Chem. B* **2004**, *108*, 11753.
26. (a) Kim, H. S. *Chem. Phys. Lett.* **2000**, *317*, 553; *321*, 262; *330*, 570. (b) Kim. H. S. *Chem. Phys.* **2000**, *253*, 305; *257*, 183; **2001**, *269*, 295. (c) Kim. H. S. *THEOCHEM* **2005**, *722*, 1; **2001**, *540*, 79; *541*, 59. (d) Kim. H.-S. *Bull. Korean Chem. Soc.* **2006**, *2*, 315; *12*, 2011.
27. Gorkel, G. W. *Crown Ethers and Cryptands*; The Royal Society of Chemistry: London. 1990.
28. Jorgensen, W. L. *Free Energy Changes in Solution* in *Encyclopedia of Computational Chemistry*; Schielyer. P. v. R., Ed.; Wiley: New York. 1998; Vol. 2, p 1061.
29. Zwanzig. R. W. *J. Chem. Phys.* **1954**, *22*, 1420.
30. Jorgensen, W. L.; Blake, J. F.; Buckner. J. K. *Chem. Phys.* **1989**, *129*, 193.
31. Christian, R. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: 2003; p 389.
32. Groth. P. *Acta. Chem. Scand A* **1978**, *32*, 279.
33. Bockris. J. O'M.; Reddy. A. K. N. *Modern Electrochemistry*; Plenum Press: New York. 1970; Vol. 1. Chapter 2. p 45.
34. Chung, J. J.; Kim. H.-S. *Bull. Korean Chem. Soc.* **1993**, *14*, 220.
35. Enderby, J. E.; Neilson, G. W. *Rep. Progr. Phys.* **1981**, *44*, 38.
36. Mezei. M.; Beveridge. D. L. *J. Chem. Phys.* **1981**, *74*, 6902.
37. Eerden. J. v.; Harkeman. S.; Feil. D. *J. Phys. Chem.* **1988**, *92*, 5076.
38. Mazor. M. H.; McCammon, J. A.; Lybrand, T. P. *J. Am. Chem. Soc.* **1990**, *112*, 4411.