ORIGINAL ARTICLE

The associations of macrocyclic ethers with cations in 1,4-dioxane/water mixtures; potentiometric Na$^+$ and K$^+$ binding measurements and computational study
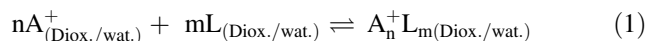
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Abstract This paper deals with the study of different degrees of association constants of Na$^+$ and K$^+$ ions with macrocycles of [12]crown-4, [15]crown-5, [18]crown-6, and Diaza[18]crown-6 in (1:1)dioxane/water mixture using the sodium and potassium ion selective electrodes (ISE). The gas phase molecular mechanical and quantum chemical calculations of [18]crown-6 and diaza[18]crown-6 were performed at MM+, AM1, MINDO/3, HF/6-31G(d), and B3LYP/6-31G(d) levels with the help of Gaussian03 program. Conformational abilities were compared with the ion binding results of ISE measurements. The results were also discussed in terms of oxygen charges and enthalpy stabilized association mechanism.

Keywords Azacrown ether · Potentiometry, DFT · Semiemprical methods

Introduction

The associations of the macrocycles with cations in various solvents have been investigated for several cation-macrocycles systems [1–4]. However, the work on mother solvent due to cation-macrocycles-ion–dipole effects and conformational role of macrocyclic ligand with different methods is quite essential [5–11]. Therefore, the ensembles of molecular interactions of the macrocyclic ether and cation have to be examined. Several macrocyclic ethers and their complexes have been synthesized and characterized with suitable analytical methods [10–15]. We have developed a formalism

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for the estimation of association constants and reported the thermodynamic association constants using different analytical methods of dipolar relaxation rate measurements [10–12], calorimetric titrations [13], conductance [14], and ISE measurements [1, 15, 16] The association constants were calculated using Eqs. 1–5 [10–14]

$$nA^+_{(Diox./wat.)} + mL_{(Diox./wat.)} \rightleftharpoons A^+_n L_{m(Diox./wat.)} \tag{1}$$

$$K = \left[A^+_n L_m\right]_{(Diox./wat.)} / [A^+]^n_{(Diox./wat.)} [L]^m_{(Diox./wat.)} \tag{2}$$

$$1/K_a[L_0] = (1 - P)^2 / P \tag{3}$$

$$1/\left\{K_a[L_0]^{n+m-1}\right\} = (1 - nP')^n (1 - mP')^m / P' \tag{4}$$

$$1/\{K_a[Lo]\} = (1 - -P')^2 / P'$$
$$(\text{if } n = 1, \ m = 1 \text{ and } P = P') \tag{5}$$

In this expressions, [L] is concentration of uncomplexed crown ether. [A$^+$] is the concentrations of uncomplexed cation, [A$_n$ L$_m$] is complex concentration. However, the identical initial cation and ligand concentrations, [L$_o$] = [A$_0^+$] are used in the solution, then Eqs. 1–5 are established. The mole fraction of a complexed ligand, P= [A^+_n L$_m$]/{[L] + [A$_n$ + L$_m$]} and P' = P/[1+ (m-1)P] would be used in mole balance relationships in Eqs. 1, 2 to obtain the simple expressions, Eqs. 4, 2 [10–14]. K$_a$ values were determined with the relationship, Equation 4, for various stoichiometries, (n:m), where P' is the mole fraction of the complexed cation.

The estimations using linear least squares and correlation coefficients gave the K precisely as we studied the Na$^+$ ion association constants with various macrocycles using sodium ISE, in 1:1 dioxane/water [1, 15]. In complexes, different binding mechanisms may involve different estimation methods [17], in particular ion pair formation should affect the association mechanisms [21].

Herein, we would like to report the results of association constants of Na$^+$ and K$^+$ ions with macrocycles of [12]crown-4, [15]crown-5, [18]crown-6, and diaza[18]crown-6 in 1:1 dioxane/water mixture using the sodium and potassium ion selective electrodes (ISE). These experimental findings were also supported by theoretical computations.

Experimental

The chemicals and macrocyclic ethers from FLUKA were used without further purification. 1,4-Dioxane was purified on metallic sodium and mixed with deionised water to form 1:1 (v/v) solution mixtures. Both solutions of the free cation and the macrocycle were prepared in volumetric flasks and were then mixed in 1:1 ratio. The mixture was then placed into a thermostated cell, equipped with combined sodium ISE from Orion (model ROSS) for sodium complexation measurements. Potassium ion measurements were conducted on Orion 9002. The mV values were measured, (+0.05 mV) with an ORION millivolt meter (model 920 A) in the thermostated bath [15, 17]. The log K_a and ΔG^0 = -2.303RT log K_a (2.303 × 4.18 × 298.15 × logK_a) values were obtained from Eqs. 1–5 with the minimum correlation coefficients (Table 1). The geometry optimizations and energy calculations of macrocrocyclic ethers studied herein were conducted with MM+ force field, AM1, MINDO3, HF/6-31G(d), B3LYP/6-31G(d) [18, 19] and estimated theoretically with a Gaussian03 program [20].

Results and discussion

This paper deals with the estimation of the association constants of Na$^+$ and K$^+$ ions with [18]crown-6 (**I**) and

Diaza[18]crown-6 (**II**), [15]crown-5 (**III**) and [12]crown-4 (**IV**) in 1:1 dioxane/water mixture using sodium and potassium ion selective electrodes. Table 1 and Fig. 1 display the results using Eqs. 1–5. The most stable complex is formed between K$^+$ and compound **I**, in dioxane/water while, **II** shows smaller Na$^+$ and K$^+$ binding efficiency [5, 8, 9]. However, weak complexes such as compound **II** and Na$^+$ represent moderate agreements with Eqs. 1–5, (see Fig. 1). Preliminary theoretical barrier energy estimations of macrocyclic backbone of compounds **I** and **II** exhibited the importance of the localized hetero atom charges on binding effects of macrocyclic backbones [22–24]. On the other hand, the results of [15]crown-5 (**III**) and [12]crown-4 (**IV**) are in accordance with the earlier results [5–9]. The association constants found apparently larger compared to those found in water as presented in Table 1 [4].

Recently, theoretical molecular mechanics studies on the estimation of relative conformational energies and the factors determining complex formation showed interesting result [23–25]. In this respect, [18]crown-6 (**I**) has been widely studied with the different computational methods [12, 22–24]. Accordingly, in this work we survived the gas phase quantum mechanical and chemical calculations of **I** and **II** at MM+, AM1, MINDO/3, HF/6-31G(d), B3LYP/6-31G(d) levels (Fig. 2).

Molecular mechanics studies of [18]crown-6 (**I**) and diaza [18]crown-6 (**II**) were conducted with MM+ using the parameters obtained from semi-empirical AM1 and MINDO3 [12, 22–25]. The [18]crown-6, used as a model compound, has been the subject of earlier theoretical studies with different software [22–24]. We examined both structures of C$_2$ conformations at similar computational conditions in the present work. It is known that C$_2$ is mostly the preferred conformation of a six oxygen

Table 1 The association constants of Na$^+$ and K$^+$ in 1:1 dioxane/water 298.15 K for different cation/ligand (n/m) ratios, ΔG^o are in kJ/mol, Eqs. 1–5

Crown Ether[a]	log K^b	$\Delta G^{o\ b}$	log K^c	$\Delta G^{o\ c}$	log K^d	$\Delta G^{o\ d}$
[12]-crown-4/NaClO$_4$	0.51	−2.90	2.57	−14.62	2.26	−12.85
[15]-crown-5/NaClO$_4$	1.46	−8.29	3.64	−20.68	3.28	−18.66
[18]-crown-6/NaClO$_4$	2.10	−11.98	4.43	−25.18	4.25	−24.03
Diaza[18]crown-6/ KClO$_4$	0.99	−5.60	3.08	−17.48	2.75	−15.63
[18]crown-6/KClO$_4$	3.94	−22.36	6.49	−36.86	5.57	−31.87
Diaza[18]crown-6/ KClO$_4$	2.05	−11.62	4.28	−24.34	3.96	−22.49

[a] Equimolar cation/salt, [b]1:1(n:m) ratio, [c]1:2 (n:m) ratio, [d]2:1 (n:m) ratio
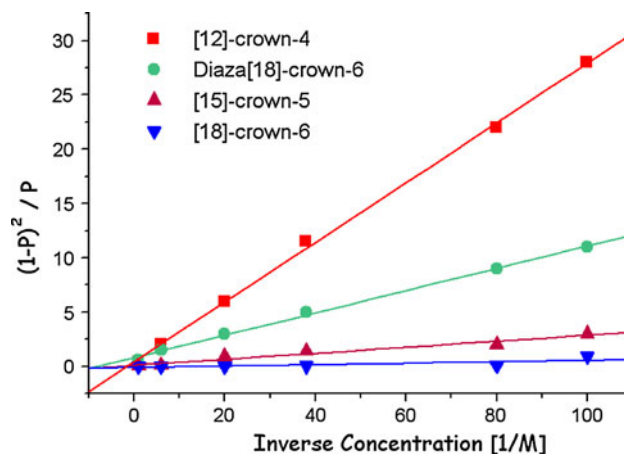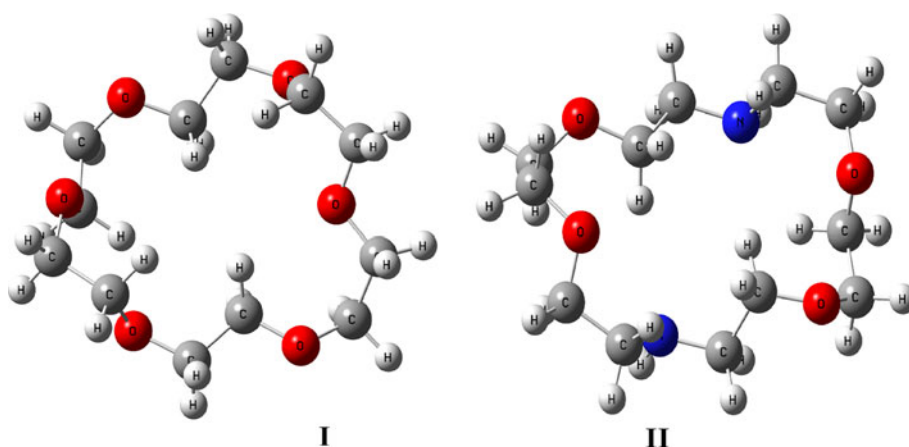

Fig. 1 The 1:1 ratio of Na$^+$ complexation plots of macrocyclic ethers **I, II, III** and **IV** at 298.15 K. Note that the compound-**II** shows large y-intercept

Fig. 2 Optimized molecular structures of **I** and **II** at B3LYP/ 6-31G(d)

macrocycle in aqueous solvents [26, 27]. We have initially performed semi-empirical calculations of AM1 and MIN-DO3 to estimate the local charges so that two different sets of oxygen and nitrogen polarization charges were applied in MM+ calculations (Table 2). Results primarily indicated the role of delocalized oxygen charges on the torsional barrier of gauche oxyethylene units of a macrocyles which could optimize charge densities and therefore the preferred conformations. This also influenced the polarization balances of the rest of atoms in a macromolecule governing the power of macrocycle-cation interactions. However, this did not explain the low binding effect of compound **II** since the barrier energies of different charges of **II** are similar to those found for **I** (Table 2). The hydrogen bonding of nitrogen atoms is responsible for poor complexation of **II** as was indicated by Buschmann [8, 9]. This effect diminished the nitrogen charge density to bind a

cation and limited the rearrangement of spatial conformations of macrocyclic backbone.

The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of chemical species are quite important to define its reactivity. Fukui et al. [28] was the first to recognize this. E_{HOMO} is often associated with the electron donating ability of the molecules. E_{HOMO} indicates that the molecular ability in donating electrons to appropriate acceptor molecules with low energy, empty molecular orbital. On the other hand E_{LUMO} indicates the ability of the molecule to accept electrons. The lower value of E_{LUMO}, means that the molecule would accept electrons. Therefore, concerning the value of the energy gap, $\Delta E(E_{LUMO}-E_{HOMO})$, higher values of ΔE will provide lower reactivity to a chemical species. Lower values of ΔE will indicate the higher reactivity of the molecules, because the energy to remove

Table 2 The theoretical estimations on [18]crown-6 (**I**) and diaza [18]crown-6 (**II**) with various computational methods*

Crown ethhers	φN^a	φO^b	Angel^c	Tors.En.^{d}	Method	Total Energy
[18]crown-6 (**I**)	–	0.000	±50.6	3.66	MM+	19.34
[18]crown-6 (**I**)	–	−0.255	±58.1	4.50	AM1/MM+	34.24
[18]crown-6 (**I**)	–	−0.418	±55.4,	61.40	MINDO3/MM+	155.69
[18]crown-6 (**I**)	–	−0.660	±52.7	–	HF/6-31G(d)	−917,473
[18]crown-6 (**I**)	–	−0.590	±59.5	–	B3LYP/6-31G(d)	−922.975
Diaza[18]crown-6 (**II**)	0.000	0.000	±44.0	4.22	MM+	22.86
Diaza[18]crown-6 (**II**)	−0.307	−0.268	±58.5	3.16	AM1/MM+	34.98
Diaza[18]crown-6 (**II**)	−0.307	−0.268	±58.5	3.16	AM1/MM+	34.98
Diaza[18]crown-6 (**II**)	−0.750	−0.658	54.4	–	HF/6-31G(d)	−877.806
Diaza[18]crown-6 (**II**)	−0.550	−0.470	71.1	–	B3LYP/6-31G(d)	−883.237

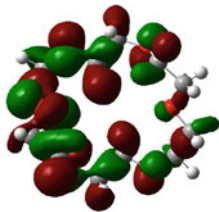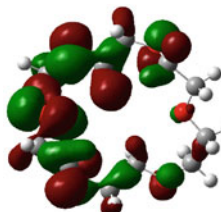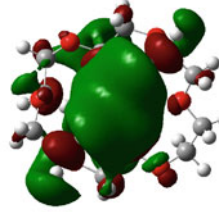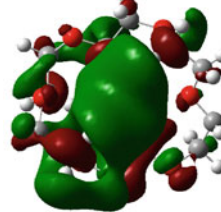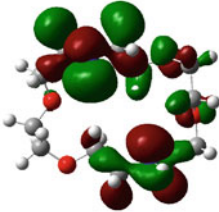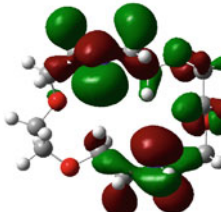* Only one central symmetry conformer of C_2 point group was investigated, see ref [23]
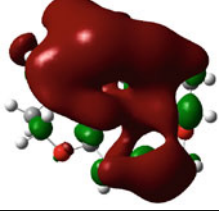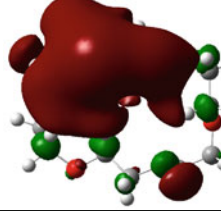
^{a} Nitrogen charge

^{b} Oxygen charge

^{c} Torsional gauche angles

^{d} Torsional barrier energies of ± a,g, atorsios, [kcal/M] of the macrocyclic backbone

Table 3 Frontier molecular Orbital Diagrams and Energies of **I** and **II** by the HF/6-31G(d) and B3LYP/6-31G(d)

I (HF/6-31G(d))	**I**(B3LYP/6-31G(d))
$E_{HOMO}=-0.396$	$E_{HOMO}=-0.240$
$E_{LUMO}=0.213$	$E_{LUMO}=0.070$
$\Delta E^a= 0.609$	$\Delta E^a= 0.310$
II (HF/6-31G(d))	**II**(B3LYP/6-31G(d))
$E_{HOMO}=-0.357$	$E_{HOMO}=-0.216$
$E_{LUMO}=0.223$	$E_{LUMO}=0.076$
$\Delta E^a= 0.580$	$\Delta E^a=0.292$

[a] $\Delta E(E_{LUMO}- E_{HOMO})$

an electron from the HOMO to the LOMO orbital will be low [29–31]. The frontier molecular orbital energies also play an important role in the electric and optical properties, as well as in UV–Vis spectra and chemical reactions in the conjugated molecules [32, 33].

Frontier molecular orbital diagrams and energies of **I** and **II**, such as E_{LUMO}, E_{HOMO}, and ΔE (in eV) estimated by the HF/6-31G(d) and B3LYP/6-31G(d) levels are represented in Table 3. The values of E_{HOMO} show the relation: **II** > **I** for this property. In addition, the values of ΔE show this order: **I** > **II**. Consequently, the electron-donating ability of **I** is lower than **II**. As can be seen from the pictures of HOMO and LUMO in Table 3, the majority of HOMO and LUMO are found on the donor atoms in the crown ether ring, suggesting the high electron-donating ability of heteroatoms.

Our conclusion is actually that the dissociation of the complexes has more pronounced effect on the binding properties as we previously reported that the enthalpy stabilized cation binding is involved in dioxane/water solvent mixtures [4, 16, 25]. The K^+ binding of highest power is not only due to conformational ability of D_{3h} point group of minimum strain energy which is probably C_2 in our case but also the poorest hydration tendency of K^+/[18]crown-6 complex. Accordingly, the binding powers of [15]crown-5, in particular [12]crown-4, in dioxane/water have already been outlined in our earlier reports [1, 14–16]. We additionally showed that higher degree of cation/macrocyle

associations, like1:2 or 2:1 are more likely to be involved in case of [18]crown-6(see Table 2). This is in fact a direct evidence of the formation of discrete oligomolecular or polymolecular-cation assemblies of a supramolecular behavior [2–4, 34].

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