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Molecular Design of Crown Ethers. 12.[1] Complexation Thermodynamics of 12- to 16-Crown-4: Thermodynamic Origin of High Lithium Selectivity of 14-Crown-4

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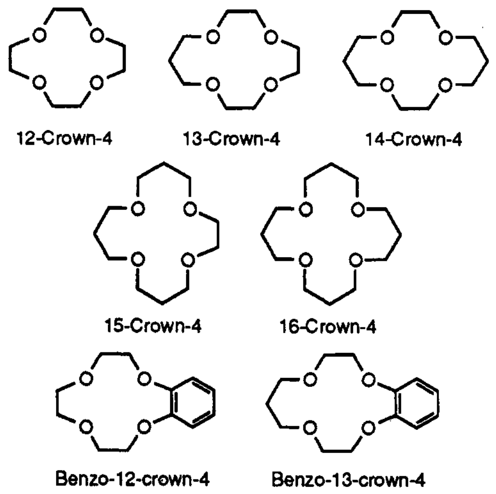
Calorimetric titrations have been performed in methanol at 25 °C to give the complex stability constants (K_s) and the thermodynamic parameters for the stoichiometric 1:1 complexation of lithium and sodium ions with 12- to 16-crown-4: 1,4,7,10-tetraoxacyclododecane (12-crown-4), 1,4,7,10-tetraoxacyclotridecane (13-crown-4), 1,4,8,11-tetraoxacyclotetradecane (14-crown-4), 1,4,8,12-tetraoxacyclopentadecane (15-crown-4), and 1,5,9,13-tetraoxacyclohexadecane (16-crown-4). Possessing a less-symmetrical structure, 14-crown-4 gave the highest K_s for Li^+ and the lowest for Na^+ among the crown-4 series, eventually showing the highest cation selectivity for Li^+ over Na^+. The highly selective binding of Li^+ by 14-crown-4 has shown to originate from the cooperative entropic and enthalpic contribution at this ring size, both of which may be attributable to the least conformational changes and the most extensive desolvation caused by the size-fitted combination of cation and cavity diameters.

Since the first synthesis of crown ether,[2] the symmetrical $3m$-crown-m ($m \geq 4$) skeletons have widely been adopted as the most preferable structures in the syntheses of various crown ethers, because of the synthetic feasibility and their generally high cation-binding abilities.[3-7] However, recent investigations[7-19] have revealed that less-symmetrical ($3m + n$)-crown-m's ($m \geq 4$, $n \neq 0$) are not always inferior to the symmetrical ones in view of the relative cation selectivity as well as the binding ability. In contrast to the mostly negative influences on the binding properties caused by the ring enlargement of medium- to large-sized crown ethers,[10-12] introduction of extra methylene(s) into small-sized 12-crown-4 and 15-crown-5 endows the resulting less-symmetrical 14-crown-4[17-19] and 16-crown-5[7,8,10-16] with much higher cation selectivities for lithium and sodium ions, respectively, than the parent crown ethers. It has been proposed that the rigid structure, the precise size-matching between the cavity and cation diameters, and the favorable orientation of donor oxygens are jointly responsible for the enhanced cation selectivities.[7,12] Unfortunately, the complexation thermodynamics of these less-symmetrical crown ethers have not been investigated systematically and the thermodynamic origin of the specific cation selectivity is left unanswered.

Chart I



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In the present study, we synthesized unsubstituted 13- to 16-crown-4 and investigated the thermodynamic behavior of these crown-4 homologs in the homogeneous-phase complexation with lithium and sodium ions in order to elucidate the thermodynamic origin of the high lithium selectivity of 14-crown-4 derivatives.

Experimental Section

Materials. Commercially available 12-crown-4 was used as received. Less-symmetrical 13-crown-4, 14-crown-4, 15-crown-4, and 16-crown-4 were synthesized in 11–36% yields in the reactions of appropriate glycols with glycol ditosylates in the presence of mixed alkali hydroxides (LiOH–NaOH) in tetrahydrofuran, according to the procedures reported previously.[19] The solvent methanol was refluxed over magnesium turnings and then distilled fractionally. Analytical grade lithium chloride and sodium thiocyanate were dried in vacuo prior to use.

Apparatus and Procedures. Calorimetric titrations were performed at atmospheric pressure in a temperature-controlled water bath maintained at 25.0 °C, by using an LKB 8721-2 precision calorimeter connected to a personal computer for automated titration and data processing.[20] The principle of the measurement and the detailed experimental procedures were reported elsewhere.[21] Typically, a methanol solution of sodium thiocyanate (0.15 M) was introduced continuously at a rate of 0.43 mL/min into a crown ether solution (5.0–10.0 mM) placed in the calorimeter. A titration curve was obtained by plotting the temperature change (measured by E/mV) against the amount of the metal salt solution added, from which the complex stability constant (K_s) and the enthalpy change (ΔH) are calculated. Reliability of the whole system and the calculation procedures were doubly checked as previously by comparing the obtained thermodynamic parameters with the reported values,[22,23] and satisfactory results were obtained.

Results

Assuming the 1:1 stoichiometry for the complexation of lithium and sodium ions with 12-crown-4 to 16-crown-4, the complex stability constant (K_s) and the enthalpy change (ΔH) were calculated by using the least-squares method to minimize the U value:[20]

$$U(K_S,\Delta H) = \sum_{t=1}^{m}(Q_t - \Delta H \times N_t)^2$$

where Q_t refers to the net heat of complexation measured at time t in minutes and N_t denotes the amount in moles of the complex formed at time t and is directly related to the complex stability constant K_s.

The stability constant K_s and the enthalpy change ΔH of complexation were calculated by computer simulation with continuously changing K_s, i.e., N_t, to minimize the U value. For each cation–ligand combination, the measurement was repeated more than three times and the U value obtained was minimized satisfactorily to give the optimized set of K_s and ΔH with standard deviations. No serious deviation was found in the fitting process, verifying the 1:1 stoichiometry of complexation as assumed above. The complex stability constants and thermodynamic parameters obtained are listed in Table I, along with those reported for the complexation with benzo-12-crown-4 and benzo-13-crown-4 in methanol.[25]

Table I. Complex Stability Constant (K_S) and Thermodynamic Parameters in kcal/mol for Complexation of Lithium and Sodium Ions with 12- to 16-Crown-4 and Some of Their Benzo Analogues in Methanol at 25 °C[a]

ligand	cation	log K_S	$-\Delta G$	$-\Delta H$	$T\Delta S$
12-crown-4	Li^+	2.14 ± 0.03	2.92	0.13 ± 0.03	2.79
	Na^+	2.66 ± 0.02	3.63	3.07 ± 0.08	0.56
13-crown-4	Li^+	2.01 ± 0.05	2.74	0.12 ± 0.04	2.62
	Na^+	2.06 ± 0.04	2.81	0.82 ± 0.02	1.99
14-crown-4	Li^+	2.34 ± 0.06	3.19	0.35 ± 0.05	2.84
	Na^+	1.63 ± 0.03	2.22	1.15 ± 0.05	1.07
15-crown-4	Li^+	1.85 ± 0.04	2.52	0.15 ± 0.03	2.37
	Na^+	1.80 ± 0.02	2.46	1.05 ± 0.03	1.41
16-crown-4	Li^+	<1.50			
	Na^+	<1.15			
benzo-12-crown-4[b]	Li^+	1.34 ± 0.01	1.83	1.66 ± 0.01	−0.17
benzo-13-crown-4[b]	Li^+	1.26 ± 0.05	1.72	1.23 ± 0.38	−0.49

[a] Averages of more than three independent measurements. [b] Reference 25.

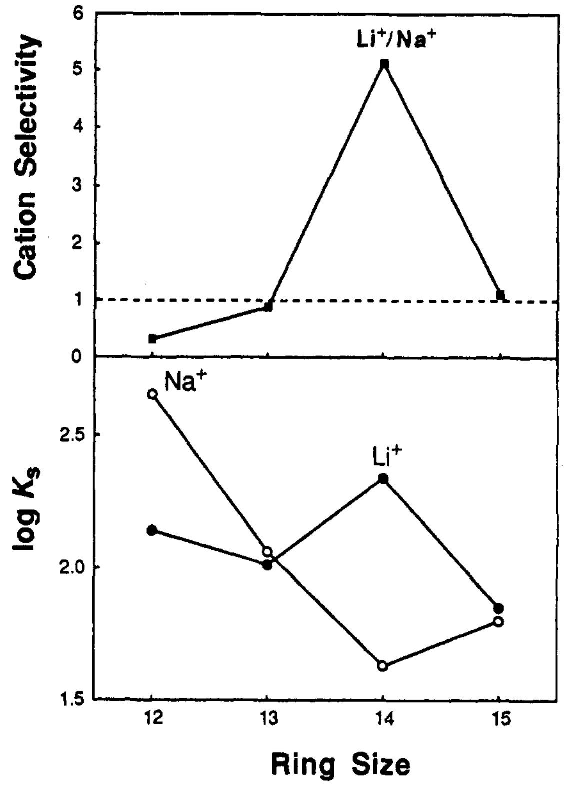

Figure 1. Complex stability constant (K_s) and cation selectivity (K_s^{Li}/K_s^{Na}) (■) for complexation of lithium (●)and sodium (○) ions with 12- to 15-crown-4 in methanol at 25 °C.

Discussion

Binding Constants. In order to visualize the cation-binding properties of 12- to 16-crown-4, the changing profiles of the complex stability constant (K_s) and the relative cation selectivity for lithium over sodium ion (K_s^{Li}/K_s^{Na}) are plotted as a function of crown ether's ring size in Figure 1 .

As can be seen from Figure 1, the K_s^{Na} value sharply decreases with increasing ring size up to 14 and then

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recovers slightly thereafter, probably owing to their unfitted ring sizes and improper donor orientations for sodium ion. On the other hand, the K_s^{Li} value displays a distinctly different profile. Thus, the serial ring enlargement scarcely affects the K_s^{Li} value up to ring size 13, as is the case with the benzo analogues (Table I), but dramatically enhances K_s^{Li} at ring size 14, and finally affords a rapid decrease at 15. The appearance of a peak in K_s^{Li} may be attributed to the appropriate ring size and donor orientation of 14-crown-4 for lithium ion, as has been pointed out in the solvent extraction with these crown-4's.[19] As a consequence of the opposite behavior of K_s^{Li} and K_s^{Na} values, the profile of the relative cation selectivity K_s^{Li}/K_s^{Na} is remarkably exaggerated, giving a distinctive peak of the cation selectivity for 14-crown-4, as shown in the upper trace of Figure 1. It is concluded therefore that, although the crown-4's are believed in general to be useful for complexing small cations like lithium, actually 14-crown-4 is the only ligand that possesses the definitive lithium selectivity as demonstrated in the solvent extraction[19] and the homogeneous-phase complexation.

Thermodynamic Parameters. The thermodynamic quantities for the complexation of lithium and sodium ions with 12- to 15-crown-5 are plotted as functions of ring size in Figure 2 . Possessing distinct cation diameters (Li^+, 1.52 Å; Na^+, 2.04 Å)[26] and free energies of hydration (Li^+, 115 kcal/mol; Na^+, 90 kcal/mol),[27] lithium and sodium ions display completely different thermodynamic behavior upon the complexation with 12- to 16-crown-4. It is conspicuous that the complexation of lithium ion is absolutely entropy-driven with only trivial positive enthalpic contribution for all the crown-4's employed, whereas both the enthalpy and entropy terms contribute significantly to the stability of sodium complexes with the crown-4's. As can be recognized from Figure 2b, the gradually declining pattern of complex stability ($-\Delta G$) for sodium primarily reflects the enthalpy change ($-\Delta H$), although the compensating contribution of entropy change ($T\Delta S$) does play a minor but appreciable role.

It should be emphasized that, in the typical entropy-driven complexation of lithium ion, not only the $T\Delta S$ value but also the $-\Delta H$ value give the highest values at ring size 14, maximizing the complex stability ($-\Delta G$) for lithium, as shown in Figure 2a. This collaborative behavior of $-\Delta H$ and $T\Delta S$ is characteristic to the lithium complexation and quite different from their mutually compensating changes observed for the sodium complexation. The maximal enthalpic and entropic gains obtained for the lithium complexation with 14-crown-4 indicate that the cavity size of 14-crown-4 is best size-fitted to the cation diameter of lithium, as shown by the examination of CPK molecular models, and therefore the complexation causes the least conformational change of ligand and the most extensive desolvation of cation and ligand, affording the most stable lithium complex. On the other hand, the complexation of larger sodium ion in the small cavity of crown-4's must involve substantial conformational changes and less-extensive desolvation, affording the mutually-compensating moderate enthalpy and entropy changes. In this context, it is rather natural that the tailoring of crown ether's ring size by introducing extra methylene(s) is a convenient and powerful tool to enhance the cation-binding ability and relative cation selectivity of crown ethers, but is applicable only to the small-sized crown ethers such as crown-4 and crown-5, both of which possess relatively rigid skeletons and do not appear to cause drastic conformational changes upon complexation.

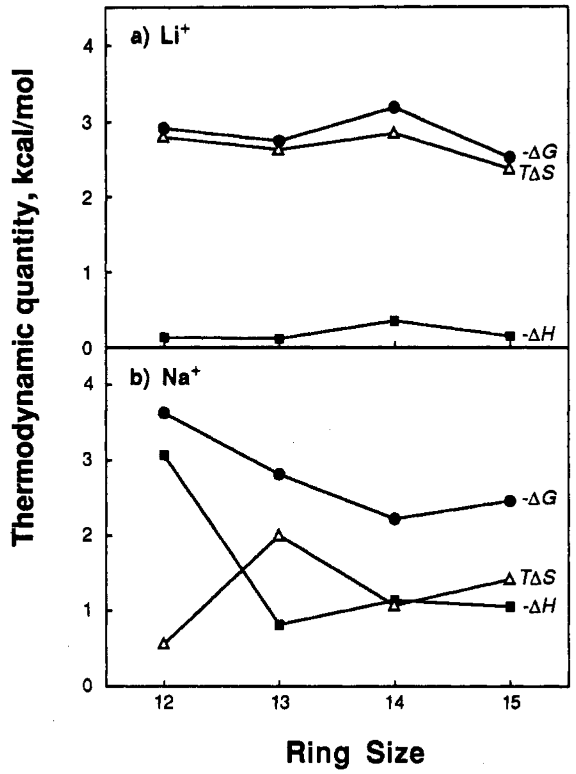

Figure 2. Thermodynamic parameters for complexation of (a) lithium and (b) sodium ions with 12- to 15-crown-4 in methanol at 25 °C.

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