Complexation Thermodynamics of Crown Ethers. Part 3.[1,2] 12-Crown-4 to 36-Crown-12: from Rigid to Flexible Ligand†

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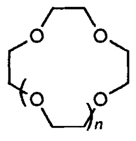
Complex stability constants and thermodynamic parameters have been determined for the complexation of alkali metal ions with large-sized crown ethers, *i.e.* 24-crown-8 to 36-crown-12, in methanol at 25 °C. Using the present and reported data, the complexation behaviour of 12-crown-4 through 36-crown-12 is discussed comparatively and globally from the thermodynamic point of view. The complex stability sequence for each cation as a function of ring size shows a characteristic two-peak profile with a global maximum and a smaller local maximum at a larger ring size, both of which may be interpreted in terms of the size-fit concept. Thermodynamically, the complexation of alkali metal ions with the crown ethers is absolutely enthalpy-driven in methanol, but the cation selectivity determined by the size–fit relationship is shown to be mostly entropy-governed. The large, but ring size insensitive, enthalpy and entropy changes for large crown ethers are rationalized by the mutually resembling cation–ligand interaction, degree of desolvation, and substantial structural freezing upon encapsulating complexation forming a highly flexible 3D cavity. However, the size–fit concept still appears to play a subsidiary role even in the complexation by larger crown ethers, although its control becomes fairly loose.

In contrast to the intensive thermodynamic studies concentrated on the complexation of cationic species with small to medium sized crown ethers (3*m*-crown-*m*; $m = 4$–6),[3,4] the complexation thermodynamics of large-sized crown ethers ($m \geqslant 7$) have not been extensively investigated so far, except for the works on some large benzocrown ethers.[3–12] Although the complexation behaviour has been believed, and partly demonstrated indeed, to depend significantly on the ring size and flexibility of crown ether,[3,5,7,13–15] no systematic study has been done of the complexation thermodynamics of unsubstituted crown ethers possessing ring sizes larger than 21.

Recent investigations using a series of unsubstituted[16] or substituted[17,18] crown ethers of various ring sizes ($m = 4$–12) have revealed that the complex stability sequence for several univalent cations shows a global maximum for the crown ether with a hole size-fitted to the specific cation and, in addition, a smaller but distinct local maximum for the crown ether of a larger ring size, displaying characteristic two-peak profile. The local maxima at the larger ring-sizes have been ascribed to the encapsulating complexation,[16–19] and therefore the large-sized crown ethers are often regarded as formal mimics of antibiotic ionophores like valinomycin.[17]

In this study, we have determined the complex stability constants and thermodynamic parameters for the complexation of alkali metal ions with large-sized crown ethers, *i.e.* 24-crown-8 (24C8), 27-crown-9 (27C9), 30-crown-10 (30C10), 33-crown-11 (33C11), 36-crown-12 (36C12), in methanol at 25 °C by means of titration calorimetry. Using the present results and the thermodynamic parameters reported for the complexation of small to medium sized 12-crown-4 (12C4),[14,19] 15-crown-5 (15C5),[13,14,20] 18-crown-6 (18C6),[13,14,20] and 21-crown-7 (21C7),[13] we discuss globally the complexation thermodynamics of rigid 12-crown-4 to highly flexible 36-crown-12, and deduce the thermodynamic origin of the characteristic two-peak profile of the stability constant as a function of the crown ether's ring size.



12C4 $n = 1$
15C5 $n = 2$
18C6 $n = 3$
21C7 $n = 4$
24C8 $n = 5$
27C9 $n = 6$
30C10 $n = 7$
33C11 $n = 8$
36C12 $n = 9$

Experimental

Materials.—The large-sized 3*m*-crown-*m* ($m = 8$–12), i.e. 24-crown-8 to 36-crown-12, were synthesized in the reactions of the appropriate combinations of oligoethylene glycol and oligoethylene glycol ditoluene-*p*-sulfonate in the presence of alkali hydroxide in tetrahydrofuran, according to the procedures reported previously.[16] The crude products obtained after the basic work-up procedures[16] were purified by distillation under reduced pressure followed by column chromatography over alumina to give the pure crown ethers in 3–19% yields.

The solvent methanol was refluxed over magnesium turnings and distilled fractionally prior to use. All alkali metal salts used were analytical grade reagents. Sodium and potassium chlorides were recrystallized respectively from water or from

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† Non SI-unit employed: 1 cal = 4.184 J. Abbreviations: 12-crown-4: 1,4,7,10-tetraoxacyclododecane; 15-crown-5: 1,4,7,10,13-pentaoxacyclopentadecane; 18-crown-6; 1,4,7,10,13,16-hexaoxacyclooctadecane; 21-crown-7: 1,4,7,10,13,16,19-heptaoxacyclohenicosane; 24-crown-8: 1,4,7,10,13,16,19,22-octaoxacyclotetracosane; 27-crown-9: 1,4,7,10,13,16,19,22,25-nonaoxacycloheptacosane; 30-crown-10: 1,4,7,10,13,16,19,22,25,28-decaoxacyclotriacontane; 33-crown-11: 1,4,7,10,13,16,19,22,25,28,31-undecaoxacyclotritriacontane; 36-crown-12: 1,4,7,10,13,16,19,22,25,28,31,34-dodecaoxacyclohexatriacontane.

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water and ethanol, while caesium chloride was used as received. All the metal salts obtained 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.[21] The principle of measurement and the detailed experimental procedures were reported elsewhere.[22] Typically, a methanol solution of sodium chloride (0.15 mol dm^{-3}) was introduced continuously at a rate of 0.43 cm^3 min^{-1} into a methanol solution of crown ether (3-5 mmol dm^{-3}) placed in the calorimeter. In order to obtain the net heat of complexation [Q(net)], the total apparent heat observed [Q(obs)] was corrected for the dilution of titrant (Q_D), the non-chemical contributions (Q_{HL}), including agitation, heat flow between the vessel and its surroundings and resistance heating by the thermistor used, and the temperature difference between titrant and titrate (Q_{TC}) in each run: $Q(\text{net}) = Q(\text{obs}) - Q_D - Q_{HL} - Q_{TC}$. A titration curve was obtained by plotting the net temperature change (measured by E/mV) against the amount of the sodium chloride solution added, from which the complex stability constant (K_s) and the enthalpy change ($\Delta H°$) are calculated. The reliability of the whole system and the calculation procedures were doubly checked by test runs on the reported reaction systems: (i) the enthalpy change ($\Delta H° = -11.34$ kcal mol^{-1} at 25 °C) upon titration of TRIS [tris(hydroxymethyl)aminomethane] with hydrochloric acid was consistent with that reported (-11.35 kcal mol^{-1});[23] (ii) $\Delta H°$ (-6.22 kcal mol^{-1} at 25 °C) for the complexation of 18-crown-6 with potassium chloride in aqueous solution was also in good agreement with the reported value (-6.21 kcal mol^{-1}).[24]

Results

Since no formation of sandwich or dicationic complex with large-sized crown ethers has been reported in the homogeneous phase,[3,4,15] we assumed the 1:1 stoichiometry for the complexation of sodium, potassium, and caesium ions with 24-crown-8 to 36-crown-12. The complex stability constant (K_s) and the enthalpy change ($\Delta H°$) were calculated by using the least-squares method to minimize the error square sum (U),[21]

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

where Q_t refers to the net heat [Q(net)] 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 $\Delta H°$ 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 was minimized satisfactorily to give the optimized sets of K_s and $\Delta H°$ with standard deviations. No serious deviation was found in the fitting process, consistent with the 1:1 stoichiometry of complexation assumed above. The complex stability constants and thermodynamic parameters obtained in the present study are listed in Table 1, along with those reported for the complexation of alkali metal ions with 12-crown-4 to 21-crown-7 in methanol.[13,19,20]

Discussion

As can be seen from Table 1, the complexation thermodynamics of common crown ethers, *i.e.* 12C4, 15C5 and 18C6, have been examined independently by a few research groups. For most cation–ligand combinations, the consistency of the thermodynamic parameters reported for the same system is quite satisfactory in spite of the different calorimeter, titration procedures and source of reagents employed, so that the choice of thermodynamic parameters may not cause serious discrepancies in the comparative study described below. However, appreciable inconsistencies (>1 kcal mol^{-1}) are found in the $\Delta H°$ and/or $T\Delta S°$ values reported for 12-crown-4. This may be attributable at least in part to the much larger errors resulting from the fairly small heat produced upon complexation by 12-crown-4. Hence, we will employ the data[19] with the smallest reported errors in the following discussion and plots.

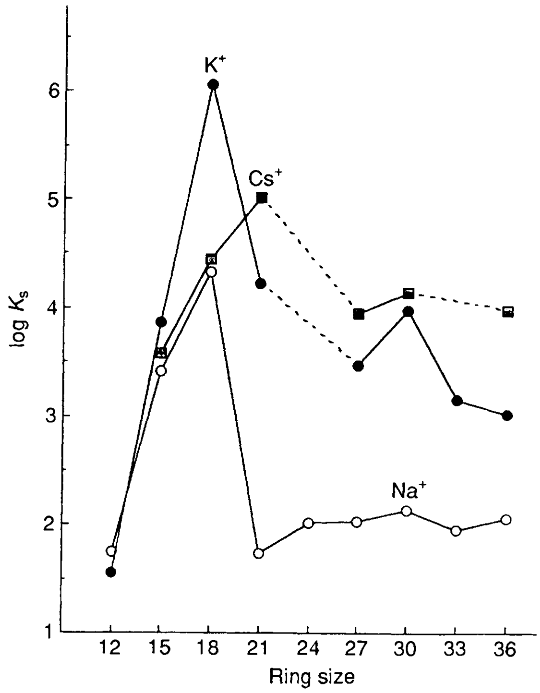

Fig. 1 Complex stability constant (log K_s) as a function of crown ether's ring size for complexation of sodium (○), potassium (●), and caesium (▨) ions with 3m-crown-m (m = 4–12) in methanol at 25 °C

Complex Stability.—As has been demonstrated in the solvent extraction of aqueous metal picrates with unsubstituted 3m-crown-m (m = 4–12)[16] and in the homogeneous-phase complexation with some substituted crown ethers,[17,18] the complex stability constants (K_s) for alkali metal ions display the characteristic two-peak profiles for all cations examined; see Fig. 1. The global maxima, observed for K^+ with 18C6 and for Cs^+ with 21C7, are reasonably accounted for in terms of the size–fit relationship between the formal cavity of crown ether and the ion diameter, while the global peak for Na^+ at the ring size 18 seems somewhat deviated from the apparently best-fitted ring size of 15. Since the solvent extraction with 15C5 gives the highest extractability for Na^+ in accord with the size–fit relationship,[16] this deviation observed in homogeneous solution may need another explanation. As proposed by Schultz *et al.*,[25] the tendency of alkali metal ions to form hexa-coordinated complexes with crown ethers may be the driving force to give the higher K_s for 18C6 rather than 15C5 in homogeneous methanol solution, where only free cations are involved in the complexation process and the counter anions have little effect. In the solvent extraction, metal salt is extracted from the aqueous to organic phase producing a contact ion-pair complex with crown ether, in which the counter anion occupies one

Table 1 Complex stability constant (log K_s) and thermodynamic parameters in kcal mol^{-1} for complexation of alkali metal ions with 3*m*-crown-*m* (*m* = 4–12) in methanol at 25 °C

Ligand	Cation	log K_s	$-\Delta G°$	$-\Delta H°$	$T\Delta S°$	Ref.
12C4	Na^+	1.75	2.39	2.01	0.36	*a*, *b*
		1.5	2.0	3.0	−1.0	*c*
	K^+	1.55	2.11	3.22	−1.12	*a*, *b*
		1.58	2.16	5.10	−2.94	*c*
15C5	Na^+	3.42	4.67	5.26	−0.64	*b*, *d*
		3.13	4.27	5.50	−1.23	*c*
		3.48	4.75	4.99	−0.24	*e*
	K^+	3.86	5.26	7.41	−2.21	*b*, *d*
		3.59	4.90	7.70	−2.80	*c*
		3.77	5.13	7.7	−2.57	*e*
	Rb^+	4.07	5.55	6.76	−0.50	*b*, *d*
	Cs^+	3.58	4.88	5.07	−0.21	*b*, *d*
18C6	Na^+	4.32	5.89	8.13	−3.28	*b*, *d*
		4.36	5.95	7.50	−1.55	*c*
		4.36	5.95	8.36	−2.41	*e*
	K^+	6.06	8.27	13.12	−4.85	*b*, *d*
		6.16	8.40	12.70	−4.30	*c*
		6.06	8.27	13.41	−5.14	*e*
	Rb^+	5.32	7.26	11.85	−4.56	*b*, *d*
		5.32	7.26	12.09	−4.83	*e*
	Cs^+	4.44	6.06	11.93	−5.91	*b*, *d*
		4.79	6.54	11.29	−4.75	*e*
21C7	Na^+	1.73	2.36	10.37	−8.00	*b*, *e*
	K^+	4.22	5.75	8.59	−2.83	*b*, *e*
	Rb^+	4.86	6.63	9.66	−3.03	*b*, *e*
	Cs^+	5.01	6.83	11.18	−4.34	*b*, *e*
24C8	Na^+	2.02 ± 0.08	2.76	6.44 ± 0.09	−3.68	*f*
27C9	Na^+	2.03 ± 0.03	2.77	6.47 ± 0.07	−3.70	*f*
	K^+	3.47 ± 0.07	4.73	10.40 ± 0.15	−5.67	*f*
	Cs^+	3.95 ± 0.08	5.39	8.72 ± 0.06	−3.33	*f*
30C10	Na^+	2.14 ± 0.07	2.92	6.11 ± 0.08	−3.19	*f*
	K^+	3.98 ± 0.02	5.43	11.64 ± 0.11	−6.21	*f*
	Cs^+	4.15 ± 0.02	5.66	11.22 ± 0.05	−5.56	*f*
33C11	Na^+	1.96 ± 0.02	2.67	8.11 ± 0.09	−5.44	*f*
	K^+	3.16 ± 0.05	4.31	11.69 ± 0.06	−7.38	*f*
36C12	Na^+	2.06 ± 0.02	2.81	7.44 ± 0.01	−4.63	*f*
	K^+	3.03 ± 0.03	4.13	12.03 ± 0.10	−7.90	*f*
	Cs^+	3.98 ± 0.04	5.43	10.91 ± 0.06	−5.48	*f*

[a] Ref. 19. [b] Data employed in Figs. 1 and 2. [c] Ref. 14. [d] Ref. 20. [e] Ref. 13. [f] This work.

coordination site of the complexed cation. Hence, the cation selectivity sequence in homogeneous solution may differ from that observed in solvent extraction.[26]

In addition to the global ones, smaller local maxima of K_s are seen at larger ring sizes for all cations examined. The second peak for K^+ appears at ring size 30, while a much broader peak, or plateau, is found at ring sizes 24–30 and 30–33 for Na^+ and Cs^+, respectively. These local maxima may be attributed to the encapsulating complexation by the large-sized crown ethers, which also recognize cations by size, but less strictly, through the three-dimensional (3D) cavity created upon encapsulating complexation. Formation of the 3D cavity inherently accompanies substantial structural changes of the ligand, and the induced cavity is much more flexible in size and shape than the inherent two-dimensional one. These points will be discussed below from the thermodynamic point of view.

Complexation Thermodynamics.—It should be noted that the complexation of alkali metal ions with rigid 12C4 through highly flexible 36C12 is exclusively enthalpy-driven in methanol, irrespective of the ring size of crown ether; see Table 1 and Fig. 2. For all alkali metal ions examined, the enthalpic gain ($-\Delta H°$) increases with increasing ring size up to 18 or 21, then decreases a little, and finally levels off thereafter. The entropic loss ($T\Delta S°$), though smaller than $-\Delta H°$ in magnitude, displays a similar tendency throughout the ring sizes of 12 to 36, and therefore cancels the enthalpic gain to a considerable extent, affording the characteristic two-peak profile of K_s as a consequence of the critical balance between $-\Delta H°$ and $T\Delta S°$.

The entropy change, being mostly negative, is particularly small or even positive in the complexations with 12C4 and 15C5, for which their fairly rigid skeletons and the minimal structural changes upon complexation must be jointly responsible. The gradual increases up to 18C6 of both $-\Delta H°$ and $T\Delta S°$ for all cations may be related to the preferred coordination number of alkali metal ions. Thus, the formal six coordination sites of alkali metal ions,[27,28] initially occupied by methanol molecules, are substituted successively by the donor oxygen atoms of 3*m*-crown-*m* until the substitution completes at *m* = 6. The enthalpic gain from the substitution increases with the number of donor oxygens (*m*) at least up to 6, while the entropic loss arising from the molecular association and the structural freezing of the crown ether skeleton is partially compensated by the entropic gain from the release of solvating methanol upon complexation.

It is interesting to discuss the thermodynamic behaviour of the formally best size-fitted combinations of cation and ligand, *i.e.* Na^+ and 15C5 or 18C6, K^+ and 18C6, and Cs^+ and 21C7. The global maxima for Na^+, K^+ and Cs^+ do not always accompany the greatest enthalpic gains, but are rather accomplished by the less negative entropic losses, probably resulting from the minimal structural changes upon complexation of size-fitted cations. As can be seen from Fig. 2, in the complexation of Na^+, the enthalpic gains for 15C5 and 18C6

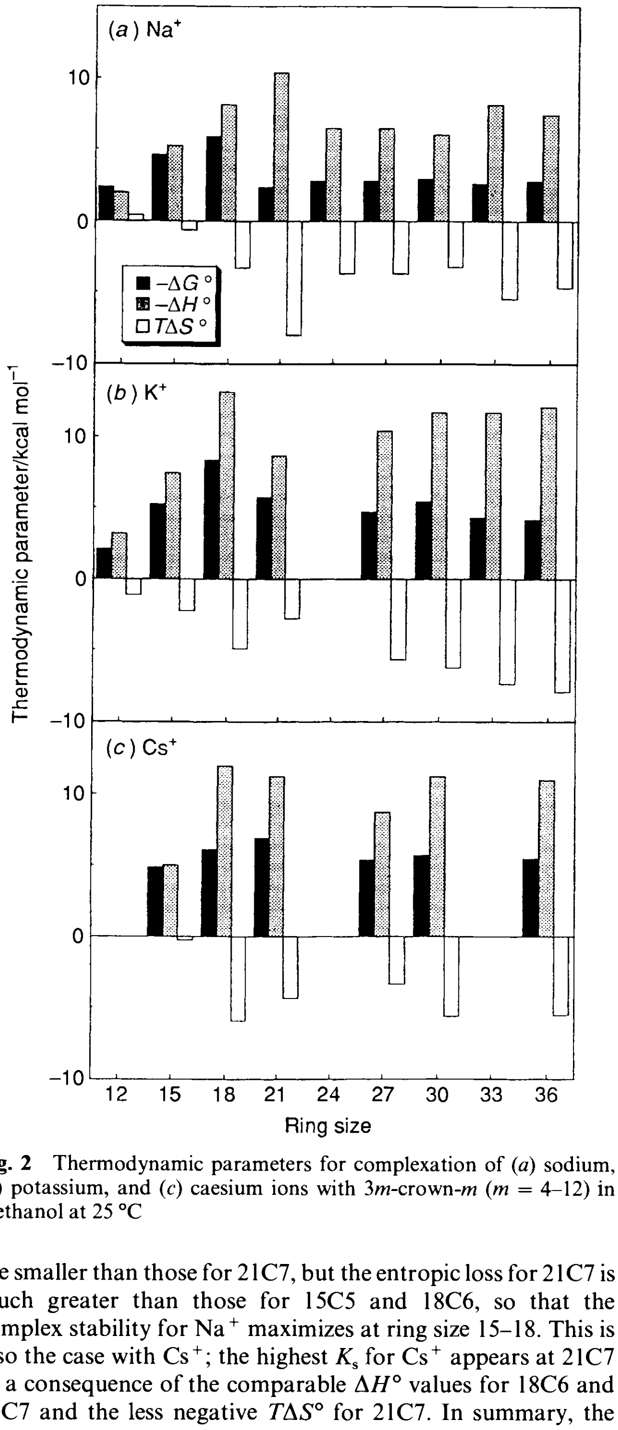

Fig. 2 Thermodynamic parameters for complexation of (*a*) sodium, (*b*) potassium, and (*c*) caesium ions with 3*m*-crown-*m* (*m* = 4–12) in methanol at 25 °C

are smaller than those for 21C7, but the entropic loss for 21C7 is much greater than those for 15C5 and 18C6, so that the complex stability for Na^+ maximizes at ring size 15–18. This is also the case with Cs^+; the highest K_s for Cs^+ appears at 21C7 as a consequence of the comparable ΔH° values for 18C6 and 21C7 and the less negative $T\Delta S^\circ$ for 21C7. In summary, the complexation itself is evidently enthalpy-driven, but the cation selectivity is mostly entropy-governed.

In contrast to the highly ring size-sensitive thermodynamic parameters for 12C4 to 21C7, the ΔH° and $T\Delta S^\circ$ values for 24C8 to 36C12 are kept high and insensitive to the ring size, as can be seen from Fig. 2. The local maxima of K_s are not always attributable to single thermodynamic parameters. Thus, the smaller entropic loss for 30C10 is mainly responsible for the small peak of K_s for Na^+ at that ring size, while the larger enthalpic gains for 30C10 appear to contribute to the local K_s maxima observed for K^+ and Cs^+. These large and ring size insensitive thermodynamic parameters indicate that both the structural change and the extent of desolvation are fairly extensive and mutually resemble in the encapsulating complexation of these large-sized crown ethers. Hence, the size recognition in encapsulating complexation is not so strict as in the formally size-fitted complexation by small to medium sized crown ethers, probably owing to the induced 3D cavity which can flexibly adjust its diameter to the size of cation accommodated. Thermodynamically, the size–fit concept is shown to have the entropic, rather than enthalpic, origin both for the formal 2D and induced 3D size-fitted complexations, although its control is fairly loose for the latter case.

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