Molecular Design of Crown Ethers. Part 9.[1] Complexation Thermodynamics of 1,4,7,10,13-Pentaoxacyclohexadecane (16-Crown-5) and its Lariat Derivative in Methanol–Water: Solvent Effect upon Lariat Complexation

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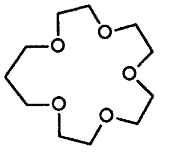
Calorimetric titrations have been performed in 60–100% methanol at 25 °C in order to obtain the complex stability constants (K_s) and the thermodynamic parameters for the stoichiometric 1:1 complexation of some alkali (Na^+ and K^+) and heavy metal (Ag^+ and Tl^+) ions with less symmetrical crown ethers, 1,4,7,10,13-pentaoxacyclohexadecane (16-crown-5) (**1**) and 15,15-dimethyl-16-crown-5 (**2**), and the lariat ether, 15-(2,5-dioxahexyl)-15-methyl-16-crown-5 (**3**). The thermodynamic quantities clearly indicate that the complex stability sequence is essentially entropy governed, although the complex formation itself is evidently enthalpy driven. The lower complex stabilities for **2** are attributed to the reduced enthalpic gains caused by the steric hindrance between the methyl substituents and the cation. This steric hindrance, however, helps to lock the ring conformation such that complexation can occur, as indicated by the less negative entropic changes for **2**. The lariat effect is shown to be sensitive to solvent composition; the complex stability sequence for Na^+ is **3** > **1** > **2** in 60–80% methanol but **1** > **3** > **2** in 100% methanol. Thermodynamically, the partial inversion of the stability sequence is attributed to the smaller entropic gain arising from the less effective desolvation by the lariat side arm in 100% methanol.

Lariat ethers, possessing additional donor atom(s) in the side arm(s), were originally designed[2] and are indeed known to enhance the cation binding ability and selectivity of the parent crown ether through further ligation of sidearm donor(s) to a cation accommodated in the crown cavity.[2–8] Contrary to the pronounced lariat effect reported for several *C*- and *N*-pivot lariats with 3*m*-crown-*m* skeletons,[2–8] we have recently demonstrated that, in the 16-crown-5 series (**1**–**3**), the lariat effect does not always function as an effective tool for enhancing cation binding ability or selectivity, but is invalid or even negative under certain conditions.[1] As far as the binding constant can be evaluated by the solvent extraction technique in a water–dichloromethane system, 16-crown-5 lariat **3** shows much higher cation-binding ability and selectivity for the size-matched Na^+ over K^+ than the reference crown ether **2**, proving effective lariat ligation of the sidearm. By contrast, the conductometric measurement in methanol solution does not indicate any positive participation of the side arm donor, affording almost comparable or even smaller binding constants for **3** than those for **2**. This obviously conflicts with the basic concept of lariat ether and therefore prompted us to investigate thermodynamically the mechanism and validity of the lariat effect in the other solvent systems.

The failure of lariat ligation in the homogeneous methanol solution was attributed to a combined effect of flexible ring/side arm and heavy solvation of methanol to a cation accommodated in the cavity.[1] The validity of the lariat effect is considered to be governed by a critical balance between the entropic loss from further structural freezing and the gain from accompanying desolvation, both induced by the lariat ligation. The 16-crown-5 lariat **3** appears to be a borderline case; the balance is negative at least in methanol. In this context, it is interesting to draw a thermodynamic profile of the lariat effect in the 16-crown-5 series, although the solvent effect upon complexation thermodynamics of crown ethers has not been studied extensively.[9] In the present study, we report the calorimetric titrations of the complex formation of **1**–**3** with the size-matched Na^+ (effective ionic radius for coordination number 6 = 102 pm)[10] and the slightly less well fitting Ag^+ (115 pm)[10] and also with the larger K^+ (138 pm)[10] and Tl^+ (150 pm)[10] in 60–100% aqueous methanol at 25 °C, and discuss the effects of ring substitution and solvent composition on the complexation behaviour of the 16-crown-5 series from the thermodynamic point of view.



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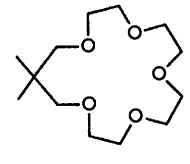

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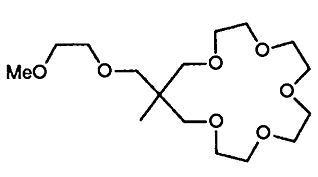

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Experimental

Materials.—The crown ethers **1**–**3** were prepared according to the procedures reported earlier.[5,11] Reagent-grade methanol was refluxed over magnesium turnings and then distilled fractionally to give dry methanol for calorimetry. The purified methanol was used without further treatment, or mixed with distilled, deionized water [$(1.0\text{–}1.2) \times 10^{-6}$ S cm^{-1}] to make a mixed solvent which contains 60 or 80% methanol by volume. Analytical grade sodium thiocyanate, sodium and potassium chlorides, and silver and thallium(I) nitrates were used as received. All metal salts were dried *in vacuo* prior to use.

Table 1 Complex stability constant (log K_s) and thermodynamic parameters (kcal mol^{-1}) for complexation of crown ether **1**–**3** with some alkali and heavy metal ions in methanol–water mixed solvents at 25 °C[a]

Ligand	Cation	Solvent (MeOH:H_2O)[b]	log K_s	$-\Delta G^\circ$	$-\Delta H^\circ$	$T\Delta S^\circ$
1	Na^{+c}	6:4	2.02 ± 0.08	2.76	7.91 ± 0.06	−5.15
	Na^{+c}	8:2	2.89 ± 0.06	3.94	8.20 ± 0.06	−4.26
	Na^{+c}	10:0	4.07 ± 0.06	5.55	7.07 ± 0.07	−1.52
	Na^{+d}	8:2	2.83 ± 0.03	3.86	8.56 ± 0.18	−4.70
	K^{+d}	8:2	2.17 ± 0.03	2.96	5.20 ± 0.19	−2.24
	Ag^{+e}	8:2	2.70 ± 0.07	3.68	6.36 ± 0.13	−2.68
	Tl^{+e}	8:2	2.66 ± 0.04	3.63	3.16 ± 0.11	0.47
2	Na^{+c}	6:4	1.93 ± 0.03	2.63	6.65 ± 0.04	−4.02
	Na^{+c}	8:2	2.78 ± 0.08	3.79	6.61 ± 0.15	−2.82
	Na^{+c}	10:0	3.54 ± 0.05	4.83	5.65 ± 0.06	−0.82
	Na^{+d}	8:2	2.66 ± 0.05	3.63	7.42 ± 0.31	−3.79
	K^{+d}	8:2	1.88 ± 0.05	2.56	4.27 ± 0.11	−1.71
	Ag^{+e}	8:2	2.50 ± 0.04	3.41	6.72 ± 0.02	−3.33
	Tl^{+e}	8:2	2.39 ± 0.03	3.26	2.10 ± 0.05	1.16
3	Na^{+c}	6:4	2.06 ± 0.02	2.81	6.79 ± 0.03	−3.98
	Na^{+c}	8:2	3.09 ± 0.05	4.21	6.02 ± 0.09	−1.81
	Na^{+c}	10:0	3.70 ± 0.03	5.05	5.86 ± 0.06	−0.81
	Na^{+d}	8:2	3.02 ± 0.06	4.12	5.25 ± 0.36	−1.13
	K^{+d}	8:2	2.01 ± 0.03	2.74	3.18 ± 0.18	−0.44
	Ag^{+e}	8:2	2.64 ± 0.01	3.60	5.15 ± 0.07	−1.55
	Tl^{+e}	8:2	2.48 ± 0.01	3.38	3.17 ± 0.07	0.21

[a] Values are the averages of more than three independent runs. [b] By volume. [c] Sodium thiocyanate. [d] Metal chloride. [e] Metal nitrate.

Apparatus and Procedures.—Calorimetric titrations were performed under atmospheric pressure in a water bath thermostatted at 25 °C, by using an LKB 8721-2 precision calorimeter connected to a personal computer for automated titration and data processing.[12] The principle of measurement and the detailed experimental procedures were reported elsewhere.[13,14] For the reasons of solubility in pure methanol, the effect of solvent composition was examined in 60–100% methanol by using sodium thiocyanate, while metal chlorides or nitrates were used in the other runs in 80% methanol. Typically, a salt solution (0.15 mol dm^{-3}) was continuously introduced at a rate of 0.43 cm^3 min^{-1} into a crown ether solution (2.0–5.0 mmol dm^{-3}) placed in the calorimeter. A titration curve was obtained by plotting the temperature change (measured by E/mV) against the amount of the salt solution added, from which the complex stability constant (K_s) and the enthalpy change (ΔH°) were calculated. The reliability of the whole system and the calculation procedures were doubly checked as previously[15] by comparison of the obtained thermodynamic data with the reported values,[2a,16] and satisfactory results were obtained.

Results

Assuming a 1:1 stoichiometry[1,5] for the complexation of sodium, potassium, silver and thallium ions with ligands **1**–**3**, the complex stability constant (K_s) and the enthalpy change (ΔH°) were determined by using the least-squares method to minimize the U value [eqn. (1)], where $Q_{c,t}$ refers to the heat of

$$U(K_s,\Delta H^\circ) = \sum_{t=1}^{m} (Q_{c,t} - \Delta H^\circ n_t)^2 \qquad (1)$$

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 stability constant K_s.

The stability constant K_s and the enthalpy change ΔH° for the complexation of **1**–**3** were calculated by simulation on a computer with continuously changing K_s, *i.e.*, n_t, to minimize the U value. For all cation–ligand combinations examined, the U value was minimized satisfactorily to give the optimized sets of K_s and ΔH° listed in Table 1. No serious deviation was observed in the fitting process, verifying the 1:1 stoichiometry of complexation as assumed above.

Discussion

Substitution Effect.—Before moving on to the lariat effect in a mixed solvent, we first discuss the effect of ring substitution on the complexation behaviour. As reported previously,[11,17–19] less symmetrical 16-crown-5 shows higher $\mathrm{Na}^+/\mathrm{K}^+$ and $\mathrm{Ag}^+/\mathrm{Tl}^+$ selectivities than symmetrical 15-crown-5 both in the solvent extraction[11,17,18] and in the homogeneous phase complexation.[19] Introduction of non-donating alkyl group(s) to 16-crown-5 at the 15- or 14/16-position is known to lower the extraction equilibrium constant significantly without serious accompanying changes in the relative cation selectivity.[20]

As shown in Table 1, an analogous tendency is seen in the complex stability constant (K_s) for all cations examined in the homogenous solution. Changes caused by methylation of **1** may be visualized more clearly through the differences in thermodynamic parameters ($\delta\Delta G^\circ$, $\delta\Delta H^\circ$, $\delta T\Delta S^\circ$) between **1** and **2**, which are summarized in Table 2. The methylation of **1** diminishes the ΔG° value for Na^+ by 0.13–0.72 kcal mol^{-1}[*] in 60–100% methanol and those for Na^+–Tl^+ by 0.23–0.40 kcal mol^{-1} in 80% methanol. The observed loss in free energy gain ($-\Delta G^\circ$), indicated by negative $\delta\Delta G^\circ$ shown in Table 2, is ascribed to the more drastic decrease in enthalpic gain ($-\Delta H^\circ$), or more negative $\delta\Delta H^\circ$, for most cations except for Ag^+, while less negative $T\Delta S^\circ$ for **2**, or negative $\delta T\Delta S^\circ$, compensates to some extent the drastic enthalpic loss caused by methylation, moderating the decrease in ΔG°. The smaller enthalpic gains ($-\Delta H^\circ$) for **2** than for **1** indicate that the ion–dipole interaction is weakened in the substituted 16-crown-5 (**2**), probably owing to the steric hindrance between the axial methyl group introduced at C-15 and the cation accommodated, as suggested previously.[20] On the other hand, the less negative $T\Delta S^\circ$, or smaller entropic loss, for **2** than for **1** indicates that the

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[*] 1 cal = 4.18 J.

Table 2 Differential thermodynamic parameters (kcal mol^{-1}) between **1** and **2** and between **2** and **3**[a]

Ligand pair	Cation	Solvent (MeOH:H$_2$O)[b]	$\delta\Delta G°$	$\delta\Delta H°$	$\delta T\Delta S°$
1–**2**	Na^{+c}	10:0	−0.72	−1.42	−0.70
	Na^{+c}	8:2	−0.17	−1.59	−1.44
	Na^{+c}	6:4	−0.13	−1.26	−1.13
	Na^{+d}	8:2	−0.23	−1.14	−0.91
	K^{+d}	8:2	−0.40	−0.93	−0.53
	Ag^{+e}	8:2	−0.27	0.36	0.65
	Tl^{+e}	8:2	−0.37	−1.06	−0.70
2–**3**	Na^{+c}	10:0	0.22	0.21	−0.01
	Na^{+c}	8:2	0.42	−0.59	−1.01
	Na^{+c}	6:4	0.18	0.14	−0.04
	Na^{+d}	8:2	0.49	−2.17	−2.66
	K^{+d}	8:2	0.18	−1.09	−1.27
	Ag^{+e}	8:2	0.19	−1.57	−1.78
	Tl^{+e}	8:2	0.12	1.07	0.95

[a] Calculated from data in Table 1. [b] By volume. [c] Sodium thiocyanate. [d] Metal chloride. [e] Metal nitrate.

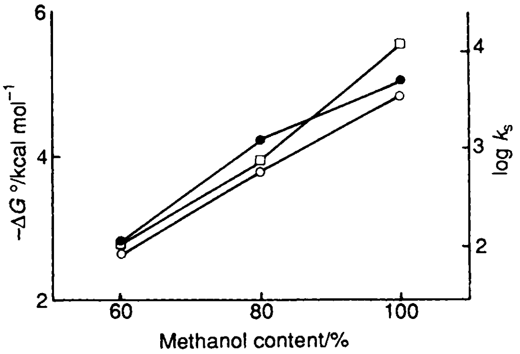

Fig. 1 Free energy change ($-\Delta G°$) as a function of methanol content for complexation of **1** (□), **2** (○) and **3** (●) with Na$^+$ in methanol–water at 25 °C

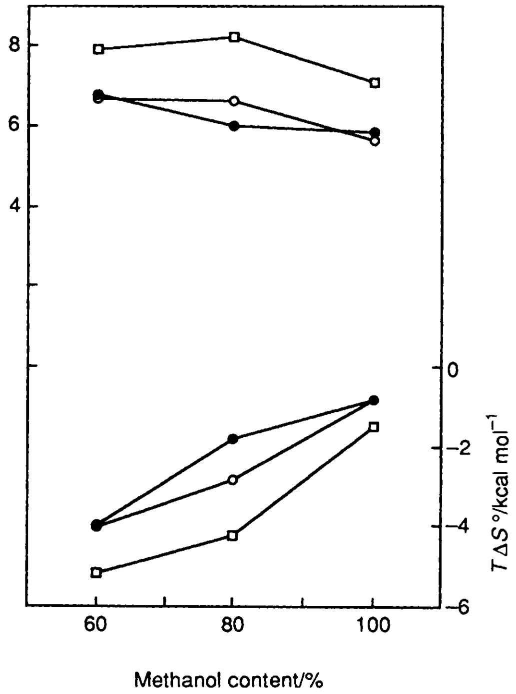

Fig. 2 Enthalpy ($-\Delta H°$, upper plots) and entropy changes ($T\Delta S°$, lower plots) as functions of methanol content for complexation of **1** (□), **2** (○) and **3** (●) with Na$^+$ in methanol–water at 25 °C

conformational change upon complexation is smaller in **2** than in **1**, and that the two methyl groups at C-15 contribute to lock the 16-crown-5 framework in a conformation favourable for complexation.

Lariat Effect.—Since the alkylation of crown ethers alters the binding constants significantly, the dimethyl analogue **2** (not the parent crown ether **1**) is employed as the reference ligand in discussing the lariat effect of **3**. As shown in Table 2 (lower half), the introduction of an electron-donating side arm enhances the complex stability, *i.e.*, positive $\delta\Delta G°$, in all cases examined, although the extent of enhancement varies with the combination of cation and the solvent composition employed. Contrary to our previous result,[1] no obvious inversion in the stability constant for Na$^+$ is seen between the reference crown compound **2** and the lariat ether **3**, although their stability constants become fairly close in 100% methanol. The different salts employed in the previous[1] and present works, *i.e.*, NaCl *versus* NaSCN, may be responsible for this inconsistency. It is thus inferred that the counter-anion affects the lariat ligation in this critical case.

The lariat effect is found to be very sensitive to the solvent composition. In Fig. 1, the stabilities ($-\Delta G°$ and $\log K_s$) of sodium complexes of **1**–**3** are plotted as functions of the methanol content. The complex stability of each ligand gradually increases with increasing methanol content, as reported for the complexation of Na$^+$ with benzo-15-crown-5 in 20–100% aqueous methanol,[21,22] but the changing profile substantially differs between crown ether **1** or **2** and lariat ether **3**. Increasing the methanol content from 60 to 80% leads to an almost comparable increment in $-\Delta G°$ for **1**–**3**, while further augmentation to 100% affords a steady (or rather enhanced) rise for **1** and **2**, but a much reduced increment for **3**. Hence the stability sequence is partially inverted in 100% methanol.

In order to discuss the solvent effect upon lariat ligation from the thermodynamic point of view, the $-\Delta H°$ and $T\Delta S°$ values are plotted as functions of methanol content in Fig. 2. It is noted that the enthalpic gain ($-\Delta H°$) is relatively insensitive to the methanol content, while the entropic loss ($T\Delta S°$) augments more drastically at higher methanol contents. As can readily be recognized from the similar profiles of the $-\Delta G°$ and $T\Delta S°$ plots in Figs. 1 and 2, the complex stability sequence is essentially entropy governed, although the complex formation itself is evidently enthalpy driven. The small and somewhat fluctuating, but steady decline in $-\Delta H°$ at higher methanol contents may be rationalized by the smaller enthalpic gain upon replacement of methanol by ligand oxygens, rather than by water molecules, occupying the solvation sites of Na$^+$.

Major, and mutually conflicting, contributors to the entropy change upon complexation are the entropic gain from desolvation and the loss from structural freezing of ligand conformation.[9] In the present case, the less negative entropy changes ($T\Delta S^\circ$) for ligands **1**–**3** at higher methanol contents may indicate that, as the methanol content increases, the desolvation generally becomes more extensive upon complexation of the solvated cation and ligand. However, in sharp contrast with the ever-rising $T\Delta S^\circ$ for **1** and **2** with increasing methanol content, the increment of $T\Delta S^\circ$ for **3** abruptly decreases in 100% methanol, as shown in Fig. 2. This supports our previous speculation [1] that the balance between the entropic loss from further structural freezing of side arm and the gain from accompanying desolvation induced by lariat ligation, becomes negative for a lariat ether with a flexible side arm/ring like **3**. This is especially so in the absence of water molecules which solvate preferentially to a cation in the mixed solvent.[23]

Relative Cation Selectivity.—Although the lariat sidearm introduced in **3** enhances the complex stability in the homogeneous solution, the extent of enhancement differs substantially with the cation encapsulated. As shown in Table 2, the increment in $\delta\Delta G^\circ$ is larger for Na^+ and Ag^+ than for K^+ and Tl^+, respectively, thus affording much enhanced Na^+/K^+ and Ag^+/Tl^+ selectivities for **3**. Thermodynamically, the larger increments for the size-matched Na^+ (102 pm)[10] and Ag^+ (115 pm)[10] are attributed to their higher entropic gains, probably arising from the more extensive desolvation upon lariat ligation of the side arm, than those for the larger K^+ (138 pm)[10] and Tl^+ (150 pm).[10] It is also interesting to note that the sequence of the absolute differential thermodynamic parameters between **2** and **3** is in good agreement with that of the ionic radii, *i.e.*, $Na^+ > Ag^+ > K^+ > Tl^+$, as shown in Table 2. This indicates that the size-fit between the cavity and the cation controls the complex stability entropically through desolvation and structural freezing upon complexation, while the enthalpic contribution is negative in most cases.

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