Molecular Design of Crown Ethers. Part 8.[1] Substitution and Lariat Effect upon Cation Complexation with 1,4,7,10,13-Pentaoxacyclohexadecane (16-Crown-5) Derivatives in Solvent Extraction and in Homogeneous Solution†

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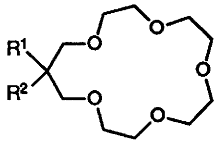
The effects of a donating sidearm introduced into 1,4,7,10,13-pentaoxacyclohexadecane (16-crown-5) upon its binding abilities and relative cation selectivities for alkali-metal ions were examined comparatively in solvent extraction and in the homogeneous phase. In sharp contrast to much enhanced extractabilities and relative cation selectivities observed in the solvent extraction of aqueous alkali-metal picrates with a 16-crown-5 lariat, rather reduced complex stability constants and selectivities were obtained in a conductance study in methanol. This obviously conflicts with the basic concept of the lariat effect and may require further verification of its applicability to other ligand and solvent systems.

From their first synthesis, lariat ethers were designed to enhance the cation-binding ability of crown ethers through ligation of additional donor atom(s) introduced in a sidearm, and also to mimic the dynamic complexation exhibited by natural macrocyclic ligands.[2] Indeed, various *C*- and *N*-pivot lariat ethers have shown more or less higher performance in cation binding and/or transport than the parent or reference crown ethers.[2–9] Positive participation of sidearm donor(s) has been demonstrated in the complexation of metal ions with some *C*- and *N*-lariat ethers in the homogeneous phase,[2a,c] in solvent extraction[6b] as well as in the solid state.[2b,d] Thus this strategy has been successful so far.

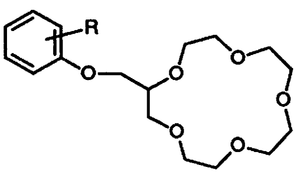
We now report quite opposite effects of a sidearm in the solvent extraction and in the homogeneous-phase complexation of alkali-metal ions. In contrast to much enhanced extractabilities for 16-crown-5 (1,4,7,10,13-pentaoxacyclohexadecane) lariats in solvent extraction, rather reduced complex stability constants were obtained in a conductance study in methanol. This obviously conflicts with the basic concept of the lariat effect and may require further verifications of its applicability to other ligand and solvent systems.

Results and Discussion

Our earlier studies on 16-crown-5[10,11] and its lariat derivatives[6] have shown that: (1) 16-crown-5 derivatives, merely possessing an extra methylene in the ring, exhibit much higher selectivities for Na^+ over K^+ and larger cations than does 15-crown-5; (2) dual alkylations at C^{15} lead to serious decreases in extractability, which are quite comparable for all 15,15-disubstituted 16-crown-5 derivatives, irrespective of the substituents introduced; and (3) the introduction of ligating sidearm(s) at C^{15} enhances the cation-binding ability as measured by the solvent extraction technique. In this study, we performed both quantitative solvent extraction in water–dichloromethane and conductance measurements in methanol with 16-crown-5 **1**, 15,15-dimethyl-16-crown-5 **2**, and 15-(2,5-dioxahexyl)-15-methyl-16-crown-5 (16-crown-5 lariat, **3**). The extraction equilibrium constants (K_{ex}) and the complex stability constants (K_s) obtained are listed in Table 1. The cation selectivities, relative to Na^+, were also calculated from K_{ex} or K_s for both systems (Table 2). Also listed in these tables are the corresponding values for *o*- and *p*-methoxyphenoxymethyl-15-crown-5 **4** and **5**.[2a]



1 $R^1 = R^2 = H$
2 $R^1 = R^2 = CH_3$
3 $R^1 = CH_3$, $R^2 = CH_3OCH_2CH_2OCH_2$



4 R = *o*-CH_3O
5 R = *p*-CH_3O

In solvent extraction the K_{ex} values of compound **2** for all cations examined are considerably smaller than those of **1**, which is in good agreement with our previous qualitative work.[6a] However, the substitution of ligating 2,5-dioxahexyl for one methyl in **2** substantially raises the K_{ex} value of **3** especially for the size-matched cation Na^+, while the values for size-mismatched larger cations increase only slightly or are almost unchanged. This is reasonably accounted for in terms of the steric requirement upon sidearm ligation; only the size-matched cation accommodated in the cavity of 16-crown-5 fully enjoys

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† *Non-SI unit employed:* cal = 4.184 J.

Table 1 Extraction equilibrium constants (K_{ex}) and complex stability constant (K_s) obtained by solvent extraction in dichloromethane–water and by conductance or calorimetric study in methanol at 25 °C, respectively

	log K_{ex}[a]				log K_s[b]			
Ligand	Na^+	K^+	Rb^+	Cs^+	Na^+	K^+	Rb^+	Cs^+
1 16-crown-5	4.55[c]	3.65[c]	3.52[c]	3.14[c]	4.10[d]	2.92[d]	2.46[d]	2.09[d]
	4.54	3.60	3.48					
2 dimethyl-16-crown-5	4.29	3.25	3.22	2.92	3.73	2.54	2.06	1.73
3 16-crown-5 lariat	4.57[e]	3.39[e]	3.24[e]	2.86[e]	3.53	2.43	2.05	1.57
	4.70	3.40	3.25					
4 15-crown-5 *o*-lariat					3.24[f]	3.32[f]		
5 15-crown-5 *p*-lariat					2.90[f]	3.17[f]		2.62[f]

[a] Measured in this work, unless stated otherwise, by solvent extraction of the aqueous metal picrate with the ligand in dichloromethane; see refs. 6 and 10 for detailed conditions. [b] Measured in this work, unless stated otherwise, by conductance study of the homogeneous-phase complexation of the metal chloride with the ligand in methanol; see ref. 11*a*. [c] Ref. 10*a*. [d] Ref. 11*a*. [e] Ref. 6*a*. [f] Ref. 2*a*.

Table 2 Relative cation selectivities[a] of compounds **1**–**5** for solvent extraction in dichloromethane–water and for homogeneous-phase complexation in methanol at 25 °C

	Solvent extraction				Homogeneous phase			
Ligand	Na^+	K^+	Rb^+	Cs^+	Na^+	K^+	Rb^+	Cs^+
1	1.0	0.11	0.087	0.040	1.0	0.066	0.023	0.010
2	1.0	0.091	0.085	0.043	1.0	0.065	0.021	0.010
3	1.0	0.050	0.035	0.014	1.0	0.079	0.033	0.011
4[b]					1.0	1.20		
5[b]					1.0	1.86		0.52

[a] Calculated from the binding constants (K_{ex} or K_s) in Table 1, the value for Na^+ being taken as unity in each case; the revised values, where available, are used for solvent extraction. [b] Calculated from data in ref. 2*a*.

further ligation by the donating sidearm. As a consequence of the specific enhancement in extractability, the cation selectivity for Na^+ over the larger cations much increases with **3**. As can be seen from Table 2, the relative cation selectivity of the 16-crown-5 series does not appreciably change upon substitution with non-donating methyl groups in solvent extraction, in contrast to the sizeable decrease in extractability. However, substitution with a donating sidearm enhances not only the extractability but also the selectivity for Na^+ by a factor of 2–3.

Contrary to the pronounced lariat effect reported for several *C*- and *N*-lariats with symmetrical 3*m*-crown-*m* skeletons,[2,8] the homogeneous-phase complexation by 16-crown-5 lariat **3** does not display any positive lariat effect. The K_s values for all cations examined decrease in going from **1** to **2**, as is the case with solvent extraction, but unexpectedly the K_s values for **3** show further declines to give the smallest values among these three ligands. Apparently, the potentially versatile sidearm, which does function in solvent extraction, behaves as a burden in homogeneous-phase complexation. In sharp contrast to the solvent extraction case, substitution with a donating sidearm does not enhance but rather lowers the cation selectivity for Na^+, as shown in Table 2.

Although this difference in complexation behaviour of 15- and 16-crown-5 lariats cannot be attributed to a single cause, the increased rotational and vibrational freedom of the 16-crown-5 skeleton is inferred to be playing an important role. The invalid or negative lariat effect observed for 16-crown-5 lariat **3** in methanol may be attributed to a combined effect of the increased flexibility of 16-crown-5 and the heavy solvation of a cation accommodated in the cavity and also to the donor oxygen atom in the sidearm. In methanol, the accommodated cation, either nestling in or perching on the crown ether cavity, is still solvated by methanol.* Consequently, lariat ligation involving a sidearm requires extensive desolvation of methanol molecules bound to a cation and the donor oxygen in the sidearm. From the enthalpic point of view, this process is obviously unfavourable, since the gain from the ion–dipole interaction produced in the lariat ligation must be smaller than the total loss upon breaking both the ion–dipole interaction between the cation and solvating methanol and the hydrogen bonding between the sidearm oxygen and methanol. However, this enthalpic loss upon lariat ligation is compensated or overcome by the entropic gain from the increased freedom of the liberated methanol molecules, exhibiting a positive lariat effect in several cases.[2,8]† The thermodynamic parameters reported for *C*-lariats, *o*- and *p*-methoxyphenoxymethyl-15-crown-5 **4** and **5**,[2a] are compatible with this situation. The higher log K_s value of Na^+ (3.24) for lariat ether **4** than that (2.90) for the reference ligand **5** is accounted for in terms of the less negative entropy change ($T\Delta S^{\circ}$) of −0.92 kcal mol^{-1} that overcomes the somewhat smaller enthalpic gain ($-\Delta H^{\circ}$) of 5.34 kcal mol^{-1} for **4** as compared with the respective parameters for **5** ($T\Delta S^{\circ}$ −1.46 kcal mol^{-1}, $-\Delta H^{\circ}$ 5.41 kcal mol^{-1}). However this scenario may not be readily applicable to lariat ethers with more flexible sidearms and framework. These lariats are considered to suffer substantial entropic loss in order to swing back and fix the extended sidearm to the cation accommodated in the cavity and also to readjust the conformation of the crown ring. Hence, the validity of the lariat effect may be a consequence of a critical balance between the possible entropic loss from further structural freezing and the gain from accompanying desolvation, both induced by the lariat ligation. For the 16-

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* Hydration of accommodated cations in the axial direction has recently been reported in an X-ray diffraction study of 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane) complexes of alkali-metal ions in dense aqueous solution.[12]

† We have recently published[13] a thermodynamic study on the solvent extraction of metal picrates with several crown ethers, including 16-crown-5 **1** and lariat ether **3**. The higher K_{ex} value for complexation of Na^+ with **3** than with **1** observed in solvent extraction is well accounted for in terms of the less negative entropic gain ($T\Delta S^{\circ}$ = −5.23 kcal mol^{-1}) for **3** than that for **1** ($T\Delta S^{\circ}$ = −6.70 kcal mol^{-1}), which may be ascribed to the extensive desolvation upon sidearm ligation, exceeding the entropic loss induced by the reduced freedom of the sidearm.

crown-5 lariat **3** the balance appears to be negative at least in methanol, judging from the present results.

In this context, the effective lariat effect observed in solvent extraction may need further consideration, since the lariat complexation process would appear to be analogous in both systems. However the ion-pair extraction of aqueous metal picrates into the organic phase is inherently dehydrating* and essentially all (98.3%) lariat ether **3** is distributed to the organic phase. Hence, the lariat ligation process is deduced to take place predominantly in the organic medium in the absence, or in the presence of a very small amount, of participating water, thus affording a distinctly different result from the homogeneous-phase complexation in methanol.

We may conclude that, in the homogeneous phase, the lariat sidearm does not always function as an enhancer of cation-binding ability and relative cation selectivity, especially with lariat ethers carrying a flexible sidearm and/or ring system, but its effect is more promising in solvent extraction and probably in membrane transport.

Experimental

Materials.—Dichloromethane was distilled prior to use. Distilled deionized water was used throughout this work. Methanol was purified as described previously;[15] the conductivity of the purified methanol was less than 2×10^{-7} S cm^{-1}. Alkali-metal chlorides were purchased from Merck and used without further purification.

The crown ethers **1–3** were prepared by the procedures reported earlier and purified by distillation under reduced pressure.[6a]

Solvent Extraction.—Equal volumes (10 cm^3) of a dichloromethane solution of the respective crown ether at various concentrations (1–10 mmol dm^{-3}) and of an aqueous solution of each metal picrate (3.0 mmol dm^{-3}) were introduced into an Erlenmeyer flask and the mixture was shaken for 10 min in a Taiyo M100L incubator thermostatted at 25.0 ± 0.1 °C. The equilibrated mixture was then allowed to stand for at least 2 h at that temperature in order to complete phase separation. The concentration of the metal picrates in the organic phase was determined photometrically with a JASCO UVIDEC-660 instrument, according to reported procedures.[6,10]

Conductance Measurement.—A methanol solution of the crown ether (6.0 mmol dm^{-3}, 200 cm^3) was placed in a conductance cell maintained at 25 ± 0.005 °C, to which was added stepwise a solution of a metal salt (10 mmol dm^{-3}). Upon each addition the resistance of the solution was measured repeatedly, using a Fuso model 362A conductivity apparatus, as reported previously.[11a]

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* T. Iwachido *et al.*[14] reported that water of hydration, associated with an ion pair extracted into a nitromethane phase with dibenzo-18-crown-6 (6,7,9,10,17,18,20,21-octahydrodibenzo[*b*,*k*][1,4,7,10,13,16]hexaoxacyclooctadecine), is as low as 1.2 molecules for Na$^+$ and 0.1 for K$^+$ and Cs$^+$.