

Articles

Thermodynamics of Macrocyclic Complexation Chemistry. Interactions of Metal Ions with Double-Armed N-Pivot Lariat Ethers in Methanol and Methanol–Water Solutions at 25.0 °C

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The log K , ΔH , and $T\Delta S$ values for interactions of Na^+ , K^+ , Cu^{2+} , and Ca^{2+} with a series of N,N'-dipivot lariat ethers have been determined from calorimetric titration data valid in 9:1 (v/v) $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ and absolute methanol at 25.0 °C. Complex stability is increased greatly by introducing pendant arms containing oxygen or nitrogen atoms to the parent macrocycles. The enthalpy and entropy changes support the idea that the side arms interact with the cations. Formation of complexes of Ca^{2+} is both enthalpy and entropy stabilized. All other interactions are enthalpy driven, and the entropy changes are unfavorable. Effects of pendant-arm length and substituents on the complexation of the cations are discussed on the basis of the thermodynamic data. The large negative ΔH values for complexation of Cu^{2+} with lariat ethers indicate a strong interaction between Cu^{2+} and the nitrogen atoms of the ligands. Large entropic losses for some of the cation–ligand interactions indicate that the lariat ethers are flexible and readily change their conformations to accommodate the cations.

Introduction

The lariat ethers have been recognized as a new class of synthetic cation binders^{1–4} and are considered as promising candidates for effective cation-transport carriers^{5–7} because of their three-dimensional coordination with metal ions and the high flexibility of ligating pendant arms. Various types of lariat ethers have been prepared for investigation of cation-binding and transport properties.^{8–15} Some lariat ethers have high selectivities for certain metal ions.^{4–9} Nitrogen-pivot lariat ethers were shown to have better cation-binding properties than carbon-pivot lariat ethers since the general lack of binding strength exhibited by carbon-pivot lariat ethers and the problem of sidedness can be overcome by the nitrogen-pivot lariat ethers.¹⁶ Most double-armed lariat ethers exhibit increased cation-binding ability as compared to their single-armed analogs.^{1,4} However, further increase in the

number of pendant arms on the macrocycle usually results in decreased complexing ability.^{1,4}

In general, the presence of side arms in macrocycles causes these molecules not to adhere to the "hole-size" rule. For example, in cases of nitrogen-pivot lariat ethers with single side arms, peak binding for Na^+ was observed when six oxygen atoms were present in the ligand irrespective of whether the donors were contributed by the macrocoring or the side arm.¹⁷ For nitrogen-pivot lariat ethers with a single arm containing one donor atom, the binding strength of both Na^+ and K^+ increased as the ring size of the parent macrocycle was increased from 15 members to 18 members.¹⁸ But for some lariat ethers with two side arms, the K^+ -binding strength increased while the Na^+ -binding strength decreased when the size of the parent macrocycle was changed from a 15-membered ring to an 18-membered ring.¹⁹ It was concluded that both the parent macrocoring and the pendant arm(s) have significant effects on cation complexation and selectivity.^{1–5}

The importance of thermodynamics in understanding the cation-binding process by lariat ethers has been emphasized.⁴ There have been few reports on thermodynamics of lariat ether–cation interactions.^{18,20,21} In order to more fully understand the complexation process of cations with lariat ethers and the effects of different pendant-arm substituents and lengths on cation binding, log K , ΔH , and $T\Delta S$ values for interactions of Na^+ , K^+ , Cu^{2+} , and Ca^{2+} with a series of N,N'-disubstituted derivatives of 1,4-diaza-15-crown-5 (**1a–g**) and 1,4-diaza-18-crown-6 (**2a–g**) (Figure 1) were determined in 100% methanol and 90%

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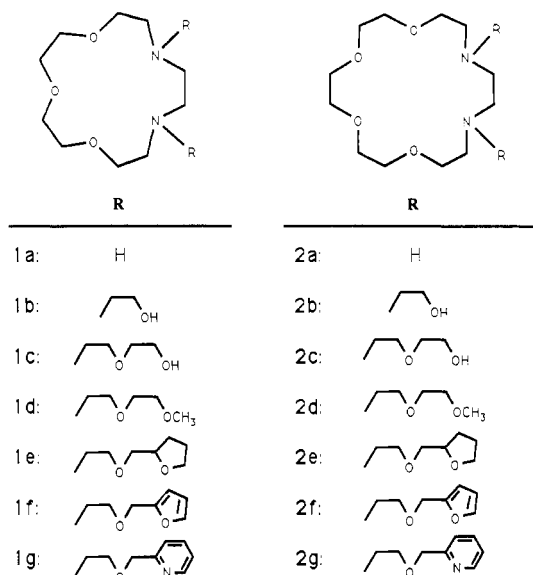


Figure 1. Structure of double-armed N-pivot lariat ethers.

methanol-water solutions at 25.0 °C. The thermodynamic parameters provide useful information on cation complexation with lariat ethers and give insight into the interaction mechanisms.

Experimental Section

The syntheses of N,N'-disubstituted derivatives of 1,4-diaza-15-crown-5 and 1,4-diaza-18-crown-6 have been reported.¹³ NaBr (J. T. Baker, reagent), KBr (Wasatch, reagent), Cu(NO₃)₂·3H₂O (Fisher, reagent), and CaCl₂·2H₂O (Spectrum Chemical, reagent ACS) were used as received. The absolute methanol (Fisher HPLC grade) used had a water content of less than 0.05%. Concentrations of NaBr and KBr were obtained from the weight of the salt which had been dried overnight at 120 °C, and those of Cu²⁺ and Ca²⁺, from an EDTA titration. Lariat ether solutions were standardized by thermometric titration with NaBr or KBr.²² NaBr and KBr were used because they have greater solubility in methanol than the corresponding chlorides. The effect of the anion (Br⁻) was tested by titrating NaBr into 18-crown-6 (18C6) in 100% methanol solution. No difference was found between the use of NaBr and NaCl (log *K* and Δ*H* values for NaBr-18C6 interaction are 4.38 and -35.12 kJ/mol, respectively, as compared with literature values of 4.36 and -34.98 kJ/mol²³ for NaCl-18C6 interaction).

The thermodynamic quantities were determined as described earlier²⁴ at 25.0 ± 0.1 °C by titration calorimetry using a Tronac Model 450 calorimeter equipped with a 20-mL reaction vessel. The metal ion solutions (0.12–0.20 M) were titrated into lariat ether solutions (2 × 10⁻³–6 × 10⁻³ M) and the titrations were carried out to a 2-fold excess of the metal ions, since in that way lower amounts of macrocycle were consumed for each calorimeter run. The number of data points for each run were 100–150 depending on titrant and titrate concentrations. Reliability was checked by comparing results when the metal ion was titrated into the macrocyclic ligand solution and when the macrocyclic ligand was titrated into the metal ion solution. No difference was seen within the experimental error of the measurements. The measurements were made at variable (but very low) ionic strength. Studies performed by Popov²⁵ and Reisse²⁶ and their co-workers show that the ionic strength effect can be neglected for complexation reactions of neutral macrocyclic ligands with cations as long as the ionic strength is < 0.05 M. Because the maximum ionic strength attained in our titration processes was 0.02 M, the concentration

equilibrium constants reported in this paper can be assumed to closely approximate the thermodynamic constants. A 1:1 metal-ligand interaction was assumed since a 1:2 interaction was not detected either from observation of the thermograms or from calculation of log *K* and Δ*H* values for 1:2 reactions by the computer program REACTIONS.²⁷ The method used to process the calorimetric data and to calculate the log *K* and Δ*H* values has been described elsewhere.²⁸

Results and Discussion

The log *K*, Δ*H*, and *T*Δ*S* values for interactions of Na⁺, K⁺, Cu²⁺, and Ca²⁺ with nitrogen-pivot lariat ethers in 9:1 (v/v) methanol/water are given in Table 1. The complexation of the metal ions with lariat ethers is exothermic in each case, and the *T*Δ*S* value is negative except in the case of Ca²⁺. These facts indicate that the interactions of Na⁺, K⁺, and Cu²⁺ with the lariat ethers are enthalpy driven.

Side-Arm Effect. Since no significant amount of heat was produced in the 9:1 (v/v) methanol-water system for Na⁺ and K⁺ interactions with **1a** and **2a**, the binding strength of parent macrocycles with Na⁺ and K⁺ was expected to be very weak. Therefore, the large -Δ*H* values for Na⁺ and K⁺ interactions with double-armed lariat ethers (**1b–g** and **2b–g**) indicate a participation of the side arms in the cation binding. This participation is confirmed by the data determined in absolute methanol (Table 2). The log *K* values for complexation of Na⁺ and K⁺ with **2a** are 1.92 and 2.31, respectively. However, by the attachment of side arms to **2a**, the increase in log *K* values demonstrated by the double-armed lariat ethers **2c,d,f** is over 2 orders of magnitude. As can be seen from Table 2, the large increase in K⁺-binding constants is due to increasingly favorable enthalpy changes. The Δ*H* values for K⁺ interactions with **2c,d,f** are 16–19 kJ/mol more negative than that for K⁺ interaction with **2a** while the *T*Δ*S* values are nearly constant for all interactions. This result indicates that the increased enthalpy gain arises from the interaction between the side arms and ring-bound cations. On the other hand, both enthalpy and entropy changes contribute to the increased Na⁺-binding constants with **2d,f** and **1f**. The favorable change in Δ*H* values is attributed to the binding of the side arms with the Na⁺, while the favorable change in Δ*S* values suggests that additional solvent molecules are replaced by the side arms. Therefore, the thermodynamic data provide clear evidence for side-arm involvement in cation binding.

Lengthening the side arms has a small effect on the binding constants. Comparisons of Na⁺-**1b** with Na⁺-**1c** and K⁺-**2b** with K⁺-**2c** complexes in Table 1 show small increased values of log *K* (0.36 and 0.28 for Na⁺ and K⁺, respectively). These increases in log *K* values result mainly from favorable enthalpy changes, which suggests that the oxygen atoms at the end of the side arms interact with Na⁺ and K⁺ and cause a small increase in the cation-binding constants.

Substituents on Side Arms. The differences among the lariat ethers **1c–g** and **2c–g** are in the type of end substituents on the side arms. Some substituent effect on the cation-binding constants is seen although the difference is within 1 log *K* unit (see Table 1) either for interactions of Na⁺ with 15-membered-ring lariat ethers (**1c–g**) or for K⁺ complexation with 18-membered-ring ligands (**2c–g**).

Having two methoxyethoxyethyl groups (-CH₂CH₂OCH₂CH₂-OCH₃) as the side arms, ligand **2d** forms a more stable complex with K⁺ than do any of the other 18-membered-ring lariat ethers. The lower K⁺-binding constant in the case of **2c** may result from weaker K⁺ interaction with the side arms since hydroxyl groups of the side arms may interact strongly with solvent molecules. Evidence for this is seen in the large negative *T*Δ*S* value (-12.6

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Table 1. Log *K*, ΔH (kJ/mol), and $T\Delta S$ (kJ/mol) Values^a for Interactions of Lariat Ethers with Metal Cations in 9:1 (v/v) CH₃OH/H₂O at 25.0 °C

ligand	param	Na ⁺	K ⁺	Cu ²⁺	Ca ²⁺
1a		<i>b</i>	<i>b</i>	ND	ND
1b	log <i>K</i>	3.14 ± 0.02	2.43 ± 0.02	3.5 ± 0.2	4.13 ± 0.05
	ΔH	-24.9 ± 0.3	-33.0 ± 0.2	-53.9 ± 0.8	-16.1 ± 0.3
	$T\Delta S$	-7.0	-19.1	-34.1	7.5
1c	log <i>K</i>	3.50 ± 0.02	ND	ND	ND
	ΔH	-26.7 ± 0.3			
	$T\Delta S$	-6.8			
1d	log <i>K</i>	3.41 ± 0.03	ND	4.48 ± 0.08	ND
	ΔH	-28.0 ± 0.5		-42.5 ± 0.3	
	$T\Delta S$	-8.6		-16.9	
1e	log <i>K</i>	3.82 ± 0.04	3.59 ± 0.05	4.92 ± 0.09 ^c	3.2 ± 0.1 ^c
	ΔH	-27.7 ± 0.3	-43.2 ± 0.4	-42.9 ± 0.3 ^c	-9.9 ± 0.9 ^c
	$T\Delta S$	-5.9	-22.7	-14.8	8.1
1f	log <i>K</i>	3.35 ± 0.04	ND	4.43 ± 0.06	ND
	ΔH	-27.2 ± 0.3		-41.8 ± 0.5	
	$T\Delta S$	-8.1		-16.5	
1g	log <i>K</i>	3.95 ± 0.05	ND	4.17 ± 0.08	ND
	ΔH	-30.0 ± 0.3		-69.5 ± 0.3	
	$T\Delta S$	-7.5		-45.7	
2a		<i>b</i>	<i>b</i>	ND	ND
2b	log <i>K</i>	4.35 ± 0.05	4.00 ± 0.04	ND	ND
	ΔH	-41.0 ± 0.3	-23.9 ± 0.5		
	$T\Delta S$	-16.2	-1.1		
2c	log <i>K</i>	ND	4.28 ± 0.04	4.4 ± 0.1 ^c	4.38 ^d
	ΔH		-37.1 ± 0.3	-48.3 ± 0.9 ^c	-13.8 ^d
	$T\Delta S$		-12.6	-23.1	11.2
2d	log <i>K</i>	3.5 ± 0.2 ^c	4.81 ± 0.08	ND	ND
	ΔH	-30.6 ± 0.6 ^c	-35.2 ± 0.3		
	$T\Delta S$	-10.5	-7.7		
2e	log <i>K</i>	3.62 ± 0.03	4.38 ± 0.06	4.42 ± 0.08	ND
	ΔH	-29.5 ± 0.3	-30.2 ± 0.3	-52.9 ± 0.3	
	$T\Delta S$	-8.8	-5.2	-27.7	
2f	log <i>K</i>	ND	4.52 ± 0.06	4.50 ± 0.07	4.25 ^d
	ΔH		-34.9 ± 0.6	-50.9 ± 0.5	-15.3 ^d
	$T\Delta S$		-9.1	-25.2	9.0
2g	log <i>K</i>	ND	4.26 ± 0.06	4.5 ± 0.1 ^c	ND
	ΔH		-38.1 ± 0.4	-78 ± 1 ^c	
	$T\Delta S$		-13.7	-52	

^a Averages of at least three determinations except as indicated by footnotes *c* and *d*. ND means not determined. The measurements were made at variable (but very low) ionic strengths (from 0.002 to 0.02 M; see Experimental Section). ^b No measurable heat other than heat of dilution indicating that ΔH and/or log *K* are small. ^c Averages of two determinations. ^d Sufficient ligand available to make only one experimental determination.

Table 2. Log *K*, ΔH (kJ/mol), and $T\Delta S$ (kJ/mol) Values^a for Interactions of Lariat Ethers with Na⁺ and K⁺ in Methanol at 25.0 °C

ligand	param	Na ⁺	K ⁺
2a	log <i>K</i>	1.92 ± 0.09	2.31 ± 0.06
	ΔH	-18.1 ± 0.9	-28.9 ± 0.3
	$T\Delta S$	-7.2	-15.7
2c	log <i>K</i>	ND	4.79 ± 0.04
	ΔH		-45.1 ± 0.3
	$T\Delta S$		-17.8
2d	log <i>K</i>	4.61 ± 0.08	>5.5
	ΔH	-29.0 ± 0.5	-47.4 ± 0.3
	$T\Delta S$	-2.8	>-15.9
2f	log <i>K</i>	4.5 ± 0.1	>5.5
	ΔH	-28.6 ± 0.8	-48.2 ± 0.2
	$T\Delta S$	-3.0	>-16.7
1f	log <i>K</i>	4.09 ± 0.08	3.53 ± 0.04
	ΔH	-21.8 ± 0.6	-37.2 ± 0.3
	$T\Delta S$	1.6	-17.1

^a Averages of three determinations. ND means not determined.

kJ/mol in 90% methanol), which probably results from incomplete desolvation due to strong hydrogen-bond interaction of the hydroxyl groups with the solvent molecules. The rigidity of the ring substituents on side arms of **2e,f,g** may bring a stronger steric hindrance for access of the donor atoms at the side arms to K⁺ than that of methoxy on **2d**. Moreover, the change from oxygen to nitrogen atoms for the side arms of **2g** weakens the coordination of K⁺; hence, the methoxyethoxyethyl group of **2d** is the best side arm for K⁺-binding by an 18-membered macrocycle.

It can be seen from Table 1 that the ΔH values for Na⁺ interactions with **1c-f** are almost the same. As a result, the entropy effect plays an important role in the complex stability sequence. Similar situations have been noted by Liu et al.²⁰ and Gokel et al.²¹ Among the Na⁺ complexes of **1c-f**, the highest binding constant by **1e** is obviously attributed to the smallest entropic loss. This may result from an extensive desolvation of **1e**, since the same entropy behavior can be observed for Cu²⁺ interaction with 15-membered-ring lariat ethers and K⁺ with 18-membered-ring macrocycles (except **2b**); i.e., the smallest entropic losses are also found for complexation of **1e** with Cu²⁺ and of **2e** with K⁺ (see Table 1). These facts suggest that the envelope form of the tetrahydrofuran (the side-arm substituent of **1e** and **2e**) favors the desolvation process.

Complexation of Cu²⁺ and Ca²⁺. The nitrogen atoms included in this series of lariat ethers are expected to have good binding characteristics to transition metal ions. Indeed, the complexation of Cu²⁺ with 15-membered-ring lariat ethers is stronger than that of Na⁺ by the same lariat ethers (see Table 1). In the cases of **1d-f**, the binding constants for Cu²⁺ are 10-fold larger than those for Na⁺. The much larger negative ΔH values probably arise from a strong interaction between Cu²⁺ and the nitrogen atoms of the lariat ethers. The large $-\Delta H$ values for Cu²⁺ complexation with **1g** and **2g** (-69.5 and -78 kJ/mol) indicate strong Cu²⁺-N interactions. All four nitrogen atoms in **1g** and **2g** may coordinate to Cu²⁺. The large $-T\Delta S$ values (-45.7 and -52 kJ/mol for Cu²⁺-**1g** and Cu²⁺-**2g**, respectively) indicate that **1g** and **2g** undergo an extensive conformation change in order to

arrange the four nitrogen atoms in an optimal geometric sense for Cu^{2+} coordination.

Both enthalpy and entropy changes for complexation of Ca^{2+} are favorable, but the negative ΔH values for Ca^{2+} are smaller than those for any of the other metal ions. It has been reported²⁹ that the number of water molecules associated with Ca^{2+} can be as many as 13 and those replaced by several crown ethers upon complexation in nitrobenzene number more than seven, which is much more than those replaced by dibenzo-18-crown-6 from K^+ and Na^+ .³⁰ Thus, the positive $T\Delta S$ values for Ca^{2+} complexation can be attributed to the extensive cation desolvation. However, the replacement of a large number of solvent molecules consumes much of the heat produced by cation interaction with the donor atoms and, consequently, small negative ΔH values are observed.

Summary

The stability of lariat ether complexes is affected by more factors than that of crown ether and cryptand complexes because of the high flexibility of both the pendant arms and the macroring. When forming complexes with cations, lariat ethers usually undergo a large conformational change. Optimization of the formation constant would be obtained if every donor atom could interact with the cation without constraining the lariat ether to change its conformation.

Usually, two factors, pivot nitrogen atoms and proper donor(s) on the arms (oxygen, nitrogen, etc.), result in ligating pendant arms which increase the cation-binding constants by providing

additional coordination sites. The influence of the side arms on cation complexation depends on the flexibility, length, and donor groups of the arms. The effect of the flexibility is shown by **2d** in which the flexible methoxy groups demonstrate a higher K^+ -binding ability than the rigid ring substituents. The arm length should not be too long. For ethoxy $(-\text{CH}_2\text{CH}_2\text{O}-)_n$ type side arms, two $-\text{CH}_2\text{CH}_2\text{O}-$ units in length are long enough for most cation-binding. For Na^+ interactions with 18-membered-ring lariat ethers, two short hydroxyethyl arms $(-\text{CH}_2\text{CH}_2\text{OH})$ are more effective than the long arms since the long arms bring about strong steric hindrance. Donor groups which are weakly solvated in the solvent are more effective for cation complexation. The methoxy group $(-\text{OCH}_3)$ is better than the hydroxyl group $(-\text{OH})$ since the $-\text{OH}$ may interact with solvent molecule(s) through hydrogen bonding. In addition, nitrogen atoms on the side arms increase binding ability for transition metal ions.

The function of the parent macroring in cation binding is displayed not only by its size but also by its cooperativity with the side arms to accommodate the cation. In most cases, an 18-membered ring is better than a 15-membered ring for cation complexation because the former is more flexible and has more donor atoms. Therefore, the structure of a lariat ether can be pre-organized by modifying both the pendant arm and macroring to obtain a unique selectivity for a particular cation.

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