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Analysis of cation–macrocycle complexation by fast atom bombardment mass spectrometry

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Fast atom bombardment mass spectrometry has been used to analyse the cation complexation behaviour of a systematically varied array of crown and lariat ethers having one or two sidearms. Sandwich complexation, apparent when the cation is somewhat larger than the crown cavity, is observed for several systems but the presence of donor-group-containing sidearms in lariat ethers suppresses this phenomenon. Calcium cation complexation proved to be especially interesting.

INTRODUCTION

One of the most compelling aspects of crown ether chemistry[1] has proved to be the remarkable ability of these compounds to bind alkali and alkaline earth metal cations. Prior to the discovery of crown ethers in July 1962, complexation of cations such as sodium, potassium, or calcium by proteins and naturally occurring ionophores was documented, but model systems were unavailable. Since the initial report of crowns,[2] literally thousands of macrocycles have been prepared and studied. The simple crown ethers represent a 'two-dimensional' binding array for spherical cations, whereas the cryptands[3] and spherands[4] add a third dimension. The latter are less dynamic in binding kinetics than the former but are generally more binding and more selective.[5] The lariat ethers[6] were designed to find a middle ground between these systems: strong binding and fast binding dynamics. This was accomplished by use of a macroring and one or more donor-group-containing flexible sidearms.

Once synthetic access to these compounds was accomplished, it became necessary to assess the complexation properties.[7] Several methods exist to accomplish this and vary in both difficulty and the value of the results obtained. A very popular method has been the so-called picrate extraction technique which is convenient but suffers from the difficulty that the binding constants, expressed as percentages, are directly comparable only with values obtained in precisely the same way. Homogeneous cation binding constants may be obtained by a variety of techniques (NMR, thermochemistry, conductometry, ion selective electrodes, etc.) and are directly comparable so long as temperature and solvent are the same.[8] Most of our previous work has involved cation selective electrode techniques but these are somewhat difficult to apply in the case of calcium cations. Commercially available calcium-selective electrodes can be used only in water or with just a tiny fraction of co-solvent in the aqueous medium. We solved this problem some years ago by developing a competitive technique but the method had some limitations.[9]

In the past several years, fast atom bombardment mass spectrometry (FAB/MS) has proved useful as an alternative means of assessing cation binding.[10] In the FAB technique[11] the sample, dissolved in a non-volatile matrix, is desorbed by a beam of energetic fast atoms. The resulting desorption process involves a relatively low energy transfer so that fragmentation, the process associated with the better known electron impact mass spectrometry, is minimized. In the case of macrocycle–cation complexation, the desorption process does not disrupt the dissociation and the intact complex can be observed as a major ion. It is important to note that the gas phase results, observed in the mass spectrometer, reflect the chemistry that takes place in the non-volatile matrix (i.e. in solution) rather than any reaction in the spectrometer's analyser. This

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technique is proving convenient because small samples can be utilized and also because very complex systems can be analysed. Moreover, complexation of cations for which other methods are either inconvenient or unavailable may be attractive to probe by the FAB/MS technique. The importance of this developing technique is clear from recent reports from Johnstone and Lewis,[12] Dearden *et al.*,[13] Liou and Brodbelt[14] and others.[15] We now report application of the FAB/MS technique to a systematically varied series of lariat ethers complexed by both alkali and alkaline earth metal cations. In particular, we show that the complexation behaviour of these ligands toward Ca^{2+} has been successfully probed by using this emerging technique.

RESULTS AND DISCUSSIONS

FAB/MS is a convenient and rapid technique that can be used to investigate complexation between crown ethers and various metal ions in solution. In the present study, we have applied the FAB/MS method to the analysis of several crown and lariat ether complexes formed in a matrix solution. An important advance of this technique in the study of cation binding is that the complexes tend to retain their integrity once desorbed and can thus be observed directly.

The FAB technique is generally thought to produce results that reflect the corresponding solution chemistry.[10,16] We have determined Li^+, Na^+, K^+, and Ca^{2+} complexation values for nitrogen-pivot lariat ethers in *m*-nitrobenzyl alcohol solution (the FAB matrix) by determining the intensity of the $(\text{lariat}\cdot\text{metal})^+$ ion relative to that of the uncomplexed, protonated ligand $(\text{lariat}\cdot\text{H})^+$. When no sidearm is present in a crown, binding with an appropriately sized cation usually involves formation of a 1:1 (cation: macrocycle) complex in which the macrocycle surrounds the cation's equator. The apical positions are usually occupied either by counterion or solvent. When the cation is larger than the crown's hole size, sandwich (1:2, cation:macrocycle) complexation may be observed. Lariat ethers differ from simple crowns by their ability to provide a bound cation with three-dimensional solvation without requiring formation of a sandwich structure.

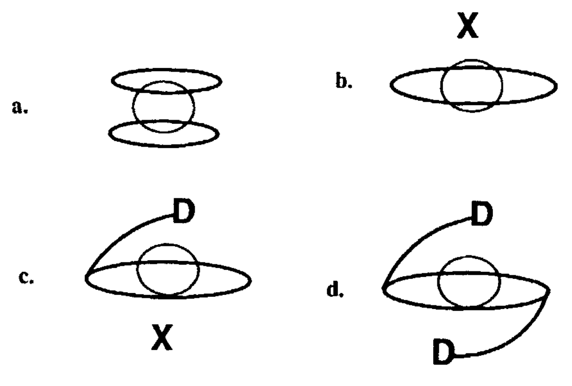
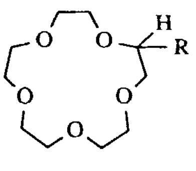


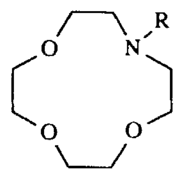
Figure 1 Complexation mechanisms for crown ethers (D is a donor group and X is a counteranion). **a.** Sandwich complex formation with a crown that is smaller than the cation. **b.** Monocyclic crown ether complex formation between a crown and cation of similar size. **c.** Lariat ether complexation involving a single sidearm. **d.** Bibracchial lariat ether complexation of a cation.

Ligands used

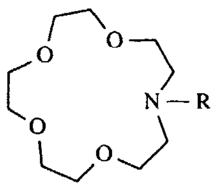
The present study involves both crown and lariat ethers. The lariats were of the single-sidearm[17] and double-sidearm (bibracchial) types.[18] All of the compounds utilized in the present study (i.e. **1–23**) were obtained commercially or were prepared as previously described (see Experimental section). The structures are illustrated below.



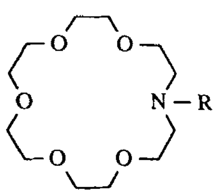
1, R = H
2, R = $CH_2OCH_2CH_2OCH_3$
3, R = $CH_2OCH_2CH_2O\text{-n-Bu}$
4, R = $CH_2O(CH_2CH_2O)_2CH_3$
5, R = $CH_2O(CH_2CH_2O)_3OCH_2Ph$



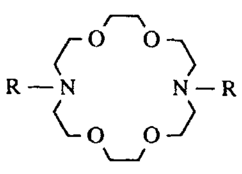
6, R = $C_6H_4\text{-p-OCH}_3$
7, R = $CH_2CH_2CH_2OH$
8, R = $C_6H_4\text{-o-OCH}_3$



9, R = H
10, R = CH_3
11, R = $CH_2CH_2CH_2CH_3$
12, R = $CH_2C_6H_5$
13, R = $(CH_2CH_2O)_3CH_3$
14, R = $CH_2CO\text{-O-t-Bu}$



15, R = H
16, R = $CH_2C_6H_5$
17, R = $(CH_2CH_2O)_3CH_3$
18, R = $(CH_2CH_2O)_2CH_3$
19, R = $CH_2CH_2OCH_3$



20, R = H
21, R = $CH_2C_6H_5$
22, R = $C_6H_4\text{-o-OCH}_3$
23, R = $CH_2CH_2OCH_3$

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Complexation of cations by simple crowns

We were particularly interested in the complexation of K^+ by 15-crown-5 (**1**). Although the cavity size of **1** is estimated to be *ca.* 2 Å (the size of Na^+), **1** binds K^+ more strongly in methanol solution. We thought that FAB/MS might show that complexation of this species occurs by sandwich formation, i.e. K^+ bound by two 15-crown-5 rings (presumably in parallel). A 1:1 mixture of 15-crown-5 and KCl was dissolved in *m*-nitrobenzyl alcohol and subjected to FAB/MS analysis. The most intense peak (100%) in the spectrum was observed at *m/z* 259 $(\text{15-crown-5}\cdot K)^+$. A second ion at *m/z* 479 (10%), consistent with the formulation $[(\text{15-crown-5})_2\cdot K]^+$, was also observed. Quantitative sandwich complexation requires a 2:1 (crown:K^+) concentration ratio in solution. In the present case, a 1:1 mixture was used but a significant amount of the sandwich complex was still formed. This suggests that the 2:1 complex of 15-crown-5 with KCl is quite favourable. The experiment clearly shows the value of FAB/MS in assessing the complex species formed in solution.

Aza-15-crown-5 (**9**) and aza-18-crown-6 (**15**) are similar in size to their counterparts, 15-crown-5 and 18-crown-6, but they are more basic because of the NH for O substitution. Moreover, they have the ability to hydrogen bond either to each other or to the medium. This is reflected in cation binding constants in anhydrous methanol solution that are far lower for the aza-analogues than for the respective $(OCH_2CH_2)_n$ structures. These compounds were subjected to FAB/MS analysis with the following results. In the FAB/MS spectrum of aza-15-crown-5 (1:1 mixture with KCl, *m*-nitrobenzyl alcohol), the protonated molecular ion $(\mathbf{9}\cdot H)^+$ was the base peak. This contrasts with the 15-crown-5 case in which the protonated molecular ion represented <5% of the base peak. This is not surprising given the low basicity of ether oxygens compared with amine. The 1:1 complex between **9** and K^+ (*m/z* 258) had a relative intensity of 44% and the sandwich structure $(\mathbf{9}_2\cdot K)^+$ (*m/z* 477) had an intensity of 1.5%. Though this is substantially lower than the 10% relative abundance observed for **1**, the formation of the 2:1 complex was observed in this case.

The FAB/MS spectrum of aza-18-crown-6 (**15**, conditions as above) showed a base peak corresponding to a 1:1 crown:cation complex, $(\mathbf{15}\cdot K)^+$ at *m/z* 302. The protonated molecular ion, the base peak for **9**, was observed at *m/z* 264 with a relative abundance of 33%. Because the cavity size of **15** corresponds to the ionic diameter of K^+, no sandwich complex formation was expected and, indeed, none was observed. In solution, complexation of K^+ is favoured by 18-membered rings over those having only 15 members. This trend is observed here as well leading to a predominance of protonated molecular ion for **9** when binding of K^+ is weaker. When binding of K^+ is stronger (**15**) the abundance of protonated molecular ion is reduced correspondingly.

Lariat ether complexes

The lariat ethers differ from monocyclic crowns having no sidearms in the sense that sidearm donors may also solvate the ring-bound cation and add the third dimension of solvation that might come from sandwich complexation. Four carbon-pivot and five nitrogen-pivot aza-15-crown-5 compounds were studied. In the carbon-pivot cases, a sidearm was attached to 15-crown-5 by using a CH_2OR linkage to the macroring. Compounds **2–5** are thus chemically stable species but are relatively inflexible due to the non-invertability of carbon. Cation binding studies of these compounds in anhydrous methanol solution has revealed that they are relatively poor binders and that the sidearms do not play as significant a role in binding as do the N-pivot molecules. The five N-pivot structures (**10–14**) are based upon aza-15-crown-5 (**9**). These compounds are inherently more flexible than the C-pivot structures but only compounds **13** and **14** have sidearms that contain donor groups.

The FAB spectra of compounds **2–5** mixed with KCl and show that the corresponding $[(\text{C-lariat})_2\cdot K]^+$ peaks, along with $(\text{C-lariat}\cdot K)^+$ peaks, are less intense than observed for the 15-crown-5/KCl mixture. The relative abundances of the $[(\text{crown})_2\cdot K]^+$ peaks are listed in the Table 1. The relative intensities of the $[(\text{lariat})_2\cdot K]^+$ peaks decrease with increasing sidearm length. For 1:1 mixtures of the 15-membered-ring derivatives with NaCl, the compounds having short sidearms showed weak $[(\text{lariat})_2\cdot Na]^+$ ions and the FAB spectra of derivatives having longer sidearms showed no $[(\text{lariat})_2\cdot Na]^+$ (see Table 1). The data show that formation of the 2:1 complexes becomes less favourable as cation size is decreased. In addition, in the case of the mixtures with NaCl, the relative abundance of the $[(\text{lariat})_2\cdot Na]^+$ peak correlates (for **2** and **3**) with sidearm length. The relative abundance of the $[(\text{lariat})_2\cdot \text{metal}]^+$ peaks in the FAB spectra of 12-membered and 15-membered-ring N-pivot lariat ethers are also summarized in Table 1.

Although the $[(\text{lariat})_2\cdot \text{metal}]^+$ peaks of N-pivot lariat ethers were much less intense than those observed for C-pivot lariat ether mixtures, the data suggest that the presence of the sidearms decreases 2:1 complex formation in solution. Furthermore, for 12-membered-ring lariat ethers, $[(\text{lariat})_2\cdot Na]^+$ peaks decrease in the order ($\log K_S$ is in CH_3OH): **6** (1.38) > **7** (2.35) > **8** (2.75). Note that as the steric accessibility of the sidearm donor group increases, the

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Table 1 Relative intensities of $[(\text{crown})_2\cdot\text{M}]^+/(\text{crown}\cdot\text{M})^+$

Compound no.	*C/N pivot*	*Ring size*	*Sidearm*	*Ratio A*[a] *For K*$^+$	*for Na*$^+$	*Ratio B*[b]	*log K*$_S$ *(Na*$^+$*)*[c]
1	CA	15	H	9.7	–	–	3.24
2	C	15	$CH_2OCH_2CH_2OCH_3$	5.0	1.3	–	3.01
3	C	15	$CH_2OCH_2CH_2OBu$	0.6	0.1	–	3.09
4	C	15	$CH_2O(CH_2CH_2O)_2CH_3$	0.3	0.0	–	3.13
5	C	15	$CH_2O(CH_2CH_2O)_3CH_2Ph$	0.2	0.0	–	3.51
6	N	12	C_6H_4-*4*-OCH_3	1.9	1.7	0.52	1.18
7	N	12	$CH_2CH_2CH_2OH$	1.0	0.5	0.95	2.35
8	N	12	C_6H_4-*2*-OCH_3	1.0	0.4	1.52	2.75
9	N	15	H	3.5	0.7	1.02	1.70
10	N	15	CH_3	1.0	0.3	2.63	3.39
11	N	15	$CH_2CH_2CH_2CH_3$	0.7	0.0	2.66	3.02
12	N	15	$CH_2C_6H_5$	0.5	0.0	2.11	2.77
13	N	15	$(CH_2CH_2O)_3CH_3$	–	–	–	4.32
14	N	15	CH_2CO-O-*t*-Bu	0.5	0.0	4.16	4.20
15	N	18	H	–	–	0.81	2.69
16	N	18	$CH_2C_6H_5$	–	–	3.57	3.41
17	N	18	$(CH_2CH_2O)_3CH_3$	–	–	3.87	4.28
18	N	18	$(CH_2CH_2O)_2CH_3$	–	–	5.16	4.33
19	N	18	$CH_2CH_2OCH_3$	–	–	8.30	4.58
20	N	18	H	–	–	0.38	1.50
21	N	18	$CH_2C_6H_5$	–	–	2.33	2.72
22	N	18	C_6H_4-*2*-OCH_3	–	–	2.60	3.65
23	N	18	$CH_2CH_2OCH_3$	–	–	6.48	4.75

[a] Ratio A is $100[(\text{crown})_2\cdot\text{M}]^+/(\text{crown}\cdot\text{M})^+$. [b] Ratio B is $(\text{crown}\cdot\text{Na})^+/(\text{crown}\cdot\text{H})^+$. [c] Binding constants ($\log K_S$) were determined in anhydrous methanol at 25°C.

tendency for the system to form 2:1 complexes diminishes. As expected from solution studies, 18-membered-ring N-pivot lariat ethers and BiBLEs (bibracchial, i.e. two armed, lariat ethers) showed no peak attributable to $[(\text{BiBLE})_2\cdot\text{K}]^+$ indicating that the 2:1 complex with KCl is not formed in the matrix.

It should be noted that no sandwich structures were observed for any of the 18-membered ring lariat ethers. In Table 1, blank values have been included in columns 5 and 6 (ratio A) because the lack of any sandwich structure would necessitate division by zero. The lack of sandwich structures in these cases is reasonable since the macroring is as large as any of the cation complexes and a third dimension of solvation is added by the complexing sidearm.

Complexation of Ca^{2+} by lariat ethers

The FAB/MS technique is especially valuable in the case of Ca^{2+} for which other binding assessment methods are cumbersome or unreliable. Divalent calcium is expected to make a higher solvation demand on the ligand and complexation was thus studied with BiBLEs **20–23**. Of these, only **22** and **23** have donor-group-containing sidearms. It should be noted that for singly charged ions to be observed in the mass spectrum, divalent calcium must have one of its two charges neutralized by a counteranion that is present in the observed complex (Table 2).

It might be assumed that ion peaks corresponding to the monocalcium complex would diminish in intensity along the series **20–23** because the binding constant increases in the opposite sense. The decrease in $(\text{C}\cdot\text{Ca}\cdot X)^+$ would thus be attributable to the formation of increasing amounts of $(\text{C}\cdot\text{Ca})^{2+}$. Although this seems intuitively reasonable, no significant ions corresponding to the doubly charged species were observed. These should certainly be apparent if they are present in the FAB matrix; this is an intrinsic assumption of the method. Our inability to observe the doubly charged peaks may be due to the energy beam being too high and therefore decomposing them, but the energies used (*ca.* 6 keV) make this possibility seem unlikely. At present we cannot account for this discrepancy between expectation and observation although work to clarify this particular issue further is in progress.

CONCLUSIONS

The FAB/MS method is a fast and sensitive method that can be used with a variety of macrocycles to assess complexation strength and selectivity. By using the

Table 2 Calcium complexation by diaza-18-crown-6 derivatives

Compound no.	*R*	*log K_S*	*Relative abundance (%)* $(C\cdot Ca\cdot X)^+$	$(C\cdot H)^+$	$(C\cdot Ca\cdot X)^+/(C\cdot H)^+$
20	H		100	44	2.3
21	CH_2Ph	2.79	100	36	2.8
22	$CH_2C_6H_4$-2-OCH_3	3.27	69	100	0.7
23	$CH_2CH_2OCH_3$	4.48	6	100	0.06

method, we were able to detect sandwich complexation and to analyse the effect of sidearms on complexation. Why complexation of calcium cations seems to differ both from expectations and from results observed with alkali metal cations remains a conundrum that is under investigation.

EXPERIMENTAL SECTION

^{1}H-NMR spectra were recorded on a Varian XR-400 NMR Spectrometer or on a Hitachi Perkin-Elmer R-600 High Resolution NMR Spectrometer in $CDCl_3$ solvents and are reported in ppm (δ) downfield from internal $(CH_3)_4Si$. ^{13}C-NMR were recorded on a JEOL FX90Q or Varian XL-400 NMR Spectrometer or as noted above. Infrared spectra were recorded on a Perkin-Elmer 1310 Infrared Spectrophotometer and were calibrated against the 1601 cm^{-1} band of polystyrene. Melting points were determined on a Thomas Hoover apparatus in open capillaries and are uncorrected. Thin layer chromatographic analyses were performed on aluminum oxide 60 F-254 neutral (Type E) with a 0.2 mm layer thickness or on silica gel 60 F-254 with a 0.2 mm layer thickness. Preparative chromatography columns were packed with activated aluminum oxide (MCB 80–325 mesh, chromatographic grade, AX 611) or with Kieselgel 60 (70–230 mesh). Chromatron chromatography was performed on a Harrison Research Model 7924 Chromatotron with 2 mm thick circular plates prepared from Kieselgel 60 PF-254. Gas chromatographic analyses were conducted on a Hewlett-Packard model 5720 gas chromatograph equipped with a flame ionization detector and a 5 ft × 0.25 in. column packed with 1.5% OV-101 on 100/120 mesh Chromosorb G. Helium was used as the carrier gas, and the flow rate was *ca.* 60 ml/min.

All reactions were conducted under dry N_2 unless otherwise noted. All reagents were the best grade commercially available and were distilled, recrystallized, or used without further purification, as appropriate. Molecular distillation temperatures refer to the oven temperature of a Kugelrohr apparatus. Combustion analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and are reported as percentages.

Cation binding constants were measured in absolute MeOH at 25.0 ± 1.0°C using a Corning 476210 electrode and an Orion model 701A 'ionalyzer' meter according to the method of Frensdorff[19] as described recently in detail.[9] Values for the equilibrium constants are reported as log K_S. Samples suitable for single crystal X-ray analysis were grown by slow cooling of a warm saturated solution, by evaporation of a saturated solution, or by vapour diffusion.

FAB spectra were acquired by using a JEOL DX 303 with a 6–8 KeV Xe primary beam and a *m*-nitrobenzyl alcohol matrix. The spectra reported herein were peak averaged over four scans using a DA 5000 data system. The compounds reported in this paper were prepared as previously described.[20] In a typical experiment, *m*-nitrobenzyl alcohol (1 μl), 1 μl of a 50 mM lariat ether solution ($CHCl_3$), and a 1 μl of a 50 mM aqueous solution of metal chloride were carefully mixed on the FAB probe. Binding constants for the lariat ethers were determined potentiometrically in anhydrous methanol as previously described.[9]

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