

Estimation of Selectivities and Relative Cationization Efficiencies of Different [Crown + M]⁺ by Electrospray Mass Spectrometry

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The selectivity of the lariat crown ethers toward metal ions can be estimated easily using electrospray mass spectrometry. Two lariat crown ethers in the *sym*-dibenzo-16-crown-5 series were shown to be more selective towards Li⁺ than Na⁺ ions in methanol. Calibration for the relative cationization efficiencies of the metallated crowns [crown + M]⁺ was shown to be essential for comparison of the selectivities in ligand–metal interactions. The two *sym*-dibenzo-16-crown-5 ethers show the best selectivity towards Li⁺ ion in methanol with their Li⁺ complexes being the most stable among Li⁺, Na⁺ and K⁺ ions. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

Most host–guest studies that have been performed under controlled conditions can be achieved inside a mass spectrometer.¹ Fast atom bombardment mass spectrometry (FAB-MS) is a simple and rapid method for studying the selective capture of metal cations by crown ethers in a matrix solution. However, FAB matrices are not used as solvents in solution chemistry studies, which limits the application of information obtained by FAB-MS. Besides FAB, among the other recently developed mass spectrometric techniques for detecting host–guest complexes, electrospray ionization (ESI) is no doubt the best choice, as fragmentation is seldom observed in ESI-MS and no fragmentation has been observed in our studies with cationized crowns [C + M]⁺, where C is a lariat crown and M⁺ is an alkali metal ion. In addition, charged particles formed by desolvation of ions from liquids are amenable to mass spectrometry² and common solvents such as water, methanol and acetonitrile can be used. Moreover, it demands little experimental effort. Thus information obtained from the ESI technique has much wider application than that from other methods. Although the formation mechanism in ESI is still controversial,³ there are reports suggesting that ESI mass

spectra reflect the equilibrium between the host and guest in the matrix solutions.⁴

Bartsch and co-workers⁵ have reported that *sym*-dibenzo-16-crown-5 ethers had the best selectivity towards Na⁺ ion among alkali metal ions in aqueous solution. Since Li⁺ is classified as a harder species than Na⁺, it will preferentially coordinate with the harder oxygen donor ligands in non-aqueous solvents. Recently, Chapeaurouge *et al.*⁶ used ESI-MS to predict chemical behavior and demonstrated that alkoxyethyl-substituted acylsilanes complexed better with Li⁺ than Na⁺ in methanol. Bonding between oxygen and lithium will be stronger because they belong to the same period thus their orbital sizes and energy levels are closer to each other. Since the chelating atoms in these alkoxyethylacylsilanes are oxygen, so this series of lariat crown ethers will be expected to behave similarly and show better selectivity towards Li⁺ ion in methanol. To test this point, we carried out selective complexation between lariat crown ethers and different cations, using ESI-MS with suitable calibration as was used by Langley *et al.*^{7a} and Johnstone *et al.*^{7b} in FAB MS studies. Two lariat crown ethers; one with a hydroxy side arm (*hydroxy-sym*-dibenzo-16-crown-5) and the other with a benzyloxy side arm (*benzyl-sym*-dibenzo-16-crown-5 ether) were chosen to study the complexation behaviors with alkali metal ions. A large excess of salts was used to minimize the impurity effect observed in ESI-MS⁶ caused by cations (Na⁺, K⁺) persisting in methanol, and relative cationization efficiencies were adequately calibrated for each set of the metallated lariat crowns [crown + M]⁺ versus varied

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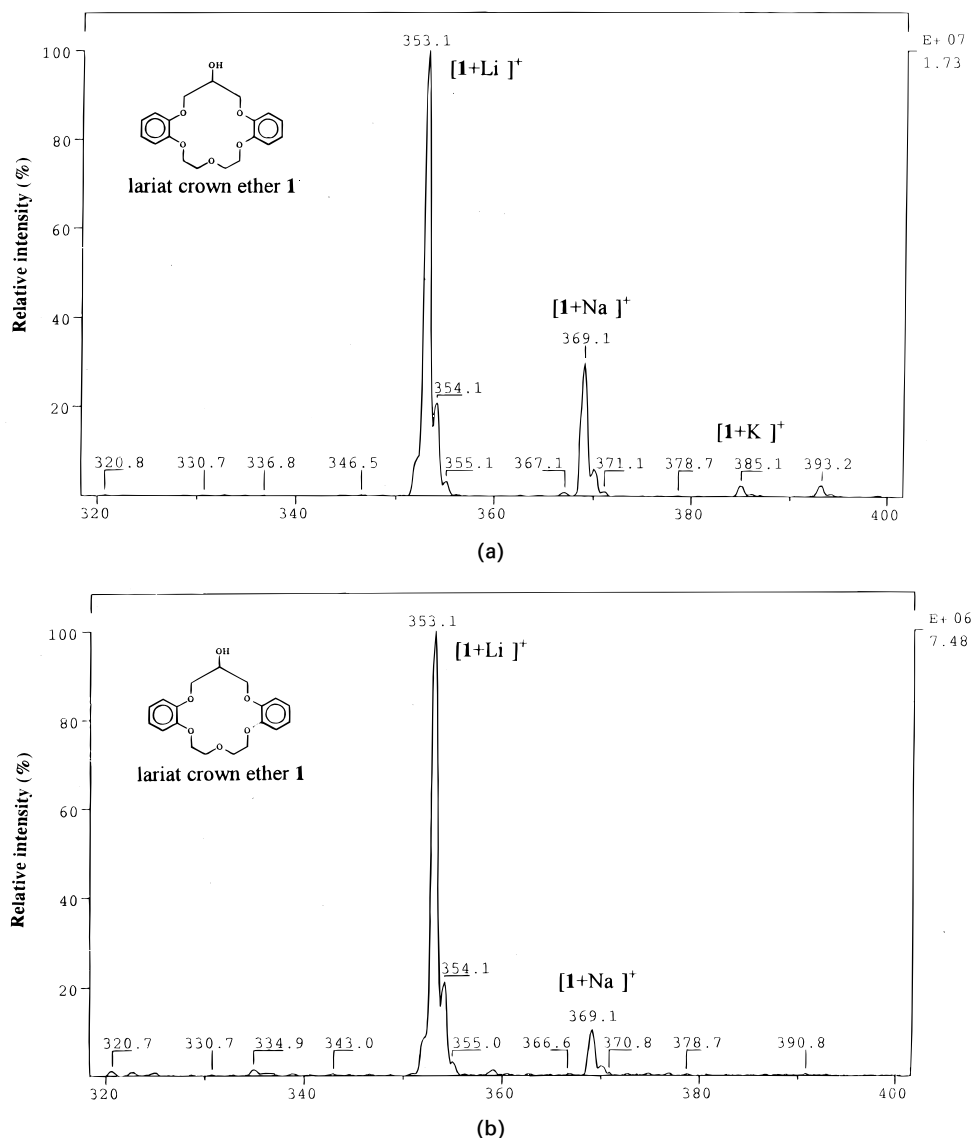


Figure 1. ESI mass spectra of compound **1** (0.1 mM) measured in methanol–LiCl–NaCl–KCl (each 10 mM). (a) Tube lens at normal voltage and (b) tube lens at normal voltage + 100 V.

molar ratio of M_1/M_2 as carried out by Langley *et al.*^{7a} and Johnstone *et al.*^{7b} in FAB-MS studies. The results revealed the preference of Li^+ complexation of these lariat crown ethers in methanol. In addition, a quantitative estimation of selectivity can be obtained from the calibrated peak intensity ratio. The present method is fast and simple and is adaptable to other macrocyclic ring systems, and our recent results are reported in this paper.

EXPERIMENTAL

Materials

Alkali metal salts (LiCl, NaCl and KCl) and methanol (Uvasolv grade) of the highest quality were purchased from Merck. Hydroxy-*sym*-dibenzo-16-crown-5 (**1**) was synthesized by modifying the procedures of Cram and co-workers⁸ and Bartsch and co-workers.⁹ Benzyl-*sym*-dibenzo-16-crown-5 ether (**2**) (m.p. reported as 140–142 °C¹⁰) was prepared by heating NaH (0.72 g, 24

mmol), compound **1** (1.00 g, 2.89 mmol) and benzyl chloride (0.52 g, 3 mmol) in anhydrous tetrahydrofuran (50 ml) with magnetic stirring for 2 h under reflux. Compound **2** was obtained in 91% yield after purification by column chromatography (silica gel, 70–230 mesh, CHCl_3 as eluent), m.p. 105.5–106 °C. Elemental analysis: calculated for $\text{C}_{26}\text{H}_{28}\text{O}_6$, C 71.53, H 6.47; found, C 71.53, H 6.52%.

Alkali metal salt solutions were prepared with methanol in PP volumetric flasks. The lariat crown ethers were freshly prepared in glass volumetric flasks. To compare the cationization efficiencies, sample solutions (0.1 M in the lariat crown **1** and 0.02 M in the lariat crown **2**, owing to the poorer solubility, and 1 mM in the alkali metal salts) were prepared with methanol. Calibration experiments were performed by changing the alkali metal salt concentrations from 1 mM + 1 mM to 1 mM + 5 mM (v/v), so the molar ratio of two salts varied from 1:1 to 5:1. Then they were added to a fixed amount of lariat crown ether, so at least a 16.6-fold excess of lariat crown ether **1** and a 3.3-fold excess of lariat crown ether **2** were used, which ensured that

nearly all of the cations became complexes. In the selective complexation experiments, after thoroughly mixed methanolic solutions of LiCl, NaCl and KCl (10 mM each), a fixed amount of lariat crown ether solution (0.1 mM) was added and stirring was continued for 30 min before carrying out ESI-MS measurements. The stirring time was determined experimentally (see below). A 100-fold excess of salts was necessary to minimize the impurities that may be caused by the cations (Na^+ and K^+) presented in the background.⁶

Mass spectrometry

A Finnigan MAT TSQ-700 (Finnigan, San Jose, CA, USA) triple-sector quadrupole mass spectrometer equipped with an electrospray source was used. Nitrogen was used as the nebulizing gas at a back-pressure of 5×10^{-6} – 6×10^{-6} Torr (1 Torr = Z133.3 Pa). The electrospray needle was maintained at 4.5 kV with the tube voltage setting at 54.4 V and the heated capillary temperature was set at 200 °C. The lens, tube and quadrupole voltages were optimized to obtain maximum ion

current for electrospray. The sample was introduced into the ESI source at a rate of $7 \mu\text{l min}^{-1}$ with a syringe pump (Harvard Apparatus, Cambridge, MA, USA). Ions were detected by scanning the first quadrupole and the scans were monitored over the mass range 300–600 in 0.45 s. At least 30 scans were averaged to obtain representative spectra. When the stabilities of each lariat crown ether and cation complex were compared, an additional offset voltage (100 V for 1 and 50 V for 2) was applied to the tube lens.⁶ This caused a decrease in intensity for the less stable metallated crown (Figs 1(b) and 2(b)).

RESULTS AND DISCUSSION

Selectivity of lariat crown ether with different alkali metal cations

To determine the selective complexation of lariat crown ethers 1 and 2 with lithium, sodium and potassium ions, a competitive experiment with each lariat crown ether

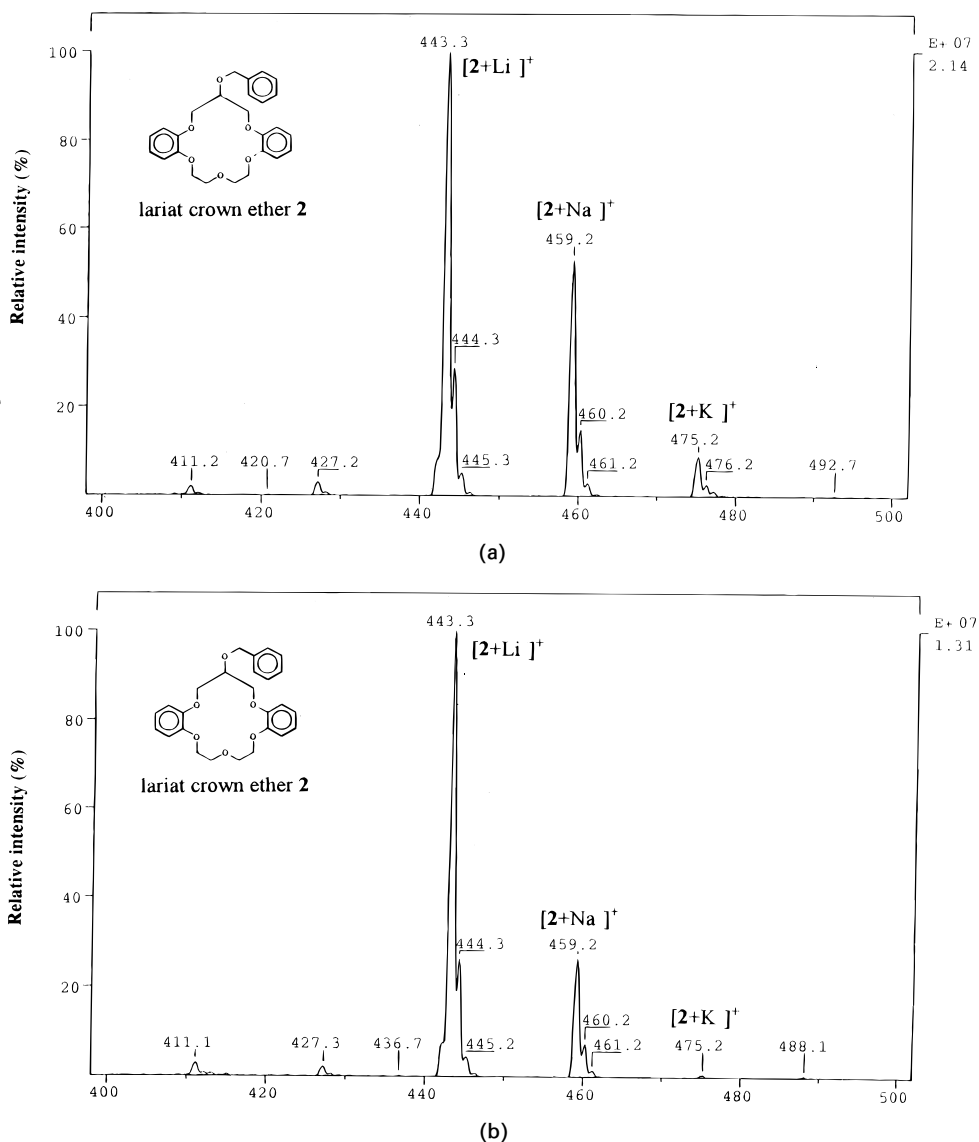


Figure 2. ESI mass spectra of compound 2 (0.1 mM) measured in methanol–LiCl–NaCl–KCl (each 10 mM). (a) Tube lens at normal voltage and (b) tube lens at normal voltage + 50 V.

with all three cations in equimolar amounts was carried out. Cationization occurred readily, giving [crown + M]⁺ with correct isotopic ratios which were consistent with the calculated values for each proposed ion structure. Apparent ion distributions [crown + Li]⁺: [crown + Na]⁺: [crown + K]⁺ of ~100:30:2.5 for **1** (Fig. 1(a)) and 100:56.6:9.2 for **2** (Fig. 2(a)) were obtained. These ratios are related to the concentration relationship of the respective species in methanolic solution. This indicates that both lariat crowns (**1** and **2**) are more selective towards Li⁺ than Na⁺ and K⁺ ions in methanol, as expected.

This result is different from that reported by Bartsch and co-workers,⁵ who observed a preference of **1** towards Na⁺ in aqueous solution. The selectivity varied with the different solvent systems, and our results show that Li⁺ forms the most stable complexes with lariat crown ethers in methanol. This can be confirmed by a tandem mass spectrometry-type experiment.⁶ In fact, when the voltage at the tube lens was increased by 100 V with **1** and 50 V with **2** (an experimental set-up that gives rise energy transfer to ions in the gas phase and hence leads to a decrease in intensity for the less stable metallated crown), the stabilities of the lariat crown ether-cation complexes were found to be $S_{C-Li^+} > S_{C-Na^+} > S_{C-K^+}$ (Figs 1(b) and 2(b)), as expected. Selective coordination of lithium towards oxygen ligands is well known in organic chemistry and Chapeaurouge and co-workers⁶ observed similar ESI results with alkoxymethyl-substituted acylsilanes. These results indicate that the lariat crown ether forms the most stable complex with Li⁺ among the three alkali metal cations in methanol.

Although there are reports which assume that the ESI mass spectrum represents the condition of ions in solution,⁴ there is a risk of mistaking the peak intensities for the true concentrations, even if the species were already in an ionized state before they entered the mass spectrometer.¹¹ The peak intensities may represent the stabilities of ions in the mass spectrometer, but they do not represent the absolute amounts in solution. Since different species have different cationization effi-

ciencies,⁷ it is necessary to calibrate the cationization efficiencies of [crown + Li]⁺: [crown + Na]⁺: [crown + K]⁺ before comparing the peak intensities of [crown + M]⁺ and drawing any conclusions about selectivity.

Relative cationization efficiencies for lariat crown ether with different alkali metal cations

In a FAB-MS study of ligand-cation interactions, Langley *et al.*^{7a} and Johnstone *et al.*^{7b} investigated the relative abundances of protonated ions, [crown + H]⁺ and metallated ions, [crown + M]⁺, of some crown ethers. By modifying their method, we can obtain the cationization efficiency for each metallated crown. Calibration experiments were performed by changing the molar ratio of the two salts from 1:1 to 5:1. Varying the molar ratio of LiCl to KCl from 1:1 to 5:1 and adding the mixture to a fixed amount of **1**, ESI mass spectra were recorded after stirring the mixture for 30 min. The results are presented in Table 1.

The stability constants (K_s) of the *sym*-dibenzo-16-crown-5 ethers with alkali metal cations are in the range 10³–10⁴ according to the literature.¹² Since the crown ethers studied all had the same cavity size and the same oxygen donor atoms, the stability constants of **1** and **2** should be of the same order of magnitude.¹³ Therefore, complex formation will nearly approach completion with an excess amount of crown ether, thus [crown + M]⁺ ≈ M⁺. Using the peak intensity of [crown + K]⁺ as an internal standard, a plot of the peak intensity ratio against the molar ratio of Li⁺ to K⁺ reveals a linear relationship (Table 1), and the peak intensity ratio is proportional to the increase in molar ratio of the cation. One axis (abscissa) reveals the true ratio of metallated ions and the other (ordinate) represents the apparent results, and the slope of the line is the ratio of the cationization efficiency of [crown + Li]⁺ to [crown + K]⁺.

The cavity diameter of *sym*-dibenzo-16-crown-5 has been estimated as 2.0–2.4 Å,⁵ while alkali metal ion

Table 1. Variation of ratio of metallated ion peak intensities (*I*) relative to molar ratio of alkali metal cations

Molar ratio	$I_{[1+K]^+}/I_{[1+Na]^+}$	$I_{[1+Li]^+}/I_{[1+Na]^+}$	$I_{[1+Li]^+}/I_{[1+K]^+}$
1	0.68	0.0878	0.47
2	1.48	0.112	0.92
3	2.08	0.131	1.47
4	2.27	0.2045	1.88
5	3.44	0.36	2.65
Equation	$y = 0.631 + 0.097x$	$y = 0.3388x + 0.0243$	$y = 0.532x - 0.118$
r^2	0.9559	0.9961	0.9887
Molar ratio	$I_{[2+K]^+}/I_{[2+Na]^+}$	$I_{[2+Li]^+}/I_{[2+Na]^+}$	$I_{[2+Li]^+}/I_{[2+K]^+}$
1	1.27	0.33	0.6699
2	2.84	0.58	0.077
3	4.08	0.73	0.085
4	6.12	0.86	0.12
5	6.81	1.00	0.17
Equation	$y = 1.43 - 0.084x$	$y = 0.162 + 0.214x$	$y = 0.1264 + 0.0468x$
r^2	0.9846	0.98	0.9812

Table 2. Cationization efficiencies between two metallated ions of compounds 1 and 2

Compound	Ionization efficiency		
	$[\text{crown} + \text{Li}]^+ : [\text{crown} + \text{Na}]^+$	$[\text{crown} + \text{Li}]^+ : [\text{crown} + \text{K}]^+$	$[\text{crown} + \text{Na}]^+ : [\text{crown} + \text{K}]^+$
1	1 : 2.9	1 : 1.9	1.6 : 1
2	1 : 6.2	1 : 7.9	1 : 1.4

diameters have been reported¹⁴ as 1.36 Å (Li⁺), 1.96 Å (Na⁺) and 2.66 Å (K⁺). Using this information, one can anticipate that Li⁺ and Na⁺ will be accommodated within the crown ether cavity and form stabler inclusion complexes (we have isolated an inclusion complex between Na⁺ and hydroxy-*sym*-dibenzo-16-crown-5 ether¹⁵) whereas K⁺ is too large to fit within the cavity and will sit on the top of the ring formed by the crown ring oxygens. Hence the $[\text{crown} + \text{K}]^+$ complex formation may be slower than that of the $[\text{crown} + \text{Li}]^+$ complex; however, the results reported here are the equilibrium values, because no noticeable change in the spectra was observed after stirring for either 30 min or 1 h. Therefore, equilibrium had been reached, and we fixed the stirring time at 30 min for subsequent measurements. The cationization efficiency ratio of $[\mathbf{1} + \text{Li}]^+$ to $[\mathbf{1} + \text{K}]^+$ can be determined as 0.532 from the slope of the plot of $y = 0.532x - 0.118$ (Table 1). Similarly, we can determine the cationization efficiency ratio of $[\mathbf{1} + \text{Li}]^+$ to $[\mathbf{1} + \text{Na}]^+$ as 0.3388 (Table 1). From these two results, we can calculate the cationization efficiency ratio of $[\mathbf{1} + \text{K}]^+$ to $[\mathbf{1} + \text{Na}]^+$ as 0.63. To check this result, we then verified the molar ratio between Na⁺ and K⁺ similarly and determined the cationization efficiency ratio of $[\mathbf{1} + \text{K}]^+$ to $[\mathbf{1} + \text{Na}]^+$ as 0.631 (Table 1), which is in excellent agreement with the calculated value. Hence the cationization efficiency ratio $[\mathbf{1} + \text{Li}]^+ : [\mathbf{1} + \text{Na}]^+ : [\mathbf{1} + \text{K}]^+$ is 1 : 2.9 : 1.9 (Table 2). For the lariat crown ether 2, which has a benzyloxy side-arm, the results obtained similarly are presented in Table 1 and the cationization efficiency ratio $[\mathbf{2} + \text{Li}]^+ : [\mathbf{2} + \text{Na}]^+ : [\mathbf{2} + \text{K}]^+$ is 1 : 6.2 : 7.9 (Table 2).

Determination of the accurate selectivity ratio of lariat crown ether and alkali metal cations

The cationization efficiencies of $[\text{crown} + \text{M}]^+$ will not be different with an excess amount of either the crown ether or the cation. According to the mechanism of ESI ionization,² the emitted droplets carries off only the analytical species, $[\text{crown} + \text{M}]^+$ and solvent molecules, while most of the excess amount of crown ethers or electrolytes will be left in the parent droplets which will not enter the mass spectrometer. Since $[\text{crown} + \text{M}]^+$ is a complexed ion, its formation is related only to its stability constant. No cluster ions such as $[\text{crown}_x + \text{M}]^+$ or $[\text{crown} + \text{M}_y]^{y+}$ are observed under our ESI experimental conditions, so the cationization efficiencies of $[\text{crown} + \text{M}]^+$ should be

the same with either the crown ether or cation present in excess.

As shown previously, the apparent ion distributions of lariat crown ethers toward Li⁺, Na⁺ and K⁺ ions were 100:30:2.5 for 1 and 100:56.6:9.2 for 2 (Figs 1(a) and 2(a)). In this paper, we have shown that different species have different cationization efficiencies and exhibit different peak intensities even when their concentrations are the same. It is erroneous to compare selectivities using the unmodified results. By carrying out calibration as described above, we adjust the selectivity ratio between lariat crown ethers towards Li⁺, Na⁺ and K⁺ ions as 100:10.3:1.3 for 1 and 100:9.1:1.2 for 2. From these results, we conclude that the lariat crown ethers favor complexation with Li⁺ over Na⁺ and K⁺ ions in methanol.

CONCLUSION

The results obtained with both 1 and 2 reveal that the lariat crown ethers are more selective towards Li⁺ ion and the lariat crown ether–Li⁺ complexes are more stable than the corresponding complexes with Na⁺ or K⁺ in methanol. Experiments conducted in aqueous solution showed that Na⁺ had a better complexation ability than the other two alkali metal cations.¹³ Hence selective complexation of lariat crown ethers with cations changes with the solvent system; this may due in part to the difference in solvation between solvent and cation. We have conducted experiments showing that different species have different cationization efficiencies and provided a method for calibration. Owing to the ease of application and its inherent sensitivity, using ESI-MS to study cation–ligand interactions has great appeal. To be confident with one's results, the adjustment of the cationization efficiency ratio is a necessary step before making a comparison of selectivities in complexation.

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