

# Ag<sup>+</sup> Ion-selective lariat ethers: high pressure syntheses and cation recognition properties

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A new series of lariat ethers have been prepared by a high pressure S<sub>N</sub>Ar reaction, in which various heteroaromatics are directly connected to the nitrogens of 12-, 15- and 18-membered aza-crown ethers. Liquid membrane transport studies demonstrated that lariat ethers having thiazole, oxazole, pyrazine and pyridazine rings on their sidearms exhibited excellent Ag<sup>+</sup> ion selectivity. <sup>13</sup>C NMR binding experiments revealed that these lariat ethers selectively formed encapsulated Ag<sup>+</sup> complexes in a different fashion from that of double armed crown ethers. Cooperative action between the heteroaromatic sidearm and the aza-crown ring afforded unique cation recognition.

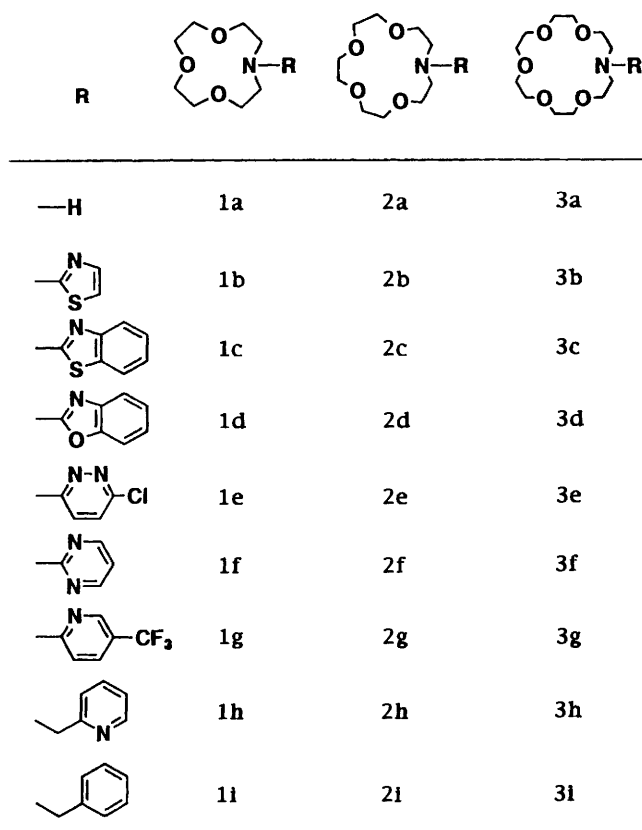
Lariat ethers and double armed crown ethers have been recognized as potential cation-binders and are characterized by a parent crown ring with cation-ligating sidearms.<sup>1</sup> They offer three dimensional complexation suitable for selective recognition and a modification of the cation binding ability of the parent crown ethers.<sup>2</sup> Although a variety of armed crown ethers have been reported, their syntheses have mostly been based upon common organic reactions and therefore variations in molecular structures have been limited.<sup>3</sup> Thus, new synthetic methodology is desirable to develop new cation-selective binders of this type. We have recently prepared a novel type of double armed crown ether, with heteroaromatic substituents on their sidearms, by means of a high pressure S<sub>N</sub>Ar reaction.<sup>4</sup> They selectively coordinated Ag<sup>+</sup> ions by the cooperative binding of two types of nitrogen atoms and mediated its selective transport. Highly selective reagents for Ag<sup>+</sup> ions are of commercial interest, because Ag<sup>+</sup> ions occur in nature together with Pb<sup>2+</sup> and other metal cations. Furthermore, some stable Ag<sup>+</sup> complexes have been reported to have potential in cancer radioimmunotherapy.<sup>5</sup>

We have applied the high pressure S<sub>N</sub>Ar reaction to the synthesis of a new series of lariat ethers,<sup>6</sup> since there are methods available for the synthesis of the parent aza-12-crown-4,<sup>7,8</sup> aza-15-crown-5,<sup>8,9</sup> and aza-18-crown-6<sup>8,9</sup> which are neither difficult experimentally nor involve high dilution. They exhibited excellent Ag<sup>+</sup> ion selectivity in binding and transport processes. Based upon extraction and <sup>13</sup>C NMR binding experiments, it has been proved that the new lariat ethers recognize Ag<sup>+</sup> ions in a different fashion from that of double armed crown ethers.<sup>4</sup> Although high pressure techniques have recently been employed as a facile and useful methodology in various synthetic reactions,<sup>10</sup> few examples have been reported in the field of host-guest chemistry.<sup>11</sup> The present study describes a further synthetic application of this technique for the synthesis of metal-selective lariat ethers.

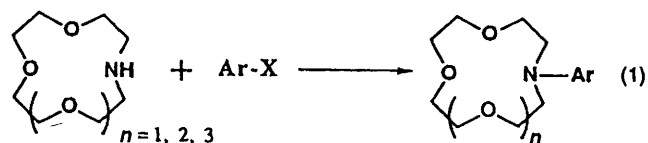
## Results and discussion

### High pressure functionalization of aza-crown ethers

High pressure (0.8 GPa) S<sub>N</sub>Ar reactions of unsubstituted aza-crowns **1a**, **2a** and **3a** with halogenoheteroaromatics gave a variety of new lariat ethers in practical yields [eqn. (1)]. The yields were generally higher than those of the corresponding double armed crown ethers reported before.<sup>4</sup> In particular, medium-sized crown ethers **2b–2g** and **3b–3g** were almost quantitatively obtained by the one-step reaction. In contrast,



Structures of the lariat ethers and related aza-crown ethers



similar reactions in a sealed tube only gave very low yields of the products. Thus, the high pressure reaction is useful for the synthesis of lariat ethers having heteroaromatic substituents on their sidearms. Since our high pressure functionalization requires neither a high-dilution technique nor other laborious

procedures, it should have wide application in the synthesis of various functionalized materials.<sup>12</sup>

Double armed crown ethers with two similar heteroaromatics on their sidearms form two types of Ag<sup>+</sup> complexes.<sup>4</sup> Fig. 1 shows the ligand topology of our new lariat ethers along with those of double armed crown ethers. Both have a parent crown ring with functionalized sidearms for Ag<sup>+</sup> ion binding, but their donor arrangement and ligand topology are apparently

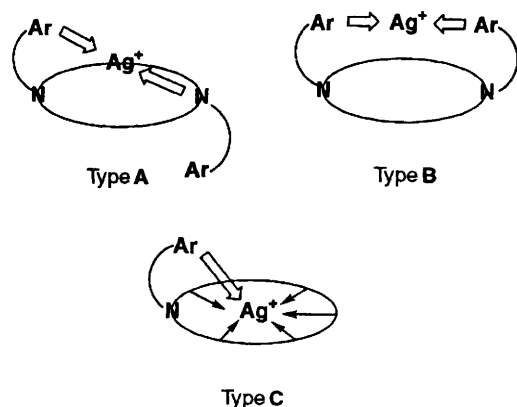


Fig. 1 Cation binding modes of lariat ethers and double armed crown ethers

different. Ag<sup>+</sup> ions coordinate with crown-nitrogen/heteroaromatics (Type A) or heteroaromatic/heteroaromatic (Type B) in the double armed crown ether complexes. Such cooperative binding of the crown nitrogen and heteroaromatics on the sidearm are restricted by steric factors in the lariat ether complex. Since an N-substituted mono-aza crown ring is more flexible and effective at surrounding the Ag<sup>+</sup> ion than the N,N'-disubstituted diaza-crown ring, the present lariat ethers are expected to form an encapsulated Ag<sup>+</sup> complex of Type C.

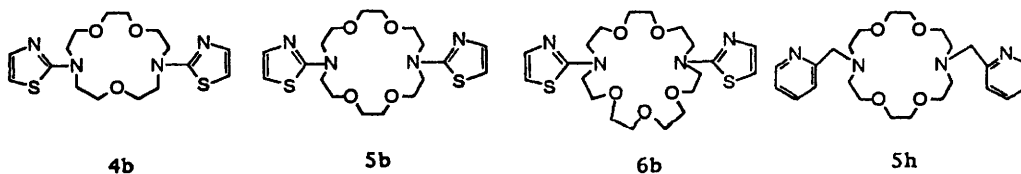
#### Ag<sup>+</sup> Ion-selective transport across a liquid membrane

We examined three kinds of aza-crown ethers as synthetic carriers using a CH<sub>2</sub>Cl<sub>2</sub> liquid membrane system: the aza-crown ethers directly connected to heteroaromatics **1b–1g**, **2b–2g** and **3b–3g**, the aza-crown ethers having flexible pyridyl-methyl sidearms **1h**, **2h** and **3h** and the simple aza-crown ethers **1i**, **2i**<sup>9</sup> and **3i**.<sup>9</sup> Table 1 summarizes their initial transport rates for Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Ag<sup>+</sup>, Pb<sup>2+</sup>, Cu<sup>2+</sup> and Cd<sup>2+</sup> ions, along with those measured for the related double armed crown ethers **4b**, **5b**, **6b** and **5h**.<sup>4</sup>

The aza-crown ethers **1b–1f**, **2b–2f** and **3b–3f** possessing heteroaromatics on their sidearms selectively transported Ag<sup>+</sup> ions, whereas they hardly carried any of the Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Pb<sup>2+</sup>, Cu<sup>2+</sup> and Cd<sup>2+</sup> ions (Table 1). In contrast, lariat ethers **1h**, **2h** and **3h** with flexible pyridylmethyl sidearms effectively transported Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Pb<sup>2+</sup> and Cu<sup>2+</sup> cations. Since the

Table 1 Transport properties of new lariat ethers<sup>a</sup>

Ether	Transport rate/10 <sup>6</sup> mol h <sup>-1</sup>						
	Li <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup>	Ag <sup>+</sup>	Pb <sup>2+</sup>	Cu <sup>2+</sup>	Cd <sup>2+</sup>
<b>1b</b>	<0.3	<0.3	<0.3	1.9	<0.3	<0.3	<0.3
<b>2b</b>	<0.3	<0.3	<0.3	1.4	<0.3	<0.3	<0.3
<b>3b</b>	<0.3	<0.3	<0.3	2.5	<0.3	<0.3	<0.3
<b>1c</b>	<0.3	<0.3	<0.3	1.5	<0.3	<0.3	<0.3
<b>2c</b>	<0.3	<0.3	<0.3	0.4	<0.3	<0.3	<0.3
<b>3c</b>	<0.3	<0.3	<0.3	1.6	<0.3	<0.3	<0.3
<b>1d</b>	<0.3	<0.3	<0.3	1.9	<0.3	<0.3	<0.3
<b>2d</b>	<0.3	<0.3	<0.3	1.8	<0.3	<0.3	<0.3
<b>3d</b>	<0.3	<0.3	<0.3	2.2	<0.3	<0.3	<0.3
<b>1e</b>	<0.3	<0.3	<0.3	0.4	<0.3	<0.3	<0.3
<b>2e</b>	<0.3	<0.3	<0.3	1.3	<0.3	<0.3	<0.3
<b>3e</b>	<0.3	<0.3	<0.3	1.5	<0.3	<0.3	<0.3
<b>1f</b>	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
<b>2f</b>	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
<b>3f</b>	<0.3	<0.3	<0.3	1.3	<0.3	<0.3	<0.3
<b>1g</b>	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
<b>2g</b>	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
<b>3g</b>	<0.3	<0.3	<0.3	0.4	<0.3	<0.3	<0.3
<b>1h<sup>b</sup></b>	0.7	0.9	0.4	0.9	<0.3	<0.3	<0.3
<b>2h</b>	4.4	4.0	2.8	0.3	0.6	<0.3	0.6
<b>3h<sup>b</sup></b>	1.7	8.3	8.9	<0.3	2.3	1.8	<i>c</i>
<b>1i<sup>b</sup></b>	<0.3	<0.3	<0.3	9.2	<0.3	<0.3	<0.3
<b>2i<sup>b</sup></b>	<0.3	0.9	0.4	2.8	<0.3	<0.3	<0.3
<b>3i<sup>b</sup></b>	<0.3	1.8	9.4	2.2	2.5	<0.3	<i>c</i>
<b>4b<sup>b</sup></b>	<0.3	<0.3	<0.3	7.9	<0.3	<0.3	<i>c</i>
<b>5b<sup>b</sup></b>	<0.3	<0.3	<0.3	4.9	<0.3	<0.3	<i>c</i>
<b>6b<sup>b</sup></b>	<0.3	<0.3	<0.3	5.1	<0.3	<0.3	<i>c</i>
<b>5h<sup>b</sup></b>	5.0	10.5	7.9	<0.3	1.6	2.2	<i>c</i>



<sup>a</sup> Conditions: Aq 1: guest perchlorate (0.5 mmol)–H<sub>2</sub>O (5 cm<sup>3</sup>). Membrane: ether (0.0372 mmol)–CH<sub>2</sub>Cl<sub>2</sub> (12 cm<sup>3</sup>). Aq 2: H<sub>2</sub>O (5 cm<sup>3</sup>). <sup>b</sup> Cited from literature.<sup>4a,14</sup> <sup>c</sup> Not determined.

**Table 2** Competitive cation extraction properties of lariat ethers<sup>a</sup>

Ether	Extraction percentage <sup>b</sup> (%)					
	Na <sup>+</sup>	K <sup>+</sup>	Ag <sup>+</sup>	Pb <sup>2+</sup>	Cu <sup>2+</sup>	Cd <sup>2+</sup>
<b>2b</b>	0	0	35	<1	0	<1
<b>2h</b>	<1	0	99	0	0	2
<b>2i</b>	<1	0	96	15	9	0
<b>3b</b>	0	0	43	0	0	<1
<b>3h</b>	0	0	96	24	6	<1
<b>3i<sup>c</sup></b>	0	11	99	48	76	0

<sup>a</sup> Conditions: ether (0.2 mmol)–CH<sub>2</sub>Cl<sub>2</sub> (5 cm<sup>3</sup>); NaClO<sub>4</sub> (0.05 mmol), KClO<sub>4</sub> (0.05 mmol), AgClO<sub>4</sub> (0.05 mmol), Pb(ClO<sub>4</sub>)<sub>2</sub> (0.05 mmol), Cu(ClO<sub>4</sub>)<sub>2</sub> (0.05 mmol), Cd(ClO<sub>4</sub>)<sub>2</sub> (0.05 mmol)–H<sub>2</sub>O (5 cm<sup>3</sup>), stirred for 2 h. <sup>b</sup>  $\{1 - [M^+ \text{ extracted in CH}_2\text{Cl}_2]/[M^+ \text{ initially added in H}_2\text{O}]\} \times 100$ . <sup>c</sup> Precipitate appeared and a considerable amount of metal species was removed from the aqueous phase.

*N*-benzyl crown ethers **1i**, **2i** and **3i** exhibited high carrier activities for Na<sup>+</sup>, K<sup>+</sup>, Ag<sup>+</sup> and Pb<sup>2+</sup> cations, the direct junction of a heteroaromatic unit with the nitrogen atom of crown ring is responsible for the remarkably high Ag<sup>+</sup> ion selectivity. The present type of lariat ethers showed a different effect of size of parent crown ring on Ag<sup>+</sup> ion transport rates from double armed crown ethers. Lariat ethers **3b–3g** with aza-18-crown-6 rings transported Ag<sup>+</sup> ions faster than aza-15-crown-5 and aza-12-crown-4 derivatives **1b–1g** and **2b–2g**. If an Ag<sup>+</sup> ion is nicely accommodated in the crown ring, then the lariat ether may form a stable Ag<sup>+</sup> complex of Type C (see Fig. 1), although the formation of a 2:2 complex cannot be ruled out. Thus, the cation selectivity of this lariat ether is apparently controlled by the 'ion-cavity size concept' established in crown ether chemistry<sup>2b</sup> and can be modified easily. In contrast, double armed crown ether **4b** with a 15-membered ring was a better carrier than diaza-18-crown-6 **5b** and diaza-21-crown-7 **6b**.<sup>4</sup> They formed complexes of Types A and B. Competitive cation transport experiments were carried out using a mixture of KClO<sub>4</sub>, AgClO<sub>4</sub>, Pb(ClO<sub>4</sub>)<sub>2</sub> and Cu(ClO<sub>4</sub>)<sub>2</sub> (0.1 mol m<sup>-3</sup>, each) as the Aq. 1 phase. When lariat ether **3b** with a thiazole sidearm was employed as the carrier, Ag<sup>+</sup> ions were selectively and effectively transported; transport rates were determined to be 8.4 × 10<sup>-6</sup> mol h<sup>-1</sup> for Ag<sup>+</sup>, 0.9 × 10<sup>-6</sup> mol h<sup>-1</sup> for Pb<sup>2+</sup> and <0.3 × 10<sup>-6</sup> mol h<sup>-1</sup> for K<sup>+</sup> and Cu<sup>2+</sup> cations. The transport rate of the Ag<sup>+</sup> ion was greatly enhanced probably because of the presence of an excess of perchlorate ions. On the other hand, the transport properties of aza-crown ether **3i** were quite different when four kinds of cations were present. The transport rates were much less: 1.0 × 10<sup>-6</sup> mol h<sup>-1</sup> for Ag<sup>+</sup>, 0.5 × 10<sup>-6</sup> mol h<sup>-1</sup> for Pb<sup>2+</sup> and <0.3 × 10<sup>-6</sup> mol h<sup>-1</sup> for K<sup>+</sup> and Cu<sup>2+</sup> ions. These results clearly indicate that the present lariat ethers can be used as selective carriers in a competitive transport system.

#### Ag<sup>+</sup> Ion-selective extraction

We performed liquid–liquid extraction experiments using a mixture of NaClO<sub>4</sub>, KClO<sub>4</sub>, AgClO<sub>4</sub>, Pb(ClO<sub>4</sub>)<sub>2</sub>, Cu(ClO<sub>4</sub>)<sub>2</sub> and Cd(ClO<sub>4</sub>)<sub>2</sub>. The extraction percentage was estimated on the basis of the partition of the metal perchlorate between CH<sub>2</sub>Cl<sub>2</sub> and the aqueous solution. Typical results of the competitive extractions are summarized in Table 2.

Table 2 shows that lariat ethers **2b** and **3b** with thiazole sidearms predominantly extracted Ag<sup>+</sup> ions from among the metal cations examined. Their extraction results mirror those of the transport experiments (see Table 1). They selectively bound Ag<sup>+</sup> ions, efficiently solubilized them into the CH<sub>2</sub>Cl<sub>2</sub> membrane and rapidly transported them. The extraction selectivity of Ag<sup>+</sup> ions over Pb<sup>2+</sup> and other metal cations was also found with crown ethers **2h**, **2i**, **3h** and **3i**, but their Ag<sup>+</sup> ion

selectivities were lower than those of lariat ethers **2b** and **3b**. Direct attachment of the thiazole ring to the aza-crown ring decreased extraction efficiency,<sup>†</sup> but remarkably enhanced the Ag<sup>+</sup> ion selectivity. Thus, selectivity enhancement for Ag<sup>+</sup> ions has been achieved by high pressure functionalization of aza-crown ethers, although several sulfur-containing macrocycles have recently been reported to be Ag<sup>+</sup> ion-selective ligands.<sup>13</sup>

#### Ag<sup>+</sup> Ion-selective changes in <sup>13</sup>C NMR spectra

The cation binding behaviour of the new lariat ethers was examined by <sup>13</sup>C NMR spectroscopy in DMF–D<sub>2</sub>O (4:1). DMF–D<sub>2</sub>O was chosen as the solvent system partly because of solubility problems and partly to compare the results with those previously obtained with double armed diaza-crown ethers.<sup>4a</sup> Fig. 2 illustrates Ag<sup>+</sup>- and Pb<sup>2+</sup>-induced changes in <sup>13</sup>C NMR chemical shifts of selected carbons of lariat ethers **2b** and **3b** and a mixture of aza-18-crown-6 and thiazole. The addition of AgClO<sub>4</sub> to a solution of the 15-membered lariat ether **2b** caused significant and continuous spectral changes, whereas the addition of Pb(ClO<sub>4</sub>)<sub>2</sub> offered no spectral change [Fig. 2(a)]. This indicates that the lariat ether **2b** discriminates well between Ag<sup>+</sup> and Pb<sup>2+</sup> ions even in a homogeneous solution, although they have similar metal characteristics and ion sizes. Significant shifts were observed in the signals for the carbons of the crown ring (–N–CH<sub>2</sub>–) and the heteroaromatic substituents (–C=N–) upon addition of Ag<sup>+</sup> to a DMF–D<sub>2</sub>O (4:1) solution of **2b**, supporting the formation of an encapsulated Ag<sup>+</sup> complex. Indeed, based upon the X-ray analyses of binuclear silver complexes with diaza-18-crown-6 **5b** and diaza-15-crown-5 **4b** with thiazole sidearms, each silver ion is basically coordinated by the two nitrogen atoms of the thiazole and the crown ring oxygens.<sup>‡,4b</sup> In contrast, the 18-membered lariat ether **3b** showed different complexing behaviour. Fig. 2(b) indicates that its Pb<sup>2+</sup> complex structure is very different from that of its Ag<sup>+</sup> complex; the Pb<sup>2+</sup> complex has circular coordination in the same way as simple crown ethers, while Ag<sup>+</sup> ions are wrapped in a three dimensional fashion. Even though the electron density of the crown ring-nitrogen atom was decreased by the introduction of a thiazole group, the aza-18-crown-6 ring was still effective at binding Pb<sup>2+</sup> ions. Such Pb<sup>2+</sup> binding was not observed for the double armed crown ethers **4b**, **5b** and **6b**. Disubstituted diaza-crown rings probably have a more rigid structure than single armed crown ethers and therefore were ineffective at binding Pb<sup>2+</sup> ions. Inspection of Fig. 2(c) suggests that the parent aza-18-crown-6 formed sandwich-type 2:1 complexes with Ag<sup>+</sup> and Pb<sup>2+</sup> cations, while thiazole itself interacted with Ag<sup>+</sup> cations non-stoichiometrically. These results clearly indicate that the combination of a heteroaromatic-functionalized sidearm and an N-substituted monoaza-crown ring was responsible for the selective binding of Ag<sup>+</sup> ions in a three dimensional complex.

Table 3 summarizes the results of <sup>13</sup>C NMR binding experiments for K<sup>+</sup> and Cd<sup>2+</sup> cations as well as for Ag<sup>+</sup> and Pb<sup>2+</sup> cations. Lariat ethers **3i** interacted strongly with various metal cations except for Cd<sup>2+</sup> as deduced from the induced changes in <sup>13</sup>C NMR chemical shifts. In contrast, **2b** and **3b** hardly bound K<sup>+</sup> and Cd<sup>2+</sup> cations at all, whereas they selectively formed three dimensional complexes with Ag<sup>+</sup> ions. Although the unsubstituted aza-18-crown-6 and thiazole together interacted with various metal cations, the intramolecular association of these two functional moieties gave a unique cation recognition ability.

<sup>†</sup> The thiazole substituent acts as an electron-withdrawing group and reduces the electron-density on the nitrogen atom of the aza-crown ring.  
<sup>‡</sup> Unfortunately, all our attempts to obtain crystals of **2b**–Ag and **3b**–Ag complexes were unsuccessful.

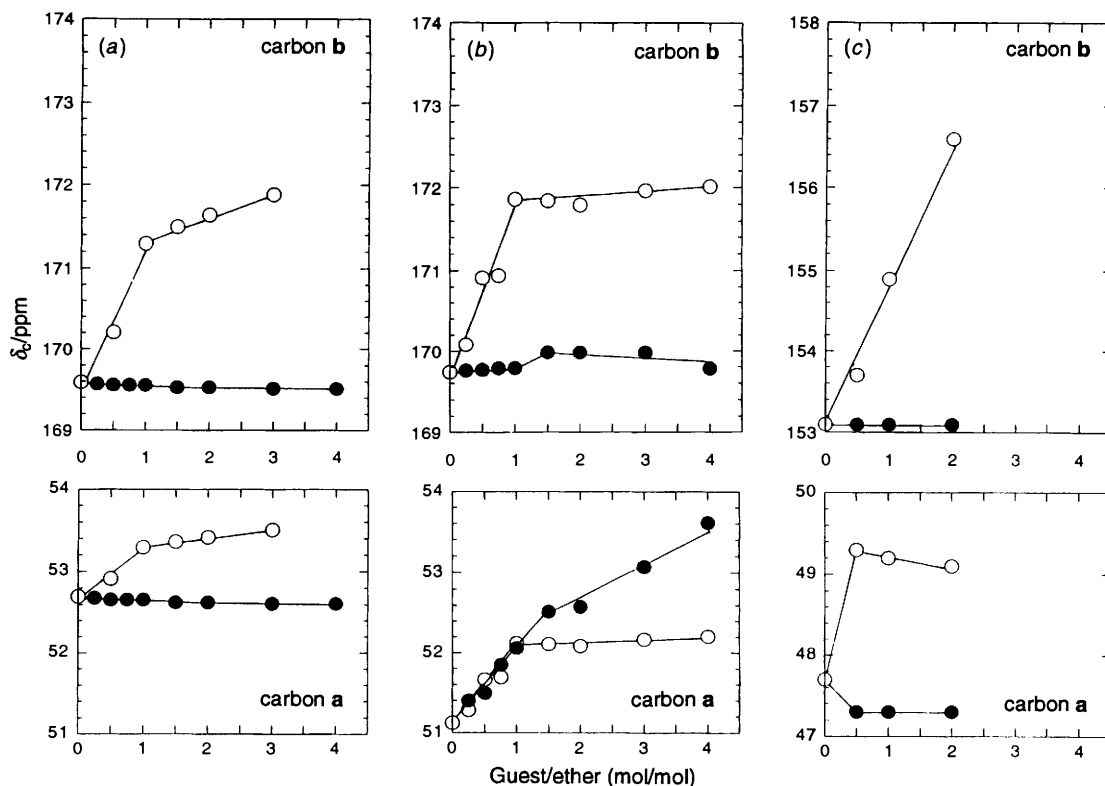
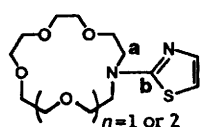


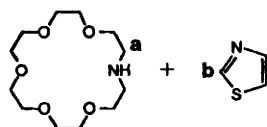
Fig. 2  $\text{Ag}^+$ - and  $\text{Pb}^{2+}$ -induced changes in  $^{13}\text{C}$  NMR chemical shifts of lariat ethers **2b** (a) and **3b** (b) and a mixture of crown **3a** and thiazole (c).  $\text{Ag}^+$ :  $\circ$ ;  $\text{Pb}^{2+}$ :  $\bullet$ . Carbons as indicated by **a** and **b** in Table 3.

Table 3 Guest-induced changes in  $^{13}\text{C}$  NMR chemical shifts of lariat ethers<sup>a</sup>

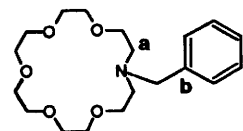
Ether	Carbon	Induced chemical shift (ppm)			
		$\text{K}^+$	$\text{Ag}^+$	$\text{Pb}^{2+}$	$\text{Cd}^{2+}$
<b>2b</b>	<b>a</b>	*	0.6	*	*
	<b>b</b>	*	1.7	*	*
<b>3b</b>	<b>a</b>	*	1.0	0.9	*
	<b>b</b>	0.1	2.1	*	*
<b>3a</b> + thiazole <sup>b</sup>	<b>a</b>	0.4	1.5	-0.4 <sup>c</sup>	-0.7
	<b>b</b>	*	1.8	* <sup>c</sup>	0.5
<b>3i</b>	<b>a</b>	1.3	1.4	-1.9	-0.1
	<b>b</b>	-7.9	*	-6.8	-4.9



**2b** or **3b**



**3a** + thiazole



**3i**

<sup>a</sup> Conditions: ether (0.025 mmol), guest perchlorate (0.025 mmol) in DMF- $\text{D}_2\text{O}$  (4:1) (0.5  $\text{cm}^3$ ). Positive values refer to downfield shifts.

<sup>b</sup> 0.025 mmol of thiazole was added. <sup>c</sup> Turbid. \*  $\pm 0.1$  ppm.

In conclusion, high pressure functionalization of the parent crown ethers **1a**, **2a** and **3b** allowed one-step synthesis of the

new lariat ethers **1b-g**, **2b-g** and **3b-g**. These lariat ethers showed modified coordination character of the parent crown ethers, and enhanced  $\text{Ag}^+$  ion selectivity. Further applications of the high pressure technique may offer new host molecules having novel binding sites and unique functions.

## Experimental

### General

Melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected.  $^1\text{H}$  NMR spectra were measured on a Hitachi R40 (90 MHz) or a JEOL JNM-EX270 (270 MHz) instrument.  $^{13}\text{C}$  NMR spectra were recorded on a JEOL JNM-FX90Q, a JNM-EX270 or a JNM-ALPHA500 spectrometer operating at 22.49 MHz, 67.80 Hz and 125.65 Hz, respectively. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane.  $J$  Values are given in Hz. Preparative medium-pressure liquid chromatography was carried out using a column (25  $\times$  310 mm) prepacked with silica gel (Lobar, LiChroprep Si60, Merck).

Crown ethers **1a**, **2a**, **3a**, **1i** and **2i** were prepared according to the methods reported in the literature.<sup>7-9</sup> Crown ethers **3h** and **3i** were also synthesized by the methods described in the literature.<sup>9,14</sup> All new compounds had the correct elemental compositions as determined by microanalysis.

The preparation and selected spectroscopic data for the compounds **1h** and **2h** are given below.

**10-(2-Pyridylmethyl)-1,4,7-trioxa-10-azacyclododecane 1h.** A solution of mono-aza crown **1a** (177 mg, 1 mmol), 2-picolyl chloride hydrochloride (246 mg, 1.5 mmol), and triethylamine (1.0 g, 10 mmol) in ethanol (20  $\text{cm}^3$ ) was refluxed for 20 h. The mixture was diluted with water and extracted with dichloromethane (50  $\text{cm}^3 \times 3$ ). The combined organic extracts were dried over anhydrous  $\text{MgSO}_4$ . After evaporation of the dichloromethane, the residue was subjected to column chromatography on alumina using hexane and hexane-ethyl acetate as eluent in a

gradient fashion to give the title compound **1h** as a pale yellow oil (149 mg, 48%) (Found: C, 63.2; H, 8.1; N, 10.5).  $C_{14}H_{22}O_3N_2$  requires C, 63.14; H, 8.33; N, 10.52%;  $\delta_H(\text{CDCl}_3)$  2.79 (4 H, t, *J* 5.0), 3.54–3.76 (12 H, s + m), 3.80 (2 H, s), 6.96–7.15 (1 H, m), 7.52–7.64 (2 H, m) and 8.36–8.48 (1 H, m);  $\delta_C(\text{CDCl}_3)$  55.1, 62.5, 70.1, 70.5, 71.3, 121.6, 123.0, 136.1, 148.7 and 160.2.

**13-(2-Pyridylmethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane 2h.** Prepared by the method described above, as a pale yellow oil (68%) (Found: C, 61.8; H, 8.7; N, 8.8).  $C_{16}H_{26}O_4N_2$  requires C, 61.91; H, 8.44; N, 9.03%;  $\delta_H(\text{CDCl}_3)$  2.79 (4 H, t, *J* 5.8), 3.13–3.47 (16 H, s + m), 3.50 (2 H, s), 6.62–7.37 (3 H, m) and 8.02–8.18 (1 H, m);  $\delta_C(\text{CDCl}_3)$  54.9, 62.5, 70.0, 70.3, 70.7, 71.1, 121.8, 123.0, 136.3, 148.4 and 160.4.

#### Functionalization of monoaza-crown ethers

**General procedure.** A mixture of unsubstituted aza-crown ether **1a**, **2a** or **3a** (1 mmol), heteroaromatic chloride (1.5 mmol) and triethylamine (3 mmol) was diluted with tetrahydrofuran (THF) in a polytetrafluoroethylene tube (4 cm<sup>3</sup>), which was compressed to 0.8 GPa (8 kbar) and heated and kept at 100 °C for several days. The high pressure instrument employed has been described elsewhere.<sup>15</sup> After cooling and depressurization, the triethylamine and THF were evaporated under reduced pressure. Benzene (*ca.* 50 cm<sup>3</sup>) was added to the residue and the quaternary salt was removed by filtration. The filtrate was then subjected to chromatography on silica gel (Wakogel C-200 or C-100), using hexane, hexane–ethyl acetate and ethyl acetate as eluent in a gradient fashion. Reaction time (days), yield (%), melting point (°C), microanalytical data, and selected spectroscopic data for the new compounds are as follows.

**10-(Thiazol-2-yl)-1,4,7-trioxa-10-azacyclododecane 1b.** 4 Days (64%), mp 30–32 °C (Found: C, 51.3; H, 7.2; N, 10.7).  $C_{11}H_{18}O_3N_2S$  requires C, 51.14; H, 7.02; N, 10.84%;  $\delta_H(\text{CDCl}_3)$  3.60 (8 H, s), 3.63–3.95 (8 H, m), 6.37 (1 H, d, *J* 3.8) and 7.04 (1 H, d, *J* 3.8);  $\delta_C(\text{CDCl}_3)$  53.9, 69.5, 70.0, 71.4, 105.9, 139.5 and 171.4.

**10-(Benzothiazol-2-yl)-1,4,7-trioxa-10-azacyclododecane 1c.** 6 Days (44%), mp 77–79 °C (Found: C, 58.4; H, 6.5; N, 9.1).  $C_{15}H_{20}O_3N_2S$  requires C, 58.42; H, 6.54; N, 9.08%;  $\delta_H(\text{CDCl}_3)$  3.54 (8 H, s), 3.60–4.00 (8 H, m) and 6.85–7.60 (4 H, m);  $\delta_C(\text{CDCl}_3)$  53.6, 69.6, 70.9, 114.9, 128.2, 145.7 and 158.2.

**10-(Benzoxazol-2-yl)-1,4,7-trioxa-10-azacyclododecane 1d.** 6 Days (57%), mp 105–107 °C (Found: C, 61.6; H, 7.0; N, 9.6).  $C_{15}H_{20}O_4N_2$  requires C, 61.63; H, 6.90; N, 9.58%;  $\delta_H(\text{CDCl}_3)$  3.58 (8 H, s), 3.63–3.95 (8 H, m) and 6.68–7.33 (4 H, m);  $\delta_C(\text{CDCl}_3)$  50.7, 69.8, 70.1, 71.2, 108.7, 116.1, 120.2, 123.8, 143.6, 149.0 and 162.7.

**10-(6-Chloropyridazin-3-yl)-1,4,7-trioxa-10-azacyclododecane 1e.** 4 Days (62%), mp 89–92 °C (Found: C, 50.3; H, 6.3; N, 14.7).  $C_{12}H_{18}O_3N_3Cl$  requires C, 50.09; H, 6.31; N, 14.60%;  $\delta_H(\text{CDCl}_3)$  3.52 (8 H, s), 3.57–3.75 (4 H, m), 3.80–3.97 (4 H, m) and 7.03 (2 H, s);  $\delta_C(\text{CDCl}_3)$  52.0, 69.4, 69.7, 71.2, 116.2, 128.2, 146.0 and 158.7.

**10-(Pyrimidin-2-yl)-1,4,7-trioxa-10-azacyclododecane 1f.** 5 Days (74%), mp 35–36 °C (Found: C, 57.1; H, 7.7; N, 16.5).  $C_{12}H_{19}O_3N_3$  requires C, 56.90; H, 7.56; N, 16.59%;  $\delta_H(\text{CDCl}_3)$  3.56 (8 H, s), 3.84 (8 H, s), 6.40 (1 H, t, *J* 4.8) and 8.22 (2 H, d, *J* 4.8);  $\delta_C(\text{CDCl}_3)$  49.6, 69.9, 70.2, 71.5, 109.4, 157.3 and 161.9.

**10-(5-Trifluoromethyl-2-pyridyl)-1,4,7-trioxa-10-azacyclododecane 1g.** 4 Days (58%), mp 70–72 °C (Found: C, 52.4; H, 6.1; N, 8.7).  $C_{14}H_{19}O_3N_2F_3$  requires C, 52.50; H, 5.98; N, 8.75%;  $\delta_H(\text{CDCl}_3)$  3.55–3.95, 3.58 (16 H, m + s), 6.64 (1 H, d, *J* 9.1), 7.50 (1 H, dd, *J* 2.6, 9.1) and 8.26 (1 H, br s);  $\delta_C(\text{CDCl}_3)$  51.2, 69.8, 71.6, 106.1, 114.3 (*J*<sub>CF</sub> 33), 125.0 (*J*<sub>CF</sub> 270), 133.8, 145.4 and 160.3.

**13-(Thiazol-2-yl)-1,4,7,10-tetraoxa-13-azacyclopentadecane 2b.** 5 Days (99%), oil (Found: C, 51.5; H, 7.3; N, 9.3).  $C_{13}H_{22}O_4N_2S$  requires C, 51.64; H, 7.33; N, 9.26%;  $\delta_H(\text{CDCl}_3)$  3.58 (4 H, s), 3.60 (8 H, s), 3.63–3.88 (8 H, m), 6.37 (1 H, d, *J* 3.6) and 7.04 (1 H, d, *J* 3.6);  $\delta_C(\text{CDCl}_3)$  53.9, 68.8, 70.3, 70.4, 71.2, 105.9, 139.6 and 170.8.

**13-(Benzothiazol-2-yl)-1,4,7,10-tetraoxa-13-azacyclopentadecane 2c.** 4 Days (99%), mp 77–79 °C (Found: C, 57.8; H, 7.0; N, 7.9).  $C_{17}H_{24}O_4N_2S$  requires C, 57.93; H, 6.86; N, 7.95%;  $\delta_H(\text{CDCl}_3)$  3.55 (4 H, s), 3.58 (8 H, s), 3.70–3.88 (8 H, m) and 6.81–7.54 (4 H, m);  $\delta_C(\text{CDCl}_3)$  53.6, 68.9, 70.3, 70.4, 71.2, 118.9, 120.5, 120.9, 125.7, 130.9, 153.2 and 167.8.

**13-(Benzoxazol-2-yl)-1,4,7,10-tetraoxa-13-azacyclopentadecane 2d.** 4 Days (99%), mp 80–82 °C (Found: C, 60.7; H, 7.1; N, 8.2).  $C_{17}H_{24}O_5N_2$  requires C, 60.70; H, 7.19; N, 8.33%;  $\delta_H(\text{CDCl}_3)$  3.55 (4 H, s), 3.62 (8 H, s), 3.75 (8 H, m) and 6.73–7.32 (4 H, m);  $\delta_C(\text{CDCl}_3)$  51.0, 69.3, 70.7, 70.4, 71.1, 108.6, 116.0, 120.1, 123.8, 143.6, 149.0 and 162.3.

**13-(6-Chloropyridazin-3-yl)-1,4,7,10-tetraoxa-13-azacyclopentadecane 2e.** 4 Days (96%), mp 74–76 °C (Found: C, 50.5; H, 6.6; N, 12.8).  $C_{14}H_{22}O_4N_3Cl$  requires C, 50.68; H, 6.68; N, 12.66%;  $\delta_H(\text{CDCl}_3)$  3.53 (4 H, s), 3.58 (8 H, s), 3.75 (8 H, br s), 6.85 (1 H, d, *J* 9.6) and 7.09 (1 H, d, *J* 9.6);  $\delta_C(\text{CDCl}_3)$  51.6, 69.1, 70.1, 70.3, 71.1, 114.8, 128.3, 145.8 and 158.0.

**13-(Pyrimidin-2-yl)-1,4,7,10-tetraoxa-13-azacyclopentadecane 2f.** 4 Days (87%), mp 57–59 °C (Found: C, 56.7; H, 7.9; N, 13.9).  $C_{14}H_{23}O_4N_3$  requires C, 56.55; H, 7.80; N, 14.13%;  $\delta_H(\text{CDCl}_3)$  3.63 (4 H, s), 3.67 (8 H, s), 3.70 (8 H, s), 6.38 (1 H, t, *J* 4.9) and 8.22 (2 H, d, *J* 4.9);  $\delta_C(\text{CDCl}_3)$  50.3, 69.4, 70.3, 109.4, 157.5 and 161.6.

**13-(5-Trifluoromethyl-2-pyridyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane 2g.** 4 Days (88%), mp 47–49 °C (Found: C, 52.8; H, 6.2; N, 7.6).  $C_{16}H_{23}O_4N_2F_3$  requires C, 52.74; H, 6.36; N, 7.69%;  $\delta_H(\text{CDCl}_3)$  3.60 (4 H, s), 3.68 (8 H, s), 3.77 (8 H, m), 6.51 (1 H, d, *J* 8.0), 7.50 (1 H, dd, *J* 2.5, 8.0) and 8.28 (1 H, br s);  $\delta_C(\text{CDCl}_3)$  51.2, 70.3, 70.4, 71.3, 114.3 (*J*<sub>CF</sub> 33), 125.0 (*J*<sub>CF</sub> 270), 133.9, 145.7 and 159.6.

**16-(Thiazol-2-yl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane 3b.** 4 Days (92%), oil (Found: C, 52.1; H, 7.8; N, 8.1).  $C_{15}H_{26}O_5N_2S$  requires C, 52.00; H, 7.56; N, 8.09%;  $\delta_H(\text{CDCl}_3)$  3.65 (16 H, s), 3.77 (8 H, s), 6.38 (1 H, d, *J* 5.0) and 7.05 (1 H, d, *J* 5.0);  $\delta_C(\text{CDCl}_3)$  52.3, 68.7, 70.5, 70.6, 70.8, 105.7, 139.5 and 170.7.

**16-(Benzothiazol-2-yl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane 3c.** 4 Days (99%), oil (Found: C, 57.3; H, 7.2; N, 6.9).  $C_{19}H_{28}O_5N_2S$  requires C, 57.55; H, 7.12; N, 7.07%;  $\delta_H(\text{CDCl}_3)$  3.53 (16 H, s), 3.72 (8 H, s) and 6.80–7.53 (4 H, m);  $\delta_C(\text{CDCl}_3)$  52.3, 69.1, 70.8, 71.0, 118.8, 120.5, 120.9, 125.8, 130.9, 153.2 and 167.9.

**16-(Benzoxazol-2-yl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane 3d.** 4 Days (96%), mp 53–54 °C (Found: C, 59.7; H, 7.6; N, 7.2).  $C_{19}H_{28}O_6N_2$  requires C, 59.99; H, 7.42; N, 7.36%;  $\delta_H(\text{CDCl}_3)$  3.60 (16 H, s), 3.75 (8 H, m) and 6.72–7.33 (4 H, m);  $\delta_C(\text{CDCl}_3)$  69.5, 70.7, 70.9, 108.6, 116.0, 120.1, 123.8, 143.6, 149.0 and 162.4.

**16-(6-Chloropyridazin-3-yl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane 3e.** 4 Days (89%), oil (Found: C, 51.1; H, 6.9; N, 11.4).  $C_{16}H_{26}O_5N_3Cl$  requires C, 51.13; H, 6.97; N, 11.18%;  $\delta_H(\text{CDCl}_3)$  3.58 (16 H, s), 3.74 (8 H, m), 6.87 (1 H, d, *J* 9.8) and 7.06 (1 H, d, *J* 9.8);  $\delta_C(\text{CDCl}_3)$  50.3, 69.3, 70.9, 114.9, 128.2, 145.7 and 158.2.

**16-(Pyrimidin-2-yl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane 3f.** 4 Days (97%), oil (Found: C, 56.2; H, 8.2; N, 12.3).  $C_{16}H_{27}O_5N_3$  requires C, 56.29; H, 7.97; N, 12.31%;  $\delta_H(\text{CDCl}_3)$  3.58–3.94 (16 H, s + m), 6.34 (1 H, t, *J* 4.6) and 8.17 (2 H, d, *J* 4.6);  $\delta_C(\text{CDCl}_3)$  48.7, 69.4, 70.7, 70.8, 71.0, 109.3, 157.5 and 161.6.

**16-(5-Trifluoromethyl-2-pyridyl)-1,4,7,10,13-pentaoxa-16-**

**azacyclooctadecane 3g**, 4 Days (92%), oil (Found: C, 52.7; H, 6.6; N, 6.9.  $C_{18}H_{27}O_5N_3F_3$  requires C, 52.94; H, 6.66; N, 6.86%);  $\delta_H$ ( $CDCl_3$ ) 3.63 (16 H, s), 3.70–3.84 (8 H, m), 6.58 (1 H, d,  $J$  9.0), 7.52 (1 H, dd,  $J$  2.8, 9.0) and 8.28 (1 H, br s);  $\delta_C$ ( $CDCl_3$ ) 50.0, 69.3, 70.9, 105.2, 114.2 ( $J_{CF}$  33), 125.1 ( $J_{CF}$  270), 134.0, 145.8 and 159.8.

#### Extraction experiment

Competitive extraction experiments were carried out as follows. A methylene chloride solution of the crown ether (0.015 mmol, 1.5  $cm^3$ ) was added to an aqueous solution of metal perchlorates (0.015 mmol, 1.5  $cm^3$  of each). After the mixture had been stirred for 2 h, the aqueous phase was separated. The concentrations of metal cations were determined by atomic absorption or flame spectroscopic methods (performed at Exlan Technical Center Co., Okayama).

#### Transport experiments

Transport experiments were performed at room temperature (ca. 20 °C) in a U-tube glass cell (2.0 cm i.d.).<sup>2a</sup> The carrier, dissolved in methylene chloride, was placed in the base of the U-tube, and two aqueous phases were placed in the tube arms, floating on the organic membrane phase. The membrane phase was constantly (50 rpm) stirred with a magnetic stirrer (MS magnetic stirrer). The transport rates indicated in Table 2 were calculated from the initial rates of appearance of co-transported  $ClO_4^-$  anion into the Aq. 2 phase, which was determined by a  $ClO_4^-$  ion-selective electrode (Orion EA940 Autochemistry System). The amount of each metal cation transported was also determined by atomic absorption or flame spectroscopic method (Shimadzu AA-630-12 Atomic Absorption/Flame Emission Spectrophotometer), and was nearly equal to that of the co-transported anion. It was confirmed that all guest salts were hardly transported at all in the absence of a carrier (transport rate  $< 0.3 \times 10^{-6}$  mol  $h^{-1}$ ).

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