Synthesis and Metal Ion Complexation Studies of Proton-Ionizable Calix[4]azacrown Ethers in the 1,3-Alternate Conformation

Jong Seung Kim,*[,†] Ok Jae Shon,[†] Jong Won Ko,[‡] Moon Hwan Cho,[‡] Ill Yong Yu,[†] and Jacques Vicens[§]

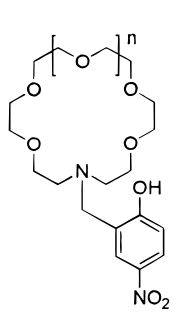
Department of Chemistry, Konyang University, Nonsan 320-711, Korea, Department of Chemistry, Kangwon National University, Chuncheon 200-701, Korea, and Ecole Europeenne de Chimie Polymeres et Materiaiaux (ECPM), 25, rue Becquerel, Strasbourg, F-67087 Cedex, France

Received August 10, 1999

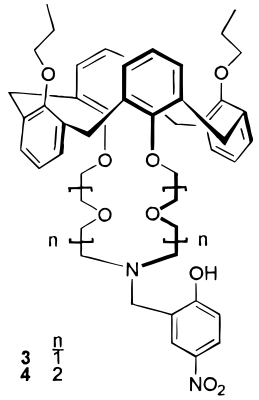
A series of novel *N*-chromogenic calix[4]arene azacrown ethers were synthesized as selective extractants of potassium ion. 1,3-Alternate calix[4]arene azacrown ethers were prepared by reacting 25,27-dipropyloxy-26,28-bis(5-chloro-3-oxapentyloxy) calix[4]arenes with *p*-toluenesulfonamide in the presence of potassium carbonate. The coupling reaction of calix[4]arene azacrown ether with 2-hydroxy-5-nitrobenzyl bromide in the presence of triethylamine in THF gave the chromogenic calix[4]arene azacrown ether in moderate yield. These compounds show high potassium selectivity over other metal ions as shown by two-phase extraction, bulk liquid membrane, and ^{1}H NMR studies on a ligand−metal complex. It is assumed that the OH of the chromogenic group attached on nitrogen can assist the complexation by encapsulation of the metal.

Introduction

Azacrown ethers are often used as precursors for structurally modified macrocyclic ion-complexing agents due to the attachment of pendant groups to the secondary nitrogen atom. Most often, pendant groups such as carboxylic acid,[1−4] chromogenic,[1] and fluorogenic groups[5] are involved in the metal ion-binding process that is centered within the macrocyclic polyether ring and alter the complexation behavior relative to that of the parent crown ether.[6,7] The use of chromogenic moieties to evaluate metal ion complexation by crown ethers was introduced by Pedersen early in the development of crown ether chemistry.[8,9] In his method, the concentration of picrate anion extracted from an aqueous phase into an organic layer using crown ether was determined by UV spectrophotometry. One of the primary goals in designing spectrophotometric reagents for the determination of metal ions is their potential use in clinical diagnostic instruments.[10] For this purpose, instead of using chromogenic anion extraction during metal ion extraction for the determination of metal ions, several researchers have developed crown ethers with a chromogenic moiety covalently attached to the crown ether structure.[11] Phenolic groups are widely used as proton-ionizable substituents.[12] Phenol-containing lariat azacrown ethers have been shown to be able to selectively extract cations from water into an organic phase. For instance, *N*-(2-hydroxy-5-nitrobenzyl)-aza-15-crown-5 (**1**) and *N*-(2-hydroxy-5-nitrobenzyl)-aza-18-crown-6 (**2**) were synthesized, and the extractability of alkali metal ions was measured. Compound **1** showed Li^+ selectivity whereas **2** showed K^+ selectivity due to size agreement between the metal ion and the cavity of the corresponding azacrown ether.[13]



1 n = 0
2 n = 1



3 n = 1
4 n = 2

Calix[4]arenes have been shown to be useful 3-D molecular building blocks for the synthesis of receptors with specific properties.[14] They can exist in four different conformations: cone, partial cone, 1,2-alternate, and 1,3-alternate.[15,16] Calixcrown ethers have also attracted intense interest as cesium-selective extractants. It has been reported that 1,3-dialkoxycalix[4]arene crown-6 derivatives are exceptionally selective ionophores for cesium ion due to the complexation of cesium ion not only with the crown ether but also with the two aromatic rings

* To whom correspondence should be addressed.
† Konyang University.
‡ Kangwon National University.
§ Ecole Europeenne de Chimie Polymeres et Materiaiaux.

(1) Takagi, M.; Ueno, K. *Top. Curr. Chem.* **1984**, *121*, 39.
(2) Sink, R. M.; Buster, D. C.; Sherry, A. D. *Inorg. Chem.* **1990**, *29*, 3645.
(3) Delgado, R.; Frasto da Silva, J. J. R. *Talanta* **1982**, *29*, 815.
(4) Reisen, A.; Zehnder, M.; Kaden, T. A. *J. Chem. Soc., Chem. Commun.* **1985**, 1336.
(5) Löhr, H.-G.; Vögtle, F. *Acc. Chem. Res.* **1985**, *18*, 65.
(6) Tsukube, H.; Adachi, H.; Morosawa, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 89.
(7) Inoue, Y.; Ouchi, M.; Hosoyama, K.; Hakushi, T.; Liu, Y.; Takeda, Y. *J. Chem. Soc., Dalton Trans.* **1991**, 1291.
(8) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495.
(9) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.
(10) Czech, B. P.; Gebauer, C. R.; Kumar, A.; Sy-Icaza, S.; Barczak, C.; Chapoteau, E.; Babb, D. A.; Czech, A.; Bartsch, R. A. *Clin. Chem.* **1986**, *32*, 1173.
(11) Vögtle, F.; Weber, E. In *Host−Guest Complex Chemistry, Macrocycles*; Springer-Verlag: Berlin, 1985; pp 84, 90, 189, 217.
(12) (a) McDaniel, C. W.; Bradshaw, J. S.; Izatt, R. M. *Heterocycles* **1990**, *30*, 665. (b) Nakamura, H.; Sakka, H.; Takagi, M.; Ueno, K. *Chem. Lett.* **1981**, 1305.

10.1021/jo9912754 CCC: $19.00
Published on Web 03/28/2000

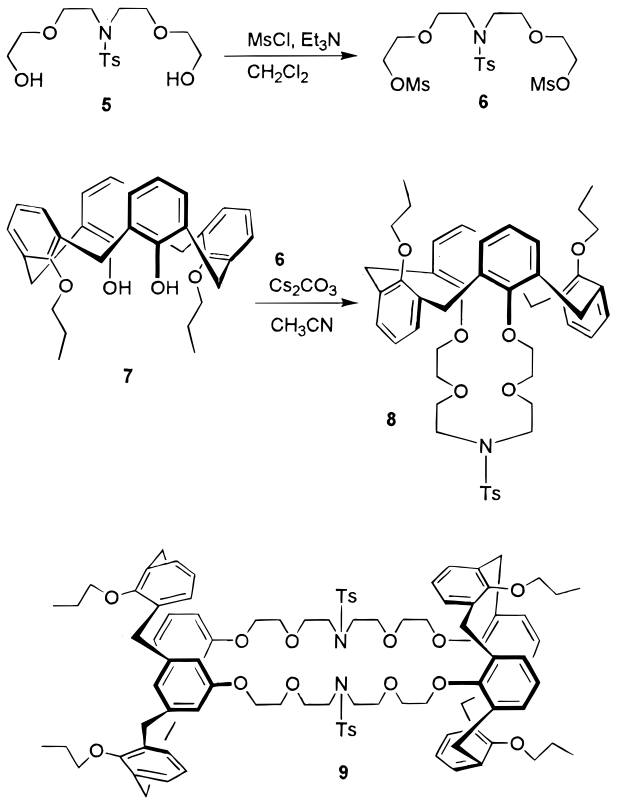
(cation/π-interaction) when fixed in the 1,3-alternate conformation.[17−21]

From this point of view, it is possible that the combination of *N*-chromogenic azacrown ether and calixcrown ether would result in an optimized structure for metal ion encapsulation due to (1) electrostatic interactions between the metal ion and both the oxygens and a nitrogen as electron donors, (2) π-metal interactions between the metal ion and two rotated aromatic nuclei of the 1,3-alternate calixarene, and (3) an extra pendant chromogenic group attached to nitrogen, which can promote metal complexation by 3-D encapsulation under basic conditions. With this in mind, we sought to synthesize chromogenic calixazacrown ethers and to investigate their complexation behavior toward alkali metal ions through bulk liquid membrane, solvent extraction, and ^{1}H NMR studies.

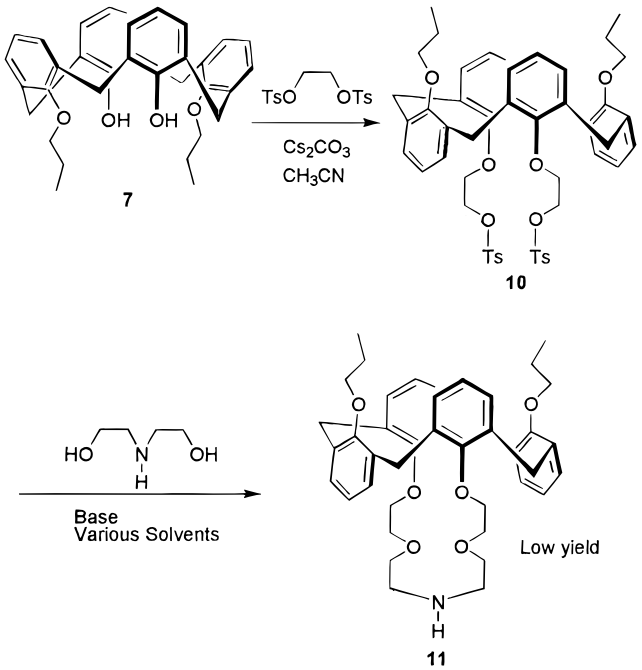
Results and Discussion

Scheme 1 shows our first approach to receptor **8**. *N*-Tosyl tetraethylene glycol **5** was prepared in good yield by reacting *p*-toluenesulfonamide with 2-(2-chloroethoxy)-ethanol in the presence of K_2CO_3 in DMF.[22] Glycol **5** was further transformed into dimesylate **6** by reaction with mesyl chloride in the presence of NEt_3 in CH_2Cl_2. 1,3-Dipropyl calix[4]arene **7** in a cone conformation was synthesized by reacting calix[4]arene with 1-iodopropane using K_2CO_3 in refluxing acetonitrile. 1,3-Dipropyl calix-[4]arene **7** was then reacted with dimesylate **6** in the presence of Cs_2CO_3 according to a "cesium effect" occurring in cyclization.[23] Surprisingly, under our experimental conditions we isolated biscalixarene **9** instead of the desired 1,3-bridged calix[4]arene **8**. The dimeric structure

Scheme 1. Proposed Synthetic Route for Compound 8



Scheme 2. Alternate Synthetic Method for Calix[4]arene Azacrown Ether 11



of **9** was confirmed by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. We then decided to use a different pathway (see Scheme 2) to receptor **11**. 1,3-Dipropyl calix[4]arene **7** was first reacted with ethylene glycol ditosylate in refluxing acetonitrile in the presence of Cs_2CO_3. The product calixarene **10** was shown to be in the 1,3-alternate conformation. Compound **10** was reacted with diethanolamine in the presence of NaH to afford 1,3-dipropyl calix[4]azacrown **11** in only 10% yield. The use

(13) (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) Gutsche, C. D. In *Synthesis of Macrocycles: Design of Selective Complexing Agents*; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1987; p 93. (c) *Calixarenes: A Versatile Class of Macrocyclic Compounds;* Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991. (d) Böhmer, V.; McKervey, M. A. *Chemie in unserer Zeit* **1991**, 195. (e) Gutsche, C. D. C*alixarenes, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, U. K., 1989; Vol. 1. (f) Gutsche, C. D. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Oxford University Press: New York, 1991; Vol. 4, pp 27−63. (g) Van Loon, J.-D.; Verboom, W.; Reinhoudt, D. N. *Org. Prep. Proc. Int.* **1992**, *24*, 437−462. (h) Ungaro. R.; Pochini, A. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Eds.; VCH: Weinheim, Germany, 1991; pp 57−81.

(14) Andreetti, G. D.; Ugozzoli, F.; Ungaro, R.; Pochini, A. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Oxford University Press: New York, 1991; Vol. 4, pp 64−125.

(15) Casnati, A.; Pochini, A.; Ungaro, R.; Ugozzoli, F.; Arnaud, F.; Fanni, S.; Schwing, M.-J.; Egberink, R. J. M.; de jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 2767.

(16) Kim, J. S.; Suh, I. H.; Kim, J. K.; Cho, M. H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2307.

(17) Kim, J. S.; Ohki, A.; Ueki, R.; Ishizuka, T.; Shimotashiro, T.; Maeda, S. *Talanta* **1999**, *48*, 705−710.

(18) Kim, J. S.; Ohki, A.; Cho, M. H.; Kim, J. K.; Ra, D. Y.; Cho, N. S.; Bartsch, R. A.; Lee, K. W.; Oh, W. Z. *Bull. Kor. Chem. Soc.* **1997**, *18*, 1014.

(19) Kim, J. S.; Lee, W. K.; Ra, D. Y.; Lee, Y. I.; Choi, W. K.; Lee, K. W.; Oh, W. Z. *Microchem. J.* **1998**, *59*, 464.

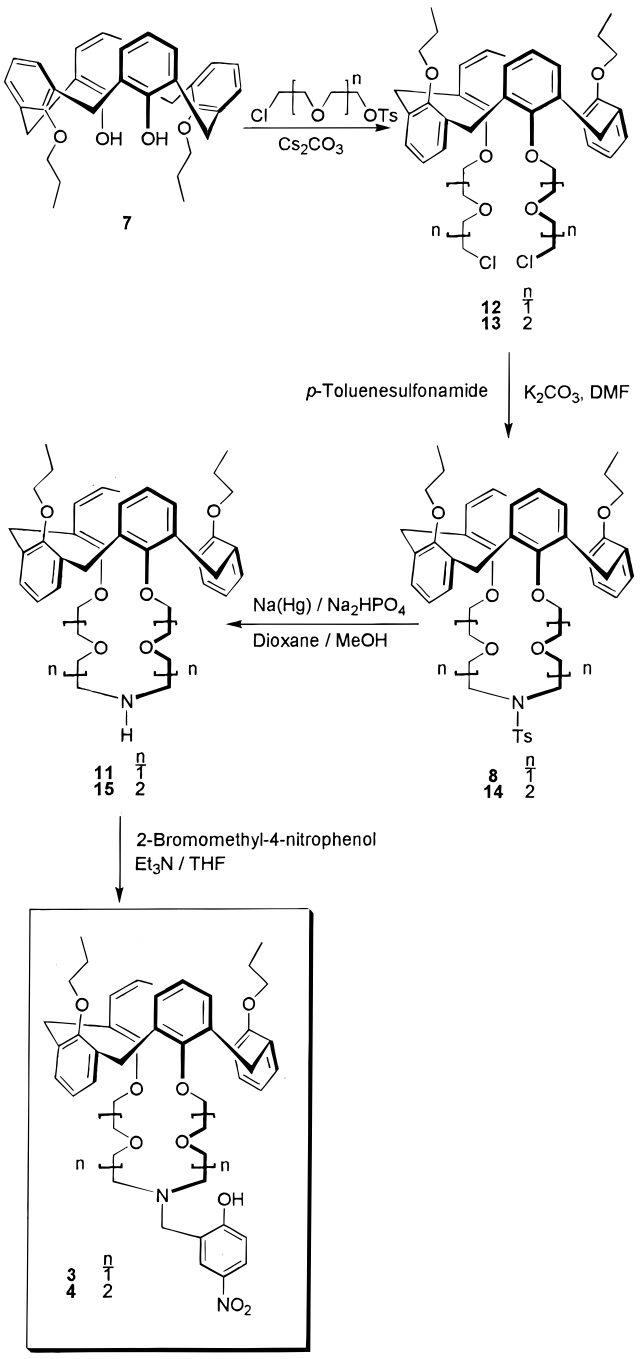
(20) Kim, J. S.; Pang, J. H.; Yu, I. Y.; Lee, W. K.; Suh, I. H.; Kim, J. K.; Cho, M. H.; Kim, E. T.; D. Y. Ra. *J. Chem. Soc., Perkin Trans. 2* **1999**, *837*.

(21) Kruizinga, W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 5183.

(22) Anelli, P. L.; Montanari, F.; Quici, S.; Ciani, G.; Sironi, A. *J. Org. Chem.* **1988**, *53*, 5292. (The reaction conditions are similar, but the workup and purification processes are somewhat different.)

(23) Gokel, G. W.; Garcia, B. J. *Tetrahedron. Lett.* **1977**, *4*, 317.

Scheme 3. Synthetic Scheme for Chromogenic Calix[4]arene Azacrown Ethers 3 and 4



of different bases (K_2CO_3, Cs_2CO_3) in various solvents (DMF, acetonitrile, THF) did not improve the yields.

Interestingly, we found that the best way to prepare cyclization products **8** and **14** was as indicated in Scheme 3. First alkylation of compound **7** with monotosylates gave tetraalkylated calix[4]arenes **12** and **13**, respectively, which are blocked in a 1,3-alternate conformation based on the ^{1}H NMR spectra ($CDCl_3$), which show a singlet peak at δ 3.70 for the bridging methylene hydrogens of the calix[4]arene framework. The ^{13}C NMR spectra for these compounds reveal one signal around 38.0 ppm, which is characteristic of the 1,3-alternate conformation. Cyclization of **12** and **13** using *p*-toluenesulfonamide in the presence of K_2CO_3 in DMF provided the desired products **8** and **14**, respectively, in moderate yield (see Experimental Section). The NMR spectra of **8** and **14** are consistent with those expected for the 1,3-alternate conformations. The use of Cs_2CO_3 as a base for this cyclization gave a lower yield than with K_2CO_3. For detosylation, sodium−mercury amalgam in a mixture of 1,4-dioxane and methanol provided **11** and **15** in good yield. A chromogenic pendant arm was attached to the nitrogens of **11** and **15** using 2-bromomethyl-4-nitrophenol in the presence of triethylamine to give final products **3** and **4**, respectively, in quantitative yield after reaction at room temperature. The synthesis of **11** and its analogues as mentioned above allows us to synthesize *N*-substituted calix[4]arene azacrown ethers for further synthesis and complexation studies.

The ratio of ligand **3** to potassium ion was assessed by high-resolution mass spectrometry. Ionophore **3** was reacted with potassium picrate in chloroform. The molecular ion peak (M + 1) for **3** occurred at *m*/*z* 817.3, and the parent ion peak appeared at *m*/*z* 855.2, which corresponds to a 1:1 complex of **3**·K^+. No other mass fragmentation (e.g., 1:2 or 2:1) complexes were observed.

Complexation selectivity was initially measured by ^{1}H NMR spectroscopy, as shown in Figure 1. Ligand **3** was chosen to investigate NMR behavior because it showed the best selectivity for potassium ion in bulk liquid membrane and solvent extraction experiments. Compound **3** is blocked in a 1,3-alternate conformation based on its NMR spectrum (A, Figure 1): a singlet peak at δ 3.84 in ^{1}H NMR for bridging four methylene hydrogens (Ar−CH_2−Ar) and one signal at 38.8 ppm in the ^{13}C NMR spectrum for bridging methylene carbons (Ar−CH_2−Ar). In the case of ligand−metal picrate complex, the NMR spectral patterns changed remarkably with respect to splitting and chemical shift, as indicated in Figure 1. First, in the case of **3**·Na^+ (spectrum B), no peaks were observed for picrate anion or complexed ligand. All of the peaks are identical to those of the parent ligand **3**, indicating that complexation with Na^+ did not occur. Interestingly, **3**·K^+ (spectrum C) gave rise to remarkable changes in both chemical shift values and splitting patterns.

The area under a picrate anion peak at δ 8.84 was 87% of that of the parent ligand, implying that 87% of the ligand−metal ion complex was formed in chloroform. This percentage was confirmed by changes in the chemical shift of bridged −CH_2− (δ 4.01) between azacrown and nitrophenol units as well as those of protons for −CH_2CH_2N− (δ 2.66). In addition, a multiplet pair of −$OCH_2CH_2CH_3$ at δ 1.21−1.15 and a triplet pair of −$OCH_2CH_2CH_3$ at δ 0.71 were shifted downfield to δ 1.51 and 1.83, respectively, which indicates strong complexation with potassium ion. In the case of **3**·Rb^+ (spectrum D), about 60% complexation was calculated from the change in the chemical shift and integration of the shifted peak. For **3**·Cs^+ (spectrum E), a tiny peak of the picrate and no significant changes in the chemical shift were observed, which indicate no complexation with cesium ion. A singlet at 3.80 ppm corresponding to ArCH_2Ar was split into a multiplet in the case of complexation with potassium and rubidium ion due to a loss of symmetry. This potassium-selective response in NMR with respect to changes in the chemical shift and peak splitting are in good agreement with the results of two-phase extraction and selective metal ion transport experiments (vide infra).

Metal-binding properties were estimated using UV−vis absorption spectroscopy. Two-phase extractions were

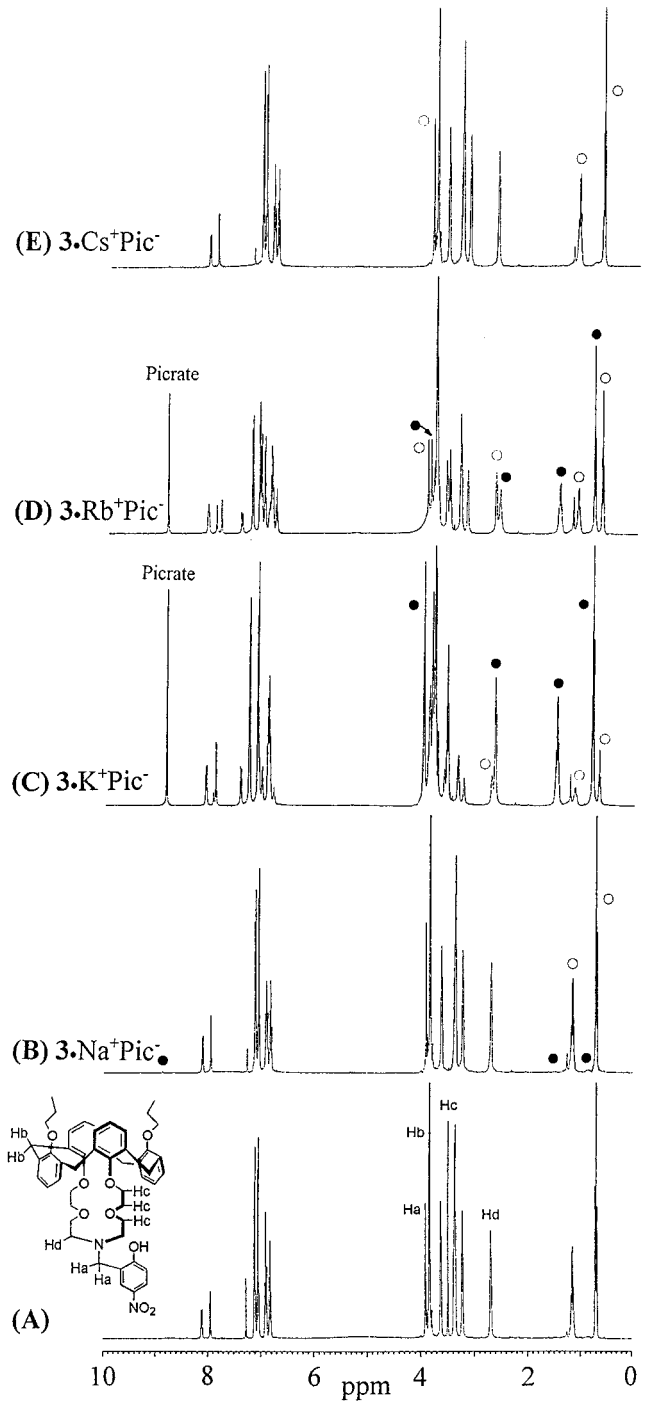


Figure 1. ^{1}H NMR spectra of **3** (A) and **3**M^+Pic^- (B−E) in $CDCl_3$. Closed (●) and open (○) circles are for complexed and uncomplexed ligand, respectively.

carried out using various organic ligands with a nitrophenol unit as a chromogenic sidearm. The proton-ionizable chromogenic calixarene can extract certain cations from a basic aqueous phase to an organic phase by complexation. Upon complexation, calixarene azacrown ether undergoes proton-dissociation on the pendant phenolic group of the chromophores to yield an anion which in turn interacts intramolecularly with a metal ion complexed by the azacrown ether moiety.[25] The ability of the calixarene azacrown ether to extract metal ion can be estimated by UV-spectral changes. In this extraction experiment, the pH of the aqueous phase was varied from 7 to 13 using tetramethylammonium hydroxide. Under neutral conditions, no significant changes in the UV spectra were observed. The most selective and distinctive UV band was observed with pH 12, as shown in Figure 2. Significant bathochromic shifts from 326 nm (parent ligand only) to 428 nm (phenoxide band) were observed upon ligand−metal complexation. In addition, for K^+, a very prominent hyperchromic shift was observed, indicating that the potassium ion is selectively encapsulated by the azacrown cavity, assisted by the simultaneous attachment of a nitrophenoxy to nitrogen. There were no detectable spectral changes upon the extraction of Na^+.

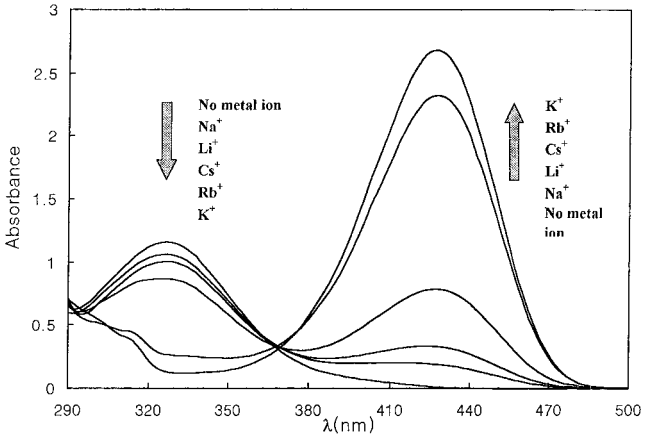


Figure 2. Metal ion-dependent changes in the UV spectrum of calixazacrown ether **3**.

Table 1. Solvent Extraction Results for Alkali Metal Ions Using Various Organic Ligands[a]

	extractability %[b]				
compound	$Lsti^+$	Na^+	K^+	Rb^+	Cs^+
1	36.05	14.19	17.55	19.89	5.41
2	9.79	10.74	65.56	26.01	9.01
3	17.44	3.57	32.24	25.47	1.57
4	7.45	5.95	30.59	13.81	10.42

[a] Source phase (aqueous solution of metal nitrate, 3 mL), MNO_3 = 1.2 mM, pH =12 adjusted by tetramethylammonium hydroxide; organic phase ($ClCH_2CH_2Cl$, 3 mL), (carrier) = 0.1 mM. [b] Extractability = (concentration of extracted metal)/(concentration of organic ligand) × 100%: the average value of three independent determinations.

Two-phase extraction experiments using various ligands were carried out, and the results are described in Table 1. pH-dependent extraction was also carried out. Under neutral conditions, a small amount of metal ion was extracted, but no selectivity was observed. At pH 12, the selectivity for potassium ion was greater than those for other alkali metal ions. An increase in the ring size of the azacrown ether (n = **1** → **2**) enhanced both K^+/Na^+ and K^+/Cs^+ selectivity, indicating that the ring size agreed with the size of the potassium ion. For calixarene **3**, extractability was not as high as that with **2**, but the selectivities toward K^+/Na^+ and K^+/Cs^+ were increased. As indicated earlier, for **4** the cavity is too large to accept the potassium ion, resulting in decreased extractability.

We also used a bulk liquid membrane to measure transport rates of metal ions from an aqueous source phase into an aqueous receiving phase through an

(24) Kimura, K.; Tanaka, M.; Iketani, S.; Shono, T. *J. Org. Chem.* **1987**, *52*, 836.
(25) Bartsch, R. A.; Yang, I. W.; Jeon, E. G.; Walkowiak, W.; Charewicz, W. A. *J. Coord. Chem.* **1992**, *27*, 75.

Table 2. Single Ion Transport Values for Alkali Metal Ions through a Bulk Liquid Membrane Using Various Organic Ligands[a]

	transport rate (10^{-8} mol·s^{-1}·m^{-2})[b]				
compound	Li^+	Na^+	K^+	Rb^+	Cs^+
2	92.54	99.99	75.38	115.31	109.17
11	0.00	4.20	128.55	117.82	19.89
3	248.75	9.87	172.11	134.21	160.74

[a] Transport conditions: source phase (aqueous solution of metal hydroxide, 0.8 mL, 0.1 M); membrane phase ($ClCH_2CH_2Cl$, 3.0 mL), (carrier) = 1.0 mM; i.d. of glass vial = 18 mm, stirred by 13 mm Teflon-coated magnetic stirring bar driven by a Hurst Synchronous motor; receiving phase (0.1 M aqueous HNO_3, 5.0 mL). [b] The average value of three independent determinations. The experimental values deviate from the reported values by an average of 10%.

Table 3. Competitive Transport Rate of Alkali Metal Ions through a Bulk Liquid Membrane Using Various Organic Ligands[a]

	transport rate (10^{-8} mole·s^{-1}·m^{-2})[b]	
compound	$K^+/Li^+/Na^+$	$K^+/Rb^+/Cs^+$
2	18.35/0.00/9.72	25.16/3.10/0.45
11	60.92/0.00/6.59	45.50/49.11/3.81
3	125.65/0.00/2.88	22.10/10.26/0.59
4	12.39/0.00/4.01	11.32/16.39/35.09

[a] Transport conditions: same as Table 1 except that the source phase (0.8 mL) is composed of 0.034 M of each metal hydroxide and 0.066 M of the corresponding metal nitrate. [b] The average value of three independent determinations. The experimental values deviate from the reported values by an average of 10%.

organic bulk membrane. The source and receiving phases consist of 0.8 mL of 0.1 M alkali metal hydroxide and 5.0 mL of 0.1 M HNO_3, respectively. Organic medium consists of a solution of 3.0 mL of 1.0 mM ligand in 1,2-dichloroethane. The measured flux values from a single transport experiment in bulk liquid membrane are shown in Table 2. For **11**, stirring for 24 h at room temperature gave transport rates of 0.00, 4.20, 128.55, 117.82, and 19.89 (unit: 10^{-8} mol s^{-1} m^{-2}) for Li, Na, K, Rb, and Cs ion, respectively, indicating potassium selectivity. No transport of lithium ion was observed. However, attachment of the nitrophenol group as a pendant group to a *N*-azacrown framework enhanced the lithium transport rate. It has been reported that the nitrophenol unit is well matched with lithium ion under pH conditions high enough for OH to be deprotonated.[12] Compound **3** shows high potassium selectivity over sodium ion, but a large amount of lithium ion was also transported. A competitive ion transport experiment, which is the most applicable in an industrial setting, provides high potassium selectivity, as shown in Table 3 i.e., lithium ion is not easily encapsulated into the calixarene cavity in the presence of potassium ion. This potassium selectivity is increased in the case of **3** suitable for potassium ion. For **4**, a slow transport rate was observed for all of the alkali metal ions. This may be due to the fact that the large-cavity azacrown has to undergo considerable folding/twisting to bring the binding sites into close proximity with the cation, and such ordering would be entropically unfavorable. High potassium ion selectivity in this single and competitive ion transport indicates that the ring size of an azacrown cavity containing a calix[4]arene network agrees well with the diameter of potassium ion. In this study, for potassium selectivity, we assume a mechanism similar to that proposed by Reinhoudt,[16] where the complexed ion interacts not only with the azacrown ether moiety but also with two aromatic nuclei (cation/π-interaction) in the 1,3-alternate conformation.

In conclusion, calix[4]arene azacrown ethers were synthesized with moderate yield in a 1,3-alternate conformation. Attachment of a proton-ionizable group as a pendant unit onto the nitrogen of the calix[4]arene azacrown framework was also successful. Complexation studies by ^{1}H NMR, two-phase extraction, and bulk liquid membrane were carried out to give high potassium ion selectivity. This potassium selectivity may be due to electrostatic interaction between the metal ion and the polyether cavity composed of oxygens and nitrogen as electron donors, and π-metal interaction between the metal ion and two aromatic rings of the 1,3-alternate calixarene. In addition, an extra pendant chromogenic nitrophenol group attached to nitrogen may play a role in this metal complexation by encapsulation under basic conditions.

Experimental Section

Unless specified otherwise, reagent-grade reactants and solvents were obtained from chemical suppliers and used as received. Dry solvents were prepared as follows: tetrahydrofuran was freshly distilled from sodium metal ribbon or chunks; benzene and pentane were stored over sodium ribbon, respectively. Acetonitrile was dried over molecular sieves (3 Å) and distilled over diphosphorus pentaoxide. DMF was dried over 4 Å molecular sieves. Compounds **1**,[12] **2**,[12] and **7**[17] were prepared according to methods described in the literature.

Synthesis. *N*-(2-Hydroxy-5-nitrobenzyl)-25,27-bis-(1-propyloxy)calix[4]arene Azacrown-5 (3), 1,3-Alternate. Under nitrogen, to a solution of 1.0 g (1.51 mmol) of calix[4]-arene azacrown ether (**11**) and 0.24 mL (3.31 mmol) of triethylamine in 100 mL of THF was added dropwise 0.38 g (1.6 mmol) of 2-bromomethyl-4-nitrophenol over 30 min at 0 °C. Upon complete addition, the reaction solution was stirred for 8 h at 0 °C, and then stirred for an additional 6 h at 65 °C. Removal of THF in vacuo gave a yellow oil. The crude product was extracted several times with CH_2Cl_2 (100 mL) and water (100 mL). Column chromatography using ethyl alcohol/ethyl acetate (v/v) = 1:1 as an eluent on silica gel gave the desired product as a yellow solid in 73% yield. Mp 150−152 °C. IR (deposit, cm^{-1}): 3358 (O−H). FAB MS *m/z* (M^+) calcd 816.20, found 816.48. Anal. Calcd for $C_{49}H_{56}N_2O_9$: C, 72.05; H, 6.86. Found: C, 72.12; H, 6.76.

***N*-(2-Hydroxy-5-nitrobenzyl)-25,27-bis-(1-propyloxy)-calix[4]arene Azacrown-5 (4), 1,3-Alternate.** Compound **4** was prepared almost the same as for **3** and isolated as a yellow oil in 75% yield. IR (neat, cm^{-1}): 3345 (O−H). FAB MS *m/z* (M^+) calcd 904.12, found 904.48. Anal. Calcd for $C_{53}H_{64}N_2O_{11}$: C,67.69; H, 7.07. Found: C, 67.71; H, 7.11.

***N,N*-Bis[2-(2-hydroxyethoxy)ethyl]-*p*-toluenesulfonamide (5).**[22] Under nitrogen, a solution of K_2CO_3 (10.49 g, 0.076 mol) and 2-(2-chloroethoxy)ethanol (9.46 g, 0.076 mol) in 70 mL of predried DMF was refluxed for 1 h. *p*-Toluenesulfonamide (5.0 g, 0.029 mol) in 20 mL of dried DMF was added dropwise for 1 h, and the reaction mixture was then refluxed for an additional 4 h. After a white precipitate was filtered, removal of DMF in vacuo gave a brownish oil. One hundred milliliters of $NaHCO_3$ and 100 mL of CH_2Cl_2 were added. The organic layer was separated and washed twice with brine. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, and evaporated in vacuo to give an oil. Column chromatography on silica gel with ethyl acetate:hexane (1:1) as an eluent (R_f = 0.2) provided 6.43 g (68% yield) of the desired product as a colorless oil. IR (neat, cm^{-1}): 3400 (O−H), 1334 (SO_2), 1153 (SO_2).

***N,N*-Bis[2-[2-[(methylsulfonyl)oxy]ethoxy]ethyl]-*p*-toluenesulfonamide (6).**[22] A solution of **5** (2.0 g, 5.76 mmol) and triethylamine (3.99 mL, 28.78 mmol) in 50 mL of CH_2Cl_2 was cooled to 0 °C. Methanesulfonyl chloride (1.7 mL, 23.02 mmol) dissolved in 10 mL of CH_2Cl_2 was added dropwise over

30 min. The reaction temperature was raised to 25 °C, and the mixture was stirred for an additional 2 h to complete the reaction. One hundred milliliters of ice−water was added carefully, and the organic solution was separated and washed with 5% $NaHCO_3$ (100 mL × 2) and brine (100 mL × 2). The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, and evaporated in vacuo to give an oil. Recrystallization using 50 mL of diethyl ether gave **6** as a white solid in 68% yield. Mp 102−103 °C. IR (KBr pellet, cm^{-1}): 1350 (SO_2), 1181 (SO_2), and 1124 (C−O).

***N*-Tosyl 25,27-Bis(1-propyloxy)calix[4]arene Azacrown-5 (8).** Under nitrogen, to a three-neck round-bottom flask were added K_2CO_3 (0.96 g, 6.95 mmol), 30 mL of predried DMF, **12** (1.00 g, 1.38 mmol), and *p*-toluenesulfonamide (0.23 g, 1.38 mmol), and the mixture was refluxed for 24 h. DMF was completely removed in vacuo, and 100 mL of 10% aqueous $NaHCO_3$ solution and 100 mL of CH_2Cl_2 were added. The organic layer was separated and washed with water (50 mL × 2), dried over $MgSO_4$, and then filtered. Evaporation of CH_2Cl_2 in vacuo gave a yellowish oil which was purified by column chromatography (R_f = 0.3) using ethyl acetate:hexane (1:8) to provide 0.9 g (72%) of **8** as a white solid. Mp 168−171 °C. IR (KBr pellet, cm^{-1}): 1340 (SO_2), 1092 (SO_2). FAB MS *m*/*z* (M^+) calcd 819.2, found 820.3. Anal. Calcd for $C_{49}H_{57}NO_8S$: C, 71.79; H, 6.96. Found: C, 71.52; H, 6.94.

Doubly 25,27-Bis(1-propyloxy)calix[4]arene Azacrown Ether (9), 1,3-Alternate. Under nitrogen, a solution of 1,3-dipropyloxy calix[4]arene **7** (1.59 g, 2.91 mmol), **6** (0.99 g, 1.97 mmol), and Cs_2CO_3 (3.2 g, 9.83 mmol) in 50 mL of acetonitrile was refluxed for 24 h. The mixture was cooled to room temperature, and excess Cs_2CO_3 was filtered out. The acetonitrile was removed in vacuo, and 50 mL of water and 50 mL of CH_2Cl_2 were then added. The organic layer was separated and washed sequentially with 10% aqueous $NaHCO_3$ solution and 100 mL of water. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, and evaporated in vacuo to give an oil. Column chromatography on silica gel with ethyl acetate:hexane (1:3) as an eluent (R_f = 0.5) provided a solid which could be recrystallized using 50 mL of diethyl ether to give **9** as a white solid (34% yield). Mp 212−214 °C. IR (KBr pellet, cm^{-1}): 1343 (SO_2), 1096 (SO_2). FAB MS *m*/*z* (M^+) calcd 1562.1, found 1695.1 (ligand Cs^+).

25,27-Bis(2-*p*-toluenesulfonyloxyethyloxy)-26,28-bis(1-propyloxy)calix[4]arene (10), 1,3-Alternate. Under nitrogen, a solution of 1,3-dipropyloxycalix[4]arene **7** (1.0 g, 1.96 mmol), ethyleneglycol di-*p*-toluenesulfonate (1.17 g, 4.1 mmol), and Cs_2CO_3 (1.41 g, 4.3 mmol) in 50 mL of acetonitrile was refluxed for 24 h. After cooling to room temperature, to this reaction mixture were added 50 mL of 10% HCl aqueous solution and 50 mL of CH_2Cl_2. The organic layer was separated and washed twice with 100 mL of 10% $NaHCO_3$ aqueous solution and brine. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, and evaporated in vacuo to give a brownish oil. Column chromatography on silica gel with ethyl acetate:hexane (1:5) as an eluent (R_f = 0.6) provided **10** as a colorless oil in 37% yield. IR (KBr pellet, cm^{-1}): 1451(SO_2), 1192(SO_2). Anal. Calcd for $C_{52}H_{56}O_{10}S_2$: C, 69.02; H, 6.19. Found: C, 69.10; H, 6.26.

25,27-Bis(1-propyloxy)calix[4]arene Azacrown-5 (11), 1,3-Alternate. Under nitrogen, to a solution of 10 mL of 1,4-dioxane and 2 mL of methanol were carefully added 0.37 g (2.56 mmol) of *N*-tosyl 25,27-bis(1-propyloxy)calix[4]arene azacrown-5 (**8**) and 6.0 g of 6% Na(Hg) amalgam. The reaction mixture was refluxed for 2 days at 80 °C. After cooling to room temperature, the solvent was evaporated in vacuo. Fifty milliliters of CH_2Cl_2 and 50 mL of water were added, and the organic layer was separated. The CH_2Cl_2 layer was washed twice with 10% aqueous Na_2HPO_4 solution and then dried over $MgSO_4$. After filtration of magnesium sulfate, removal of the solvent in vacuo gave a yellow oil. Upon recrystallization from 30 mL of diethyl ether, **11** was obtained as a crystalline solid (52% yield). Mp 187−189 °C. IR (KBr pellet, cm^{-1}): 3312 (N−H). FAB MS *m*/*z* (M^+) calcd 665.0, found 665.7. Anal. Calcd for $C_{42}H_{51}NO_6$: C, 75.78; H, 7.67. Found: C, 75.81; H, 7.65.

25,27-Bis(1-propyloxy)-26,28-bis(5-chloro-3-oxapentyloxy)calix[4]arene (12), 1,3-Alternate. A solution of 1,3-dipropyl calix[4]arene **7** (0.92 g, 1.81 mmol), 2-(2-chloroethoxy)-ethanol *p*-toluenesulfonate (1.84 g, 3.62 mmol), and Cs_2CO_3 (1.2 g, 3.62 mmol) in 50 mL of acetonitrile was heated at reflux for 24 h under nitrogen. The reaction mixture was allowed to cool to room temperature, and 100 mL of 10% HCl aqueous solution and 50 mL of CH_2Cl_2 were then added. The organic phase was separated and dried over $MgSO_4$. The organic solution was filtered and then evaporated in vacuo to afford a brownish oil. Column chromatography on silica gel with ethyl acetate:hexane (1:8) as an eluent (R_f = 0.5) provided 0.78 g (60% yield) of **12** as a white solid. Mp 149−151 °C. IR (KBr pellet, cm^{-1}): 1050 (C−O). FAB MS *m*/*z* (M^+) calcd 721.77, found 722.60. Anal. Calcd for $C_{42}H_{50}Cl_2O_6$: C, 69.90; H, 6.93. Found: C, 69.71; H, 6.96.

25,27-Bis(8-chloro-3,6-dioxaoctyloxy)-26,28-bis(1-propyloxy)calix[4]arene (13), 1,3-Alternate. Compound **13** was prepared by almost the same method that used for **12**. 78% yield. Mp 150−154 °C. IR (KBr pellet, cm^{-1}): 1050 (C−O). FAB MS *m*/*z* (M^+) calcd 809.01, found 810.10. Anal. Calcd for $C_{46}H_{58}Cl_2O_8$: C, 68.23; H, 7.17. Found: C, 68.31; H, 7.20.

***N*-Tosyl 25,27-Bis(1-propyloxy)calix[4]arene Azacrown-7 (14), 1,3-Alternate.** Compound **14** was prepared by the method that was used for **8**. 70% yield. Mp 170−172 °C. IR (KBr pellet, cm^{-1}): 1344 (SO_2), 1094(SO_2). FAB MS *m*/*z* (M^+) calcd 907.20, found 907.70. Anal. Calcd for $C_{53}H_{65}NO_{10}S$: C, 7.12; H, 7.16. Found: C, 70.20; H, 7.06.

25,27-Bis(1-propyloxy)calix[4]arene azacrown-7 (15), 1,3-Alternate. Detosylation of **14** was performed according to the method used for **11**. Yellowish oil. 48% yield, IR (neat, cm^{-1}): 3324 (N−H). FAB MS *m*/*z* (M^+) calcd 753.01, found 754.40 (M + 1). Anal. Calcd for $C_{46}H_{59}NO_8$: C, 73.30; H, 7.83. Found: C, 73.41; H, 7.71.

^{1}H NMR of Complex. ^{1}H NMR samples for metal picrate complexes were prepared as follows. A mixture of ligand **3** (20 mg) and excess metal picrate (over at least 5 equiv) in $CHCl_3$ (10 mL) was stirred for 1 h. After filtration of the precipitated metal picrate, the filtrate was dried in vacuo to give a yellow solid complex **3**·M^+Pic^-, which is soluble in $CDCl_3$.

3·Na^+Pic^-: no peak was considerably different from that with free ligand **3**.

3·K^+Pic^-: δ 8.84 (s, 2 H, Pic-*H*), 8.09 (d, 2 H, Ar-*H*), 7.90 (s, 1 H, Pic-*H*), 7.44−6.88 (m, 12 H, Ar-*H*), 4.01 (s, 2 H, NCH_2-Ar), 3.89−3.39 (m, 24 H, OCH_2CH_2O, $OCH_2CH_2CH_3$), 2.66 (s, 4 H, $OCH_2CH_2NCH_2$), 1.53−1.47 (m, 4 H, $OCH_2CH_2CH_3$), 0.70 (t, 6 H, $OCH_2CH_2CH_3$).

3·Rb^+Pic^-: δ 8.84 (s, 2 H, Pic-*H*), 8.09 (m, 3 H, Ar-*H*), 7.42−6.82 (m, 12 H, Ar-*H*), 3.97 (s, 2 H, NCH_2Ar, complexed), 3.92 (s, 2 H, NCH_2Ar, uncomplexed), 3.92−3.36 (m, 24 H, OCH_2CH_2O, $OCH_2CH_2CH_3$), 2.71 (s, 4 H, $OCH_2CH_2NCH_2$, uncomplexed), 2.63 (4 H, $OCH_2CH_2NCH_2$, complexed), 1.52−1.49 (m, 4 H, $OCH_2CH_2CH_3$, complexed), 1.22−1.13 (m, 4 H, $OCH_2CH_2CH_3$, uncomplexed), 0.85 (t, 6 H, $OCH_2CH_2CH_3$, complexed), 0.65 (t, 6 H, $OCH_2CH_2CH_3$, uncomplexed).

3·Cs^+Pic^-: δ 8.12 (d, 2 H, Ar-*H*), 7.62 (s, 1 H, Pic-*H*), 7.12−6.81 (m, 12 H, Ar-*H*), 3.89 (s, 8 H, $ArCH_2Ar$), 3.59 (s, 4 H, OCH_2CH_2O), 3.50−3.31 (m, 8 H, OCH_2CH_2O and $OCH_2CH_2CH_3$), 3.23 (s, 4 H), 2.70 (s, 4 H, $OCH_2CH_2NCH_2$), 1.22−1.13 (m, 4 H), 0.65 (t, 6 H, $OCH_2CH_2CH_3$).

Two-Phase Extraction. Solvent extraction was based on the microextraction technique reported by Bartsch and coworkers.[26] This method is fast and requires only a small amount of organic ligand. An aqueous solution (3.0 mL) of 0.1 mM alkali metal nitrate in 0.01 M tetramethylammonium hydroxide (for pH adjustment) and 0.1 mM (3.0 mL) organic ligand in 1,2-dichloroethane in a 10-mL centrifuge tube were mixed by vortex mixer for 5 min. After centrifugation, a 1.00-mL sample of the aqueous layer was taken, and the concentra-

(26) (a) Gokel, G. In *Crown Ethers & Cryptands*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: London, U. K, 1991; p 81. (b) Lee, S. S.; Jung, J. H.; Yu, S. H.; Cho, M. H. *Thermochim. Acta* **1995**, *259*, 133.

tion of metal ion in the aqueous phase was determined by an atomic absorption spectrometer.

Transport of Alkali Metal Ions in a Bulk Liquid Membrane System. Liquid membrane transport experiments were carried out using a bulk liquid membrane apparatus consisting of a bulk, stirred organic phase that separates the aqueous and receiving phases.[27] The two aqueous phases were separated by a 1,2-dichloroethane phase which constituted the membrane. The details of the transport conditions for single and competitive experiments are summarized in the footnotes of Tables 2 and 3, respectively. Each experiment was repeated three times in a room maintained at 25 ± 1 °C. Three millilters of the aqueous receiving phase was collected, and the flux values (moles transported/s m^2) were determined using a Perkin-Elmer 2380 atomic absorption spectrophotometer. Blank experiments in which no organic ligand was present were performed to determine membrane leakage.

(27) Cho, M. H.; Seon-Woo, K. W.; Hea, M. Y.; Lee, I. C.; Yoon, C. J.; Kim, S. J. *Bull. Kor. Chem. Soc.* **1988**, *9*, 5.

Acknowledgment. This research was fully supported by a Grant from the Korea Research Foundation, Korea (1998-001-D00499).

Supporting Information Available: NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9912754