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A Synthesis and Characterization of New Rigid Calixarene Analogs Capping Crown Ethers

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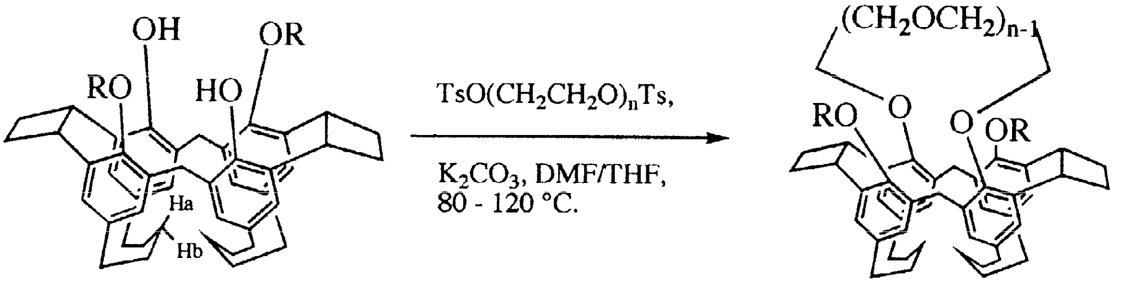
Abstract: New ionophores having different size of crown ethers were prepared from a rigid calixarene analog in 72-98% yields. They efficiently extracted the alkali metal ions. Their ion selectivity was apparently changed by the size of crown ether.

A bridging method between benzene nuclei of calix[4]arenes has been extensively studied to hold a desired conformation and to make a rigid skeleton.[1-3] The unique structures of bridged calixarenes are focused on their ion binding property as ionophores. However, a conformational change of unbridged benzene ring of calixarenes occurs by the introduction of functional groups at phenolic oxygen atoms because of original bulkiness of substituents.[4-6] Accordingly, the evaluation of substituent effects for a unique cavity formed on calixarenes is not clarified under the same conformational conditions.

Recently, we reported that new bridged calix[4]arene analogs were completely held in the cone conformation and were variously functionalized without any conformational change.[7-11] Accordingly, the rigid calixarenes can be used in order to examine the effect of substituents introduced at their phenolic moieties. Hence, we were prompted to evaluate the substituent effect under the same conformational conditions as an ionophore. We chose 1,3-dialkoxy ethers of the rigid calix[4]arene for this purpose.[12] This approach would clarify the nature of the formed cavity (hydrophilicity and lipophilicity) and the strength of interaction with metal ions caused by substituents. We would like to report here their synthesis and ion binding properties.



(1)

	R
1a	Me
b	Et

	n	R	Yield (%)
2a	3	Et	72
3a	4	Me	91
b	4	Et	91
4a	5	Me	92
b	5	Et	98

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The synthetic method is shown in Equation 1.[12] The crown ethers were prepared from calix[4]arene **1** (10 - 20 mM) by treatment with K_2CO_3 (5 equiv.) and $TsO(CH_2CH_2O)_nTs$ (n=3 - 5, 1.5 - 2 equiv.) in DMF/THF (9/1) at 80 - 120 °C for 24 - 72 h. After an acidic extraction with $CHCl_3$, pure compounds **2** - **4** were obtained in 72 - 98% yields by column chromatography (silica gel, ethyl acetate as an eluent).[13] Unfortunately, the synthesis of crown ether by the reaction of **1a** and triethylene glycol ditosylate failed because the competitive isomerization of methyl group occurred by internal S_N2 reaction of the phenoxide ion.

The structures of crown ethers **2**-**4** obtained were mainly determined on the basis of the chemical shift change by ^1H NMR spectroscopy.[12] The aromatic protons of **1a**-**b** split into four sets of doublets between δ 6.62 and 7.14. On the other hand, those of **3** and **4** having four substituents considerably shift to the low field and gather in a narrow region of δ 6.87 to 7.10, although they split into four parts. These results show that the electronic environment around aromatic ring protons becomes rather similar by the introduction of the additional ether groups. The inner protons Ha and outer ones Hb (see structure **1**) of pentamethylene bridges of **2**-**4** shift to the low field about 0.1-0.3 ppm compared with those of **1**. The methoxy protons of **3a** and **4a** shift to up-field about 0.11-0.25 ppm compared with those of **1a** owing to further steric repulsion by introducing bulky substituents. The methylene bridge protons of **1** appear as two doublets (AB type) at *ca.* δ 3.20 and 3.70 (J=13 Hz). On the other hand, those of **2**-**4** widely spread to δ 2.98-2.99 and 4.26-4.31 (J= 13-14 Hz). This behavior suggests that the rigidity around methylene bridges increased by the modification.

First, the ion binding properties of ionophores **2**-**4** were studied by the titration of alkali metal salts with ^1H NMR spectroscopy in acetone as shown in Figure 1. When $RbClO_4$ salts was added into an acetone solution of ionophore **3b** at the ratio of **3b**:$RbClO_4$=1:0.3, the new peaks due to a metal complex obviously appeared in comparison with the metal free spectrum (Figure 1(a) and (b)). When the ratio of **3b**:$RbClO_4$ was 1:1 (Figure 1(c)), all peaks became again of one component. Accordingly, **3b** formed 1:1 complex with Rb^+ ion with a slow exchange rate on the NMR time scale.

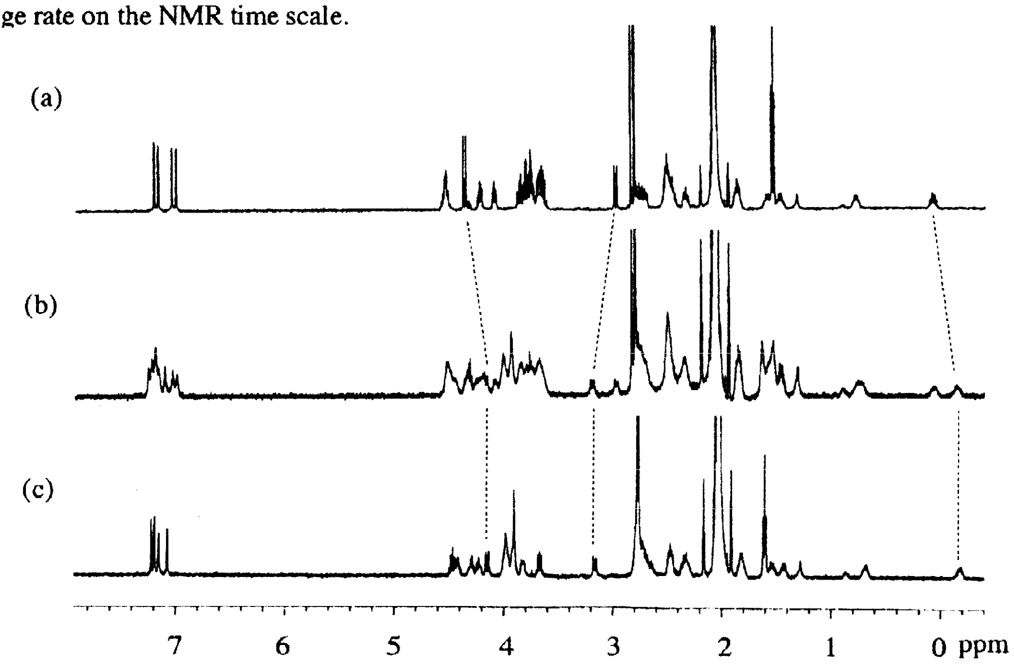

Figure 1 500 MHz ^1H NMR spectra of **3b** (1 mM) and $RbClO_4$ at the ratio of (a)1:0, (b)1:0.3, and (c)1:1 in acetone-d_6 at 25 °C.

The stoichiometry of the complexation was exactly examined by Job's plots between ionophores **2** - **4** and alkali metal perchlorates in acetone (see Figure 2). When the mole fraction of **3b** was 0.5, the complex concentration reached to maximum for Rb^+ ion. And also, **2a** and **4b** whose mole fraction was 0.5 formed the metal complex at the maximum concentration for both K^+ and Cs^+ ions, respectively. These results clearly demonstrate that ionophores **2-4** form 1:1 complex with alkali metal ions.

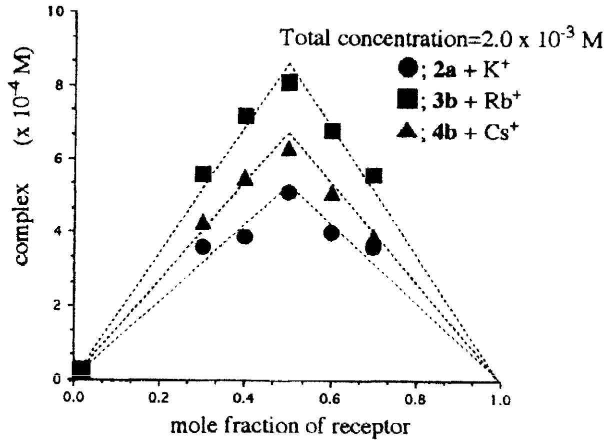

Figure 2 Job plots of complexes between ionophores and $MClO_4$ in acetone-d_6.

Based on these observations, we determined the extractability of ionophores **2-4** with alkali metal ions from aqueous phase to organic phase.[7,8] The experiments were carried out with 2.5 x 10^{-4} M of ionophores in CH_2Cl_2 and 2.5 x 10^{-5} M of picric acid in 0.01 M of aqueous metal hydroxide at 22 °C. These results are shown in Table I. Generally speaking, all ionophores show excellent extractability for alkali metal ions. Their ion selectivity dramatically changes depending on the length of ether linkage; *i.e.*, **2a** having triethylene glycol unit (n=3) apparently shows a sharp K^+ ion selectivity. Ionophores **3a** and **b** having tetraethylene glycol one (n=4) strongly interact with Rb^+ ion. Finally, **4a** and **b** having pentaethylene glycol one (n=5) show a sharp Cs^+ ion selectivity. These results clearly indicate that the ring size formed by crown ether moiety was forced to make itself the binding ion size, due to the rigid cyclophane framework.

The best extraction for alkali metal ions among all ionophores is exhibited by **3a** and **b** having tetraethylene glycol unit. In both cases of tri- and pentaethylene glycol units, their extractability considerably decreased, although their selectivity increased. The effect of alkyl groups was confirmed by the results of extraction, *i.e.*, the extractability for ionophores having ethyl groups are more effective for all alkali metal ions than that with methyl one. This is probably due to the higher lipophilicity of the larger alkyl group.

Table I Extraction (%) of alkali metal picrates in CH_2Cl_2[a]

Compd	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+
2a	<1	41.8	77.7	12.3	<1	2.3
3a	<1	12.9	84.5	97.2	93.4	68.2
3b	<1	10.6	90.6	99.2	87.7	89.4
4a	<1	3.7	18.6	43.4	90.8	5.1
4b	<1	<1	40.5	66.0	94.2	16.8

a) Extraction conditions: 2.5 x 10^{-4} M of ionophore in CH_2Cl_2; 2.5 x 10^{-5} M of picric acid in 0.01 M of MOH at 22 °C. Ionophore solution (5.0 ml) was shaken (10 min) with picrate solution (5.0 ml) and % extraction was measured by the absorbance of picrate in CH_2Cl_2. Experimental error was ± 2%.

In conclusion, ionophores **2-4** having oligoethylene glycol units efficiently extracted alkali metal ions. The ion selectivity of ionophores was apparently changed by the chain length. Further investigations including the characterization of other regioisomers are now in progress and will be reported elsewhere.

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(13) Compd.; Anal. Calcd (Found); MS (M^+); IR (υ); ^{1}H NMR δ (intensity, multiplicity, *J* in Hz). **2a**; Calcd for $C_{54}H_{66}O_6{\bullet}H_2O$: C, 78.23 (78.61); H, 8.27 (8.35); 810; 2976, 1454, 1224, 1148, 1042; 0.17 (2H, m), 0.89 (2H, m), 1.31 (2H, m), 1.46 (6H, t, 7.0), 1.70 (4H, m), 1.82 (2H, m), 2.09 (4H, m), 2.37 (2H, m), 2.55 - 2.72 (8H, m), 2.78 (2H, m), 2.98 (2H, d, 13), 3.19 (2H, m), 3.47 (2H, m), 3.68 (4H, q, 7.0), 3.73 (2H, m), 4.10 (4H, m), 4.26 (2H, d, 13), 4.32 (2H, m), 4.41 (2H, m), 4.57 (2H, q-like), 6.72 (2H, d, 2.0), 6.95 (2H, d, 2.0), 6.97 (2H, d, 2.0), 7.21 (2H, d, 2.0). **4a**; Calcd for $C_{56}H_{70}O_8{\bullet}2H_2O$: C, 74.14 (73.74); H, 8.22 (7.94); 870; 2932, 1460, 1265, 1140, 1062; -0.03 (2H, m), 0.76 (2H, m), 1.41 (2H, m), 1.52 (2H, m), 1.78 (4H, m), 2.37 (4H, m), 2.46 (8H, m), 2.68 (4H, m), 2.99 (2H, d, 13), 3.53 (6H, s), 3.72 - 4.04 (20H, m), 4.27 (2H, d, 13), 4.40 (2H, m), 4.56 (2H, q-like), 6.87 (2H, d, 2.0), 6.94 (2H, d, 2.0), 7.02 (2H, d, 2.0), 7.10 (2H, d, 2.0). **4b**; Calcd for $C_{58}H_{74}O_8{\bullet}0.5H_2O$: C, 76.72 (76.82); H, 8.32 (8.78); 898; 2946, 1456, 1220, 1134, 1040; 0.00 (2H, m), 0.78 (2H, m), 1.46 (6H, t, 7.0), 1.51 (4H, m), 1.78 (4H, m), 2.30 - 2.57 (12H, m), 2.69 (4H, m), 2.99 (2H, d, 14), 3.52 - 4.17 (20H, m), 3.72 (4H, q, 7.0), 4.31 (2H, d, 14), 4.44 (2H, m), 4.55 (2H, m), 6.91 (2H, d, 2.0), 6.94 (2H, d, 2.0), 7.03 (2H, d, 2.0), 7.08 (2H, d, 2.0).