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New Ionophores Derived from a Rigid Calixarene Regioisomer

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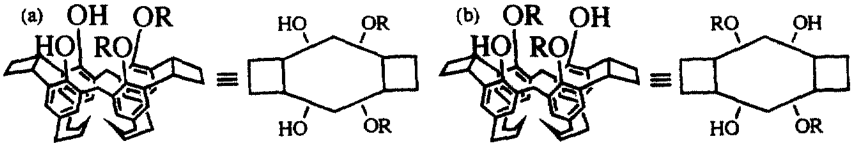
Abstract: New ionophores having a crown ether moiety were prepared from a regioisomer of rigid calixarene analog in 79-97% yields. They efficiently extracted alkali metal ions. Their ion selectivity was apparently changed by the size of crown ether.

Bridged calix[4]arenes can hold a desired conformation by their designed tethers.[1-4] They usually become a rigid framework not to rotate transannularly around the benzene nuclei.

Chart I



1,2-form Top view 1,3-form Top view

New rigid calix[4]arene analog **1a** (R=H) gave two regioisomers as shown in Chart I, namely 1,2- and 1,3-dialkoxy compounds when it was introduced two alkyl groups by the regioselective modification on the four phenol moieties.[5-10] 1,3-Dialkoxy calix[4]arenes functionalized on remaining two hydroxy groups showed the unique property such as chiral receptors of organic molecules[10] or ionophores of alkali metal ions.[11] Therefore, we were prompted to compare the difference of properties between two regioisomers to examine the character of rigid calix[4]arene analog **1b-c**. Since we characterized the calixarene regioisomers **2-4** as an ionophore based on 1,2-form, we would like to report here their synthesis and ion binding properties.

The synthetic method is shown in Equation 1.[11] The synthesis of crown ethers was performed with dialkylated calix[4]arene **1b-c** (10 - 20 mM), 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 79 - 97% yields by column chromatography (silica gel, benzene/ethyl acetate as a mobile phase).[12]

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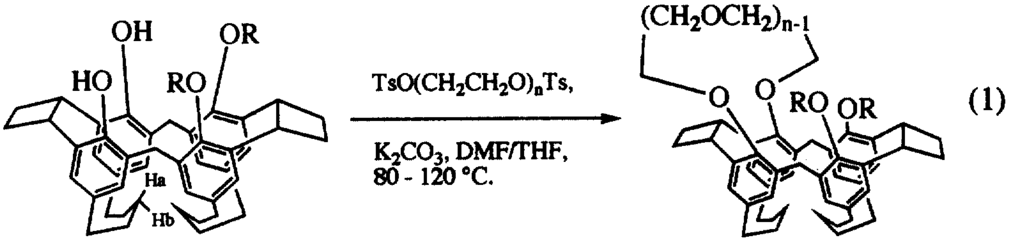

	R
1a	H
b	Me
c	Et

	n	R	Yield (%)
2a	3	Me	79
b		Et	97
3a	4	Me	94
b		Et	95
4a	5	Me	94
b		Et	93

Typical features of crown ethers **2**-**4** obtained were mainly determined from the chemical shift change by ^{1}H NMR spectroscopy.[12] The aromatic protons of **1b**-**c** split into four sets of doublet from δ 6.55 to 7.13. On the other hand, those of **2**-**4** having four substituents considerably shift to the low field and gather in a narrow range from δ 6.79 to 7.08, although they split into four parts. These results suggest that the electronic environment around aromatic ring protons becomes similar situation by the introduction of the additional alkoxy groups. The inner protons Ha and outer ones Hb (*see* structure **1**) of pentamethylene bridges for **2**-**4** shift to the low field by 0.1 - 0.2 ppm compared with those for **1b**-**c**. The methoxy protons of **2a**, **3a**, and **4a** shift to up-field by 0.28 - 0.35 ppm compared with those of **1b** due to the further steric repulsion with substituents. The methylene bridge protons of **1b**-**c** appear as AB type coupling of two doublets at *ca.* δ 3.20 and 3.70 (*J*=13-14 Hz), whereas those of **2**-**4** widely spread to δ 2.92 - 3.00 and 4.16 - 4.27 (*J*= 13 Hz). This fact shows that the rigidity around methylene bridges of calixarenes increased by the etherification.

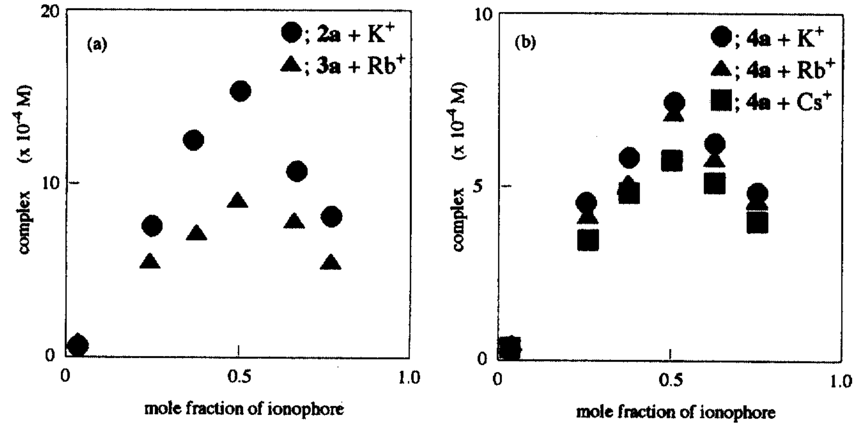

Figure 1 Job's plots (3 mmol/l) of complexes between ionophores **2**-**4** and MClO$_4$ in acetone-d_6 at 27 °C.

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

Compd	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+
2a	<1	6.3	45.0	33.2	9.7	3.6
2b	<1	2.5	45.7	32.4	11.5	5.5
3a	<1	7.5	68.9	82.1	68.1	24.2
3b	1.5	6.3	58.2	89.4	72.1	29.5
4a	<1	<1	49.5	68.9	73.4	10.2
4b	<1	<1	24.6	70.6	73.5	4.3

a) Extraction conditions: 2.5×10^{-4} M of ionophore in CH_2Cl_2; 2.5×10^{-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%.

First, the stoichiometry of the complexation was exactly examined by Job's plots between ionophores **2-4** and alkali metal perchlorates in acetone as shown in Figure 1. When the mole fraction of **2a**, **3a**, and **4a** was 0.5, the complex concentration reached to maximum for the corresponding alkali ions such as K^+, Rb^+, and Cs^+ ones, respectively. These results clearly show that ionophores **2-4** forms 1:1 complex with the corresponding alkali metal ions.

Based on these observations, we determined the extractability of ionophores **2-4** with alkali metal ions from aqueous phase to organic phase.[5,6] The extraction experiments were carried out with 2.5×10^{-4} M of ionophores in CH_2Cl_2 and 2.5×10^{-5} M of picric acid in 0.01 M of metal hydroxide at 22 °C. These results are summarized in Table I. Generally speaking, all ionophores show the excellent extractability for larger alkali metal ions like K^+, Rb^+, and Cs^+ than smaller ones like Li^+ and Na^+. Their ion selectivity dramatically changes by the length of ether linkage; *i.e.*, **2a** and **b** having triethylene glycol unit (n=3) apparently show a sharp K^+ ion selectivity. Ionophores **3a** and **b** having tetraethylene glycol one (n=4) strongly interact with Rb^+ ion. Moreover, **4a** and **b** having pentaethylene glycol one (n=5) clearly show Cs^+ ion selectivity. These results clearly suggest that crown ether was forced to form a certain ring size, due to the rigid and bulky cyclophane skeleton. In fact, CPK model examination and MM2 calculations indicate that the cavity size of crown ether on calixarenes is approximately 2.5-2.8 Å for **2**, 2.9-3.2 Å for **3**, and 3.2-3.6 Å for **4**. These are really complementary to the complexed ions, because the ionic diameters of K^+, Rb^+, and Cs^+ are 2.76, 2.98, and 3.40 Å, respectively.[13]

The best extractability for alkali metal ions among all ionophores is exhibited by **3a** and **b** possessing tetraethylene glycol unit. In both cases of tri- and pentaethylene glycol units, their extractability considerably decreased. The effect of alkyl groups was confirmed by the results of extraction; *i.e.*, the extractability and selectivity for ionophores having ethyl groups are more effective for all alkali metal ions than those for methyl ones. Accordingly, this is considered to be due to the high liphophilicity and bulkiness of the larger alkyl groups.

In conclusion, ionophores **2-4** having oligoethylene glycol unit efficiently extracted alkali metal ions.

The ion selectivity of ionophores apparently changed by the chain length. Further investigations are now in progress and will be reported elsewhere.

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(12) Compd. Mp/°C; Anal. Calcd (Found); MS (M^+); IR υ (cm^{-1}); ^1H NMR δ (intensity, multiplicity, *J* in Hz). **2a** 101 - 103; Calcd for $C_{52}H_{62}O_6\cdot 2H_2O$: C, 76.25 (76.65); H, 8.12 (7.67); m/z 782; 2935, 1476, 1220, 1150, 1020; -0.18 (1H, m), -0.10 (1H, m), 0.66 (2H, m), 1.37 (4H, m), 1.68 (4H, m), 2.26 - 2.53 (12H, m), 2.63 (4H, m), 2.92 (2H, d, 13), 3.43 (6H, s), 3.58 (2H, m), 3.74 - 3.96 (10H, m), 4.16 (2H, d, 13), 4.38 (2H, m), 4.66 (2H, m), 6.79 (2H, d, 1.8), 6.82 (2H, d, 1.8), 6.97 (2H, d, 1.8), 6.99 (2H, d, 1.8). **2b** 98 - 99; Calcd for $C_{56}H_{66}O_6\cdot 0.5H_2O$: C, 79.08 (79.28); H, 8.23 (8.26); m/z 810; 2945, 1464, 1222, 1159, 1044; -0.14 (1H, m), -0.08 (1H, m), 0.70 (2H, m), 1.47 (6H, t, 7.0), 1.47 (4H, m), 1.77 (4H, m), 2.35 - 2.60 (12H, m), 2.69 (4H, m), 3.00 (2H, d, 13), 3.53 - 4.10 (12H, m), 3.75 (4H, q, 7.0), 4.27 (2H, d, 13), 4.39 (2H, m), 4.80 (2H, m), 6.93 (2H, d, 2.0), 6.96 (2H, d, 2.0), 7.06 (2H, d, 2.0), 7.08 (2H, d, 2.0). **3a** 67 - 69; Calcd for $C_{54}H_{66}O_7\cdot 2H_2O$: C, 75.14 (74.94); H, 8.17 (8.03); m/z 826; 2950, 1482, 1220, 1140, 1024; 0.00 (2H, m), 0.77 (2H, m), 1.46 (4H, m), 1.77 (4H, m), 2.36 - 2.62 (12H, m), 2.70 (4H, m), 2.99 (2H, d, 13), 3.50 (6H, s), 3.52 - 4.06 (16H, m), 4.24 (2H, d, 13), 4.43 (2H, m), 4.59 (2H, m), 6.86 (2H, d, 2.0), 6.87 (2H, d, 2.0), 7.06 (2H, d, 2.0), 7.08 (2H, d, 2.0). **3b** 107 - 108; Calcd for $C_{56}H_{70}O_7\cdot 0.5H_2O$: C, 77.83 (77.51); H, 8.28 (8.14); m/z 854; 2935, 1472, 1210, 1131, 1031; -0.05 (2H, m), 0.72 (2H, m), 1.44 (4H, m), 1.46 (6H, t, 7.0), 1.78 (4H, m), 2.36 - 2.58 (12H, m), 2.82 (4H, m), 2.99 (2H, d, 13), 3.56 (6H, m), 3.72 - 4.10 (10H, m), 3.80 (4H, q, 7.0), 4.26 (2H, d, 13), 4.39 (2H, m), 4.65 (2H, m), 6.90 (2H, d, 2.0), 6.91 (2H, d, 2.0), 7.06 (2H, d, 2.0), 7.08 (2H, d, 2.0). **4a** 90 - 92; Calcd for $C_{56}H_{70}O_8\cdot 2H_2O$: C, 74.14 (74.46); H, 8.22 (7.98); m/z 870; 2938, 1482, 1220, 1140, 1021; 0.00 (2H, m), 0.78 (2H, m), 1.43 (4H, m), 1.74 (4H, m), 2.28 - 2.60 (12H, m), 2.66 (4H, m), 2.99 (2H, d, 13), 3.46 (6H, s), 3.52 - 4.03 (20H, m), 4.24 (2H, d, 13), 4.43 (2H, m), 4.53 (2H, m), 6.86 (2H, d, 2.0), 6.87 (2H, d, 2.0), 7.05 (2H, d, 2.0), 7.07 (2H, d, 2.0). **4b** 102 - 103; Calcd for $C_{58}H_{74}O_8$: C, 77.44 (77.33); H, 8.29 (8.77); m/z 898; 2942, 1472, 1220, 1152, 1040; -0.02 (2H, m), 0.72 (2H, m), 1.47 (6H, t, 7.0), 1.47 (4H, m), 1.80 (4H, m), 2.31 - 2.62 (12H, m), 2.70 (4H, m), 2.99 (2H, d, 13), 3.56 (4H, m), 3.70 - 4.08 (16H, m), 3.83 (4H, q, 7.0), 4.27 (2H, d, 13), 4.37 (2H, m), 4.60 (2H, m), 6.89 (2H, d, 2.0), 6.90 (2H, d, 2.0), 7.05 (2H, d, 2.0), 7.06 (2H, d, 2.0).

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