Synthesis and Application of Rigid Calix[4]arenes Partially Modified by Ester Functionality

Yukihiro Okada,*[1] Zhihui Miao,[2] Manabu Mizutani,[1] and Jun Nishimura*[2]
[1]*Department of Chemistry, Gunma University, Kiryu 376-8515*
[2]*Department of Nano-Material Systems, Gunma University, Kiryu 376-8515*

(Received December 19, 2005; CL-051552; E-mail: okada@chem.gunma-u.ac.jp)

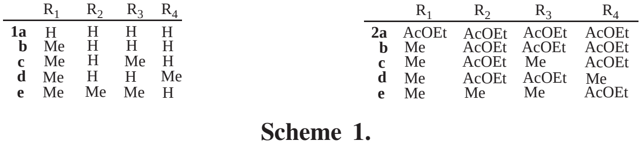
Ionophores **2** having ethyl acetate unit were found to extract efficiently alkali metal ions. Their ion selectivity was apparently changed by the number of ethyl acetate moieties introduced. Dendritic calixarenes were also obtained in excellent yields.

Bridged calixarenes have been extensively studied to hold a desired conformation and to make a rigid framework.[1,2] Their unique structures have attracted much interest in their ion binding properties. If they are partially bridged, however, a conformational change of unbridged benzene rings often occurs during the introduction of functional groups at phenolic moieties. Moreover, the effect of substituents introduced to calixarenes is not easily identified because they do not always maintain the same conformation, ideally the cone structure.

Rigid calix[4]arene analogs were reported previously always completely maintain a cone conformation and can be functionalized at their phenolic moieties with a variety of groups and more importantly the modification can be carried out without any conformational change.[3–6] Accordingly, we were prompted to evaluate the effect of the number of substituents under the same cone conformation as an ionophore. Furthermore, we converted the ionophoric calixarenes to dendritic molecules using the modification examined, aiming to the design of functional molecule used in water.[7–10] Here, we report the synthesis and properties of the calixarene esters as well as the extension to the dendritic structure.

The synthesis of calixarene esters **2** (ethoxycarbonylmethyl ether derivatives) is shown in Scheme 1.[11–16] They were prepared from calix[4]arene **1**[4] (10–20 mM) by treatment with K_2CO_3 (5 equiv.) and $BrCH_2COOEt$ (5 equiv.) in DMF/THF (9/1) at 80–90 °C for 12 h under N_2. After an acidic extraction with $CHCl_3$, pure compounds **2** were obtained in 72–98% yields by column chromatography (silica gel, ethyl acetate as an eluant).

The structures of esters **2** obtained were mainly determined on the basis of the chemical shift change by ^{1}H NMR spectroscopy.[17] The typical features are as follows: i) The methylene bridge protons between benzene rings appear as two doublets at δ 3.02–3.04 ($J = 14$ Hz) and δ 4.51–4.82 ($J = 14$ Hz) for **2a**, **2c**, and **2d** or two doublets of doublet at δ 3.02, 3.04 ($J = 14$ Hz) and δ 4.27–4.46, 4.30–4.58 ($J = 14$ Hz) for **2b** and **2e**, typically showing a cone structure like AB-type splitting.[15] ii) The methylene protons of phenyl ether moiety for all esters show AB-type coupling at δ 4.20–4.52 to exhibit the slow movement.



	R_1	R_2	R_3	R_4
1a	H	H	H	H
b	Me	H	H	H
c	Me	H	Me	H
d	Me	H	H	Me
e	Me	Me	Me	H

	R_1	R_2	R_3	R_4
2a	AcOEt	AcOEt	AcOEt	AcOEt
b	Me	AcOEt	AcOEt	AcOEt
c	Me	AcOEt	Me	AcOEt
d	Me	AcOEt	AcOEt	Me
e	Me	Me	Me	AcOEt

Scheme 1.

The ion binding properties of ionophores **2** were studied by the titration of alkali metal salts with ^{1}H NMR spectroscopy. As a result of this titration experiment, Job's plot apparently showed that **2** easily formed 1:1 complex with alkali metal ions.

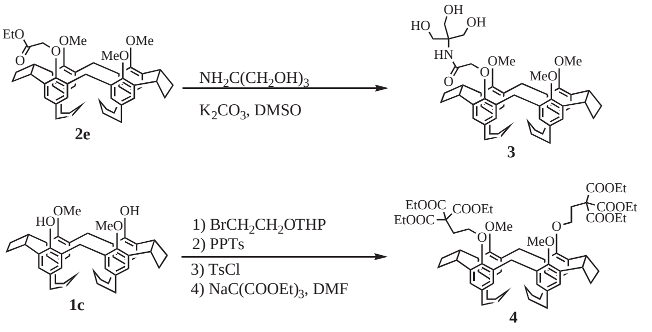
Based on these observations, we determined the extractability of all ionophores **2** with alkali metal ions from the aqueous to the organic phase.[4,11] The experiments were carried out with 2.5×10^{-4} M of ionophores in CH_2Cl_2 and 2.5×10^{-5} M of picric acid in 0.01 M of aqueous metal hydroxide at 22 °C. These results are shown in Table 1. Generally, all ionophores show excellent ion selectivity and extractability for alkali metal ions. Their ion selectivity dramatically changes depending on the number of ethyl acetate units; i.e., **2a** having four ethyl acetate units apparently shows a wide ion selectivity for larger ions like K^+, Rb^+, and Cs^+, although its extractability recorded the maximum for Rb^+ ion. On the other hand, ionophore **2b** having three ethyl acetate units shows a sharp ion selectivity for Rb^+ ion. Ionophores **2c** and **2d** having two ethyl acetate units show a sharp ion selectivity for Rb^+ ion as same as **2b**, although the extractabilities of **2c** and **2d** are clearly less than those of **2a** and **2b**. These results showed that the number of ethyl acetate units as a binding site requires more than three in order to make a potential ionophore for numerous ions. Furthermore, **2d** seems to be able to extract the alkali metal ions more than **2c** due to the difference of binding site distances between two ester moieties. Ionophore **2e** having one ethyl acetate unit shows an exclusive ion selectivity for Cs^+ ion due to the binding between ester and methoxyl groups. These results clearly indicate that the extraction selectivity of ionophores having a binding site introduced on a calixarene framework for alkali metal ions can be changed to a larger ion by the number of functional groups.

We converted **1** and **2** into a dendritic structure having a

Table 1. Extraction (%) of alkali metal picrates in CH_2Cl_2[a]

Compds	Li^+	Na^+	K^+	Rb^+	Cs^+	$NH_4{}^+$
2a[b]	15.9	32.8	90.2	95.7	88.3	33.0
2b	13.4	10.3	64.8	80.5	57.4	13.6
2c	<1	<1	9.4	24.4	16.9	2.9
2d	<1	1.6	16.0	38.2	23.7	1.9
2e	<1	3.8	1.2	<1	48.4	<1

[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%. [b]Ref. 4.



Scheme 2.

binding site to be a host molecule even in aqueous solution, as shown in Scheme 2.[8,9] Calixarene **2e** was reacted to give an arborol structure **3** with tris(hydroxymethyl)aminomethane and K_2CO_3 in DMSO in quantitative yield. As expected, arborol **3** is easily soluble in methanol/water = 9/1.

Calixarene **1c** was also converted to a dendritic structure **4** in a 80% yield for four steps via etherification with $BrCH_2CH_2OTHP$ and K_2CO_3 in DMF/THF (Y. 95%), deprotection with pyridinum *p*-toluenesulfonate in EtOH (Y. quantitative), tosylation with *p*-toluenesulfonyl chloride in pyridine (Y. 92%), and esterification with triethyl methanetricarboxylate sodium salt in DMF (Y. 92%). Thus, a potential precursor **4** toward arborol was prepared in an excellent yield.

In conclusion, ionophores **2** having ethyl acetate unit efficiently extracted alkali metal ions. The ion selectivity of **2** was apparently changed by the number of ethyl acetate units. Dendritic calixarenes **3** and **4** were also obtained in excellent yield. Further investigations are now in progress and will be reported elsewhere.

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17 Compd.; ^1H NMR in $CDCl_3$ δ (intensity, multiplicity, *J* in Hz). **2b**; 0.04 (2H, m), 0.80 (2H, m), 1.40 (4H, m), 1.42 (9H, t, 7.0), 1.76–1.86 (4H, m), 2.36 (4H, m), 2.40–2.74 (10H, m), 2.78 (2H, m), 3.02 (1H, d, 14), 3.04 (1H, d, 14), 3.65 (3H, s), 4.32 (6H, q, 7.0), 4.36 (1H, d, 15), 4.37 (1H, d, 15), 4.38 (1H, d, 15), 4.40 (1H, d, 15), 4.41 (1H, d, 15), 4.42 (2H, m), 4.44 (1H, d, 15), 4.46 (1H, d, 14), 4.58 (1H, d, 14), 4.60 (2H, m), 6.85 (2H, d, 2.0), 6.98 (4H, d, 2.0), 7.13 (2H, d, 2.0). **2c**; 0.08 (2H, m), 0.84 (2H, m), 1.26 (2H, m), 1.34 (2H, m), 1.43 (6H, t, 7.0), 1.68 (4H, m), 1.82 (2H, m), 2.24 (4H, m), 2.48–2.72 (8H, m), 2.80 (2H, m), 3.02 (2H, d, 14), 3.60 (6H, s), 4.24 (2H, m), 4.36 (4H, q, 7.0), 4.46 (2H, d, 15), 4.50 (2H, m), 4.52 (2H, d, 15), 4.82 (2H, d, 14), 6.74 (2H, d, 2.0), 6.85 (2H, d, 2.0), 7.00 (2H, d, 2.0), 7.21 (2H, d, 2.0). **2d**; −0.06 (2H, m), 0.76 (2H, m), 1.34 (4H, m), 1.42 (6H, t, 7.0), 1.50 (4H, m), 1.80 (4H, m), 2.42 (6H, m), 2.52 (2H, m), 2.72 (4H, m), 3.04 (2H, d, 14), 3.60 (6H, s), 4.20 (2H, d, 15), 4.28 (2H, d, 15), 4.36 (4H, q, 7.0), 4.44 (2H, m), 4.52 (2H, d, 14), 4.59 (2H, m), 6.92 (4H, d, 2.0), 7.06 (4H, d, 2.0). **2e**; 0.02 (2H, m), 0.80 (2H, m), 1.41 (2H, m), 1.47 (3H, t, 7.0), 1.56 (2H, m), 1.74 (2H, m), 1.82 (2H, m), 2.35 (4H, m), 2.42–2.70 (10H, m), 2.78 (2H, m), 3.02 (1H, d, 14), 3.04 (1H, d, 14), 3.52 (3H, s), 3.60 (3H, s), 3.76 (3H, s), 4.25 (2H, q, 7.0), 4.27 (1H, d, 14), 4.30 (1H, d, 14), 4.34–4.46 (4H, m), 4.38 (1H, d, 15), 4.42 (1H, d, 15), 6.83 (2H, d, 2.0), 6.96 (4H, m), 7.16 (2H, d, 2.0). **3**; −0.42 (1H, m), 0.01 (1H, m), 0.62 (1H, m), 0.80 (1H, m), 1.31 (4H, m), 1.58 (3H, m), 1.66 (2H, m), 1.82 (2H, m), 2.22–2.80 (16H, m), 3.02 (3H, s), 3.04 (1H, d, 14), 3.06 (1H, d, 14), 3.60 (3H, s), 3.64 (3H, s), 3.82 (6H, m), 4.06 (1H, d, 14), 4.16 (1H, d, 14), 4.20 (1H, d, 14), 4.34–4.56 (4H, m), 4.38 (1H, d, 14), 6.72 (1H, d, 2.0), 6.85 (1H, d, 2.0), 6.87 (1H, d, 2.0), 6.94 (1H, d, 2.0), 7.01 (1H, d, 2.0), 7.12 (1H, d, 2.0), 7.18 (1H, d, 2.0), 7.21 (1H, d, 2.0), 7.82 (1H, brs). **4**; −0.08 (2H, m), 0.72 (2H, m), 1.26 (2H, m), 1.34 (2H, m), 1.35 (18H, t, 7.0), 1.82 (6H, m), 2.24–2.72 (18H, m), 3.06 (2H, d, 14), 3.65 (6H, s), 4.20–4.62 (8H, m), 4.26 (12H, q, 7.0), 4.56 (2H, d, 14), 6.72 (2H, d, 2.0), 6.80 (2H, d, 2.0), 6.90 (2H, d, 2.0), 7.05 (2H, d, 2.0).

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