Synthesis and Characterization of Chiral Calixarene Analogs Locked in the Cone Conformation by the Photocycloaddition

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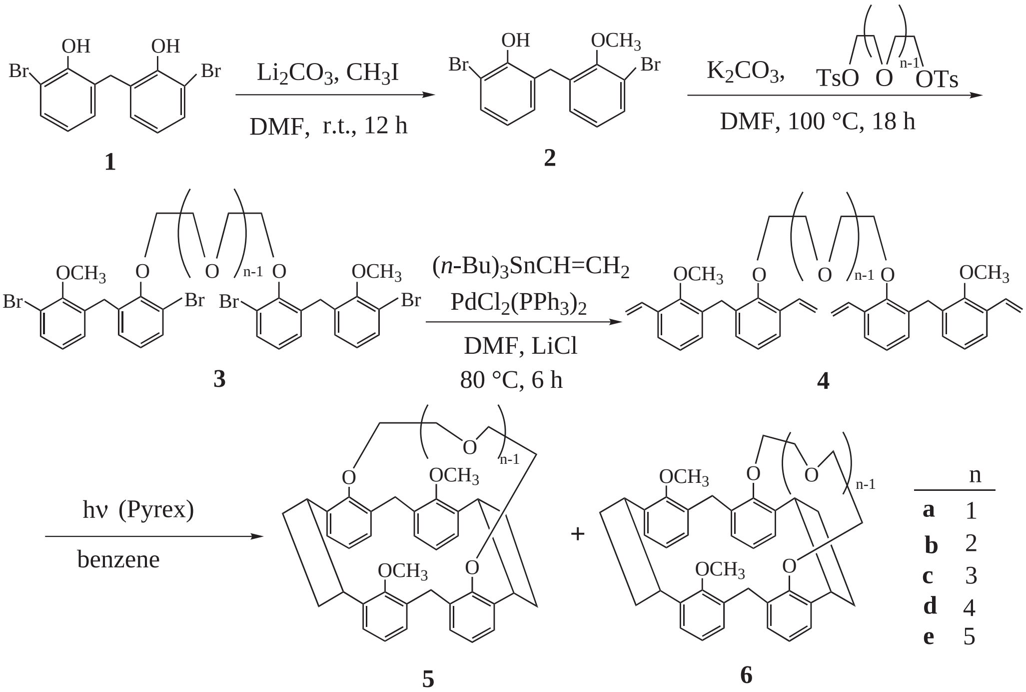
Abstract: A bisphenol derivative was used as the starting material. [2+2] Photocycloaddition of tetraolefin gave the desired calix[4]arene analogs having chiral and achiral structure in 12–77% yields. The optical resolution was successfully achieved by using the HPLC method. The calixarene analog formed a 1:1 complex with alkali metal ions and extracted large metal picrates better than small ones.

Key words: calixarene, cyclophane, photocycloaddition, alkali metal

Intramolecular [2+2] photocycloaddition of styrene derivatives is a powerful and convenient method for the formation of a cyclophane skeleton.[1,2] [2+2] Photocycloaddition easily makes the rigid cyclophane skeleton having a C_2 or C_s symmetrical unit by the transformation from the vinyl group to a cyclobutane ring.[3,4] Accordingly, this method can be adapted for the synthesis of stable enantiomers of macrocycles. Although many calix[n]arenes were reported as powerful host molecules in the last decade, difficulties in the synthesis or modification toward chiral ones still remained.[5–9] Therefore, we were prompted to develop another simple synthetic route to chiral calixarene analogs with styrene derivatives by the photocycloaddition. We would like to report here the synthesis and characterization of chiral calix[4]arene analogs by the intramolecular photocycloaddition.

The synthesis of calix[4]arenes is shown in Scheme 1 and Table 1. Bisphenol derivative **1** was used as the starting material. Monoetherification of **1** was performed with Li_2CO_3 and CH_3I in anhyd DMF at room temperature for 12 hours to give monomethyl ether **2** in 93% yield. Tetrabromides **3** were obtained in 77–95% yields by the etherification with **2**, the corresponding oligo(ethylene glycol) ditosylate, and K_2CO_3 in anhyd DMF at 100 °C for 18



Scheme 1

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hours. The vinylation of **3** was performed with tributyl(vinyl)tin, PdCl$_2$(PPh$_3$)$_2$, and LiCl in anhyd DMF at 80 °C for 6 hours to give tetraolefins **4** in 47–88% yields. [2+2] Photocycloaddition of **4** (0.31–1.2 mM) was carried out by irradiation with a 400W high-pressure Hg lamp (Pyrex filter) in benzene for 6–12 hours. After evaporation, calix[4]arenes **5** and **6** were isolated with column chromatography (SiO$_2$, benzene–ethyl acetate = 2:1). The results are summarized in Table 1. The olefin **4a** did not give any desired product at all due to the difficulty of parallel arrangement between two olefin moieties under the photocycloaddition. On the other hand, **4b** gave calixarenes in excellent 77% yield (entry 2). These results show that the chain length of **4a** is too short to make a calixarene skeleton, but that of **4b** is suitable for the formation of calixarene. In fact, MM2 calculations show that the steric energy of **5a** and **6a** is higher than that of **5b** and **6b** as shown in Figure 1. When the oligoethylene chain became longer from **4c** to **4e**, the yields of calixarenes were gradually decreased from 27% to 12% (entries 4, 7, and 10). This result shows that the molecular stability of calixarenes is decreased from n = 2 to 5, judging from the MM2 calculations as shown in Figure 1. Thus, new calix[4]arenes, which show the potential of the introduction of functional group on upper rim, were simply obtained with styrene derivatives by the [2+2] photocycloaddition.

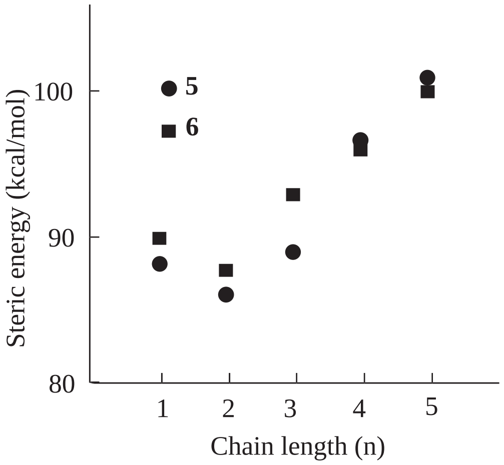

Figure 1 MM2 calculation of calixarene isomers **5** and **6**.

The product ratio of chiral or achiral isomers as regioisomers is important to prepare the new chiral calixarenes. In fact, the chiral calixarene **5** was produced more than the achiral **6** in the system of n = 2–4 in benzene solution (see Table 1). It is clear that **5** is a more stable isomer than **6**. The MM2 calculations also demonstrated that the steric energy of **5** is ca. 2–3 kcal/mol lower than that of **6** in the case of n = 2 and 3 and nearly the same in the case of n = 4 as shown in Figure 1. The highest regioselectivity for **5** and **6** is recorded as 3.6:1 in the system of n = 3.

[2+2] Photocycloaddition of cinnamoyl derivatives was reported to change the product distribution from a *trans* to a *cis* adduct by the addition of metal perchlorate in benzene due to the affinity of olefins on metal salt.[10] Therefore, we examined the conditions of photocycloaddition to be high regioselectivity by adding metal perchlorate. In fact, the product ratio (**5**:**6**) and total yield (**5** + **6**) of **4d** are dramatically changed from 1.1:1 to 2.1:1 and from 23% to 46% when KClO$_4$ (1 equiv) was added in the benzene solution (entries 7 and 8 in Table 1). Similarly, those of **4c**

Table 1 The Product Distribution of Photocycloaddition in Benzene[a]

Entry	Comp.	n	Salt	Salt equiv	Product			
					Yield (%)			Ratio
					5	**6**	Total	**5**:**6**
1	**4a**	1	–	–	–	–	–	–
2	**4b**	2	–	–	43	34	77	1.3:1
3	**4b**	2	NaClO$_4$	1	11	8.0	19	1.4:1
4	**4c**	3	–	–	21	5.8	27	3.6:1
5	**4c**	3	NaClO$_4$	1	25	5.1	30	4.9:1
6	**4c**	3	KClO$_4$	1	27	5.2	32	5.2:1
7	**4d**	4	–	–	12	11	23	1.1:1
8	**4d**	4	KClO$_4$	1	31	15	46	2.1:1
9	**4d**	4	RbClO$_4$	1	20	17	37	1.2:1
10	**4e**	5	–	–	5.1	7.0	12	0.73:1
11	**4e**	5	KClO$_4$	1	17	28	45	0.61:1
12	**4e**	5	RbClO$_4$	1	9.5	17	27	0.56:1

[a] Conditions: 0.31–1.2 mmol/L, 6–12 h.

are changed from 3.6:1 to 5.2:1 and from 27% to 32% when $KClO_4$ was added (entries 4 and 6). These results showed that **5** was more sensitive than **6** in the presence or absence of metal ions.

The structure of **5** and **6** was mainly elucidated by ^{1}H NMR spectroscopy.[11] All the protons could be assigned in the usual way by using several experiments like COSY and NOESY and considering the symmetry of C_2 for **5** and C_s for **6**. We concluded that they took completely the cone-type conformation, as depicted in Scheme 1, from the following findings: their methylene bridges show AB type coupling (δ = 3.13–3.17 and 4.16–4.22 with J = 15 Hz for **5** and δ = 3.17 and 4.21–4.26 with J = 15 Hz for **6**),[2] which is the same as those ascribed to the calixarene cone-form. Their cyclobutane methine protons resonate at δ = 4.13–4.60 to demonstrate the typical *cis* configuration.[1,3] Their methoxy groups show a singlet at δ = 3.63–3.75 for **5** and 3.20–3.26 for **6** to keep the same environment, respectively.[1] The chirality was easily demonstrated by the optical resolution of **5d** using the HPLC method (Chiralpak AD, hexane–2-propanol = 23/1 as an eluent, α_D = –40.2 and +41.1).[9]

First, the stoichiometry for the complexation was exactly examined by Job's plots (3 mmol/L) between ionophore **5d** and alkali metal thiocyanates in $CDCl_3$–CD_3OD (7:3). When the mole fraction of **5d** was 0.5, the complex concentration reached maximum for K^+, Rb^+, and Cs^+. This result clearly demonstrates that **5** forms a 1:1 complex with alkali metal ions.

Based on these observations, we determined the extractability of ionophores **5** and **6** with alkali metal ions from the aqueous phase to an organic phase.[12–16] 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 2. Generally speaking, **5** acted as excellent ionophores, but **6** did not. It is clear that the steric hindrance of cyclobutane methine protons prohibited the complexation with **6** and metal ions. Ionophores showed excellent extractability for larger alkali metal ions like K^+, Rb^+, and Cs^+ than for smaller ones like Li^+ and Na^+. The ion selectivity of **5** dramatically changes by the length of the ether linkage; i.e., **5b** having a diethylene glycol unit (n = 2) could not extract the alkali ions due to the small size of crown ether. Ionophore **5c** having a triethylene glycol unit (n = 3) apparently shows sharp K^+ ion selectivity. Ionophore **5d** having a tetraethylene glycol unit (n = 4) clearly shows Rb^+ ion selectivity. Moreover, **5e** having a pentaethylene glycol unit (n = 5) shows Cs^+ ion selectivity. These results clearly suggest that the ring size of crown ether was forced to form a suitable cavity size by the rigid calixarene skeleton. In fact, CPK model examination and MM2 calculations indicate that the cavity size of crown ether on calixarenes **5** is approximately 2.6–2.9 Å for **5c**, 2.9–3.3 Å for **5d**, and 3.3–3.7 Å for **5e**. These are really complementary to the complexed ions, because the ionic diameters of K^+, Rb^+, and Cs^+ are 2.76 Å, 2.98 Å, and 3.40 Å, respectively.[14]

The best extractability for alkali metal ions among all ionophores is exhibited by **5d** possessing a tetraethylene glycol unit. In both cases of tri- and pentaethylene glycol units, their extractability considerably decreased, although their ion selectivity increased. Thus, the regioisomers **5** and **6** showed quite different behavior for metal binding. Accordingly, this is a sophisticated modification of the calix[4]arene geometry, which dramatically changed the ion selectivity and extractability.

In conclusion, we have synthesized calix[4]arene analogs having chiral and achiral structure in excellent yield firmly locked in the cone conformation. The optical resolution of chiral calixarene was successfully achieved by using the HPLC method. The calix[4]arene analog formed a 1:1 complex with alkali metal ions and extracted larger metal picrates than small ones. Further investigation is now in progress and will be reported elsewhere.

Table 2 Extraction (%) of Alkali Metal Picrates in CH_2Cl_2[a]

Compd	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+
5b	<1	<1	<1	<1	<1	1.2
5c	2.8	7.7	20.9	4.5	2.0	1.3
5d	1.7	1.7	22.8	43.0	36.5	5.9
5e	1.9	3.4	5.6	9.4	12.8	2.6
6b	<1	<1	<1	<1	<1	<1
6c	<1	<1	3.3	<1	<1	<1
6d	<1	1.2	6.8	9.9	8.7	1.9
6e	<1	1.5	6.2	12.1	11.6	2.5

[a] Extraction conditions: 2.5×10^{-4} M of ionophore in CH_2Cl_2; 2.5×10^{-5} M of picric acid in 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%.

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(11) Compd.: MS (M^+): ^{1}H NMR δ (intensity, multiplicity, *J* in Hz). **5c**: Calcd for $C_{42}H_{46}O_6$: 646: 2.16–2.62 (8 H, m), 3.17 (2 H, d, 15), 3.52 (2 H, m), 3.58–3.70 (6 H, m), 3.75 (6 H, s), 3.77–3.83 (4 H, m), 4.13 (2 H, m), 4.22 (2 H, d, 15), 4.43 (2 H, m), 5.94 (2 H, dd, 1.8, 8.0), 6.17 (2 H, dd, 1.8, 8.0), 6.32 (2 H, t, 8.0), 7.07 (2 H, dd, 1.8, 8.0), 7.16 (2 H, t, 8.0), 7.38 (2 H, dd, 1.8, 8.0). **6c**: Calcd for $C_{42}H_{46}O_6$: 646: 2.24–2.58 (8 H, m), 3.17 (2 H, d, 15), 3.26 (6 H, s), 3.50–3.95 (12 H, m), 4.21 (2 H, d, 15), 4.16 (2 H, m), 4.60 (2 H, m), 6.44 (2 H, dd, 2.0, 7.8), 6.67 (2 H, dd, 2.0, 7.8), 6.69 (2 H, t, 7.8), 6.76 (2 H, dd, 2.0, 7.8), 6.81 (2 H, t, 7.8), 6.86 (2 H, dd, 2.0, 7.8). **5d**: Calcd for $C_{44}H_{50}O_7$: 690: 2.24–2.52 (8 H, m), 3.13 (2 H, d, 15), 3.63 (6 H, s), 3.64–4.06 (16 H, m), 4.16 (2 H, d, 15), 4.26 (2 H, m), 4.36 (2 H, m), 6.40 (2 H, dd, 1.8, 7.5), 6.56 (2 H, dd, 1.8, 7.5), 6.63 (2 H, t, 7.5), 6.67 (2 H, dd, 1.8 & 7.5), 6.86 (2 H, t, 7.5), 6.98 (2 H, dd, 1.8, 7.5). **6d**: Calcd for $C_{44}H_{50}O_7$: 690: 2.26–2.50 (8 H, m), 3.17 (2 H, d, 15), 3.20 (6 H, s), 3.58–3.94 (16 H, m), 4.26 (2 H, d, 15), 4.28 (2 H, m), 4.44 (2 H, m), 6.52 (2 H, dd, 1.8, 7.5), 6.66 (2 H, dd, 1.8, 7.5), 6.72 (2 H, dd, 1.8, 7.8), 6.76 (2 H, t, 7.5), 6.78 (2 H, dd, 1.8, 7.5), 6.83 (2 H, dd, 1.8, 7.5).

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