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Synthesis of novel calixarenes having a tweezer-type structure

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Abstract—Monobromide was used as the starting material. The [2+2]photocycloaddition of diolefins directly gave all the calix[4]-arene regioisomers having chiral and achiral structures in 20–47% yields. They formed a complex with alkali metal ions and extracted large metal picrates rather than small ones.

Intramolecular [2+2]photocycloaddition of styrene derivatives is a powerful and convenient method for the construction of a calixarene-like skeleton (e.g., transformation of diolefin **4** into macrocycle **5**).[1–3] The cyclobutane ring maintained the desired conformation of calix[4]arene analogs to suppress the benzene ring rotation at the opposite 1,3-position.[4–6] Accordingly, two bisphenol units were forced to adopt a face-to-face conformation, forming a cage structure such as calix[4]-arene. Although many calix[*n*]arenes were reported as powerful host molecules, the molecular tweezer-type calixarenes, especially those of chiral structures, are scarcely known.[7–11] Therefore, we were prompted to develop a direct synthesis of three regioisomers of this type of calixarene by using the same starting material. In this paper, we report a simple synthesis of tweezer-type calix[4]arenes by the intramolecular photocycloaddition.

The synthesis of all calix[4]arene analogs is shown in Scheme 1. Monobromide **1** was used as the starting material. Monoetherification of **1** was performed with Li_2CO_3 and CH_3I in dry DMF at rt for 12 h to give monomethylether **2a** and **b** in 68 and 17% yields, respectively. Calixarenes **5** having a crown ether (n = 3–5) apart from the cyclobutane ring were obtained as follows: dibromides **3** were obtained in 84–92% yields by the etherification with **2a**, the corresponding oligoethyleneglycol ditosylate, and K_2CO_3 in dry DMF at 100 °C for 18 h. The vinylation of **3** was performed with tributyl vinyl tin, $PdCl_2(PPh_3)_2$, and LiCl in dry DMF at 80 °C for 6 h to give diolefins **4** in 38–45% yields. [2+2]Photocycloaddition of **4** (0.11–1.2 mM) was carried out by irradiation with a 400 W high-pressure Hg lamp (pyrex filter) in dry benzene for 23 h. After evaporation, calix-[4]arenes **5** were isolated in 41–47% yields by column chromatography (SiO_2, benzene/ethyl acetate = 2/1).

Calixarenes **8** having a crown ether (n = 3–5) close to the cyclobutane ring were obtained as follows: dibromides **6** were obtained in 73–88% yields by etherification with **2b**, the corresponding oligoethyleneglycol ditosylate, and K_2CO_3 in dry DMF at 100 °C for 18 h. The vinylation of **6** was performed with tributyl vinyl tin, $PdCl_2(PPh_3)_2$, and LiCl in dry DMF at 80 °C for 6 h to give diolefins **7** in 44–50% yields. [2+2]Photocycloaddition of **7** was carried out by irradiation with a 400 W high-pressure Hg lamp (pyrex filter) in dry benzene for 23 h. After evaporation, calix[4]arenes **8** were isolated in 20–46% yields by column chromatography (SiO_2, benzene/ethyl acetate = 2/1).

Chiral calixarenes **13** were obtained as follows: monobromides **9** were obtained in quantitative yields by etherification with **2b**, the corresponding oligoethyleneglycol monotosylate, and K_2CO_3 in dry DMF at 80–90 °C for 18 h. The tosylation of **9** was performed with TsCl, triethylamine, 4-(dimethylamino)pyridine in dry CH_2Cl_2 for 24 h to give tosylates **10** in quantitative yields. Dibromides **11** were obtained in 79–83% yields by etherification with **2a**, **10**, and K_2CO_3 in dry DMF at 80–90 °C for 18 h. The vinylation of **11** was performed with tributyl vinyl tin, $PdCl_2(PPh_3)_2$, and LiCl

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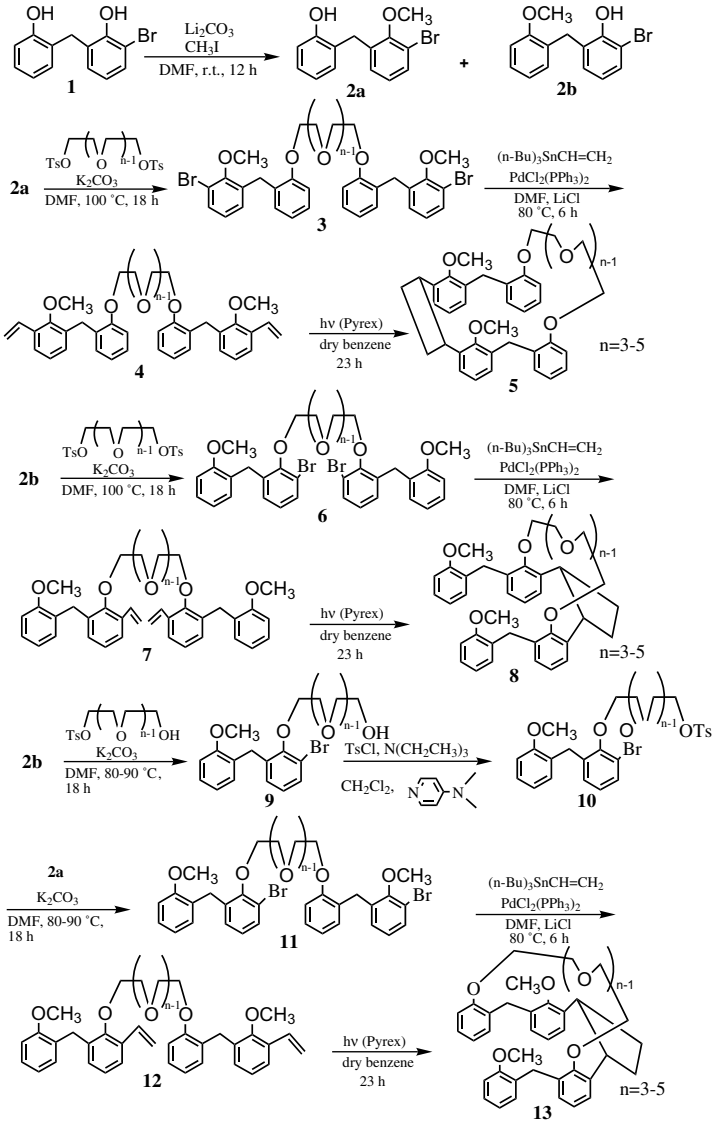

Scheme 1.

in dry DMF at 80 °C for 6 h to give diolefins **12** in 43–52% yields. [2+2]Photocycloaddition of **12** was carried out by irradiation with a 400 W high-pressure Hg lamp (pyrex filter) in dry benzene for 23 h. After evaporation, calix[4]arenes **13** were isolated in 32–45% yields by column chromatography (SiO_2, benzene/ethyl acetate = 2/1). Each enantiomer of **13** could be separated by chiral HPLC column (Chiralpak AD, hexane/2-propanol = 23/1 as an eluent).[3,11]

The structure of **5**, **8** and **13** was mainly elucidated by ^1H NMR spectroscopy.[12] All protons could be assigned in the usual way by using several experiments like COSY and NOESY and considering the molecular symmetry of achiral structure **5** and **8** and chiral structure **13**. The benzylic methylene protons of **5** and **13** show AB-type coupling (δ 3.76–3.82 and 3.86–4.02 with J = 15–16 Hz for **5** and δ 3.60–3.62 and 4.04–4.41 with J = 15 Hz for **13**),[2] which is the same as those ascribed to the parent calix[4]arene cone-form. On the other hand, those of **8** show a singlet peak at δ 3.84–3.86, which is a typical feature of the rotation around the CH_2 axis. Then, we concluded that **5** and **13** took completely the cone-type (*syn*) conformation, but **8** took several conformations like the partial-cone or the 1,2-alternate form.

The cyclobutane methine protons of **5** and **8** locate at δ 4.40–4.42 and 4.48–4.58, respectively, and those of **13** locate in two parts at δ 4.24–4.38 and 4.50–4.64 to demonstrate the typical *cis* configuration by the molecular symmetry.[1,4] The methoxy groups of **5** and **8** show a singlet at δ 3.56–3.60 and 3.70–3.76, respectively, and those of **13** show two singlets at δ 3.61–3.76 and 3.80–3.96 by the molecular symmetry.[1] Thus, the introduction of a cyclobutane ring can suppress the rotation of the neighboring benzene rings to keep the *syn* structure.

The complexation was examined by the addition of K^+ salt in solution of calixarene analogs **5**, **8**, and **13**. Most of their peaks shifted after the addition of a metal ion (1 equiv). Job's plots clearly demonstrate that

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

Compd	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+
5a	<1	<1	<1	<1	<1	<1
5b	<1	<1	<1	<1	1.6	<1
5c	<1	<1	<1	<1	1.4	<1
8a	<1	<1	<1	<1	<1	<1
8b	<1	1.5	4.6	3.7	4.3	1.5
8c	<1	1.6	9.7	13.0	10.5	2.2
13a	<1	<1	<1	<1	<1	<1
13b	<1	<1	2.0	2.8	3.9	<1
13c	<1	<1	2.1	3.3	4.7	<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%.

calixarenes can form 1:1 complex with the alkali metal ions. Based on this observation, we determined the extractability of ionophores **5**, **8**, and **13** with alkali metal ions from the aqueous phase to an organic phase.[13–17] 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 1. Generally speaking, they acted as ionophores, although the extractability is moderate. Ionophores showed the extractability for larger alkali metal ions like K^+, Rb^+, and Cs^+ rather than smaller ones like Li^+ and Na^+. The best extractability for alkali metal ions among all ionophores is exhibited by **8**. This result suggests that the crown ether ring of **8** was preorganized to bind the metal ions by the rigid calixarene moiety attaching the cyclobutane ring.

In conclusion, all regioisomers of new calix[4]arene analogs were synthesized in good yields. They formed a complex with alkali metal ions and extracted larger metal picrates rather than small ones. Further investigation is now in progress and will be reported elsewhere.

Acknowledgements

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12. Compd: ^{1}H NMR δ (intensity, multiplicity, J in Hz). **5a**: 2.38 (2H, m), 2.45 (2H, m), 3.56 (6H, s), 3.60 (6H, m), 3.66 (2H, m), 3.76 (2H, d, 16), 3.94 (4H, m), 4.02 (2H, d, 16), 4.40 (2H, m), 6.66–6.80 (8H, m), 6.92–7.05 (4H, m), 7.16 (2H, m). **5b**: 2.40 (2H, m), 2.46 (2H, m), 3.58 (6H, s), 3.62 (10H, m), 3.68 (2H, m), 3.81 (2H, d, 16), 3.87 (2H, m), 3.94 (2H, d, 16), 3.99 (2H, m), 4.41 (2H, m), 6.72–6.84 (10H, m), 7.02–7.11 (4H, m). **5c**: 2.40 (2H, m), 2.48 (2H, m), 3.40–3.80 (14H, m), 3.60 (6H, s), 3.82 (2H, d, 15), 3.82–4.16 (6H, m), 3.86 (2H, d, 15), 4.42 (2H, m), 6.70–6.90 (10H, m), 7.01–7.16 (4H, m). **8a**: 2.36 (2H, m), 2.50 (2H, m), 3.58 (2H, m), 3.62–3.96 (8H, m), 3.76 (6H, s), 3.84 (4H, s), 3.92 (2H, m), 4.58 (2H, m), 6.58–6.92 (10H, m), 7.03–7.16 (4H, m). **8b**: 2.38 (2H, m), 2.48 (2H, m), 3.56–3.80 (14H, m), 3.72 (6H, s), 3.80–3.90 (2H, m), 3.86 (4H, s), 4.53 (2H, m), 6.62–6.88 (10H, m), 7.04–7.16 (4H, m). **8c**: 2.40 (2H, m), 2.50 (2H, m), 3.58–3.80 (18H, m), 3.82–3.96 (2H, m), 3.70 (6H, s), 3.86 (4H, s), 4.48 (2H, m), 6.62–6.90 (10H, m), 7.02–7.16 (4H, m). **13a**: 2.34 (1H, m), 2.44 (1H, m), 2.61 (1H, m), 3.14 (1H, m), 3.50–3.92 (12H, m), 3.62 (2H, d, 15), 3.76 (3H, s), 3.96 (3H, s), 4.24 (1H, m), 4.41 (2H, d, 15), 4.64 (1H, m), 5.96–6.54 (4H, m), 6.65–6.98 (5H, m), 7.03–7.22 (5H, m). **13b**: 2.36 (3H, m), 2.52 (1H, m), 3.40–3.68 (10H, m), 3.60 (2H, d, 15), 3.61 (3H, s), 3.70–3.86 (4H, m), 3.80 (3H, s), 4.04 (2H, m), 4.10 (2H, d, 15), 4.24 (1H, m), 4.50 (1H, m), 6.37–6.86 (9H, m), 6.94–7.34 (5H, m). **13c**: 2.42 (2H, m), 2.52 (2H, m), 3.56–3.70 (12H, m), 3.60 (2H, d, 15), 3.62 (3H, s), 3.74–3.86 (6H, m), 3.80 (3H, s), 4.04 (2H, d, 15), 4.10 (2H, m), 4.38 (1H, m), 4.50 (1H, m), 6.54–6.82 (8H, m), 6.84–7.22 (6H, m).
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