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Synthesis and Characterization of a Calixarene Analog Locked in the Cone Conformation

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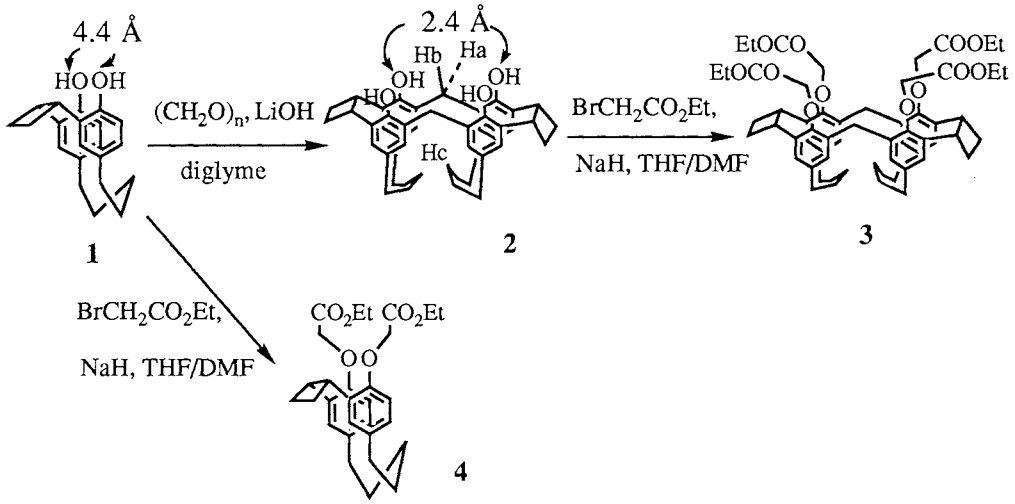
A cone-formed calix[4]arene analog (**2**) was prepared in 89% yield from dihydroxy-[2.5]metacyclophane as a building block. A rigidified calixarene analog having ethyl acetate units showed the remarkable selectivity in alkali metal ion extraction. Cyclophane **2** can easily be chiral by changing one, two, or three OH groups to some other achiral functional groups.

Many macrocyclic compounds composed of a metacyclophane skeleton were reported as artificial receptors.[1] Rigidification is one of the most important modifications of these compounds which resulted in arranging binding sites favorably for various guests and giving specific selectivities in affinity. Many successful examples in this respect are disclosed in the families of spherands[2] and calixarenes.[3] In order to make calixarenes conformationally more rigid, alkylidene bridges and/or bulky substituents were introduced and resulted in better selectivity and efficiency for binding metal ions.[4] We report here the first example of a calixarene analog firmly locked in the cone conformation, which shows remarkable selectivity in binding of metal ions.

The synthesis of calixarene analog **2** is shown in Scheme 1. *syn*-4,17-Dihydroxy[2.5]metacyclophane **1**[5] was chosen as a building block, because of easy preparation and also taking syn conformation which was



Scheme 1.

proved by NMR spectroscopic analysis.[6] Thus, cyclophane **1** (2.0 g, 6.5 mmol) was treated with LiOH (0.31 g, 13 mmol) and paraformaldehyde (2.0 g, 65 mmol) in 20 mL of diglyme at 140 - 150 °C for 12 h under N_2 to afford desired product **2**.[7] Interestingly, a remarkable template effect was observed on this condensation reaction. That is, lithium hydroxide gave **2** in excellent 89% yield. When other larger metal ions were used, the yield was gradually decreased in the order of Na^+ (42%), K^+ (15%), and Rb^+ (5%). Then finally cesium hydroxide did not give **2** at all under the same reaction conditions. Analytical and physical data of **2** as well as others mentioned above are listed in Table 1.

The structure of **2** was mainly elucidated by ^{1}H-NMR spectroscopy. Since all protons could be assigned in the usual way by using several experiments like COSY and ^{13}C-NMR, we concentrated to solve how the two metacyclophane units are arranged in **2** and concluded the head-to-head arrangement or the cone-type configuration, as depicted in Scheme 1, by the following findings: 1) The methylene bridge shows AB type coupling (Ha at δ3.28 with J=14 Hz and Hb at δ3.97 with J=14 Hz),[8] which is the same as those ascribed to the calixarene cone-form. Moreover, this same coupling constant is maintained even in pyridine-d_5 acting as a

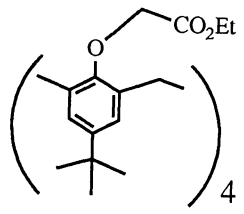
Table 1. Physical and Analytical Data of Cyclophanes **2**, **3**, and **4**

Compd.	Mp/°C; Anal. Calcd (Found)[a]; MS (M^+)[b]; IR (υ)[c]; ^{1}H NMR δ (intensity, multiplicity, *J* in Hz)[d]; ^{13}C NMR δ[d].
2	>300; For $C_{44}H_{48}O_4 \cdot H_2O$, C, 80.21 (79.91), H, 7.65 (7.59); 640; 3270, 2938, 1480, 1452, 1148; -0.22 (2H, m), 0.65 (2H, m), 1.40 (4H, m), 1.72 (4H, m), 2.30-2.62 (12H, m), 2.71 (4H, m), 3.28 (2H, d, 14), 3.97 (2H, d, 14), 4.56 (4H, m), 6.71 (4H, d, 1.9), 6.99 (4H, d, 1.9), 7.78 (4H, s), pyridine-d_5, 0.14 (2H, m), 0.73 (2H, m), 1.44 (4H, m), 1.86 (4H, m), 2.46 (12H, m), 2.84 (4H, m), 3.39 (2H, d, 14), 4.32 (2H, d, 14), 4.97 (4H, m), 6.90 (4H, d, 2.0), 7.28 (4H, d, 2.0), 10.17 (4H, bs); 22.05, 23.53, 28.70, 31.43, 33.13, 37.06, 127.11,127.48, 127.66, 128.78, 133.65, 148.24.
3	180-182; For $C_{60}H_{72}O_{12}$, C, 73.15 (73.22), H, 7.37 (7.40); 984; 2932, 1760, 1190, 1140, 1062; -0.02 (2H, m), 0.76 (2H, m), 1.32 (12 H, t, 7.0), 1.49 (4H, m), 1.76 (4H, m), 2.40 (12H, m), 2.69 (4H, m), 3.03 (2H, d, 14), 4.25 (8H, q, 7.0), 4.39 (4H, d, 15), 4.51 (4H, d, 15), 4.51 (2H, d, 14), 4.55 (4H, m), 6.88 (4H, d, 1.9), 7.03 (4H, d, 1.9); 14.28, 23.01, 24.23, 26.86, 27.75, 33.36, 38.41, 60.74, 72.00, 128.14, 129.04, 133.77, 133.94, 136.18, 152.19, 170.12.
4	67-69; For $C_{29}H_{36}O_6$, C, 72.47 (72.66), H, 7.55 (7.63); 480; 2948, 1770, 1500, 1214, 1136, 1080; 0.15 (1H, m), 0.88 (1H, m), 1.27 (6H, t, 7.2),1.53 (2H, m), 1.73 (2H, m), 2.48 (6H, m), 2.67 (2H, m), 4.22 (4H, q, 7.2), 4.35 (2H, d, 15), 4.47 (2H, d, 15), 4.65 (2H, m), 6.37 (2H, d, 8.3), 6.62 (2H, dd, 8.3 & 2.1), 7.11 (2H, d, 2.1).

a) Microanalytical Center, Faculty of Engineering, Gunma University. b) A JEOL JMS-DX 302 mass spectrometer. c) A Hitachi 270-50 infrared spectrophotometer with KBr-disc method. d) A Varian Gemini-200 FT NMR spectrometer. In $CDCl_3$, using TMS as an internal standard.

hydrogen bond acceptor solvent [8] (Ha at δ3.39 with J=14 Hz and Hb at δ4.32 with J=14 Hz). 2) The Hc proton resonance (δ-0.22) shifts to a higher field by ca. 0.4 ppm from that of the parent metacyclophane **1**, due to the additional shielding effect (calcd 0.4 ppm)[9] coming from another cyclophane system. 3) The hydroxy protons of **1**, whose OH-OH distance is estimated 4.4 Å in a CPK model, resonate at δ5.04, just the typical chemical shift value for simple monomeric phenols, suggesting the lack of hydrogen bond in a molecule. On the contrary, the hydroxy protons of **2** resonate at much lower field, δ7.78. This large down-field shift clearly suggests the presence of intramolecular hydrogen bonding between two adjacent hydroxy groups, attaching upon each of two metacyclophane units, whose OH-OH distance is estimated to be 2.4 Å by a CPK model.

Tetraester **3** was obtained from **2** by the treatment of ethyl bromoacetate (5 equiv.), NaH (1.5 equiv.) in THF/DMF=10/1 for 12 h at 60-70 °C under N_2 in 89% yield (see Scheme 1). The NMR titration of tetraester **3** with alkali metal thiocyanate in CD_3OD and $CDCl_3$ was carried out.[4c,11] When an equimolar amount of thiocyanate was added to the host, the chemical shift difference of the methylene bridge resonance was leveled. Hence, ester **3** obviously formed a 1:1 complex with alkali metal ions. The selectivity of **3** at the metal ion binding was determined by the extraction of metal picrates into CH_2Cl_2. Results are summarized in Table 2. The effect of the restricted ring conformation clearly appears in the ion selectivity; i.e., ester **3** extracted large ions like K^+ and Rb^+ more efficiently than small ones like Li^+ and Na^+. This behavior makes a remarkable contrast to that of rather flexible parent calix[4]arene tetraester **5** which shows notable Na^+ selectivity.[10] Actually, the binding sites of **3** on aromatic rings cannot approach closely to each other to make the hole size as small as to fit smaller ions, due to the rigid framework constructed by the three bridged cyclophane skeletons.



5

It is noteworthy that cyclophane **2** can be made chiral by the displacement of one, two, or three hydroxyl groups with some achiral functional groups. In fact, a chiral cyclophane derived from **2** by displacing three OH groups with methoxyl ones was found to be a racemic mixture whose enantiomeric components were successfully separated by a chiral HPLC column composed of amylose units.[12]

Table 2. Extraction (%) of alkali metal picrates by ionophores in CH_2Cl_2[a]

Ionophore	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+
3	15.9	32.8	90.2	95.7	88.3	33.0
4[b]	<1	<1	<1	<1	<1	<1
5[c]	15.0	94.6	49.1	23.6	48.9	---
18-crown-6	3.6	17.6	82.8	81.5	65.5	39.2

a) Extraction conditions: 2.5×10^{-4} M of ionophore in CH_2Cl_2; 2.5×10^{-4} M of picric acid in 0.1 M of MOH at 22 °C. Ionophore solution (5.0 ml) was shaken for 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) Actually the compound, the half of **3**, did not bind any alkali metal ions. c) Ref. 10.

In conclusion, we synthesized a calixarene analog firmly locked in the cone confor-mation in excellent yield. The new receptor shows different properties and selectivities from common calixarene derivatives on the binding of alkali metal ions. Further works are now in progress and will be reported elsewhere.

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References

1) "Synthesis of Macrocycles," ed by R. M. Izatt and J. J. Christensen, John Wiley & Sons, New York (1987); D. J. Cram, *Science,* **219**, 1177 (1983); K. Koga and K. Odashima, *J. Incl. Phenom.*, **7**, 53 (1989).

2) K. N. Trueblood, C. B. Knobler, E. Maverick, R. C. Helgeson, S. B. Brown, and D. J. Cram, *J. Am. Chem. Soc.*, **103**, 5594 (1981).

3) C. D. Gutsche, *Acc. Chem. Res.*, **16**, 161 (1983); S. Shinkai, *J. Incl. Phenom.*, **7**, 193 (1989).

4) a) C. Alfieri, E. Dradi, A. Pochini, R. Ungaro, and G. D. Andreetti, *J. Chem. Soc. Chem. Commun.*, **1983**, 1075; b) V. Böhmer, H. Goldmann, and W. Vogt, *ibid.*, **1985**, 667; c) A. Arduini, A. Pochini, S. Reverberi, and R. Ungaro, *Tetrahedron*, **42**, 2089 (1986); d) P. J. Dijkstra, J. A. J. Brunink, K.-E. Bugge, D. N. Reinhoudt, S. Harkema, R. Ungaro, F. Ugozzoli, and E. Ghidini, *J. Am. Chem. Soc.*, **111**, 7567 (1989); e) V. Böhmer, W. Vogt, and H. Goldmann, *J. Org. Chem.*, **55**, 2569 (1990).

5) J. Nishimura, H. Doi, E. Ueda, A. Ohbayashi, and A. Oku, *J. Am. Chem. Soc.*, **109**, 5293 (1987); Y. Okada, S. Mabuchi, M. Kurahayashi, and J. Nishimura, *Chem. Lett.*, **1991**, 1345.

6) Y. Okada, K. Sugiyama, Y. Wada, and J. Nishimura, *Tetrahedron Lett.*, **31**, 107 (1990); Y. Okada, K. Sugiyama, M. Kurahayashi, and J. Nishimura, *ibid.*, **32**, 2367 (1991).

7) C. D. Gutsche, B. Dhawan, K. H. No, and R. Muthukrishnan, *J. Am. Chem. Soc.*, **103**, 3782 (1981); D. W. Chasar, *J. Org. Chem.*, **50**, 545 (1985); C. D. Gutsche, M. Iqbal, and D. Stewart, *ibid.*, **51**, 742 (1986).

8) C. D. Gutsche and L. J. Bauer, *Tetrahedron Lett.*, **22**, 4763 (1981).

9) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," ed by F. A. Bovey, Academic Press, New York (1988), p.106. This result was estimated by isoshielding line ($z=2.3$, $\rho=1.8$). If **2** has an alternative situation (coupled head-to-tail), the shielding effect was less than 0.1 ppm ($z=2.3$, $\rho=3.5$).

10) M. A. McKervey, E. M. Seward, G. Ferguson, B. Ruhl, and S. J. Harris, *J. Chem. Soc.,Chem. Commun.*, **1985**, 388; F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, E. Marques, B. L. Ruhl, M. J. Schwing-Weill, and E. M. Seward, *J. Am. Chem. Soc.*, **111**, 8681 (1989).

11) D. Live and S. I. Chan, *J. Am. Chem. Soc.*, **98**, 3769 (1976); J. Rebek, Jr., T. Costello, L. Marshall, R. Wattley, R. C. Gadwood, and K. Onan, *ibid.*, **107**, 7481 (1985).

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