Synthesis and Characterization of Macrocycles as Enlarged Calix[4]arene Analogues

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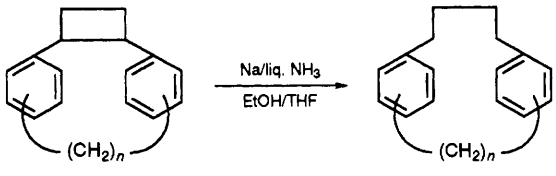
Macrocycle **2**, which is obtained in 86% yield from calixarene analogue **1** by Birch reduction, does not undergo intramolecular benzene-ring rotation between room temp. and 125 °C according to variable temperature (VT) NMR experiments and derivative **3** is an ionophore for alkali metals, transition metals and lanthanoids.

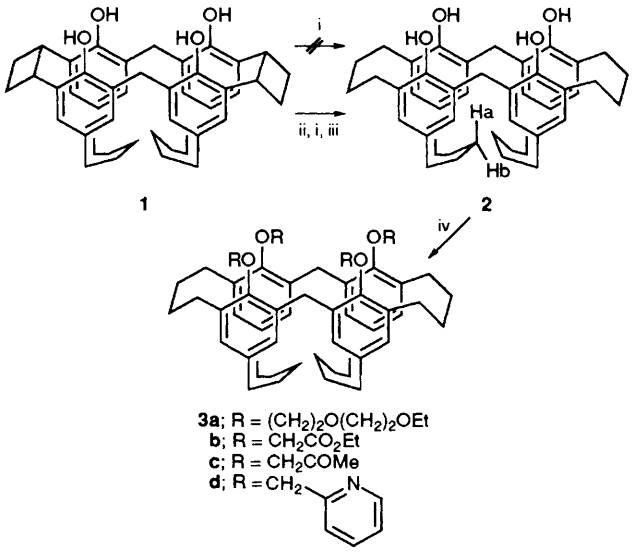
Calixarenes have a versatile molecular framework as ionophores and molecular receptors. And modifications to obtain new functionalized and/or bridged calixarenes have been studied extensively. We recently reported the synthesis and characterization of the calixarene analogue **1** as a bridged calixarene.[1] Analogue **1** derived from metacyclophane, has several attracting features: (*i*) its three-bridged structure retains the cone conformation. (*ii*) Two located hydrogen bonding sites are made between each pair of neighbouring OH groups, while calix[4]arene has only one at the centre. (*iii*) Several derivatives of **1** act as excellent ionophores for alkali metals, transition metals and lanthanoids.[2] Accordingly, we were prompted to study the modification of **1** in order to alter its hydrogen-bonding nature and ionophoric behaviour. First, we tried Birch reduction, because it conveniently transforms [2.*n*]cyclophanes to [4.*n*]cyclophanes and got intriguing results as shown in eqn. (1).[3] In this communication, we report this modification and the characterization of the new macrocycle **2**.



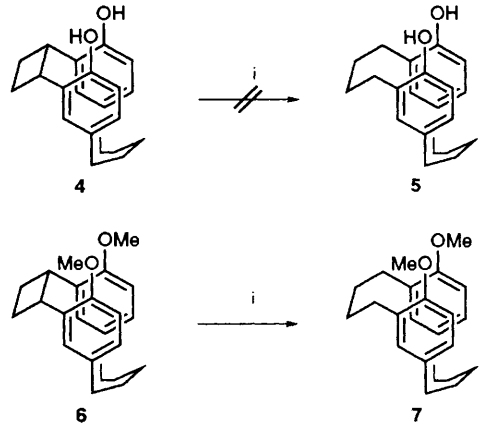
(1)

The synthetic route is shown in Scheme 1. We examined direct Birch reduction of **1** under reported conditions.[3,4] The reduction, however, did not occur and only the starting material was recovered, which suggests that phenoxide ion generated in the media prevented radical anion from forming, owing to electronic repulsion between solvated electrons and phenoxides. Dihydroxy[2.5]metacyclophane **4** did not give any reduced product as shown in Scheme 2. On the other hand, *syn*-dimethoxy[2.5]metacyclophane **6** quantitatively afforded the desired *syn*-dimethoxy[4.5]metacyclophane **7**.

Based on these observations, phenolic OH group was protected by the etherification before Birch reduction as shown in Scheme 1. A methoxymethyl (mom) group was chosen, because its protection and deprotection are readily done under mild conditions.[5] The methoxymethylation was



Scheme 1 *Reagent and conditions*: i, Na/liq. NH_3/EtOH/THF; ii, $ClCH_2OMe$/NaH/THF; iii, THF/HCl; iv, R–X/NaH/THF/DMF



Scheme 2 *Reagents and conditions*: i, Na/liq. NH_3/EtOH/THF

performed with **1** (31 mmol dm^{-3}), chloromethyl methyl ether (10 equiv.), and NaH (2 equiv.) in dry tetrahydrofuran/dimethylformamide (THF/DMF) (9/1) at 40–45 °C for 12 h under N_2. After column chromatography (benzene/ethyl acetate 19/1), the ether was obtained in 90% yield. Birch reduction was carried out with the ether (4.3 mmol dm^{-3}), Na (150 equiv.), and EtOH (4 equiv.) in liq. NH_3/dry THF (1/1) at −60 °C for 4 h under N_2. The deprotection was carried out with the crude product (1 mmol dm^{-3}) in THF/aq. HCl (1/1) at 50 °C for 12 h. After column chromatography (benzene/ethyl acetate, 8/2), pure **2** was obtained in overall 95% yield.† The structure was determined by ^1H NMR, including COSY, NOESY and ^{13}C NMR[1] judged by the following findings: (*i*) after Birch reduction, cyclobutane ring methine protons (δ 4.56) of **1** are disappeared. (*ii*) The AB type coupling of methano-bridges is shifted from δ 3.28 and 3.97 for **1** to δ 3.33 and 4.16 for **2**, owing to the release of strain. (*iii*) The inner methine protons (Ha) of **2** resonate at normal chemical shift δ 0.59 in contrast with **1** at δ −0.22. This result suggests that the distance between benzene nuclei is spread to make the shielding effect to these protons decrease. Furthermore, Ha and Hb lie in inequivalent environments so that they resonate at different positions, δ 0.59 and 0.84. (*iv*) The hydroxy proton chemical shift of **2** (δ 6.14) reveals that it has weaker hydrogen bonding than that of cyclophane **1** (δ 7.78), and, therefore, **2** has rather apart benzene rings by the reduction of cyclobutane ring. (*v*) Interestingly, **2** did not undergo intramolecular benzene ring rotation, which was proved by VT NMR experiments; *i.e.* **2** kept the cone conformation between room temp. and 125 °C in $(CD_3)_2SO$ or from room temp. to 100 °C in [$^2H_5$]pyridine. Macrocycle **2** is rather limited in its inner movements, even if it is more flexible than **1**.

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

	Receptor			
Cation	**3a**	**3b**	**3c**	**3d**
Li^+	<1	<1	<1	<1
Na^+	4.9	4.7	<1	<1
K^+	5.1	5.4	<1	<1
Rb^+	6.2	6.3	<1	<1
Cs^+	6.8	6.7	<1	<1
NH_4^+	<1	<1	<1	<1
Cr^{3+}	4.2	11.8	8.2	77.6
Mn^{2+}	<1	2.7	<1	26.6
Ni^{2+}	<1	3.2	<1	21.1
Cu^{2+}	<1	<1	<1	25.7
Zn^{2+}	<1	2.8	<1	33.2
Ag^+	<1	2.9	<1	98.4
Hg^{2+}	1.7	17.6	12.3	97.6

[a] Extraction conditions: 2.5×10^{-4} mol dm^{-3} of receptor in CH_2Cl_2; 2.5×10^{-4} mol dm^{-3} of picric acid in 0.1 mol dm^{-3} of MOH for alkali metals or 2.5×10^{-5} mol dm^{-3} of picric acid in 1×10^{-3} mol dm^{-3} of metal nitrate for transition metals at 22 °C. Receptor 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%.

Since **2** has several interesting features mentioned above, we investigated its metal ion extraction to clarify the difference between molecular structures of **1** and **2**.[2] The derivatization of **2** is shown in Scheme 1. Ethers **3** were obtained in 63–87% yields with **2** (45 mmol dm^{-3}), R–X (3 equiv.), and NaH (2 equiv.) in THF/DMF (9/1) at 70–80 °C for 12 h under N_2. The structures were determined by ^1H NMR spectroscopy.[2] The essential spectroscopic features are as follows: (*i*) the protons of methylene bridges for **3**, which show AB type coupling mode, appear more separately at δ 3.10–3.23 and 4.40–4.51 than those for **2** at δ 3.33 and 4.16. (*ii*) The phenyl ether α-methylene protons of **3** are considerably restricted from the free rotation and exhibit AB type coupling (H_1:

† All new compounds gave satisfactory physical and analytical data. Physical and analytical data of cyclophanes **2** and **3**. **2** m.p. >300 °C; IR ν/cm^{-1} 3400, 2925, 1482, 1230; ^1H NMR δ 0.59 (2H, m), 0.84 (2H, m), 1.10–1.90 (16H, m), 2.23–2.80 (16H, m), 3.33 (2H, d, *J* 14 Hz), 4.16 (2H, d, *J* 14 Hz), 6.14 (4H, bs), 6.53 (4H, d, *J* 2.0 Hz), 6.75 (4H, d, *J* 2.0 Hz). **3a** m.p. 84–87 °C; ν/cm^{-1} 2910, 1472, 1220, 1125, 1055; δ 0.65 (2H, m), 0.90 (2H, m), 1.20 (12H, t, *J* 7.0 Hz), 1.09–1.38 (8H, m), 1.67 (8H, m), 2.20 (4H, bd-like), 2.51 (8H, m), 2.88 (4H, bd-like), 3.10 (2H, d, *J* 14 Hz). 3.35–4.00 (40H, m), 4.51 (2H, d, *J* 14 Hz), 6.71 (4H, d, *J* 2.0 Hz), 6.94 (4H, d, *J* 2.0 Hz). **3b** m.p. 180–183 °C; ν/cm^{-1} 2924, 1762, 1198, 1076; δ 0.65 (2H, m), 0.92 (2H, m), 1.30 (12H, t, *J* 7.1 Hz), 1.06–1.40 (8H, m), 1.78 (8H, m), 2.25 (4H, m), 2.54 (8H, m), 2.95 (4H, m), 3.19 (2H, d, *J* 14 Hz), 3.92 (4H, d, *J* 15 Hz), 4.25 (4H, d, *J* 15 Hz), 4.25 (8H, m), 4.49 (2H, d, *J* 14 Hz), 6.76 (4H, d, *J* 2.0 Hz), 7.03 (4H, d, *J* 2.0 Hz). **3c** m.p. 208–209 °C; ν/cm^{-1} 2924, 1720, 1470, 1212, 1052; δ 0.69 (2H, m), 0.87 (2H, m), 1.02–1.48 (8H, m), 1.72 (8H, m), 2.13–2.38 (4H, m), 2.21 (12H, s), 2.52 (8H, m), 2.70 (4H, m), 3.13 (2H, d, *J* 13 Hz), 4.01 (4H, d, *J* 16 Hz), 4.14 (4H, d, *J* 16 Hz), 4.40 (2H, d, *J* 13 Hz), 6.75 (4H, d, *J* 2.0 Hz), 6.98 (4H, d, *J* 2.0 Hz). **3d** m.p. 89–91 °C; ν/cm^{-1} 2925, 1593, 1480, 1435, 1370, 1220, 1040, 755; 0.74 (2H, m), 0.90 (2H, m), 1.31 (4H, m), 1.60 (8H, m), 1.80 (4H, m), 2.05–2.70 (16H, m), 3.23 (2H, d, *J* 13 Hz), 4.50 (2H, d, *J* 13 Hz), 4.65 (4H, d, *J* 15 Hz), 4.71 (4H, d, *J* 15 Hz), 6.74 (4H, d, *J* 1.8 Hz), 6.94 (4H, td, *J* 6.0, 0.8 Hz), 6.97 (4H, d, *J* 1.8 Hz), 7.10 (4H, td, *J* 7.6, 0.8 Hz), 7.20 (4H, dd, *J* 7.6, 0.8 Hz), 8.32 (4H, dd, *J* 6.0, 0.8 Hz).

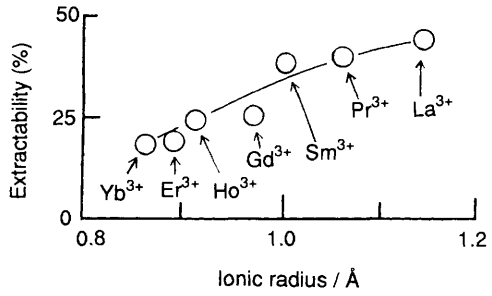


Fig. 1 The extraction results of lanthanoids by **3d**; 2.5×10^{-4} mol dm^{-3} of **3d** in CH_2Cl_2 and 2.5×10^{-5} mol dm^{-3} of picric acid in 1×10^{-3} mol dm^{-3} of metal nitrate at 22 °C

δ 3.92–4.65, *J* 10–16 Hz and H_2: δ 4.01–4.71, *J* 10–16 Hz) in contrast with a singlet of calix[4]arenes,[6] although **2** takes a less strained structure, compared with **1**. (*iii*) And moreover, these methylene protons of **3** appear at upfield region (*ca.* δ 0.1–0.5) more than those of derivatives of **1**, owing to the electronic effect of benzene rings. These findings show that methylene protons considerably interfere with butano and methylene bridges even after reduction.

Ethers **3** did extract metal ions into organic phase. The results are listed in Table 1 and also depicted in Fig. 1.[2,7] The remarkable points of extraction are summarized: (*i*) ionophore **3** showed moderate extraction for alkali metals. (*ii*) The ion selectivity of **3** is recognized for Cs^+ ion. This selectivity for largest Cs^+ ion shows that the binding sites of **3** exist apart from each other by the modification. (*iii*) **3** has high selectivity and moderate extractability for transition metals. In particular, **3d** having picolyl groups is an excellent ionophore in respect to both selectivity and extractability for Ag^+ and Hg^{2+}. (*iv*) **3d** also sufficiently extracted lanthanoids (see Fig. 1). The largest La^{3+} ion was most sufficiently extracted to organic phase by the reason as mentioned above. (*v*) The extractability of **3d** was gradually decreased for smaller lanthanoids.

In conclusion, calixarene analogue **1** having mom groups was transformed to macrocycle **2** in overall 95% yield by Birch reduction as a key step. Ethers **3** derived from **2** selectively extracted large alkali metals, transition metals, and lanthanoids. Further investigation now proceeds and will be reported elsewhere.

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