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Regioselective Synthesis of 1,2- and 1,3-Bridged Calix[4]crowns. What Are the Factors Controlling the Regioselectivity?

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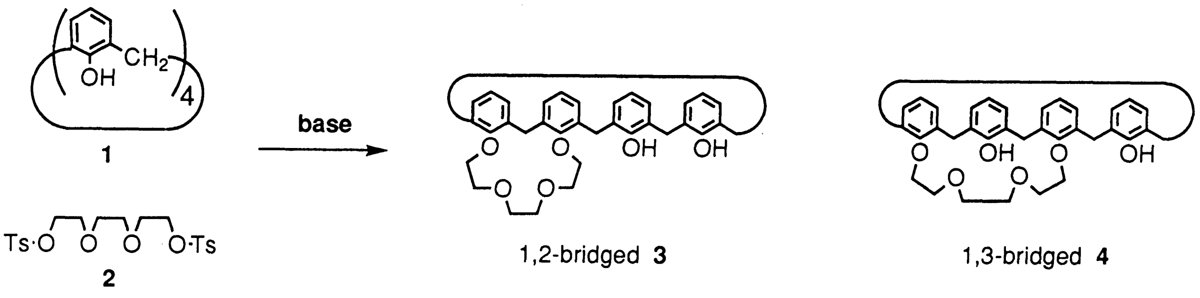
The product distribution in the synthesis of calix[4]crowns from calix[4]arene-25,26,27,28-tetrol and 3,6-dioxaoctane-1,8-ditosylate was investigated in detail. It was shown that the 1,2- vs. 1,3-bridging regioselectivity is governed by the basicity and the metal cation of the used base. The findings enable us to regioselectively synthesize desired calix[4]crowns in good yields, which has been believed to be too difficult to control.

Calix[4]crowns in which an oligo(ethylene oxide) chain is capped on the lower rim of a calix[4]arene ring have been reported by several groups and applied as ionophores for alkali and alkaline earth metal cations.[1-5] They generally shows high ion selectivity because of the rigidification effect arising from the calix[4]arene ring. We are also interested in this class of calix[4]arenes to design ionophores for ion-selective electrodes.[2-5] The survey of the past literatures taught us that the bridging occurs sometimes at 1,2-position (proximal phenyl units) but sometimes at 1,3-position (distal phenyl units) and the reason why such a change in product distribution takes place is not specified at all. We planned to design a calix[4]crown with a small ionophoric cavity from calix[4]arene-25,26,27,28-tetrol (**1**) and 3,6-diaxaoctane-1,8-ditosylate (**2**) to realize either Li$^+$ or Na$^+$ selectivity. We have found on the basis of careful product analyses in this reaction that several identifiable products plus a few unidentified products are formed and the ratio of 1,2-bridged (**3**) vs. 1,3-bridged (**4**) is profoundly affected by the base used for the Williamson-type reaction. The results reported here are important to reasonably explain confusion existing in the 1,2- vs. 1,3-bridging and to systematically classify the synthetic methods for calix[4]crowns.



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2

1,2-bridged **3**

1,3-bridged **4**

The reaction of **1** and **2** was carried out under various conditions as shown in Table 1. Figure 1 shows typical HPLC chromatograms of the product mixture. These compounds were isolated either by column chromatography (silica gel, chloroform-methanol) or by exclusion chromatography (JAIGEL-2H) and identified by ^{1}H NMR and mass spectral evidence. We thus succeeded in identifying 7 products (**3-5**, **7-10**).

Table 1. Reaction conditions and distribution of products

Run	Reaction conditions$^{a)}$			Product yield$^{b)}$ /%	Distribution of products /%							
	Base (equiv. of **1**)	Solvent	Temp ℃		3	4	5	6	7	8	9	10
1	LiH (4.2)	DMF	70	18	21	41	—	3	13	—	3	—
2	NaH (4.2)	DMF	70	66$^{c)}$	96	—	—	—	—	—	4	—
3	KH (4.2)	DMF	70	52$^{c)}$	91	—	2	6	—	—	1	—
4	NaH (3.0)	THF-toluene$^{d)}$	reflux	44$^{c)}$	64	—	18	—	—	5	4	9
5	Li_2CO_3 (10.0)	CH_3CN	reflux	10	—	10	—	—	90	—	—	—
6	Na_2CO_3(10.0)	CH_3CN	reflux	65$^{c)}$	6	71	10	—	5	6	2	—
7	Na_2CO_3(10.0)	DMF	70	52$^{c)}$	8	64	1	—	9	—	13	—
8	K_2CO_3 (10.0)	CH_3CN	reflux	60$^{c)}$	3	63	25	2	3	—	3	—

a) 1.05 equiv. (for **1**) of **2** is used unless otherwise mentioned. b) The product yields are estimated from all of the isolated products, the residue being unreacted **1** unless otherwise mentioned. c) Less than 5% (estimated from UV intensity) of unidentified products are included. d) THF:toluene = 10:1 v/v.

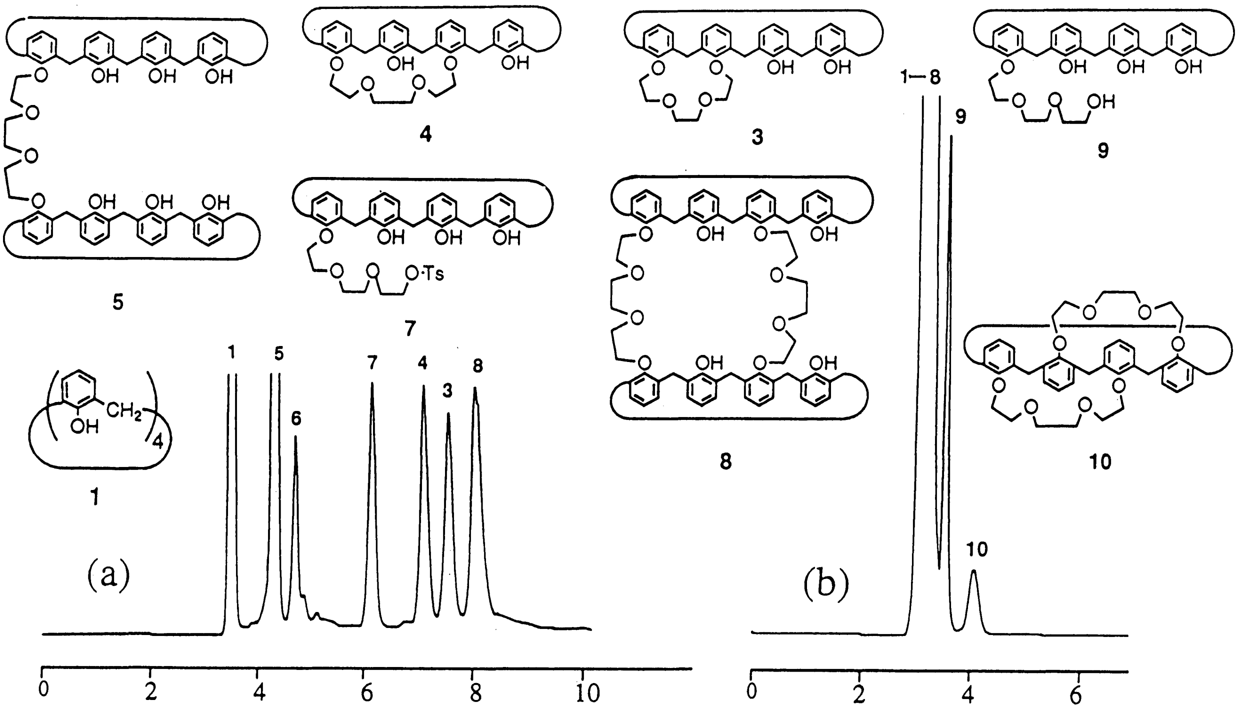
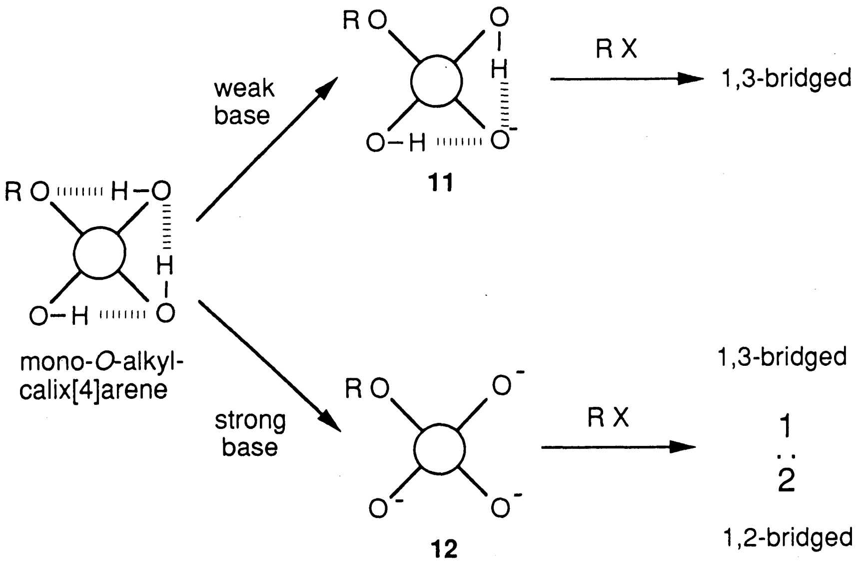


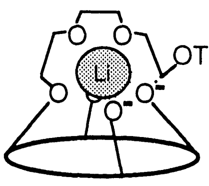
Fig. 1. HPLC chromatograms of the product mixture (column, silica gel): (a) eluent, chloroform:*n*-hexane = 65:35 v/v, (b) eluent, chloroform:methanol = 95:5 v/v.

Compounds **3**6) and **4**7) are desired 1,2- and 1,3-bridged calix[4]crowns with a cone conformation (determined by ^{1}H NMR). Compounds **10** is doubly-bridged calix[4]arenes which has a 1,3-alternate conformation8)(determined by ^{1}H NMR). This compound is yielded from **4** and the 1,3-alternate is the sole allowed conformation. Compounds **5** and **8** are mono-bridged and di-bridged biscalix[4]arenes, respectively: that is, intermolecular cross-link takes place in preference to intramolecular cross-link to give **3** and **4**. The ^{1}H NMR spectrum of **8** is very similar to that of **4** but mass spectroscopy (EI) established that **8** is a biscalix[4]arene (M^+ 1076). Compound **7** is a half-reacted species and **9** is its hydrolysis product by concomitant water. We could not identify **6** but the ^{1}H NMR spectrum showed that the structure is very similar to **5**.

The product distribution is summarized in Table 1. The yields were determined by HPLC assuming the same ε (at 270 nm) for each phenyl unit. The data in Table 1 are averaged values of two experiments. The reproducibility was generally good. Examination of Table 1 reveals that (i) when MH is used as a base, **3** is exclusively yielded in the presence of NaH and KH, whereas **4** becomes the major product in the presence of LiH, (ii) when M_2CO_3 is used as a base, **4** is yielded in preference to **3** and the yield of half-reacted **7** is increased, and (iii) the production of **10** is detected when THF-toluene (10:1 v/v) is used as a solvent (run 4). How can we explain these base effects on the product distribution?



Previously, we thoroughly investigated the base effect on the regioselectivity in 1,2- vs. 1,3-di-*O*-alkylation of calix[4]arenes.9) The problem is reduced to be a point that, when an alkylation reagent reacts with mono-*O*-alkylcalix[4]arene, it enters into the proximal position or into the distal position. When weak bases such as M_2CO_3 are used, they partly dissociate the OH groups and result mainly in **11**. This species predominantly yields 1,3-di-alkylated calix[4]arenes.9) The data for M_2CO_3 in Table 1 show that this rationale is valid also in the present system. When strong bases such as MH are used, three OH groups in mono-*O*-alkylcalix[4]arene are all dissociated (as in **12**) and *O*-alkylation occurs according to the probability to afford 1,2 : 1,3 in a 2:1 ratio.9) The product distribution for LiH, NaH, and KH reveals that this rationale is not necessarily valid in the present system and suggests that some additional effect must be taken into consideration. Provided that the oligo(ethylene oxide) chain in **7** acts like that in "lariat crowns",10) the reaction site may be subject to the metal template effect. Examination of CPK molecular models suggests that Li^+ complexation with **7** allows the terminal tosylate to react with the distal phenol (as in **13**), whereas Na^+ or K^+ complexation with **7** allows it to react with the proximal phenol (as in **14**). The difference is related to the size of alkali metal cations. This metal template effect reasonably elucidates **4** selectivity of LiH and **3** selectivity of NaH and KH.



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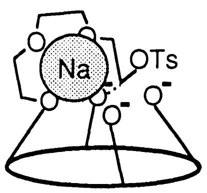

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The present study established the regioselective synthetic methods of 1,2- and 1,3-bridged calix[4]crowns. In conclusion, the regioselectivity is governed by the basicity of and the metal cation in the used base. We believe that this work has brought the controversial problem on the regioselectivity in the synthesis of calix[4]crowns to an end.

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6) Compound **3**: colorless crystal, mp 226-228 °C; mass spectrum (EI), m/e 538 (M^+); ^1H NMR ($CDCl_3$, 300MHz) δ 8.91 (s, 2H, OH), 7.12 (d, J=7.5 Hz, 2H, ArH), 7.01 (d, J=7.5 Hz, 2H, ArH), 6.99 (d, J= 7.5 Hz, 4H, ArH), 6.81 (t, J=7.5 Hz, 2H, ArH), 6.64 (t, J=7.5 Hz, 2H, ArH), 4.72 (d, J=ca.13 Hz, 1H, $ArCH_2Ar$), 4.34 (d, J=ca.13 Hz, 1H, $ArCH_2Ar$), 4.31 (d, J=ca.13 Hz, 2H, $ArCH_2Ar$), 4.29-4.24 (m, 6H, OCH_2), AA'BB'system, A; 4.18-4.11 (m, 2H, OCH_2), B; 3.97-3.88 (m, 2H, OCH_2), 4.05 (m, 2H, OCH_2), 3.42 (d, J=ca.13 Hz, 1H, $ArCH_2Ar$), 3.41 (d, J=ca.13 Hz, 2H, $ArCH_2Ar$), 3.38 (d, J=ca.13 Hz, 1H, $ArCH_2Ar$).
7) Compound **4**: colorless crystal, mp>400 °C (dec.); mass spectrum (EI), m/e 538 (M^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.76 (s, 2H, OH), 7.05 (d, J=7.5 Hz, 4H, ArH), 7.02 (d, J=7.5 Hz, 4H, ArH), 6.82 (t, J= 7.5 Hz, 2H, ArH), 6.60 (t, J=7.5 Hz, 2H, ArH), 4.38 (d, J=12.6 Hz, 4H, $ArCH_2Ar$), AA'BB'system, 4.25-4.18 (8H, $ArOCH_2CH_2O$), 4.02 (s, 4H, $CH_2OC\underline{H_2}C\underline{H_2}OCH_2$), 3.39 (d, J=12.6 Hz, 4H, $ArCH_2Ar$).
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