

Synthesis of *p*-*tert*-Butyl-calix[6]-biscrown-3 via Intramolecular Ring-closure of 1,4-Bis(2-(2-chloroethoxy)ethoxy)-*p*-*tert*-butyl-calix[6]arene

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With a variation in reaction conditions, 1,4-bis(2-(2-chloroethoxy)ethoxy)-calix[6]arene (3) and 1,3,5-tris(2-(2-chloroethoxy)ethoxy)-calix[6]arene (4) or 4 and 4-chloroethoxyethoxy-calix[6]crown-3 (5) were selectively synthesized from *p*-*tert*-butyl-calix[6]arene and 2-(2-chloroethoxy)ethyltosylate. 1,3,4,6-*p*-*tert*-butylcalix[6]-biscrown-3 (6) with (u,u,u,d,d,d) conformation and 1,3,4,5-*p*-*tert*-butylcalix[6]-biscrown-3 (7) with self-anchored (u,u,u,u,u,d) conformation were synthesized through an intramolecularly ring-closing condensation of 1,4-bis(2-(2-chloroethoxy)ethoxy)-*p*-*tert*-butyl-calix[6]arene (3) in 25% and 15% yield, respectively. Using 5 instead of 3, only 7 was obtained in 65% high yield. 6 and 7 show different complexation properties toward alkali metal and ammonium ions.

Keywords Calix[6]arene, crown ether, calixcrown, synthesis

Introduction

Calixcrowns constitute a family of calixarenes, in which phenolic oxygens are bridged intramolecularly with an oligo(oxyethylene) chain. As calixcrowns possess well preorganized structures and more rigid binding sites when compared with calixarenes and crowns, they exhibit a more outstanding recognition ability toward alkali metal cations than the latter two.¹ At present, the calix[4]crown chemistry is approaching maturity. Not only all types of calix[4]monocrowns but also all types of calix[4]-biscrowns have been synthesized, and their recog-

nition ability toward ions and molecules was extensively studied.²⁻⁵ In contrast, the calix[6]crown chemistry has been receiving little attention, though it is regarded as the next candidate for close scrutiny. In 1995, Ungaro *et al.* reported the synthesis of lower-rim-1,4-bridged calix[6]crown-5.⁶ Recently, two types of calix[6]-biscrown-4s: *p*-*tert*-butylcalix[6]-1,4-2,5-biscrown-4⁷ and 1,4-diallyloxy-calix[6]-2,3-5,6-biscrown-4⁸ have been synthesized. The latter exhibits high Cs⁺/Na⁺ selectivity.

As an extension of our previous studies on the synthesis of calix[6]-biscrowns⁷, in this paper we wish to report a new and facile method for synthesizing two isomers of *p*-*tert*-butylcalix[6]-biscrown-3 and their complexation properties toward alkali metal and ammonium ions.

Synthesis and characterization

Investigation of the functionalization of *p*-*tert*-butylcalix[6]arene (1) with 2-(2-chloroethoxy)ethyltosylate (2) shows that the products depend on the reaction conditions. Reaction of *p*-*tert*-butylcalix[6]arene (1) with 2-(2-chloroethoxy)ethyltosylate (2) (2.0 eqivs) took place in the presence of weak base-K₂CO₃ (2.0 eqivs) in a refluxing acetonitrile for 15 h; 1,4-bis(2-(2-chloroethoxy)ethylcalix[6]arene (3) and 1,3,5-tris(2-(2-chloroethoxy)ethoxy)-calix[6]arene (4) could be separated in 35% and 12% yields, respective-

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Received August 21, 2000; accepted November 16, 2000.

Project supported by the National Natural Science Foundation of China (No.29772026).

ly. If the amount of base was increased to 20 equivs and the reaction time was extended to 72 h, 1,3,5-tris(2-(2-chloroethoxy)ethoxy)calix[6]arene (**4**) and a self-monobridged compound of **3**, 4-(2-(2-chloroethoxy)ethoxy)-*p*-*tert*-butylcalix[6]crown-3 (**5**) were obtained in 45% and 17% yields, respectively. Further treatment of **3** with NaH (4.0 equivs.) in refluxing benzene resulted in the self-intrabridging reaction to afford two isomers; 1,3-4,6-calix[6]-bis-crown-3 (**6**) and 1,3-4,5-calix[6]-biscrown-3 (**7**) in 25% and 15% yields, respectively. Using **5** instead of **3**, the yield of **7** increased to 65%. It is worthy to note that 1,4 and 1,3,5-substituted products were firstly obtained in the same mixture; **3** and **4** are very useful intermediates for constructing calix[6]cryptands and calix[6]crowns.

The structures of compounds **3**, **4**, **5**, **6** and **7** were characterized by FAB-MS spectra, elemental analyses, and ^1H NMR spectra. The ^1H NMR spectra of **3** show two singlets (ratio 1:2) for the *tert*-butyl groups as well as for the aromatic protons and one singlet for the hydroxyl proton, indicating that the calix[6]arene moiety is 1,4-substituted. However, no defined conformation of **3** at ambient temperature can be presented due to the overlapping signals for the diaryl methylene and oxyethylene moieties in the region of δ 3.10–4.10.

The ^1H NMR spectra of **4** show two singlets in a 1:1 ratio for the *tert*-butyl groups as well as for the aromatic protons and one singlet for the hydroxyl proton, indicating that the calix[6]arene moiety is 1,3,5-substituted. Several papers concerning 1,3,5-substituted or 1,3,5-triply bridged calix[6]arene⁹ have been published, and suggested that those compounds adopt cone conformation with C_{3v} -symmetry, and the ^1H NMR signals of the diaryl methylene protons in those compounds exhibit one pair of doublets. However, the ^1H NMR of **4** is different, the ArCH_2Ar protons in calixarene skeleton give three pairs of AB doublets in a 1:1:1 ratio. There is a rule that ArCH_2Ar protons function as a pair of AB doublets in the ^1H NMR spectrum if the two neighboring aryl groups are *syn* to one another, on the other hand, a singlet for the methylene hydrogen atoms indicates that the aryl groups are *anti* to one another.¹⁰ In this account, the (u,u,u,u,u,d) or (u,u,u,d,d,d) conformations can be ruled out. The $\Delta\delta_{\text{H}}$ values of the doublets of the ArCH_2Ar protons may provide another criterion for judging the relative direction of the neighboring phenyl groups. The $\Delta\delta_{\text{H}}$ values for the three pairs of the dou-

blets are 1.20, 1.02 and 0.18, respectively. Since $\Delta\delta_{\text{H}}$ for a regular cone conformation is *ca.* 0.9, the small $\Delta\delta_{\text{H}}$ value (*ca.* 0.18) indicates that one phenyl unit flanked by the C methylenes is flattened and the five residual phenyl units adopt a regular cone position.⁹ Furthermore, two types of $\text{OCH}_2\text{CH}_2\text{O}$ signals in a 1:2 ratio support that **4** exists in (u,u,u,u,u,ui) conformation (as shown in Scheme 1).⁹

In the ^1H NMR spectra of **5**, six singlets in a 1:1:1:1:1:1 ratio for the *tert*-butyl protons as well as for the aromatic protons indicate the calixarene moiety being 1,3,4- or 1,2,4-substituted. Five singlets in a 2:1:1:1:1 ratio for the ArCH_2Ar protons indicate that **5** adopts 1,3,5-alternate conformation.¹¹ Thus, the 1,2,4-isomer can be ruled out because it can not adopt this conformation.

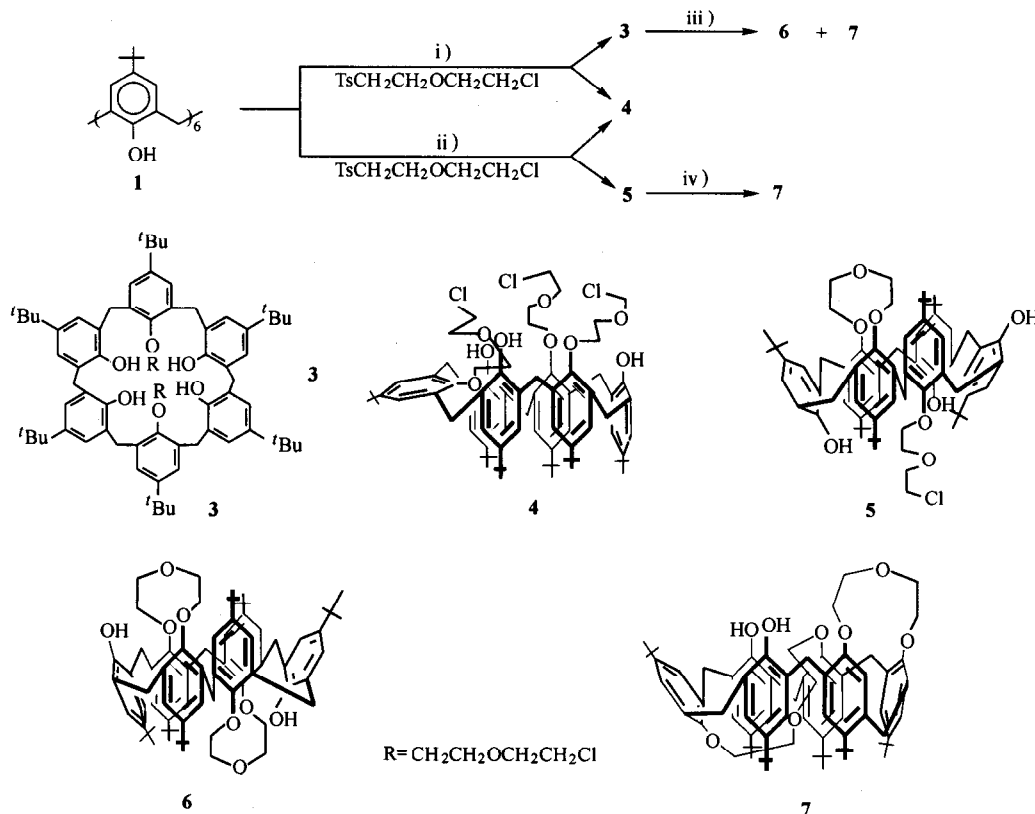
The existence of two ether bridges in compound **6** and **7** was deduced from FAB-MS data and signals in its ^1H NMR spectra. The ^1H NMR spectra of **6** show two singlets (ratio 1:2) for the *tert*-butyl groups indicating that it is a 1,2-4,5- or 1,3-4,6-isomer; one pair of AB doublets (8H) and one singlet (4H) for aryl methylene protons indicate that **6** is 1,3-4,6-*p*-*tert*-butylcalix[6]-biscrown-3 with (u,u,u,d,d,d) conformation.⁸ The 1,2-4,5-isomer in cone conformation must be ruled out because it should possess two pairs of doublets, and the 1,2-4,5-isomer in 1,2,3-alternate conformation may be ruled out by the two singlets in 1:2 ratio for the *p*-*tert*-butyl protons.

As compound **7** was derived from **5**, it should be one of the two possible isomers; *i. e.* 1,3-4,5 or 1,3-4,6-calix[6]-biscrown-3. However, the six singlets at 1.037, 1.150, 1.337, 1.419, 1.261 and 1.269 (overlapped) in a ratio of 1:1:1:1:1:1 for the *tert*-butyl supported the asymmetrical one, *i. e.* 1,3-4,5-calix[6]-biscrown-3. With the aid of H-HCOSY, four pairs of AB doublets and two singlets are assigned to the diaryl methylene protons, which indicate the conformation of **5** being (u,u,u,u,u,d). The signal pattern of diaryl methylene protons in a ratio of 1:1:1:1:1:1 is in agreement with the completely asymmetrical one, *i. e.* *p*-*tert*-butyl-calix[6]-1,3-4,5-biscrown-3. The upfield shift of protons of the $\text{OCH}_2\text{CH}_2\text{O}$ group from (3.7–3.9) to (2.62–2.9) suggests that **5** is a kind of self-anchored rotaxane,¹² in which one polyether chain is crossing through the cavity of calix[6]arene and the other is over the cavity, as depicted in Scheme 1.

Examination of the CPK molecule reveals that the compounds **6** and **7** are well preorganized for binding cations. The *p*-*tert*-butylcalix[6]-1,4-2,5-biscrown-4 (**8**)⁷ is used as a reference compound for extraction experiments. Percentage extraction of **6** and **7** toward picrate salts from water into CHCl₃ at 25 °C is summarized

in Table 1. It is useful to note that the compounds **6** and **7** show very high extraction ability toward cations as compared with *p*-*tert*-butylcalix[6]-1,4-2,5-biscrown-4 (**8**). Especially, 1,3-4,6-*p*-*tert*-butylcalix[6]-biscrown-3 (**6**) shows high selectivity toward Cs⁺, also **6** exhibits high extraction ability toward Et₃NH⁺.

Scheme 1



Reagents and conditions: i) K₂CO₃ (2.0 equivs) / CH₃CN, reflux, 15 h; ii) K₂CO₃ (20 equivs) / CH₃CN, reflux, 3 d; iii) NaH (4.0 equivs) / dry benzene, reflux, 8 h; iv) NaH (4.0 equivs) / dry benzene, reflux, 8 h.

Table 1 Percentage extraction (%E) of picrate salts from water into CHCl₃ at 25 °C

Host ^a	%E ^c							
	Li ⁺	Na ⁺	K ⁺	Cs ⁺	NH ₄ ⁺	<i>n</i> -PrNH ₃ ⁺	Et ₂ NH ₂ ⁺	Et ₃ NH ⁺
6	0.08	0.2	0.5	19.5	0.2	0.8	0.6	23.8
7	19.8	18.6	15.5	25.6	1.8	13.8	37.8	0.9
8 ^b	1.4	5.2	4.1	/	16.2	4.8	12.1	/

^a[Host] = [Guest] = 0.0001 mol/dm³. ^b These data were quoted from Ref. 7. ^c The percentage extraction (%E) was measured from the decrease in the aqueous phase (absorbance at 354 nm), and reconfirmed by the increase in the chloroform layer (absorbance at 380 nm)

Experimental

Melting points are uncorrected. ^1H NMR spectra were recorded on Bruker-ARX 300 instruments at ambient temperature. TMS was used as an internal standard. FAB-MS spectra were obtained from a Kratos MS80RF mass spectrometry service, with *m*-nitrobenzyl alcohol as a matrix. Elemental analyses were performed by the Analytical Laboratory of the Department of Chemistry. All chemicals were analytically pure and purified according to the known procedure.

Preparation of 3 and 4

A mixture of *p*-*tert*-butylcalix[6]arene (3.0 mmol) and $\text{TsCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{Cl}$ (6.0 mmol) in dry CH_3CN (250 mL) was refluxed under nitrogen atmosphere in the presence of K_2CO_3 (6.0 mmol) for 15 h. After the evaporation of CH_3CN under reduced pressure, a portion of 100 mL of CH_2Cl_2 was added, and the organic phase was washed with water (2×100 mL) and dried over MgSO_4 . The solvent was evaporated and the crude product was purified by column chromatography (silica gel, CH_2Cl_2) and recrystallized from $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$.

Compound 3 Yield 35%, $R_f = 0.72$ (CH_2Cl_2), m.p. 271–273 °C; ^1H NMR (300 MHz, CDCl_3) δ : 1.22 (s, 18H, $\text{C}(\text{CH}_3)_3$), 1.23 (s, 36H, $\text{C}(\text{CH}_3)_3$), 3.10–4.22 (overlapped, 28H, $\text{OCH}_2\text{CH}_2\text{O}$ and ArCH_2Ar), 7.01 (s, 4H, ArH), 7.12 (s, 8H, ArH), 7.28 (s, 4H, ArOH); MS (FAB) m/z (%): 1186 [$\text{M} + 2\text{H}$] $^+$; Anal. calcd. for $\text{C}_{74}\text{H}_{98}\text{O}_8\text{Cl}_2$: C 74.95, H 8.32; found C 74.67, H 8.25.

Compound 4 Yield 12%, $R_f = 0.28$ (CH_2Cl_2), m.p. 234–236 °C; ^1H NMR (300 MHz, CDCl_3) δ : 1.27 (s, 27H, $\text{C}(\text{CH}_3)_3$), 1.14 (s, 27H, $\text{C}(\text{CH}_3)_3$), 3.35 (d, $J = 15.6$ Hz, 2H, ArCH_2Ar), 3.49 (d, $J = 14.7$ Hz, 2H, ArCH_2Ar), 3.60 (d, $J = 13.8$ Hz, 2H, ArCH_2Ar), 3.71 (br, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.78 (d, $J = 13.8$ Hz, 2H, ArCH_2Ar), 3.93 (br, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.99–4.12 (overlapped, 16H, $\text{OCH}_2\text{CH}_2\text{O}$ and $\text{OCH}_2\text{-CH}_2\text{Cl}$), 4.37 (d, $J = 15.6$ Hz, 2H, ArCH_2Ar), 4.71 (d, $J = 14.7$ Hz, 2H, ArCH_2Ar), 6.89 (s, 6H, ArH), 7.12 (bs, 9H, ArH and ArOH); MS (FAB) m/z (%) 1292 [$\text{M} + \text{H}$] $^+$; Anal. calcd. for $\text{C}_{78}\text{H}_{105}\text{O}_9\text{Cl}_3$: C 72.45, H 8.18; found C 72.11, H 8.28.

Preparation of 4 and 5

A mixture of *p*-*tert*-butylcalix[6]arene (3.0 mmol) and $\text{TsCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{Cl}$ (9.0 mmol) in dry CH_3CN (250 mL) was refluxed under nitrogen atmosphere in the presence of K_2CO_3 (60.0 mmol) for 72 h. After the evaporation of CH_3CN under reduced pressure, a portion of 100 mL of CH_2Cl_2 was added and the organic phase was washed with water (2×100 mL) and dried over MgSO_4 . The solvent was evaporated and the crude product was purified by column chromatography (silica gel, CH_2Cl_2) and recrystallized from $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$.

Compound 4 Yield increased to 45%.

Compound 5 Yield 17%, $R_f = 0.34$ (CH_2Cl_2), m.p. 265–267 °C; ^1H NMR (300 MHz, CDCl_3) δ : 1.18, 1.19, 1.21, 1.21, 1.23, 1.23 (s, 9H each, $\text{C}(\text{CH}_3)_3$), 3.36 (br, 4H, $\text{OCH}_2\text{CH}_2\text{Cl}$), 3.50 (s, 2H, ArCH_2Ar), 3.66 (br, 8H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.94 (br, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 4.26 (s, 4H, ArCH_2Ar), 4.48 (s, 2H, ArCH_2Ar), 4.70 (s, 2H, ArCH_2Ar), 4.88 (s, 2H, ArCH_2Ar), 6.96, 6.99, 7.03, 7.06, 7.12, 7.18 (s, 2H each, ArH), 7.19, 7.49, 8.50 (s, 1H each, ArOH); MS (FAB) m/z (%): 1149 [$\text{M} + \text{H}$] $^+$; Anal. calcd. for $\text{C}_{74}\text{H}_{97}\text{O}_8\text{Cl}$: C 77.29, H 8.50; found: C 77.56, H 8.42.

Preparation of 6 and 7

3 (1 mmol) was refluxed in 30 mL of dry benzene in the presence of NaH (4.0 mmol) for 8 hours. After evaporation of benzene under reduced pressure, a portion of 100 mL of CH_2Cl_2 was added and the organic phase was washed with water (2×100 mL) and dried over MgSO_4 . The solvent was evaporated and the crude product was purified by column chromatography (silica gel, chloroform/*n*-hexane = 2:1) and recrystallized from $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$. 6 and 7 were obtained in 25% and 15% yields, respectively.

Compound 6 $R_f = 0.68$ (CH_2Cl_2), m.p. 234–236 °C; ^1H NMR (300 MHz, CDCl_3) δ : 1.01 (s, 18H, $\text{C}(\text{CH}_3)_3$), 1.15 (s, 36H, $\text{C}(\text{CH}_3)_3$), 3.40 (d, $J = 14.7$ Hz, 4H, ArCH_2Ar), 3.69–3.71 (m, 16H, $\text{OCH}_2\text{CH}_2\text{O}$), 4.01 (s, 4H, ArCH_2Ar), 4.32 (d, $J = 14.7$ Hz, 4H, ArCH_2Ar), 6.89 (d, $J = 14.7$ Hz, 4H, ArH), 7.12 (s, 4H, ArH), 7.19

(d, $J = 14.7$ Hz, 4H, ArH), 7.36 (br, 2H, ArOH); MS (FAB) m/z (%): 1113 $[M + H]^+$; Anal. calcd. for $C_{74}H_{96}O_8$: C 79.81, H 8.69; found: C 79.49, H 8.63.

Compound 7 $R_f = 0.46$ (CH_2Cl_2), m. p. 235—237 °C; 1H NMR (300 MHz, $CDCl_3$) δ : 1.03 (s, 9H, $C(CH_3)_3$), 1.14 (s, 9H, $C(CH_3)_3$), 1.25 and 1.26 (overlapped, 18H, $C(CH_3)_3$), 1.33 (s, 9H, $C(CH_3)_3$), 1.41 (s, 9H, $C(CH_3)_3$), 2.62—2.90 (m, 2H, OCH_2CH_2O), 3.02 (d, $J = 13.5$ Hz, 1H, $ArCH_2Ar$), 3.18 (d, $J = 12.9$ Hz, 1H, $ArCH_2Ar$), 3.34 (m, 6H, OCH_2CH_2O), 3.50 (d, $J = 16.2$ Hz, 1H, $ArCH_2Ar$), 3.55 (m, 2H, OCH_2CH_2O), 3.64 (d, $J = 16.8$ Hz, 1H, $ArCH_2Ar$), 3.81 (d, $J = 13.5$ Hz, 1H, $ArCH_2Ar$), 3.90 (s, 2H, $ArCH_2Ar$), 3.96 (s, 2H, $ArCH_2Ar$), 4.03—4.32 (m, 6H, OCH_2CH_2O), 4.51 (d, $J = 16.8$ Hz, 1H, $ArCH_2Ar$), 4.59 (d, $J = 16.2$ Hz, 1H, $ArCH_2Ar$), 4.80 (d, $J = 12.9$ Hz, 1H, $ArCH_2Ar$), 6.38, 6.56, 6.71, 6.94, 7.04, 7.21 (s, 1H each, ArH), 7.01, 7.17, 7.24 (s, 2H each, ArH), 7.35 (s, 2H, ArOH), 7.38 (s, 2H, ArOH); MS (FAB) m/z (%) 1112 (M^+ , 30), 1135 (MNa^+ , 45); Anal. calcd for $C_{74}H_{96}O_8$: C 79.81, H 8.69; found: C 79.65; H 8.60. Using 5 instead of 3, the yield of 7 was increased to 65%.

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(E200008165 LI, L.T.; DONG, L.J.)