

Regioselective intramolecular bridging of *p*-*tert*-butylcalix[10]arene

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Abstract The synthesis and characterization of a series of regioselective intramolecular bridging of calix[10]arene are described for the first time. Reacting *p*-*tert*-butylcalix[10]arene with tri-ethylene glycol ditosylate using K_2CO_3 as a base in toluene, 1,2-calix[10]crown-4 **2a**, 1,4-calix[10]crown-4 **2b** and 1,6-calix[10]crown-4 **2c** were obtained in yields of 9%, 14% and 7%, respectively. While using Cs_2CO_3 /acetone instead of K_2CO_3 /toluene, the 1,4-calix[10]crown-4 **2b** was obtained selectively in good yield up to 50%.

Keywords Calixcrowns · Calix[10]arene · Intramolecular · Bridging

Introduction

Calixcrowns comprise a family of calixarenes in which the phenolic oxygens are linked intramolecularly via flexible poly(oxyethylene) chains [1]. As they possess preorganized structures and more rigid binding sites in comparison with calixarenes and crown ethers, they exhibit superior recognition of ability toward alkali metal ions and other ions by the cooperation of calixarene and crown moieties. For instance, the Na^+/K^+ selectivity attainable with crown ethers has been saturated at the 10^2 order, with calixarenes the selectivity can reach $10^{3.1}$, but it is $10^{5.3}$ for diethoxycalix[4]crown-4 in a partial cone conformation [1]. And also, calix[4]arene crown-6 hosts have been

investigated for the sequestration and removal of radioactive ^{137}Cs from aqueous waste mixtures [2]. These successes have sparked a general interest in synthesis of calixcrowns, leading to almost of the possible regio- and atrop-isomers of single- and double-crowned calix[4,6,8]-arenes reported [3–5]. Although the greatest attention has been paid to calix[4,6,8]crowns, interesting results have recently been obtained also with ‘minor’ calix[5]crowns [6] and calix[7]crowns [7]. In contrast to the ‘major’ calix[*n*]arenes ($n = 4,6,8$), the large octamer [8] has remained largely less studied and the bridged calix[10]crowns are unknown, because the synthesis of parent *p*-*tert*-butylcalix[10]arene has remained difficult and the yield is less efficient [9]. Until 1999, Gutsche and co-workers have synthesized *p*-*tert*-butylcalix[10]arene in a rational yield from the acid-catalyzed condensation of *p*-*tert*-butylphenol and formaldehyde which has opened the door for the calix[10]arene chemistry [10]. Here we report the investigation of intramolecular bridging of calix[10]arene by an alkylation of *p*-*tert*-butylcalix[10]arene and tri-ethylene glycol ditosylate. Under selected conditions, a series of 1,2-, 1,4- and 1,6-bridged *p*-*tert*-butylcalix[10]crown-4 have been synthesized.

Experimental

Materials and methods

The 1H NMR was recorded at 400 MHz, on Varian Mercury 400 spectrometer. ESI mass spectra was obtained from a Finnigan LCQ Advantage mass spectrometry service. *p*-*tert*-butylcalix[10]arene was synthesized according to the literature procedures [10]. All solvents were purified by standard procedures. Petroleum ether refers to the

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fraction with b.p. 60–90 °C. All other chemicals were commercially available and used without further purification.

General procedure for the synthesis of compounds **2a**, **2b** and **2c** (K₂CO₃/toluene)

A suspension of *p*-*tert*-butylcalix[10]arene (**1**) (200 mg, 0.123 mmol) and anhydrous K₂CO₃ (221 mg, 1.60 mmol, see Table 1) in toluene (20 mL) was stirred for 1 h. Triethylene glycol ditosylate (62 mg, 0.135 mmol, 1.1 equiv., see Table 1) was added in four portions. The reaction mixture was stirred for 2 days under reflux. After the solvent was removed under reduced pressure, the residue was treated with 0.1 M HCl (20 mL) and extracted with CH₂Cl₂ (3 × 20 mL). After the organic phase was washed with H₂O (3 × 20 mL), the combined organic phase was evaporated to dryness again. The crude product was subjected to column chromatography to afford the isolated compounds (Table 1).

General procedure for the synthesis of compounds **2b** (Cs₂CO₃/acetone)

A suspension of *p*-*tert*-butylcalix[10]arene (**1**) (200 mg, 0.123 mmol) and anhydrous Cs₂CO₃ (401 mg, 1.23 mmol, see Table 1) in acetone (20 mL) was stirred for 1 h under reflux. Then a solution of the tri-ethylene glycol ditosylate (62 mg, 0.135 mmol, 1.1 equiv., see Table 1) dissolved in acetone (5 mL) was slowly added. The reaction mixture was stirred for 2 days under reflux. After the solvent was removed under reduced pressure, the residue was treated with 0.1 M HCl (20 mL) and extracted with CH₂Cl₂ (3 × 20 mL). After the organic phase was washed with H₂O (3 × 20 mL), the combined organic phase was evaporated to dryness. The crude product was subjected to column chromatography to give the only compound **2b**, yield 50%.

Compound **2a** was isolated by flash chromatography (SiO₂, gradient dichloromethane: petroleum ether 10:1 v/v)

white powder. m.p 200–202 °C ESI(+) MS *m/z* 1735.0 (MH⁺); ¹H NMR (400 MHz, CDCl₃): δ 1.19, 1.20, 1.22, 1.25, 1.27 (s each, C(CH₃)₃, each 18H), 3.88–4.26 (m, overlapped, 32H), 6.89 (d, ArH, 2H, J = 1.8 Hz), 7.00 (d, ArH, 2H, J = 1.6 Hz), 7.04 (d, ArH, 2H, J = 1.8 Hz), 7.10 (d, ArH, 2H, J = 1.8 Hz), 7.14–7.20 (m, overlapped, ArH, 12H), 8.86, 9.25, 9.48, 9.64 (br s each, ArOH, 2H each). Anal. Calcd. for C₁₁₆H₁₅₀O₁₂: C, 80.24; H, 8.71. Found: C, 80.17; H, 8.75.

Compound **2b** was isolated by column chromatography (SiO₂, gradient dichloromethane: petroleum ether 8:1 v/v) white powder. m.p 235–238 °C ESI(+) MS *m/z* 1735.6 (MH⁺) ¹H NMR (400 MHz, CDCl₃) δ 1.18, 1.21, 1.23, 1.25, 1.26 (s each, C(CH₃)₃, each 18H), 3.84–4.23 (m, overlapped, 24H), 4.29, 4.32 (t, 2H, OCH₂CH₂), 4.31(t, 4H, OCH₂CH₂), 7.00 (d, ArH, 2H, J = 2.0 Hz), 7.17 (d, ArH, 2H, J = 2.0 Hz), 7.07–7.16 (m, overlapped, ArH, 16H), 8.25, 8.75, 9.19, 9.20 (br s each, ArOH, 2H each). Anal. Calcd. for C₁₁₆H₁₅₀O₁₂: C, 80.24; H, 8.71. Found: C, 80.31; H, 8.69.

Compound **2c** was isolated by column chromatography (SiO₂, gradient dichloromethane: petroleum ether 6:1 v/v) white powder. m.p 266–268 °C ESI(+) MS *m/z* 1735.8 (MH⁺) ¹H NMR (400 MHz, CDCl₃) δ 1.24, 1.25, 1.26 (s, C(CH₃)₃, 18H, 36H, 36H), 3.80–4.14 (m, overlapped, 32H), 6.92 (s, ArH, 2H), 6.80 (s, ArH, 2H), 7.00–7.22 (m, overlapped, 16H), 8.57, 8.87 (br s each, ArOH, 4H each) Anal. Calcd. for C₁₁₆H₁₅₀O₁₂ · H₂O: C, 79.41; H, 8.73. Found: C, 79.39, H, 8.76.

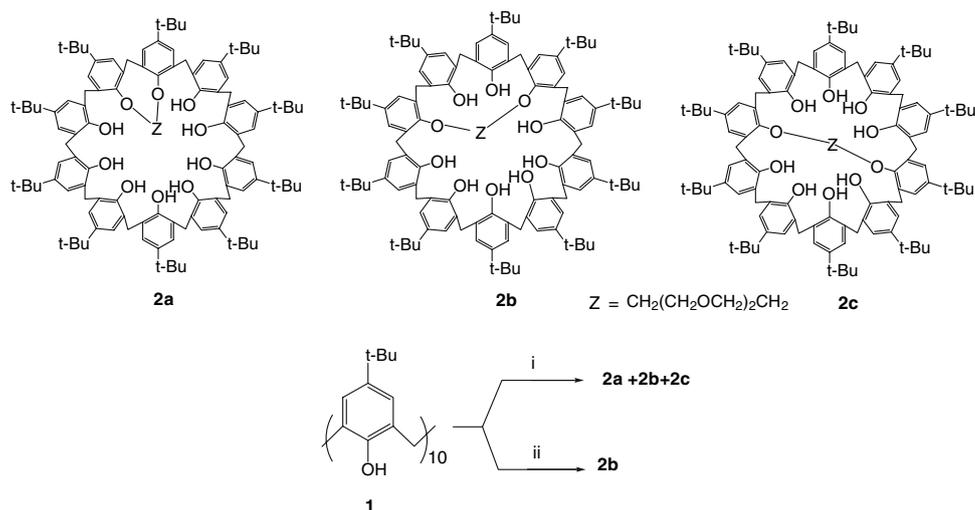
Results and discussion

The synthetic route is depicted in Scheme 1. Reacting *p*-*tert*-butylcalix[10]arene **1** with tri-ethylene glycol ditosylate in the presence of K₂CO₃ as the base in toluene (Table 1, entry 1), gave the corresponding 1,2-calix[10]-crown-4 **2a**, 1,4-calix[10]-crown-4 **2b** and 1,6-calix[10]-crown-4 **2c** in yields of 9%, 14% and 7%, respectively. With acetonitrile instead of toluene, the reaction is speeded up but the complex mixtures of products have been obtained. At the same time using the acetone instead of toluene no reaction occurred. After much effort, it was found that by treating *p*-*tert*-butylcalix[10]arene (**1**) with tri-ethylene glycol ditosylate in the presence of Cs₂CO₃ in acetone (Table 1, entry 4), the only 1,4-calix[10]crown-4 **2b** was obtained in good yield (50%) and the product was separated easily with the recovery of the starting material. With other solvent such as DMF or toluene instead of acetone, most of the calix[10]arene did not react, even after prolonging the reaction time to 3 days and finally the complex mixtures of products have been obtained. The different reactivity may be the result of the solubility of the

Table 1 Yield of 1,2- 1,4- 1,6-calix[10]crown-4

Entry	Base (equiv.)	Solvent	Isolated compd. (%)
1	K ₂ CO ₃ (13)	Toluene	2a (9), 2b (14), 2c (7)
2	K ₂ CO ₃ (13)	Acetonitrile	Complex mixtures of products
3	K ₂ CO ₃ (13)	Acetone	No reaction
4	Cs ₂ CO ₃ (10)	Acetone	2b (50)
5	Cs ₂ CO ₃ (10)	Toluene	Complex mixtures of products
6	Cs ₂ CO ₃ (10)	DMF	Complex mixtures of products

Scheme 1 Regioselective intramolecular bridging of *p*-*tert*-butylcalix[10]. Reagents and conditions: (i) K_2CO_3 /toluene; (ii) Cs_2CO_3 /acetone



base in the solvents examined. Cs_2CO_3 dissolves in acetone but is insoluble in other organic solvents. It is worth noting that the use of Cs_2CO_3 increase the yield of **2b** up to 50% indicating that cesium cation maybe give the effective templation in acetone.

All new compounds were characterized by ESI-MS, 1H NMR spectroscopy and elemental analysis. The structure assignment for intrabridged calix[10]arenes **2a**, **2b**, and **2c** was mainly based on spectral data. In particular, elemental analysis and ESI(+)-MS confirmed the molecular formula, while 1H NMR spectroscopy was used to assign the bridging pattern. For example, the ESI(+)-MS spectrum of **2a**, **2b** and **2c** shows the expected molecular ion peak in accordance with the molecular weight of the *p*-*tert*-butylcalix[10]-crown-4 which certainly indicates that in compound **2a**, **2b**, and **2c**, the calix[10]arene moiety is intramolecularly bridged by the tri-ethylene glycolic spacer at the adjacent phenolic hydroxyl positions. The 1H NMR spectrum of **2c** possess the highest symmetry (double Ar-Ar) characterized by a three-resonance pattern (ratio 1:2:2) for *tert*-butyl groups and two singlet (1:1) for the phenolic hydroxyl protons. The expected three *tert*-butyl singlets were clearly seen at δ 1.24, 1.25, 1.26 (1:2:2) and two phenolic hydroxyl singlets were seen at δ 8.57, 8.87 (1:1). This is in accordance with the structure of 1, 6-calix[10]-crown-4. It is worth noting that 1,2-bridged and 1,4-bridged possesses the same CH_2-CH_2 symmetry. Consequently, their 1H NMR spectra should display a five-singlet pattern (1:1:1:1:1) for *tert*-butyl groups and a four-singlet pattern (1:1:1:1) for the phenolic hydroxyl groups. From the 1H NMR spectrum of **2a**, **2b** they indicated the two possible bridging patterns: 1,2- or 1,4-bridging. Therefore, discrimination between these two bridging modes required additional information. Neri et al. have previously pointed out that the chemical shift values for the phenolic hydroxyl group can be used as a sensitive structural probe to

distinguish the 1,2-bridged and 1,4-bridged in the case of calix[8]arenes intramolecularly bridged at the lower rim [5a, 11d]. Therefore we used the chemical shift of OH groups for assignment of the bridging pattern. In fact, this value is neatly increasing in accordance with the number of H-bonds with proximal OH groups, allowing their classification as ‘isolated’ (i), ‘singly-H-bonded’ (s), and ‘doubly-H-bonded’ (d) [11]. 1,2-bridged calix[10]arenes should give rise to four ‘s, d, d, d’ OH signals in a 1:1:1:1 ratio, while the 1,4-bridged would give to ‘s, s, d, d’ (1:1:1:1) patterns, respectively. As shown in Fig. 1, the 1H NMR spectrum of 1,2-calix[10]crown-4 **2a** shows four OH singlets at 8.86, 9.25, 9.48 and 9.64 ppm (1:1:1:1) clearly attributable to an ‘s, d, d, d’ pattern while 1,4-calix[10]-crown-4 **2b** shows four OH singlets at 8.25, 8.75, 9.19 and 9.20 ppm (1:1:1:1) clearly attributable to an ‘s, s, d, d’ pattern. It is worth pointing out that the doubly-H-bonded signal appears at higher field with respect to compounds **2b** because of the reduced cooperativity in the shorter ‘semi-circular’ H-bond [11d].

In conclusion, intramolecular bridging of calix[10]arene is not only an important route to synthesize new host molecules, but also as a very convenient method to shape and preorganize calixarene macrocycles. A series of 1,2-; 1,4- and 1,6-bridged *p*-*tert*-butylcalix[10]crown-4 have been synthesized and characterized. In Cs_2CO_3 /acetone

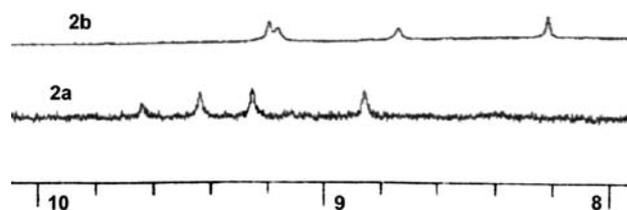


Fig. 1 OH region of the 1H NMR spectra of 1,2-calix[10]crown-4 **2a** (400 MHz, $CDCl_3$) and 1,4-calix[10]crown-4 **2b** (400 MHz, $CDCl_3$)

system, the 1,4-calix[10]crown-4 **2b** was obtained selectively in good yield up to 50%. The work may promote the syntheses of new types of intramolecular bridging calix[10]arenes, which can be considered as useful molecular scaffolds for shaping new calix[10] arene-based molecular hosts. Further research was investigated of bridging of calix[10]arene with polyfunctional agents.

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