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An Approach to Calix[6]cryptands with Bridgehead Carbon Atom : Stabilized in- and out- Stereoisomers

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Abstract: A new approach to cap 1,3,5-trimethyloxy-*p-tert*-butyl calix[6]arene with 1,1,1-tri(tosyloxyethoxyethoxymethyl)propane to form a pair of separable stabilized in- and out- calix[6]cryptands was reported. After heating **5a** or **5b** at 280℃, the interconversion between them was not detected by TLC, which provides a direct and non-spectral methodology to obtain unambiguous evidence for the ring immobilization in calix[6]arenes with stereoisomers. © 1998 Elsevier Science Ltd. All rights reserved.

Calixarenes have been proved to be useful building blocks for artificial receptors in supramolecular chemistry.[1] In order to preorganize the host it is usually desirable to derive the calixarenes with well-defined structures suitable for complexation. It is well-known that in calix[4]arene the oxygen-through-the-annulus rotation is inhibited simply through the introduce of substituents bulkier than ethyl group onto the lower rim and the calix[4]arene conformation thus can be immobilized, but the same attempt failed for calix[6]arenes even the introduced substituents are bulky groups, e.g. cholesterol group.[2-5] The reason is, as Shinkai *et al.* pointed out, that the calix[6]arene enjoys not only the oxygen-through-the-annulus rotation, but also the para-substituent-through-the-annulus rotation.[5]

In 1994, Reinhoudt *et al.* and Shinkai *et al.* put forward independently that capping-strategy is a key to suppress the ring inversion and control the structure of calix[6]arene in defined conformation, in general, cone conformation. Reinhoudt *et al.* synthesized cryptocalix[6]arenes by covalent three-point linking of a 1,3,5-trimethyloxy-*p-tert*-butylcalix[6]arene to a cyclotriveratrylene.[6] Shinkai *et al.* reported their capping-strategy in several reports.[7-9] In each case the starting materials were 1,3,5-trimethyloxy-*p-tert*-butylcalix[6]arene and a capping compound, i.e. the 1,3,5-triazine, the mesitylenyl, or the 1,3,5-tri(mercaptomethyl)benzene derivative. However, no in- and out- steric isomerism can be found in these compounds without bridgehead carbon atoms.

In this paper, we report for the first time a synthetic strategy to synthesize calix[6]cryptand with a bridgehead carbon atom. The key is selecting a starlike trifunctional reagent with three long and flexible

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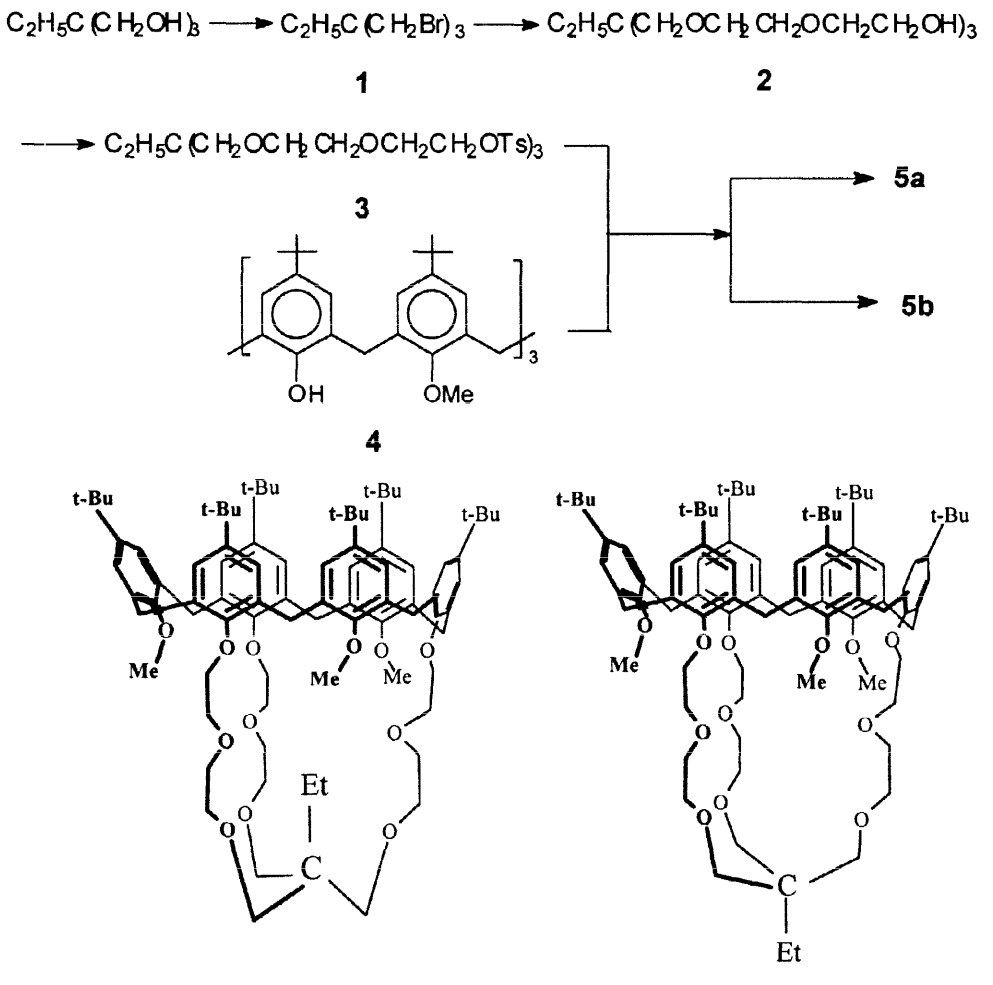
spacers as capping reagent. The synthetic routine is shown in Scheme 1.

Scheme 1



5a **5b**

The elemental analysis data indicate that the two compounds **5a** and **5b** have same composition. The FAB-MS spectra show identical and expected molecular ion peaks for **5a** and **5b**, too. The ^{1}H NMR spectra of **5a** and **5b** show two singlets for the *tert*-butyl groups, one AB system for the methylene bridges of the calix[6]arene skeleton, two singlets for the aromatic protons, one singlet and two pairs of triplets (or distorted triplets) for the protons in the cryptand moiety. Both **5a** and **5b** have the methoxy groups at δ 2.39 and 2.60 respectively,which reveal that the methoxy groups are flattened into the calix[6]arene cavity.[3,7] Thus, conclusions may be derived as follows: (i) **5a** and **5b** are calix[6]cryptands (ii) they are isomers (iii) **5a** and **5b** adopt a flattened cone conformation.[3,6,7]

However, the signals for the ethyl groups in **5a** and **5b** are different. Such signals in **5b** and the precursor **3** appear at δ 0.82 (CH_3, t, J = 7.3Hz), 1.12 ($-CH_2-$, q, J = 7.3Hz) and δ 0.79 (CH_3, t, J = 7.2Hz), 1.21 ($-CH_2-$, q, J = 7.2Hz); whereas that in **5a** shift to low field appearing at δ 0.92 (CH_3, t, J =

7.6Hz) and 1.49 (-CH_2-, q, J = 7.6Hz). In 1984, Allwood reported the synthesis of [3,3,3]cryptand starting from 2,3-O-isopropylidene-D-glycerol and 2,3-di-O-benzyl-L-glyecrol. This compound has two conformers: in, in- and out,out- ones. Allwood found that in the in, in- isomer, the bridgehead hydrogens included in the cryptand show signals at lower field in ^1H NMR spectra, in comparison with that of the out, out- isomer.[10] Thus, we can deduce that **5b** is the out- conformer of which the bridgehead ethyl group is out of the cryptand and **5a** is the in- conformer. Examination of the CPK molecular models reveals that the flexible spacers of **3** are long enough and the sites of both **3** and **4** for reaction are matchable. Thus, the direct condensation of **3** and **4** to form the in- and out- conformers is reasonable.

Table 1. Association Constants (Ka) of Complexes of Hosts with Picrate Salts in $CHCl_3$ Saturated with H_2O at 25 °C [a]

Host	$Ka\times10^{-5}$, $mol^{-1}\cdot L$			
	Li^+	**Na^+**	**K^+**	**NH_4^+**
5a	1.7	2.1	1.2	0.7
5b	20.3	18.1	8.1	2.9

[a] The association constants were determined as described by Cram *et al.*[11] Values were average results of three measurements.

The complexation ability of the two conformers also supports the above conclusion. Their association constants with alkali metal picrates were determined by the two phase (H_2O, $CHCl_3$) extraction method[11] and are summarized in Table 1. The complexation ability of **5a** is much lower than that of **5b**. This can be explained as the spacer oxygen atoms near the ethyl contribute with difficulty to form the host-guest complexes in **5a** due to steric hindrance, while there is not such steric hindrance in **5b**.

The similar isomerism was generally observed in the syntheses of cryptands with bridgehead carbon atoms.[10,12-14] Recently, Alder has thoroughly reviewed such interesting phenomena.[13] In most cases, the isomers were separated by column chromatography. Some difficulties were encountered in the separating process due to (i) very similar Rf values so that each isomer was obtained in low yield by collecting early and late fractions and (ii) conformational mobilities of the isomers so that the chromatography separation must be carried out at low temperature. In principle, the interconversion of **5a** and **5b** can be accomplished through two pathways (i) homeomorphic isomerization, i.e. interconverting by a process in which one chain passes through the ring formed by the other two chains and the bridgehead atom.[12-14] (ii) interconverting through the oxygen-through-the-annulus rotation, i.e. a flip-flop-type ring inversion. In the case of **5a** and **5b**, the two pathways are proved to be suppressed by the following experiments. Heating **5a** at 280℃ in a sealed tube, no **5b** was detected in the cooled substance by TLC. A similar result was also obtained for **5b** under the same conditions (silica gel, dichloromethane: diethyl ether = 4:1).[15] Thus, we can say that **5a** and **5b** are a pair of stabilized stereoisomers but not conformers.

Recently, Shinkai *et al.* suggested that no exchange between H_{ax} and H_{eq} in the $ArCH_2Ar$ methylene protons be observed in 2D EXSY [7] is an indirect evidence for the immobilization of the ring inversion in calix[6]arenes.[16] In 1996, Shinkai *et al.* reported an optically resolved calix[6]arene, the 1,3-phenyl units of which is bridged by an asymmetrical 4-methoxy-m-xylenyl unit.[16] This compound does not racemize at 100°C providing an unambiguous evidence in chiral calix[6]arenes. We can say that the separation of stabilized in- and out- isomers provides another effective methodology to obtain unambiguous evidence for the immobilization of the ring inversion in calix[6]arenes with stereoisomers.

EXPERIMENTAL

General. Where necessary solvents were purified and dried prior to use using standard procedures. Commercial grade chemicals were used without further purification. 1,3,5-trimethyloxy-*p*-*tert*-butylcalix[6]arene **(4)**[17] was prepared by published procedures. Melting points were recorded on a Gallenkamp melting point apparatus in open capillaries and were uncorrected. Nuclear magnetic resonance spectra were recorded using tetramethylsilane (TMS) as a reference. Electron impact and Fast atom bombardment mass spectra were obtained from a Kratos MS80RF mass spectrometry service.

1,1,1-tri(bromomethyl)propane (1). 70 ml (1.04 mol) of phosphorus tribromide was added slowly to 100 g (0.754 mol) of 1,1,1-trihydroxymethyl propane at 80°C (**CAUTION!**). The mixture was then heated slowly to 160°C and was maintained at that temperature for 18 h. The obtained solid was washed three times with 300 ml hot water, dried and purified by recrystallization from 95% ethyl alcohol to give 110 g of **1** in 46% yield, m.p 94~94.5°C. ^1H NMR ($CDCl_3$, 60MHz): δ 0.83 (t, 3H, J=7.0Hz, CH_3), 1.52 (q, 2H, J=7.0Hz, $-CH_2-$), 3.40 (bs, 6H, CH_2Br). Anal. Calcd for $C_6H_{11}Br_3$: C, 22.32; H, 3.43. Found: C, 22.24; H, 3.54.

1,1,1-tri(hydroxyethoxyethoxymethyl)propane (2). Under nitrogen, 42.3 g (1.84 mol) of sodiun was added by portion to 624 ml (6.58 mol) of diethyleneglycol (**CAUTION!**). After stirring for 0.5 h, 44 g (0.14 mol) of **1** was added to the solution. The mixture was stirred at 160°C for 20 h, and then quenched with 129 ml (1.48 mol) of 36% HCl. Most of the excess diethyleneglycol was removed under reduced pressure, the residue was extracted with 100 ml of acetone, filtered, and purified by column chromatography (silica gel, diethyl ether : acetone = 100:10~10:100) to give 41.9 g of **2** as a viscous liquid in 77.3% yield. ^1H NMR ($CDCl_3$, 60MHz): δ 0.78 (t, 3H, J=7.0Hz, CH_3), 1.24 (q, 2H, J=7.0Hz, $-CH_2-$), 3.27 (bs, 9H, $-CH_2O-$ and OH), 3.57 (bs, 24H, $-CH_2CH_2O-$). MS (EI, 70ev): m/z = 398 (M^+). Anal. Calcd for $C_{18}H_{38}O_9$: C, 54.25; H, 9.61. Found: C, 54.61; H, 9.73.

1,1,1-tri(tosyloxyethoxyethoxymethyl)propane (3). A solution of 48.5 g (0.25 mol) of tosyl chloride in 110 ml of pyridine was added slowly to a solution of 31.5 g (0.079 mol) of **2** at 0°C. After stirring for 12 h at 5°C, the mixture was poured into ice water, acidified to pH=1 with 36% HCl and extracted three times with 100 ml portions of chloroform. The combined organic phase was washed four times with 100 ml portions of water and dried with magnesium sulfate. Pure compound **3** was isolated by column chromatography (silica gel, dichloromethane : diethyl ether = 9:1)as pale yellow viscous liquid (30.6 g) in 45% yield. ^{1}H NMR ($CDCl_3$, 60MHz): δ 0.79 (t, 3H, J=7.2Hz, CH_3), 1.21 (q, 2H, J=7.2Hz, -CH_2-), 2.33 (s, 9H, ArCH_3), 3.17 (s, 6H, -CH_2O-), 3.33~3.80 (m, 18H, -CH_2CH_2O-), 3.92~4.20 (m, 6H, -CH_2CH_2O-), 7.39 (d, 6H, J=7.6Hz, ArH), 7.72 (d, 6H, J=7.6Hz, ArH). MS (EI, 70ev): m/z = 860 (M^+). Anal. Calcd for $C_{39}H_{56}O_{15}S_3$: C, 54.40; H, 6.56; S, 11.17. Found: C, 54.73; H, 6.97; S, 11.47.

Compound (5a) and **(5b)**. To a solution of 1.55 g (1.53 mmol) of **4** in 100 ml of dry dioxane, 0.20 g (6.67 mmol) of sodium hydride (80%) was added under nitrogen and the mixture was refluxed for 0.5 h. Then a solution of 1.32 g (1.53 mmol) of **3** in 100 ml of dry dioxane was added dropwise to the boiling mixture with stirring. After 24 h of refluxing, 20 ml of methanol was added. The solvents was evaporated and the residue was dissolved in 100 ml of chloroform, washed three times with 50 ml portions of brine and dried with magnesium sulfate. The crude product was separated by column chromatography (silica gel, dichloromethane : diethyl ether = 10:1) to give **5a**, 0.67 g, 32.3% yield, m.p. > 298℃ (dec.), R_f = 0.72 (silica gel, dichloromethane : diethyl ether = 4:1) and **5b**, 0.45 g, 21.7% yield, m.p > 320℃ (dec.), R_f = 0.34 (silica gel, dichloromethane : diethyl ether= 4:1). **5a** ^{1}H NMR ($CDCl_3$, 500MHz): δ 0.82 (s, 27H, $C(CH_3)_3$), 0.92 (t, 3H, J=7.6Hz, CH_3), 1.39 (s, 27H, $C(CH_3)_3$), 1.49 (q, 2H, J=7.6Hz, -CH_2-), 2.39 (s, 9H, ArOCH_3), 3.41 (d, 6H, J=15.2Hz, ArCH_{eq}-Ar), 3.45 (s, 6H, $C(CH_2O)_3$), 3.73 (t, 6H, J=5.6Hz, -CH_2O-CH_2-$C\underline{H}_2$-), 3.87 (t, 6H, J=5.6Hz,-CH_2O-CH_2-$C\underline{H}_2$-), 4.01 (t, 6H, J=4.4Hz, -$CH_2OCH_2CH_2O$-CH_2-CH_2-), 4.11 (t, 6H, J=4.4Hz,-$CH_2OCH_2CH_2OCH_2$-CH_2-), 4.66 (d, 6H, J=15.2Hz, ArCH_{ax}-Ar), 6.71 (s, 6H, ArH), 7.26 (s, 6H, ArH). ^{13}C NMR (75MHz, $CDCl_3$): δ 7.75, 22.8, 29.5, 30.9, 31.5, 33.8, 34.1, 43.3, 59.9, 70.5, 70.7, 71.0, 71.7, 72.1, 123.4, 127.8, 133.0, 133.6, 145.5, 145.6, 151.1, 154.3. MS (FAB): m/z = 1358 (M^+, 20%), 1381 (M^++ Na^+, 18%). Anal. Calcd for $C_{87}H_{122}O_{12}$: C,76.84; H, 9.04. Found: C, 76.95; H, 9.25. **5b** ^{1}H NMR (500MHz, $CDCl_3$): δ 0.82 (t, 3H, J=7.3Hz,CH_3), 0.94 (s, 27H, $C(CH_3)_3$), 1.12 (q, 2H, J=7.3Hz, -CH_2-), 1.22 (s, 27H, $C(CH_3)_3$), 2.60 (s, 9H, ArOCH_3), 3.26 (s, 6H, $C(CH_2O)_3$), 3.41 (d, 6H, J=15.1Hz, ArCH_{eq}-Ar), 3.69 (t, 6H, J=4.9Hz, -$CH_2OC\underline{H}_2$-CH_2-), 3.77 (t, 6H, J=4.9Hz, -CH_2OCH_2-$C\underline{H}_2$-), 3.91 (bs, 6H, -$CH_2OCH_2CH_2O$-$C\underline{H}_2$-CH_2-), 3.97 (bs, 6H, -$CH_2OCH_2CH_2OCH_2$-$C\underline{H}_2$-), 4.60 (d, 6H, J=15.1Hz, ArCH_{ax}-Ar), 6.83 (s, 6H, ArH), 7.11 (s, 6H, ArH). ^{13}C NMR (75MHz, $CDCl_3$): δ 7.1, 20.4, 29.6, 31.1, 31.4, 33.9, 34.0, 43.6, 60.4, 68.9, 70.0, 70.4, 70.6, 72.0, 124.3, 126.8, 133.0, 133.7, 145.3, 145.6, 151.7, 154.2. MS (FAB): m/z = 1359 (MH^+, 30%), 1381 (M^+ + Na^+, 29%). Anal. Calcd for $C_{87}H_{122}O_{12}$: C, 76.84; H, 9.04. Found: C, 76.71; H, 9.15.

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