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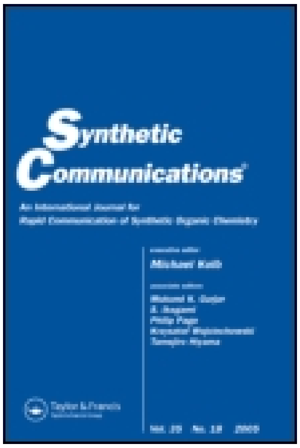

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# Catalytic Approach for the Synthesis of bis-Calixarenes

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# Catalytic Approach for the Synthesis of bis-Calixarenes

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**Abstract:** Three new tail-to-tail linked biscalix[6]arenes joined via ether linkages have been synthesized. These bis calix[6]arenes have been characterized by $^1H$ NMR, $^{13}C$ NMR, and mass spectroscopy and elemental analysis.

**Keywords:** bis-calix[6]arenes, methyl calix[6]arenes, phase-transfer catalyst

bis-Calixarenes have attracted great interest because of their peculiar multicavity structure and molecular recognition abilities. In the case of tail-to-tail linkage, the bis-calixarenes, providing two diverging cavities, have been used as tectons for poly-cap self-assemblies. bis-Calixarene derivatives lend themselves well to many applications like cation complexation, anion recognization, organic neutral and charged molecular recognization, redox active ionophore, ion selective electrodes, and ditopic receptors.[1–10]

In this article we have for the first time reported the single-step synthesis of methyl calix[6]arene **(3)**, which was obtained by the acid-catalyzed condensation of p-cresol **(1)** and formaldehyde **(2)**. Methyl calix[6]arene **(3)** was refluxed with bis[2-chloroethyl]ether **(4)** in the presence of NaOH and phase-transfer catalyst triethyl benzyl ammonium chloride using acetone as a solvent at 50–55°C for 18 h to yield bis-calix[6]arene **(5)** (Fig. 1).

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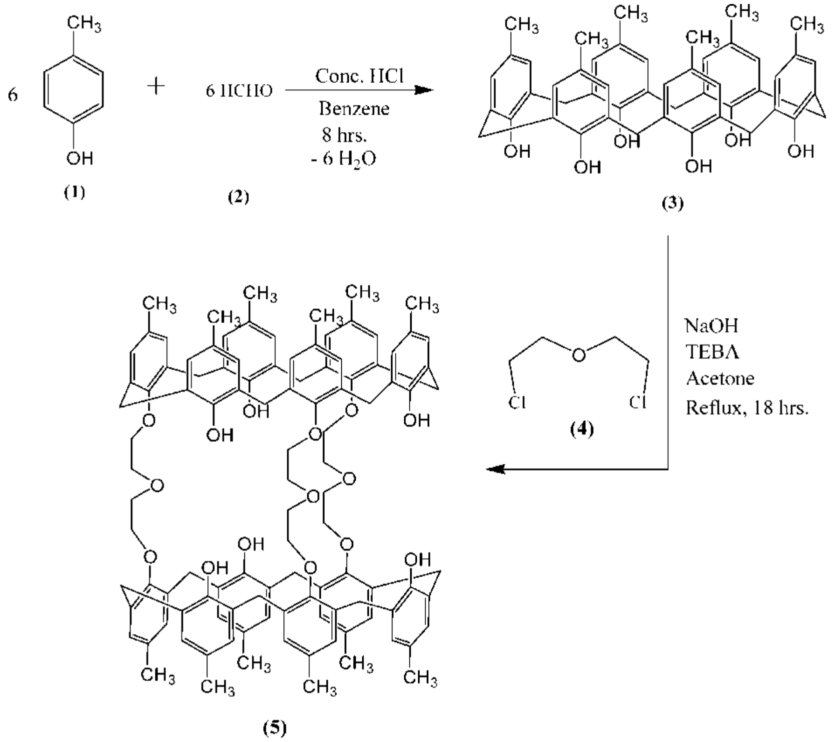

*Figure 1.* Synthetic scheme for compound **5**.

Tetra carboxy methyl calix[6]arene (**7**) was obtained by refluxing methyl calix[6]arene (**3**) and bromo acetic acid (**6**) for 24 h. Compound (**7**) was refluxed with bis[2-chloroethyl]ether (**4**) in the presence of NaOH and phase-transfer catalyst triethyl benzyl ammonium chloride using acetone as a solvent at 50–55°C for 15 h to yield the bis-calix[6]arene derivative, which possesses carboxy functional groups as ligating sites (**8**) (Fig. 2).

The bis-calix[6]arene hydroxamic acid (**10**) was synthesized to explore good metal ion receptors based on bis-calixarenes. Compound (**8**) was refluxed with thionylchloride at 75–80°C for 6–8 h to obtain corresponding acid chloride (**9**), which was condensed with N-phenylhydroxylamine in the presence of an aqueous suspension of sodium carbonate at 0–1°C for 2 h to form bis-calix[6]arene hydroxamic acid (**10**) (Fig. 3).

If the synthesis of bis-calix[6]arene derivatives was carried out without using a phase-transfer catalyst, the reactions required a large amount of solvents and a long time for completion (Table 1).

All new synthesized tail-to-tail linked bis-calix[6]arenes have been characterized by $^{1}H$ NMR, $^{13}C$ NMR, and fast atom bombardment (FAB) mass spectrometry and elemental analysis.

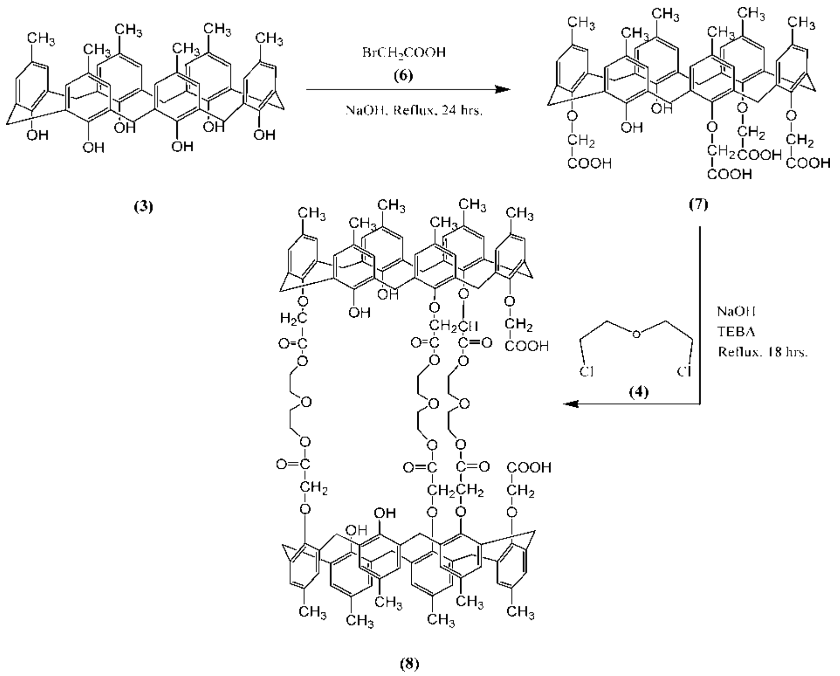

*Figure 2.* Synthetic scheme for compound **8**.

The $^1$H NMR dimethylsulphoxide (DMSO) spectrum of compound **5** displayed two singletes at 6.64 and 6.77 ppm for ArH and 2.06–2.20 ppm for $CH_3$, and compound **8** and **10** displayed four singletes at 6.64–6.88 ppm for ArH and 2.06–2.39 ppm for $CH_3$. Compound **5, 8**, and **10** displayed a singlet at 8.55 ppm for OH, 3.72–3.86 ppm for Ar-$\underline{CH_2}$-Ar, and 4.65–4.81 ppm for ArO$\underline{CH_2}$. In addition, compound **8** displayed a singlet at 9.55 ppm for COOH, and compound **10** displayed singlet at 10.50 ppm for N-OH.

The $^{13}$C NMR (DMSO) spectrum of compound **5** displayed aromatic carbon adsorption in the region between 128.7 and 150.7 ppm, compound **8** displayed aromatic carbon adsorption in the region between 112.0 and 153.1 ppm, and compound **10** displayed aromatic carbon adsorption in the region between 112.0 and 153.1 ppm. In addition, compound **5** displayed a singlet at 21.29 ppm for $CH_3$ and 31.26 ppm for Ar-$\underline{CH_2}$-Ar; compound **8** and **10** displayed a singlet at 21.30 ppm for $CH_3$ and 31.16 ppm for A-$\underline{CH_2}$-Ar. In addition, compound **10** displayed a singlet at 161.5 ppm for $\underline{CO}$-N(OH).

In conclusion, the three different bis-calix[6]arene derivatives have been synthesized using a phase-transfer catalyst. This methodology is a rapid and convenient approach for the synthesis of a multicavity calixarene framework.

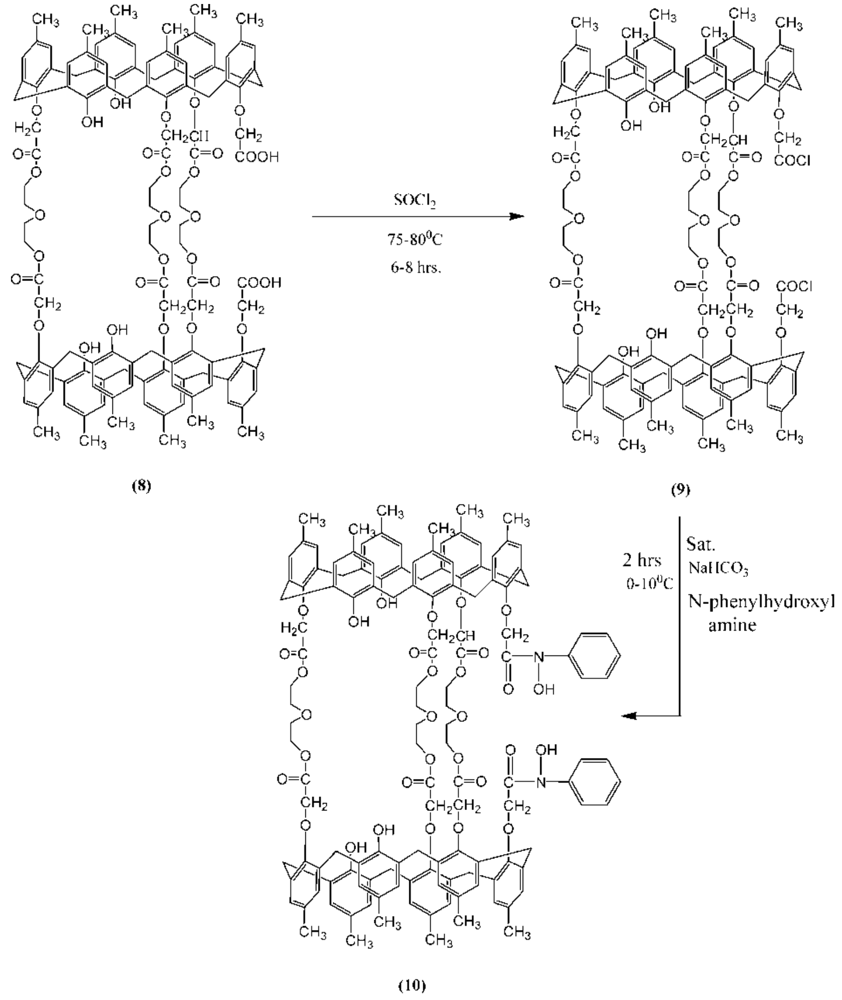

*Figure 3.* Synthetic scheme for compound **10**.

*Table 1.* Comparison of conventional and phase transfer catalyzed synthetic methodologies for bis-calix[6]arenes

| | Conventional method | | Phase transfer catalyzed method | |
|---|---|---|---|---|
| Compounds | Mp (°C) | Reaction time | Mp (°C) | Reaction time |
| **5** | 215–220 | 18 h | 215–220 | 50 h |
| **8** | 178–182 | 15 h | 178–182 | 48 h |

## EXPERIMENTAL

Melting points were determined in a sealed capillary tube using a Toshniwal (India) melting-point apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded on a DRX 300 spectrophotometer operating at 300 MHz in DMSO-d$^6$ with TMS as an internal standard.

### Synthesis of Compound (3)

The synthesis of methyl calix[6]arene **3** was achieved by reacting *p*-cresol (23.6 ml, 0.22 M) and formaldehyde (35%, 33.0 ml, 1.10 M) in the presence of benzene (75 ml) and concentrated HCl (23.6 ml) at reflux temperature for 8 h. The obtained product was resinous in nature. The crude product was washed with hot distilled water. After washing, the product was passed through column containing silica gel (60 mm size) with the use of $CHCl_3$–toluene (9:1 v/v) to obtained cyclic hexamer methyl calix[6]arene.

Data

Yield 90%, mp $> 37°$C. $^1$H NMR (DMSO, $\delta$): 8.99 (s, 6H, OH), 6.79 (s, 12H, ArH), 3.77 (s, 12H, Ar$\underline{CH_2}$Ar), 2.16 (s, 18H, $CH_3$).$^{13}$C NMR (DMSO, $\delta$): 21.5 (s, $CH_3$), 31.4 (s, Ar$\underline{CH_2}$Ar), 115.9–150.7 (s, ArC). The FAB-MS spectra of compound **3** showed a molecular ion peak at 743 $(M + Na)^+$. Anal. calcd. for $C_{48}H_{48}O_6$: C, 79.97; H, 6.71; O, 13.32. Found: C, 79.92; H, 6.66; O, 13.30.

### Synthesis of Compound (5)

With Phase-Transfer Catalyst

The bis-calix[6]arene **5** was synthesized by reacting methyl calix[6]arene (1.0 g, 0.001 M), NaOH (0.16 g), and bis-[2-chloro ethyl] ether (1.1 ml, 0.007 M) in refluxing acetone medium for 18 h in the presence of a catalytic amount of triethyl benzyl ammonium chloride. The resulted alkaline solution was neutralized with 50% HCl. The colorless product was filtered and isolated.

Without Phase-Transfer Catalyst

The bis-calix[6]arene **5** was synthesized by reacting methyl calix[6]arene (1.0 g, 0.001 M), NaOH (0.3 g), and bis-[2-chloro ethyl] ether (2.1 ml, 0.015 M) in refluxing acetone medium for 50 h. The resulted alkaline solution was neutralized with 50% HCl. The colorless product was filtered and isolated.

Data

Yield 43%, mp 215–220°C (decom). $^1$H NMR (DMSO, $\delta$): 8.55 (s, 6H, OH), 6.64–6.77 (s, 24H, ArH), 3.72–3.85 (s, 36H, Ar$\underline{CH_2}$Ar and $CH_2OCH_2$), 2.06–2.20 (s, 36H, $CH_3$), 4.65–4.81 (s, 12H, ArO$\underline{CH_2}$).$^{13}$C NMR (DMSO, $\delta$): 21.29 (s, $CH_3$), 31.26 (s, Ar$\underline{CH_2}$Ar), 128.7–150.7 (s, ArC). m/z = 1635 $[M\text{-}CH_3]^+$. Anal. calcd. for $C_{108}H_{114}O_{15}$: C, 78.52; H, 6.96; O, 14.53. Found: C, 78.46; H, 6.94; O, 14.50.

## Synthesis of Compound (8)

The tetra carboxy calix[6]arene **7** was synthesized by reacting methyl calix[6]arene (1.0 g, 0.001 M), NaOH (0.2 g), and bromo acetic acid (2.0 g, 0.015 M) in refluxing acetone for 24 h. After completion of the reaction, the reaction mass was kept at room temperature for 0.5 h. The reaction mixture was filtered, and the collected product was washed with distilled water to obtain tetracarboxy calix[6]arene as a colorless powder (mp 130–135°C).

With Phase-Transfer Catalyst

The carboxy bis-calix[6]arene **8** was synthesized by reacting tetra carboxy methyl calix[6]arene **7** (1.0 g, 0.001 M), NaOH (0.16 g), and bis-[2-chloro ethyl] ether (0.89 ml, 0.006 M) in the presence of a catalytic amount of triethyl benzyl ammonium chloride in refluxing acetone for 15 h. The resulted alkaline solution was neutralized with 50% HCl. The light brown product was filtered and isolated.

Without Phase-Transfer Catalyst

The carboxy bis-calix[6]arene **8** was synthesized by reacting tetra carboxy methyl calix[6]arene **7** (1.0 g, 0.001 M), NaOH (0.3 g), and bis-[2-chloro ethyl] ether (2.1 ml, 0.015 M) in refluxing acetone medium for 48 h. The resulted alkaline solution was neutralized with 50% HCl. The light brown product was filtered and isolated.

Data

Yield 37%, mp 178–182°C (decom). $^1$H NMR (DMSO, $\delta$): 8.56 (s, 4H, OH), 9.55 (s, 2H, COOH), 6.64–6.88 (s, 24H, ArH), 3.72–3.86 (s, 36H, Ar$\underline{CH_2}$Ar and $CH_2OCH_2$), 2.06–2.39 (s, 36H, $CH_3$), 4.66–4.81 (s, 16H, ArO$\underline{CH_2}$), 4.53 (s, 12H, $\underline{CH_2}$ $CH_2O$ $CH_2$ $\underline{CH_2}$). $^{13}$C NMR (DMSO, $\delta$): 21.30 (s, $CH_3$), 31.16 (s, Ar$\underline{CH_2}$Ar), 112.0–153.1 (s, ArC). m/z = 2114 $[M]^+$. Anal. calcd. for $C_{124}H_{130}O_{31}$: C, 70.37; H, 6.19; O, 23.44. Found: C, 70.32; H, 6.15; O, 23.41.

## Synthesis of Compound (10)

A mixture of carboxy bis-calix[6]arene **8** (1.0 g, 0.0004 M) and thionyl chloride (0.11 ml, 0.0009 M) was stirred at 75–80°C for 6–8 h. The acid chloride was condensed with freshly prepared N-phenylhydroxylamine (0.3 g, 0.002 M) in the presence of an aqueous suspension of sodium carbonate (1.5 g) at 0–10°C for 2 h to obtain compound **10**.

Data

Yield 30%, mp 225–230°C (decom). $^{1}$H NMR (DMSO, $\delta$): 8.56 (s, 4H, OH), 6.64–6.88 (s, 24H, ArH), 3.72–3.86 (s, 36H, Ar$\underline{CH_2}$Ar and $CH_2OCH_2$), 2.06–2.39 (s, 36H, $CH_3$), 4.66–4.81 (s, 16H, ArO$\underline{CH_2}$), 4.53 (s, 12H, $\underline{CH_2}$ $CH_2O$ $CH_2$ $\underline{CH_2}$), 10.50 (s, 2H, N-OH), 7.00 (t, $J = 6$ Hz, 2H, ArH), 7.24 (t, $J = 6$ Hz, 4H, ArH), 7.64 (d, $J = 6$ Hz, 4H, ArH). $^{13}$C NMR (DMSO, $\delta$): 21.30 (s, $CH_3$), 31.16 (s, Ar$\underline{CH_2}$Ar), 112.0–153.1 (s, ArC) 161.5 (s, CO). $m/z = 2296$ $[M]^{+}$. Anal. calcd. for $C_{124}H_{130}O_{31}$: C, 70.37; H, 6.19; O, 23.44. Found: C, 70.32; H, 6.15; O, 23.41.

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