Direct Synthesis of Singly-Bridged Biscalixarenes and Crowned-Calixarenes

*Abha Naveen Kumar

*Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai 400085, India

Abstract: Two tail-to-tail linked singly-bridged biscalix[6]/[4]arenes were directly synthesized by reaction of calix[6]/[4]arenes with diethyleneglycol ditosylate in presence of KHCO$_3$ as the base. It was found that this coupling depended on the kind of calixarene. With calix[4]arene, both corresponding biscalixarene and crowned-calixarene were obtained in this reaction. But in case of p-tert-butylcalix[4]arene, this reaction afforded corresponding crowned-calixarene only. In addition to that, coupling reaction also depends on the linker as evident by the synthesis of corresponding crowned-calixarenes/mono-O-alkylated derivatives, in case of p-tert-butylcalix[6]arene.


Introduction

In the quest to design hosts with defined structures and functions, calixarenes are widely utilized for building elaborate systems containing more than one cyclic structure. Biscalixarenes and crowned-calixarenes are examples of two such molecular systems, where inter/intra-molecular bridging provide not only new cavities for binding but also restricted flexibility of calixarenes. For the synthesis of these macrobicyclic compounds, calixarenes are coupled with bifunctional reagents which results in inter- and/or intra-molecular bridging depending on the reaction conditions. For example, 5,11,17,23-tetrakis[(propargyloxy)methyl]-25,26,27,28-tetra(benzyloxy)calix[4]arene in 1,3-alternate conformation afforded both kinds of products when oxidatively coupled, though intermolecularly coupled product is obtained in just 7% yield.

In the past, I along with my co-workers have been involved in developing protocols for regioselective functionalization of calixarenes, and in utilizing hosts based on calixarenes for targets like cesium and fullerenes. Recently, we have succeeded in accomplishing synthesis of biscalixarene 2 in single step by using KHCO$_3$-diethyleneglycol ditosylate combination (Figure 1). During this study, we found out that outcome of this coupling is sensitive to both base and linker.


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Figure 1: Synthesis of compounds 2 and 3 (taken from our previous work)\textsuperscript{10}

In the literature, direct reaction of calix[4]/[6]arenes with oligoethyleneglycol ditosylates afforded crowned-calixarenes\textsuperscript{11-13} and/or multi-bridged biscalixarenes\textsuperscript{31-33} as the reaction products; and in only few of the reports, formation of singly-bridged biscalixarenes like 2 was mentioned\textsuperscript{10,34}.

Keeping in view of these literature reports\textsuperscript{11-34} and the novel finding of one-step synthesis of biscalixarene 2\textsuperscript{10}, the present study to afford singly-bridged biscalixarenes using KHCO\textsubscript{3}-diethyleneglycol ditosylate is undertaken. Also, the coupling of 1a with oligoethyleneglycol ditosylates and 1,ω-dibromoalkanes was further investigated in this report, to get better insight about this reaction.

Experimental

All the chemicals (Fluka and Aldrich) were of analytical grade and used as received, if not mentioned otherwise. Compound 1a, 1b, 1c and 1d were dried under vacuum at 100 °C for 6 h before use. Anhydrous KHCO\textsubscript{3} was obtained by heating material on flame and then stored in a desiccator. Acetonitrile was dried and distilled over P\textsubscript{2}O\textsubscript{5}. All the reactions were carried out in flame dried glass apparatus kept under an argon atmosphere. Melting points were taken on Fisher-Johns melting point apparatus and are uncorrected. \textsuperscript{1}H NMR spectra were recorded with a Bruker AC 200 spectrometer at ambient temperature. Mass spectra were measured with a Q-TOF (YA-105) instrument.

General procedure for the synthesis of calixarene compounds 4-12: Compound 1a/1b/1c/1d (5.1 mmol) and KHCO\textsubscript{3} (8.2 mmol) were dissolved in CH\textsubscript{2}CN (100 mL) and stirred at reflux temperature for 3 h. The mixture was cooled to rt and oligoethyleneglycol ditosylate/1,ω-dibromoalkane (3.1 mmol) was added to it and further stirred at reflux temperature for 7 days. The solvent was removed under vacuo and water was added to the residue. The mixture was acidified with 1 N HCl and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The organic layer was washed with water, brine and dried (Na\textsubscript{2}SO\textsubscript{4}) and then concentrated to dryness. The residue was subjected to either column chromatography or preparative thin layer chromatography over silica gel (CH\textsubscript{2}Cl\textsubscript{2}/Hex) to yield the corresponding biscalixarene, crowned-calixarene or mono-O-alkylated derivative as the product.

Spectral data of compounds

**Bis[2-(37,38,39,40,41-pentahydroxy-42-calix[6]arenyloxy)ethyl] ether (4):** White solid. mp: 178-180 °C. \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): δ 3.64 -3.84 (m, 26H), 4.45-4.47 (m, 6H), 6.68-6.81 (m, 10H), 6.84-7.00 (m, 16H), 7.07-7.14 (m, 10H), 8.69 (s, OH), 9.79 (br s, OH). ESI-MS: m/z 1341.8 ([M-H]\textsuperscript{+}, calcd. 1341.5). Anal. calcd. for C\textsubscript{88}H\textsubscript{76}O\textsubscript{18}: C 78.67, H 5.85; found: C 78.60, H 5.87.

**Bis[2-(25,26,27-trihydroxy-28-calix[4]arenyloxy)ethyl] ether (5):** White solid. mp: 293-295 °C. \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): δ 3.29-3.48 (m, 8H), 4.21-4.28 (m, 4H), 4.41-4.53 (m, 12H), 6.61-6.69 (m, 6H),
6.86-7.08 (m, 18H), 9.38 (s, 4H), 9.96 (s, 2H). ESI-MS: m/z 917.8 ([M-H]^+, calcd. 917.4). Anal. calcd. for C_{60}H_{54}O_{2}: C 78.41, H 5.92; found: C 78.30, H 5.94.

25,26-Dihydroxycalix[4]arene-27,28-(crown-3) (6): White solid. mp: 120-122 °C (lit.\(^{35}\) mp: 119-121 °C). \(^1\)H NMR: δ 3.38-3.50 (m, 4H), 4.06-4.17 (m, 4H), 4.36-4.51 (m, 7H), 4.93 (d, J = 12.2 Hz, 1H), 6.70 (t, J = 7.4 Hz, 2H), 6.91-7.26 (m, 10H), 8.67 (s, 2H). ESI-MS: m/z 493.3 ([M-H]^+, calcd. 493.2). Anal. calcd. for C_{32}H_{30}O_{5}: C 77.71, H 6.11; found: C 77.76, H 6.10.

5,11,17,23-Tetra-tert-butyl-25,27-dihydroxycalix[4]arene-26,28-(crown-3) (7): White solid. mp: 246-248 °C. \(^1\)H NMR: δ 0.93 (s, 18H), 1.30 (s, 18H), 3.33 (d, J = 13.0 Hz, 4H), 3.94 (s, 8H), 4.28 (d, J = 12.8 Hz, 4H), 6.76 (s, 4H), 7.07 (s, 4H); ESI-MS: m/z 717.7 ([M-H]^+, calcd. 717.5). Anal. calcd. for C_{48}H_{42}O_{5}: C 80.18, H 8.69; found: C 80.23, H 8.68.

5,11,17,23,29,35-Hexa-tert-butyl-37,38,40,41-tetrahydroxycalix[6]arene-39,42-(crown-5) (8): White solid. mp: 180-182 °C (lit.\(^{15}\) mp: 184-185 °C). \(^1\)H NMR: δ 1.13 (s, 18H), 1.23 (s, 36H), 3.53-3.59 (m, 6H), 3.70-3.85 (m, 14H), 4.09 (m, 4H), 4.38 (d, J = 14.4 Hz, 4H), 6.99-7.06 (m, 12H), 7.79 (s, OH); ESI-MS: m/z 1130.4 ([M]^+, calcd. 1130.7). Anal. calcd. for C_{74}H_{66}O_{5}: C 78.55, H 8.73; found: C 78.67, H 8.70.

5,11,17,23,29,35-Hexa-tert-butyl-37,38,40,41-tetrahydroxycalix[6]arene-39,42-(crown-6) (9): White solid. mp: 227-229 °C. \(^1\)H NMR: δ 1.12 (s, 18H), 1.28 (s, 36H), 3.51 (m, 8H), 4.05-4.20 (m, 20H), 4.38-4.44 (m, 4H), 6.97 (s, 4H), 7.10-7.11 (m, 8H), 7.76 (s, 4H); ESI-MS: m/z 1174.5 ([M]^+, calcd. 1174.8). Anal. calcd. for C_{76}H_{70}O_{10}: C 77.65, H 8.75; found: C 77.74, H 8.73.

5,11,17,23,29,35-Hexa-tert-butyl-37-monotosyloxyethoxy-38,39,40,41,42-pentahydroxycalix[6]arene (10): White solid. mp: 176-178 °C. \(^1\)H NMR: δ 1.21-1.28 (m, 45 H), 2.04-2.46 (m, 3H), 3.40-3.60 (m, 6H), 3.91 (d, J = 13.6 Hz, 2H), 4.18-4.32 (m, 6H), 4.66 (s, 2H), 6.96 (s, 4H), 7.11 (s, 10H), 7.81 (d, J = 6.4 Hz, 2H), 8.47 (s, 2H), 9.43 (s, 1H), 9.62 (s, 2H); ESI-MS: m/z 1169.9 ([M-H]^+, calcd. 1169.7). Anal. calcd. for C_{76}H_{70}O_{10}: C 76.89, H 8.09; found: C 76.97, H 8.10.

5,11,17,23,29,35-Hexa-tert-butyl-37,38,40,41-tetrahydroxy-39,42-(pentanyldioxy)calix[6]arene (11): White solid. mp: 190-192 °C. \(^1\)H NMR: δ 1.20 (s, 18H), 1.30 (s, 36H), 2.07 (s, 4H), 2.33 (s, 2H), 3.59 (br s, 8H), 4.15 (m, 4H), 4.29 (s, 4H), 7.13-7.24 (m, 12H), 9.32 (s, 4H); \(^{13}\)C NMR: δ 29.6, 31.3, 31.7, 32.2, 32.3, 32.9, 34.2, 75.2, 125.4, 126.0, 126.2, 127.3, 132.5, 142.4, 147.5, 150.0, 150.3; ESI-MS: m/z 1040.3 ([M]^+, calcd. 1040.7). Anal. calcd. for C_{71}H_{68}O_{5}: C 81.88, H 8.90; found: C 81.97, H 8.88.

5,11,17,23,29,35-Hexa-tert-butyl-37,38,40,41-tetrahydroxy-39,42-(hexanyldioxy)calix[6]arene (12): White solid. mp: 238-240 °C. \(^1\)H NMR: δ 1.20 (s, 18H), 1.33 (s, 36H), 2.04-2.18 (m, 8H), 3.32-3.54 (m, 6H), 4.11 (m, 6H), 4.40 (d, J = 12 Hz, 4H), 7.09-7.19 (m, 12H), 9.08 (s, 4H); ESI-MS: m/z 1054.1 ([M-H]^+, calcd. 1053.7). Anal. calcd. for C_{72}H_{80}O_{6}: C 81.93, H 8.98; found: C 81.99, H 8.97.

Results and Discussion

Piqued by the previous work\(^{10}\), KHCO\(_3\)-diethyleneglycol ditosylate combination have been further explored in this report to afford singly-brided biscalixarenes. Thus, the substrates calix[6]arene (1b), calix[4]arene (1c) and p-tert-butylcalix[4]arene (1d) were reacted with KHCO\(_3\) and diethyleneglycol ditosylate as shown in Scheme 1.
Scheme 1: Reagents and conditions: (i) KHCO$_3$, diethyleneglycol ditosylate, CH$_3$CN, reflux.

Using calix[6]arene 1b as the substrate, biscalix[6]arene 4 was obtained in 21% yield. When calix[4]arene 1c was used as the substrate, biscalix[4]arene 5 was obtained in only 5% yield along with the (1,2)-calix[4]arenecrown-3 (6) product in 23% yield. When p-tert-butylcalix[4]arene 1d was used as the substrate, (1,3)-p-tert-butylcalix[4]arenecrown-3 (7) was obtained in 29% yield. All the compounds synthesized were characterized by their respective analytical and spectral data.

During the previous work on synthesis of biscalix[6]arene 2 from 1a, it was observed that changing the linker to triethyleneglycol ditosylate led to formation of calix[6]crown $3^{10}$. This part of the study was conducted to further investigate the effect of linker over the outcome of this KHCO$_3$ mediated reaction of bifunctional linkers with 1a (Scheme 2).
Thus, coupling of 1a was carried out using tetra- and penta-ethylene glycol ditosylates under the similar reaction conditions. In both the cases, respective calixcrowns 8 and 9 were obtained. But with a long spacer like pentaethylene glycol ditosylate, percentage yield of the calixcrown 9 has decreased substantially to 18% (in the TLC analysis, few more bands were observed which were difficult to purify and analyze). Assignment of the 1,4-substitution pattern in the calixcrowns 8 and 9 was done unambiguously by their 1H NMR spectrum; and was further substantiated in case of compound 8 where its melting point and spectral data matches well with the data for the reported compound13, leaving no scope for ambiguity.

With ethylene glycol ditosylate, corresponding mono-O-tosyloxy derivative 10 was obtained in 26% yield. Elemental analysis and spectral data of the compound 10 provide clear evidence for its formation. Its 1H NMR spectrum contains two signals at 8 1.12 and 1.21-1.28 for tert-butyl protons in a 1:5 intensity ratio, attributable to the tert-butyl groups of O-substituted and hydroxyl-bearing aromatic rings, respectively. The spectrum contains three hydroxyl signals at 8 8.47, 9.43 and 9.62 in the intensity ratio of 2:1:2, respectively. The signal at 8 8.47 is due to OH groups, sandwiched between one OCH₂ group and one OH group. The signals at 8 9.43 and 9.52 are due to OH groups, sandwiched between two OH groups.

To check the effect of alkyl spacers on this reaction, 1,5-dibromopentane and 1,6-dibromohexane were used for the coupling under the similar reaction conditions (Scheme 2). In both the cases, corresponding crowned-calixarenes 11 and 12 were obtained in 58 and 45% yield, respectively. Elemental analysis and spectral data of the compounds 11 and 12 provide clear evidence for formation of the intramolecularly coupled product. Assignment of their structure was done unambiguously by NMR data and was further confirmed in case of compound 12 where its data matches well with the data for the reported compound16.
Conclusion

In conclusion, two tail-to-tail linked singly-bridged biscalixarenes 4 and 5 are synthesized in one-step by direct condensation of diethyleneglycol ditosylate with corresponding calixarenes in presence of KHCO₃ as the base. Also investigation of reaction of 1a with oligoethyleneglycol ditosylates/1,2-dibromoalkanes in presence of KHCO₃ as the base, revealed this coupling reaction to be sensitive to the bifunctional linker. Thus one-step syntheses of singly-bridged biscalixarenes, crowned-calixarenes and mono-O-alkylated derivative are achieved depending upon the reaction conditions (parent calixarene and linker). In addition to its synthetic utility, this study in conjunction with the previous literature reports contributes towards understanding of coupling of bifunctional linkers with calixarenes.

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References


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