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Synthesis of *p*-tert-Butylcalix[4] Arenes with Diester Bridge Spanning the 1,3-(Distal) Positions on the Lower Rim

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p-tert-Butylcalix[4]crown ether esters have been synthesized in good yield using two synthetic methods.

Calixarenes which structurally resemble spherands and natural cyclodextrins have received much attention over the past decade.[1] These are useful building blocks for preorganized lipophilic or water soluble cation receptors and carriers.[2] In particular *p*-tert-butylcalix[4]arene which is easily accessible in large quantities is a popular building block[3] or platform for assembling more elaborate structures with ligating side arms or podands. The introduction of substituents on the phenolic OH groups of *p*-tert-butylcalix[4]arene produces derivatives with different shapes and conformational mobilities depending upon the nature and number of these substituents. Several tetra and disubstituted calix[4]arenes have been synthesized some of which are now well established as selective receptors for metal cations.[4–7] There are examples in which two calixarenes are joined by a single bridge[8], the singly bridged calixcrowns [poly(oxyethylene)bridge][9–11], calixspherands (m-teranisyl bridge)[12], and double and triple calixarenes with metallocene (ferrocene) bridges.[13] Use of various conformationally constrained spacers such as phthaloyl dichloride or biphenyl-4,4′-disulfonyl dichloride led to the formation of 1,2 bridged single calixarenes and bridged triple calixarenes.[14,15] In all these examples the parent *p*-tert-butylcalix[4]arene is reacted with an activated bifunctional reagent such as diacid dichloride, an oligoethylene glycol ditosyl ester or a bisbromomethylated teranisyl system. Calixarenes with diamide bridges spanning the 1,3-(distal) positions on the lower rim have been synthesized from syn 1,3 diacid dichloride of *p*-tert-butylcalix[4]arene and various bifunctional amines.[16] Interestingly calixarenes with diester bridges spanning the 1,3 distal positions on the lower rim have not been synthesized either from the parent *p*-tert-butylcalix[4]arene or from syn 1,3 diacid dichloride of *p*-tert-butylcalix[4]arene. The ester moieties are known to decrease the complexing ability of the ligand but increases the decomplexation property of their complexes – a combination of both

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these phenomena is one of the factors responsible for the selective ionophore character of naturally occuring nactins which possess ester moieties. In the present manuscript we have synthesized the calixcrown ether esters (Scheme 1) by using two synthetic methodolgies. On the one hand we have used the easily prepared polyethylene(dibromoacetate) and combined it with *p-tert*-butylcalix[4]arene to give calixcrown ether esters in yields ranging from 50–60% and on the other hand we have used the easily available syn 1,3-diacidichloride of *p*-tert-butylcalix[4]arene and combined it with polyethylene glycols under phase transfer conditions to give a calixcrown ether esters (Scheme 1) in good yields (65–75%). While this work was in progress Zheng et al reported[17] the synthesis of these compounds using polyethylene(dichloracetate) instead of polyethylene(dibromoacetate) when bromine is a better leaving group as compared to chlorine. The bromoacetates of polyethylene glycols and 2-ethoxyethanol were prepared either by refluxing together glycol and bromoacetic acid in dry benzene in the presence of *p*-toluenesulphonic acid as catalyst or by stirring together a mixture of poyethylene glycols and bromoacetyl chloride in dry dichloromethane under phase transfer conditions. The structures of these bromoacetates were confirmed from their ^{1}H NMR and I.R. spectra. In the I.R. spectra an absorption band appears at 1750cm^{-1} (ester). The ^{1}H NMR spectrum of "**2b**" shows a singlet at δ 3.65 (4H, $OCOCH_2$) and triplets at δ 3.76 (4H, OCH_2), δ3.91 (4H, OCH_2) and at δ 4.34 (4H, OCH_2). Two synthetic strategies (method A and method B) were used for all cyclization reactions. In method A a mixture of calix[4]arene, bisbromoacetate of glycol and potassium carbonate were refluxed in dry acetone under nitrogen for 14–18 hrs. Similar procedure was adopted for the synthesis of compund **3a**. In method B a mixture of diacid dichloride of calix[4]arene and glycols were refluxed with stirring in the presence of tetrabutylammonium hydrogen sulfate($TBHSO_4$) catalyst for 6–12 hrs in dry dichloromethane. The products were isolated and purified by chromatography. Mass spectrometric analysis showed that the capped calixarenes were the dominant products. Double or triple calixarenes were not isolated although there formation can not be ruled out. The ^{1}HNMR of compounds **3b-d** could be assigned completely and are fully consistent with capped structures all in the cone conformation.

The ^{1}H NMR spectral features for the calixarene skelton for example for **3d**, are: two singlets at δ1.00 and at δ1.25 for the tert-butyl protons and two singlets at δ7.01 and at δ6.83 for the aromatic protons; two doublets at δ 3.33 and at δ4.44 for the methylene protons, $ArCH_2Ar$ (indicating the equivalence of all the four methylene groups); a singlet at δ 4.76 for the $-OCH_2CO-$ protons and another singlet at δ7.16 for OH protons; and for the crown ring, three triplets centered at δ3.87 (J = 6Hz, OCH_2), δ3.72 (t, 4H, J = 6Hz, OCH_2), δ3.66 (t, 4H, J = 5.4Hz, OCH_2) appear in the spectrum. In its I.R. spectrum, an absorption band appears at 1750 cm^{-1} (ester). The ^{13}C NMR spectrum further corroborates the structure of this compound. The presence of an AB system for the benzylic protons and a signal at δ33.78 ppm in the ^{13}C NMR respectively showed that the compound 3d exists in cone conformation. The spectral data of other compounds is similar and is given in the experimental.

X-ray diffraction analysis was also used to probe the solid state conformations of compound **3d** (Fig. 1). The major conformation determining features in this molecule are the presence of two intramolecular O-H...O hydrogen bonds between the phenolic oxygens and the proximal ethereal oxygens[O10...O1 2.89(1) Å, H10A...O1 2.14(1) Å, angleO10A-H10A....O1 152.3(7)° and O11....O7 3.00(1) Å, H11A...O7 2.23(7) Å, angle O11-H11A....O7 156.9(6) °. These intramolecular hydrogen bonds are mainly responsible for the cone conformation of **3d**.

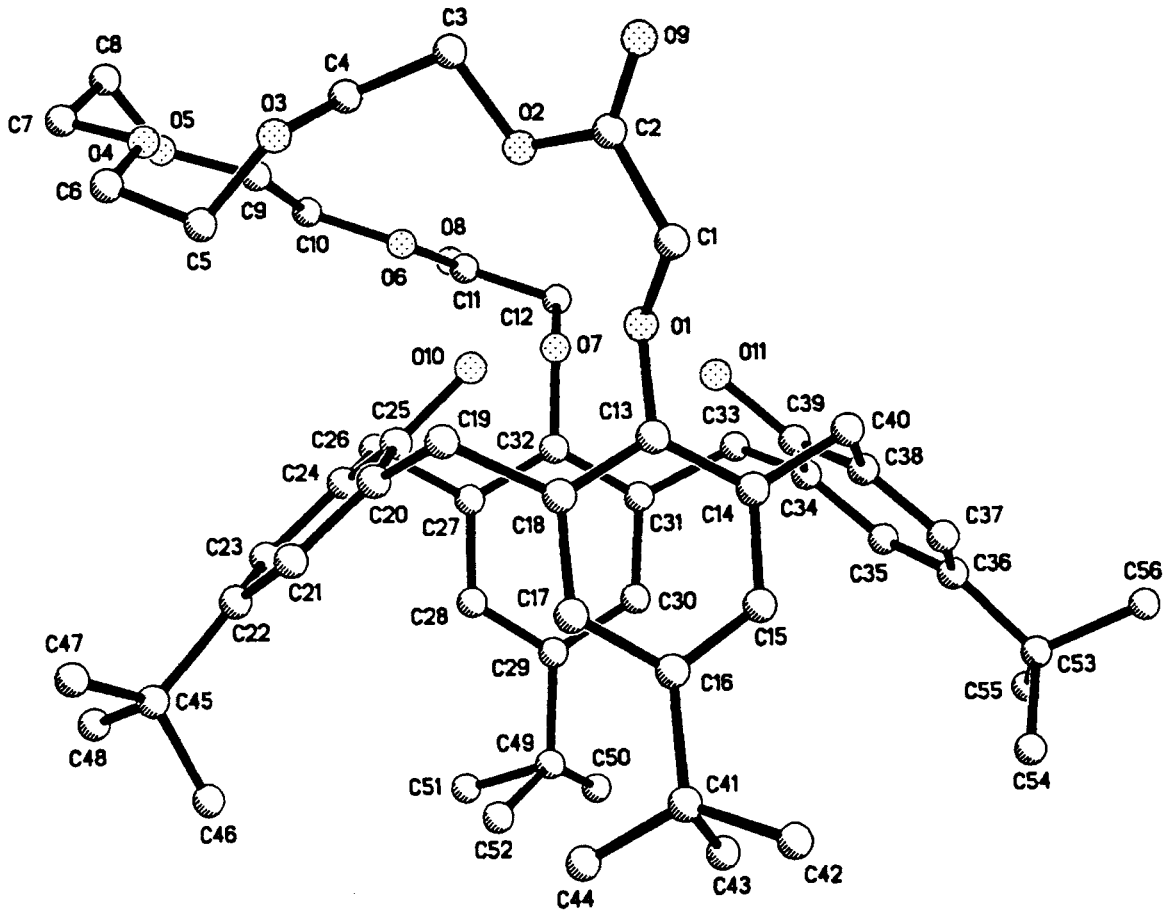


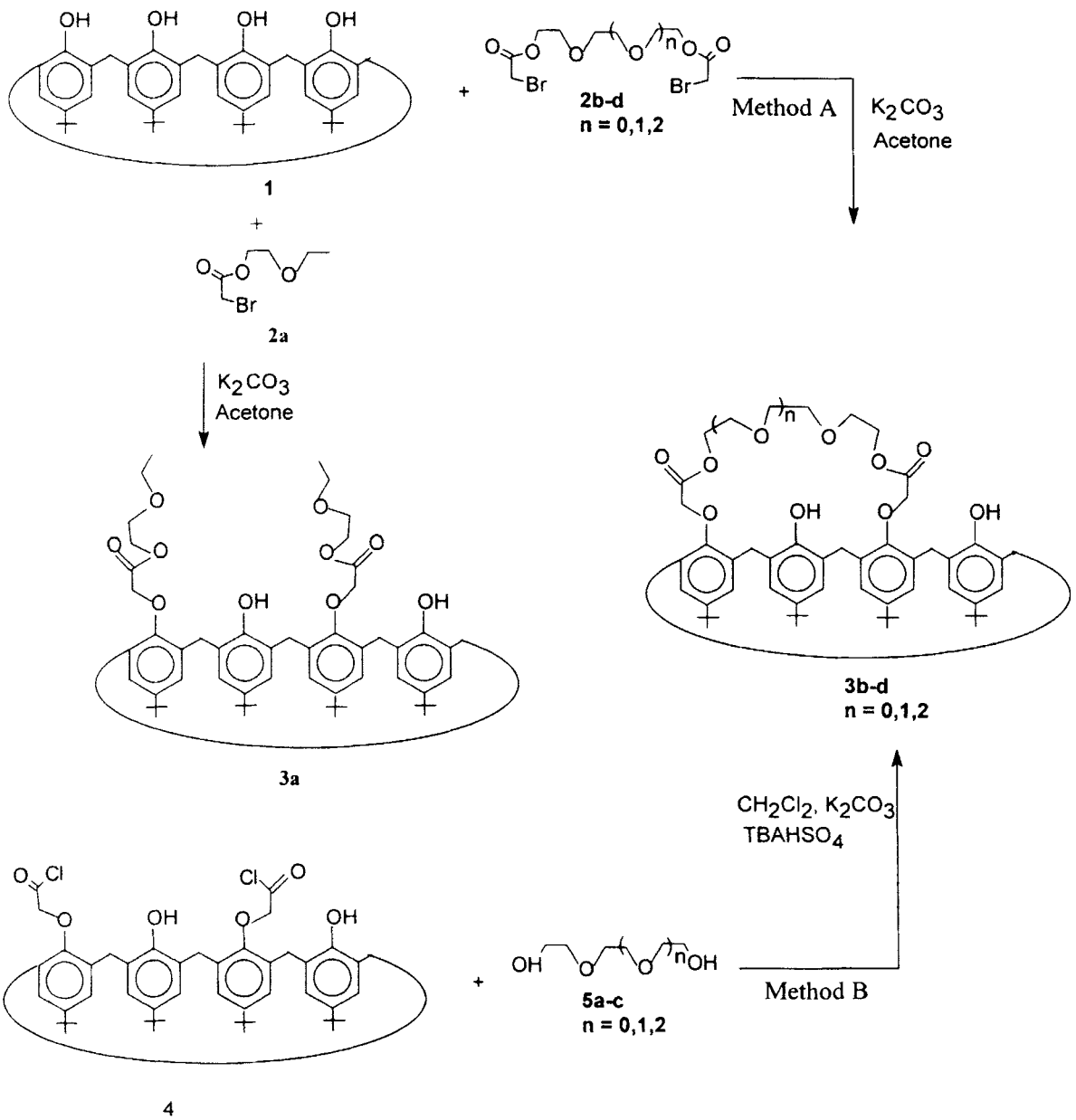
FIGURE 1 A view of the molecule showing labelling scheme. Hydrogens have been omitted for the sake of clarity

EXPERIMENTAL

M.p's were determined in capillaries and are uncorrected. ^{1}H NMR spectra were recorded on Bruker Acc 200 MHz spectrometer using TMS as an internal standard and $CDCl_3$ as solvent. FAB Mass spectra were recorded on a JEOL S ×102/DA-6000 mass spectrometer using Xenon (6KV, 10mA) as the FAB gas.

General Procedure for the Preparation of Bromoacetates: A solution of bromoacetic acid (9.313 g, 67 mmol), triethylene glycol **5b** (5g, 33.3 mmol) and a pinch of *p*-toluenesulphonic acid in dry benzene were refluxed together for five hours. The water and benzene were collected in Dean and Stark apparatus. When no more water separated, reaction was considered complete. The reaction mixture was transfered to a separatory funnel and washed with 1% sodium carbonate solution. Organic layer was separated and dried over anhydrous sodium sulphate and distilled off. The yield of these bromoacetates were quantitative.

Compound **2a**: ν_{max} ($CHCl_3$) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (t,3H,OCH_2CH_3), 3.56 (q,2H,OCH_2CH_3), 3.66 (t,2H,OCH_2), 3.88 (s,2H,$BrCH_2CO$), 4.33 (t,2H,$COOCH_2$).



SCHEME 1

Compound **2b**: ν_{max} ($CHCl_3$) 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (t,4H,OCH_2), 3.83 (4H,O CO CH_2), 4.33 (t, 4H, OCH_2).

Compound **2c**: ν_{max} ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65 (s,4H,$OCOCH_2$), 3.76 (t,4H,OCH_2), 3.91 (t,4H,OCH_2), 4.34 (t,4H,OCH_2).

Condensation of Compound 1 with Compound 2a

A solution of compound 1 (1g, 1.54 mmol), compound **2a** (0.65g, 3 mmol) and K_2CO_3 (0.42g, 3.08 mmol) in dry acetone were refluxed together for 20 hours. After the completion of the reaction (tlc) the reaction mixture was cooled and passed through a bed of celite. The filtrate and dichloromethane washings of the celite were combined and distilled to remove the solvent. The residue was purified by column chromatography over silica using petroleum ether and ethyl acetate as eluent. Method A: Yield 80%. m.p. 127°c. ν_{max} ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (s,18H,$C(CH_3)_3$), 1.16 (t,6H,CH_3), 1.26 (s,18H,$C(CH_3)_3$), 3.32 (d,4H,$ArCH_2Ar$), 3.50 (q,4H,CH_2), 3.68–3.70 (m,4H,OCH_2), 4.36–4.41 (m,8H, $ArCH_2Ar$,OCH_2), 4.76 (s,4H,OCH_2CO), 6.79 (s,4H,ArH), 6.97 (s,2H,OH),7.01(s,4H,ArH). ^{13}C NMR(Normal/DEPT-135) ($CDCl_3$) δ15.04 (CH_2CH_3)/+ ve phase, 31.00 $[C(CH_3)]_3$/+ve phase, 31.64 ($ArCH_2Ar$)/-ve phase, 31.78 $[C(CH_3)]_3$/+ve phase, 33.79 $[C(CH_3)]_3$/ no signal, 64.41 (OCH_2)/-ve phase, 66.68 (OCH_2)/-ve phase, 68.10 (OCH_2)/-ve phase, 72.27 ($PhOCH_2$)/-ve phase, 125.06 (Ar)/+ve phase, 125.71 (Ar)/+ve phase, 127.98 (Ar)/ no signal, 132.36 (Ar)/ no signal, 147.05 (Ar)/ no signal, 150.27 (Ar)/ no signal. Mass spectrum(FAB, NBA): m/z 909(M^+ +1)

Synthesis of Calixcrown Ether-Esters

Method A

General Procedure: A solution of compound 1 (1g, 1.54 mmol), compound **2d** (0.65g, 3.0 mmol) and potassium carbonate (0.46g, 3.30 mmol) in dry acetone was refluxed for 20 hrs. After the reaction was complete (t.l.c.) the solution was filtered through celite. The filtrate and dichloromethane washings of the celite were combined and distilled to remove the solvent. The solid residue was purified by column chromatography over silica gel using petroleum ether and ethyl acetate as eluent. Similar procedure was used to prepare compounds **3a, 3b** and **3c**.

Method B

General Procedure : A solution of 1,3-diacidchloride of p-tert-butylcalix[4]arene **4**[18] (2g, 2.50 mmol) and diethylene glycol **5a** (0.266g, 2.50 mmol) in 100 ml of dry dichlormethane containing a suspension of K_2CO_3 (0.632g, 5 mmol) and tetrabutylammonium hydrogen sulfate ($TBHSO_4$) catalyst was stirred at room temperature and then refluxed. After the completion of the reaction (TLC, 10h), the suspension was filtered and the residue was washed with ethyl acetate. The combined filtrate and the washings were distilled and the crude reaction product was chromatographed on silica gel column using hexane-ethyl acetate as eluent to isolate the pure compound. Similarly **4** reacts with oligoethylene glycols and under the above reaction conditions to provide calixcrowns **3c** and **3d** respectively.

Compound 3b: Method A: Yield 60%., Method B: Yield 75%, m.p. 216°C(dec.). ν_{max}/cm^{-1} (KBr) 1750cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.95 (s,18H,$C(CH_3)_3$), 1.25 (s,18H,$C(CH_3)_3$), 3.31 (d, J = 13.2 Hz, 4H,$ArCH_2Ar$), 3.85 (t, J = 6Hz,4H,OCH_2), 4.31–4.35 (m,8H,$ArCH_2Ar$, OCH_2), 4.75 (s,4H,OCH_2CO), 6.78 (s,4H,ArH), 6.96 (s,4H,ArH). Mass spectrum(FAB, NBA): m/z 834(M^+ +1).

Compound 3c: Method A: Yield 50%., Method B: Yield 70%, m.p. 178–80°C. ν_{max}/cm^{-1}(KBr) 1750cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.97 (s,18H,$C(CH_3)_3$), 1.25 (s,18H,$C(CH_3)_3$), 3.31 (d, J = !3.2 Hz, 4H,$ArCH_2Ar$), 3.85 (t, J = 6Hz, 4H,OCH_2), 3.71 (s,4H,OCH_2), 4.39–4.45 (m,8H,$ArCH_2Ar$,OCH_2), 4.75 (s,4H,OCH_2CO), 6.78 (s,4H,ArH), 6.96 (s,4H,ArH). Mass spectrum(FAB, NBA): m/z 878(M^++1).

Compound 3d: Method A: Yield 60%., Method B: Yield 65%, m.p. 151–2°C. I.R. $\nu_{max}./cm^{-1}$(KBr) 1750 (ester). ^1H NMR ($CDCl_3$): δ 1.00 (s, 18H, $C(CH_3)_3$), 1.25 (s, 18H, $C(CH_3)_3$), 3.33 (d, 4H, J = 13.2 Hz, $ArCH_2Ar$), 3.66 (t, 4H, J = 5.4 Hz,

OCH_2), 3.72 (t, 4H, J = 6.0, Hz, OCH_2), 3.87 (t, 4H, J = 6.0, Hz, OCH_2), 4.39–4.46 (m, 8H, $ArCH_2Ar$, OCH_2), 4.76 (s, 4H, OCH_2CO), 6.83 (s, 4H, ArH), 7.01 (s, 4H, ArH), 7.16 (s, 2H, ArOH); ^{13}C NMR ($CDCl_3$): δ 31.46 (CH_3), 33.78 (CH_2), 33.93 ($C(CH_3)_3$), 64.74 (OCH_2), 66.85 (OCH_2), 70.99 (OCH_2), 72.39 ($PhOCH_2$), 125.06 (ArC), 125.78 (ArC), 127.99 (ArC), 132.59 (ArC), 141.57 (ArC), 147.23 (ArC), 150.11 (ArC), 150.55 (ArC), 169.18 (CO). Mass spectrum(FAB, NBA): m/z 922(M^+).

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