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Synthesis of *p*-benzylcalix[4]arene and its sulfonated water soluble derivative

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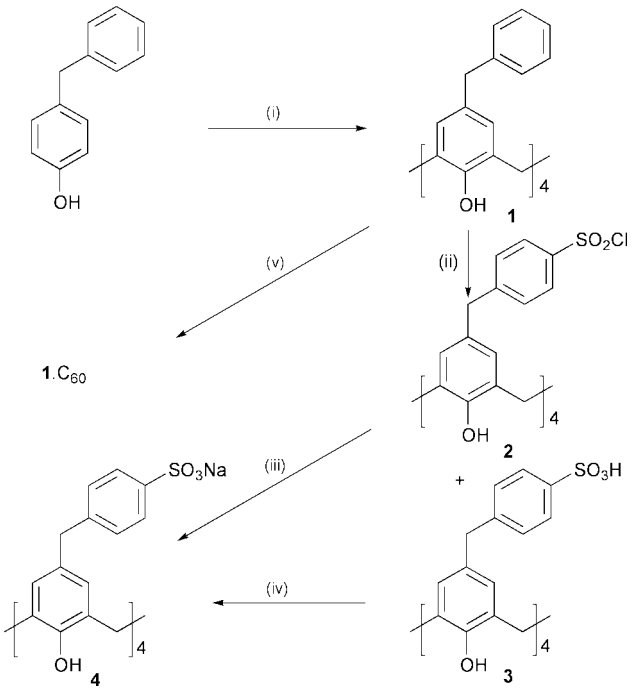
p-Benzylcalix[4]arene is formed in good yield by a direct "one pot" reaction involving *p*-benzylphenol and formaldehyde, selectively converted to the corresponding chlorosulfonyl and sulfonate analogues.

There is a growing interest in cyclooligomeric compounds called calix[*n*]arenes.[1] These bowl shaped (usually $n = 4, 5$) or more flexible ($n \geqslant 6$) macrocycles can form a diverse range of molecular assemblies. The synthesis of calixarenes has been widely investigated by Gutsche *et al.* and others, leading to well-established procedures for their preparation in reasonable yields.[2,8] However, these focus mainly on *p*-^{t}Bu- calix[*n*]arenes derived from base or acid catalysed condensation of *p*-^{t}Bu-phenol and formaldehyde, leading to the major calixarenes (n = 4, 5, 6, and 8) and other higher calixarenes.[2,3] In contrast, the direct syntheses of calixarenes derived from other *p*-alkylphenols are not extensively investigated and are generally formed in low yields;[6] this is an impediment to developing their chemistry. Base catalysed condensation of *p*-benzylphenol and formaldehyde, for example, leads to a mixture of *p*-benzylcalix-[5,6,8]arenes in 33%, 16% and 12% yields respectively,[5–7] as well as *p*-benzylcalix[7 and 10]arenes,[4,9,10] with no evidence for the formation of the *p*-benzylcalix[4]arene. Herein we report the synthesis of *p*-benzylcalix[4]arene as the first 'major' calixarene of the *p*-benzylcalix[*n*]arene family now available in good yield. The calix[4]arene is new and its availability offers scope for further elaboration such as *O*-alkylation, aromatic substitution of the benzyl groups, and as a receptor molecule, both aspects being established herein with the synthesis of the water soluble sulfonated *p*-benzylcalix[4]arene and the formation of a discrete 1 : 1 complex of the calixarene with C_{60} (Scheme 1).

The rigid cone structure of the phenolic-containing array with the flexibility of the benzyl moieties, offers scope for complexation of a range of substrates, of varying shape and electronic characteristics.

The base induced condensation reaction of *p*-benzylphenol and formaldehyde, proceeds smoothly and quickly relative to the similar condensation of its *p*-^{t}Bu-phenol analogue.[2] Oligomerization of *p*-benzylphenol formed at 120 °C using aqueous formaldehyde as the reaction medium with a catalytic amount of sodium hydroxide, affording a clear beige glass, consisting exclusively of *p*-benzylcalix[8]arene as the sole calixarene formed (TLC, NMR), with the consumption of all the starting phenol. Other products presumably are linear oligomers, noting that corresponding oligomers are formed in the condensation of *p*-^{t}Bu-phenol. Upon addition of diphenyl ether to this material and increasing the temperature quickly to 260 °C over half-an-hour and holding the temperature at reflux for 3 hours affords *p*-benzylcalix[4]arene, **1** in 60% isolated yield.†

It is noteworthy that the outcome of the reaction changes dramatically when either the ramping period or the reflux temperature is altered. For instance when the ramping is over one hour instead of half-an-hour and the reflux temperature is 220 °C instead of 260 °C and even over an extended period of reflux (10 h) the conversion to *p*-benzylcalix[4]arene accounts for only 16% of the starting material.



Scheme 1 Reagents and conditions: (i) Ph_2O, NaOH, H_2CO, 260 °C, 3 h; (ii) Anh. DCM, $ClSO_3H$, rt, 5 h, Argon; (iii) Py–H_2O, $NaHCO_3$, 100 °C; (iv) NaOH; (v) C_{60}, Tol.

The organic free solvent condensation to give the *p*-benzylcalix[8]arene also depends on the reaction conditions, notably, the molar ratio of the base to *p*-benzylphenol and the amount of formaldehyde used. Interestingly, this reaction always gives *p*-benzylcalix[8]arene in varying amounts which is easily separated, precipitating from the reaction mixture upon addition of acetonitrile. The mother liquor contains a mixture of *p*-benzylcalix[4,5,6,7]arenes which can be recycled and, if desired, separated (Table 1).

The ready availability of compound **1** allowed the preparation of the water soluble sulfonated derivative. This adds a novel lipophilic and highly charged calixarene to the expanding

Table 1 Product distribution of solvent free base induced condensation of *p*-benzylphenol (10 g) and formaldehyde (15 ml) using different molar ratios of base to *p*-benzylphenol at 110 °C

Molar ratio	*p*-Benzylcalix[*n*]arene distributions
0.045 NaOH	$n = 8$, 30%[a]
0.045 KOH	$n = 8$, 30%[a]
0.26 NaOH	$n = 8 > 6 > 4 > 7$
0.26 KOH	$n = 8 > 7 > 4$
0.34 NaOH	$n = 8 > 5 > 4$
0.34 KOH	$n = 6 > 5 > 8$

[a] Isolated yield, no other calixarenes present.

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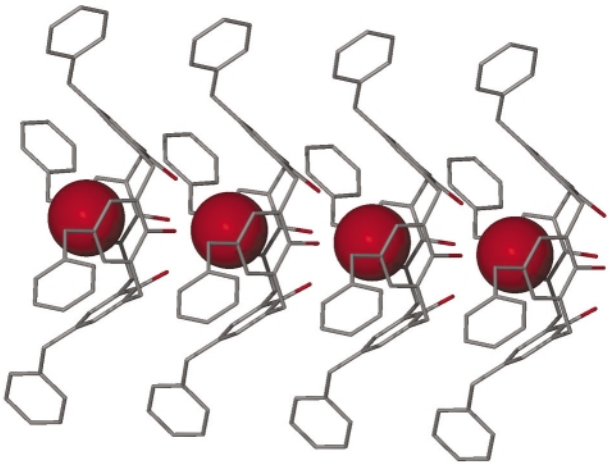

Fig. 1 Molecular structure of *p*-benzylcalix[4]arene showing the inclusion of water (space filling) within a self inclusion leading to a columnar array (hydrogen atoms have been removed for clarity).

chemistry of the water soluble calixarenes. The sulfonated *p*-benzylcalix[4]arene was prepared using the chlorosulfonation approach, isolated either in 60% yield as the sulfonic acid **3**, which slowly absorbs moisture as a deliquescent solid or as the sodium salt **4**. The chlorosulfonyl analogue, **2** can be intercepted and isolated in 30% yield (this yield can be improved under dry forcing reaction condition).†

The structure of *p*-benzylcalix[4]arene (Fig. 1) was established using diffraction data,‡ and shown to be an inclusion complex with water sandwiched between calixarenes in a columnar array, Fig. 1. The water resides deep in the cavity of the cone conformation, hydrogen bonded to the lower rim hydroxy groups. This is different to the water inclusion complex of sulfonated calix[4]arene with water in the cavity whereby the O–H groups are H-bonded (H$\cdots\pi$) to adjacent aromatic rings.[11,12] Another structural feature is the columnar π-stacking of the 1 : 1 supermolecules.

The C_{60} inclusion complex of **1** was prepared by slow evaporation of an equimolar toluene solution of both components. While crystals suitable for X-ray-diffraction studies were available, solution of the structure has proved elusive. Nevertheless, the structure is likely to be similar to those reported by Atwood *et al.*[13,14] where the fullerenes form columnar arrays. Indeed the cell dimensions are remarkably similar for the 1 : 1 complex of C_{60} with *C*-ethylphenylcalix[4]resorcinarene (tetragonal, $a = b = 18.9296(7)$, $c = 27.2702(13)$ Å,[13] and tetragonal, $a = b = 19.2183(3)$, $c = 27.7911(6)$ Å for **1**.C_{60}). Moreover, the similarity of the two cells supports the assignment of the 1 : 1 ratio of the two components.

In conclusion, we have demonstrated the accessibility of *p*-benzylcalix[4]arene in good yield and its water soluble sulfonated derivatives, opening the challenge to expand and diversify the chemistry. Moreover, the results give insight into the advantage of organic solvent free oligomerisation reactions.[15,16]

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Notes and references

† *Synthesis* of compound **1**. *p*-Benzylcalix[4]arene was prepared by an adapted method described in ref. 2. A mixture of *p*-benzylphenol (20.1 g, 0.109 mol), 13 ml of formaldehyde solution and (0.19 g, 0.0049 mol) of 10 M sodium hydroxide was stirred and heated at 120 °C for *ca.* 2 h forming a gummy beige material. 165 ml of warm diphenyl ether was added and the contents were heated first for 2 h at 120 °C, before ramping the temperature to 260 °C over half-an-hour. Refluxing at 260 °C was maintained for 3 h forming a dark amber solution, and the mixture then allowed to cool to rt. Diphenyl ether was evaporated and the viscous material obtained was washed and dried *in vacuo* affording an amber oil which crystallized slowly on standing, and upon addition of acetone (150 ml), *p*-benzylcalix[4]arene, **1** was obtained as a micro-crystalline white powder. Yield 60%, mp 204.5–205.6 °C, MS (ESI$^+$): *m/z* 807.34 [M.Na$^+$], 844.44 [M(H_2O).K$^+$], $C_{56}H_{48}O_4$ (784.34). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.39 (d, 4H, Ar-CH_2-Ar), 3.76 (s, 8H, Ar-CH_2-Ph), 4.18 (d, 4H, Ar-CH_2-Ar), 6.78 (s, 8H; Ar-H), 7.11–7.30 (m, 20H, Ph), 10.13 (s, 4H, OH), ^{13}C NMR: ($CDCl_3$, 300 MHz) δ 32.1 (Ar-CH_2-Ar), 41.3 (ArCH_2-Ph), 126.2 (Ar), 128.4 (Ar), 128.6 (Ar), 129.0 (Ar) 129.5 (Ar), 134.7 (Ar), 141.3 (Ar), 147.2 (Ar-OH). *Synthesis* of compounds **2** and **3**. To a solution of *p*-benzylcalix[4]arene (0.4 g, 0.51 mmol) dissolved in 20 ml of dry dichloromethane, 1 ml of chlorosulfonic acid was added dropwise. The biphasic mixture was stirred at rt for *ca.* 5 h with formation of a viscous amber coloured material. The reaction mixture was poured over ice, and the organic phase was separated, treated successively with 1 M sodium bicarbonate ($\times$ 2), brine solution ($\times$ 2), water and dried ($MgSO_4$) affording the tetrachlorosulfonyl of *p*-benzylcalix[4]arene, **2**. Yield 56%, decomp. 180–195 °C, MS (ESI$^+$): *m/z* 1201.9 [M.Na$^+$], 1218.1 [M.K$^+$], $C_{56}H_{44}O_{12}S_4Cl_4$ (1179.01). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.45 (d, 4H, Ar-CH_2-Ar, J_{AB} 13.2 Hz), 3.87 (s, 8H, Ar-CH_2-Ph), 4.24 (d, 4H, Ar-CH_2-Ar), 6.79 (s, 8H, Ar-H), 7.36 (AA′XX′, 8H, Ph-H), 7.94 (AA′XX′, 8H, Ph-H), 10.15 (s, 4H; OH), ^{13}C NMR ($CDCl_3$, 300 MHz) δ 32.1 (Ar-CH_2-Ar), 41.3 (ArCH_2-Ph), 127.4 (Ar), 128.7 (Ar), 129.8 (Ar), 130.1 (Ar) 132.7 (Ar), 142.4 (Ar), 147.9 (Ar), 149.7 (Ar-OH). The aqueous phase was filtered and treated with activated charcoal ($\times$ 2) leaving a clear light amber solution. Water was evaporated affording a deliquescent light gray solid, which crystallized from acetone to afford the sulfonic acid of *p*-benzylcalix[4]arene, **3**. Yield 80% decomp. 166–170 °C, MS (ESI$^+$): *m/z* 1105.2 [M.H$^+$], 1127.2 [M.Na$^+$], $C_{56}H_{48}S_4O_{16}$ (1104.2). ^{1}H NMR (d_6-DMSO, 300 MHz) δ 3.68 (s, 8H; Ar-CH_2-Ph), 4.08 (br s, 8H, Ar-CH_2-Ar), 6.25 (br s, COH/SOH, shifts downfield with increasing [H_2SO_4]), 6.88 (s, 8H, Ar-H), 7.15 (AA′XX′, 8H, Ph-H), 7.53 (AA′XX′, 8H, Ph-H), ^{13}C NMR (d_6-DMSO, 300 MHz) δ 49.2 (Ar-CH_2-Ar), 49.5 (ArCH_2-Ph), 126.2 (Ar), 128.7 (Ar), 129.1 (Ar), 129.7 (Ar) 134.2 (Ar), 143.2 (Ar), 145.3 (Ar), 148.2 (Ar-OH). Compound **4** was prepared by titration of compound **3** with 1 M sodium hydroxide to neutral pH. Treatment with methanol afforded sodium sulfonates of *p*-benzylcalix[4]arene, **4**, decomp. 200–210 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 3.65–3.95 (m, 8H, Ar-CH_2-Ar), 3.81 (s, 8H, Ar-CH_2-Ph), 4.82 (s, 4H, COH), 6.90 (s, 8H, Ar-H), 7.22 (AA′XX′, 8H, Ph-H), 7.73 (AA′XX′, 8H, Ph-H).

‡ *Crystal data*. Crystals of **1** for X-ray structural determination were grown from a moist acetone–propan-2-ol solution of *p*-benzylcalix[4]arene affording [*p*-benzylcalix[4]arene]·[H_2O]$_{0.5}$: $C_{56}H_{48}O_{4.5}$, space group *P*4/*n*, $a = b = 19.0703(3)$, $c = 5.6631(11)$ Å, $V = 2059.4(6)$ Å^3, $T = 173(2)$ K, $\rho_{calc.} = 1.279$ g cm^{-3}, $\mu = 0.080$ cm^{-1} (no correction), $Z = 2$, Mo-K$_\alpha$ radiation, $2\theta_{max} = 50°$ (1484 observed, $I > 2\sigma(I)$, 139 parameters, no restraints, $R_1 = 0.0455$, $wR_2 = 0.1245$ (all data), Data were collected at 173(1) K on an Enraf-Nonius Kappa CCD diffractometer. The structure was solved by direct methods (SHELXS-97) and refined with a full matrix least-squares refinement on F^2 (SHELXL-97), hydrogens included at calculated positions, $S = 1.079$. CCDC 172616. See http://www.rsc.org/suppdata/cc/b1/b106161p/ for crystallographic data in .cif or other electronic format.

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