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Direct synthesis of calixarenes with extended arms: *p*-phenylcalix[4,5,6,8]arenes and their water-soluble sulfonated derivatives

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Abstract—*p*-Phenylcalix[4,5,6,8]arenes have been isolated from the base catalysed condensation of *p*-phenylphenol with formaldehyde in tetralin, and selectively converted to the corresponding sulfonated derivatives using sulfuric or chlorosulfonic acids.

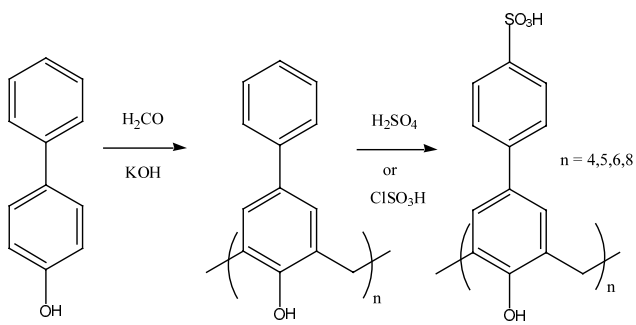
Macrocyclic calixarenes are noted for their diversity and flexibility in supramolecular chemistry, having attracted attention in the last two decades as candidates in mimicking the structure or function of enzymes, crystal engineering, separation science and molecular recognition.[1–3] For example, calix[4,5]arenes and their *p*-sulfonate derivatives have been shown to bind a wide range of molecules and ions.[4,5] Constructing calixarenes with larger/deeper cavities is of interest in confining large molecules and as an entry to new supramolecular arrays. In this context *p*-phenylcalix[*n*]arenes are potential candidates; for $n=4$ and 5, rigid hydrophobic cavities capable of binding large molecules are likely. However, they are not readily available. In the search for deep-cavity calixarenes, various researchers have introduced groups other than Bu^t at the *para* position of calix[4]arene such as benzoyl[7] and piperidinomethyl moieties.[6]

Some procedures for the preparation of *p*-phenylcalix[*n*]arenes have been reported, including the synthesis of *p*-phenylcalix[6 and 8]arenes using a one-pot synthesis involving condensation of *p*-phenylphenol and formaldehyde, with 10 and 7% isolated yields, respectively.[7] However, there is no detailed report on the synthesis of *p*-phenylcalix[4 and 5]arenes using this approach.[7]

There are a few reports using indirect approaches, on the synthesis of *p*-phenylcalix[4]arene, notably by Gutsche et al. using a stepwise route;[8,9] by Anduini et al. using mercury- or thallium-containing calix[4]arene,[10] and by Atwood et al. starting from the *tetra*-methylether of *p*-bromocalix[4]arene, employing the Suzuki palladium-catalysed reaction of arylboronic acids.[11] Also, there is a report on the synthesis of *p*-phenylcalix[5]arene by a '3+2' fragmentation condensation.[12]

Herein we report the direct synthesis of *p*-phenylcalix[*n*]arenes, $n=4$, 5, 6 and 8, which have been isolated in relatively moderate yields (Scheme 1).

In addition, we report the synthesis and characterisation of their water soluble sulfonate derivatives, which have exciting possibilities as phase transfer catalysts, in transport processes and more.



Scheme 1. Synthesis of *p*-phenylcalix[*n*]arenes and their sulfonated analogues.

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It is well known that base-catalysed condensation reactions of *p*-substituted phenols with formaldehyde depends on temperature (and temperature gradient), the type of base and molar ratio of phenol to base.[13]

In the present study we systematically varied the ratio of phenol to potassium or sodium hydroxide, with all reactions conducted in tetralin. A higher molar ratio of base (KOH, ca. 0.45)[14] is required to achieve the optimal production of *p*-phenylcalix[4]arene, whereas *p*-phenylcalix[5]arene preparation is optimized at 0.045. Results of the optimisation experiments are summarised in Table 1.

The *p*-phenylcalixarenes were sulfonated either by a direct method using sulfuric acid, as described in the literature for other classes of calixarenes[15] or by chlorosulfonation.[17] The exception is the case of $n=8$, where the former method is preferred because of solubility considerations of the starting material.[16] The lipophilic character of these novel sulfonic acids with appreciable solubilities in polar solvents render their isolation rather difficult and multiple precipitations from ether/ethanol or acetone/ethanol mixtures were required. They were characterised by ^{1}H and ^{13}C NMR spectroscopy and display similar resonance signals to the parent sulfonic acids of calix[*n*]arenes; a broad singlet for $ArCH_2Ar$ ($\sim$4 ppm) and a singlet ($\sim$7.3 ppm), an AA′XX′ system (7.3–7.6 ppm) for the aromatic region and one resonance for the bridging methylene carbons at about 32 ppm[17] (Figs. 1a and 1b).

All sulfonic acids of *p*-phenylcalix[*n*]arenes can be easily converted to the corresponding sodium salts by simple titration with sodium hydroxide.[18]

Table 1. Molar ratio of base to phenol and the resulting isolated yields of *p*-phenylcalix[*n*]arenes

Molar ratio	% Yields			
Base:phenol	$n=4$	$n=5$	$n=6$	$n=8$
0.045 NaOH	0	3	10	30
0.045 KOH	3	15	11	18
0.18 NaOH	0	0	0	0
0.18 KOH	0	2	8	0
0.45 NaOH	2	5	10	20
0.45 KOH	10	5	7.4	38
0.75 NaOH	0	0	0	0
0.75 KOH	0	0	0	0

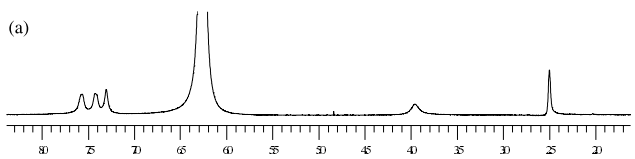

Figure 1a. ^{1}H NMR spectra of the octa-sulfonic acid derivative of *p*-phenylcalix[8]arene in DMSO-d_6.

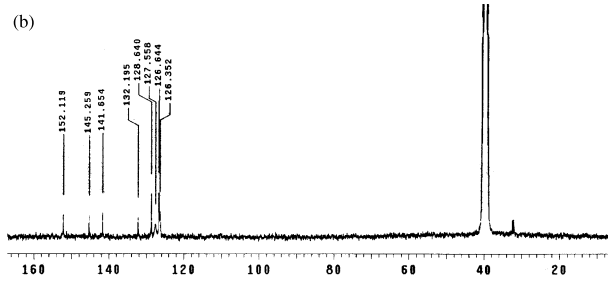

Figure 1b. ^{13}C NMR spectra of the octa-sulfonic acid derivative of *p*-phenylcalix[8]arene in DMSO-d_6.

Overall we have established a simple, direct route to *p*-phenylcalix[*n*]arenes and their sulfonated derivatives. The inclusion/self assembly chemistry of these large macromolecules is currently under investigation.

Acknowledgements

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14. To a slurry of *p*-phenylphenol (10 g, 58.7 mmol) and 5.5 g of paraformaldehyde in 200 ml of tetralin in a 250 ml round-bottomed flask equipped with a condenser and a Dean–Stark water trap; 2 ml of 15 M KOH (26.4 mmol)

was added dropwise at 80°C under a stream of nitrogen. The reaction vessel was lowered into a 200°C preheated heating mantle and kept at this temperature for 2.5 h. After 1 min the reactants dissolved and after 15 min a precipitate began to form. Tetralin was evaporated in vacuo from the cooled reaction mixture and the residue was stirred in 200 ml of warm chloroform containing 2 M HCl (250 ml). The chloroform layer was separated, filtered, washed with water and dried ($MgSO_4$) to afford a yellowish solid, after removal of the solvent. The yellowish solid was triturated in refluxing methanol, filtration affords 3 g of a beige powder which consisted of a mixture of *p*-phenylcalix[*n*]arenes ($n=4$, 5 and 6). The beige solid was then heated in an acetone/methanol mixture and upon standing 0.80 g (7.4%) of *p*-phenylcalix[6]arene precipitated: IR (KBr) 3173 cm^{-1} (OH stretching); ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta=4.05$ (s-br, 12H; $ArCH_2Ar$), 7.22–7.49 (m, 42H; ArH), 10.57 (s, 6H; OH); ^{13}C NMR (300 MHz, $CDCl_3$, 25°C): $\delta=$ 32.93 ($ArCH_2Ar$), 127.00 (Ar), 127.15 (Ar), 127.74 (Ar), 128.63 (Ar), 128.84 (Ar), 135.56 (Ar), 140.88 (Ar), 149.35 (Ar-OH), MS (ESI^-): *m*/*z* (%): 1091.6 (100) [$M-H^+$], 1092.3 (68) [M], 1093.5 (33) [$M+H^+$]; $C_{78}H_{60}O_6$ (1092.43): requires C, 85.68; H, 5.54; found: C, 85.40; H, 6.30. The filtrate was then evaporated and the residue triturated in acetone/methylene chloride, affording 0.5 g (5%) of a crystalline solid shown to be *p*-phenylcalix[5]arene: IR (KBr) 3282 cm^{-1} (OH stretching); ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta=4.01$ (s-br, 10H; $ArCH_2Ar$), 7.25–7.49 (m, 35H; ArH), 9.11 (s, 5H; OH); ^{13}C NMR (300 MHz, $CDCl_3$, 25°C): $\delta=32.14$ ($ArCH_2Ar$), 127.00 (Ar), 127.08 (Ar), 127.20 (Ar), 128.36 (Ar), 128.86 (Ar), 135.30 (Ar), 140.88 (Ar), 149.87 (Ar-OH), MS (ESI^+): *m*/*z* (%): 933.35 (100) [$M+Na^+$]; $C_{65}H_{50}O_5$ (910.36): requires C, 85.68; H, 5.54; found: C, 84.06; H, 5.24; mp >350°C [dec.]. After evaporation of the filtrate, the residue obtained was triturated with acetone affording 1 g (9%) of *p*-phenylcalix[4]arene: IR (KBr) 3200 cm^{-1} (OH stretching); ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta=3.67$ (d, 4H; $ArCH_2Ar$; $J_{AB}=13.5$ Hz), 4.38 (d, 4H; $ArCH_2Ar$; $J_{AB}=$ 13.5 Hz) 7.20–7.49 (m, 28H; ArH), 10.43 (s, 4H; OH); ^{13}C NMR (300 MHz, $CDCl_3$, 25°C,): $\delta=31.33$ ($ArCH_2Ar$), 127.08 (Ar), 127.12 (Ar), 128.26 (Ar), 128.64 (Ar), 128.90 (Ar), 135.99 (Ar), 140.96 (Ar), 148.69 (Ar-OH), MS (ESI^-): *m*/*z* (%): 727.4 (100) [$M-H^+$]; $C_{52}H_{40}O_4$ (728.29): requires C, 85.68; H, 5.54; found: C, 85.50; H, 6.06.

Chromatographic separation of *p*-phenylcalix[4,5,6]-arenes can also be achieved on a silica gel column using acetone/methylene chloride/hexane as eluents at ratios of 1:1:2 with R_f values of 0.23, 0.64 and 0.46, respectively. The chloroform insoluble material (5.7 g) contaminated with *p*-phenylphenol was triturated several times with hot acetone/chloroform to give 4.1 g (38%) of a white solid *p*-phenylcalix[8]arene.

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16. 2 g of *p*-phenylcalix[8] arene was stirred at 80°C in 10 ml of neat sulfuric acid for ca. 12 h whereupon cooling, the reaction mixture was poured over ice, then the aqueous mixture was filtered and treated with activated charcoal (×2) leaving a clear light greenish solution. Water was evaporated affording a deliquiscent light green solid, which was crystallized from acetone to afford the per-sulfonic acid of *p*-phenylcalix[8]arene. IR (KBr): *v*(OH) 2900; 3200 cm^{-1}; $v_a(SO_2)$ 1006–1068 cm^{-1}; $v_s(SO_2)$ 1176 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25°C): $\delta=7.56$ (br-d, 16H; PhH_{AX}), 7.42 (br-d, 16H; PhH_{AX}), 7.30 (s, 16H; Ar-H), 6.25 (s. br; COH/SOH, shifts downfield with increasing [H_2SO_4]), 3.95 (br, 16H; Ar-CH_2-Ar). ^{13}C NMR (300 MHz, DMSO-d_6, 25°C): $\delta=32.03$ ($ArCH_2Ar$), 126.35 (Ar), 126.64 (Ar), 127.55 (Ar), 128.64 (Ar), 132.19 (Ar), 141.65 (Ar), 145.25 (Ar), 152.11 (Ar-OH).
17. **General procedure for $n=4$, 5 and 6**: To a solution of *p*-phenylcalix[5]arene (0.4 g, 0.51 mmol) dissolved in 20 ml of dry chloroform, 1 ml of chlorosulfonic acid was added dropwise at 0°C under argon. The mixture was stirred at room temperature for ca. 12 h to form a bright rose biphasic mixture. The reaction mixture was poured over ice, and the aqueous phase was separated and treated with activated charcoal (×2) leaving a clear light greenish solution. Water was then evaporated affording a deliquiscent green solid and upon addition of acetone/methanol mixture, a fine gray precipitate formed which was filtered over Celite to afford sulfonic acid of *p*-phenylcalix[5]arene. IR (KBr): *v*(OH) 2900; 3413 cm^{-1}, $v_a(SO_2)$ 1007–1068 cm^{-1}; $v_s(SO_2)$ 1174 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25°C): $\delta=7.58$ (br-d, 10H; PhH_{AX}), 7.46 (br-d, 10H; PhH_{AX}), 7.40 (s, 10H; Ar-H), 6.27 (s. br; COH/SOH, shifts downfield with increasing [H_2SO_4]), 3.91 (br, 10H; Ar-CH_2-Ar). ^{13}C NMR (300 MHz, DMSO-d_6, 25°C): $\delta=31.48$ ($ArCH_2Ar$), 126.42 (Ar), 126.66 (Ar), 127.82 (Ar), 128.75 (Ar), 132.40 (Ar), 141.55 (Ar), 145.52 (Ar), 151.75 (Ar-OH).

Sulfonic acid of *p*-phenylcalix[4]arene: IR (KBr): *v*(OH) 2900; 3421 cm^{-1}, $v_a(SO_2)$ 1004–1059 cm^{-1}; $v_s(SO_2)$ 1171 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25°C): $\delta=7.6$ (br-d, 8H; PhH_{AX}), 7.4 (br-d, 8H; PhH_{AX}), 7.27 (s, 8H; Ar-H), 5.74 (s; COH/SOH, shifts downfield with increasing [H_2SO_4]), 4.01 (br-s, 8H; Ar-CH_2-Ar). ^{13}C NMR (300 MHz, DMSO-d_6, 25°C): $\delta=31.66$ ($ArCH_2Ar$), 125.92 (Ar), 126.70 (Ar), 127.48 (Ar), 128.73 (Ar), 131.90 (Ar), 141.34 (Ar), 146.40 (Ar), 152.80 (Ar-OH).

Sulfonic acid of *p*-phenylcalix[6]arene: IR (KBr): *v*(OH) 2953; 3441 cm^{-1}, $v_a(SO_2)$ 1007–1067 cm^{-1}; $v_s(SO_2)$ 1173 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25°C): $\delta=7.52$ (d, 12H; PhH_{AX}; $J_{AX}=6.3$ Hz), 7.43 (d, 12H; PhH_{AX}; $J_{AX}=$ 6.3 Hz), 7.32 (s, 12H; Ar-H), 8.75 (s. br, COH/SOH, shifts downfield with increasing [H_2SO_4]), 3.85 (br, 12H; Ar-CH_2-Ar). ^{13}C NMR (300 MHz, DMSO-d_6, 25°C): $\delta=31.68$ ($ArCH_2Ar$), 126.25 (Ar), 126.40 (Ar), 127.35 (Ar), 128.75 (Ar), 132.95 (Ar), 143.01 (Ar), 145.52 (Ar), 151.70 (Ar-OH).
18. Sodium sulfonates of *p*-phenylcalix[4]arene, IR (KBr): *v*(OH) 3475 cm^{-1}, $v_a(SO_2)$ 1008–1042 cm^{-1}; $v_s(SO_2)$ 1126; 1452 cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6, 25°C): $\delta=$ 7.56 (d, 8H; PhH_{AX}; $J_{AX}=7.2$ Hz), 7.44 (d, 8H; PhH_{AX}), 7.37 (s, 8H; Ar-H), 3.91 (br-s, 8H; Ar-CH_2-Ar).