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Tetra-*O*-benzylated Calix[8]arenes with C_4 Symmetry

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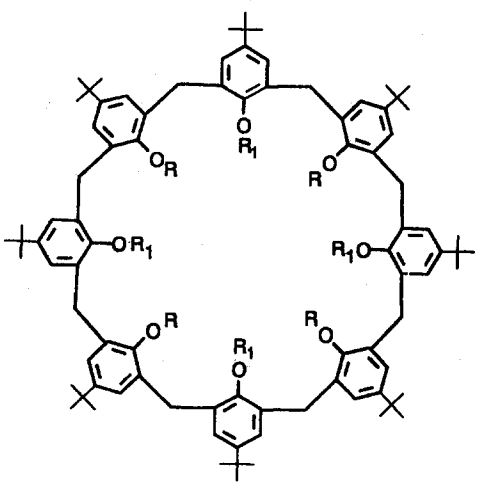
Abstract: The first procedure for the selective partial *O*-alkylation of *p-tert*-butylcalix[8]arene **1** affording well defined products is described. Treatment of **1** with *p*-X-benzyl bromides (X = H, Me, *tert*-Bu, NO_2, CN) and K_2CO_3 in THF/DMF gives the corresponding 1,3,5,7-tetrabenzyl ethers **2-6** having C_4 symmetry. Their structures were firmly established by FAB(+) MS, ^{1}H- and ^{13}C-NMR. Variable temperature NMR studies evidenced conformational flexibility for **2-6**. A possible rationale is proposed in order to explain the origin of the 1,3,5,7-substitution pattern.

Calixarenes are macrocyclic compounds of great interest in supramolecular chemistry as basic skeletons for the construction of new molecules with remarkable host properties.[1] To this end, the selective functionalization at the lower rim is an important tool that has been extensively used in the chemistry of calix[4]arenes.[1] Partially *O*-substituted calix[6]arenes with defined structures have been reported only very recently.[2]

In the case of calix[8]arenes, mixtures of regioisomers or structurally undefined di-, hexa-, and tetra-*O*-substituted derivatives have been reported by Gutsche,[3] whereas an unidentified *p*-nitrophenyl pentasubstituted product has been patented by japanese researchers.[4]

Here we wish to report the synthesis of the first partially substituted calix[8]arenes with defined structure, **2-6**, having a 1,3,5,7-tetrasubstitution pattern and C_4 symmetry.[5]



Compd	R	R_1
1	H	H
2	H	Bn
3	H	*p*-Bu^t-Bn
4	H	*p*-Me-Bn
5	H	*p*-NO_2-Bn
6	H	*p*-CN-Bn
7	Ac	*p*-Bu^t-Bn

Bn = Benzyl

Compounds **2-4** were obtained in 20-41% yield by treating *p-tert*-butylcalix[8]arene **1** with the appropriate benzyl bromide (8 equiv) and K_2CO_3 (16 equiv) in THF/DMF (10:1 v/v) at 60 °C, followed by column chromatography on silica gel.[6] More reactive benzyl bromides (*p*-NO_2-BnBr and *p*-CN-BnBr) in the same experimental conditions gave mainly the relevant octa-*O*-substituted derivatives. However, in these instances the 1,3,5,7-tetrasubstituted derivatives **5** and **6** can be obtained, albeit in low yields (10-15%), by limiting the amounts of electrophile and base (4 equiv each).[6]

Structures **2-6** were established upon analysis of ^{1}H- and ^{13}C- NMR and FAB(+) MS spectra. The ^{1}H-NMR spectra, as examplified in Figure 1 by the spectrum of **3**, were highly symmetrical displaying two singlets for the *tert*-butyl groups of the calixarene skeleton, one singlet for the bridging methylenes ($ArCH_2Ar$), one singlet for the $ArCH_2O$ methylenes, and two other aromatic singlets for alkylated and unalkylated phenolic rings.

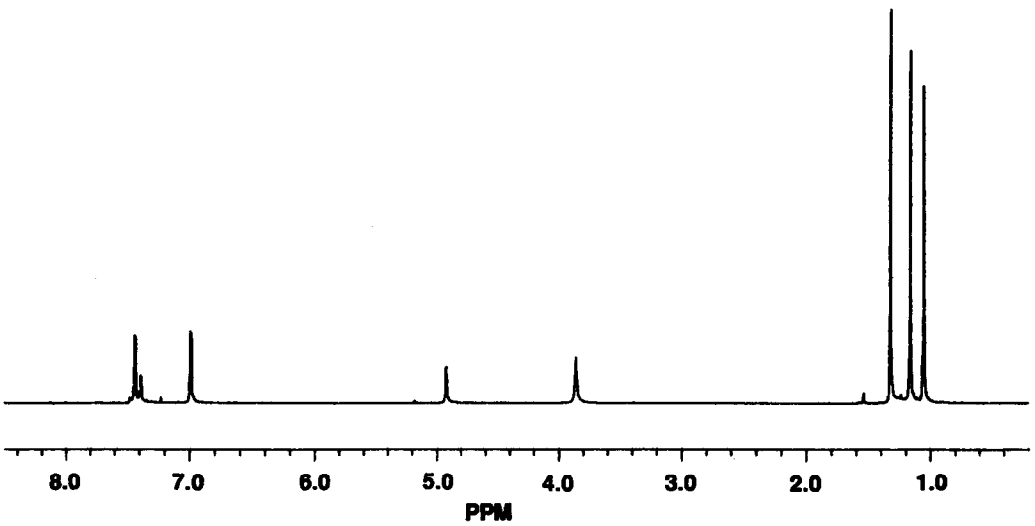


Fig. 1. The ^{1}H-NMR spectrum of **3** (250 MHz, $CDCl_3$, 295 K).

In addition, an aromatic AB or a three-spin system was observed in the spectra of **3-6** and **2**, respectively. A singlet for a *tert*-butyl or a methyl group on aromatic ring completed the spectra of **3** and **4**, respectively. The 2:1 intensity ratio between $ArCH_2Ar$ and $ArCH_2O$ singlets promptly indicated a tetrasubstitution in the calix[8]arene ring, that was confirmed by the expected molecular ion mass peaks in the FAB(+) MS spectra. Furthermore, the relatively sharp appearance of the signals of the bridging methylenes suggested a mobile structure for compounds **2-6**. This was confirmed by VT-^{1}H-NMR studies ($CDCl_3$, 220-350 K) that evidenced further sharpening of the signals at higher temperatures, while broadening and coalescence occurred upon cooling giving complicated spectra.

The 1,3,5,7-substitution pattern was deduced from the very high symmetry of the ^{1}H-NMR spectra. In fact, among the eight possible tetrasubstituted regioisomers only the 1,3,5,7 with C_4 symmetry is compatible with the presence of two *tert*-butyl signals in 1:1 ratio and one singlet for the eight bridging methylenes. The 1,2,5,6-isomer, possessing two C_2 symmetry axes, was ruled out because it should give three singlets in a 1:2:1

intensity ratio for the $ArCH_2Ar$, instead of the observed one. Accidental isochrony of signals was excluded by running for each compound several spectra in different solvents at various temperatures.

The broad-band decoupled and DEPT ^{13}C-NMR spectra of **2-6** were compatible with the above considerations showing the expected 13 signals for the calix[8]arene skeleton.

The above described calix[8]arene derivatives may be easily converted into octasubstituted compounds with alternating groups at the lower rim. As an example, treatment of **3** with acetic anhydride in pyridine gave the mixed 1,3,5,7-tetraether-2,4,6,8-tetraester **7** whose ^1H- and ^{13}C-NMR spectra showed the same symmetry as the parent compound with additional signals for the four equivalent $COCH_3$ groups.[5]

The 1,3,5,7 regioselectivity of the alkylation of calix[8]arene **1** appears to be not dependent on the nature of the alkali metal cation, since replacement of potassium carbonate with sodium carbonate did not change appreciably the composition of the reaction products. Instead, it seems plausible that, as suggested for the alkylation of calix[4]arenes in the presence of a weak base,[7] the reaction proceeds *via* a sequence of cycles of two steps, monodeprotonation by the base and reaction of the phenoxide anion with the alkylating agent. The monoalkylated calix[8]arene formed initially would be in turn deprotonated to give preferentially the monoanions most stabilized by hydrogen bonds, i.e. those resulting from removal of a proton from one of the phenolic groups flanked with two hydroxyls. These monoanions would undergo alkylation and the procedure would continue until a dead-end is reached when no more a phenoxide monoanion stabilized by two hydrogen bonds can be formed. The 1,3,5,7-tetrasubstituted derivative should be the most probable dead-end product, but other dead-points can be accumulated besides it. This is substantiated by the presence of additional spots in the TLC plate of the crude reaction mixtures. However, further studies are needed to gain a deeper insight into the alkylation mechanism of calix[8]arenes and to test the above hypothesis.

Due to their large annulus calix[8]arenes have a great potential in supramolecular chemistry that so far has been relatively unexploited mainly because of their complicate chemistry and conformational flexibility. This preliminary report paves the way for the synthesis of a new class of selectively substituted calix[8]arenes with C_4 symmetry whose potential applications in host-guest chemistry are the subject of ongoing studies.

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5. Satisfactory microanalytical and spectral data were obtained for compounds **2-7**. Molecular weights were deduced by FAB(+) MS using 3-nitrobenzyl alcohol as matrix. The molecular-ion peak was generally weak, only for **7** it was the base-peak. Compound **2**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 1.05, 1.17 [s, $C(CH_3)_3$, 36 H each], 3.86 (s, $ArCH_2Ar$, 16 H), 4.88 (s, $ArCH_2O$, 8 H), 6.97, 6.99 (s, ArH, 8 H each), and 7.24-7.45 (m, $CH_2C_6H_5$, 20 H). Compound **3**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 1.05, 1.16, 1.32 [s, $C(CH_3)_3$, 36 H each], 3.85 (s, $ArCH_2Ar$, 16 H), 4.92 (s, $ArCH_2O$, 8 H), 6.97, 6.98 (s, ArH, 8 H each), 7.38 (s, OH, 4 H), 7.42 and 7.43 (AB, J = 8.7 Hz, *p-tert*-Bu-C_6H_4, 16 H). Compound **4**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 1.03, 1.17 [s, $C(CH_3)_3$, 36 H each], 2.34 (s, $C_6H_4CH_3$, 12 H), 3.86 (s, $ArCH_2Ar$, 16 H), 4.85 (s, $ArCH_2O$, 8 H), 6.96, 6.99 (s, ArH, 8 H each), 7.14 and 7.36 (AB, J = 7.5 Hz, *p*-Me-C_6H_4, 16 H). Compound **5**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 1.04, 1.18 [s, $C(CH_3)_3$, 36 H each], 3.84 (s, $ArCH_2Ar$, 16 H), 4.94 (s, $ArCH_2O$, 8 H), 6.96, 6.98 (s, ArH, 8 H each), 7.49 and 8.08 (AB, J = 8.5 Hz, *p*-NO_2-C_6H_4, 16 H). Compound **6**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 1.05, 1.19 [s, $C(CH_3)_3$, 36 H each], 3.91 (s, $ArCH_2Ar$, 16 H), 4.89 (s, $ArCH_2O$, 8 H), 6.96, 6.97 (s, ArH, 8 H each), 7.31 (s, OH, 4 H), 7.37 and 7.38 (AB, J = 8.9 Hz, *p*-CN-C_6H_4, 16 H). Compound **7**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 1.01, 1.16, 1.29 [s, $C(CH_3)_3$, 36 H each], 1.52 (s, $COCH_3$, 12 H), 3.83 (s, $ArCH_2Ar$, 16 H), 4.62 (s, $ArCH_2O$, 8 H), 6.80, 7.09 (s, ArH, 8 H each), 7.31 and 7.33 (AB, J = 8.5 Hz, *p-tert*-Bu-C_6H_4, 16 H).

6. As a typical example the preparation of **3** is described: Compound **1** (0.50 g, 0.385 mmol) in 44 mL of THF/DMF (10:1 v/v) was stirred at 60 °C until a clear solution was obtained (20 min), then 0.85 g (6.15 mmol) of K_2CO_3 were added and stirring was continued for additional 20 min under nitrogen. A solution of *p-tert*-butylbenzyl bromide (0.70 g, 3.08 mmol) in 6 mL of THF was added. The mixture was stirred at 60 °C for 20 h, THF was evaporated under reduced pressure, and 0.1 N HCl (100 mL) was added. The colourless precipitate was collected by filtration, washed with MeOH (10 mL) and dried. Column chromatography of the crude product (LiChroprep Si-60, 25-40 μm, CH_2Cl_2/*n*-hexane 2:3) gave **3** (298 mg, 41%) as a white powder (m.p. 153-155 °C, R_f = 0.47, CH_2Cl_2/*n*-hexane 1:1). Reaction times for compounds **2** and **4-6** were 6-8 h.

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