

## New Syntheses of Calixarene-*p*-sulphonates and *p*-Nitrocalixarenes †

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Calixarene-*p*-sulphonates (tetramer, hexamer, and octamer) have been prepared (75–88%) and used to give *p*-nitrocalixarenes (15–22% yields based on the starting calixarenes). The novel nitration has two advantages: (i) calixarenes are protected from nitric acid oxidation by the electron-withdrawing sulphonate groups and (ii) the difference in the water-solubility of the *p*-nitrocalixarenes from the sulphonate-containing, lower nitration products, allows ready isolation of the former. The *p*-nitrocalixarenes thus obtained have potential as intermediates in the synthesis of a variety of functionalised calixarenes.

The host-guest chemistry of cyclodextrins has been of considerable interest for decades, many functionalised cyclodextrins which can partly mimic the action of enzymes having been exploited.<sup>1,2</sup> Recently, Gutsche and others<sup>3,4</sup> have described a new series of cyclic molecules called 'calixarenes' (**1**; *n*) which possess a cylindrical structure similar to cyclodextrins and are, therefore, expected to be useful in the design of totally synthetic enzyme mimics. Such systems should be (i) water-soluble so that host-guest-type complexation in an aqueous system can take place and (ii) suitably substituted in order to prepare functionalised derivatives. Substituted calixarenes have been prepared by Gutsche and others,<sup>3–10</sup> but few of them are either water-soluble or useful as intermediates to prepare biomimetic calixarenes.

Here, we report the sulphonation of calixarenes (tetramer, hexamer, and octamer) and subsequent conversion of the products into *p*-nitrocalixarenes. This is the first successful method to the latter, which offer potential as intermediates to other functionalised calixarenes *via* the amino derivatives.<sup>11</sup>

The starting materials, calix[*n*]arenes (**1**; *n*) were prepared by debutylation of *p*-*t*-butylcalix[*n*]arenes.<sup>12,13</sup> Calix[4]arene (**1**;

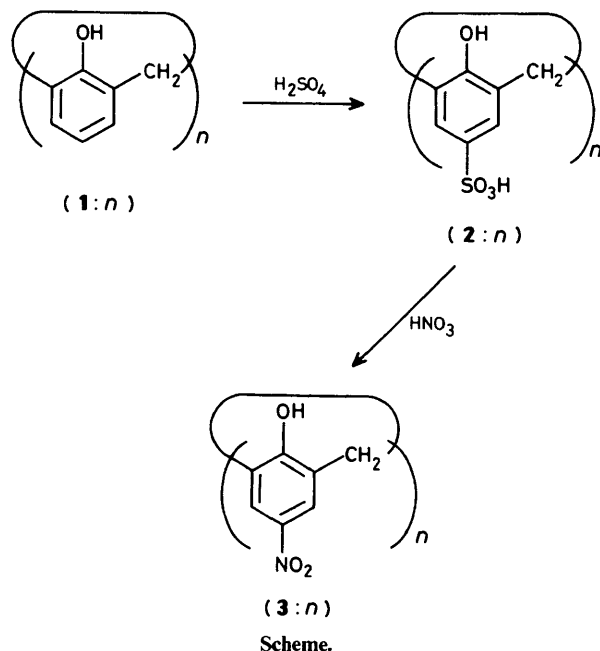


Table. Yields of calixarene-*p*-sulphonates (**2**; *n*) and *p*-nitrocalixarenes (**3**; *n*)

Starting material	Yield of ( <b>2</b> ; <i>n</i> ) (%)	Yield of ( <b>3</b> ; <i>n</i> ) <sup>a</sup> (%)	
		Method A <sup>b</sup>	Method B <sup>c</sup>
( <b>1</b> ; <i>n</i> = 4)	78		21
( <b>1</b> ; <i>n</i> = 6)	75		15
( <b>1</b> ; <i>n</i> = 8)	88	27	22

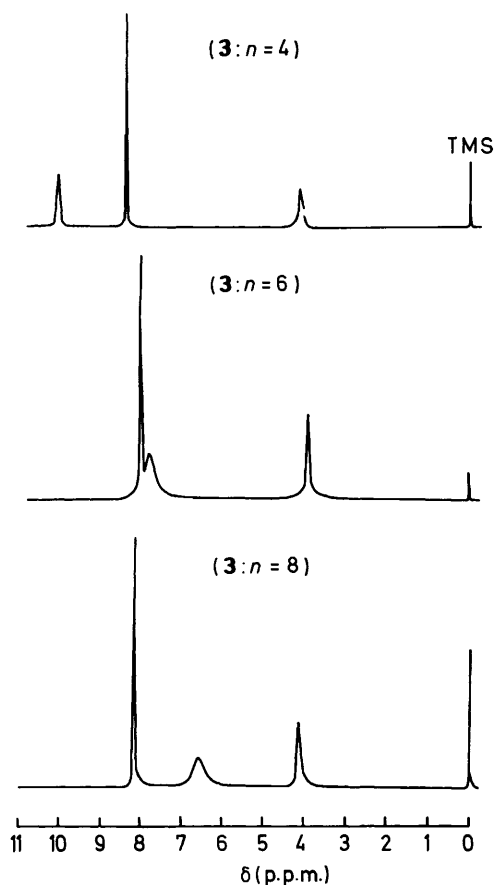
<sup>a</sup> The yield is calculated on the basis of (**1**; *n*). <sup>b</sup> Compound (**2**; *n*) was isolated and then treated with nitric acid. <sup>c</sup> One-pot synthesis without the isolation of (**2**; *n*).

*n* = 4) and calix[8]arene (**1**; *n* = 8) were sulphonated in good yield in a manner similar to that previously described for calix[6]arene;<sup>14,15</sup> the yields were unaffected by the ring size (see Table). Elemental analyses for the hygroscopic products were adjusted to the calculated values by including several water molecules. The <sup>1</sup>H n.m.r. spectra of (**2**; *n* = 4), (**2**; *n* = 6), and (**2**; *n* = 8) in D<sub>2</sub>O at room temperature gave singlets at 4.32, 4.32, and 4.11 p.p.m. which are assigned to ArCH<sub>2</sub>Ar. This implies that the calixarene is not fixed in the 'cone' conformation in D<sub>2</sub>O at room temperature since if it were a double doublet would be expected for the methylene protons.<sup>3,4</sup>

Direct nitration of calixarenes has been reported<sup>3,4,16,17</sup> to give decomposition products, probably resulting from partial oxidation of the calixarene ring. We found that direct nitration of calixarenes in chloroform at 0 °C gave carbonyl compounds ( $\nu_{\text{C=O}}$  at 1710 and 1750 cm<sup>-1</sup>) which were not removed by repeated recrystallisation. Since other attempts at direct nitration failed, we explored the possibility of developing a milder method of nitration by substituting the sulphonate groups in (**2**; *n*) (see Scheme). Compound (**3**; *n*) would be easily isolated from the reaction mixture since its water solubility would be less than that of the sulphonate-containing products.

The synthesis of (**3**; *n*) was attempted by two different methods. In method A, (**2**; *n*) was first isolated and then treated with nitric acid, and in method B (**1**; *n*) was sulphonated and then directly nitrated. In method A, we examined the effect of the H<sub>2</sub>SO<sub>4</sub> concentration on the nitration yield. At 5 °C in the presence of 65% HNO<sub>3</sub> [2.2 g in 71.3 g of dilute H<sub>2</sub>SO<sub>4</sub> and (**2**; *n* = 8) (2.0 g, 1.2 mmol)], replacement of the sulphonate groups by nitro groups failed above 55% H<sub>2</sub>SO<sub>4</sub> and below 22% H<sub>2</sub>SO<sub>4</sub>; the highest yield (27%) was obtained with a concentration of 40–50%. The one-pot synthesis of (**3**; *n*) from (**1**; *n*) was thus carried out at this H<sub>2</sub>SO<sub>4</sub> concentration: after sulphonation, the reaction mixture was diluted to ca. 40% H<sub>2</sub>SO<sub>4</sub> with cold water and then conc. HNO<sub>3</sub> was added at 0–5 °C. Since method B gave similar yields to method A, this is the method of choice if (**2**; *n*) is not the desired product.

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**Figure.**  $^1\text{H}$  N.m.r. spectra of (3;  $n$ ) in  $(\text{CD}_3)_2\text{SO}$  at  $20^\circ\text{C}$ ; compound (3;  $n = 4$ ) is an anhydrous sample. On the other hand, (3;  $n = 6$ ) and (3;  $n = 8$ ) contain  $4\text{H}_2\text{O}$  and  $12\text{H}_2\text{O}$  per one calixarene, respectively, and the chemical shifts move to higher magnetic field with increasing water concentration

Three *p*-nitrocalixarenes had m.p.s  $> 360^\circ\text{C}$ ; above  $300^\circ\text{C}$  the colour (slightly yellow) gradually changed to brown but there was no sharp decomposition point. These observations are not surprising since *p*-*t*-butylcalixarenes have m.p.s in the range  $334\text{--}412^\circ\text{C}$ ,<sup>12,13</sup> and *p*-nitrocalixarenes are expected to be less stable to heat. Although anhydrous (3;  $n = 4$ ) could be isolated, removal of water from (3;  $n = 6$ ) and (3;  $n = 8$ ) was difficult and not effected at 1 mmHg at room temperature. At  $120\text{--}150^\circ\text{C}$  the compounds gradually decomposed and their elemental analysis data became worse. Possibly, the OH groups of (3;  $n$ ), the acidity of which should be much higher than those of *p*-*t*-butylcalixarenes, interact strongly with occluded water molecules.

The  $^1\text{H}$  n.m.r. spectra of (3;  $n = 4$ ), (3;  $n = 6$ ), and (3;  $n = 8$ ) in  $(\text{CD}_3)_2\text{SO}$  at room temperature gave relatively broad singlets at  $\delta$  4.18, 3.98, and 4.06, respectively, which are assigned to  $\text{ArCH}_2\text{Ar}$ , (Figure). This suggests that (3;  $n$ ) in  $(\text{CD}_3)_2\text{SO}$  does not exist in the 'cone' conformation. In the  $^1\text{H}$  n.m.r. spectrum of (3;  $n = 4$ ) in (Figure) the peak for the OH protons, which disappeared on the addition of  $\text{D}_2\text{O}$ , appeared at 10.10 p.p.m. The unusual shift to the lower magnetic field is rationalised in terms of strong intramolecular hydrogen-bonding among the OH groups.<sup>3-5</sup>

## Experimental

**Calix[4]arene-*p*-tetrasulphonic Acid (2;  $n = 4$ ).**—Calix[4]-arene (1.0 g, 2.4 mmol) was mixed with concentrated  $\text{H}_2\text{SO}_4$

(10 ml) and the solution was heated at  $60^\circ\text{C}$  for 4 h. An aliquot was withdrawn from the reaction mixture and poured into water. The reaction was completed when no water-insoluble material was detected in the aliquot. After cooling, the precipitate was filtered off through a glass filter. The precipitate was dissolved in water and the aqueous solution was neutralised by  $\text{BaCO}_3$ . Precipitated  $\text{BaCO}_3$  was filtered off and washed with hot water and the combined filtrate and washings were evaporated to dryness under reduced pressure. The residue was dissolved in hot water (15 ml) and the solution was adjusted to pH 8 by  $\text{Na}_2\text{CO}_3$ . After filtration, methanol was added to the filtrate to afford a white precipitate (yield 78%), m.p.  $> 300^\circ\text{C}$ ;  $\delta(\text{D}_2\text{O})$  4.32 (8 H, s,  $\text{ArCH}_2\text{Ar}$ ) and 7.96 (8 H, s, ArH);  $\nu_{\text{max.}}$ (KBr) 3 440 (OH) and 1 040 and 1 180 ( $\text{SO}_3$ )  $\text{cm}^{-1}$  (Found: C, 34.5; H, 2.9%. Calc. for  $\text{C}_{28}\text{H}_{17}\text{O}_{16}\text{S}_4\text{Na}_7 \cdot 6\text{H}_2\text{O}$ : C, 34.9; H, 2.9%). The elemental analysis shows that three of the four phenol units are the sodium phenolate salts.

**Calix[8]arene-*p*-octasulphonic Acid (2;  $n = 8$ ).**—This compound was prepared from (1;  $n = 8$ ) according to the method similar to that of (2;  $n = 4$ ), (yield 88%), m.p.  $> 300^\circ\text{C}$ ;  $\delta(\text{D}_2\text{O})$  4.11 (16 H, s,  $\text{ArCH}_2\text{Ar}$ ) and 7.61 (16 H, s, ArH);  $\nu_{\text{max.}}$ (KBr) 3 460 (OH) and 1 050 and 1 190 ( $\text{SO}_3$ )  $\text{cm}^{-1}$  (Found: C, 32.1; H, 3.4. Calc. for  $\text{C}_{56}\text{H}_{35}\text{O}_{32}\text{S}_8\text{Na}_{13} \cdot 18\text{H}_2\text{O}$ : C, 32.1; H, 3.4%).

***p*-Nitrocalix[8]arene (3;  $n = 8$ ) by Method A.**—65%  $\text{HNO}_3$  (2.2 g) was added dropwise at  $0\text{--}5^\circ\text{C}$  to compound (2;  $n = 8$ ) (2.0 g, 1.2 mmol) dissolved in 52%  $\text{H}_2\text{SO}_4$  (71.3 g) at  $0^\circ\text{C}$  and the solution was stirred below  $10^\circ\text{C}$  for 10 h. Dilution of the reaction mixture with water gave a finely dispersed precipitate which since it could not be recovered by the conventional filtration was isolated by centrifugation and washed with water. It was then dissolved in alkaline solution and treated with active charcoal. After filtration, NaOH was added (up to 5 mol%) to the filtrate to salt out the octasodium salt. The salt was filtered off, washed with brine, and dissolved in water (15 ml). The aqueous solution was added dropwise into 2M HCl. The precipitate was recovered by centrifugation (yield 27%) and had m.p. (decomp.)  $> 360^\circ\text{C}$ ;  $\delta[(\text{CD}_3)_2\text{SO}]$  4.06 (16 H, s,  $\text{ArCH}_2\text{Ar}$ ) and 7.93 (16 H, s, ArH);  $\nu_{\text{max.}}$ (KBr) 3 300 (OH) and 1 340 and 1 510 ( $\text{NO}_2$ )  $\text{cm}^{-1}$  (Found: C, 47.5; H, 4.8; N, 7.5%. Calc. for  $\text{C}_{56}\text{H}_{40}\text{N}_8\text{O}_{24} \cdot 12\text{H}_2\text{O}$ : C, 47.2; H, 4.5; N, 7.9%).

***p*-Nitrocalix[8]arene (3;  $n = 8$ ) by Method B.**—Compound (1;  $n = 8$ ) (2.0 g, 2.3 mmol) was dissolved in concentrated  $\text{H}_2\text{SO}_4$  (40 ml) and the solution heated at  $80^\circ\text{C}$  for 4 h. After cooling, the reaction mixture was diluted with cold water (67 ml) (the  $\text{H}_2\text{SO}_4$  concentration is 37% at this stage) and then treated with 65%  $\text{HNO}_3$  (4.8 g) at  $5\text{--}10^\circ\text{C}$  for 10 h. The purification method is similar to that of method A [yield from (1;  $n = 8$ ) 22%]. The analytical data are similar to those of method A.

***p*-Nitrocalix[4]arene (3;  $n = 4$ ) by Method B.**—Compound (3;  $n = 4$ ) was prepared from (1;  $n = 4$ ) according to the method similar to that of (3;  $n = 8$ ), yield [from (1;  $n = 4$ )] 21%, m.p. (decomp.)  $> 360^\circ\text{C}$ ;  $\delta[(\text{CD}_3)_2\text{SO}]$  4.18 (8 H, s,  $\text{ArCH}_2\text{Ar}$ ), 8.53 (8 H, s, ArH), and 10.10 (4 H, s, OH);  $\nu_{\text{max.}}$ (KBr) 3 300 (OH) and 1 325 and 1 585 ( $\text{NO}_2$ )  $\text{cm}^{-1}$  (Found: C, 55.7; H, 3.3; N, 8.9%. Calc. for  $\text{C}_{28}\text{H}_{20}\text{N}_4\text{O}_{12}$ : C, 55.6; H, 3.3; N, 9.2%).

***p*-Nitrocalix[6]arene (3;  $n = 6$ ) by Method B.**—Compound (3;  $n = 6$ ) was prepared from (1;  $n = 6$ ) according to the method similar to that of (3;  $n = 8$ ) [yield from (1;  $n = 4$ ) 15%], m.p. (decomp.)  $> 360^\circ\text{C}$ ;  $\delta[(\text{CD}_3)_2\text{SO}]$  3.98 (12 H, s,  $\text{ArCH}_2\text{Ar}$ ) and 8.19 (12 H, s, ArH);  $\nu_{\text{max.}}$ (KBr) 3 400 (OH) and 1 320, and 1 500 ( $\text{NO}_2$ )  $\text{cm}^{-1}$  (Found: C, 51.9; H, 3.4; N, 8.6%. Calc. for  $\text{C}_{42}\text{H}_{30}\text{N}_6\text{O}_{18} \cdot 4\text{H}_2\text{O}$ : C, 51.5; H, 3.9; N, 8.6%).

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### References

- 1 R. Breslow, *Acc. Chem. Res.*, 1980, **13**, 170.
- 2 I. Tabushi, *Acc. Chem. Res.*, 1982, **15**, 66.
- 3 C. D. Gutsche, *Acc. Chem. Res.*, 1983, **16**, 161.
- 4 C. D. Gutsche, 'Host Guest Complex Chemistry/Macrocycles,' eds. F. Vögtle and E. Weber, Springer-Verlag, Berlin, 1985, p. 375 and references cited therein.
- 5 C. D. Gutsche and L. J. Bauer, *J. Am. Chem. Soc.*, 1985, **107**, 6052, 6059, 6063.
- 6 S.-K. Chang and I. Cho, *Chem. Lett.*, 1984, 477.
- 7 R. Ungaro, A. Pochini, and G. D. Andreetti, *J. Inclusion Phenom.*, 1984, **2**, 199.
- 8 C. Alfieri, E. Dradi, A. Pochini, R. Ungaro, and G. D. Andreetti, *J. Chem. Soc., Chem. Commun.*, 1983, 1075.
- 9 A. Arduini, A. Pochini, S. Reverberi, and R. Ungaro, *J. Chem. Soc., Chem. Commun.*, 1984, 981.
- 10 M. A. McKervey, E. M. Seward, G. Ferguson, B. Ruhl, and S. J. Harris, *J. Chem. Soc., Chem. Commun.*, 1985, 388.
- 11 S. Shinkai and T. Tsubaki, unpublished results.
- 12 V. Bocchi, F. A. Pochini, R. Ungaro, and G. D. Andreetti, *Tetrahedron Lett.*, 1982, **38**, 373.
- 13 C. D. Gutsche and L.-G. Lin, *Tetrahedron*, 1986, **42**, 1633.
- 14 S. Shinkai, S. Mori, T. Tsubaki, T. Sone, and O. Manabe, *Tetrahedron Lett.*, 1984, **25**, 5315.
- 15 S. Shinkai, S. Mori, H. Koreishi, T. Tsubaki, and O. Manabe, *J. Am. Chem. Soc.*, 1986, **108**, 2409.
- 16 A. Zinke, R. Ott, and F. H. Garrana, *Monatsh. Chem.*, 1958, **89**, 135.
- 17 C. D. Gutsche, personal communication.

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