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# The acidity of calix[5]arenes and their linear analogues

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**Abstract:** Five new calix[5]arenes containing a single *p*-nitrophenol unit as the most acidic phenolic unit have been synthesised by (3+2) fragment condensation of a trimer with a *p*-nitrophenol in the middle with various bishydroxymethylated alkanediyl diphenols. Their first acid constant ($pK_{a1}$) has been determined in 2-methoxyethanol/water (9:1) at 22 °C by optical titration. The $pK_{a1}$ values are distinctly lower ($\Delta pK_a > 2$) than for the trimer, while no difference has been found in comparison to structurally analogous calix[4]arenes. Rigidification of the calix[5]arene skeleton by introducing a single alkanediyl bridge opposite to the *p*-nitrophenol unit has no effect on $pK_{a1}$. All values are in agreement with a stabilisation of the monoanion via two chains of consecutive intramolecular hydrogen bonds O-H···O-H···$O^{(-)}$, a system which is favoured, if the acidity of the first donating O-H group is increased. This effect is observed also in linear pentamers which show $pK_{a1}$-values higher by only 0.8-1 units than those of the calix[5]arenes. 

Keywords: Acidity, Calixarenes, Macrocycles

## *Introduction*

The name calixarenes was initially coined for macrocyclic compounds consisting of phenolic units connected via methylene bridges *ortho* to the phenolic hydroxyl groups [1]. In a broader sense the name may be used for [1$_n$]metacyclophanes in general [2], including also compounds with *exo* hydroxyl groups. One of the remarkable properties of calixarenes, realised already in the very beginning, is their high acidity in comparison to that of the single phenolic units [3]. This phenomenon was attributed to the cyclic array of intramolecular hydrogen bonds, which obviously leads to a stronger stabilisation of the monoanion than of the undissociated calixarene (although a proton is lacking in this "cyclic array" of the monoanion).

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The determination of $pK_a$-values for calixarenes [4] consisting of identical phenolic units, e.g. by potentiometric titration, was seriously hampered by their low solubility, especially in water or water containing solvent mixtures. Thus, some of the early values had to be corrected later [5,6]. Reliable values confirmed by different groups are available now for the dissociation of the phenolic hydroxyl groups in the tetraanion of the *p*-sulfonated calix[4]arene [6,7].

In contrast to calixarenes consisting of identical phenolic units, the investigation of compounds containing a single *p*-nitrophenol unit has some pronounced advantages. Due to its distinctly higher acidity, the *p*-nitrophenol unit will be deprotonated as the first phenolic unit. This step can be easily followed spectroscopically via the spectral difference between *p*-nitrophenol and *p*-nitrophenolate which both absorb at higher wavelengths than other phenol units (e.g. alkyl phenols). This allows more detailed studies of the relations between acidity and various structural factors [8].

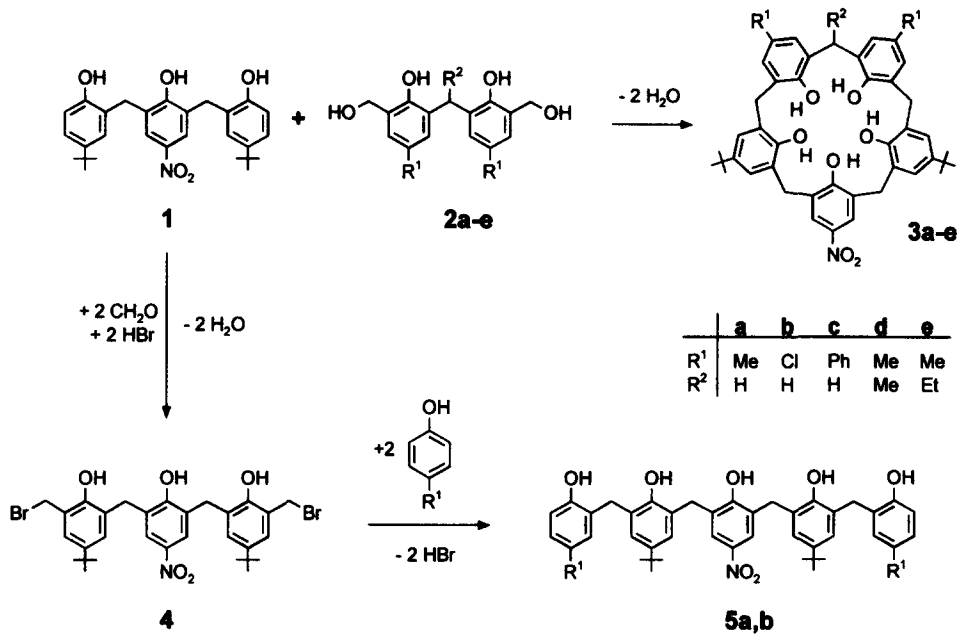
In a recent paper we have reported the $pK_{a1}$-values of calix[4]arenes in 2-methoxyethanol-water (9:1), a solvent system which allows the comparison of a variety of compounds [9]. We now extend these studies to calix[5]arenes, in which the intramolecular hydrogen bonds are weaker (as estimated by IR- [10] and $^1$H NMR-spectroscopy [11] in solution and by the O-O-distances in the crystalline state [12]). We include in these studies the corresponding linear pentamers, as well as calix[5]arenes with a single alkanediyl bridge where one cone conformation is strongly preferred [13].

***Syntheses***

Calix[5]arenes consisting of different *p*-substituted phenolic units can be easily prepared now by "heat induced" (3+2) fragment condensation of a trimer with a bis-hydroxymethylated dimer using the conditions first described explicitly by No and Kwan [14]. Compounds **3a-e** were thus obtained in 16-22% (not optimised) by refluxing a solution of stoichiometric amounts of **1** and **2a-c** in xylene. A yield of about 20% still compares favourably with the one-pot synthesis of *t*-butyl calix[5]arene [15] The calix[5]arenes are easily isolated by column chromatography, since obviously other calixarenes are not formed under these reaction conditions.

The structure of calix[5]arenes **3** has been confirmed by FD-mass spectrometry, but it follows already, unambiguously from their $^1$H NMR spectra. As an example, **3d** shows

- three singlets for OH protons (ratio 1:2:2),
- one singlet and four pairs of m-coupled doublets each for two aromatic protons,
- two pairs of doublets with geminal coupling for the two different methylene bridges,
- a quartet and a doublet (ratio 1:3) for the ethanediyl bridge,
- two singlets (ratio 1:3) for the aryl bound methyl and *t*-butyl groups.




This set of signals (no other signals are observed) in the correct ratio can be explained only by the expected calix[5]arene **3d** [16]. It should be mentioned that **3b** and **3c** obviously assume one of two possible cone conformations in which the substituent $R^2$ assumes the equatorial position [13].

Bromomethylation of trimer **1** and condensation of the resulting bisbromomethylated trimer **4** with an excess of *p*-cresol or *p*-chlorophenol led to the linear pentamers **5a,b** as analogues of the calix[5]arenes **3a,b**. Their structure was established in a similar way, and the purity of all compounds was checked and confirmed by t.l.c.

### *$pK_a$-values*

The purpose of our studies was to determine apparent equilibrium constants

$$K_a = \frac{c(CalH_4^-)\, c(BH^+)}{c(CalH_5)} \qquad (1)$$

for the equilibrium $CalH_5 + B \rightleftharpoons CalH_4^- + BH^+$ (2)

which are comparable within a series of calixarenes and model compounds. For experimental reasons (solubility of calixarenes and buffer substances, reproducible potentials of a glass electrode) outlined in detail in a previous publication [9] we have chosen 2-methoxyethanol/water (9:1) as solvent. (This mixture is represented by B in

eqs. (1,2), while $BH^+$ represents the mixture of protonated species eventually present.) The determination of $K_a$ requires then the potentiometric measurement of $BH^+$ (from the apparent pH) and the spectroscopic determination of

$$\frac{c(CalH_4^-)}{c(CalH_5)} = \frac{\varepsilon - \varepsilon(HA)}{\varepsilon(A^-) - \varepsilon} \qquad (3)$$

where ε, ε(HA), and ε($A^-$) represent the (standardised) absorbances of the compound at a given pH, in acidic and basic solution. The equations (1) and (3) may be combined to

$$\log \frac{\varepsilon - \varepsilon(HA)}{\varepsilon(A^-) - \varepsilon} = pH - pK_a \qquad (4)$$

which is used for the evaluation of $pK_a$ from a series of measurements.

Fig. 1 shows as an example the UV spectra of **5a** as a function of the apparent pH, while typical linear plots according to eqn. (4) are shown in Fig. 2. The isosbestic behaviour over the whole pH range (Fig. 1) is found for all compounds, demonstrating that the spectral changes are caused by a single equilibrium. This means that only the *p*-nitrophenol unit is deprotonated, as expected. The linearity of the plots in Fig. 2 illustrates the accuracy of the measurements and shows, that values of $\Delta pK_a > 0.1$ may be discussed as real differences.

The $pK_{a1}$-values thus obtained are collected in Table 1. For all calix[5]arenes **3** they are lower by more than 2 units in comparison to the trimer **1** ($pK_{a1}$ = 6.15). This is easily explained by a further stabilisation of the monoanion [17] by two additional intramolecular hydrogen bonds (β) as indicated in formula **I**. In line with this explanation is the decrease observed in the order **3a** > **3c** > **3b**, since with increasing acidity of the phenolic units opposite to the *p*-nitrophenol unit they become stronger hydrogen bond donors. The intensity of their hydrogen bonds β increases and consequently also that of hydrogen bonds α. Surprisingly the $pK_{a1}$ values of calix[5]arenes **3a-c** are identical within

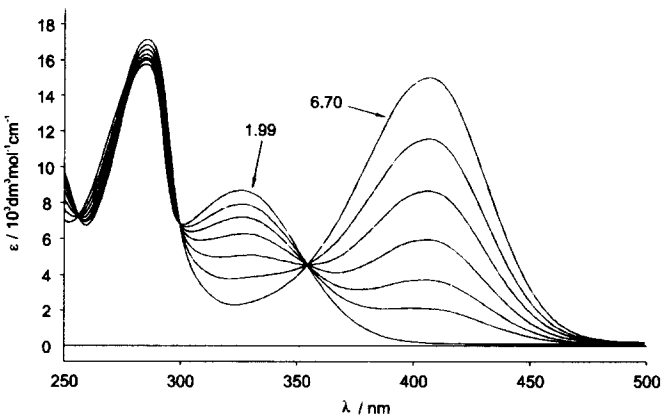



**Fig. 1** UV spectrum of compound **5a** as a function of the apparent pH ( pH values of the single curves: 1.99, 3.93, 4.30, 4.62, 4.97, 5.39, 6.70).

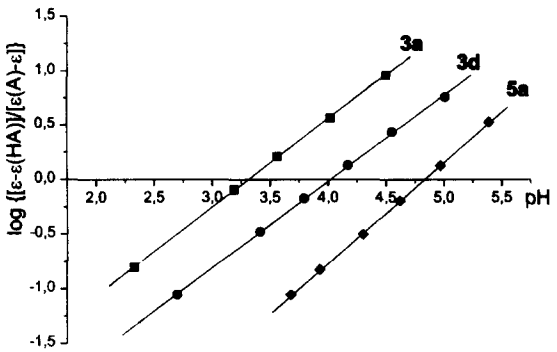


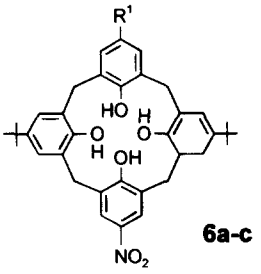

**Fig. 2** Evaluation of the $pK_{a1}$ values for the compounds **3a**, **3d** and **5a**; typical plots using eqn. (4).

the experimental errors to those of the analogous calix[4]arenes **6a-c**, where only one hydrogen bond of type β is possible (formula **II**). Probably this is compensated by the generally shorter O-O-distances in calix[4]-arenes in comparison to calix[5]arenes.

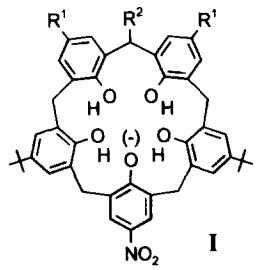
The only other $pK_a$-values reported in the literature for calix[5]arenes are those for the pentaanion of *p*-sulfonatocalix[5]arene [18]. Here $pK_{a1}$ = 4.31 is distinctly higher, than the values reported for the corresponding calix[4]arene (3.26 [6], 3.34 [8]), while for the hexaanion of *p*-sulfonatocalix[6]arene again a $pK_{a1}$ (3.37 [19], 3.45 [20]) similar to that of the calix[4]arene was reported.

A strong decrease of $pK_{a1}$ in comparison to **1** is also observed for the linear analogues **5** and again **5b** is more acidic than **5a**, which supports the explanation given above[21]. The acidity of these linear oligomers **5** is already remarkably close to that of the analogous calix[5]arenes **3** and the difference of 0.8-1.0 in $pK_{a1}$ may be mainly caused by entropic factors, since the calix[5]arenes are better preorganised for a hydrogen bonded monoanion **I**.

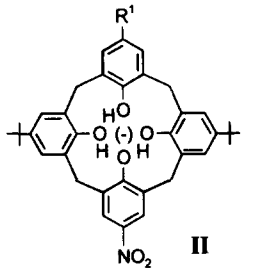
Introduction of a substituent $R^2$ at one of the methylene bridges favours the cone-conformation with the equatorial position of $R^2$ and raises the energy barrier for the ring inversion [13]. Calix[5]arenes **3d,e** were studied to see, how this restriction of the conformational mobility influences the acidity. However, if there is an effect ($pK_{a1}$ of **3e** is lower by 0.08 compared to **3a**) it is too small to be unambiguously established under our conditions.



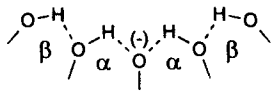

**6a-c**




**I**




**II**



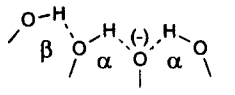



**Table 1** Apparent first acid constants ($pK_{a1}$ values) for calix[5]arenes **3** and their linear analogs **5**. In parantheses the $pK_{a1}$ values for the analogous calix[4]arenes **6** are given for comparison. The absorption of the monoanion is characterised by $\lambda_{max}$ and $\varepsilon_{max}$ (see text).

| Compound | $R^1$ | $R^2$ | $pK_{a1}$ | $\lambda_{max}(A^-)$ [nm] | $\varepsilon_{max}(A^-)/\varepsilon_{max}(HA)$ |
|---|---|---|---|---|---|
| **3a** | Me | H | 4.02 [4.01] | 405.8 | 1.91 |
| **3b** | Cl | H | 3.34 [3.27] | 400.7 | 1.65 |
| **3c** | Ph | H | 3.71 [3.76] | 402.8 | 1.74 |
| **3d** | Me | Me | 4.01 | 405.2 | 1.59 |
| **3e** | Me | Et | 3.94 | 405.4 | 1.59 |
| **5a** | Me | | 4.83 | 406.7 | 1.73 |
| **5b** | Cl | | 4.37 | 404.6 | 1.73 |

A stabilisation of the monoanion by intramolecular hydrogen bonds is usually accompanied by an hypsochromic shift of the *p*-nitrophenolate absorption together with an hypochromic effect. This has been clearly demonstrated, for instance, for various linear oligomers with a *p*-nitrophenol unit at the end [22]. These effects can be seen also in the present systems if analogous compounds are compared. For instance $\lambda_{max}$ decreases in the series **3a** > **3c** > **3b** in the same order as $pK_{a1}$ (Table 1), and the same is true for **5a** > **5b**, while the highest value ($\lambda_{max}$ = 409 nm) is found for the trimer **1**. A comparison of the absorption coefficient $\varepsilon_{max}$ which requires the knowledge of the exact concentration [23], was not intended, but the ratio $R = \varepsilon_{max}(A^-)/\varepsilon_{max}(HA)$, using $\varepsilon_{max}(HA)$ as an "internal standard", may be discussed instead. A decrease for R in the series **3a** > **3c** > **3b** suggests that indeed stronger intramolecular hydrogen bonding in the monoanion is the main effect. It should be noted, however, that also the linear compounds **5** have a lower R than **3a** and that the lowest values are found for the "stiff" calixarenes **3d/e**.

***Conclusion***

In summary it can be stated that under the conditions chosen

- calix[5]arenes have the same acidity than the analogous calix[4]arenes,
- the stabilisation of one cone conformation by an alkanediyl bridge has no pronounced effect,
- calix[5]arenes are more acidic than the corresponding linear pentamers.

The main reason for the observed $pK_{a1}$-values is the stabilisation of the monoanion by a pair of consecutive intramolecular hydrogen bonds. Via these hydrogen bonds the acidity is influenced still by the overnext phenolic unit.

We presently try to extend these studies to larger calixarenes (and their linear analogues) since co-operative hydrogen bonding is an important factor determining the properties of natural compounds (e.g. enzymes) as well as those of artificial systems (e.g. self assembled structures in solution or in the solid state).

## *Experimental*

### Syntheses

The trimer **1** [9] and the hydroxymethylated dimers **2a-e** [13] have been described before. $^1$H NMR spectra were recorded on a Bruker AC200, FD mass spectra on a Finnigan MAT 8230 spectrometer. Melting points are uncorrected.

**General procedure for the synthesis of calix[5]arenes 3a-e**

A suspension of the trimer **1** (460 mg, 1 mmol) and the bisbromomethylated dimer **2** (1 mmol) in 300 ml xylene was refluxed for three days. The xylene was removed under reduced pressure and the remaining residue was submitted to column chromatography, using first hexane:acetone (6:1) and then hexane:chloroform (7:3) as eluent. The isolated calix[5]arenes were identified by $^1$H NMR and mass spectrometry.

**5-Nitro-11,29-di-*tert*-butyl-17,23-dimethyl-31,32,33,34,35-pentahydroxy calix[5]arene (3a)**

116 mg (16%) of a pale yellow solid. m.p. 307 °C. - $^1$H NMR (200 MHz): δ/ppm = 10.01 (s, 1H, ArOH), 8.71 (s, 2H, ArOH), 8.56 (s, 2H, ArOH), 8.16 (s, 2H, Ar($NO_2$)H), 7.20 (d, $^4$J = 2.5 Hz, 2H, ArH), 7.17 (d, $^4$J = 2.5 Hz, 2H, ArH), 6.99 (s, 4H, ArH), 3.85, 3.69 (br s, 10H, $CH_2$), 2.22 (s, 6H, $CH_3$), 1.25 (s, 18H, $C(CH_3)_3$) - MS; m/z 715.9 (%) (100, $M^+$)

**5-Nitro-11,29-di-*tert*-butyl-17,23-dichloro-31,32,33,34,35-pentahydroxy calix[5]arene (3b)**

135 mg (18%) of a pale yellow solid. m.p. 234 °C. - $^1$H NMR (200 MHz): δ/ppm = 9.87 (s, 1H, ArOH), 8.86 (s, 2H, ArOH), 8.43 (s, 2H, ArOH), 8.16 (s, 2H, Ar($NO_2$)H), 7.20 (d, $^4$J = 2.1 Hz, 2H, ArH), 7.18 (d, $^4$J = 2.3 Hz, 2H, ArH), 7.17 (d, $^4$J = 2.4 Hz, 2H, ArH), 7.14 (d, $^4$J = 2.6 Hz, 2H, ArH), 3.79, 3.87 (br s, 10H, $CH_2$), 1.25 (s, 18H, $C(CH_3)_3$) - MS; m/z (%): 755.8 (100, $M^+$).

**5-Nitro-11,29-di-*tert*-butyl-17,23-diphenyl-31,32,33,34,35-pentahydroxy calix[5]arene (3c)**

185 mg (22%) of a pale yellow solid. m.p. 227 °C. - $^1$H NMR (200 MHz): δ/ppm = 9.99 (s, 1H, ArOH), 8.99 (s, 2H, ArOH), 8.56 (s, 2H, ArOH), 8.16 (s, 2H, Ar($NO_2$)H), 7.51-7.20 (m, 18H, ArH), 3.91 (br s, 10H, $CH_2$), 1.25 (s, 18H, $C(CH_3)_3$) - MS; m/z (%): 839.7 (100, $M^+$).

**5-Nitro-11,29-di-*tert*-butyl-17,20,23-trimethyl-31,32,33,34,35-pentahydroxy calix[5]arene (3d)**

145 mg (20%) of a pale yellow solid. m.p. 198 °C. - $^1$H NMR (200 MHz): δ/ppm = 9.95 (s, 1H, ArOH), 8.51 (s, 2H, ArOH), 8.49 (s, 2H, ArOH), 8.16 (s, 2H, Ar($NO_2$)H), 7.21 (d, $^4$J = 2.4 Hz, 2H, ArH), 7.18 (d, $^4$J = 2.5 Hz, 2H, ArH), 7.07 (d, $^4$J = 1.5 Hz, 2H, ArH), 6.97 (d, $^4$J = 1.5 Hz, 2H, ArH), 4.59 (q, $^3$J = 7.3 Hz, 1H, $Ar_2CHR$), 4.13 (d, $^2$J = 14.2 Hz, 2H, $CH_2$), 4.11 (d, $^2$J = 14.2 Hz, 2H, $CH_2$), 3.61 (d, $^2$J = 14.7 Hz, 2H, $CH_2$), 3.49 (d, $^2$J = 14.2 Hz, 2H, $CH_2$), 2.31 (s, 6H, $CH_3$), 1.56 (d, $^3$J = 6.8 Hz, 3H, $CH_3$), 1.31 (s, 18H, $C(CH_3)_3$) - MS; m/z (%): 729.7 (100, $M^+$).

**5-Nitro-11,29-di-*tert*-butyl-17,23-dimethyl-20-ethyl-31,32,33,34,35-pentahydroxy calix[5]arene (3e)**

150 mg (20%) of a pale yellow solid. m.p. 194 °C. - $^1$H NMR (200 MHz): δ/ppm = 9.91 (s, 1H, ArOH), 8.49 (s, 2H, ArOH), 8.41 (s, 2H, ArOH), 8.14 (s, 2H, Ar($NO_2$)H), 7.19 (d, $^4$J = 2.4 Hz, 2H, ArH), 7.15 (d, $^4$J = 2.4 Hz, 2H, ArH), 6.99 (br d, 2H, ArH), 6.94 (br d, 2H, ArH), 4.22 (t, $^3$J = 7.8 Hz, 1H, $Ar_2CHR$), 4.11 (d, $^2$J = 14.6 Hz, 2H, $CH_2$), 4.09 (d, $^2$J = 14.2 Hz, 2H, $CH_2$), 3.59 (d, $^2$J = 14.7 Hz, 2H, $CH_2$), 3.47 (d, $^2$J = 14.2 Hz, 2H, $CH_2$), 2.30 (s, 6H, $CH_3$), 2.01 (m, 2H, $CH_2$), 1.24 (s, 18H, $C(CH_3)_3$), 0.78 (t, $^2$J = 7.3 Hz, 3H, $CH_3$) - MS; m/z (%): 743.7 (100, $M^+$).

**Synthesis of the linear pentamers 5a,b**

***a)*** Bromomethylation: 2,6-Di-(2-hydroxy-5-*tert*-butylbenzyl)-4-nitrophenol (**1**, 1.86 g, 4 mmol), paraformaldehyde (1.2 g, 40 mmol) and a solution of HBr (33%) in glacial acetic acid (10 ml) were heated with stirring to 70 °C. After 20 min a clear solution was obtained, from which a crystalline product precipitated after about 60 min. After 2 h the mixture was cooled, the precipitate filtered and washed with a small amount of acetic acid, followed by petroleum ether. Thus 1.9 g (73 %) of 2,6-di-(2-hydroxy-3-bromomethyl-5-*tert*-butylbenzyl)-4-nitrophenol (**4**) were obtained, pure enough for the subsequent reaction; m.p. 134-136 °C (decomp.); $^1$H NMR (200 MHz): δ/ppm = 9.09 (br s, 1H, OH), 8.06 (s, 2H, ArH) 7.28, 7.14 (d, $^4$J = 2,4 Hz, d, 2H each, ArH), 6.73 (br s, 2H, OH), 4.54 (s, 4H, $CH_2Br$), 3.96 (s, 4H, $ArCH_2Ar$), 1.25 (s, 18H, $C(CH_3)_3$)

***b)*** Condensation: A solution of the bisbromomethylated trimer **4** (300 mg, 0.46 mmol) in 4 ml glacial acetic acid was heated to 90 °C and the *p*-substituted phenol (7 mmol) was added. After 22 h the solution was cooled to room temperature and purified as indicated for the individual compounds.

**2,6-Bis(2-hydroxy-5-*tert*-butyl-3-(2-hydroxy-5-methyl)benzyl)benzyl-4-nitrophenol (5a)**

A precipitate separated from the reaction mixture which was filtered, washed with glacial acetic acid and recrystallised from glacial acetic acid to give 59 mg (18%) of a pale yellow solid. m.p. 170 °C. The yield can be increased by working up the mother liquors as described below.- $^1$H NMR (200 MHz): δ/ppm = 9.3 (br s, 5H,

OH), 8.06 (s, 2H, Ar($NO_2$)H), 7.24 (m, 8H, ArH), 6.91 (m, 6H, ArH), 3.90 (s, 4H, $CH_2$), 3.80 (s, 4H, $CH_2$), 2.25 (s, 6H, $CH_3$), 1.28 (s, 18H, $C(CH_3)_3$) - MS; m/z (%): 705.6 (100, $M^+$).

**2,6-Bis(2-hydroxy-5-*tert*-butyl-3-(2-hydroxy-5-chloro-benzyl)-benzyl-4-nitrophenol (5b)**

Water (15 ml) was added to the reaction mixture which then was extracted three times with 20 ml dichloromethane. The combined organic phases were washed with water, the solvent was evaporated and the excess *p*-chlorophenol was removed by steam distillation. The crude product was then purified by flash chromatography with chloroform-methanol (20:1) to give 94 mg (27%) of a pale yellow solid. m.p. 166 °C. - $^1$H NMR (200 MHz): δ/ppm = 9.00 (br s, 5H, OH), 8.07 (s, 2H, Ar($NO_2$)H), 7.27 - 7.06 (m, 8H, ArH), 6.88 (br d, $^3$J = 8.3 Hz, 2H, ArH), 3.87 (s, 4H, $CH_2$), 3.82 (s, 4H, $CH_2$), 1.27 (s, 18H, $C(CH_3)_3$) - MS; m/z (%): 745.3 (100, $M^+$).

**Determination of $pK_a$-values**

A buffer solution was made by dissolving 100 mg citric acid (Aldrich), 50 mg malonic acid (Aldrich) and 70 µl triethylamine (freshly distilled) in 450 ml 2-methoxyethanol and 50 ml water. In a typical experiment 0.8 mg of the nitrocalix[5]arene was dissolved in 25 ml of this solution ($c = 5 \cdot 10^{-5}$ mol/l) using an ultrasonic bath. 20 ml of this solution were placed in a thermostated vessel of an automatic titration apparatus (Metrohm E510) at 22°C and acidified with conc. HCl. Titration with NaOH (c = 1 mol/l) was carried out, using a glass electrode, which was calibrated against aqueous buffer standards. At the desired apparent pH-values the titration was stopped, 2 min were waited before the final reading to obtain a constant value, a sample was transferred by a pipette to a 1cm cuvette, and its UV-VIS spectrum was measured with a Perkin-Elmer Lambda 17 spectrometer connected to a computer.

The sample was afterwards transferred back into the titration vessel, and the titration was continued. The accuracy of this procedure is demonstrated by Figure 1, where the volume increase (usually a total of 100-150 µl until to the final pH) is taken into account for the single spectra.

In this way usually 10-15 spectra were recorded, including a spectrum at low pH, before the titration starts, and at high pH (at least pH > $pK_a$+3). The $pK_a$ was obtained from plots according to Eq. (4). For different wavelengths (usually between 390 - 425 nm) deviations less than 0.02 were observed for a single titration experiment. Usually three titrations were carried out, including also different or independently calibrated electrodes. The deviations for these repeated experiments were in the range of ±0.05.

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