The first acid constant of calix[4]arenes

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A series of calix[4]arenes containing a single *p*-nitrophenol unit (or two *p*-nitrophenol units) have been synthesized by fragment condensation. Their first acid constant (pK_{a1}) has been determined in 2-methoxyethanol–water (9:1) by optical titration. Relative to the corresponding linear trimers with a *p*-nitrophenol in the middle, a decrease of pK_{a1} by 2.1 units or more is observed, which can be explained entirely by intramolecular hydrogen bonds stabilising the monoanion. In this way electron-withdrawing *p*-substituents in the opposite phenolic unit lead to a further decrease in pK_{a1}, while a distortion of the cone conformation by *m*-methyl groups causes a slight increase. The structure of one calix[4]arene was further confirmed by single crystal X-ray analysis showing the molecule in the usual cone conformation.

Introduction

Calixarenes are macrocyclic molecules in which phenolic units are linked together *via* methylene bridges *ortho* to the phenolic hydroxy groups.[1] Calix[4]arenes,† the smallest members of the family, normally assume the so-called cone conformation which is stabilised by a cyclic array of intramolecular hydrogen bonds between the *endo* hydroxy groups. This close vicinity of OH groups must have a pronounced influence on their acidity due to both intramolecular hydrogen bonding and electrostatic interactions.

The determination of pK_a values for calixarenes is complicated by the fact that one is dealing with at least tetraprotonic acids. Furthermore, most of the usual calixarenes are only sparingly soluble, especially in water or water-containing solvents, which seriously hampers the application of standard techniques like potentiometric titration. Thus, the first studies of *p*-nitrocalix[4]arene led to rather divergent values,[2,3] especially for pK_{a2}, although they were in agreement with theoretical calculations[4] that pK_{a1} is much lower than in comparable model compounds. Meanwhile more reliable values were found for the dissociation of the first two phenolic OH groups in calix[4]arene-tetrasulfonate. For instance pK_a values of 3.34 and 11.5[5] and 3.26 and 11.8,[6] respectively, were reported by two groups.

Our own interest has been directed towards calix[4]arenes containing just one *p*-nitrophenol unit, which represents the most acidic phenolic unit, the dissociation of which can be easily monitored by the change in UV absorption. Thus, structural influences on pK_{a1} caused by the other phenolic units can be studied conveniently, following a strategy which has been successfully applied to various linear oligomers.[7] An early result obtained in methanol–water (1:1) indicated the influence of the *p*-substituent in the phenolic unit opposite to the *p*-nitrophenol unit,[8] which seemed to be even more pronounced for two series of calix[4]arenes in methanol–water (9:1).[9] Although a tentative explanation could be a conformational distortion of the cone conformation, this explanation remained unsatisfactory since such a distortion could not be found by other methods, including single crystal X-ray analysis.[10]

We therefore extended these studies to other calix[4]arenes and we present in this paper pK_{a1} values, which are consistent within this series, showing steric and electronic effects exerted by substituents in the other phenolic units.

The aim of our studies was the comparison of different calix[4]arenes ($CalH_4$) and their corresponding model compounds with respect to their acidity [equilibrium (1)], or more

$$CalH_4 + B \rightleftharpoons CalH_3^- + BH^+ \quad (1)$$

precisely their first acid constants [eqn. (2)]. In principle this

$$K_{a1} = \frac{[CalH_3^-][BH^+]}{[CalH_4]} \quad (2)$$

equilibrium, where B represents the (basic) solvent (or even a mixture of solvent bases) being present in excess and BH^+ the protonated solvent (or the respective mixture of protonated solvents), can be studied in any solvent (mixture). Relative values for K_{a1}, which can be compared with a series of compounds, are obtained as long as all members of this series are studied under identical conditions.

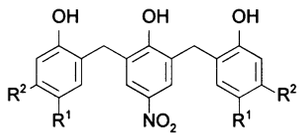
The choice of an appropriate solvent was, nevertheless, a difficult problem. Most of the calixarenes are sparingly soluble, especially in aqueous solvents, while many buffer systems are of low solubility (at least in some pH regions) in more organic mixtures. After numerous tests we have chosen for the present study 2-methoxyethanol–water (9:1) [only some control measurements were made for comparison in methanol–water (9:1)], which enabled a convenient continuous variation in [BH^+] by the titration of a mixture of weak acids by a strong base. In this solvent, a glass electrode assumes a stable potential within reasonably short times. Thus, a potentiometric characterisation of [BH^+] was possible by an apparent pH value, while the ratio [$CalH_3^-$]/[$CalH_4$] of monoanion and calixarenes was determined by measurement of the UV–VIS absorption.

Results and discussion

Syntheses

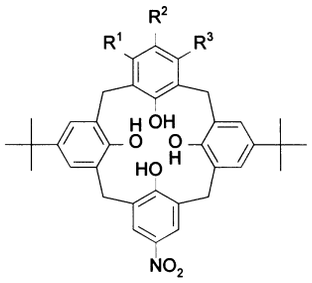
All compounds were prepared by the well known fragment condensation[11–14] of linear trimers **1**, containing the *p*-nitrophenol unit in the middle, with the bis(bromomethyl)ated [or

† IUPAC name: calix[4]arene = 1^2,3^2,5^2,7^2-tetrahydroxy-1,3,5,7(1,3)-tetrabenzena-cyclooctaphane.



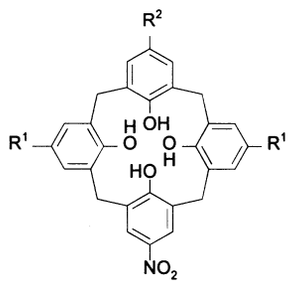
1 R^1 R^2

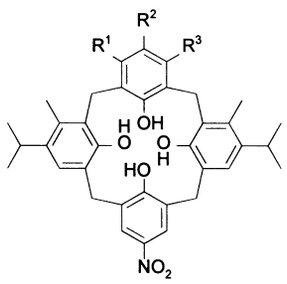
a	CH_3	H
b	$C(CH_3)_3$	H
c	C_6H_{11}	H
d	CH_3	CH_3
e	$CH(CH_3)_2$	CH_3



5 R^1 R^2 R^3

a	CH_3	CH_3	H
b	CH_3	Cl	H
c	CH_3	Cl	CH_3



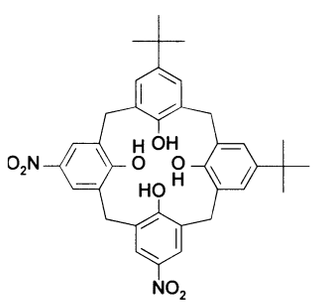


2 $R^1 = CH_3$ **3** $R^1 = C(CH_3)_3$

2 R^2		**3** R^2	
a	$COOC_2H_5$	**a**	CH_3
b	COOH	**b**	$C(CH_3)_3$
c	CH_2COOCH_3	**c**	$C_{12}H_{25}$
d	CH_2COOH	**d**	C_6H_{11}
		e	C_6H_5
		f	Cl
		g	$COOC_2H_5$
		h	COOH
		i	NO_2

6 R^1 R^2 R^3

a	H	CH_3	H
b	CH_3	CH_3	H
c	H	Cl	H
d	CH_3	Cl	H
e	CH_3	Cl	CH_3



4

bis(hydroxymethyl)ated] phenol that has to form the opposite phenolic unit in the calix[4]arene. Compounds **1** themselves were obtained in yields of 65–75% by condensation of 2,6-bis(bromomethyl)-4-nitrophenol with an excess of a 4-alkyl- or 3,4-dialkyl-phenol. The macrocyclisation reaction was carried out in dioxane using $TiCl_4$ as the Friedel–Crafts catalyst and (probably) as template. The calix[4]arenes **2**–**6** are easily isolated and purified by flash chromatography (in the case of **2a**, **2c** and **3g** after complete reesterification of the crude product); the yield of pure product, which is not optimised for the special examples, varies between 8–27% for compounds **2** and **3**, the lowest yields (**2a** and **3g**) being obtained with the bis(bromomethyl)ated ester of *p*-hydroxybenzoic acid. However, no general conclusions on the influence of the *p*-substituent in the bromomethylated phenol should be drawn from these results. The yield is significantly lower if *m*-methyl groups are present in the bis(bromomethyl)ated phenol and in the trimer (3% for **6b** and **6d**) and drops to 0.6% for **6e**. Compound **4** was obtained in a similar way by 2 + 2-fragment condensation[11] of the *p*-*tert*-butylphenol dimer and the bis(bromomethyl)ated dimer of *p*-nitrophenol. The acids **2b**, **2d** and **3h** were obtained by alkaline hydrolysis of the respective esters **2a**, **2c** and **3g**.

The structure of all calix[4]arenes was unambiguously confirmed by ^{1}H NMR and mass spectra and in the case of **3e**, also by a single crystal X-ray analysis.

Table 1 Apparent pK_{a1} values of *p*-nitrophenol (pN), selected trimers and calix[4]arenes in methanol–water 9:1

Compound	pK_{a1}	Compound	pK_{a1}
pN	8.90	**3a**	4.99
		3b	4.77
1b	6.97	**3c**	4.97
1c	7.03	**3d**	4.82

Table 2 Apparent pK_{a1} values obtained in 2-methoxyethanol–water 9:1

Compound	pK_{a1}	Compound	pK_{a1}
pN	8.73	**3f**	3.27
		3g	3.15
1b	6.15	**3h**	3.27
1c	6.11	**3i**	2.40
1d	6.14		
1e	6.31	**4**	1.98
2a	3.24	**5a**	4.01
2b	3.30	**5b**	3.30
2c	3.87	**5c**	3.58
2d	3.75		
		6a	4.37
3a	4.01	**6b**	4.68
3b	3.95	**6c**	3.88
3c	4.01	**6d**	4.03
3d	4.00	**6e**	4.18
3e	3.76		

pK_a values

First determinations of pK_{a1} were made for compounds **3a**–**d** in methanol–water (9:1), the solvent mixture formerly used.[9] These results are collected in Table 1. As expected, the trinuclear compounds **1b**,**c** show a decrease in pK_{a1} of *ca.* 1.9 units when compared with *p*-nitrophenol, which is easily explained by a stabilisation of the monoanion by intramolecular hydrogen bonds. A further decrease of *ca.* 2.0–2.2 units (3.9–4.1 relative to *p*-nitrophenol) is observed for all calix[4]arenes studied and an alkyl substituent in the *p*-position of the opposite phenolic unit [$CH_3C(CH_3)_3$, C_6H_{11}, $C_{12}H_{25}$ in this series] obviously has no remarkable influence.

To obtain a broader view, we switched to 2-methoxyethanol–water (9:1) as the solvent system, and the pK_{a1} values obtained here are collected in Table 2. For compounds **3a** and **4**, the UV spectra are shown as a function of the apparent pH (optical titration) in Fig. 1.The spectra of all the compounds containing one *p*-nitrophenol unit show an isosbestic behaviour over the whole pH range [Fig. 1(*a*)]. For the calix[4]arenes **3i** and **4** containing two *p*-nitrophenol units no deviations from a first set of isosbestic points are found for pH < (pK_{a1} + 3), while all spectra pass a second set of isosbestic points above pH = 10 [*cf.* Fig. 1(*b*)].

The evaluation of the pK_{a1} values is illustrated by typical plots in Fig. 2. From eqn. (2), eqn. (3) may be deduced, where

$$\log \frac{\varepsilon - \varepsilon(\mathrm{HA})}{\varepsilon(\mathrm{A}^-) - \varepsilon} = \mathrm{pH} - \mathrm{p}K_a \qquad (3)$$

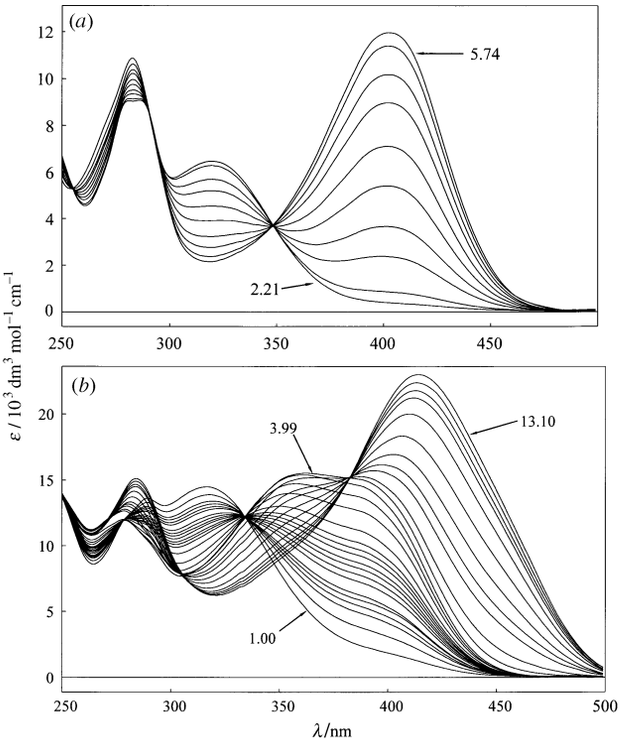


Fig. 1 (*a*) UV spectra of compound **3a** as a function of the apparent pH (pH values of the single curves: 2.21, 2.71, 3.29, 3.57, 3.83, 4.19, 4.40, 4.66, 5.10 and 5.74); (*b*) UV spectra of compound **4** as function of the apparent pH (pH values of the single curves: 1.29, 1.47, 1.55, 1.62, 1.68, 1.74, 1.81, 1.88, 1.94, 2.00, 2.08, 2.14, 2.23, 2.40, 2.81, 3.43, 3.99, 5.05, 10.12, 10.23, 11.58, 12.20, 12.40, 12.60, 12.79, 12.98 and 13.10)

ε is the molar absorption coefficient obtained at a given wavelength at the apparent pH, and ε(HA) and $\varepsilon(A^-)$ are the molar absorption coefficients in acidic and in alkaline solutions, respectively (see Experimental section). Plots of eqn. (3) are linear with a slope of 1, and the apparent pK_a is obtained as the intercept with the pH axis. Repeated determinations and evaluations at different wavelengths usually led to deviations <0.05 (for details see the Experimental section), but for the following discussion only differences greater than 0.10 are considered.

As in methanol–water (9:1), the pK_{a1} values of the trimers **1b–e** are nearly identical (6.1–6.3), but are lower than *p*-nitrophenol (8.7) by *ca.* 2.5 units. Again a further decrease in pK_{a1} by more than 2 units is observed when this trimeric unit is incorporated in a calix[4]arene. Comparison of the pK_{a1} values of compounds **3a–d** (3.9–4.0) shows again that different alkyl groups in the *para* position of the opposite phenolic unit have no influence on the acidity of the *p*-nitrophenol unit. A slight decrease is observed for $R^2 = C_6H_5$ (**3e**, 3.75) and for electron-withdrawing substituents like R^2 = Cl, COOR and NO_2, the pK_{a1} decreases by 0.75, 0.85 and 1.30.‡

All these results can be entirely understood by stabilisation of the monoanion by two intramolecular hydrogen bonds (α), as indicated in Scheme 1. Such hydrogen bonds are possible also in the trimers **1**, but their influence is less pronounced due to the higher rotational freedom. Additional stabilisation stems from the hydrogen bond (β) of the opposite phenolic unit, an effect which was also observed in linear compounds.[7] (The formation of a 'three-centred' hydrogen bond or a direct hydrogen bond from the opposite hydroxy group seems less likely, since the distance between distal phenolic oxygens in calix[4]arenes is in the range of 3.7–3.8 Å; compare the X-ray structure below.) The increased acidity of the opposite phenolic unit in **3e–3i** favours or strengthens the H-bond (β) and consequently the H-bonds (α), which explains the observed decrease in pK_{a1} for these compounds.

‡ When comparing the calix[4]arene **3i** containing two *p*-nitrophenol units with the other compounds, it must be kept in mind that already for statistical reasons the pK_{a1} of a diprotonic acid is lower by log 2 = 0.3 (while pK_{a1} is higher by log 2) in comparison with the corresponding monoprotonic acid, even if there is no mutual influence of the two acidic functions.

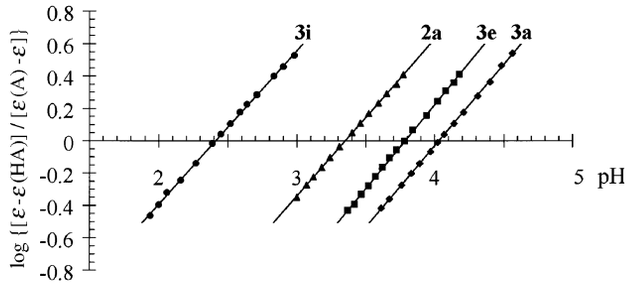


Fig. 2 Evaluation of the pK_{a1} values for the calix[4]arenes **2a**, **3a**, **3e** and **3i**; typical plots using eqn. (2)

Stronger intramolecular hydrogen bonding in the monoanions of the calix[4]arenes is also indicated by the wavelength of the absorption maximum, which is found at lower values (396–404 nm) than in the case of the linear trimers (409–411 nm). A similar hypsochromic effect was observed for the linear oligomers with the *p*-nitrophenol at the end for an increasing number of phenolic units.[7]

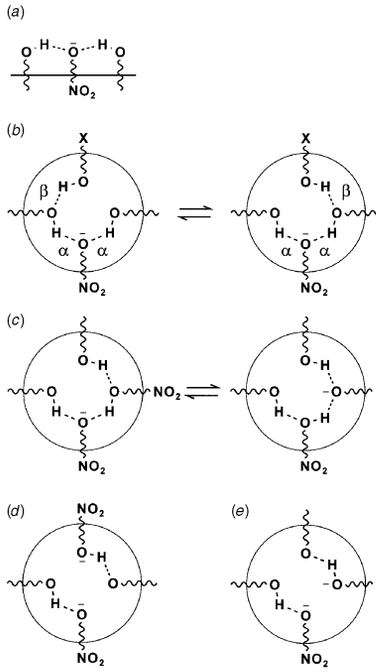
Not unexpectedly, the pK_{a1} value of **4**, with two adjacent *p*-nitrophenol units, is further decreased by 0.42 in comparison with the isomeric **3i**, while the pK_{a2} value for both compounds is 13.2 (±0.2). This is in agreement with the most probable hydrogen bond pattern for the mono- and di-anion, as sketched in Scheme 1.

Most probably the carboxylic groups in **2b** and **3h** are deprotonated in a similar pH range as the *p*-nitrophenol unit.§ However, obviously this dissociation, if it occurs, does not intervene with our determinations in a measurable way, since neither the isosbestic behaviour of the UV spectra is disturbed, nor the linearity or the slope of plots according to eqn. (3). Perhaps the slightly higher pK_{a1} values for **2b** and **3h** in comparison with **2a** and **3g** are an indication for the dissociation of the carboxylic groups. However, like the opposite difference in **2c**/**2d**, this should not be overinterpreted. Comparison of **2a**/**2b** and **3g**/**3h** shows that the alkyl substituent R^1 (Me/Bu^t) has no remarkable influence on pK_{a1}, which is also the basis for the following discussion.

Methyl groups in the *meta* position to the phenolic hydroxy groups should not change the acidity of this phenolic unit but should generally cause a distortion of the C_4 symmetrical cone conformation of calix[4]arenes. This has been demonstrated by the X-ray structures for octamethyl calix[4]arenes derived from 3,4-dimethylphenol[15] (four *m*-methyl groups) and 3,5-dimethylphenol[16] (eight *m*-methyl groups), and in the latter case also by low temperature ^{1}H NMR spectroscopy in solution. We were interested if such a distortion, caused by the opposite phenolic unit (*cf.* ref. 10), influences the dissociation of the *p*-nitrophenol unit. Comparison of **3a** with **5a** and **3b** with **5b** shows that a single *m*-methyl group has no detectable effect, which is in agreement with the X-ray structure of a similar calix[4]arene with a single *m*-methylphenol unit.[17] Two *m*-methyl groups at the opposite phenolic unit, *e.g.* as in **5b**, cause an increase in pK_{a1} of 0.3 in comparison with **3c**.

The deformation may be stronger if two *meta* positions adjacent to each other are substituted, which prompted us, to

§ The pK_{a1} of *p*-hydroxybenzoic acid is lower by *ca.* 2.5 than the pK_a of *p*-nitrophenol (in aqueous solution), which is not too different from the decrease in the pK_{a1} observed for the *p*-nitrophenol unit in a calix[4]arene in comparison with *p*-nitrophenol itself.



Scheme 1 Schematic representation of intramolecular hydrogen bonds in (*a*) trimers **1**, (*b*) calix[4]arenes **2**, **3**, (*c*) **4** and of (*d*) the dianions of **3i** (only one direction is shown) and (*e*) **4**

synthesize calix[4]arenes **6**. Comparison of **3a** with **6a** and especially of **3f** with **6c** shows an increase in pK_{a1} by 0.36 and 0.6, respectively, which most probably is due to a similar steric influence of the two *m*-methyl groups as discussed above, causing a distortion of the cone conformation. (A slight increase in pK_{a1} is seen, however, also for the trimer **3e** in comparison with **3b**.) If now one or two methyl groups are 'introduced' in positions R^1 and R^3 of **6c**, pK_{a1} increases by 0.15 (**6d**) and 0.3 (**6e**).

In conclusion, a deformation of the calix[4]arene skeleton by *m*-methyl groups in the phenolic unit opposite to the dissociating *p*-nitrophenol unit weakens the intramolecular hydrogen bonds and causes changes in pK_{a1} up to 0.9, the difference for **3f** and **6e**. It is reasonable to assume that a similar deformation of the calixarene skeleton by *m*-methyl groups 'between' the *p*-nitrophenol and the adjacent phenol units leads to a larger increase in pK_{a1}.

X-Ray structure of 3e

Single crystals of **3e** suitable for X-ray diffraction studies were obtained by allowing a chloroform solution to evaporate to dryness. Details of the X-ray experimental conditions, cell data, structure solution and refinement are shown in Table 3.¶

The asymmetric unit contains two crystallographically independent molecules of **3e** which have similar open-cone conformations as a result of the formation of eight-membered intramolecular hydrogen-bonded rings with O···O 2.652(4)–2.701(4) Å (Fig. 3). The calix[4]arene conformation is described by the interplanar angles between the aromatic rings and the plane of the CH_2 groups which join them. For the plane C17, C27, C37, C47, these values are 122.9(1)° [C11–C16], 126.8(1)° [C21–C26], C124.6(1)° [C31–C36] and 124.5(1)° [C41–C46]. The corresponding values for the second molecule and the C57, C67, C77, C87 plane are 122.9(1)° [C51–C56], 129.5(1)° [C61–C66], C121.2(1)° [C71–C76] and 131.0(1)° [C81–C86]. The exocyclic phenyl rings make angles of 38.1(1)° [C38–C313] and 30.4(2)° [C78–C713] with the calixarene aromatic ring to which they are bonded. The nitro group in each molecule is rotated away from coplanarity with its associated aromatic ring, but in different directions [+15.8(3)° (N18, O19, O110) and −8.7(3)° (N58, O59, O510)].

The two calixarenes pack around independent inversion centres such that a *tert*-butyl group of one molecule is inside the cavity of the inversion related one and *vice versa* (Fig. 4). In one such pair, the interplanar distance between ring C21–C26 and that related by the inversion centre at (0, 0.5, 0.5) is 3.53 Å; the corresponding distance for the second pair between ring C81–C86 and the molecule related by the inversion centre at (0.5, 0, 0) is much larger (4.95 Å). This difference found for the two analogous pairs is clearly caused by packing effects. It demonstrates how carefully such intermolecular distances of host–guest interactions must be discussed. The shortest intramolecular contacts are between disordered methyl C atoms (C211, C214) and atom C23 (at $-x$, $1-y$, $1-z$) with distances 3.60 and 3.61 Å; in the other dimer the corresponding separations (3.71 and 3.62 Å) are between (C811, C814) and C81 and C86 (at $1-x$, $-y$, $-z$). Comparable packing of dimers has been previously observed[10] in a calix[4]arene very similar to **3e** with the exocyclic phenyl ring replaced by a methyl group.

Table 3 Summary of crystal data, data collection, structure solution and refinement details

	3e
(*a*) Crystal data	
Formula	$2(C_{42}H_{43}NO_6)$, $0.57(CHCl_3)$
Molar mass	1383.7
Colour, habit	Colourless, block
Crystal size/mm	0.40 × 0.36 × 0.33
Crystal system	Triclinic
a/Å	13.893(3)
b/Å	15.266(2)
c/Å	20.065(4)
α/°	75.14(2)
β/°	75.40(2)
γ/°	81.548(4)
V/Å^3	3964.9(13)
Space group	$P\bar{1}$
Z	2
F(000)	1466
D_{calc}/g cm^{-3}	1.159
μ/mm^{-1}	0.132
(*b*) Data acquisition[a]	
Temp./K	294(1)
Unit-cell reflcns (*θ* range°)	25 (16.2 20.5)
Max. *θ*/° for reflcns	26.9
hkl Range of reflcns	−17 to 17; 0 to 19; −24 to 25
Variation in 3 standard reflcns	1.0%
Reflcns measured	17 226
Unique reflcns	17 226
Reflcns with $I > 2\sigma(I)$	6695
(*c*) Structure solution and refinement[b]	
Refinement on	F^2
Solution method	Direct methods
H-atom treatment	Riding
No. of variables in L.S.	928
Weights:	
k in $w = 1/[\sigma^2(F_o^2) + k]$ $[P = (F_o^2 + 2F_c^2)/3]$	$(0.1077P)^2$
R(obs, *F*), R_wF^2 (all), g.o.f.	0.079, 0.233, 1.01
Density range in final Δ-map/e Å^{-3}	−0.352, 0.433
Final shift/error ratio	−0.002

[a] Data collection on an Enraf-Nonius CAD4 diffractometer with graphite monochromatised Mo-Kα radiation (*λ* 0.7107 Å). [b] All calculations were done on an IBM Aptiva 166 MHz system with the NRCVAX system of programs (E. J. Gabe, Y. Le Page, J.-P. Charland, F. L. Lee and P. S. White, *J. Appl. Cryst.*, 1989, **22**, 384) for refinement with observed data on *F*, or with SHELXL-93 (G. M. Sheldrick, 1993) for refinement with all data on F^2.

¶ Atomic coordinates, displacement parameters and dimension tables have been deposited at the Cambridge Crystallographic Data Centre. See 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1997, Issue 1. Any request to the CCDC for the material should quote the full literature citation and reference number 188/68.

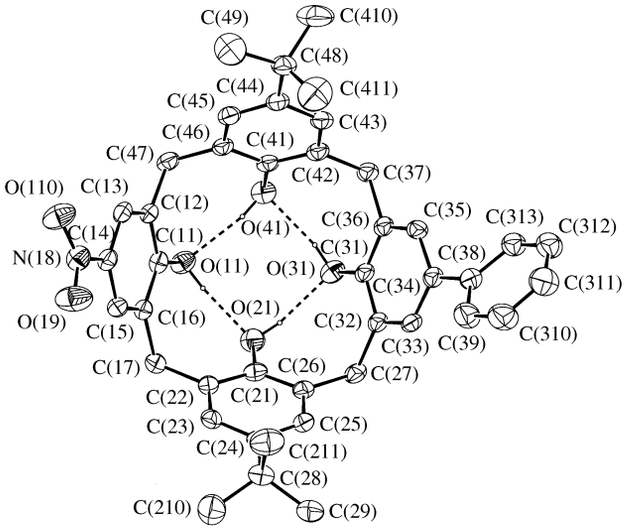


Fig. 3 View of one of the two independent calixarene molecules **3e** and our numbering scheme. Anisotropic displacement ellipsoids are drawn at the 30% probability level.

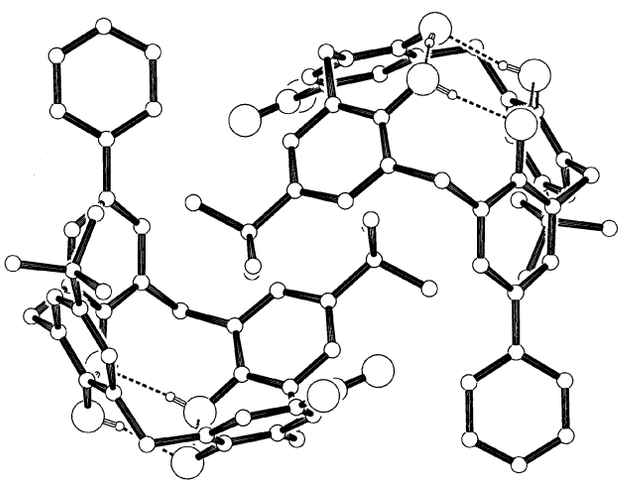


Fig. 4 View of the dimeric arrangements shown for one of the two independent calixarene molecules **3e**

The disordered trichloromethane molecules lay in a volume element centred on (0.5, 0.5, 0.5) in the unit cell effectively between calixarene dimers centred at (0.5, 0, 0) and (0, 0.5, 0.5) molecules. As a result of the dimer packing adopted by the calixarenes effectively filling the calix[4]arene cones, it was not possible for any solvent molecule to take part in C–H $\cdots\pi$ interactions inside the cones as we have reported previously.

Experimental

Syntheses

Hydroxymethylated and bromomethylated phenols,[12,13] the dimers of *p-tert*-butylphenol[18] and *p*-nitrophenol,[19] its bis-(bromomethyl)ated derivative and the trimer **1a**[20] were pepared as described in the literature or in analogy to literature prescriptions.

General procedure for the synthesis of linear trimers

Method A. 2,6-Bis(bromomethyl)-4-nitrophenol (10 g, 31 mmol) was added to an excess of molten *p*-alkylphenol (0.3 mol). After 5 h at 120 °C, the evolution of HBr finished, the mixture was cooled to room temperature and the excess phenol was removed by steam distillation. The residue was purified as described for the individual compounds.

Method B. A solution of *p*-alkylphenol (0.3 mol) in 80 ml glacial acetic acid was heated to 90 °C and 2,6-bis(bromomethyl)-4-nitrophenol (10 g, 31 mmol) was added. After 5 h the solution was cooled to room temperature and 80 ml water was added. The precipitate was filtered, washed with water and purified as indicated for the individual compounds.

2,6-*Bis*(2-*hydroxy*-5-*methylbenzyl*)-4-*nitrophenol* (**1a**). Method A: recrystallisation from chloroform gave 8.4 g (71%) of light-yellow crystals, mp 219 °C (lit.[20]: 51%; mp 219 °C) (Found: C, 69.0; H, 5.65; N, 3.7. $C_{22}H_{21}NO_5$ requires C, 69.65; H, 5.6; N, 3.7%).

2,6-*Bis*(2-*hydroxy*-5-tert-*butylbenzyl*)-4-*nitrophenol* (**1b**). Method A: recrystallisation from chloroform gave 9.7 g (68%) of white crystals, mp 212 °C; δ_H(200 MHz; $CDCl_3$) 8.11 (2 H, s, ArH), 7.28 (2 H, d, *J* 2, ArH), 7.10 (2 H, dd, *J* 2, 9, ArH), 6.74 (2 H, d, *J* 9, ArH), 3.97 (4 H, s, $ArCH_2Ar$) and 1.25 [18 H, s, $C(CH_3)_3$].

2,6-*Bis*(2-*hydroxy*-5-*cyclohexylbenzyl*)-4-*nitrophenol* (**1c**). Method A: recrystallisation from chloroform gave 11.1 g (70%) of light-yellow crystals, mp 216 °C; δ_H(200 MHz; $CDCl_3$) 8.11 (2 H, s, ArH), 7.10 (2 H, s, ArH), 6.91 (2 H, d, *J* 8, ArH), 6.72 (2 H, d, *J* 8, ArH), 3.94 (4 H, s, $ArCH_2Ar$), 2.40 (2 H, br, ArCH), 1.77 (10 H, br, CH_2) and 1.31 (10 H, br s, CH_2).

2,6-*Bis*(2-*hydroxy*-4,5-*dimethylbenzyl*)-4-*nitrophenol* (**1d**). Method A: recrystallisation from chloroform gave 9.5 g (76%) of white crystals, mp 224 °C (decomp.); δ_H(200 MHz; [$^2H_6$]-DMSO) 10.03 (1 H, s, ArOH), 9.31 (2 H, s, ArOH), 7.62 (2 H, s, ArH), 6.85 (2 H, s, ArH), 6.65 (2 H, s, ArH), 3.83 (4 H, s, $ArCH_2Ar$), 2.12 (6 H, s, CH_3) and 2.07 (6 H, s, CH_3).

2,6-*Bis*(2-*hydroxy*-4-*methyl*-5-*isopropylbenzyl*)-4-*nitrophenol* (**1e**). Method B: the precipitate was dissolved in chloroform, extracted three times with water and the solution dried over sodium sulfate. The solvent was evaporated and the crude product purified by flash chromatography with light petroleum (bp 40–60 °C)–acetone (4:1) to give 9.2 g (65%) of pale yellow crystals, mp 191 °C (Found: C, 72.2; H, 7.15; N, 3.0. $C_{28}H_{33}NO_5$ requires C, 72.55; H, 7.2; N, 3.0%); δ_H(200 MHz; $CDCl_3$) 8.09 (2 H, s, ArH), 7.11 (2 H, s, ArH), 6.62 (2 H, s, ArH), 3.93 (4 H, s, $ArCH_2Ar$), 3.01 [2 H, sept., *J* 6.8, $CH(CH_3)_2$], 2.21 (6 H, s, CH_3) and 1.20 [12 H, d, *J* 6.8, $CH(CH_3)_2$].

General procedure for the synthesis of calix[4]arenes

To a suspension of $TiCl_4$ (3.3 ml, 30 mmol) in dry dioxan (250 ml) a solution of the appropriate 2,6-bis(bromomethyl)ated phenol (5 mmol) [for the synthesis of **5b**,**c** and **6a**,**c**–**e** the 2,6-bis(hydroxymethyl)ated phenol was used instead] and **1** (5 mmol) was slowly added (over 24 h) at 100 °C. The reaction mixture was stirred at 110 °C for a further 12 h. The dark red solution was evaporated in vacuum (eventually reesterified), the residue was dissolved in 400 ml chloroform, silica gel (50 g) was added and the resultant mixture was evaporated again. The silica gel was extracted for 24 h with chloroform in a Soxhlet apparatus. The crude product thus obtained after evaporation was purified by flash chromatography. Further details are given for the individual compounds.

17-Ethoxycarbonyl-11,23-dimethyl-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (2a). The crude product was reesterified by refluxing with ethanol for 3 h prior to the Soxhlet extraction. Purification by flash chromatography with chloroform–ethyl acetate (10:1) and recrystallisation from chloroform–methanol gave 235 mg (12%) of colourless crystals, mp 327 °C (decomp.) (Found: C, 69.7; H, 5.45; N, 2.35. $C_{33}H_{31}NO_8$ requires C, 69.6; H, 5.5; N, 2.5%); δ_H(200 MHz; [$^2H_6$]DMSO) 8.08 (2 H, s, ArH), 7.72 (2 H, s, ArH), 6.86 (2 H, s, ArH), 6.81 (2 H, s, ArH), 4.23 (2 H, q, *J* 7, CH_2CH_3), 3.88 (8 H, br s, $ArCH_2Ar$), 2.01 (6 H, s, CH_3) and 1.27 (3 H, t, *J* 7, CH_2CH_3).

17-(1-Methoxycarbonylmethyl)-11,23-dimethyl-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (2c). The crude product was reesterified by refluxing with methanol for 3 h prior to the Soxhlet extraction. Purification by flash chromatography with chloroform–ethyl acetate (10:1) and recrystallisation from

chloroform–methanol gave 210 mg (8%) of colourless crystals, mp 332 °C (Found: C, 69.55; H, 5.6; N, 2.35. $C_{33}H_{31}NO_8$ requires C, 69.6; H, 5.5; N, 2.5%); δ_H(200 MHz; [$^2H_6$]DMSO) 8.07 (2 H, s, ArH), 6.97 (2 H, s, ArH), 6.88 (2 H, s, ArH), 6.80 (2 H, s, ArH), 3.88 (4 H, br s, $ArCH_2Ar$), 3.77 (4 H, br s, $ArCH_2Ar$), 3.56 (3 H, s, $COOCH_3$), 3.41 (2 H, s, $ArCH_2$) and 2.02 (6 H, s, CH_3).

11,23-Di-*tert*-butyl-17-methyl-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (3a). Purification by flash chromatography with chloroform and recrystallisation from chloroform–methanol gave 450 mg (15%) of colourless crystals, mp 352 °C (Found: C, 74.5; H, 7.1; N, 2.15. $C_{37}H_{41}NO_6$ requires C, 74.6; H, 6.95; N, 2.35%); δ_H(200 MHz; $CDCl_3$) 10.20 (4 H, s, ArOH), 7.96 (2 H, s, ArH), 7.10 (4 H, s, ArH), 6.81 (2 H, s, ArH), 4.21 (4 H, br m, $ArCH_2Ar$), 3.54 (4 H, br m, $ArCH_2Ar$), 2.09 (3 H, s, CH_3) and 1.24 [18 H, s, $C(CH_3)_3$].

11,17,23-Tri-*tert*-butyl-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (3b). Purification by flash chromatography with chloroform and recrystallisation from chloroform–methanol gave 450 mg (14%) of colourless crystals, mp 300 °C; δ_H(200 MHz; $CDCl_3$) 10.30 (4 H, s, ArOH), 7.99 (2 H, s, ArH), 7.10 (2 H, d, *J* 2.2, ArH), 7.06 (2 H, d, *J* 2.2, ArH), 7.02 (2 H, s, ArH), 4.20 (4 H, br s, $ArCH_2Ar$), 3.60 (4 H, br s, $ArCH_2Ar$), 1.22 [18 H, s, $C(CH_3)_3$] and 1.18 [9 H, s, $C(CH_3)_3$].

11,23-Di-*tert*-butyl-17-dodecyl-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (3c). Purification by flash chromatography with chloroform and recrystallisation from chloroform–methanol gave 450 mg (12%) of colourless crystals, mp 209 °C; δ_H(200 MHz; $CDCl_3$) 10.23 (4 H, s, ArOH), 7.95 (2 H, s, ArH), 7.09 (4 H, s, ArH), 6.80 (2 H, s, ArH), 4.25 (4 H, br m, $ArCH_2Ar$), 3.50 (4 H, br m, $ArCH_2Ar$), 2.31 (2 H, t, *J* 6, $ArCH_2$), 1.46 (2 H, m, $ArCH_2CH_2$), 1.22 [18 H, s, $C(CH_3)_3$ and CH_2] and 0.85 (3 H, t, *J* 6, CH_3).

17-Cyclohexyl-11,23-di-*tert*-butyl-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (3d). Purification by flash chromatography with chloroform and recrystallisation from chloroform–methanol gave 720 mg (22%) of colourless crystals, mp 324 °C; δ_H(200 MHz; $CDCl_3$) 10.27 (4 H, s, ArOH), 7.97 (2 H, s, ArH), 7.10 (2 H, d, *J* 2.3, ArH), 7.08 (2 H, d, *J* 2.3, ArH), 6.85 (2 H, s, ArH), 4.24 (4 H, br m, $ArCH_2Ar$), 3.53 (4 H, br m, $ArCH_2Ar$), 2.24 (1 H, m, ArCH), 1.73 (4 H, m, CH_2) and 1.23 [24 H, s, CH_2 and $C(CH_3)_3$].

11,23-Di-*tert*-butyl-5-nitro-17-phenyl-25,26,27,28-tetrahydroxycalix[4]arene (3e). Purification by flash chromatography with chloroform and recrystallisation from chloroform–methanol gave 890 mg (27%) of colourless crystals, mp 278 °C (Found: C, 76.55; H, 6.5; N, 1.95. $C_{42}H_{43}NO_6$ requires C, 76.7; H, 6.6; N, 2.15%); δ_H(200 MHz; $CDCl_3$) 10.27 (4 H, s, ArOH), 7.97 (2 H, s, ArH), 7.35–7.22 (5 H, m, ArH), 7.16 (2 H, d, *J* 2.1, ArH), 7.12 (2 H, d, *J* 2.1, ArH), 4.29 (4 H, br m, $ArCH_2Ar$), 3.64 (4 H, br m, $ArCH_2Ar$) and 1.23 [18 H, s, $C(CH_3)_3$].

11,23-Di-*tert*-butyl-17-chloro-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (3f). Purification by flash chromatography with carbon tetrachloride–chloroform (1.5:1) and recrystallisation from chloroform–methanol gave 750 mg (25%) of colourless crystals, mp 290–300 °C (decomp.) (Found: C, 60.45; H, 5.4; N, 1.8. $C_{36}H_{38}ClNO_6$ + 1 $CHCl_3$ requires C, 60.55; H, 5.35; N, 1.9%); δ_H(200 MHz; $CDCl_3$) 10.14 (4 H, s, ArOH), 7.97 (2 H, s, ArH), 7.13 (2 H, d, *J* 2.3, ArH), 7.09 (2 H, d, *J* 2.3, ArH), 6.98 (2 H, s, ArH), 3.90 (8 H, br s, $ArCH_2Ar$) and 1.24 [18 H, s, $C(CH_3)_3$].

11,23-Di-*tert*-butyl-17-ethoxycarbonyl-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (3g). The crude product was reesterified by refluxing with ethanol for 3 h prior to the Soxhlet extraction. Purification by flash chromatography with chloroform–ethyl acetate (3:1) and recrystallisation from chloroform–methanol gave 260 mg (8%) of pale yellow crystals, mp 336 °C (decomp.) (Found: C, 71.5; H, 6.45; N, 2.05. $C_{39}H_{43}NO_8$ requires C, 71.65; H, 6.65; N, 2.15%); δ_H(200 MHz; [$^2H_6$]DMSO) 8.00 (2 H, s, ArH), 7.64 (2 H, s, ArH), 7.16 (4 H, s, ArH), 4.14 (2 H, q, *J* 7, CH_2CH_3), 3.88 (8 H, br s, $ArCH_2Ar$), 1.25 (3 H, t, *J* 7, CH_2CH_3) and 1.16 [18 H, s, $C(CH_3)_3$].

11,23-Di-*tert*-butyl-5,17-dinitro-25,26,27,28-tetrahydroxycalix[4]arene (3i). Purification by flash chromatography with chloroform–ethyl acetate (3:1) and recrystallisation from chloroform–methanol gave 590 mg (19%) of light-yellow crystals, mp 305 °C (decomp.); δ_H(200 MHz; [$^2H_6$]DMSO) 8.01 (4 H, s, ArH), 7.18 (4 H, s, ArH), 3.90 (8 H, br s, $ArCH_2Ar$) and 1.16 [18 H, s, $C(CH_3)_3$].

11,23-Di-*tert*-butyl-16,17-dimethyl-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (5a). Purification by flash chromatography with carbon tetrachloride–chloroform (1.5:1) and recrystallisation from chloroform–methanol gave 200 mg (7%) of colourless crystals, mp 290–300 °C (decomp.) (Found: C, 70.75; H, 6.85; N, 2.0. $C_{38}H_{43}NO_6$ + 0.33 $CHCl_3$ requires C, 70.9; H, 6.7; N, 2.15%); δ_H(200 MHz; $CDCl_3$) 10.35 (4 H, s, ArOH), 7.96 (1 H, d, *J* 2.8, ArH), 7.94 (1 H, d, *J* 2.8, ArH), 7.27 (1 H, d, *J* 2.3, ArH), 7.11 (1 H, d, *J* 2.3, ArH), 7.09 (1 H, d, *J* 2.3, ArH), 7.08 (1 H, d, *J* 2.3, ArH), 6.83 (1 H, s, ArH), 4.00 (8 H, br m, $ArCH_2Ar$), 2.33 (3 H, s, CH_3), 2.05 (3 H, s, CH_3) and 1.25 [18 H, s, $C(CH_3)_3$].

11,23-Di-*tert*-butyl-17-chloro-16-methyl-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (5b). Purification by flash chromatography with carbon tetrachloride–chloroform (1.5:1) and recrystallisation from chloroform–methanol gave 380 mg (12%) of colourless crystals, mp 290–300 °C (decomp.) (Found: C, 65.35; H, 5.9; N, 1.9. $C_{37}H_{40}ClNO_6$ + 0.5 $CHCl_3$ requires C, 65.3; H, 5.9; N, 2.05%); δ_H(200 MHz; $CDCl_3$) 10.27 (4 H, s, ArOH), 7.98 (1 H, d, *J* 2.7, ArH), 7.95 (1 H, d, *J* 2.7, ArH), 7.14–7.08 (4 H, m, ArH), 7.06 (1 H, s, ArH), 3.90 (8 H, br m, $ArCH_2Ar$) and 1.24 [18 H, s, $C(CH_3)_3$].

11,23-Di-*tert*-butyl-17-chloro-16,18-dimethyl-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (5c). Purification by flash chromatography with carbon tetrachloride–chloroform (1.5:1) and recrystallisation from chloroform–methanol gave 250 mg (8%) of colourless crystals, mp 290–300 °C (decomp.) (Found: C, 68.1; H, 6.2; N, 2.0. $C_{38}H_{42}ClNO_6$ + 0.25 $CHCl_3$ requires C, 68.15; H, 6.3; N, 2.1%); δ_H(200 MHz; $CDCl_3$) 10.41 (4 H, s, ArOH), 7.95 (2 H, s, ArH), 7.27 (2 H, d, *J* 2.3, ArH), 7.12 (2 H, d, *J* 2.3, ArH), 4.00 (8 H, br m, $ArCH_2Ar$), 2.53 (6 H, s, CH_3) and 1.24 [18 H, s, $C(CH_3)_3$].

12,17,22-Trimethyl-5-nitro-11,23-diisopropyl-5,26,27,28-tetrahydroxycalix[4]arene (6a). Purification by flash chromatography with carbon tetrachloride–chloroform (1.5:1) and recrystallisation from chloroform–methanol gave 600 mg (21%) of colourless crystals, mp 290–300 °C (decomp.) (Found: C, 71.6; H, 6.6; N, 2.15. $C_{37}H_{41}NO_6$ + 0.25 $CHCl_3$ requires C, 71.5; H, 6.65; N, 2.25%); δ_H(200 MHz; $CDCl_3$) 10.49 (4 H, s, ArOH), 7.98 (2 H, s, ArH), 6.98 (2 H, s, ArH), 6.97 (2 H, s, ArH), 4.07 (4 H, br s, $ArCH_2Ar$), 3.97 (4 H, br s, $ArCH_2Ar$), 3.03 [2 H, sept., *J* 6.8, $CH(CH_3)_2$], 2.42 (6 H, s, CH_3), 2.11 (3 H, s, CH_3) and 1.13 [12 H, d, *J* 6.8, $CH(CH_3)_2$].

12,16,17,22-Tetramethyl-5-nitro-11,23-diisopropyl-25,26,27,28-tetrahydroxycalix[4]arene (6b). Purification by flash chromatography with carbon tetrachloride–chloroform (1.5:1) and recrystallisation from chloroform–methanol gave 100 mg (3%) of pale yellow crystals, mp 290–300 °C (decomp.) (Found: C, 64.4; H, 6.0; N, 1.8. $C_{38}H_{43}NO_6$ + 1 $CHCl_3$ requires C, 64.35; H, 6.1; N, 1.9%); δ_H(200 MHz; $CDCl_3$) 10.03 (4 H, s, ArOH), 8.01 (2 H, s, ArH), 6.98 (1 H, s, ArH), 6.96 (2 H, s, ArH), 3.92 (8 H, m, $ArCH_2Ar$), 2.98 [2 H, sept., *J* 6.3, $CH(CH_3)_2$], 2.33 (3 H, s, CH_3), 2.31 (3 H, s, CH_3), 2.21 (3 H, s, CH_3), 2.15 (3 H, s, CH_3) and 1.13 [12 H, d, *J* 6.3, $CH(CH_3)_2$].

17-Chloro-12,22-dimethyl-5-nitro-11,23-diisopropyl-25,26,27,28-tetrahydroxycalix[4]arene (6c). Purification by flash chromatography with carbon tetrachloride–chloroform (1.25:1) and recrystallisation from chloroform–methanol gave 1.15 g of a complex mixture (probably of calixarenes different

ringsize) from which the desired calix[4]arene could be separated by preparative TLC with chloroform. A final recrystallisation from chloroform–methanol gave colourless crystals, mp 290–300 °C (decomp.) (Found: C, 60.1; H, 5.1; N, 1.8. $C_{36}H_{38}ClNO_6$ + 0.66 $CHCl_3$ requires C, 60.0; H, 5.05; N, 1.8%); δ_H(200 MHz; $CDCl_3$) 10.40 (4 H, s, ArOH), 7.99 (2 H, s, ArH), 7.14 (2 H, s, ArH), 7.02 (2 H, s, ArH), 3.96 (8 H, br s, $ArCH_2Ar$), 3.01 [2 H, sept., *J* 6.8, C*H*(CH_3)$_2$], 2.41 (6 H, s, CH_3) and 1.15 [12 H, d, *J* 6.8, CH(C*H*$_3$)$_2$].

17-Chloro-12,16,22-trimethyl-5-nitro-11,23-diisopropyl-25,26,27,28-tetrahydroxycalix[4]arene (6d). Purification by flash chromatography with carbon tetrachloride–chloroform (1.5:1) and recrystallisation from chloroform–methanol gave 100 mg (3%) of colourless crystals, mp 290–300 °C (decomp.) (Found: C, 61.5; H, 5.6; N, 1.85. $C_{37}H_{40}ClNO_6$ + 1 $CHCl_3$ requires C, 61.0; H, 5.55; N, 1.9%); δ_H(200 MHz; $CDCl_3$) 9.45 (4 H, s, ArOH), 8.03 (2 H, s, ArH), 7.22 (1 H, s, ArH), 7.20 (1 H, s, ArH), 7.09 (1 H, s, ArH), 4.00 (8 H, br s, $ArCH_2Ar$), 2.99 [2 H, sept., *J* 6.8, C*H*(CH_3)$_2$], 2.47 (3 H, s, CH_3), 2.32 (3 H, s, CH_3), 2.25 (3 H, s, CH_3) and 1.13 [12 H, d, *d* 6.8, CH(C*H*$_3$)$_2$].

17-Chloro-12,16,18,22-tetramethyl-5-nitro-11,23-diisopropyl-25,26,27,28-tetrahydroxycalix[4]arene (6e). Purification by flash chromatography with carbon tetrachloride–chloroform (1.5:1) and recrystallisation from chloroform–methanol gave 20 mg (0.6%) of colourless crystals, mp 290–300 °C (decomp.); δ_H(200 MHz; $CDCl_3$) 10.03 (4 H, s, ArOH), 8.08 (2 H, s, ArH), 7.07 (2 H, s, ArH), 3.97 (8 H, br m, $ArCH_2Ar$), 3.05 [2 H, sept., *J* 6.8, C*H*(CH_3)$_2$], 2.47 (6 H, s, CH_3), 2.38 (6 H, s, CH_3) and 1.15 [12 H, d, *J* 6.8, CH(C*H*$_3$)$_2$].

17,23-Di-*tert*-butyl-5,11-dinitro-25,26,27,28-tetrahydroxycalix[4]arene (4). The dimer of *p*-*tert*-butylphenol and the bis(bromomethyl)ated dimer of *p*-nitrophenol were reacted as described above for the 3 + 1-fragment condensations. Purification by flash chromatography with dichloromethane and recrystallisation from hexane gave 1.0 g (32%) of light yellow crystals, mp 340 °C (decomp.) (Found: C, 68.8; H, 6.0; N, 4.4. $C_{36}H_{38}N_2O_8$ requires C, 69.0; H, 6.1; N, 4.5%); δ_H(200 MHz; [$^2H_6$]DMSO) 8.85 (4 H, br s, ArOH), 8.11 (2 H, d, *J* 2.5, ArH), 8.05 (2 H, d, *J* 2.5, ArH), 7.10 (2 H, s, ArH), 7.08 (2 H, s, ArH), 3.90 (8 H, br s, $ArCH_2Ar$) and 1.12 [18 H, s, C(CH_3)$_3$].

Hydrolysis of esters

The calix[4]arene (50 mg) was suspended in a solution of 3 ml methanol, 1.5 ml water and 50 mg sodium hydroxide and allowed to stand overnight. The resulting clear solution was neutralised with acetic acid and dropped into 10 ml water to form a white precipitate which was filtered and dried.

17-Carboxy-11,23-dimethyl-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (2b). 2b gave 41 mg (87%) of white powder, mp 355 °C; δ_H(200 MHz; [$^2H_6$]DMSO) 8.06 (2 H, s, ArH), 7.68 (2 H, s, ArH), 6.85 (2 H, s, ArH), 6.81 (2 H, s, ArH), 3.86 (8 H, br s, $ArCH_2Ar$) and 2.01 (6 H, s, CH_3).

17-Carboxymethyl-11,23-dimethyl-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (2d). 2d gave 42 mg (89%) of white powder, mp 346 °C; δ_H(200 MHz; [$^2H_6$]DMSO) 8.05 (2 H, s, ArH), 6.95 (2 H, s, ArH), 6.87 (2 H, s, ArH), 6.81 (2 H, s, ArH), 3.86 (8 H, br s, $ArCH_2Ar$), 3.29 (2 H, s, $ArCH_2$) and 2.02 (6 H, s, CH_3).

11,23-Di-*tert*-butyl-17-carboxy-5-nitro-25,26,27,28-tetrahydroxycalix[4]arene (3h). 3h gave 41 mg (85%) of white powder, mp 300–305 °C (decomp.); δ_H(200 MHz; $CDCl_3$) 10.10 (4 H, s, ArOH), 7.95 (2 H, s, ArH), 7.76 (2 H, s, ArH), 7.15 (2 H, d, *J* 2.5, ArH), 7.12 (2 H, d, *J* 2.5, ArH), 4.20 (8 H, br s, $ArCH_2Ar$) and 1.22 [18 H, s, C(CH_3)$_3$].

Determination of pK_a values

A buffer solution was made by dissolving 97 mg citric acid (Aldrich), 53 mg malonic acid (Aldrich) and 69 μl triethylamine (freshly distilled) in 450 ml 2-methoxyethanol and 50 ml water. In a typical experiment 0.8 mg of the nitrocalix[4]arene was dissolved in 25 ml of this solution (5×10^{-5} mol l^{-1}) using an ultrasonic bath. 20 ml of this solution were placed in a thermostatted vessel of an automatic titration apparatus (Metrohm E510) at 22 °C and acidified with conc. HCl. Titration with NaOH (1 mol l^{-1}) was carried out using a glass electrode, which was calibrated against aqueous buffer standards. At the desired apparent pH values (2 min elapsed before the final reading to obtain a constant value) the titration was stopped, a sample was transferred by a pipette to a 1 cm cuvette and its UV–VIS spectrum was measured with a Perkin-Elmer Lambda 17 apparatus 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 in Fig. 1, where the volume increase (usually a total of 100–150 μl until the final pH) is taken into account for the single spectra.

In this way, usually 15–20 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 eqn. (3). 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.

For the dinitrocalix[4]arenes **3i** and **4** the absorbance for the undissociated form $\varepsilon(H_2A)$ and for the dianion $\varepsilon(A^{2-})$ cannot be obtained exactly at low and at high pH. Therefore plots of eqns. (4) and (5) were used to determine K_{a1} and K_{a2}. The absorption

$$\frac{\varepsilon - \varepsilon(HA^-)}{[H^+]} = \frac{\varepsilon(H_2A)}{K_{a1}} - \frac{\varepsilon}{K_{a1}} \quad (4)$$

$$[H^+][\varepsilon - \varepsilon(HA^-)] = K_{a2}\varepsilon(A^{2-}) - K_{a2}\varepsilon \quad (5)$$

coefficient $\varepsilon(HA^-)$ was easily measured at medium pH (pK_{a1} + 3 < pH < pK_{a2} − 3) and [H^+] was calculated from the apparent pH. Deviations up to 0.1 were observed in this case for repeated experiments.

X-Ray structure analysis

The data crystal only diffracted weakly [only 6695 (38%) of the 17 726 measured reflections could be labelled as observed]. The asymmetric unit contains two independent calixarene molecules and it became obvious early on in the analysis that there were also molecules of solvation (which could only be chloroform) occupying what would otherwise have been voids in the crystal lattice. Difference maps revealed locations of all hydroxy H atoms (which were then allowed for with the SHELXL AFIX 147 command in the refinement). It was also clear that all *tert*-butyl methyl groups were slightly disordered (equally over two adjacent sites) and this was allowed for by suitable DFIX restraints in the refinement cycles. It was clear that the chloroform molecules of solvation which lay between calixarene molecules in what would have been a void centred at (0.5, 0.5, 0.5), were seriously disordered over two distinct sites in the asymmetric unit and, from the electron-density peak heights, had only partial occupancy. Attempts at modelling various disordered chloroform moieties in the two locations were not successful and, before the final refinement cycles, the contributions of the disordered solvent molecules to the observed structure amplitudes were subtracted using the SQUEEZE option in PLATON.[21] This showed that the combined occupancy of the two chloroform sites in the asymmetric unit was 0.57. In the final refinement cycles, all the calixarene non-H atoms were allowed anisotropic motion.

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