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1,3-Alternate calix[4]arenes, selectively functionalized by amino groups

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General strategies are described to synthesize calix[4]arenes which are fixed in the *1,3-alternate* conformation and substituted selectively by amino groups. These derivatives are useful starting materials for the attachment of various groups *via* amide bonds, as demonstrated by several examples, but may be converted also to ureas, imides or azomethines. Four amino groups may be attached to the narrow rim *via* (several) methylene groups as spacer by O-alkylation with ω-bromophthalimides or ω-bromonitriles. From the resulting tetraethers the amino functions are obtained by cleavage with hydrazine or by hydrolysis, allowing a selective functionalisation of both sides of the molecule (phenolic units A, C *versus* B, D). Amino functions at the wide rim are introduced by *ipso*-nitration of the respective *t*-butylcalix[4]arene derivatives and subsequent reduction. Selective *ipso*-nitration of a 1,3-diether, followed by *O*-alkylation with allylbromide to obtain the tetraether in the *1,3-alternate* conformation, hydrogenation of allyl and nitro groups (in one step), protection of the amino functions as phthalimides followed by *ipso*-nitration of the remaining *t*-butyl phenol rings, allows again to distinguish both sides of the molecule (units A, C *versus* B, D). Reaction of a wide rim tetraamine in the *1,3-alternate* conformation by Boc-anhydride allows not only to obtain the mono- and tri-Boc derivative, but also in nearly 60% yield the C_2-symmetrical di-Boc derivative, in which two adjacent phenolic units are protected (distinction of A, B from C, D). This paves the way for the preparation of chiral derivatives or assemblies. *O*-Alkylation with ω-bromophthalimides followed by *ipso*-nitration leads to precursors for octaamines in the *1,3-alternate* conformation, in which the potential amino functions on both rims can be selectively "activated" by reduction or hydrazinolysis. The structures of the newly synthesized molecules were mainly confirmed by their ^{1}H NMR spectra, which allow a distinction from isomeric derivatives in the *cone* and partial *cone* conformation. Single crystal X-ray analyses were obtained for two analogous derivatives in the *1,3-alternate* conformation (**27**, $n = 3,4$), an isomeric compound in the *cone* conformation (**27**, $n = 3,4$), and a derivative in the *partial cone* conformation (**11**).

Introduction

Calixarenes represent a class of cyclic oligomers, which is readily available in larger quantities and amenable to chemical modifications.[1] Thus, they have been frequently used as building blocks for larger molecular structures or assemblies or as platforms on which various kinds of functional groups may be assembled. For these aims calixarenes bearing amino functions may be considered as the most versatile starting material to which further residues can be attached easily *via* amide,[2] imide,[3] (thio)urea[4] or azomethine[5] links. *N*-Alkylation even allows the attachment of two residues per amino group[6] or the formation of cationic sites by quaternisation.[7] In general calixarenes can be decorated by amino groups at the narrow rim, attached to the phenolic hydroxyl groups *via* $(CH_2)_n$-spacers, or at the wide rim, directly attached to the *para*-positions or again *via* $(CH_2)_n$-spacers. In the calix[4]arene series the introduction of ether residues (≥propyl) restricts the conformational mobility and tetraethers can be fixed in one of the four basic conformations (*cone*, *partial cone*, *1,2-* and *1,3-alternate*) among which the *cone*-conformation is best explored. Thus, CMPO-like functions[8] have been attached to the wide[9] and to the narrow rim[10] to obtain extractants for lanthanides and actinides. Anion receptors were obtained as narrow (or wide) rim di- or tetra-(thio)urea derivatives[11] or by the attachment of various amide groups including cobaltocenium.[12] The self-assembly of wide rim tetra-urea derivatives to form hydrogen bonded dimeric capsules has been extensively studied,[13] and similar capsules have been found for calix[4]arenes bearing dipeptide residues at the wide rim.[14] The *1,3-alternate* conformation has been less frequently used as platform or building block. Di-urea derivatives as anion receptors[15,16] or self-assembled dimers[17] may be mentioned as examples, which were derived from the respective amino calix[4]arenes. In general it may be stated that the selective preparation of amino derivatives of calix[4]arenes fixed in the *cone* conformation is well established, using selective etherification (ω-bromonitriles, ω-bromoalkylphthalimides) for the narrow rim, and selective substitutions (*e.g.* (*ipso*)nitration[18] followed by hydrogenation) or protection strategies (Boc,[19] phthalimide[20]) for amino groups attached to the wide rim. In this manuscript we discuss general possibilities and describe new strategies for the selective introduction or protection of amino functions in *1,3-alternate* calix[4]arenes.

Results and discussion

Tetraamines, narrow rim

The introduction of aminoalkyl ether residues can be achieved by *O*-alkylation of **1** with ω-bromoalkylphthalimides[10,21] or ω-bromonitriles.[22] Bromopropionitrile ($BrCH_2CH_2$ CN, $m = 2$) cannot be used for the *O*-alkylation, since elimination to acrylnitrile predominates while only two ether residues are introduced with bromoacetonitrile.[23] Elimination cannot be avoided also with bromoethylphthalimide but hydroxy-ethylphthalimide has been used recently to obtain the 1,3-diether from *t*-butylthiacalix[4]arene under Mitsunobu conditions.[24] The *O*-alkylation with Boc-protected chloroethylamine[25] seems to be another alternative to introduce aminoethyl ether groups.[26]

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Via the *syn*-1,3-diether **2** or **3**, obtained in excellent yield in the presence of K_2CO_3, (or under Mitsunobu conditions in the case of **2** ($n = 2$) a mixed tetraether **4**, fixed (mainly) in the *1,3-alternate* conformation is available if the second etherification is done with an excess of Cs_2CO_3[27] as base. The amount of Cs_2CO_3 required as template can vary between 8- and 15-fold, with respect to the hydroxyl groups, depending on the nature of the existing ether residue and the *p*-substituent in the phenolic unit (see below). *Partial cone* and *cone* isomers[28] are always observed as side products. The formation of tetraethers with four identical ether residues (*e.g.* alkylphthalimides), can be achieved in one step with Cs_2CO_3, but two steps, as outlined in Scheme 1, are preferable according to our experience.

Compounds of type **4** contain two different precursors for amino functions which are in principle "orthogonal". The cleavage of the phthalimido groups with hydrazine in refluxing ethanol occurs without reduction of the nitrile functions. As an example, diamine **5** was obtained in 88% yield. After acetylation of the amino functions (92% of **6**) the reduction of the nitrile groups is possible by hydrogenation (Raney-Ni, room temperature) under alkaline conditions. In the final step a different residue may be attached to the diamine **7**, as shown by the *p*-nitrobenzamide **8** chosen as an example.

Contrary to our expectations the reduction of the nitrile functions in **4** was not possible without a partial hydrolysis of one of the phthalimido groups. Under various conditions, *e.g.* lowering the temperature from 50 °C to room temperature, replacing Raney-Ni by Pd/C, using LiOH as weaker base instead of NaOH, the monophthalamide **9** was formed and isolated in yields up to 62%.[29] Attempts to hydrogenate the nitrile functions with Raney-Ni in toluene at 60 °C left the starting material unreacted.[30]

However, the sequence **1** to **8** as outlined in Scheme 1 and realized for one example allows in principle to attach two different residues in alternate sequence to amino groups on the narrow rim of a *1,3-alternate* calix[4]arene. Evidently diamines and their derivatives are available analogously.[31]

Tetraamines, wide rim

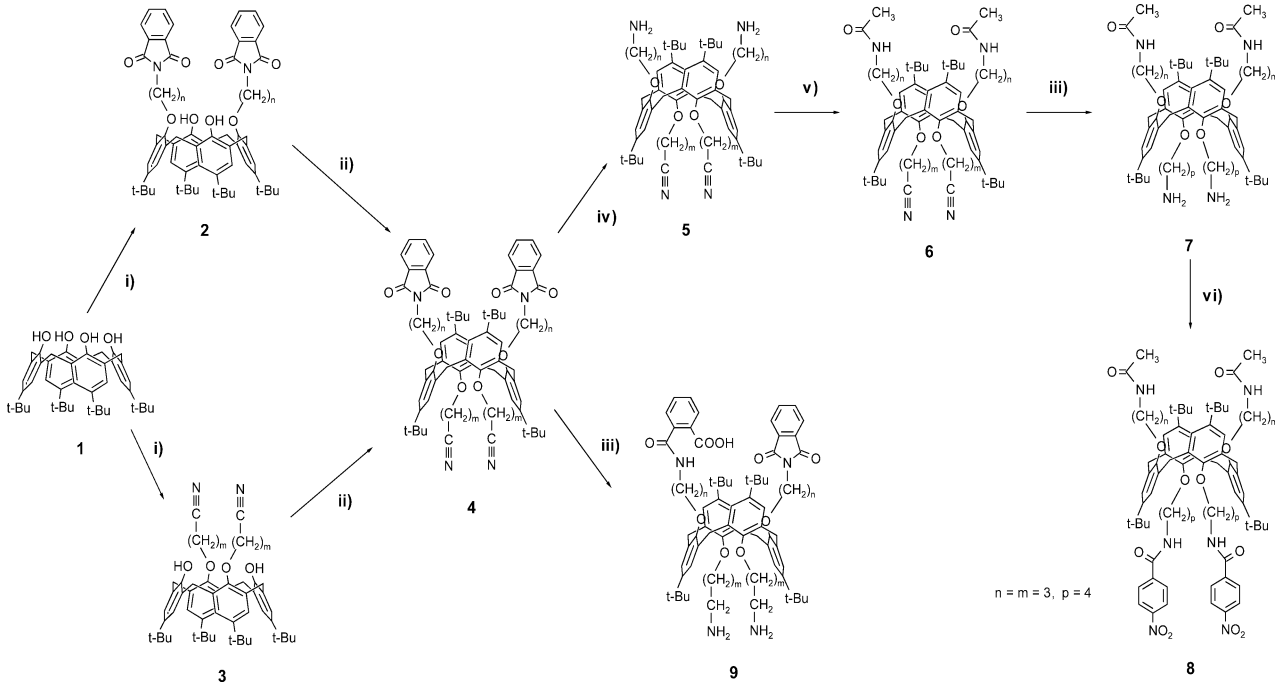
Introduction of amino functions attached to the wide rim is possible by *ipso*-nitration of a tetraether followed by reduction of the nitro groups. This sequence is possible also with tetraethers in *1,3-alternate* conformation[32] (and other conformations) and leads to a tetraamine (bearing eventually two different ether residues) where no differentiation of the amino functions is possible.

Selective *ipso*-nitration of *syn*-1,3-diethers, however, is possible in good yield in the phenolic units.[18] *O*-Alkylation of **10**, taken as an example for such a dinitro-diether, with allylbromide leads to **11** in the *1,3-alternate* conformation (accompanied by the *partial cone* isomer). Simultaneous reduction of the nitro groups and hydrogenation of the C=C double bonds (Raney-Ni, rt) gives the diamine **12**, in which the amino groups can be protected as phthalimide (**13**). *Ipso*-nitration of the *t*-butylphenyl ether units in **13** is possible in a clean fashion (without attack on the phthalimide units).[20] In the special case we even found conditions (high dilution) to obtain the *mono*-nitro compound **14** in 79% yield, which could be used to synthesize wide rim triamines. Subsequent *ipso*-nitration of **14** gave the dinitro compound **15** in 83% yield. Compounds of type **14** and **15** contain two independent (orthogonal) precursors of amino groups. In analogy to similar derivatives in the *cone*-conformation[20,33] either the phthalimide group can be cleaved by hydrazine (**16**) or the nitro groups can be hydrogenated (**17**). All steps are summarized in Scheme 2.

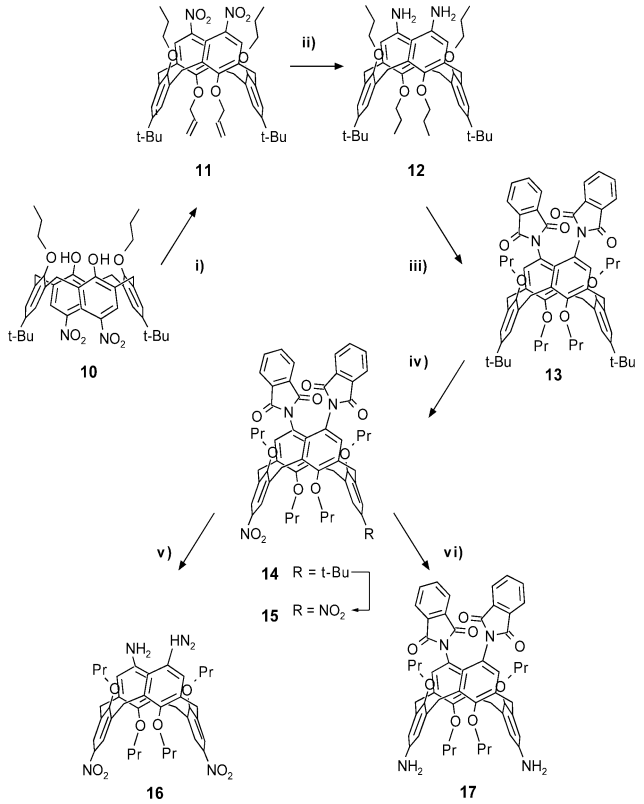
Thus, derivatives with two different amide residues are available from **15** (or **14**) by deprotection (or reduction), acylation, reduction (or deprotection) and final acylation. The appropriate reaction sequence may be chosen with respect to the special example.

It should be mentioned that the *O*-alkylation of **10** requires a reactive bromide, like allylbromide (eventually benzylbromide, ethylbromoacetate), due to the lower nucleophilicity of the *p*-nitrophenolate units, while usual alkyl bromides are not reactive enough in the presence of Cs_2CO_3. However, the first ether residue can be chosen more or less freely,[34] and the allyl group is easily hydrogenated to the propyl group.

The two different precursors of the amino function in **15** point (in pairs) in one or the other direction. The molecule has C_{2v}-symmetry. An alternative to differentiate between amino functions attached to the wide rim consists in a partial protection by Boc. When 1 mol of tetraamine[35] **18** is treated with 1.9 mol of



Scheme 1 (i) Alkyl bromide, K_2CO3; (i′) for $n = 2$: *N*-(β-hydroxyethylphthalimide, triphenylphosphine, DIAD, THF; (ii) alkyl bromide, Cs_2CO_3, DMF, 50 °C; (iii) H_2, Raney-Ni, NaOH; (iv) hydrazine, EtOH, reflux; (v) Ac_2O; (vi) *p*-nitrobenzoylchloride.



Scheme 2 (i) Allylbromide, Cs_2CO_3, DMF, 50 °C; (ii) H_2, Raney-Ni, EtOH, rt; (iii) phthalic anhydride, toluene, reflux; (iv) HNO_3, CH_2Cl_2/AcOH; (v) hydrazine, EtOH, reflux; (vi) H_2, Raney-Ni, toluene/THF, rt.

Boc-anhydride (Scheme 3), 58% of the 1,2-diprotected derivative **20** can be isolated by chromatography, in addition to 23% of the monoprotected compound **19**. (The yield of **20** can be increased to 65% and decreased to 18% for **19** using 2 mol of Boc-anhydride). If 3 mol of Boc-anhydride are used, the triprotected compound **22** is available in 63% yield from **18**, and the tetra-Boc protected compound was formed as a side product. Similar to the *cone*-derivative the formation of a 1,3-diprotected **21** compound is not observed.

Compound **20** is chiral (C_2-symmetry), an aspect which is not further discussed in this article and the two protected, as well as the not-protected, amino functions point in different directions which contrasts to **15**. Tetraamides with two different amide functions are available from **20** by acylation, deprotection and a second acylation as shown for one example. The acylation of **20** with acetanhydride leads quantitatively to **24** which after deprotection is easily acylated to tetraamide **25**.

Tetraamines, narrow/wide rim

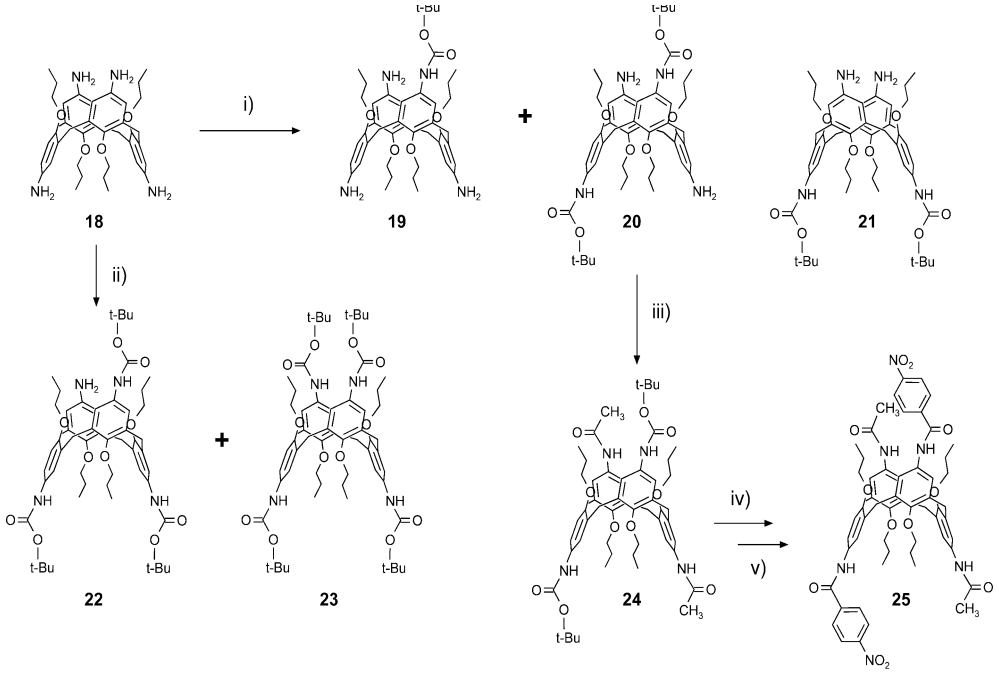
If four amino functions attached to a *1,3-alternate* calix[4]arene point in one direction, two of them must be attached at the narrow rim (with different length of the alkyl spacer, *e.g.* two, three or four carbon atoms) and two at the wide rim.

A possible reaction sequence to achieve this goal is shown in Scheme 4:

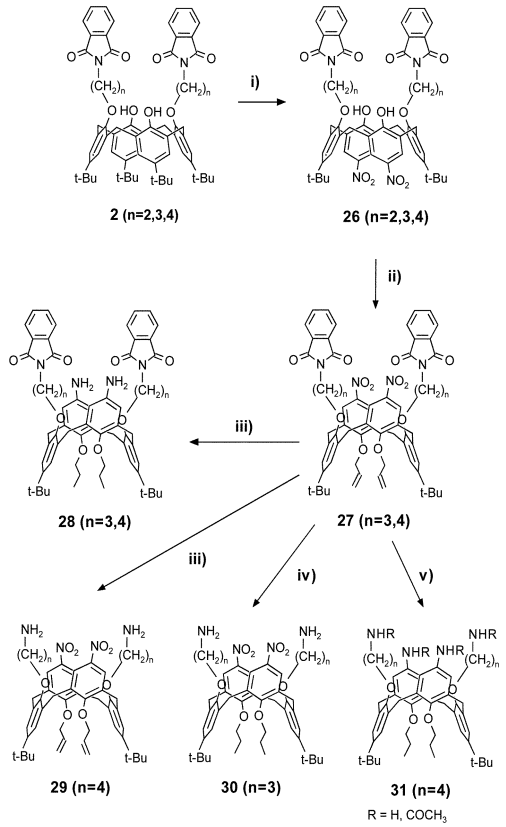
Ipso-nitration of the syn-1,3-diether **2**, followed by *O*-alkylation of **26** with allylbromide leads to compounds **27** in a reaction sequence analogous to Scheme 3.

The crucial step of the sequence, the *O*-alkylation with allylbromide (compare Scheme 2, step (i)), was tried under different conditions in the presence of Cs_2CO_3. While the reaction is too slow at room-temperature, an increase of the temperature favours the formation of the *partial cone* conformation over the desired *1,3-alternate*. The best results in our hands were found for a concentrated reaction mixture (base and calixarene) in DMF at 40–50 °C for 5–7 days. A higher yield of **27** was obtained for $n = 4$ (53%) than for $n = 3$ (19%). This may be due to some steric hindrance between the phthalimido groups and the nitro groups of the inverted phenolic units, which is more pronounced for the shorter chains ($n = 3$ *vs.* $n = 4$). This could also explain why the *partial cone* (19%) and *cone* (2%) conformers were isolated as side products in the case of **27** ($n = 3$) while the formation of the *partial cone* conformer was detected only by NMR for **27** ($n = 4$).

Compounds **27** again contain two independent precursors of amino functions. Catalytic hydrogenation leads to the wide rim diamines **28** ($n = 3, 4$) which can be *N*-acylated at the wide rim, deprotected and acylated again on the narrow rim to furnish a tetraamide with two different amide residues on the same side of the platform. Cleavage of the phthalimide groups by hydrazine in boiling ethanol leads to aliphatic diamines **30**, as shown for



Scheme 3 (i) 2 mol Boc_2O; (ii) 3 mol Boc_2O; (iii) Ac_2O; (iv) CF_3COOH, $CHCl_3$, 0 °C; (v) *p*-nitrobenzoylchloride, $CHCl_3$, NEt_3, rt.



Scheme 4 (i) HNO_3, CH_2Cl_2/AcOH; (ii) allylbromide, Cs_2CO_3, DMF, 40–50 °C; (iii) H_2, Raney-Ni, THF, rt; (iv) hydrazine, EtOH, reflux; (v) hydrazine, Pd/C, EtOH, reflux.

$n = 3$ (57%), in which the nitro groups are retained. After a first *N*-acylation at the narrow rim, reduction of the nitro groups followed by a second acylation at the wide rim will lead to a mixed tetraamide again. The choice of the appropriate reaction sequence will be due to the acyl residues to be introduced.

The example of **30** ($n = 3$) shows that the allyl ether groups are converted to propyl ether groups during the hydrazinolysis of the phthalimide groups. After shorter reaction times products were isolated, in which all phthaloyl residues were cleaved, while allyl groups were still present. This suggests that conditions might be found under which the allyl groups remain unchanged, if this would be desired. However, up to now we could not obtain a pure compound **29**.

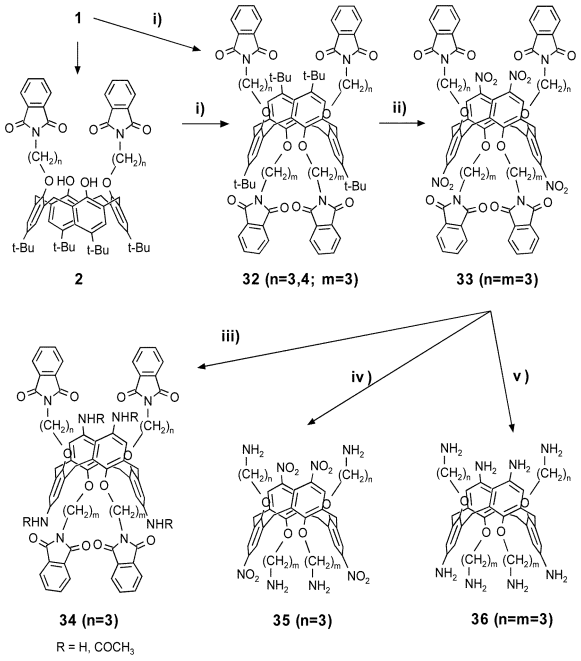
Finally, a direct conversion of **27** into tetraamines **31** (R = H) should be also possible if the cleavage reaction with hydrazine is done in the presence of Pd/C (compare the preparation of **36** below). The resulting tetraamines show (in the case of $n = 4$) very broad ^{1}H-NMR signals under all conditions studied, and also the unambiguous characterization as tetraacetamide **31** (R = $COCH_3$) failed so far.[36]

Octaamines

As illustrated in Scheme 5, it is possible also to create four amino functions on each side of a *1,3-alternate* calix[4]arene.

The tetraether **32** ($n = m = 3$) can be obtained from the respective *syn*-1,3-diether **2** or directly in one step from **1**. The two step synthesis makes it possible also to have two different spacer lengths *n* and *m*, as shown for **32** ($n = 4$, $m = 3$), which is obtained in 60% yield starting from 1,3-*syn*-diether **2** ($n = 4$), while the yield was lower for **32** ($n = m = 3$) (compare the synthesis of **27** discussed above). *Ipso*-nitration yields **33** (64%), a compound again containing two independent precursors for amino functions. The catalytic hydrogenation of the nitro groups (Raney-Ni, H_2) was complicated by the low solubility of **33** ($n = m = 3$) in usual solvents or solvent mixtures, and **34** (R = H) was directly acylated and characterised as the tetraacetamide **34** (R = $COCH_3$). Cleavage of the phthalimido groups in **33** led to the narrow rim tetraamine **35** and simultaneous reduction of the nitro groups (hydrazine, Raney-Ni) gave octaamine **36**.

As already mentioned, the formation of tetraethers in the *1,3-alternate* conformation starting with *syn*-1,3-diethers **2** is usually accompanied by *partial cone* and *cone* isomers as side products.[37] With calixarenes (*e.g.* **1**) as starting material the *1,2-alternate* conformer must be considered additionally as a potential product which was isolated in the case of **32** ($n = m = 3$) in 31%.



Scheme 5 (i) Alkylbromide, Cs_2CO_3, THF reflux or DMF 50 °C; (ii) HNO_3, CH_2Cl_2/AcOH; (iii) H_2, Raney-Ni, THF/DMF, 50°; then Ac_2O; (iv) hydrazine, EtOH, reflux; (v) hydrazine, Pd/C, EtOH, reflux.

Characterization by NMR

^{1}H NMR spectroscopy is the most valuable tool to distinguish these different isomers, especially during their separation, while the ^{13}C signals of the methylene bridges are of limited value.[38] The attribution of the structure is mainly based on the well known pattern of the Ar–CH_2–Ar bridges, and of the aromatic protons.[39] Substituents R in *p*-position and ether residues Y may furnish additional information.

In the following we will discuss typical examples proceeding mainly in the sequence given by Schemes 1 to 5. In many cases the molecular structure was additionally proved by X-ray analysis, for which some characteristic examples are presented the next section.

Due to the different ether residues in **4** the methylene protons are not identical and appear as a pair of doublets (AB system, $J = 13.8$ Hz) at $\delta = 3.86$ and 3.78 ppm. The *1,3-alternate* conformation follows nevertheless unambiguously from the small difference in their chemical shift ($\Delta\delta = 0.08$ ppm), since a *cone* conformation would require a difference of about 1.2 ppm, and a *partial cone* conformer would not show a single pair of doublets. For *ArH* protons, the ^{1}H-NMR displays two close singlets at 6.97 and 7.00 ppm, respectively. Two singlets are also found for *t*-Bu protons at 1.20 and 1.28 ppm. More pronounced are the differences in the chemical shift for the methylene protons in compound **11** ($\Delta\delta = 0.13$ ppm), while two strongly separated singlets at 6.96 and 7.95 ppm for aromatic protons are due to the different substituents at the wide rim (*t*-Bu *vs.* NO_2).

Two ^{1}H-NMR spectra measured in $CDCl_3$ and C_6D_6 are required for the complete identification of the chiral C_2-

symmetry of compound **20**, where a two-fold axis intersects the carbon atoms of two opposite methylene bridges. Two singlets (3.28, 3.41 ppm) and a pair of doublets (3.32, 3.37 ppm) for the methylene protons are found in $CDCl_3$. Two AB systems for the aromatic protons of **20** (doublets at 6.45/6.47 and 7.23/7.27 ppm) are shown only in C_6D_6, while this clear splitting cannot be seen in $CDCl_3$. The compounds **19** and **22** show a similar pattern of signals reflecting the same C_s-symmetry in both cases, with the symmetry plane intersecting two opposite phenolic units (protected and unprotected).

Even a small difference in the length of the ether chains is reflected in the ^{1}H-NMR spectrum of **32** ($n = 3$, $m = 4$). While the D_{2d}-symmetrical compound **32** ($n = m = 3$) shows one singlet for the protons of the methylene bridges (3.67 ppm) and one for the aromatic protons (6.92 ppm), two doublets with geminal coupling (~3.67, 3.70 ppm) for methylene protons and two close singlets (6.91, 6.96 ppm) for the aromatic protons are found for **32** ($n = 3$, $m = 4$), where the symmetry is reduced to C_{2v}

The proton signals displayed in ^{1}H-NMR spectrum show that all further amines (**34**, **35** and **36**) generated from the **33** precursor have the same D_{2d}-symmetry indicated by the presence of two singlets, one for methylene protons and the other one for the aromatic protons.

Single crystal X-ray analyses

Four compounds, **27** (*1,3-alt*) with $n = 3$, 4, **27** (*cone*, $n = 3$) and **11** (*paco*) have been additionally confirmed by X-ray analysis. The results will be briefly discussed, using the general numbering scheme presented in Fig. 1. The molecular conformation and shape is shown in Fig. 2a–d, while Fig. 3 contains selected packing diagrams.

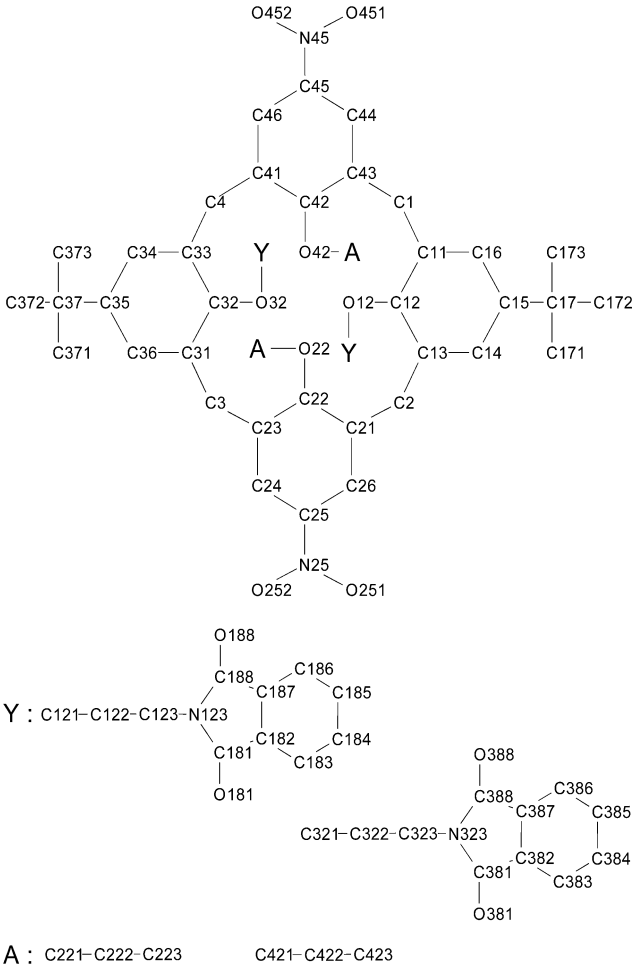


Fig. 1 General atomic numbering scheme illustrated by **27** ($n = 3$).

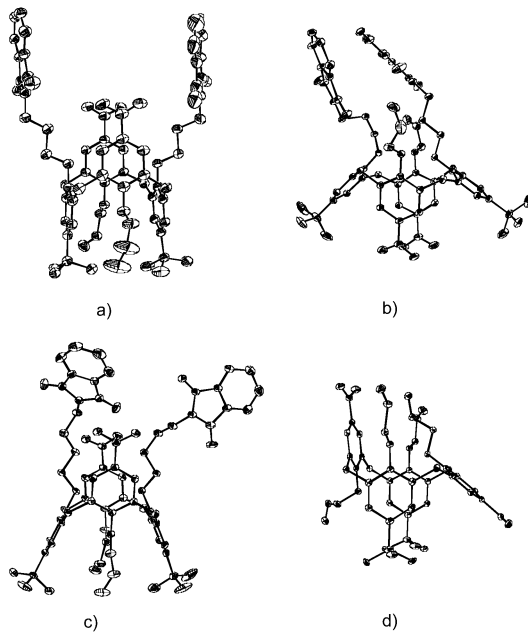


Fig. 2 Molecular conformation of four calix[4]arenes: (a) **27** (*1,3-alt*, $n = 3$); (b) **27** (*cone*, $n = 3$); (c) **27** (*1,3-alt*, $n = 4$); (d) **11** (*paco*).

For all compounds bond lengths and bond angles are in the usual range, and the following discussion refers mainly to the shape of the calixarene skeleton. A general and unambiguous description of the conformation of calixarenes is possible, using the torsion angles around the σ-bonds connecting the methylene bridges and the aromatic units (Table 1). The conformation of a given calix[4]arene is characterised by a typical sequence of the signs of these torsion angles, and these sequences are found for all compounds: (+,−)(+,−)(+,−)(+,−) for a *cone* conformation (**27** (*cone*, $n = 3$)), (−,−)(+,+)(−,−)(+,+) for *1,3-alternate* (**27** (*1,3-alt*)), and (+,−)(+,−)(−,−)(+,+) for a *partial cone* (**11** (*paco*)).[40] While all torsions are in the range of 60° to 69° (absolute values) for **27** (*1,3-alt*, $n = 3$), smaller values down to 37° are found for **27** (*1,3-alt*, $n = 4$). To visualize the consequences for the shape of these two molecules in the *1,3-alternate* conformation, and in general for a more vivid description of the conformation of calix[4]arenes the inclination of the single phenolic units with respect to a reference plane, the best plane through the four methylene carbon atoms (C1–C4), may be used. These δ values[41] are also included in Table 1. Surprisingly the strongest deviation from an ideal regular square for C1–C4 is observed for the compound in the *cone* conformation. The two diagonals differ by about 0.74 Å, and pairs of opposite sides differ by 0.14 Å. Also the average deviation from the best plane (0.23 Å) is significantly higher than for the other three compounds ($\leq$ 0.06 Å). Small but still significant differences are even found for the two molecules in the *1,3-alternate* conformation, where the average side length for $n = 4$ is larger by 0.04 Å, compared with the analogue with $n = 3$.

For **27** (*1,3-alt*, $n = 3$) all δ-values are close to 90°, only one nitrophenol unit is bent 5.1° inward and one *t*-butylphenol unit 4.3° outwards. Rather different is the shape of **27** (*1,3-alt*, $n = 4$), where both the nitrophenol units (12.4°, 16.7°) and the *t*-butylphenol units (26.3°, 20.9°) are strongly bent outwards. This "deformation" of the ideal *1,3-alternate* conformation cannot be due to an intramolecular influence of the spacer (consisting of four instead of three carbon atoms). Therefore it must be caused by packing effects (see below) and gives an example of how strong these effects can be.

27 (*cone*, $n = 3$) is found in an extremely *pinched cone* conformation, where both nitrophenol units are bent inwards (11.1°, 10.2°) and both *t*-butyl phenol units are bent outwards

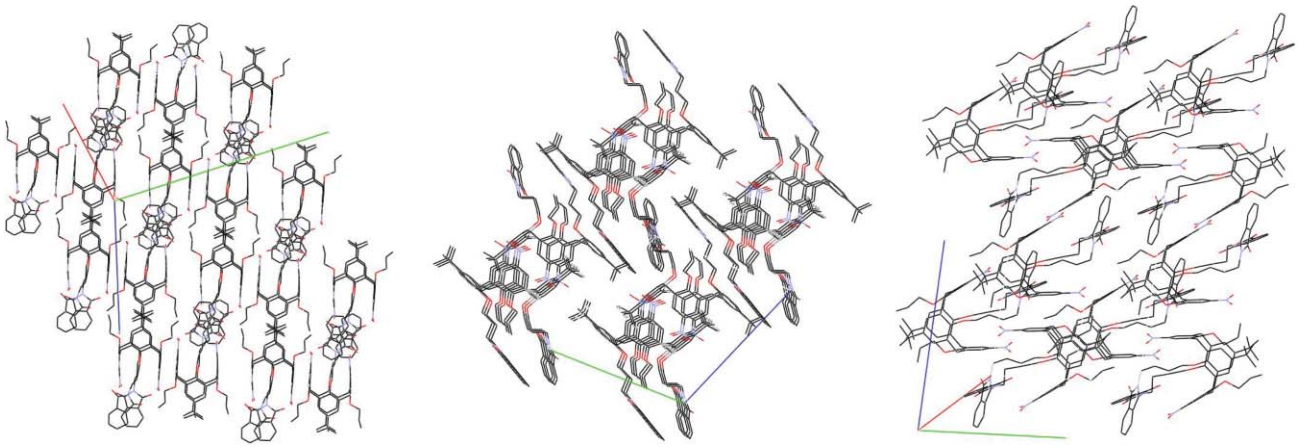


Fig. 3 The packing diagram of (a) **27** (*1,3-alt*, $n = 3$); (b) **27** (*cone*, $n = 3$); (c) **27** (*1,3-alt*, $n = 4$).

Table 1 Selected crystallographic data: (I) Torsion angles (in °) around the Ar–CH_2 bonds; (II) Distances within the reference plane (in Å), the best plane through the carbon atoms of the methylene bridges; (III) Inclination δ (in °) of the aromatic units with respect to the reference plane

	(a)	(b)	(c)	(d)
I. Torsion angles				
C12–C11–C1–C43	−60.5	66.8	−46.6	−112.7
C11–C1–C43–C42	−69.3	−115.4	−54.5	74.8
C22–C21–C2–C13	65.5	136.6	68.4	61.3
C21–C2–C13–C12	61.8	−78.4	37.2	58.9
C32–C31–C3–C23	−60.2	61.3	−45.2	−70.0
C31–C3–C23–C22	−64.1	−113.6	−61.0	−59.9
C42–C41–C4–C33	68.5	133.2	60.3	−69.9
C41–C4–C33–C32	60.3	−71.1	46.6	119.6
II. Reference planes C1–C4				
rmsd	0.006	0.23	0.062	0.037
Distance C1–C2	5.060	4.962	5.129	5.077
Distance C2–C3	5.097	5.122	5.109	5.111
Distance C3–C4	5.059	4.988	5.112	5.061
Distance C1–C4	5.090	5.117	5.121	5.042
Distance C1–C3	7.182	7.471	7.306	7.131
Distance C2–C4	7.177	6.729	7.164	7.215
III. Inclination of the aromatic units(δ)				
C11–C16	91.4	134.4	116.3	99.0
C21–C26	91.6	78.9	102.4	95.4
C31–C36	94.3	142.4	110.9	84.4
C41–C46	84.9	79.8	106.7	139.3

(a) **27** (*1,3-alt*, $n = 3$) (b) **27** (*cone*, $n = 3$) (c) **27** (*1,3-alt*, $n = 4$) (d) **11** (*paco*)

(44.4°, 52.4°). The *partial cone* compound **11** (*paco*) can be roughly described as containing structural elements of a *1,3-alternate* (aromatic rings 1 to 3) and a *pinched cone* (aromatic rings 3 to 1) conformer. The deviation of the former rings from an orientation perpendicular to the reference plane is ≤9°. The orientation of the *t*-butylphenol units is nearly parallel; one of them is bent outwards (9°) and the other one bent inwards (5.6°). Both *p*-nitrophenol units in-between are outwards oriented by 5.4° and 49.3°, respectively.

Molecular conformations of all four compounds are shown in Fig. 2, while Fig. 3 shows a representative section of the packing for the three phthaloyl substituted compounds.

Intermolecular forces between neighbouring molecules comprise π–π stacking between phthaloyl residues and aromatic units of the calixarenes (mainly between nitrophenol ether units). However, the inspection of the packing of the two *1,3-alternate* derivatives **27** ($n = 3,4$) did not give obvious reasons for the differences found in their conformation.

Conclusions

General strategies have been developed and realized for representative examples to synthesize amino derivatives of calix[4]arenes fixed in the *1,3-alternate* conformation. Four amino functions can be attached either to the narrow or to the wide rim, or just to one side of the molecule. Both sides or both rims, respectively, are completely substituted by amino functions in octaamines. The use of protective groups or two independent precursors of amino groups allows a further differentiation, leading to the preparation of mixed amides. Since amino groups are readily substituted by further residues, the compounds and synthetic strategies described will be useful for the synthesis of various selectively substituted calix[4]arenes.

Experimental

Materials

Solvents and all other chemicals were purchased from Acros, Aldrich and Lancaster and used without further purification. Silica gel (Merck, 0.040–0.063 mm) was used for column chromatography. ^{1}H-NMR spectra were reordered on a Bruker AC200, AC300 and Brucker DRX400 Avance instrument (400 MHz). FD and ESI mass spectra were measured on a Finningan MAT 8230 spectrometer. Melting points are uncorrected.

5,11,17,23-Tetra-*t*-butyl 26,28-dihydroxy 25,27-diphthalimido-ethoxy-calix[4]arene 2 ($n = 2$) (*cone*)

A solution of triphenylphosphine (6,0 g, 23 mmol) in THF (40 ml) was cooled down to 0–5 °C (ice bath) and di-*iso*-propyl azodicarboxylate (DIAD) (23 mmol, 4.5 ml) was added dropwise under nitrogen. After 30 min a white precipitate was formed and a suspension of *t*-butyl calix[4]arene (5.0 g, 7.7 mmol) and *N*-(hydroxyethyl)-phthalimide (4.4 g, 23 mmol) in THF (100 ml) and DMF (15 ml) was slowly added. The reaction mixture was stirred 1 h at 0–5 °C and after it was warmed to rt until the suspension became clear (5 h). Then the solvent was partially removed under reduced pressure until a pale yellow precipitate was formed. It was filtered off, washed with water (50 ml) and methanol (30 ml) to give the pure product as a white powder (4.6 g, 60%). mp 297–298 °C (Found: C 77.21, H 7.17, N 12.80. $C_{64}H_{70}N_2O_8$ requires C 77.24, H 7.09, N 12.86).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86, 1.25 (2s, 36H, *t*-Bu), 3.25, 4.19 (2d, 8H, $^2J = 13.2$ Hz, Ar–CH_2–Ar), 4.24 (t, 4H, $^3J = 6.6$ Hz, -CH_2–N), 4.42 (t, 4H, $^3J = 6.9$ Hz, O–CH_2-), 6.69 (s, 4H, Ar*H*), 6.77 (s, 2H, O*H*), 6.98 (s, 4H, Ar*H*), 7.67–7.92 (m, 8H, Phth-*H*).

5,11,17,23-Tetra-*t*-butyl-25,27-*bis*-phthalimidopropoxy-26,28-*bis*-cyanopropoxy-calix[4]arene 4 (*1,3-alternate*)

(a) By *O*-alkylation of 3. A suspension of diether **3** (3.9 g, 5 mmol) and Cs_2CO_3 (16.25 g, 50 mmol) in dry DMF (40 ml) was heated to 50 °C under argon for 1 h. A solution of *N*-(3-bromopropyl)-phthalimide (13.34 g, 50 mmol) in DMF (10 ml) was added and the heating was continued for 7 days under argon. The solvent was removed under reduced pressure and the yellow residue was dissolved in chloroform. The solution was washed with water (2 × 75 ml), dried ($MgSO_4$), concentrated and the product was precipitated with methanol to give 3.3 g (60%) of **4** (*1,3-alt*) as a white powder. From the filtrate 0.63 g (11%) a yellow powder was separated after several days which consisted mainly of the *partial cone* isomer.

4 *(*1,3-alt*).* mp 241–243 °C, (Found: C 74.55, H 7.16, N 4.48. $C_{74}H_{84}N_4O_8{\cdot}2H_2O$ requires C 74.47, H 7.43, N 4.69).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20, 1.28 (2s, 36H, *t*-Bu), 1.32–1.42 (m, 8H, -CH_2–CH_2–CH_2-), 1.86 (t, 4H, ^3J = 7.5 Hz, -CH_2–CN), 3.38 (t, 4H, ^3J = 8.0 Hz, -CH_2–N), 3.46, 3.52 (2t, 8H, ^3J = 7.0, 6.63 Hz, O–CH_2-), 3.86, 3.78 (2d, 8H, ^2J = 13.8 Hz, Ar–CH_2–Ar), 6.97, 7.00 (2s, 8H, Ar*H*), 7.68–7.82 (m, 8H, Phth-*H*).

4 *(*paco*).* mp 233–235 °C after recrystallisation from chloroform–methanol (15 ml, 1 : 2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01, 1.25, 1.27 (3s, 18/9/9H, *t*-Bu),1.74 (m, 2H, -CH_2–CH_2–CH_2-), 1.89 (m, 2H, -CH_2–CH_2–CH_2-), 2.11 (m, 4H, -CH_2–CH_2–CH_2-), 2.57 (t, 4H, ^3J = 7.0 Hz, -CH_2–CN), 3.09 (d, 2H, ^2J = 12.5 Hz, Ar–CH_2–Ar), 3.30 (t, 4H, ^3J = 7.3 Hz, -CH_2–N), 3.55–3.88 (m, 12H, O–CH_2-, Ar–CH_2–Ar), 4.00 (d, 2H, ^2J = 12.1 Hz, Ar–CH_2–Ar), 6.67, 6.86 (2d, 4H, ^2J = 2.2 Hz Ar*H*), 7.01, 7.10 (2s, 4H, Ar*H*), 7.68–7.84 (m, 8H, Phth-*H*).

(b) By *O*-alkylation of 2. Diether **2** (1.0 g, 0.97 mmol), γ-bromo butyronitrile (0.97 ml, 9.7 mmol), and Cs_2CO_3 (3.16 g, 9.7 mmol) were suspended in DMF (15 ml) at 50 °C. The reaction was conducted as described above. The sticky mass formed after evaporation was treated twice with chloroform (50 ml) and slightly acidified water (75 ml). The organic phase was dried ($MgSO_4$) and the product was isolated and purified by precipitation from chloroform–methanol to give 0.45 g (40%) of **4** (*1,3-alt*) as white powder, identical in all aspects to the product described above. The filtrate contained the *partial cone* isomer (tlc) which was not isolated in this case.

5,11,17,23-Tetra-*t*-butyl-25,27-*bis*-aminopropoxy-26,28-*bis*-cyanopropoxycalix[4]arene 5 (*1,3-alternate*)

A suspension of **4** (0.60 g, 0.5 mmol) in ethanol (40 ml) was refluxed with hydrazine (12 ml) for 2 h after which a clear solution was formed. The solvent was evaporated, the organic residue was dissolved in $CHCl_3$ and washed several times with water. The organic solution was dried ($MgSO_4$) and the solvent evaporated again. The final product was purified by crystallization from $CHCl_3$–hexane (20 ml, 1 : 10) to give a yellow powder; yield 0.42 g, 88%; mp 303 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18–1.37 (m, 8H, -CH_2–CH_2–CH_2-), 1.30, 1.31 (2s, 36H, *t*-Bu), 1.91 (t, 4H, ^3J = 7.7 Hz. CH_2–CN), 2.16 (bs, 4H, -NH_2), 2.50 (t, 4H, ^3J = 6.9 Hz, CH_2–NH_2), 3.45–3.50 (2t, 8H, -CH_2–O), 3.85, 3.86 (2d, 8H, ^2J = 17.3 Hz, Ar–CH_2–Ar), 7.01, 7.03 (2s, 8H, Ar*H*).

5,11,17,23-Tetra-*t*-butyl-25,27-*bis*-acetamidopropoxy-26,28-*bis*-cyanopropoxy-calix[4]arene 6 (*1,3 alternate*)

Diamine **5** (0.42 g, 0.46 mmol) was dissolved in acetanhydride (5 ml) containing a few drops of triethylamine. After 12 h stirring at room temperature a white precipitate had formed which was filtered off and washed with water (30 ml). The desired diamide **6** was obtained as a white powder; (0.42 g, 93%); mp 285–286 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13–1.41 (m, 8H, -CH_2–CH_2–CH_2-), 1.25, 1.30 (2s, 36H, *t*-Bu), 1.88 (t, 4H, ^3J = 7.3 Hz, CH_2–CN), 1.94 (s, 6H, -CH_3), 2.28–2.94 (m, 4H, -CH_2–NH), 3.26 (t, 4H, ^3J = 9.0 Hz, -CH_2–O), 3.49 (t, 4H, ^3J = 6.0 Hz, -CH_2–O), 3.84 (s, 8H, Ar–CH_2–Ar), 6.4 (bs, 2H, N*H*), 6.96, 7.01 (2s, 8H, Ar*H*).

5,11,17,23-Tetra-*t*-butyl-25,27-*bis*-acetamidopropoxy-26,28-*bis*-aminobutyloxy-calix[4]arene 7 (*1,3 alternate*)

A suspension of **6** (0.25 g, 0.25 mmol) in ethanol–THF (1 : 4, 8 ml) and aqueous NaOH (6%, 8 ml) was stirred with Raney-Ni under hydrogen atmosphere. After the hydrogen uptake was complete the catalyst was removed by filtration through sea sand and the solvent removed under reduced pressure. The white residue was extracted with chloroform, the solution washed several times with water, dried ($MgSO_4$) and evaporated. The residue was triturated with CH_2Cl_2–hexane (1 : 10, 10 ml) to give a yellow oil, yield 0.2 g, 50%.

^{1}H NMR (300 MHz, $CDCl_3$) while most of the signals are broad signals characteristic signals for aromatic protons, -NH, and terminal methyl groups can be distinguished: δ 1.25 (bm, 48H, -CH_2–CH_2–CH_2-, *t*-Bu), 1.91 (s, 6H, -CH_3), 2.50–3.81 (bm, 28H, -CH_2–NH_2, -NH_2, -CH_2–O, Ar–CH_2–Ar), 6.43 (bs, 2H, N*H*), 6.96 (bs, 8H, Ar*H*).

5,11,17,23-Tetra-*t*-butyl-25,27-*bis*-acetamidopropoxy-26,28-*bis*-(*p*-nitrobenzoylamino)-butyloxy-calix[4]arene 8 (*1,3-alternate*)

A solution of *p*-nitrobenzoylchloride (93 mg, 0.5 mmol) and triethylamine (0.07 ml, 0.5 mmol) were added to a stirred solution of **7** (0.247 g, 0.25 mmol) in chloroform (30 ml). After 12 h at room temperature the solvent was removed under reduced pressure, and the residue was purified by column chromatography (chloroform), to give a yellow powder; yield 0.15 g, 50%; mp 123 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13–1.41 (m, 8H, -CH_2–CH_2–CH_2-), 1.25, 1.30 (2s, 36H, *t*-Bu), 1.46 (m, 4H, -CH_2–CH_2–CH_2-), 1.92 (s, 6H, -CH_3), 2.28–2.94 (m, 4H, CH_2–CH_2–CH_2), 3.19–3.33 (m, 12H, -CH_2–O, -CH_2–N), 3.82 (s, 8H, Ar–CH_2–Ar), 6.2 (bs, 2H, N*H*), 6.89 (bs, 2H, N*H*), 6.94, 6.97 (2s, 8H, Ar*H*), 7.94, 8.23 (2d, 8H, ^4J = 8.8 Hz, Ar*H*).

5,11,17,23-Tetra-*t*-butyl-25-phthalimidopropoxy-27-phthaloyl-aminopropoxy-26,28-*bis*-aminobutyloxy-calix[4]arene 9 (*1,3 alternate*)

The dinitrile **4** (0.63 g, 0.54 mmol) was dissolved in ethanol–THF (1 : 4, 10 ml). A suspension of Pd/C (300 mg) in NaOH solution (10 ml, 6%) was added, and the reaction mixture was stirred under hydrogen atmosphere at 50 °C for 3 h. After the catalyst was filtered off, the solvents were removed under reduced pressure and the residue was treated with a mixture of CH_2Cl_2 (25 ml) and water (50 ml). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 ml) and the combined organic phase was dried ($MgSO_4$) and evaporated. The diamine **9** was obtained as a white powder, yield 0.39 g, 62%; mp 152–154 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13, 1.27 (2s + m, 48H, *t*-Bu, -CH_2–CH_2–CH_2-), 1.97 (t, 4H, ^3J = 7.3 Hz, -CH_2–NH_2), 3.05 (bs, 4H, N–CH_2-), 3.40 (bm, 12H, -O–CH_2-, -NH_2), 3.78, 3.95 (2d, 8H, ^2J = 16.5 Hz, Ar–CH_2–Ar), 7.03, 7.09 (2s, 8H, Ar*H*), 7.28–7.35 (m, 4H, Phth-*H*), 7.50, 7.62 (2d, 4H, ^2J = 7.0 Hz, $Phth_{COOH}$-*H*), 10.29 (bs, 1H, -COO*H*).

5,17-Di-*t*-butyl-11,23-dinitro-25,27-diallyloxy-26,28-dipropoxy-calix[4]arene 11 (*1,3-alternate*) and 11 (*partial cone*)

A stirred suspension of dinitro-calixarene **10** (2.0 g, 2.8 mmol) and Cs_2CO_3 (13.6 g, 42 mmol) in dry DMF (50 ml) was heated to 40 °C under nitrogen. After 1 h allylbromide (3.6 ml, 42 mmol) was added and the reaction was continued for 7 days. The DMF was removed under reduced pressure and the residue was treated

with chloroform (25 ml) and water (75 ml). The organic phase was washed with water (2 × 75 ml), dried ($MgSO_4$) and the solvent was evaporated to give a yellow oil. Analysis by TLC showed the presence of two compounds, which were separated and purified by column chromatography (CH_2Cl_2–hexane 2 : 3) and identified by NMR as the *1,3-alternate* and the *partial cone* isomers.

11 (*1,3-alt*). White-yellow powder, yield 1.4 g, 63%; mp 278–279 °C; (Found: C 72.88, H 7.39, N 3.59 $C_{48}H_{58}N_2O_8$ requires C 72.89, H 7.39, N 3.54)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.79 (t, 6H, $^3J = 7.7$ Hz, -CH_2–CH_3), 1.21 (s, 18H, *t*-Bu), 1.45 (m, 4H, -CH_2–CH_2–CH_3), 3.56 (t, 4H, $^3J = 7.7$ Hz, O–CH_2), 3.68, 3.81 (2d, 8H, $^2J = 15.0$ Hz, Ar–CH_2–Ar), 3.94 (d, 4H, $^4J = 5.1$ Hz, CH_2=CH–CH_2–O-), 5.05 (m, 4H, CH_2=CH-), 5.70 (m, 2H, CH_2=CH-), 6.96, 7.95 (2s, 8H, Ar*H*).

11 (*paco*). Colorless crystals, yield 0.38 g, 18%; mp 248–249 °C;

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.98 (m, 24H, *t*-Bu, -CH_2–CH_3), 1.89 (m, 4H, -CH_2–CH_3), 3.19 (d, 2H, $^2J = 12.9$ Hz, Ar–CH_2–Ar), 3.52 (m, 2H, O–CH_2-), 3.64 (d, 2H, $^2J = 13.6$ Hz, Ar–CH_2–Ar), 3.77 (m, 2H, O–CH_2), 3.83 (d, 2H, $^2J = 13.6$ Hz, Ar–CH_2–Ar), 4.08 (d, 2H, $^2J = 13.2$ Hz, Ar–CH_2–Ar), 4.16, 4.31 (2d, 4H, $^4J = 5.9$ Hz, -O–CH_2–CH=CH_2), 4.90, 5.29 (2m, 4H, -CH=CH_2), 5.65, 6.07 (2m, 2H, -CH=CH_2), 6.50, 6.87 (2d, 4H, $^4J = 2.2$, 2.6 Hz, Ar*H*), 8.02, 8.23 (2s, 4H, Ar*H*)

5,17-Di-*t*-butyl-11,23-diamino-25,26,27,28-tetrapropoxy calix[4]arene 12 (*1,3-alternate*)

Raney-Ni (0.5 g) was added to a solution of the dinitro compound **11** (0.7 g, 0.88 mmol) in THF (20 ml) and the suspension was stirred under hydrogen atmosphere at rt. After the hydrogen uptake was complete, the catalyst was filtered off and the solvent was evaporated. The residue was dissolved in chloroform (10 ml) and reprecipitated by hexane (25 ml) to give the pure diamine as a pink powder, yield 0.28 g, 45%; mp 198 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.68, 0.76 (2t, 12H, $^3J = 7.3$, 7.7 Hz, -CH_2–CH_3), 1.13–1.38 (m, 26H, *t*-Bu, -CH_2–CH_3), 3.23–3.71 (m, 12H, O–CH_2-, -NH_2), 3.68, 3.80 (2d, 8H, $^2J = 15.4$ Hz, Ar–CH_2–Ar), 6.64, 6.91 (2s, 8H, Ar*H*).

5,17-Di-*t*-butyl-11,23-diphthalimido-25,26,27,28-tetrapropoxy-calix[4]arene 13 (*1,3-alternate*)

A solution of diamine **12** (0.7 g, 1.3 mmol), phthalic acid anhydride (0.45 g, 3 mmol) and triethylamine (1 ml) in toluene (25 ml) was refluxed for 12 h. The solvent was removed under reduced pressure to give a red sticky mass, which was dissolved in chloroform (5 ml) and passed through a silica column (chloroform) to remove the excess anhydride. **13** was isolated as a pink powder, yield 0.53 g, 42%; mp 384–385 °C; (Found: C 74.63, H 7.10, N 2.66 $C_{64}H_{70}N_2O_8$ requires C 77.24, H 7.09, N 2.81).

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.58–0.67 (m, 12H, -CH_2–CH_3), 1.04 (m, 4H, CH_3–CH_2-), 1.28 (m, 22H, *t*-Bu, -CH_2–CH_3), 3.39 (m, 8H, O–CH_2-), 3.84, 3.87 (2d, 8H, $^2J = 16.5$ Hz, Ar–CH_2–Ar), 6.97, 7.12 (2s, 8H, Ar*H*), 7.70 (m, 8H, Phth-*H*).

5-Nitro-17-*t*-butyl-11,23-diphthalimido-25,27,26,28-tetrapropoxy-calix[4]arene 14 (*1,3-alternate*)

Glacial acetic acid (3 ml) and fuming nitric acid (0.22 ml) were added to a vigorously stirred, clear solution of diphthalimido **13** (0.5 g, 0.5 mmol) in dry CH_2Cl_2 (50 ml) at rt. After a certain time (around 7–15 min) when the color of the solution had changed from black-indigo to yellow, water (50 ml) was added and the reaction mixture was stirred for further 30 min. The organic solution was washed several times with water, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by precipitation from CH_2Cl_2–CH_3OH (20 ml, 1 : 1) to give a yellow powder, yield 0.38 g, 78%; mp 313–315 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80, 0.88 (2t, 6H, $^3J = 7.3$ Hz, -CH_2–CH_3), 1.03 (t, 6H, $^3J = 7.3$ Hz, -CH_2–CH_3), 1.17 (s, 9H, t-Bu), 1.66–1.91 (m, 8H, -CH_2–CH_2–CH_3), 3.55 (d, 2H, $^2J = 14.0$ Hz, Ar–CH_2–Ar), 3.61–3.83 (m, 12H, Ar–CH_2–Ar, O–CH_2-), 3.81 (t, 2H, $^3J = 7.7$ Hz, O–CH_2-), 6.98 (s, 2H, Ar*H*), 7.15, 7.20 (2d, 4H, $^4J = 2.6$ Hz, Ar*H*), 7.47–7.57 (m, 8H, Phth-*H*), 7.94 (s, 2H, Ar*H*).

5,17-Dinitro-11,23-diphthalimido-25,27,26,28-tetrapropoxy-calix[4]arene 15 (*1,3alternate*)

Glacial acetic acid (0.32 ml) and fuming nitric acid (0.02 ml) were added to a vigorously stirred, clear solution of diphthalimide **13** (0.03 g, 0.03 mmol) in dry CH_2Cl_2 (6 ml) at rt. The reaction was monitored by tlc. After 5 h the color of the solution had changed from black-indigo to yellow. Water (50 ml) was added and the reaction mixture was stirred for further 30 min. The organic solution was washed twice with water (2 × 10 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by precipitation from CH_2Cl_2–CH_3OH (20 ml, 1 : 1) to give the dinitro compound **15** as yellow powder, yield 0.013 g, 45% (Found: C 69.10, H 5.87, N 5.41. $C_{56}H_{52}N_4O_{12}$ requires C 69.12, H 5.39, N 5.76). mp. 338–340 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89, 1.07 (2t, 12H, $^3J = 7.3$ Hz, -CH_2–CH_3), 1.82 (m, 8H, -CH_2–CH_2–CH_3), 3.68 (s, 8H, Ar–CH_2–Ar), 3.74 (m, 8H, O–CH_2-), 7.19 (s, 4H, Ar*H*), 7.47–7.57 (m, 8H, Phth-*H*), 7.96 (s, 4H, Ar*H*).

Dinitro compound **15** was obtained also from the mononitro compound **14** using similar conditions. Glacial acetic acid (1.97 ml) and fuming nitric acid (0.11 ml) were added to a stirred solution of **14** (0.37 g, 0.375 mmol) in CH_2Cl_2 (25 ml). The reaction was followed by tlc and stopped (the color of the solution had changed from black to yellow) by adding water (50 ml). The organic solution was washed several times with water, dried ($MgSO_4$) and the solvent was removed under reduced pressure. Precipitation from CH_2Cl_2–CH_3OH (20 ml, 1 : 1) gave **15** as yellow powder (0.3 g, 83%).

5,17-Dinitro-11,23-diamino-25,27,26,28-tetrapropoxy-calix[4]-arene 16 (*1,3-alternate*)

A solution of **15** (0.2 g, 0.2 mmol) in EtOH (10 ml) was refluxed with hydrazine (3 ml). After 2 h the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (10 ml), washed with water (2 × 25 ml), dried ($MgSO_4$) and the solvent was evaporated. The formed powder was dissolved in chloroform (5 ml) and precipitated with hexane (15 ml) to give the pure diamine **15** as a yellow powder, yield 0.11 g, 79%; mp 216 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69, 0.78 (2t, 12H, $^3J = 7.3$ Hz, -CH_2–CH_3), 1.30–1.43 (m, 8H, -CH_2–CH_2–CH_3), 2.69 (bs, 4H, -NH_2), 3.27, 3.35 (2t, 8H, $^3J = 7.3$ Hz, O–CH_2), 3.65, 3.66 (2d, 8H, $^2J = 15.4$ Hz, Ar–CH_2–Ar), 6.4, 6.93 (2s, 8H, Ar*H*).

5,17-Diamino-11,23-diphthalimido-25,27,26,28-tetrapropoxy-calix[4]arene 17 (*1,3-alternate*)

The dinitro compound **15** (0.11 g, 0.11 mmol) was dissolved in toluene (2 ml) and THF (8 ml) and hydrogenated under atmospheric pressure in the presence of Raney-Ni at rt. After the hydrogen uptake was complete, the catalyst was filtered off and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (5 ml) and reprecipitated with hexane (15 ml) to give the pure diamine **17** as a yellow powder, yield; 0.05 g, 50%; mp. 278–280 °C. FD-MS, $(M^+ + H)$ $m/z = 914.4$.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.52, 0.71 (2t, 12H, $^3J = 7.4$ Hz, -CH_2–CH_3), 1.17–1.24 (m, 8H, -CH_2–CH_2–CH_3), 3.12 (bt, 4H, O–CH_2-), 3.20 (bs, 4H, O–CH_2-), 3.64, 3.72 (2d, 8H,

^2J = 15.6 Hz, Ar–CH_2–Ar), 4.33 (bs, 4H, -NH_2), 6.28, 7.07 (2s, 8H, ArH), 7.88, 7.91 (2bs, 8H, Phth-H).

Mono- and di-protection by Boc; calix[4]arenes 19 and 20 (*1,3-alternate*)

A solution of Boc-anhydride (0.59 g, 2.7 mmol) in dichloromethane (10 ml) was added dropwise to a stirred solution of the tetraamine **18** (1.0 g, 1.5 mmol) in dichloromethane (100 ml). After 24 h of stirring at ambient temperature the solvent was evaporated. The mono- and di-Boc protected compounds **19** and **20** were isolated by column chromatography (EtOAc–hexane = 1 : 1) in 23% (0.25 g), 58% (0.65 g) respectively.

Mono-Boc derivative **19**: pink powder, mp 138–140 °C (Found: C 71.34, H 7.90, N 6.53 $C_{44}H_{58}N_4O_6$ requires C 71.52, H 7.91, N 7.58)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87–1.24 (m, 12H, -CH_2–CH_3), 1.50 (s, 9H, t-Bu), 1.86 (m, 8H, -CH_2–CH_2–CH_3), 3.11–3.6 (m, 22H, Ar–CH_2–Ar, O–CH_2-, Ar–NH_2), 6.34, 6.44 (2s, 4H, ArH), 6.98 (bs, 4H, ArH).

Di-Boc derivative **20**: yellow powder, mp 251 °C (Found: C 70.21, H 7.71, N 6.56 $C_{49}H_{66}N_4O_8$ requires C 70.14, H 7.93, N 6.68)

^{1}H NMR (400 MHz, C_6D_6) δ 0.99 (t, 12H, ^3J = 7.3 Hz, -CH_2–CH_3), 1.66 (s, 18H, t-Bu), 1.71 (m, 8H, -CH_2–CH_2–CH_3), 2.94 (bs, 4H, -NH_2), 3.42–3.55 (m, 16H, Ar–CH_2–Ar, O–CH_2-), 6.45, 6.47 (2d, 4H, ^4J = 2.9 Hz, ArH), 7.23, 7.27 (2d, 4H, ^4J = 2.4 Hz, ArH), 7.5 (bs, 2H, -NH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.29 (bm, 12H, -CH_2–CH_3), 1.48 (s, 18H, t-Bu), 1.87 (m, 8H, -CH_2–CH_2–CH_3), 3.28 (s, 2H, Ar–CH_2–Ar), 3.32 (d, 2H, ^2J = 12.5 Hz, Ar–CH_2–Ar), 3.37 (d, 2H, ^2J = 13.0 Hz, Ar–CH_2–Ar), 3.41 (s, 2H, Ar–CH_2–Ar), 3.57–3.65 (m, 12H, O–CH_2-, -NH_2), 6.44, 6.93, 6.95 (3s, 4/2/2H, ArH), 7.82 (bs, 2H, -NH).

Tri- and tetra protection by Boc; calix[4]arenes 22 and 23 (*1,3-alternate*)

The tri-Boc compound was prepared in the same way, starting from a solution of tetraamino-calixarene **18** (1.0 g, 1.5 mmol) in CH_2Cl_2 (100 ml) and Boc-anhydride (0.948 g, 4.35 mmol). Isolation and purification by column chromatography (EtOAc–hexane = 1 : 1) gave pure tri-Boc derivative **22** (0.8 g, 60%). mp 242–244 °C (Found: C 66.90, H 7.68, N 5.05 $C_{54}H_{74}N_4O_{10}$·0.5 CH_2Cl_2 requires C 66.68, H 7.70, N 5.71)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98, 1.12 (2t, 12H, ^3J = 7.3 Hz. -CH_2–CH_3), 1.50, 1.52 (2s, 18/9H, t-Bu), 1.59, 1.73 (2m, 4H, -CH_2–CH_2–CH_3), 1.91 (m, 4H, -CH_2–CH_2–CH_3), 3.33–3.69 (m, 18H, O–CH_2, Ar–CH_2–Ar, NH_2), 6.14, 6.56 (2s, 1/2H, NH), 6.95, 6.98 (2s, 6/2H, ArH).

The tetra-Boc derivative **23** is formed as side product, but can be obtained in nearly quantitative yield, using 20–30% excess of Boc-anhydride. *E.g.*, starting from a solution of tetraamino-calixarene **18** (1.0 g, 1.5 mmol) in CH_2Cl_2 (100 ml), pure tetra-Boc compound **23** (1.35 g, 90%) was obtained after purification by reprecipitation from $CHCl_3$–hexane (1 : 5) as a white powder, mp 268–270 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, 12H, ^3J = 7.3 Hz, -CH_2–CH_3), 1.44–1.53 (m, 8H, -CH_2–CH_2–CH_3), 1.50 (s, 36H, t-Bu) 3.41 (t, 8H, ^3J = 7.3 Hz, -CH_2–CH_2–CH_3), 3.60 (s, 8H, Ar–CH_2–Ar), 6.18 (s, 4H, -NH), 6.99 (s, 8H, ArH).

5,11-Bis-*t*-butyloxycarbonylamino-17,23-bis-acetamido-25,26,27,28-tetrapropoxy-calix[4]arene 24 (*1,3-alternate*)

Di-Boc compound **20** (70 mg, 0.084 mmol) was stirred in acetic anhydride (5 ml) with a few drops of triethylamine at rt. After 12 h the reaction mixture was poured on ice and the desired diacetamide precipitated as white solid to give 79 mg of pure **24** (85% yield). mp 262–263 °C. (Found: C 68.58, H 7.86, N 5.71. $C_{54}H_{72}N_4O_{10}$·0.5H_2O requires C 68.55, H 7.78, N 5.92)

^{1}H NMR (300 MHz, DMSO) δ 0.62 (bs, 12H, -CH_2–CH_3), 1.26 (bm, 26H, t-Bu, -CH_2–CH_2–CH_3), 1.97 (s, 6H, -CO–CH_3), 3.06 (bt, 8H, O–CH_2-), 3.58 (bs, 8H, Ar–CH_2–Ar), 7.16, 7.25 (2s, 8H, ArH), 8.93, 9.51 (2s, 4H, -NH-).

5,11-Bis-*p*-nitrobenzoylamino-17,23-bis-acetamido-25,26,27,28-tetrapropoxy-calix[4]arene 25 (*1,3-alternate*)

To a stirred solution of **24** (67 mg, 0.07 mmol) in CH_2Cl_2 (7 ml) was added TFA (7 ml). The reaction mixture was stirred at rt for 2 h, then diluted with toluene (15 ml). The solvents were evaporated, the remaining yellow oil was dissolved in chloroform (15 ml) and triethylamine (0.05 ml, 0.35 mmol) and *p*-nitrobenzoyl chloride (27 mg, 0.15 mmol) were added with stirring. After 12 h the solvent was removed under reduced pressure. The dry residue was purified by column chromatography (chloroform) to obtain **25** as an orange powder (50 mg, 70% yield). mp 223 °C. FD-MS, (M^+ + H) m/z = 1036.3.

^{1}H NMR (300 MHz, DMSO) δ 0.64 (m, 12H, -CH_2–CH_3), 1.31 (bm, 8H, -CH_2–CH_2–CH_3), 1.95 (s, 6H, -CO–CH_3), 3.2 (bt, 8H, O–CH_2-), 3.66 (m, 8H, Ar–CH_2–Ar), 7.37, 7.57 (2d, 8H, ^4J = 3.7, 3.3 Hz, ArH), 8.11, 8.37 (2d, 8H, ^4J = 8.8, 8.4 Hz, ArH), 9.55, 10.26 (2s, 4H, -NH-).

5,17-Di-*t*-butyl-11,23-dinitro-26,28-diphthalimidoethoxy-calix[4]arene 26 (*n* = 2)

Nitric acid (65%, 7.5 ml) was added with stirring to a cold (0 °C) solution of **2** (n = 2) (2.5 g, 2.5 mmol) in dry CH_2Cl_2 (75 ml). After 10 min the color changed from black-indigo to yellow and the reaction was complete. Water was added (100 ml) and the mixture was stirred for 30 min. After phase separation the organic phase was washed with water (3 × 100 ml) until a neutral pH was reached, dried ($MgSO_4$) and the solvent was evaporated. The residue was dissolved in chloroform (10 ml) and the pure product was precipitated with methanol (25 ml) as yellow powder (1.6 g, 67%), m.p 298–300 °C.

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.9 (s, 18H, t-Bu), 3.41, 4.15 (2d, 8H, ^2J = 13.2 Hz, Ar–CH_2–Ar), 4.29 (t, 4H, ^3J = 6.2 Hz, -CH_2–N), 4.47 (t, 4H, ^3J = 6.3 Hz, O–CH_2-), 6.73 (s, 4H, ArH), 7.69–7.93 (m, 8H, Phth-H), 7.98 (s, 4H, ArH), 8.20 (s, 2H, OH).

5,17-Di-*t*-butyl-11,23-dinitro-26,28-diphthalimidoproxy-calix[4]arene 26 (*n* = 3)

Reaction and work up as described above. 2.0 g (1.95 mmol) **2** (n = 3) finally gave 1.5 g, (75%) of pure product as yellow powder; m.p 253.5–254 °C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 18H, t-Bu), 2.45 (m, 4H, -CH_2–CH_2–CH_2), 3.48 (d, 4H ^2J = 13.8 Hz, Ar–CH_2–Ar), 4.11 (m, 8H, O–CH_2-, -CH_2–N), 4.30 (d, 4H, ^2J = 13.8 Hz, Ar–CH_2–Ar), 6.88 (s, 4H, ArH), 7.62–7.78 (m, 8H, Phth-H), 8.04 (s, 4H, ArH), 8.94 (s, 2H, -OH).

5,17-Di-*t*-butyl-11,23-dinitro-26,28-diphthalimidobutoxy-calix[4]arene 26 (*n* = 4)

Reaction and work up as described above. 3.0 g (2.85 mmol) **2** (n = 4) finally gave 2.0 g, (70%) of pure product as yellow powder; m.p 229–231 °C; (Found: C 68.82, H 6.30, N 5.35 $C_{60}H_{60}N_4O_{10}$·H_2O requires C 68.82, H 5.97, N 5.35).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 18H, t-Bu), 2.10 (bs, 8H, -CH_2–CH_2–CH_2), 3.44 (d, 4H ^2J = 13.2 Hz, Ar-CH_2–Ar), 3.89 (bt, 4H, -CH_2–N), 4.06 (bt, 4H, O–CH_2-) 4.21 (d, 4H, ^2J = 13.2 Hz, Ar-CH_2–Ar), 6.88 (s, 4H, ArH), 7.66–7.82 (m, 8H, Phth-H), 8.00 (s, 4H, ArH), 9.07 (s, 2H, OH).

5,17-Di-*t*-butyl-11,23-dinitro-26,28-diphthalimidopropoxy-25,27-diallyloxy-calix[4]arene 27 (*n* = 3) (*1,3-alternate, partial cone, cone*)

A stirred suspension of dinitro calixarene **26** (n = 3) (0.5 g, 0.5 mmol) and Cs_2CO_3 (1.3 g, 4 mmol) in dry DMF (12.5 ml) was heated to 40 °C under nitrogen. After 1 h allylbromide

(0.34 ml, 4 mmol) was added and the reaction mixture was kept under these conditions for 7 days. The DMF was removed at reduced pressure and the residue was treated with chloroform (15 ml) and water (50 ml). The organic phase was washed twice with water (2 × 50 ml), dried ($MgSO_4$) and evaporated. TLC analysis of the residue showed the presence of two isomers (*1,3-alt* and *paco*). After column chromatography (dichloromethane–ethylacetate, 95 : 5) three different fractions were isolated which were identified as *1,3-alternate, partial cone* and *cone* conformers. Recrystallization from chloroform–methanol (10 ml, 1:4) gave **27** ($n = 3$, *1,3-alt*) as colorless crystals (0.1 g, 19%), **27** ($n = 3$, *paco*) as yellow powder (0.1 g, 19%) and **27a** ($n = 3$, *cone*) as colorless crystals (10 mg, 2%).

27 ($n = 3$, *1,3-alt*). mp 230–232 °C

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 18H, *t*-Bu), 1.88 (m, 4H, -CH_2–CH_2–CH_2-), 3.69 (m, 8H, O–CH_2-, -CH_2–N), 3.69, 3.81 (2d, 8H, ^2J = 15.6 Hz, Ar–CH_2–Ar), 3.97 (d, 4H, ^2J = 9.7 Hz, CH_2=CH–CH_2–O-), 5.03 (m, 4H, CH_2=CH-), 5.70 (m, 2H, CH_2=C*H*-), 6.95 (s, 4H, Ar*H*), 7.74 (m, 8H, Phth-*H*), 7.99 (s, 4H, Ar*H*).

27 ($n = 3$, *paco*). mp 191–192 °C

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.00, 1.24 (2s, 18H, *t*-Bu), 2.21 (m, 4H, -CH_2–CH_2–CH_2-), 3.19, 3.68 (2d, 4H, ^2J = 12.9, 13.7 Hz, Ar–CH_2–Ar), 3.88 (m, 8H, O–CH_2-, -CH_2–N), 3.90, 4.07 (2d, 4H, ^2J = 13.3, 12.9 Hz, Ar–CH_2–Ar), 4.19, 4.24 (2d, 4H, ^2J = 6.3 Hz, -O–CH_2–CH=CH_2), 4.89, 5.28 (2m, 4H, CH_2=CH-), 5.54, 6.02 (2m, 2H, CH_2=C*H*-), 6.35, 6.87 (2d, 4H, ^4J = 1.9 Hz, Ar*H*), 7.83 (m, 8H, Phth-*H*), 8.05, 8.35 (2s, 4H, Ar*H*).

27 ($n = 3$, *cone*). mp 270–272 °C

^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.28 (s, 18H, *t*-Bu), 2.28 (m, 4H, -CH_2–CH_2–CH_2-), 3.19 (d, 4H, ^2J = 13.6 Hz, Ar–CH_2–Ar), 3.81 (t, 4H, ^3J = 7.3 Hz, -CH_2–N), 4.07 (t, 4H, ^3J = 7.5 Hz, -CH_2–O-), 4.38 (d, 4H, ^2J = 5.9 Hz, -O–CH_2–CH=CH_2), 4.41 (d, 4H, ^2J = 13.6 Hz, Ar–CH_2–Ar), 5.11 (m, 4H, CH_2=CH-), 6.13 (m, 2H, CH_2=C*H*-), 7.03, 7.12 (2s, 8H, Ar*H*), 7.78 (m, 8H, Phth-*H*).

5,17-Di-*t*-butyl-11,23-dinitro-26,28-diphthalimidobutyloxy-25, 27-diallyloxy-calix[4]arene 27 ($n = 4$) (*1,3-alternate*)

Compound **27** ($n = 4$) was obtained in an analogous way starting from the dinitro compound **26** ($n = 4$) (1.6 g, 1.55 mmol) in dry DMF (40 ml) and Cs_2CO_3 (5 g, 15.5 mmol). The desired *1,3-alternate* isomer of **27** ($n = 4$) was isolated by crystallization from chloroform–methanol (25 ml, 1 : 4) as colorless crystals (0.9 g, 53%). mp 199 °C (Found: C 71.30, H 6.41, N 4.96. $C_{66}H_{68}N_4O_{12}$ requires C 71.46, H 6.18, N 5.05).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 18H, *t*-Bu), 1.55, 1.72 (2m, 8H, -CH_2–CH_2–CH_2-), 3.69 (m, 8H, O–CH_2-, -CH_2–N), 3.62, 3.66 (2d, 8H, J = 15.6 Hz, Ar–CH_2–Ar), 3.97 (d, 4H, J = 5.1 Hz, CH_2=CH–CH_2–O-), 5.12 (m, 4H, CH_2=CH-), 5.74 (m, 2H, CH_2=C*H*-), 6.95 (s, 4H, Ar*H*), 7.67 (m, 8H, Phth-*H*), 7.99 (s, 4H, Ar*H*).

5,17-Di-*t*-butyl-11,23-diamino-26,28-diphthalimidopropoxy-25, 27-dipropoxy-calix[4]arene 28 ($n = 3$) (*1,3-alternate*)

A clear solution of the dinitrocompound **27** ($n = 3$) (0.6 g, 0.55 mmol) in THF (20 ml) was hydrogenated under atmospheric pressure in the presence of Raney-Ni at rt. After the hydrogen uptake was complete the catalyst was filtered off and the solvent was evaporated. The dry residue was dissolved in chloroform (5 ml) and the diamine was reprecipitated with hexane (10 ml) as a yellow powder (0.4 g, 80%). mp 133 °C. FD-MS, ($M^+ + H$) m/z = 1026.3.

^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.58 (t, 6H, ^3J = 7.3 Hz, CH_3–CH_2-), 1.04–1.18 (m, 22H, CH_3–CH_2–CH_2-, *t*–Bu), 1.55 (m, 4H, -CH_2–CH_2–CH_2-), 3.18 (bt, 4H, ^3J = 6.8 Hz, -CH_2–N), 3.33–3.3.45 (bm, 12H, O–CH_2-, -NH_2), 3.57, 3.68 (2d, 8H, ^2J = 15.5 Hz Ar–CH_2–Ar), 6.38 (s, 4H, Ar*H*), 6.88 (s, 4H, Ar*H*), 7.59–7.76 (bm, 8H, Phth-*H*)

5,17-Di-*t*-butyl-11,23-diamino-26,28-diphthalimidobutoxy-25, 27-dipropoxy-calix[4]arene 28 ($n = 4$) (*1,3-alternate*)

The diamine **28** ($n = 4$) was obtained as described above for the analogous compound **28** ($n = 3$) starting from a clear solution of **27** ($n = 4$) (0.2 g, 0.18 mmol) in THF (15 ml). Analogous work up gave a beige powder (0.16 g, 90%); mp 129 °C.

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.65 (t, 6H, ^3J = 7.7 Hz, CH_3–CH_2-), 1.03–1.46 (m, 26H, -CH_2-, *t*-Bu), 1.81 (m, 4H, -CH_2-), 3.18–3.69 (m, 24H, -CH_2–N, O–CH_2-, -NH_2, Ar–CH_2–Ar), 6.40, 6.92 (2s, 8H, Ar*H*), 7.67–7.80 (bm, 8H, Phth-*H*).

5,17-Di-*t*-butyl-11,23-dinitro-26,28-diaminopropoxy-25, 27-dipropoxy-calix[4]arene 30 ($n = 3$) (*1,3-alternate*)

A solution of **27** ($n = 3$) (0.58 g, 0.53 mmol) in EtOH (60 ml) was refluxed with hydrazine hydrate (4.5 ml) for 3 h. Then solvent was evaporated til dry and the residue was dissolved in CH_2Cl_2 (10 ml) and washed with water (2 × 20 ml). The organic phase was dried ($MgSO_4$) and evaporated again. The resulting powder was dissolved in CH_2Cl_2 (5 ml) and the desired diamine was reprecipitated with hexane (10 ml) as a yellow powder (0.25 g, 57%), mp 155–157 °C. (Found: C 67.99, H 7.48, N 6.29. $C_{48}H_{66}N_4O_8 \cdot 0.25CHCl_3$ requires C 67.63, H 7.79, N 6.54) FD-MS, (M^+) m/z = 825.05.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.79 (t, 6H, ^3J = 7.3 Hz, -CH_2–CH_3), 1.23 (s, 18H, *t*-Bu) 1.39–1.58 (m, 8H, -CH_2-), 2.64 (t, 4H,^3J = 7.0 Hz -CH_2–NH_2), 3.50 (t, 4H, ^3J = 7.3 Hz, O–CH_2-) 3.66–3.73 (m, 8H, O–CH_2-, Ar–CH_2–Ar), 3.84 (d, 4H, ^2J = 15.0 Hz Ar–CH_2–Ar), 6.89, 7.98 (2s, 8H, Ar*H*).

5,17,11,23-Tetra-*t*-butyl-25,27,26,28-tetra-phthalimidopropoxy-calix[4]arene 32 ($n = m = 3$) (*1,3-alternate*)

(a) Starting from *t*-butyl-calix[4]arene 1. A suspension of **1** (5 g, 7.7 mmol) in THF (400 ml) and Cs_2CO_3 (25 g, 77 mmol) was stirred at rt for 1 h under nitrogen. A solution of *N*-(3-bromopropyl)-phthalimide (20.6 g, 77 mmol) in THF (15 ml) was added and the mixture was refluxed under nitrogen for 7 days. The solvent was removed under reduced pressure and the dry residue was dissolved in chloroform (25 ml) and washed with water (3 × 100 ml). The organic phase was dried ($MgSO_4$) and the solvent was evaporated. The pure *1,3-alternate* isomer was obtained as white crystals (3.45 g, 33%) by two-fold recrystallization from dichloromethane–methanol (30 ml, 1 : 5). The *1,2-alternate* isomer was found in the mother liquors and was isolated as white powder by precipitation with methanol (1.8 g, 22%). The filtrate was evaporated to dryness and the white residue was dissolved in chloroform and methanol (40 ml, 1 : 1). The *partial cone* isomer of **32** precipitated as white powder upon slow evaporation of the solvents (3.2 g, 31%).

32 *(*n = m = *3,* 1,3-alt*).* mp 255–257 °C (Found: C 75.60, H 7.02, N 4.05. $C_{88}H_{92}N_4O_{12}$ requires C 75.60, H 6.63, N 4.01)

^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.15 (s, 36H, *t*-Bu), 1.67 (m, 8H, -CH_2–CH_2–CH_2-), 3.44 (t, 8H, ^3J = 7.8 Hz, -CH_2–N), 3.62 (t, 8H, ^3J = 6.8 Hz, -CH_2–O), 3.67 (s, 8H, Ar–CH_2–Ar), 6.92 (s, 8H, Ar*H*), 7.65–7.82 (m, 16H, Phth-*H*).

32 *(*n = m = *3,* 1,2-alt*).* mp 197–199 °C

^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.05 (m, 4H, -CH_2–CH_2–CH_2-) 1.26 (s, 36H, *t*-Bu), 1.60 (m, 4H, -CH_2–CH_2–CH_2-), 3.00 (d, 2H, ^2J = 12.1 Hz, Ar–CH_2–Ar), 3.54–3.87 (m, 16H, -CH_2–N, -CH_2–O), 3.88 (s, 4H, Ar–CH_2–Ar), 4.07 (d, 2H, ^2J = 12.1 Hz, Ar–CH_2–Ar), 7.05, 7.09 (2d, 8H, ^2J = 2.2 Hz, Ar*H*), 7.51–7.66 (m, 16H, Phth-*H*).

32 *(*n = m = *3,* paco*).* mp 278–280 °C

^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.95, 1.25, 1.28 (3s, 18/9/9H, *t*-Bu), 1.87, 2.09, 2.22 (3m, 2/2/4H, -CH_2–CH_2–CH_2-), 2.99

(d, 2H, ^2J = 8.5 Hz Ar–CH_2–Ar), 3.54–3.87(m, 20H, -CH_2–N, -CH_2–O, Ar–CH_2–Ar), 4.01 (d, 2H, ^2J = 8.3 Hz, Ar–CH_2–Ar), 6.53, 6.78 (2d, 4H, ^4J = 1.4, 2.5 Hz, Ar*H*), 7.02, 7.17 (2s, 4H, Ar*H*), 7.52–7.71 (m, 16H, Phth-*H*).

b) Starting from the *syn*-diether 2 ($n = 3$). A suspension of **2** ($n = 3$) (4.0 g, 3.9 mmol) and Cs_2CO_3 (10 g, 31.2 mmol) in dry DMF (50 ml) was heated to 50 °C under argon for 1 h. A solution of *N*-(3-bromopropyl)-phthalimide (8.3 g, 31.2 mmol) in DMF (10 ml) was added and the heating was continued for 5 days under argon. The solvent was removed under reduced pressure and the white residue was dissolved in chloroform. The solution was washed with water (2 × 75ml), dried ($MgSO_4$), concentrated and the product was precipitated with methanol to give 2.0 g (36%) of **32** ($n = m = 3$, *1,3-alt*) as a white powder. The filtrate was contained mainly in the *partial cone* isomer of **32** (tlc) which was not isolated in this case.

5,17,11,23-Tetra-*t*-butyl-25,27-diphthalimidobutyloxy-26,28-diphthalimidopropoxy-calix[4]arene 32 ($n = 4$, $m = 3$) (*1,3-alternate*)

Compound **32** ($n = 4$, $m = 3$) was obtained as described for **32** ($n = m = 3$), starting from **2** ($n = 4$) (0.5 g, 0.47 mmol), *N*-(3-bromopropyl)-phthalimide (1,0 g, 3.76 mmol) and Cs_2CO_3 (1.2 g, 3.76 mmol) in dry DMF (15 ml). The desired *1,3-alternate* isomer of **32** ($n = 4$, $m = 3$) was isolated by crystallization from chloroform–methanol (20 ml, 1 : 4) as white powder (0.4 g, 60%) mp 204 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.18, 1.19 (2s, 36H, *t*-Bu), 1.32, 1.71 (2m, 16H, -CH_2–CH_2–CH_2-), 3.38–3.66 (m, 20H, O–CH_2-, -CH_2–N Ar–CH_2–Ar), 3.70 (d, 4H, ^2J = 16.53 Hz Ar–CH_2–Ar), 6.91, 6.96 (2s, 8H, Ar*H*), 7.66–7.83 (m, 16H, Phth-*H*).

^{1}H-NMR (400 MHz, C_6D_6) δ 1.39, 1.41 (2s, 36H, *t*-Bu), 1.59, 1.86 (2m, 8H, -CH_2–CH_2–CH_2-), 3.38 (t, 4H ^3J = 7.4 Hz, -CH_2–N), 3.57–3.66 (m, 12H, O–CH_2-, -CH_2–N), 3.87, 3.92 (2d, 8H, ^2J = 15.6 Hz Ar–CH_2–Ar), 6.86–6.88 (m, 8H, Phth-*H*), 7.11, 7.26 (2s, 8H, Ar*H*), 7.46–7.49 (m, 8H, Phth-*H*).

5,11,17,23-Tetra-nitro-25,26,27,28-tetraphthalimidopropoxy-calix[4]arene 33 (*1,3-alternate*)

Glacial acetic acid (13.5 ml) and fuming nitric acid (8 ml) were added to a vigorously stirred suspension of tetraphthalimido compound **32** ($n = m = 3$) in dry CH_2Cl_2 (50 ml) at rt. The reaction was complete when the color of the solution had changed from black-indigo to yellow (about 12 h). Then water (100 ml) was added and the mixture was stirred for 30 min. The organic phase was washed several times with water (3 × 100 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by slow crystallization from CH_2Cl_2–CH_3OH (40 ml, 1 : 2) which gave yellow crystals (1.12 g, 71%). mp. 387–389 °C (Found: C 62.85, H 4.29, N 8.16. $C_{72}H_{56}N_8O_{20}\cdot H_2O$ requires C 63.06, H 4.26, N 8.17).

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.26 (m, 8H, -CH_2–CH_2–CH_2-), 3.84 (s, 8H, Ar–CH_2–Ar), 3.95 (m, 16H, -CH_2–N, O–CH_2-), 7.68–7.86 (m, 16H, Phth-*H*), 8.06 (s, 8H, Ar*H*).

5,11,17,23-Tetra-acetamido-25,26,27,28-tetraphthalimidopropoxy-calix[4]arene 34 (*1,3-alternate*)

A clear solution of the tetranitro compound **33** ($n = m = 3$) (0.75 g, 0.55 mmol) in THF–DMF (50 ml, 1 : 1) at 50 °C was hydrogenated under atmospheric pressure in the presence of Raney-Ni. After the hydrogen uptake was complete the catalyst was filtered off and the solvent was evaporated. The dry residue was dissolved in chloroform (10 ml) and the tetraamine **34** (R = H) was reprecipitated with hexane (20 ml) as pale yellow powder (0.53 g, 85%) which shows a broad ^{1}H-NMR spectrum in $CDCl_3$ as well as in DMSO. Therefore it was characterized as tetraacetamide **34** (R = $COCH_3$). The solution of the tetra amine (0.2 g, 0.16 mmol) in acetic anhydride (5ml) and a few drops of triethylamine was stirred for 12 h at rt. The reaction mixture was poured in ice to form a sticky brown mass which was dissolved in chloroform (10 ml). After separation the organic phase was dried and the solvent was evaporated. The tetra-acetamide **34** (R = $COCH_3$) was obtained after column chromatography using ($CHCl_3$–MeOH; 9.8 : 0.2) as eluent as a yellow powder (0.14 g, 64%). m.p 335 °C. FD-MS, ($M^+ + H$) m/z = 1403.5.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (bm, 20H, CH_2–CH_2–CH_2-, -CH_3), 3.45 (s, 8H, Ar–CH_2–Ar), 3.79 (t, 8H, ^3J = 4.7 Hz, O–CH_2-), 4.24 (t, 8H, ^3J = 7.8 Hz, -CH_2–N), 7.36 (s, 8H, Ar*H*), 7.70–7.81 (m, 16H, Phth-*H*), 8.09 (s, 4H, N*H*).

5,11,17,23-Tetra-nitro-25,26,27,28-tetra-aminopropoxy-calix[4]arene 35 (*1,3-alternate*)

A suspension of **33** (1.12 g, 0.83 mmol) in EtOH (60 ml) was refluxed with hydrazine hydrate (20 ml) for 4 h (the solution became clear). After the solvent was evaporated in *vacuo* til dry the residue was dissolved in CH_2Cl_2 (15 ml) and washed twice with water (2 × 30 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed in *vacuo.* The residue was dissolved in chloroform (10 ml) and the tetraamine **35** was reprecipitated with hexane to give a yellow powder (0.39 g, 57%). mp 249–251 °C. (Found: C 56.34, H 6.30, N 12.41 $C_{40}H_{50}N_8O_{12}\cdot H_2O$ requires C 56.33, H 6.15, N 13.14). FD-MS, ($M^+ + H$) m/z = 835.2

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.85 (m, 16H, -NH_2, -CH_2–CH_2–CH_2-), 2.79 (t, 8H, ^3J = 6.3 Hz, -CH_2–N), 3.53 (s, 8H, Ar–CH_2–Ar), 3.78 (t, 8H, ^3J = 6.5 Hz, O–CH_2-), 7.78 (s, 8H, Ar*H*).

5,11,17,23-Tetra-amino-25,26,27,28-tetra-aminopropoxy-calix[4]arene 36 (*1,3-alternate*)

A suspension of **33** (0.4 g, 0.4 mmol) and Pd/C (100 mg) in EtOH (30 ml) was refluxed with hydrazine hydrate (8 ml) for 4 h. Then, the solvent was evaporated under reduced pressure the residue was dissolved in $CHCl_3$ (10 ml) and washed twice with water (2 × 25 ml). The organic solution was dried ($MgSO_4$) and the solvent was removed in *vacuo.* The formed powder was dissolved in chloroform (5 ml) and the octaamine was obtained as bright yellow powder by reprecipitation with hexane (0.39 g, 57%). mp 259 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98–2.06 (m, 8H, -CH_2–CH_2–CH_2-), 3.00 (t, 8H, ^3J = 6.6 Hz, -CH_2–N), 3.73 (s, 8H, Ar–CH_2–Ar), 3.98 (t, 8H, ^3J = 6.6 Hz, O–CH_2-), 8.00 (s, 8H, Ar*H*).

Crystallographic data

Data were collected on a STOE-IPDS-II two-circle diffractometer employing graphite-monochromated Mo Kα radiation (0.71073 Å). Data reduction was performed with the X-Area software.[42] For **27** (*1,3-alt*, $n = 4$) an empirical absorption correction was performed using the MULABS[43] option in PLATON.[44] Structures were solved by direct methods with SHELXS-90[45] and refined by full-matrix least-squares techniques with SHELXL-97.[46] All non-H atoms were refined with anisotropic displacement parameters. Hydrogens were included at calculated positions and allowed to ride on their parent atoms. Table 2 lists the most important parameters of the X-ray analysis.

One of the *tert*-butyl groups of **27** (*cone*, $n = 3$) is disordered over two positions with a ratio of the site occupation factors of 0.471(8) : 0.529(8). For **11** (*paco*) the tert-butyl groups are disordered over two positions with a ratio of the site occupation factors of 0.461(3) : 0.539(3) and 0.483(6) : 0.517(6), respectively and also, one of the methylene bridges is disordered over two positions with a ratio of the site occupation factors of 0.319(6) : 0.681(6). Residual electron densities: **27** (*1,3-alt*, $n = 3$) 1.89 e Å^{-3} at 0.5000, 0.1015, 0.2500, **27** (*cone*, $n = 3$) 1.02 *e* Å^{-3} at 0.4964, 0.2884, 0.0518, **27** (*1,3-alt*, $n = 4$) 3.00 e Å^{-3} at 0.8438, 0.0734, 0.2070. Crystallographic data in

Table 2 Summary of crystal data

Compound	**27** (*1,3-alt*, $n = 3$)	**27** (*cone*, $n = 3$)	**27** (*1,3-alt*, $n = 3$)	**11** (*paco*)
Formula	$C_{64}H_{64}N_4O_{12}$	$C_{64}H_{64}N_4O_{12}$	$C_{67}H_{70}Cl_2N_4O_{12}$	$C_{48}H_{58}N_2O_8$
M_w	1081.19	1081.19	1194.17	790.96
Crystal system	monoclinic	triclinic	triclinic	triclinic
Space group	$C2/c$ (No. 15)	$P\bar{1}$ (No. 2)	$P\bar{1}$ (No. 2)	$P\bar{1}$ (No. 2)
T/K	173	173	173	100
a/Å	16.7651(15)	14.1953(7)	13.4904(6)	10.3423(7)
b/Å	29.395(3)	14.6587(7)	14.1373(7)	13.1610(9)
c/Å	24.507(2)	15.3671(7)	17.7409(8)	16.5605(7)
α/°			83.459(4)	101.868(5)
β/°	95.993(7)	92.666(4)	69.464(4)	96.988(5)
γ/°			76.454(4)	91.968(5)
V/Å	12011.3(19)	2923.2(2)	3078.5(2)	2185.5(3)
Z	8	2	2	2
μ/mm^{-1}	0.083	0.085	0.171	0.081
Unique refins. Measured	61211	62074	83961	31174
Unique refins.[$I > 2\sigma(I)$]	11107	17077	14584	9295
$wR(F^2)$	0.3033	0.1492	0.3124	0.1077

CIF format have been deposited with the Cambridge Crystallographic Data Centre: CCDC reference numbers 249854–249857. See http://www.rsc.org/suppdata/ob/b4/b414173c/ for crystallographic data in .cif or other electronic format.

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References

1 For reviews on calixarenes see:(*a*) *Calixarenes 2001*, ed. V. Böhmer, Z. Asfari, J. Harrowfield, J. Vicens, Kluwer Academic Publishers, Dordrecht, 2001.; (*b*) C. D. Gutsche in *Calixarenes Revisited*, ed. J. F. Stoddart, The Royal Society of Chemistry, Cambridge, 1998.; (*c*) V. Böhmer, *Angew. Chem.*, 1995, **107**, 785–818; V. Böhmer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 713–745.
2 A. Casnati, F. Bonetti, F. Sansone, F. F. Ugozzoli and R. Ungaro, *Collect. Czech. Chem. Commun.*, 2004, **69**, 1063–1079.
3 (*a*) J. Y. Kim, Y. H. Kim, J.-I. Choe and S. K. Chang, *Bull. Korean Chem. Soc.*, 2001, **22**, 635–637; (*b*) M. O. Vysotsky, V. Böhmer, F. Würthner, C.-C. You and K. Rissanen, *Org. Lett.*, 2002, **4**, 2901–2904.
4 S. J. Kim, M. G. Jo, J. Y. Lee and B. H. Kim, *Org. Lett.*, 2004, **6**, 1963–1966.
5 J.-A. Pérez-Adelmar, H. Abraham, C. Sánchez, K. Rissanen, P. Prados and J. de Mendoza, *Angew. Chem., Int. Ed. Engl.*, 1996, **9**, 1009–1011.
6 P. Wang, M. Saadioui, C. Schmidt, V. Böhmer, V. Host, J. F. Desreux and J.-F. Dozol, *Tetrahedron*, 2004, **60**, 2509–2515.
7 S. Shinkai, Y. Shirahama, T. Tsubaki and O. Manabe, *J. Am. Chem. Soc*, 1989, **111**, 5477–5478.
8 CMPO = carbamoylmethyl phosphine oxide; the (*N*,*N*-diisobutyl carbamoylethyl) octylphenyl phosphine oxide is used in the TRUEX process: E. P. Horwitz, D. G. Kalina, H. Diamond, D. G. Vandegrift and W. W. Schultz, *Solvent Extr. Ion Exch.*, 1985, **3**, 75.
9 (*a*) F. Arnaud-Neu, V. Böhmer, J.-F. Dozol, C. Grüttner, R. A. Jakobi, D. Kraft, O. Mauprivez, H. Rouquette, M.-J. Schwing Weill, N. Simon and W. Vogt, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1175–1182; (*b*) C. Schmidt, M. Saadioui, V. Böhmer, V. Host, M.-R. Spirlet, J. F. Desreux, F. Brisach, F. Arnaud-Neu and J.-F. Dozol, *Org. Biomol. Chem.*, 2003, **1**, 4089–4096.
10 S. Barboso, A. Garcia Carrera, S. E. Matthews, F. Arnaud-Neu, V. Böhmer, J. F. Dozol, H. Rouquette and M.-J. Schwing-Weill, *Perkin Trans. 2*, 1999, 719–723.
11 (*a*) J. Scheerder, M. Fochi, J. F. J. Engbersen and D. N. Reinhoudt, *J. Org. Chem.*, 1994, **59**, 7815–7820; (*b*) K. C. Nam, S. O. Kang, H. S. Jeong and S. Jeon, *Tetrahedron Lett.*, 1999, **40**, 7343–7346; (*c*) A. Casnati, M. Fochi, P. Minari, A. Pochini, M. Reggiani, R. Ungaro and D. N. Reinhoudt, *Gazz. Chim. Ital.*, 1996, **126**, 99–106.
12 P. D. Beer, *Chem. Commun.*, 1996, **6**, 689–696.
13 J. Rebek Jr., *Chem. Commun.*, 2000, **8**, 637–643.
14 (*a*) A. Rincon, M. P. Prados and J. de Mendoza, *J. Am. Chem. Soc.*, 2001, **123**, 3493–3498; (*b*) F. Sansone, L. Baldini, A. Casnati, E. Chierici, G. Faimani, F. Ugozzoli and R. Ungaro, *J. Am. Chem. Soc.*, 2004, **126**, 6204–6205.
15 J. Budka, P. Lothak, V. Michlova and I. Stibor, *Tetrahedron Lett.*, 2001, **42**, 1583–1586.
16 J. Scheerder, J. P. M. van Duynhoven, J. F. G. Engbersen and D. N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1090–1093.
17 J. J. Gonzalez, P. Prados and J. de Mendoza, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 525–528.
18 O. Mogck, V. Böhmer, G. Ferguson and W. Vogt, *J. Chem. Soc., Perkin Trans. 1*, 1966, 1711–1715.
19 M. Saadioui, A. Shivanyuk, V. Böhmer and W. Vogt, *J. Org. Chem.*, 1999, **64**, 3774–3777.
20 A. Pop, M. O. Vysotsky and V. Böhmer, *Coll. Czech. Chem. Commun.*, 2004, **69**, 1009–1026.
21 L. A. J. Chrisstoffels, F. de Jong, D. N. Reinhoudt, S. Sivelli, S. Gazzola, A. Casnati and R. Ungaro, *J. Am. Chem. Soc.*, 1999, **121**, 10142–10151.
22 J. Scheerder, M. Fochi, J. F. J. Engbersen and D. N. Reinhoudt, *J. Org. Chem.*, 1994, **59**, 7815–7820.
23 E. M. Collins, M. A. McKervey, E. Madigan, M. B. Moran, M. Owens, G. Ferguson and S. J. Harris, *J. Chem. Soc., Perkin Trans. 1*, 1991, 3137–3142.
24 I. Bitter and V. Csokai, *Tetrahedron Lett.*, 2003, **44**, 2261–2265.
25 O. Seneque and O. Reinaud, *Tetrahedron*, 2003, **59**, 5563–5568.
26 For the formation of Y = $CH_2CH_2NH_2$ *via* azides see ref. 10.
27 (*a*) W. Veerboom, S. Datta, Z. Asfari, S. Harkema and D. N. Reinhoudt, *J. Org. Chem.*, 1992, **57**, 5394–5398; (*b*) K. Iwamoto and S. Shinkai, *J. Org. Chem.*, 1992, **57**, 7066–7073.
28 With Na_2CO_3 the *cone* isomer is formed as main product.
29 Similar experiences were made with a mixed tetraether in the *cone* conformation, where both phthalimide groups were hydrolyzed to the monoamide: P. Wang and V. Böhmer, unpublished.
30 These conditions were successfully applied for monocyano-hepthyloxy surrounded by tripropyloxy residue attached to calixarenes by Y. Rudzevich and V. Böhmer, unpublished results.
31 S. E. Matthews, P. Parzuchowski, A. G. Carrera, C. Grüttner, J. D. Böhmer and V. Böhmer, *Chem. Commun.*, 2001, **5**, 417–418.
32 P. Lhoták, J. Svoboda, I. Stibor and J. Sykora, *Tetrahedron Lett*, 2002, **43**, 7413–7417.
33 A. Pop, M. O. Vystosky, M. Saadioui and V. Böhmer, *Chem. Commun.*, 2003, **10**, 1124–1125.
34 The use of bromoalkyl phthalimides or bromonitriles in the first *O*-alkylation step leads to hexaamines with two amino groups attached to the narrow rim.
35 A. Soi, W. Bauer, H. Mauser, C. Moll, F. Hampel and A. Hirsch, *J. Chem. Soc., Perkin Trans. 2*, 1998, 1471–1478.
36 A tetra-CMPO derivative could be obtained from **28** ($n = 3$) in three steps by acylation, cleavage of the phthalimide groups and acylation again: C. Danila and V. Böhmer, unpublished.
37 Tetraethers in the *cone*-conformation can be obtained much more selectively.

38 J. Oriol Magrans, J. de Mendoza, M. Pons and P. Prados, *J. Org. Chem.*, 1997, **62**, 4518–4520.
39 V. Böhmer in Calixarenes, *The Chemistry of Phenols*, ed. Z. Rappoport, Wiley, Chichester, 2003..
40 Since starting point and direction are in principle arbitrary, the sequence (+,−)(+,−)(−,−)(+,+) is identical to (−,+)(+,+)(−,−)(−,+), listed in Table 1.
41 M. Perrin and D. Oehler in *Calixarenes, A Versatile Class of Macrocyclic Compounds*, ed. J. Vicens and V. Böhmer, Kluwer Academic Publishers, Dordrecht, 1991; values >90° mean that the phenolic unit is bent outwards.
42 Stoe & Cie 2001. *X-Area. Area-Detector Control and Integration, Software*. Stoe & Cie, Darmstadt, Germany.
43 R. H. Blessing, *Acta Crystallogr., Sect. A*, 1995, **51**, 33–38.
44 A. L. Spek, *Acta Crystallogr., Sect. A*, 1990, **46**, C-34.
45 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467–473.
46 G. M. Sheldrick, *SHELXL-97, Program for refinement of crystal structures*, University of Göttingen, Germany, 1997.