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A Novel Approach to Inherently Chiral Calix[4]arenes by Direct Introduction of a Substituent at the meta Position

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Abstract. A novel method for the preparation of inherently chiral calix[4]arenes is described by direct introduction of a substituent in para-acetamido substituted calix[4]arenes. Bromination and nitration of mono(acetamido)calix[4]arenes **5**, **6** afforded calix[4]arenes **7-10**, in which the substituent was selectively introduced adjacent to the acetamido moiety, in 58-98% yield. Bromination of bis(acetamido)calix[4]arene **13** gave a mixture from which dibromo- (**14**) and tribromocalix[4]arene **15** were isolated in 10% and 22% yield, respectively. The structure of **14** was confirmed by single-crystal X-ray structure determination. Nitration of **13** gave 4,16-dinitro- (**16**) and 4,18-dinitrocalix[4]arene **17** in 53% and 18% yield, respectively.

INTRODUCTION

Calixarenes[1,2] represent a very interesting class of compounds in supramolecular chemistry, because they are useful building blocks for the design of selective receptors for cations,[3] anions,[4] and neutral molecules.[5] Receptors with a chiral cavity are of particular interest, and this has led to the development of chiral calixarenes. Most attention has been paid to calix[4]arenes of which the undesired ring inversion can be inhibited by introduction of substituents larger than ethyl on the phenolic OH groups (lower rim).[6]

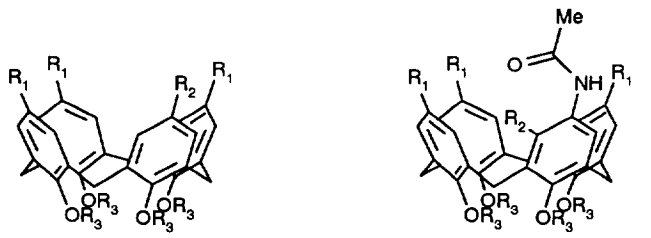
Several approaches have been reported for the synthesis of chiral calix[4]arenes. The most simple way to synthesize chiral calix[4]arenes involves the introduction of chiral substituents to the calix[4]arene skeleton.[7] The other, more interesting, approaches involve the synthesis of *inherently* chiral calix[4]arenes, which are built up of nonchiral units and owe their chirality to the fact that the calixarene molecule is not planar. One strategy to prepare this type of chiral calix[4]arenes involves asymmetrical arrangement of different substituents at the lower or upper rim.[8]

Another possibility comprises the incorporation of a substituent in the meta position of one or more of the phenol rings of the calix[4]arene. This type of chiral calix[4]arenes has been prepared by the

laborious fragment condensation procedure[9] and by direct introduction of the meta substituent.[10,11] Meta-substituted calix[4]arenes have been obtained as minor products in a nonselective substitution reaction in tricarbonylchromium calix[4]arene complexes by Shinkai et al.[10] Finally, Reddy and Gutsche[11] reported the 1,4-conjugate addition reaction in calix[4]monoquinones to give meta-substituted calix[4]arenes. In the present paper we describe a very simple, novel method for the preparation of chiral, meta-substituted calix[4]arenes by direct introduction of a substituent in para-acetamido-substituted calix[4]arenes.

RESULTS AND DISCUSSION

The starting mono(acetamido)-substituted calix[4]arenes **5** and **6**, having at the para positions of the other alkoxybenzene rings a *tert*-butyl group and a hydrogen atom, respectively, were prepared by reduction of the known mononitrocalix[4]arenes **1**[12] and **2**[13] (cone conformation) with Raney nickel and hydrazine followed by acylation of the resulting monoaminocalix[4]arenes **3** and **4** with acetyl chloride in the presence of triethylamine as a base in 60% and 66% overall yields, respectively. The formation of **5** and **6** clearly followed from their spectral data. The presence in the ^{1}H NMR spectra of singlets at δ 1.92 and 1.95 and in the ^{13}C NMR spectra at δ 167.0 and 167.8, respectively, proves the introduction of the acetyl group.



$R_3 = CH_2CH_2OEt$

1 R_1 = *t*-Bu, $R_2 = NO_2$
2 R_1 = H, $R_2 = NO_2$
3 R_1 = *t*-Bu, $R_2 = NH_2$
4 R_1 = H, $R_2 = NH_2$
5 R_1 = *t*-Bu, R_2 = NHC(O)Me
6 R_1 = H, R_2 = NHC(O)Me

7 R_1 = *t*-Bu, R_2 = Br
8 R_1 = H, R_2 = Br
9 R_1 = *t*-Bu, $R_2 = NO_2$
10 R_1 = H, $R_2 = NO_2$

Chart I

Reaction of **5** with 1.2 equiv of NBS in 2-butanone for 24 h at room temperature gave after column chromatography monobromocalix[4]arene **7** in 64% yield. Its ^{1}H NMR spectrum clearly shows the asymmetry of the molecule with among others five doublets (one other doublet hidden under the

OCH_2CH_2 multiplet) for the hydrogen atoms of the methylene bridges and three signals for the *tert*-butyl groups at δ 1.11, 1.09, and 0.98. The introduction of the bromo atom adjacent to the acetamido moiety could be deduced from the ^{13}C NMR spectrum. Compared with the ^{13}C NMR spectrum of the starting compound **5** no significant changes could be observed for the absorptions of the *tert*-butyl containing aromatic rings. However, C-5 (containing $NHC(O)CH_3$) shifted from δ 132.0 in **5** to δ 135.3 in **7**. The ortho positions C-4 and C-6, a doublet at δ 119.2 in **5**, are now present as a singlet at δ 113.6 (C-Br) and a doublet at δ 121.5, respectively. When the reaction was performed with 2.2 equiv of NBS compound **7** could still be isolated in 60% yield.

Bromination of 5-acetamidocalix[4]arene **6**, having no para-*tert*-butyl groups at the other aromatic rings, with 1.2 equiv of NBS in 2-butanone afforded compound **8** in 58% yield after chromatography. In this case bromination did also take place adjacent to the acetamido group and not at the free para positions of the three alkoxybenzene rings. The ^1H NMR spectrum of **8** exhibits for CH-6 (acetamido-C-CH) a singlet at δ 7.63 (1H) while in the spectrum of **6** a singlet is present at δ 6.77 (2H) for both CH-4 and CH-6. The structure of **8** also followed from the ^{13}C NMR spectrum following the same arguments as described above for **7**.

In addition to the bromination, we also studied the nitration of acetamidocalix[4]arenes **5** and **6**. Reaction of **5** with 6 equiv of 65% HNO_3 for 24 h gave 5-acetamido-4-nitrocalix[4]arene **9** in 98% yield. The selective introduction of a nitro group at the C-4 position could also in this case be proven by comparison of the ^{13}C NMR spectra of **5** and **9**. C-5 shifts from δ 132.0 in **5** to δ 124.6 in **9**. The most significant shift was observed for C-4 viz. from δ 119.2 (d) in **5** to δ 138.9 (s, $C\text{-}NO_2$) in **9**. Acetamidocalix[4]arene **6** exhibited the same behavior; reaction with 1.5 equiv of 65% HNO_3 afforded *exclusively* the 4-nitro-substituted calix[4]arene **10** in 91% yield. When the reaction was carried out with 10 equiv of 65% HNO_3 **10** was isolated in 85% yield.[14]

The doubling of ^1H NMR patterns of products **7-10** in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) [$Eu(hfc)_3$] reveals that **7-10** consist of a pair of enantiomers. Illustrative parts of the ^1H NMR spectra of **9** and **10**, with and without chiral shift reagent, are depicted in Figure 1.

Subsequently, we also investigated the behavior of the bis(acetamido)calix[4]arene **13** towards meta substitution. This compound was prepared starting from the corresponding dinitrocalix[4]arene **11**[15] by reduction with Raney nickel and hydrazine and subsequent treatment with 2.2 equiv of acetyl chloride in the presence of triethylamine at -15°C in 74% overall yield. Bromination of **13** with 2.4 equiv of NBS in 2-butanone at room temperature for 18 h gave a complicated reaction mixture from which two compounds could be isolated in a pure state, namely the desired 5,17-bis(acetamido)-4,16-dibromocalix[4]arene **14** and the tribromocalix[4]arene **15** in yields of 10% and 22%, respectively. The ^1H NMR spectrum of **14** exhibits for the aromatic region one singlet at δ 7.65 (2H) and a multiplet at δ

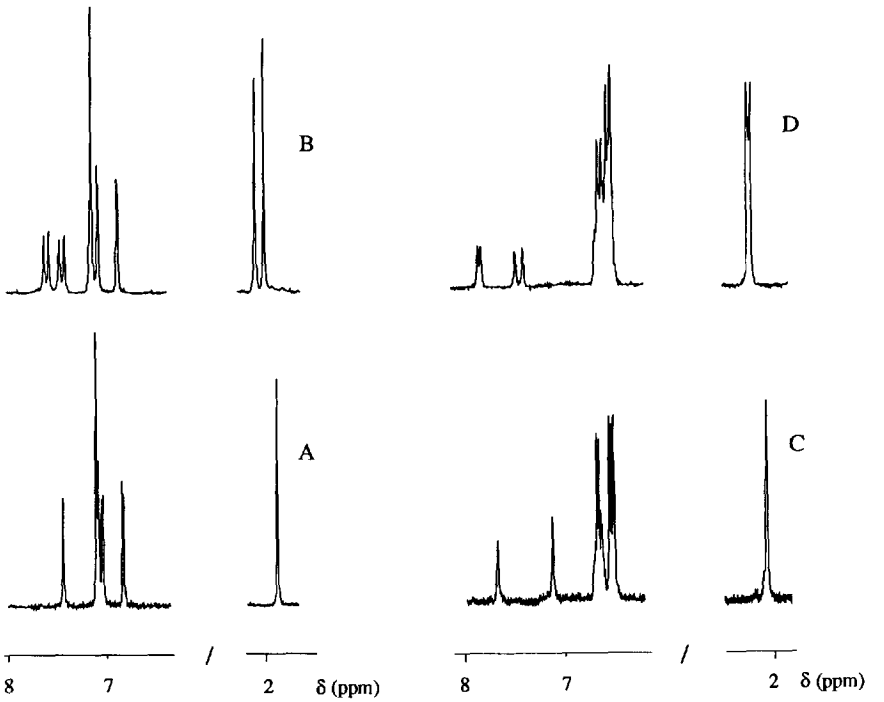
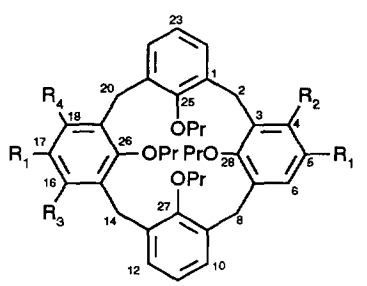


Figure 1 Parts of the ^{1}H NMR spectra of **9**, a) without and b) with chiral shift reagent, and **10**, c) without and d) with chiral shift reagent.



11 $R_1 = NO_2$, $R_2 = R_3 = R_4 = H$

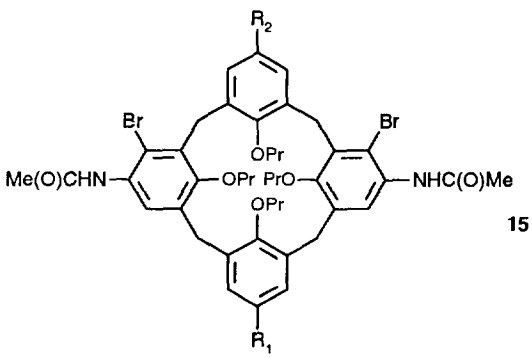
12 $R_1 = NH_2$, $R_2 = R_3 = R_4 = H$

13 $R_1 = NHC(O)Me$, $R_2 = R_3 = R_4 = H$

14 $R_1 = NHC(O)Me$, $R_2 = R_3 = Br$, $R_4 = H$

16 $R_1 = NHC(O)Me$, $R_2 = R_3 = NO_2$, $R_4 = H$

17 $R_1 = NHC(O)Me$, $R_2 = R_4 = NO_2$, $R_3 = H$



15 $R_1 = Br$, $R_2 = H$ or $R_1 = H$, $R_2 = Br$

Chart II

6.25-6.05 (6H) indicating that the bromination had taken place at the acetamido containing aromatic rings. The structure of **14** was unequivocally proven by a single crystal X-ray determination. The results of the X-ray diffraction experiment are shown in Figures 2 and 3. The asymmetric unit of the crystal structure contains one half calixarene molecule, the other half being generated by a 2-fold axis. The figures clearly show the so-called pinched cone conformation[16] of the calixarene molecule. The angle between the best plane fitted to the connecting methylene carbons and the planes of the phenyl rings are 143.4° and 81.3°, respectively. The molecules are connected by hydrogen bonds between the amide hydrogens and the amide oxygens (distance N...O: 2.96(2)Å, N-H...O angle: 164(1)°). These hydrogen bonds are also shown in Figure 3.

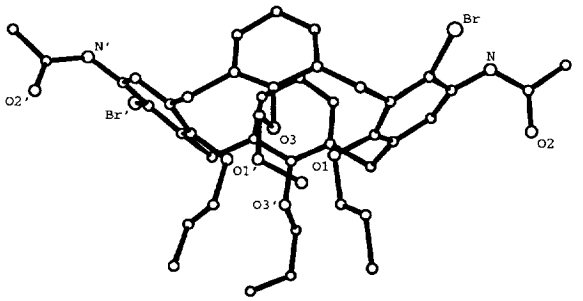


Figure 2 PLUTO view of dibromocalix[4]arene **14**.

In the case of **15** in the mass spectrum the molecular ion of *m/e* 940.8 [$(M + 1)^+$, calculated 941.1] and the isotope pattern together with the elemental analysis proved the introduction of three bromo atoms. The ^{1}H NMR spectrum of **15** shows for the aromatic hydrogen atoms two singlets at δ 6.16 (2H) and δ 7.67 (2H) and one triplet at δ 6.45 (1H) and one doublet at δ 6.09 (2H). These data imply a symmetry in which bromo atoms are introduced at the C-4 and C-18 positions. However, from the spectroscopic data available it is not clear whether the third bromo atom is located at the C-11 or the C-23 position.

Nitration of **13** with 2.7 equiv of 65% HNO_3 at room temperature for 17 h gave, after chromatography, the 4,16-dinitro- (**16**) and the 4,18-dinitrocalix[4]arene **17** in 53% and 18% yield, respectively. In both cases the mass spectrum shows the presence of two nitro groups while the presence of one singlet (2H) and a multiplet (6H) in the ^{1}H NMR spectrum proves the meta substitution. The two isomers could be distinguished on the basis of the different patterns of the OCH_2 absorptions in the ^{1}H NMR spectra. In the case of 4,16-dinitro **16** a multiplet of two hydrogen atoms is present at δ 4.1-3.95 and a multiplet of six hydrogen atoms at δ 3.85-3.7. 4,18-Dinitro **17** shows two very close sets of triplets (each 2H) at δ 3.97, 3.96 and δ 3.74, 3.71. A ROESY spectrum of **16** exhibits cross peaks between the two multiplets present, indicating that the two hydrogen atoms of two of the four OCH_2 groups are

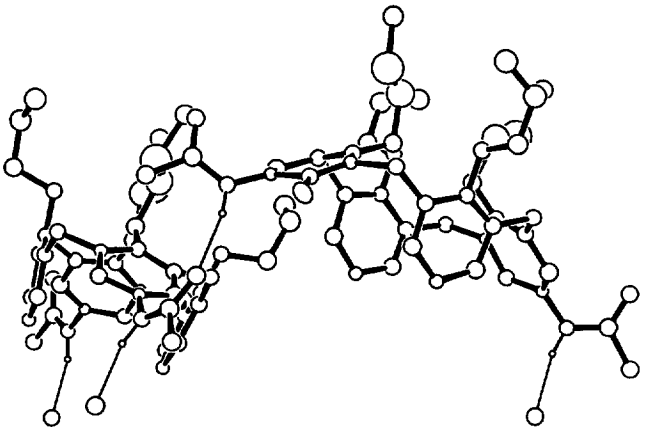


Figure 3 ORTEP view showing the pinched cone conformation of the calix[4]arene molecule. Thermal ellipsoids are scaled to include 12.5% probability. Only the amide hydrogen atoms involved in hydrogen bonding are shown. The other hydrogens are omitted for clarity. Two complete molecules are shown. Hydrogen bonds are indicated by thin lines.

chemically not equivalent.[17] However, in a ROESY spectrum of **17** in this area no cross peaks are present. These data correspond with the proposed structures because in **16** the hydrogen atoms of the OCH_2 groups of the aromatic rings without para substituent are diastereotopic, while the corresponding hydrogen atoms in **17** are enantiotopic.

The formation of 4,16-dinitro **16** is favored over that of 4,18-dinitro **17** (ratio about 3:1). After the introduction of the first nitro group the accessibility of the meta positions of the opposite aromatic ring is unequal and consequently the second nitro group will be preferably introduced at the less hindered position.[18] The chirality of compounds **14** and **16** followed from the splittings in the ^1H NMR spectra upon addition of $Eu(hfc)_3$.

Recently, we reported that tetrakis(ethoxyethoxy)calix[4]arene could be diametrically nitrated at the upper rim using a large excess of 65% HNO_3.[13] Now we have demonstrated that in calix[4]arenes a para-acetamido group is activating the meta positon in such a way that under carefully controlled conditions electrophilic substitution at this position is favored over that at free para places of the other aromatic rings. Although under the conditions used, nitration is somewhat more selective than bromination, we feel that the results described in this paper represent a novel, direct approach to meta-substituted, inherently chiral calix[4]arenes. Moreover, compared with the other methods for the preparation of this type of chiral calix[4]arenes[9-11] (vide supra), this approach is much simpler and gives rise to better overall yields.

EXPERIMENTAL

Melting points were determined with a Reichert melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AC 250 spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were obtained with a Finnigan MAT 90 spectrometer. Positive-ion fast-atom-bombardement (FAB) mass spectra were obtained with *m*-nitrobenzyl alcohol as a matrix. IR spectra were recorded with a Nicolet 5 SCX FT or a BIO-RAD FTS-60 FT spectrophotometer. Elemental analyses were carried out by a Model 1106 Carlo Erba Strumentazione Elemental Analyzer. Petroleum ether refers to the fraction boiling at 60-80°C. Petroleum ether, CH_2Cl_2 and EtOAc were distilled before use. Column chromatography was performed with silica gel (Merck; 0.040-0.63 mm). All reactions were carried out under an argon atmosphere.

5-Acetamido-11,17,23-tri-*tert*-butyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (5). To a suspension of 5-nitrocalix[4]arene **1**[12] (0.79 g, 0.85 mmol) and a catalytic amount of Raney Ni in MeOH (15 ml) was added dropwise hydrazine hydrate (0.36 ml). After 1-h reflux, the Raney Ni was filtered off using Hyflo and the solvent was evaporated. The residue was taken up in CH_2Cl_2 (50 ml) and washed with water (25 ml) and brine (25 ml). After drying over $MgSO_4$ and evaporation of the solvent 5-aminocalix[4]arene **3** was obtained which was used without further purification.

To a solution of **3** and NEt_3 (0.14 ml, 1.0 mmol) in CH_2Cl_2 (25 ml) was added dropwise acetyl chloride (0.10 ml, 1.41 mmol). After stirring of the reaction mixture for 5 min at room temperature CH_2Cl_2 (25 ml) and water (20 ml) were added. The organic layer was washed with water (2 x 20 ml) and subsequently dried over $MgSO_4$. After evaporation of the solvent the crude reaction mixture was separated with column chromatography (petroleum ether/EtOAc 3:2) to give pure **5** as an oil. Yield 60%. ^{1}H NMR δ 7.05, 7.01 (d, 2H, J=2.3 Hz, ArH), 6.51, 6.27 (s, 2H, ArH), 4.46, 4.45 and 3.11, 3.08 (ABq, 4H, J=13.0 Hz, $ArCH_2Ar$), 4.24 (t, 4H, J=6.7 Hz, $ArOCH_2$), 4.05-3.75 (m, 12H, $ArOCH_2$ and $ArOCH_2CH_2$), 3.65-3.5 (m, 8H, OCH_2CH_3), 1.92 (s, 3H, $C(O)CH_3$), 1.32 (s, 18H, $C(CH_3)_3$), 1.3-1.15 (m, 12H, OCH_2CH_3), 0.76 (s, 9H, $C(CH_3)_3$). ^{13}C NMR δ 167.0 (s, C=O), 132.0 (s, C-5), 119.2 (d, C-4,6), 31.1, 31.0 (t, $ArCH_2Ar$), 24.3 (q, $C(O)CH_3$), 15.4, 15.3 (q, OCH_2CH_3). IR (KBr) 3295 (NH), 1653 (C=O) cm^{-1}. MS (EI) *m/z* 937.605 (M^+, calcd. for $C_{58}H_{83}NO_9$ 937.607).

5-Acetamido-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (6) was prepared analogously to **5** using 5-nitrocalix[4]arene **2**[13] (1.2 g, 1.59 mmol), hydrazine hydrate (0.7 ml), NEt_3 (0.27 ml, 1.94 mmol), and acetyl chloride (0.17 ml, 2.39 mmol). The crude reaction mixture was separated with column chromatography (CH_2Cl_2/EtOAc 1:1) to afford pure **6** as an oil. Yield 66%. ^{1}H NMR δ 7.73 (s, 1H, NH), 6.77 (s, 2H, ArH), 6.65-6.45 (m, 9H, ArH), 4.51, 4.46 and 3.15, 3.09 (ABq, 4H, J=13.3

Hz, $ArCH_2Ar$), 4.2-4.05 (m, 8H, $ArOCH_2$), 3.9-3.75 (m, 8H, $ArOCH_2CH_2$), 3.65-3.5 (m, 8H, OCH_2CH_3), 1.95 (s, 3H, $C(O)CH_3$), 1.3-1.1 (m, 12H, OCH_2CH_3). ^{13}C NMR δ 167.8 (s, C=O), 131.9 (s, C-5), 120.4 (d, C-4,6), 30.9 (t, $ArCH_2Ar$), 24.3 (q, $C(O)CH_3$), 15.3 (q, OCH_2CH_3). IR (KBr) 3280 (NH), 1652 (C=O) cm^{-1}. MS (EI) *m/z* 769.417 (M^+, calcd. for $C_{46}H_{59}NO_9$ 769.419).

5-Acetamido-4-bromo-11,17,23-tri-*tert*-butyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (7). A solution of **5** (158 mg, 0.168 mmol) and NBS (36 mg, 0.202 mmol) in 2-butanone (10 ml) was stirred at room temperature in the dark for 24 h. After evaporation of the solvent, the residue was taken up in CH_2Cl_2 (50 ml) and washed with water (2 x 20 ml). After drying over $MgSO_4$ and evaporation of the CH_2Cl_2 the crude reaction mixture was separated with column chromatography (petroleum ether/EtOAc 3:1) to give pure **7** as an oil. Yield 64%. ^1H NMR δ 7.78, 7.31, 6.99, 6.63, 6.57 (br s, 1H, ArH, NH), 6.58-6.75 (m, 3H, ArH), 4.55 (d, 1H, J=13.1 Hz, $ArCHHAr$), 4.46 (d, 1H, J=12.7 Hz, $ArCHHAr$), 4.45 (d, 2H, J=13.1 Hz, $ArCH_2Ar$), 4.2-3.9 (m, 8H, $ArOCH_2$), 3.9-3.7 (m, 8H, $ArOCH_2CH_2$), 3.6-3.4 (m, 9H, OCH_2CH_3 and $ArCHHAr$), 3.15 (d, 1H, J=12.8 Hz, $ArCHHAr$), 3.13 (d, 2H, J=13.0 Hz, $ArCH_2Ar$), 2.10 (s, 3H, $C(O)CH_3$), 1.3-1.1 (m, 12H, OCH_2CH_3), 1.11, 1.09, 0.98 (s, 9H, $C(CH_3)_3$). ^{13}C NMR δ 167.4 (s, C=O), 135.3 (s, C-5), 121.5 (d, C-6), 113.6 (s, C-4), 31.43, 31.39, 31.3 (q, $C(CH_3)_3$), 30.5 (t, $ArCH_2Ar$), 24.8 (q, $C(O)CH_3$), 15.3 (q, OCH_2CH_3). IR (KBr) 3400 (NH), 1688 (C=O) cm^{-1}. MS(FAB) *m/z* 1015.8 (M^+, calcd. for $C_{58}H_{82}{}^{79}BrNO_9$ 1015.5).

5-Acetamido-4-bromo-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (8). A solution of **6** (128 mg, 0.166 mmol) and NBS (36 mg, 0.20 mmol) in 2-butanone (10 ml) was stirred at room temperature in the dark for 24 h. After workup as described for **7** and column chromatography (petroleum ether/EtOAc 1:1) pure **8** was obtained as an oil. Yield 58%. ^1H NMR δ 8.08 (s, 1H, NH), 7.63 (s, 1H, ArH), 7.15-7.0 (m, 2H, ArH), 6.9-6.8 (m, 1H, ArH), 6.3-6.1 (m, 6H, ArH), 4.5-4.35 (m, 4H, $ArCH_2Ar$), 4.3-4.15 (m, 4H, $ArOCH_2$), 3.95-3.65 (m, 13H, $ArOCH_2CH_2$ and $ArCHHAr$), 3.6-3.4 (m, 8H, OCH_2CH_3), 3.2-3.05 (m, 3H, $ArCH_2Ar$ and $ArCHHAr$), 2.25 (s, 3H, $C(O)CH_3$), 1.3-1.1 (m, 12H, OCH_2CH_3). ^{13}C NMR δ 168.0 (s, C=O), 157.9, 155.1, 154.9, 154.7 (s, C-25,26,27,28), 114.2 (s, C-4), 30.9, 30.8, 30.0 (t, $ArCH_2Ar$), 24.9 (q, $C(O)CH_3$), 15.4, 15.3 (q, OCH_2CH_3). IR (KBr) 3400 (NH), 1660 (C=O) cm^{-1}. MS (EI) *m/z* 847.328 (M^+, calcd. for $C_{46}H_{58}{}^{79}BrNO_9$ 847.330).

5-Acetamido-11,17,23-tri-*tert*-butyl-25,26,27,28-tetrakis(2-ethoxyethoxy)-4-nitrocalix[4]arene (9). First a stock solution was made of 65% HNO_3 (1 ml) in CH_2Cl_2 (200 ml) and HOAc (12 ml). To a solution of **5** (75 mg, 0.080 mmol) in CH_2Cl_2 (3 ml) was added 7.7 ml of the stock solution of 65% HNO_3 (0.52 mmol). The reaction mixture was stirred at room temperature in the dark for 24 h. After addition of water (20 ml) the mixture was extracted with CH_2Cl_2 (2 x 10 ml). The combined organic

layers were washed with water till neutral pH. After drying over $MgSO_4$ and evaporation of the solvent pure **9** was obtained as an oil. Yield 98%. ^{1}H NMR δ 7.46 (s, 1H, NH), 7.15-7.05 (m, 3H, ArH), 7.07, 6.87 (d, 1H, *J*=2.4 Hz, ArH), 6.34, 6.25 (br s, 1H, ArH), 4.56 (d, 2H, *J*=13.3 Hz, $ArCH_2Ar$), 4.48 (d, 1H, *J*=12.8 Hz, ArC*H*HAr), 4.43 (d, 1H, *J*=13.0 Hz, ArC*H*HAr), 4.35-4.15 (m, 4H, $ArOCH_2$), 4.0-3.7 (m, 12H, $ArOCH_2$ and $ArOCH_2CH_2$), 3.6-3.4 (m, 9H, OCH_2CH_3 and ArC*H*HAr), 3.17 (d, 1H, *J*=13.2 Hz, ArCH*H*Ar), 3.16 (d, 1H, *J*=12.8 Hz, ArCH*H*Ar), 3.12 (d, 1H, *J*=13.5 Hz, ArCH*H*Ar), 1.90 (s, 3H, $C(O)CH_3$), 1.3-1.1 (m, 12H, OCH_2CH_3), 1.33, 1.30, 0.83 (s, 9H, $C(CH_3)_3$). ^{13}C NMR δ 167.5 (s, C=O), 138.9 (s, C-4), 124.6 (s, C-5), 123.4 (d, C-6), 31.6, 31.4, 30.9 (q, $C(CH_3)_3$), 24.3 (q, $C(O)CH_3$). IR (KBr) 3296 (NH), 1659 (C=O) cm^{-1}. MS (EI) *m/z* 982.583 (M^+, calcd. for $C_{58}H_{82}N_2O_{11}$ 982.592).

5-Acetamido-25,26,27,28-tetrakis(2-ethoxyethoxy)-4-nitrocalix[4]arene (10). To a solution of **6** (59 mg, 0.077 mmol) in CH_2Cl_2 (3 ml) was added 1.7 ml of the stock solution (see **9**) of 65% HNO_3 (0.114 mmol). The reaction was carried out and worked up as described for **9** to give pure **10** as an oil. Yield 91%. ^{1}H NMR δ 7.72 (s, 1H, NH), 7.18 (s, 1H, ArH), 6.75-6.5 (m, 9H, ArH), 4.55 (d, 2H, *J*=14.3 Hz, $ArCH_2Ar$), 4.50 (d, 1H, *J*=13.5 Hz, ArC*H*HAr), 4.47 (d, 1H, *J*=13.8 Hz, ArC*H*HAr), 4.2-4.0 (m, 8H, $ArOCH_2$), 3.9-3.7 (m, 8H, $ArOCH_2CH_2$), 3.6-3.4 (m, 9H, $ArCH_2CH_3$ and ArCH*H*Ar), 3.21 (d, 1H, *J*=13.7 Hz, ArCH*H*Ar), 3.17 (d, 1H, *J*=13.4 Hz, ArCH*H*Ar), 3.16 (d, 1H, *J*=13.9 Hz, ArCH*H*Ar), 2.07 (s, 3H, $C(O)CH_3$), 1.25-1.1 (m, 12H, OCH_2CH_3). ^{13}C NMR δ 168.2 (s, C=O), 156.7, 156.5, 156.4 (s, C-25,26,27), 154.0 (s, C-28), 140.0 (s, C-4), 124.4 (s, C-5), 121.9 (d, C-6), 30.9, 26.9 (t, $ArCH_2Ar$), 24.4 (q, $C(O)CH_3$), 15.3 (q, OCH_2CH_3). IR (KBr) 3296 (NH), 1659 (C=O) cm^{-1}. MS (EI) *m/z* 814.400 (M^+, calcd. for $C_{46}H_{58}N_2O_{11}$ 814.404).

5,17-Bis(acetamido)-25,26,27,28-tetrapropoxycalix[4]arene (13). To a suspension of 5,17-dinitrocalix[4]arene **11**[15] (0.41 g, 0.6 mmol) and a catalytic amount of Raney Ni in MeOH (12.5 ml) was added dropwise hydrazine monohydrate (1 ml). After refluxing for 4 h, the Raney Ni was filtered off over Hyflo and the solvent was evaporated. The residue was taken up in CH_2Cl_2 (25 ml) and washed with water (15 ml) and brine (15 ml). After drying over $MgSO_4$ the solution was concentrated to about 15 ml. To this solution was added successively Et_3N (0.13 g, 1.26 mmol) and dropwise acetyl chloride (0.10 g, 1.32 mmol) at -15°C. After stirring for 2 min at this temperature the reaction was quenched by adding water (15 ml) and CH_2Cl_2 (15 ml). The organic layer was washed with water (2 x 10 ml) and subsequently dried over $MgSO_4$. After evaporation of the solvent the crude raction mixture was separated with column chromatography (petroleum ether/EtOAc 1:3) to afford pure **13** as a white solid. Yield 74%. M.p. 259-263°C (CH_2Cl_2/petroleum ether). Anal. calcd. for $C_{44}H_{54}N_2O_6 \cdot 0.45H_2O$: C, 73.91; H, 7.74; N, 3.92. Found: C, 73.58; H, 7.71; N, 3.78%. Karl-Fischer calcd. for $0.45H_2O$: 1.13. Found:

1.13%. ^{1}H NMR δ 7.03 (s, 2H, NH), 7.0-6.75 (m, 6H, ArH), 6.31 (s, 4H, ArH), 4.43, 3.13 (ABq, 8H, J=13.3 Hz, $ArCH_2Ar$), 3.95 (t, 4H, J=7.8 Hz, $ArOCH_2$), 3.69 (t, 4H, J=6.8 Hz, $ArOCH_2$), 2.1-1.8 (m, 8H, $ArOCH_2CH_2$), 1.94 (s, 6H, $C(O)CH_3$), 1.05, 0.91 (t, 6H, J=7.4 Hz, CH_2CH_3). ^{13}C NMR δ 168.7 (s, C=O), 157.3 (s, C-25,27), 153.2 (s, C-26,28), 131.2 (s, C-5,17), 121.8 (d, C-4,6,16,18), 77.0, 76.6 (t, OCH_2), 31.0 (t, $ArCH_2Ar$), 23.9 (q, $C(O)CH_3$), 10.7, 10.0 (q, CH_2CH_3). IR (KBr) 3292 (NH), 1664 (C=O) cm^{-1}. MS (FAB) *m/z* 707.2 ($[M+1]^+$, calcd. 707.4).

Bromination of 13. Formation of 14 and 15. A solution of **13** (1.0 g, 1.42 mmol) and NBS (0.60 g, 3.40 mmol) in 2-butanone (100 ml) was stirred at room temperature in the dark for 18 h. After evaporation of the solvent, the residue was taken up in CH_2Cl_2 (500 ml) and washed with water (2 x 100 ml). After drying over $MgSO_4$ the solvent was evaporated. The residue was crystallized from $MeOH/CH_2Cl_2$ to give pure **14**. The mother liquor was separated with column chromatography (CH_2Cl_2/EtOAc 95:5) to afford pure **15**.

5,17-Bis(acetamido)-4,16-dibromo-25,26,27,28-tetrapropoxycalix[4]arene (14). Yield 10%. M.p. > 300°C. Anal. calcd. for $C_{44}H_{52}Br_2N_2O_6$: C, 61.12; H, 6.06; N, 3.24. Found: C, 61.26; H, 6.22; N, 3.18%. ^{1}H NMR δ 8.09 (s, 2H, *H*ArNHAc), 7.65 (s, 2H, NH), 6.25-6.05 (m, 6H, ArH), 4.39, 3.84 (ABq, 4H, J=13.9 Hz, $ArCH_2Ar$), 4.37, 3.20 (ABq, 4H, J=13.4 Hz, $ArCH_2Ar$), 4.05-3.85 and 3.7-3.6 (m, 4H, OCH_2), 2.27 (s, 6H, $C(O)CH_3$), 2.05-1.8 (m, 8H, OCH_2CH_2), 1.09, 0.88 (t, 6H, J=7.4 Hz, CH_2CH_3). ^{13}C NMR δ 168.3 (s, C=O), 155.3, 155.2 (s, C-25,26,27,28), 136.9 (s, C-5,17), 122.7 (d, C-6,11,18,23), 114.7 (s, C-4,16), 77.3, 77.2 (t, OCH_2) 31.2, 30.2 (t, $ArCH_2Ar$), 25.2 (q, $C(O)CH_3$), 11.1, 11.0 (q, CH_2CH_3). IR (KBr) 3288 (NH), 1684 (C=O) cm^{-1}. MS (FAB) *m/z* 862.2 (M^+, calcd. 862.2).

5,17-Bis(acetamido)-4,11(23),18-tribromo-25,26,27,28-tetrapropoxycalix[4]arene (15). Yield 22%. M.p. 268-275°C. ^{1}H NMR δ 8.10 (s, 2H, *H*ArNHAc), 7.66 (s, 2H, NH), 6.45 (t, 1H, J=7.5 Hz, ArH), 6.14 (s, 2H, ArH), 6.08 (d, 2H, J=7.5 Hz, ArH), 4.37, 3.22 (ABq, 4H, OCH_2), 2.29 (s, 6H, $C(O)CH_3$), 2.0-1.75 (m, 8H, OCH_2CH_2), 1.09, 1.08 (t, 3H, J=7.5 Hz, CH_2CH_3), 0.85 (t, 6H, J=7.4 Hz, CH_2CH_3). ^{13}C NMR δ 168.1 (s, C=O), 136.6 (s, C-5,17), 123.0, 122.6 (d, C-6,11(23),16), 115.3 (s, C-4,18), 114.1 (s, C-23(11)), 30.9, 30.0 (t, $ArCH_2Ar$), 24.9 (q, $C(O)CH_3$), 10.9, 10.7, 9.7 (q, CH_2CH_3). IR (KBr) 3298 (NH), 1701 (C=O), 1686 (C=O) cm^{-1}. MS (FAB) *m/z* 940.8 (M^+, calcd. for $C_{44}H_{51}{}^{79}Br_3N_2O_6$ 941.1).

Nitration of 13. Formation of 16 and 17. To a solution of **13** (0.52 g, 0.71 mmol) in CH_2Cl_2 (15 ml) was added 28.5 ml of the stock solution (see **9**) of 65% HNO_3 (2.8 mmol). The reaction mixture was

stirred at room temperature for 24 h, whereupon a sat. solution of $NaHCO_3$ (100 ml) was added. After separation of the layers, the water layer was extracted with CH_2Cl_2 (100 ml). The combined organic layers were washed with water (2 x 50 ml) and dried over $MgSO_4$. After evaporation of the solvent the crude reaction mixture was separated with column chromatography (petroleum ether/EtOAc 3:2) to give pure **16** and **17**.

5,7-Bis(acetamido)-4,16-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (16). Yield 53%. M.p. > 300°C (CH_2Cl_2/petroleum ether). Anal. calcd. for $C_{44}H_{52}N_4O_{10}\cdot 0.2H_2O$: C, 66.02; H, 6.60; N, 7.00. Found: C, 65.58; H, 6.71; N, 6.94%. Karl-Fischer calcd. for $0.2H_2O$: 0.45. Found: 0.32%. ^{1}H NMR δ 7.56 (s, 2H, NH), 6.95-6.75 (m, 6H, ArH), 6.44 (br s, 2H, ArH), 4.49, 4.46 and 3.69, 3.21 (ABq, 4H, J=14.1 Hz, $ArCH_2Ar$), 4.1-3.95 (m, 2H, OCH_2), 3.85-3.7 (m, 6H, OCH_2), 2.01 (s, 6H, $C(O)CH_3$), 2.0-1.7 (m, 8H, OCH_2CH_2), 1.07, 0.87 (t, 6H, J=7.4 Hz, CH_2CH_3). ^{13}C NMR δ 168.1 (s, C=O), 157.1 (s, C-25,27), 154.4 (s, C-26,28), 139.4 (s, C-4,16), 122.5 (d, C-6,11,18,23), 77.4, 76.8 (t, OCH_2), 23.8 (q, $C(O)CH_3$), 10.5, 9.8 (q, CH_2CH_3). IR (KBr) 3283 (NH), 1668 (C=O) cm^{-1}. MS (FAB) *m/z* 797.3 ($[M + 1]^+$, calcd. 797.4).

5,17-Bis(acetamido)-4,18-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (17). Yield 18%. M.p. 286-287°C (CH_2Cl_2/petroleum ether). Anal. calcd. for $C_{44}H_{52}N_4O_{10}$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.24; H, 6.83; N, 6.96%. ^{1}H NMR δ 8.02 (s, 2H, NH), 7.63 (s, 2H, ArH), 6.5-6.25 (m, 6H, ArH) 4.45, 3.25 (ABq, 4H, J=13.5 Hz, $ArCH_2Ar$), 4.38, 3.50 (ABq, 4H, J=14.5 Hz, $ArCH_2Ar$), 3.97, 3.96, 3.74, 3.71 (t, 2H, J=7.3 Hz, $ArOCH_2$), 2.16 (s, 6H, $C(O)CH_3$), 2.1-1.8 (m, 8H, OCH_2CH_2), 1.0-0.85 (m, 12H, CH_2CH_3). ^{13}C NMR δ 168.5 (s, C=O), 155.7 (s, C-25,27), 154.8 (s, C-26,28), 140.8 (s, C-4,18), 124.3 (s, C-5,17), 122.8 (d, C-6,16), 31.1, 29.7 (t, $ArCH_2Ar$), 24.5 (q, $C(O)CH_3$), 10.5, 10.4, 9.9 (q, CH_2CH_3). IR (KBr) 3286 (NH), 1668 (C=O) cm^{-1}. MS (FAB) *m/z* 797.5 ($[M+1]^+$, calcd. 797.4).

X-ray structure determination of 14. The structure of **14** was determined by X-ray diffraction. The most important crystallographic data are collected in Table 1. Only small crystals of low quality could be obtained, resulting in a rather small number of observed reflections even at low temperatures. Data were collected in the $\omega/2\vartheta$ scan mode (scan width (ω): 1.60 + 0.34 $\tan\vartheta^0$), using graphite monochromated MoKα radiation. The intensity data were corrected for Lorentz and polarization effects and for long time scale variation. An empirical absorption correction was applied.[19]

The structure was solved with Patterson methods and refined by full-matrix least-squares. Weights for each reflection in the refinement (on F) were $w = 4F_0^2/\sigma(F_0^2)$, $\sigma(F_0^2) = \sigma^2(I) + (pF_0^2)^2$; the value of the instability factor p was determined as 0.04. All calculations were done with SDP.[20] Atomic scattering

factors were taken from *International Tables for X-Ray Crystallography*.[21] A PLUTO[22] view is given in Figure 2. Positions and isotropic thermal parameters of the non-hydrogens were refined. To keep the number of variables in the refinement small only the Br-atom was refined with anisotropic thermal parameters. Hydrogen atoms were put in calculated positions and treated as riding atoms. As can be seen from Figure 3 (ORTEP[23] view) two carbon atoms in one of the propoxy side chains have rather large thermal parameters, indicating disorder. The bond lengths for these atoms are affected by this disorder.[24]

Table 1. Crystallographic Data

Crystal data	
$C_{44}H_{52}Br_2N_2O_6$	D_x = 1.41 Mg.m^{-3}
M_r = 862.7	Mo Kα radiation
orthorhombic	λ = 0.7107 Å
*P*bcn	Cell parameters from repeated measurements of 25 reflections
a = 18.091(2) Å	(ϑ = 7 - 15^0)
b = 9.096(1) Å	μ = 20.2 cm^{-1}
c = 24.675(3) Å	T = 115(3) K
V = 4060(1) Å^3	
Z = 4	
Data Collection	
Enraf-Nonius CAD4 single-crystal diffractometer	ϑ_{max} = 20.0^0
$\omega/2\vartheta$ scans	h = 0 -> 17
1898 measured reflections	k = 0 -> 8
554 observed reflections	l = 0 -> 23
[I> 3.0σ(I)]	3 standard reflections, frequency 60 min., average intensity decrease 5.2%
Refinement	
Refinement on F_0	H-atoms treated as riding atoms
Final R = 0.064	Calculated weights
wR = 0.072	w = 1/[σ^2(F)]
S = 1.57	$(\Delta/\sigma)_{max}$ = 0.20
554 reflections	$\Delta\rho_{max}$ = 0.51 e Å^{-3}
115 parameters	$\Delta\rho_{max}$ = -0.56 e Å^{-3}

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