Synthesis of Neutral, Water-Soluble Calix[4]arenes

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Novel neutral water-soluble calix[4]arenes were synthesized via chlorosulfonylation of *lower rim* functionalized calix[4]arenes followed by reaction with hydroxyl group containing amines. The solubility of these calix[4]arene sulfonamides in water varies from $\sim 10^{-5}$ to $3.1 \cdot 10^{-1}$ M. A route via hydrophobically protected amines improves the purification.

Hydrophobic calix[4]arenes[1] have proven their use as building blocks in supramolecular chemistry. By (selective) functionalization[2] both at the phenolic OH groups (*lower rim*) and at the para positions of the phenol rings (*upper rim*) we could obtain selective receptors for cations,[3] anions,[4] and neutral molecules.[5] A high degree of lipophilicity is required for the successful application of calix[4]arene based ionophores in ion sensors[6] or ion transport through liquid membranes.[7] However, for *in vivo* application, such as coupling to organ specific peptides,[8] of functionalized calix[4]arenes, or for enzyme mimetics the solubility in water is a prerequisite. An obvious way to achieve this is the introduction of charged moieties as was shown by Ungaro et al.[9] who reported the preparation of *p-tert*-butylcalix[4]arene tetracarboxylic acid, while Shinkai et al.[10] synthesized the *p*-tetrasulfonato calix[4]arene. Also, *lower rim* functionalized *upper rim* sulfonato calix[4]arenes have been reported,[11] as well as *lower rim* sulfonato group containing derivatives.[11b,c] Other methods using charged species to achieve water solubility are the introduction of phosphinic acid groups,[12] cationic trialkylammonium groups,[13] or by capping of the aromatic rings of the calix[4]arene by Ru(II)-arene moieties as was shown by Atwood et al.[14]

In our investigations to develop hydrophilic ligands for ion complexation in water, we want to avoid unspecific binding of cations by anionic groups,[15] or repulsion by cationic groups in the receptor molecule and vice versa for anions. Therefore, we need neutral, water-soluble, functionalized calix[4]arenes, of which only a few examples have been reported in literature. Together with Shinkai et al.[16] we have determined the pK_a values of tetrakis[bis(2-hydroxyethyl)aminosulfonyl]calix[4]arenetetrol and Newkome et al.[17] have developed the silvanols bearing hydroxyl group containing amides at the calix[4]arene *upper rim*. Host-guest interactions of calix[4]arenes in water by means of fluorescence spectroscopy were studied by Shi et al.[18] In none of these cases are quantitative data about the water solubility given. Recently, Ungaro et al.[19] reported glycosylated calix[4]arenes of which only the tetrapropoxycalix[4]arene having four sugar moieties at the *upper rim* is water soluble up to 5 mM at room temperature. Other sugar moieties bearing calix-arenes have also been described.[20]

Recently, we reported the synthesis of calix[4]arene sulfonamides via direct chlorosulfonylation at the *upper rim* of *lower rim* functionalized calix[4]arenes, followed by reaction with an appropriate amine.[21] These sulfonamide

derivatives behave as hydrophobic, neutral anion receptors with a selectivity for hydrogen sulfate. In this paper, we describe[22] two different ways to synthesize neutral, water-soluble calix[4]arenes, namely a direct route via reaction of *lower rim* functionalized *upper rim* chlorosulfonylated calix[4]arenes with hydroxyl group containing amines and indirectly via a protection/deprotection route.

Two different tetrakis(chlorosulfonyl)calix[4]arenes, namely the tetrakis(ethoxymethoxy) 1 and the tetraethyl ester derivative 2[23] were selected as starting compounds. These chlorosulfonylated derivatives were reacted with amines that contained a different number of hydroxyl groups (Scheme 1). Reaction of 1 or 2 with ethanolamine in dichloromethane gave sulfonamide calix[4]arenes 3a and 4a both in 57% yield. From the corresponding reaction with diethanolamine, calix[4]arenes 3b and 4b were obtained in 42 and 49% yield, respectively. For solubility reasons, the reactions of 1 and 2 with tris(hydroxymethyl)aminomethane were carried out in DMSO to give derivatives 3c and 4c in 56 and 42% yield, respectively. Pure compounds were obtained after recrystallization of the crude products from ethanol in order to remove excess of amine and/or solvent. The ^{1}H NMR spectra of 3 and 4, which were recorded in polar solvents, show one singlet for the aromatic protons and one AB system for the protons of the methylene bridges.
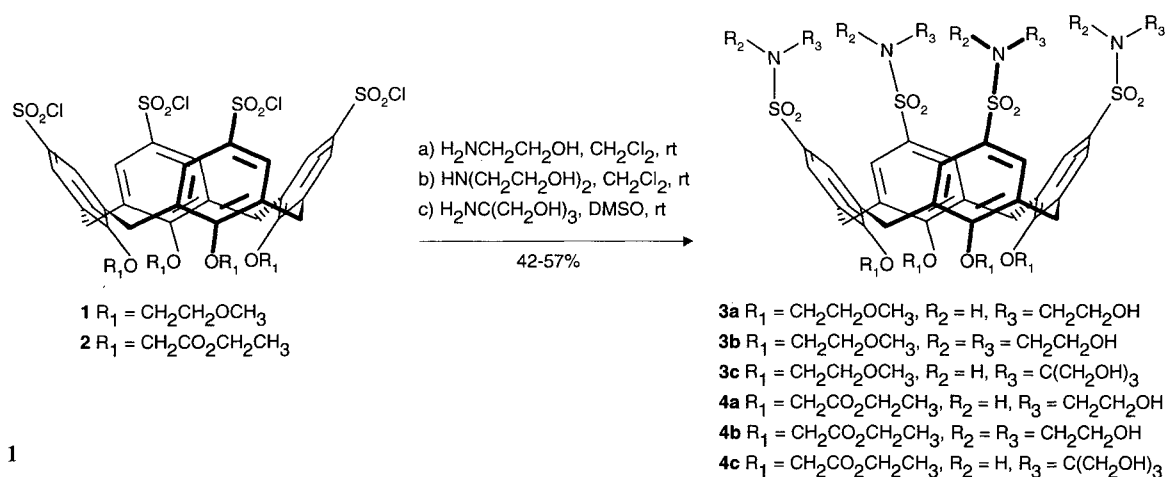
The water solubility of derivatives 3 and 4 was determined by UV spectrometry (Table). These data clearly demonstrate that the water solubility of the sulfonamide calix[4]arenes increases with the number of hydroxyl groups. Each additional hydroxyl group per aromatic unit of the calix[4]arene leads roughly to a hundred-fold increase in water solubility.

Since the purification of these calixarenes 3 and 4 is rather laborious, we decided to protect the hydroxyl groups of the amine with a *tert*-butyldimethylsilyl (TBDMS) group, comparable to what we and others[24] have done to modify cyclodextrins.
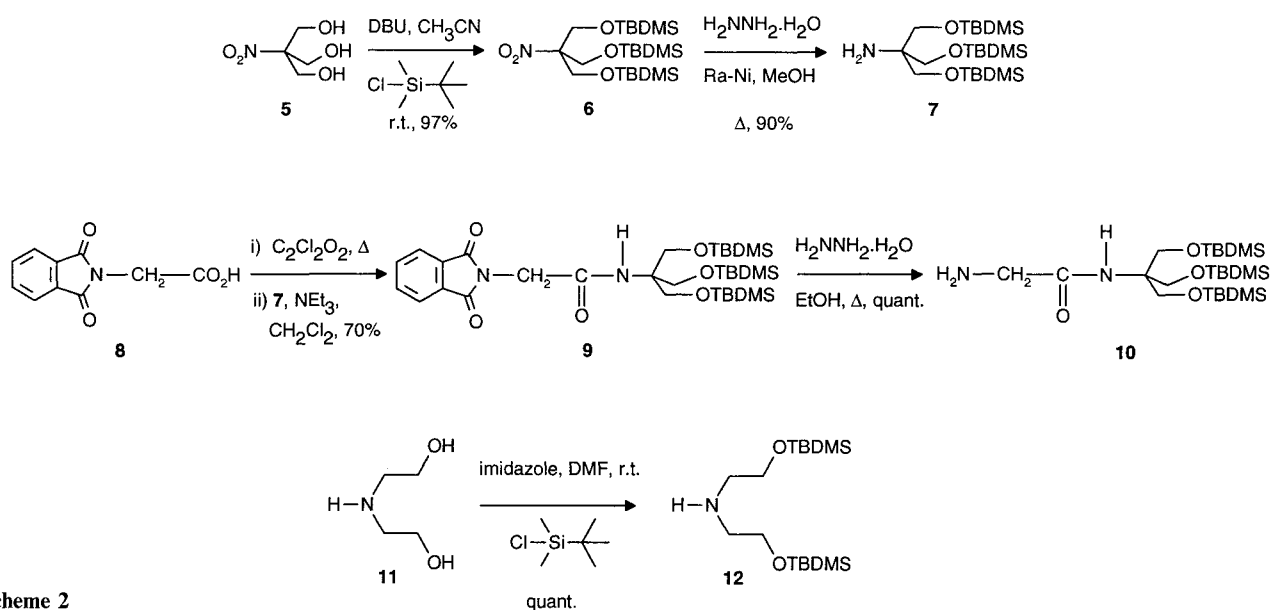
The synthesis of TBDMS-protected tris(hydroxymethyl)aminomethane (7) (Scheme 2) starts with the silylation of tris(hydroxymethyl)nitromethane (5)[25] to give tris(*tert*-

Table. Water Solubility of Neutral Calix[4]arenes at 25°C

Compound	Water Solubility (M)
3a	$\sim 10^{-5}$
3b	$(2.5 \pm 0.2) \times 10^{-3}$
3c	0.23 ± 0.02
4a	$\sim 10^{-5}$
4b	$(8.8 \pm 0.1) \times 10^{-4}$
4c	0.31 ± 0.02

Scheme 1

a) $H_2NCH_2CH_2OH$, CH_2Cl_2, rt
b) $HN(CH_2CH_2OH)_2$, CH_2Cl_2, rt
c) $H_2NC(CH_2OH)_3$, DMSO, rt

42-57%

1 $R_1 = CH_2CH_2OCH_3$
2 $R_1 = CH_2CO_2CH_2CH_3$

3a $R_1 = CH_2CH_2OCH_3$, $R_2 = H$, $R_3 = CH_2CH_2OH$
3b $R_1 = CH_2CH_2OCH_3$, $R_2 = R_3 = CH_2CH_2OH$
3c $R_1 = CH_2CH_2OCH_3$, $R_2 = H$, $R_3 = C(CH_2OH)_3$
4a $R_1 = CH_2CO_2CH_2CH_3$, $R_2 = H$, $R_3 = CH_2CH_2OH$
4b $R_1 = CH_2CO_2CH_2CH_3$, $R_2 = R_3 = CH_2CH_2OH$
4c $R_1 = CH_2CO_2CH_2CH_3$, $R_2 = H$, $R_3 = C(CH_2OH)_3$

Scheme 2

5 → DBU, CH_3CN / Cl-Si, r.t., 97% → 6 → $H_2NNH_2\cdot H_2O$ / Ra-Ni, MeOH, Δ, 90% → 7

8 → i) $C_2Cl_2O_2$, Δ / ii) 7, NEt_3, CH_2Cl_2, 70% → 9 → $H_2NNH_2\cdot H_2O$ / EtOH, Δ, quant. → 10

11 → imidazole, DMF, r.t. / Cl-Si, quant. → 12

butyldimethylsilyloxymethyl)nitromethane (6) in almost quantitative yield using 3.6 equivalents of DBU and 3.3 equivalents of TBDMSCl in acetonitrile.[26] Subsequent reduction of the nitro group of 6 using hydrazine monohydrate and a catalytic amount of Raney nickel in refluxing methanol[27] afforded the corresponding amine 7 in 90% yield. Attempts to react amine 7 directly with chlorosulfonylated calix[4]arenes 1 and 2 using different conditions failed probably due to steric hindrance between the quite bulky chlorosulfonic groups and the amino group surrounded by the three TBDMS moieties. Therefore we decided to introduce a spacer unit. The acid chloride of N-phthaloylglycine 8 was reacted with amine 7 to afford compound 9 in 70% yield. The amino group was deprotected quantitatively by refluxing 9 in ethanol with ten equivalents of hydrazine monohydrate to give amine 10; the overall yield of amine 10 starting from nitro compound 5 is 60%.

Diethanolamine 11 was selectively O-alkylated by reaction with 3.6 equivalents of TBDMSCl and 3.3 equival-

ents of imidazole in DMF to give amine 12 in quantitative yield.[28]

Reaction of chlorosulfonylated calix[4]arenes 1 and 2 with amine 10 or 12 gave sulfonamide calix[4]arenes 13–16 in 83, 86, 72 and 78% yield, respectively. These derivatives are soluble in organic solvents and can be easily purified by column chromatography.

In order to obtain water-soluble calix[4]arenes eight to twelve TBDMS-groups have to be removed from the protected derivatives 13–16. We used a method first published by Corey et al.[29] involving reaction with SiF_4 which converts the TBDMS-groups into SiF_3-groups. The advantage of this method is that the product is soluble in solvents like dichloromethane and acetonitrile (or mixtures), allowing complete substitution of the TBDMS-groups. Upon reaction with water the $OSiF_3$-groups are hydrolyzed to give the desired water-soluble calix[4]arenes 17,18,3b, and 4b in quantitative yields. ¹H NMR spectroscopy shows that the deprotection via
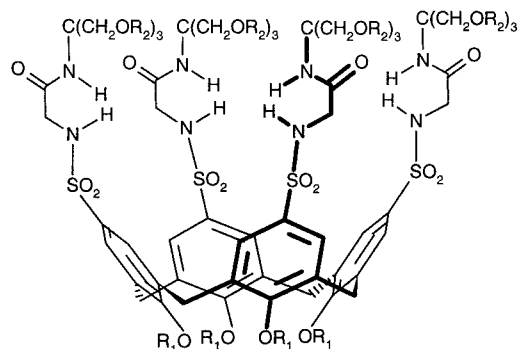
13 R₁ = CH₂CH₂OCH₃; R₂ = TBDMS
14 R₁ = CH₂CO₂CH₂CH₃; R₂ = TBDMS
17 R₁ = CH₂CH₂OCH₃; R₂ = H
18 R₁ = CH₂CO₂CH₂CH₃; R₂ = H
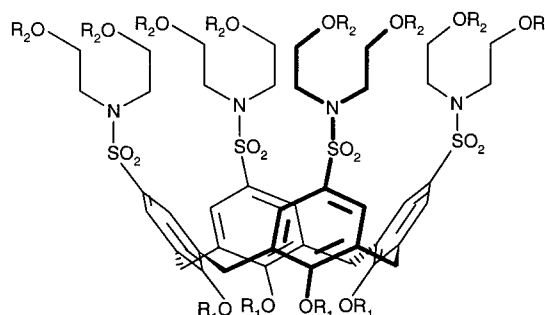
15 R₁ = CH₂CH₂OCH₃; R₂ = TBDMS
16 R₁ = CH₂CO₂CH₂CH₃; R₂ = TBDMS

this method takes place completely. Calixarenes **3b** and **4b** exhibit the same spectral data as those obtained via the direct method described above.

The ¹H NMR spectra of compounds **17** and **18**, having an additional glycine spacer compared to derivatives **3c** and **4c**, show a different behavior in water. These calix[4]arenes, synthesized via the protection route, exhibit multiple signals where singlets were expected. Upon heating the NMR samples, the multiplicity disappeared and the spectra showed the expected signals. This behavior is attributed to aggregation of these compounds caused by the presence of the glycine spacer unit. A similar observation was reported by Shinkai et al.[30] who studied the influence of the distance of water-solubilizing groups to the cavity formed by the phenolic units. They found that a larger distance leads to aggregation whereas a short distance gives derivatives that do not aggregate.

Compared to the direct method, the protection/deprotection approach enables simpler workup and purification, and gives increased yields. We feel that this methodology may find general applicability for the synthesis of neutral, water-soluble molecular building blocks.

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded with a Bruker AC250F (250 MHz) spectrometer in the absence of an internal standard. In case of silylated derivatives the protons of the SiMe₂ groups were used as an internal standard. ¹H NMR spectra at elevated temperatures were recorded with a Varian Unity 400WB spectrometer in the absence of an internal standard. FAB mass spectra were obtained with a Finnigan MAT90 mass spectrometer using *m*-nitrobenzyl alcohol (NBA) as a matrix. CH₂Cl₂ was distilled from CaCl₂ and stored over molecular sieves (4 Å), MeCN was stored over molecular sieves (3 Å), MeOH was distilled over Mg and stored over molecular sieves (4 Å), DMSO was distilled from CaO and stored over molecular sieves (4 Å). All other solvents and chemicals were of reagent grade and were used without purification. Silica gel (particle size 0.040–0.063 mm, 230–240 mesh) was obtained from Merck. All reactions were carried out under an argon atmosphere. For reasons of clarity and in order to reduce space, the name calix[4]arene was used instead of the original IUPAC name: pentacyclo[19.3.1.1³,⁷.1⁹,¹³.1¹⁵,¹⁹]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecane. The presence of solvent in the analytical samples was confirmed by ¹H NMR spectroscopy.

Sulfonamide Calix[4]arenes 3a,b and 4a,b; General Procedure:
To a solution of calix[4]arene **1** or **2** in CH₂Cl₂ (0.025 M solution) was added 2-aminoethanol (for **3a** or **4a**) (10 equiv) or 2,2′-imino-diethanol **11** (for **3b** or **4b**) (10 equiv). After stirring the reaction mixture at r.t. for 8 h it was quenched with 1 N HCl (25 mL, in the case of calix[4]arene **1**) or H₂O (25 mL, in the case of calix[4]arene **2**). The organic layer was washed with H₂O (3 × 25 mL). The combined aqueous layers were extracted with CH₂Cl₂ (3 × 25 mL). The combined organic layers were evaporated to yield the crude products, which were recrystallized from EtOH to give the pure compounds as white solids.

5,11,17,23-Tetrakis[(2-hydroxyethyl)aminosulfonyl]-25,26,27,28-tet-rakis[(2-methoxy)ethoxy]calix[4]arene (**3a**): Yield: 57%; mp 167–168 °C.

¹H NMR (250 MHz, DMSO-d₆): δ = 7.27 (s, 8 H), 7.00 (t, J = 7.1 Hz, 4 H), 4.54 (t, J = 5.1 Hz, 4 H), 4.52 (part of ABq, 4 H), 4.16 (t, J = 5.2 Hz, 8 H), 3.79 (t, J = 5.2 Hz, 8 H), 3.5–3.4 [m (including part of ABq), 12 H], 3.31 (s, 12 H), 2.56 (q, J = 5.9 Hz, 8 H).

¹³C NMR (62.9 MHz, DMSO-d₆): δ = 158.8 (s), 135.0 (s), 134.4 (s), 126.8 (d), 73.6 (t), 71.2 (t), 60.0 (t), 58.0 (q), 44.9 (t), 29.8 (t).

FAB-MS: m/z = 1149.6 [(M+H)⁺, calcd 1149.3].

Anal. Calcd for C₄₈H₆₈N₄O₂₀S₄ · 0.6H₂O: C, 49.69; H, 6.01; N, 4.83. Found: C, 49.67; H, 6.07; N, 4.58.

5,11,17,23-Tetrakis[(2-hydroxyethyl)aminosulfonyl]-25,26,27,28-tet-rakis[(ethoxycarbonyl)methoxy]calix[4]arene (**4a**): Yield: 57%; mp 237–239 °C.

¹H NMR (250 MHz, DMSO-d₆): δ = 7.29 (s, 8 H), 7.07 (br s, 4 H), 4.84 (s, 8 H), 4.79 and 3.49 (ABq, J = 13.5 Hz, 8 H), 4.57 (br s, 4 H), 4.15 (q, J = 7.1 Hz, 8 H), 3.35 (br t, 8 H), 2.57 (br t, 8 H), 1.22 (t, J = 7.1 Hz, 12 H).

¹³C NMR (62.9 MHz, DMSO-d₆): δ = 169.1 (s), 157.8 (s), 135.0 (s), 134.5 (s), 127.0 (d), 71.1 (t), 60.5 (t), 59.9 (t), 44.9 (t), 30.7 (t), 13.9 (q).

FAB-MS: m/z = 1261.7 [(M+H)⁺, calcd 1261.3].

Anal. Calcd for C₅₂H₆₈N₄O₂₄S₄·4.2H₂O: C, 46.70; H, 5.76; N, 4.19. Found: C, 46.40; H, 5.97; N, 4.46.

5,11,17,23-Tetrakis[bis(2-hydroxyethyl)aminosulfonyl]-25,26,27,28-tetrakis[(2-methoxy)ethoxy]calix[4]arene (**3b**): Yield: 42%; mp 215–216 °C.

¹H NMR (250 MHz, DMSO-d₆): δ = 7.33 (s, 8 H), 4.80 (t, J = 5.4 Hz, 8 H), 4.47 and 3.55 (ABq, J = 12.5 Hz, 8 H), 4.16 (t, J = 5.0 Hz, 8 H), 3.80 (t, J = 5.0 Hz, 8 H), 3.48 (q, J = 5.5 Hz, 16 H), 3.32 (s, 12 H), 2.86 (t, J = 5.2 Hz, 16 H).

¹³C NMR (62.9 MHz, DMSO-d₆): δ = 159.0 (s), 135.1 (s), 132.1 (s), 127.3 (d), 73.6 (t), 71.1 (t), 60.1 (t), 58.0 (q), 51.5 (t), 30.0 (t).

FAB-MS: m/z = 1325.4 [(M+H)⁺, calcd 1325.4].

Anal. Calcd for $C_{56}H_{84}N_4O_{24}S_4 \cdot 2H_2O$: C, 49.40; H, 6.51; N, 4.11. Found: C, 49.57; H, 6.42; N, 4.20.

5,11,17,23-Tetrakis[bis(2-hydroxyethyl)aminosulfonyl]-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene (**4b**): Yield: 49%; mp 211–213°C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.36 (s, 8 H), 4.86 (s, 8 H), 4.78 (t, J = 5.4 Hz, 8 H), 4.75 and 3.62 (ABq, J = 13.4 Hz, 8 H), 4.16 (q, J = 7.1 Hz, 8 H), 3.48 (q, J = 5.4 Hz, 16 H), 2.86 (br t, 16 H), 1.22 (t, J = 7.1 Hz, 12 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 169.0 (s), 158.1 (s), 134.8 (s), 132.7 (s), 127.6 (d), 71.0 (t), 60.5 (t), 60.1 (t), 51.5 (t), 30.5 (t), 13.9 (q).

FAB-MS: m/z = 1438.6 [(M+H)$^+$, calcd 1438.7].

Anal. Calcd for $C_{60}H_{84}N_4O_{28}S_4 \cdot 3.2H_2O$: C, 48.21; H, 6.09; N, 3.75. Found: C, 48.32; H, 5.96; N, 4.11.

Sulfonamide Calix[4]arenes 3c and 4c; General Procedure:

To a solution of calix[4]arene **1** or **2** in DMSO (0.22 M solution) was added tris(hydroxymethyl)aminomethane (8 equiv). After the reaction mixture had been stirred at r.t. for 8 h, CH_2Cl_2 was added. The precipitate formed was filtered off and was recrystallized several times from EtOH (until ^{1}H NMR spectroscopy showed complete removal of all DMSO and excess starting amine) to yield a white solid.

5,11,17,23-Tetrakis[tris(hydroxymethyl)methylaminosulfonyl]-25,26,27,28-tetrakis[(2-methoxy)ethoxy]calix[4]arene (**3c**): Yield: 56%; mp 153–155°C.

^{1}H NMR (250 MHz, D_2O): δ = 7.29 (s, 8 H), 4.51 and 3.44 (ABq, J = 13.2 Hz, 8 H), 4.25 (t, J = 4.7 Hz, 8 H), 3.92 (t, J = 4.7 Hz, 8 H), 3.68 (s, 24 H), 3.38 (s, 12 H).

^{13}C NMR (62.9 MHz, D_2O): δ = 158.5 (s), 137.3 (s), 135.1 (s), 126.1 (d), 73.2 (t), 72.1 (t), 61.7 (t), 59.8 (s), 58.1 (q), 30.8 (t).

FAB-MS: m/z = 1099.4 [M−SO$_2$NHC(CH$_2$OH)$_3$−C(CH$_2$OH)$_3$]$^+$, calcd 1099.3].

Anal. Calcd for $C_{56}H_{84}N_4O_{28}S_4 \cdot 10H_2O$: C, 42.85; H, 6.67; N, 3.57. Found: C, 42.81; H, 6.52; N, 3.57.

5,11,17,23-Tetrakis[tris(hydroxymethyl)methylaminosulfonyl]-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene (**4c**): Yield: 42%; mp 166–168°C.

^{1}H NMR (250 MHz, D_2O): δ = 7.32 (s, 8 H), 4.90 (s, 8 H), 4.72 and 3.49 (ABq, J = 13.6 Hz, 8 H), 4.22 (q, J = 7.1 Hz, 8 H), 3.68 (s, 24 H), 1.26 (t, J = 7.1 Hz, 12 H).

^{13}C NMR (62.9 MHz, D_2O): δ = 172.0 (s), 157.4 (s), 138.1 (s), 134.7 (s), 126.5 (d), 71.6 (t), 62.4 (t), 61.7 (s), 59.6 (t), 31.3 (t), 13.6 (q).

FAB-MS: m/z = 1133.4 [M−2×SO$_2$NHC(CH$_2$OH)$_3$+H]$^+$, calcd 1133.3].

No satisfactory elemental analysis could be obtained due to the very hygroscopic character of the compound.

Determination of the Water Solubility of Calix[4]arenes 3 and 4 by means of UV Measurements:

Solutions of the compounds in doubly distilled H_2O were measured at 25°C. The concentrations were chosen to give a maximal absorbance between 0.2 and 0.8 and a plot was drawn of the absorbance against the concentration. A saturated solution was filtered and diluted with a known amount of H_2O to give an absorbance maximum in the same region and the concentration of the saturated solution could be calculated using the plot.

Tris(tert-butyldimethylsilyloxymethyl)nitromethane (6):

Tris(hydroxymethyl)nitromethane (5.00 g, 33.1 mmol) was added to a solution of tert-butyldimethylsilyl chloride (16.54 g, 0.110 mol) and DBU (17.8 mL, 0.119 mol) in anhyd MeCN (75 mL). The mixture was stirred overnight at r.t. After evaporation of the solvent the crude product was taken up in CH_2Cl_2 (150 mL) and ice water (100 mL). Subsequently the organic layer was washed with 0.1 N HCl (100 mL) and sat. aq NaHCO$_3$ (100 mL). Evaporation of the solvent gave **6** as a red oil, which solidified under high vacuum; yield: 15.80 g (97%).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.91 (s, 6 H), 0.82 (s, 27 H), 0.00 (s, 18 H).

^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 94.8 (s), 59.7 (t), 25.7 (q), 18.1 (s), −5.7 (q).

FAB-MS: m/z = 494.1 [(M+H)$^+$, calcd 494.4].

Tris(tert-butyldimethylsilyloxymethyl)aminomethane (7):

To a solution of **6** (0.47 g, 0.95 mmol) and NH$_2$NH$_2 \cdot$H$_2$O (35 mL, 72 mmol) in MeOH (20 mL) was added a catalytic amount of Raney nickel. The mixture was refluxed until ^{1}H NMR analysis of an aliquot after workup showed complete disappearence of the signal at δ = 3.91. The mixture was filtered over Hyflo filter aid and the filter was rinsed with CH$_2$Cl$_2$ (3 × 100 mL). The solvent was evaporated and the crude product was taken up in CH$_2$Cl$_2$ (50 mL) and washed with H$_2$O (50 mL). The organic layer was dried (Na$_2$SO$_4$). Evaporation of the solvent gave **7** as a yellow oil; yield: 0.40 g (90%).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.41 (s, 6 H), 0.85 (s, 27 H), 0.00 (s, 18 H).

^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 64.1 (t), 57.4 (s), 25.9 (q), 18.2 (s), −5.6 (q).

FAB-MS: m/z = 464.8 [(M+H)$^+$, calcd 464.3].

N-[Tris(tert-butyldimethylsilyloxymethyl)methyl]-2-N'-phthaloyl-acetamide (9):

N-phthaloylglycine (**8**; 4.42 g, 21.5 mmol) was refluxed in oxalyl chloride (20 mL) for 2 h. After evaporation of the excess of oxalyl chloride, CH$_2$Cl$_2$ (75 mL) was added. To this mixture was added dropwise over 15 min a solution of amine **7** (5.00 g, 10.8 mmol) and Et$_3$N (5.6 mL, 40 mmol) in CH$_2$Cl$_2$ (25 mL). The mixture was stirred at r.t. for 3 h and quenched with H$_2$O (50 mL). The organic layer was washed with H$_2$O (2 × 100 mL). After evaporation of the solvent the crude product was purified via column chromatography (silica gel, CH$_2$Cl$_2$) to give pure **9** as a white solid; yield: 4.95 g (70%); mp 97–99°C.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.86–7.82 (m, 2 H), 7.74–7.68 (m, 2 H), 5.84 (s, 1 H), 4.25 (s, 2 H), 3.80 (s, 6 H), 0.84 (s, 27 H), 0.00 (s, 18 H).

^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 167.5 (s), 165.1 (s), 134.1 (d), 132.0 (s), 62.1 (s), 60.7 (t), 41.1 (t), 25.8 (q), 18.1 (s), −5.6 (q).

FAB-MS: m/z = 651.5 [(M+H)$^+$, calcd 651.4].

Anal. Calcd for $C_{32}H_{58}N_2O_6Si_3$: C, 59.03; H, 8.98; N, 4.30. Found: C, 59.27; H, 8.95; N, 4.37.

N-[Tris(tert-butyldimethylsilyloxymethyl)methane]-2-aminoaceta-mide (10):

A solution of phthalimide **9** (2.52 g, 3.87 mmol) and NH$_2$NH$_2 \cdot$ H$_2$O (1.9 mL, 39 mmol) in EtOH (50 mL) was refluxed for 3 h. After evaporation of the solvent the product was taken up in CH$_2$Cl$_2$ (250 mL) and 0.5 N HCl (100 mL). After separation of the layers, the organic layer was washed with 1 N NaOH (200 mL). Evaporation of the solvent yielded a white solid, which was dried by dissolving in 2,2-dimethoxypropane and subsequent evaporation of the solvent; yield: 1.98 g (98%); mp 64–65°C.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.22 (s, 1 H), 3.83 (s, 6 H), 3.20 (s, 2 H), 1.67 (s, 2 H), 0.84 (s, 27 H), 0.00 (s, 18 H).

^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 172.0 (s), 61.5 (s), 60.7 (t), 45.5 (t), 25.8 (q), 18.2 (s), −5.5 (q).

FAB-MS: m/z = 521.2 [(M+H)$^+$, calcd 521.4].

Anal. Calcd for $C_{24}H_{56}N_2O_4Si_3$: C, 55.33; H, 10.83; N, 5.38. Found: C, 55.32; H, 11.04; N, 5.36.

Bis(tert-butyldimethylsilyloxyethyl)amine (12):

To a solution of tert-butyldimethylsilyl chloride (9.75 g, 64.7 mmol) and imidazole (9.17 g, 135 mmol) in DMF (5 mL) was added diethanolamine (1.89 g, 18.0 mmol). After 30 min the solvent was evaporated, the residue was taken up in CH$_2$Cl$_2$ (100 mL) and washed with H$_2$O (5 × 100 mL). Evaporation of the solvent yielded a colorless oil; yield: 5.68 g (95%).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.67 (t, J = 5.4 Hz, 4 H), 2.79 (t, J = 5.4 Hz, 4 H), 0.85 (s, 18 H), 0.00 (s, 12 H).

^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 62.4 (t), 51.7 (t), 25.9 (q), 18.3 (s), −5.4 (q).

EI-MS: m/z = 318.229 [(M−CH$_3$)$^+$].

Calix[4]arenes 13–16; General Procedure:

To a solution of the chlorosulfonylated calix[4]arene **1** or **2** in CH$_2$Cl$_2$ were added the TBDMS-protected amine **10** or **12** (4.4 equiv) and Et$_3$N (6 equiv). The mixture was stirred at r.t. for 3 h. CH$_2$Cl$_2$ (100 mL) was added and the mixture was washed with H$_2$O (2×100 mL). The organic layer was evaporated to dryness and the residue was purified by column chromatography (silica gel, 3–10% EtOAc in CH$_2$Cl$_2$).

5,11,17,23-Tetrakis[(tris(tert-butyldimethylsilyloxymethyl)methyl-carbamoyl)methylaminosulfonyl]-25,26,27,28-tetrakis[(2-methoxy)ethoxy]calix[4]arene (13): Yield: 83%; mp 100–102°C.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.23 (s, 8 H), 6.74 (s, 4 H), 6.68 (br t, 4 H), 4.57 and 3.23 (ABq, J = 13.2 Hz, 8 H), 4.16 (t, J = 4.9 Hz, 8 H), 3.80 (s, 24 H), 3.72 (t, J = 4.9 Hz, 8 H), 3.32 (s, 12 H), 3.26–3.20 [m, (including part of ABq), 12 H], 0.84 (s, 108 H), 0.00 (s, 72 H).

^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 168.2 (s), 159.1 (s), 135.4 (s), 134.0 (s), 127.8 (d), 73.8 (t), 71.4 (t), 62.2 (s), 60.7 (t), 58.6 (q), 46.4 (t), 30.6 (t), 25.9 (q), 18.2 (s), −5.4 (q).

FAB-MS: m/z = 2987.9 [(M+H)$^+$, calcd 2987.5].

Anal. Calcd for C$_{136}$H$_{264}$N$_8$O$_{32}$S$_4$Si$_{12}$ · 2H$_2$O: C, 54.00; H, 8.93; N, 3.70. Found: C, 54.01; H, 9.04; N, 3.72.

5,11,17,23-Tetrakis[(tris(tert-butyldimethylsilyloxymethyl)methyl-carbamoyl)methylaminosulfonyl]-25,26,27,28-tetrakis[(ethoxycarbo-nyl)methoxy]calix[4]arene (14): Yield: 86%; mp 105–107°C.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.27 (s, 8 H), 6.72 (bs, 4 H), 6.62 (br s, 4 H), 4.95 and 3.33 (ABq, J = 13.5 Hz, 8 H), 4.77 (s, 8 H), 4.17 (q, J = 7.1 Hz, 8 H), 3.80 (s, 24 H), 3.36–3.30 [m, (including part of ABq], 12 H), 1.22 (t, J = 7.1 Hz, 12 H), 0.84 (s, 108 H), 0.00 (s, 72 H).

^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 169.1 (s), 168.2 (s), 158.6 (s), 134.9 (s), 134.7 (s), 128.1 (d), 71.5 (t), 62.2 (s), 61.0 (t), 60.7 (t), 46.4 (t), 31.4 (t), 25.9 (q), 18.2 (s), 14.1 (q), −5.5 (q).

FAB-MS: m/z = 3123.6 [(M+Na)$^+$, calcd 3123.7].

Anal. Calcd for C$_{140}$H$_{264}$N$_8$O$_{36}$S$_4$Si$_{12}$: C, 54.23; H, 8.58; N, 3.61. Found: C, 54.58; H, 8.75; N, 3.64.

5,11,17,23-Tetrakis[bis(2-(tert-butyldimethylsilyloxy)ethyl)amino-sulfonyl]-25,26,27,28-tetrakis[(2-methoxy)ethoxy]calix[4]arene (15): Yield: 72%; mp 109–111°C.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.18 (s, 8 H), 4.57 and 3.24 (ABq, J = 13.1 Hz, 8 H), 4.16 (t, J = 4.9 Hz, 8 H), 3.76 (t, J = 4.9 Hz, 8 H), 3.67 (t, J = 6.0 Hz, 16 H), 3.35 (s, 12 H), 3.10 (t, J = 6.0 Hz, 16 H), 0.83 (s, 72 H), 0.00 (s, 48 H).

^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 158.7 (s), 134.9 (s), 134.7 (s), 127.4 (d), 73.7 (t), 71.5 (t), 62.5 (t), 58.6 (q), 51.6 (t), 30.5 (t), 25.9 (q), 18.2 (s), −5.3 (q).

FAB-MS: m/z = 2262.2 [(M+Na)$^+$, calcd 2262.1].

Anal. Calcd for C$_{104}$H$_{196}$N$_4$O$_{24}$S$_4$Si$_8$ · 6H$_2$O: C, 53.21; H, 8.93; N, 2.39. Found: C, 53.26; H, 8.66; N, 2.36.

5,11,17,23-Tetrakis[bis(2-(tert-butyldimethylsilyloxy)ethyl)amino-sulfonyl]-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]-arene (16): Yield: 78%; mp 139–141°C.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.21 (s, 8 H), 4.97 and 3.34 (ABq, J = 13.5 Hz, 8 H), 4.79 (s, 8 H), 4.19 (q, J = 7.2 Hz, 8 H), 3.68 (t, J = 6.1 Hz, 16 H), 3.10 (t, J = 6.1 Hz, 16 H), 1.27 (t, J = 7.2 Hz, 12 H), 0.84 (s, 72 H), 0.00 (s, 48 H).

^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 169.3 (s), 158.4 (s), 135.4 (s), 134.4 (s), 127.8 (d), 71.5 (t), 62.5 (t), 60.9 (t), 51.6 (t), 31.4 (t), 25.9 (q), 18.2 (s), 14.2 (q), −5.3 (q).

FAB-MS: m/z = 2374.2 [(M+Na)$^+$, calcd 2374.1].

Anal. Calcd for C$_{108}$H$_{196}$N$_4$O$_{28}$S$_4$Si$_{12}$: C, 55.16; H, 8.40; N, 2.38. Found: C, 55.21; H, 8.73; N, 2.30.

Desilylation of 13–16; General Procedure:

A solution of the calix[4]arenes **13–16** in a mixture of CH$_2$Cl$_2$ (20 mL) and MeCN (20 mL) was stirred at r.t. for 48 h under an SiF$_4$ atmosphere. After evaporation of the solvent the residue was taken up in H$_2$O (50 mL) and washed with petroleum ether (bp 60–80°C, 50 mL). Freeze drying of the aqueous phase gave pure compounds as white solids.

5,11,17,23-Tetrakis[(tris(hydroxymethyl)methylcarbamoyl)methyl-aminosulfonyl]-25,26,27,28-tetrakis[(2-methoxy)ethoxy]calix[4]-arene (17): Yield: 93%; mp 161–163°C.

^{1}H NMR (250 MHz, D$_2$O): δ = 7.32 (br s, 8 H), 4.57 and 3.51 (br ABq, 8 H), 4.29 (br t, 8 H), 3.92 (br t, 8 H), 3.70 (br s, 24 H), 3.57 (br s, 8 H), 3.40 (br s, 12 H).

FAB-MS: m/z = 1617.9 [(M+H)$^+$, calcd 1617.5].

Anal. Calcd for C$_{64}$H$_{96}$N$_8$O$_{32}$S$_4$ · 3H$_2$O: C, 45.98; H, 6.15; N, 6.70. Found: C, 46.10; H, 6.12; N, 6.75.

5,11,17,23-Tetrakis[(tris(hydroxymethyl)methylcarbamoyl)methyl-aminosulfonyl]-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]-calix[4]arene (18): Yield: 95%; mp 157–159°C.

^{1}H NMR (250 MHz, D$_2$O): δ = 7.37 (br s, 8 H), 4.90 and 3.58 (br ABq, 8 H), 4.70 (br s, 8 H), 4.35 (br q, 8 H), 3.72 (br s, 24 H), 3.45 (br s, 8 H), 1.35 (br t, 12 H).

FAB-MS: m/z = 1751.8 [(M+Na)$^+$, calcd 1751.5].

Anal. Calcd for C$_{68}$H$_{96}$N$_8$O$_{36}$S$_4$ · 4H$_2$O: C, 45.33; H, 5.82; N, 6.22. Found: C, 45.47; H, 5.76; N, 6.35.

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