Chlorosulfonylated Calix[4]arenes: Precursors for Neutral Anion Receptors with a Selectivity for Hydrogen Sulfate

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Introduction

In nature phosphate and sulfate binding proteins are very important receptors for the active transport systems in the cell.[1,2] A very high selectivity in binding has been observed in prokaryotic, periplasmic phosphate and sulfate binding proteins, which demonstrate $>10^5$ selectivity for binding phosphate over sulfate and sulfate over phosphate, respectively.[3] In both proteins the specific binding exclusively takes place through hydrogen bonding.

Synthetic receptors that bind anions contain either positively charged guanidinium or ammonium groups[4] or Lewis acid metal centers[5] to accomplish anion binding. Recently we reported functionalized uranyl-containing salenes[6] and sulfonamides[7] derived from tris(aminoethyl)-amine (TREN) that form complexes with hard anions in CH_3CN with a selectivity for $H_2PO_4^-$. In the present paper we report anion receptors based on chlorosulfonylated calix[4]arenes.[8]

Calix[4]arenes are important building blocks in supramolecular chemistry.[10,11] They can be (selectively) functionalized both at the phenolic OH groups (lower rim) and at the para positions of the phenol rings (upper rim).[12]

Results and Discussion

The starting calixarene tetraamides **1g** and **1h** were obtained by reaction of **1a** with the appropriate *N,N*-dialkyl-2-chloroacetamide in the presence of potassium iodide and K_2CO_3 as a base in refluxing acetonitrile for 18 h in 78 and 58% yield, respectively. Reaction of calix-[4]arenes **1a,c,e,f** (all cone conformation) with 40 equiv of chlorosulfonic acid in $CHCl_3$ at room temperature for 2–3 h (method A) afforded the tetrakis(chlorosulfonyl)-calix[4]arenes **2a,c,e,f** in 52–69% yield upon recrystallization of the crude reaction mixture. The ^1H NMR spectra of **2a,c,e,f** indicate the presence of four identical rings. Under these conditions the tetrapropoxycalix[4]-arene **1b** did not give the expected tetrakis(chlorosulfonyl)-calix[4]arene **2b** but the tetrahydroxytetrakis(chloro-sulfonyl)calix[4]arene **2a** in 35% yield. Apparently under the acidic conditions, the propyl ether groups are not stable.[13] Only a few examples of calixarenes having reactive chlorosulfonyl (SO_2Cl) groups at the upper rim are known.[15,16] They were prepared in two steps viz. sulfonylation followed by treatment with thionyl chloride,[15,16] although it is known that the SO_2Cl moiety can in principle be introduced in a one step[17] like in the synthesis of chlorosulfonyl benzocrown ethers.[18]

Under the same conditions, the 1,3-alternate conformer of **1c**, calix[4]arene **1d**, gave a complex reaction mixture. However, heating of **1d** at 50 °C for 20 min (method B) gave the tetrakis(chlorosulfonyl)calix[4]arene **2d** in 54% yield. The ^1H NMR spectrum of **2d** shows a singlet at δ 3.79 for the methylene bridge protons whereas in the ^{13}C NMR spectrum the corresponding carbon absorptions are present at δ 34.5 which are both characteristic for a calix-[4]arene in the 1,3-alternate conformation.[19,20]

Surprisingly, treatment of calix[4]arene amides **1g** and **1h** (cone conformation) with chlorosulfonic acid at room temperature for 2–3 h gave the *bis*(chlorosulfonyl)calix-[4]arenes **3a** and **3b** in 42 and 27% yield, respectively. Probably under the strongly acidic conditions, the amide groups of **1g** and **1h** are protonated[21] which results in a lower reactivity of the para positions of the corresponding aromatic rings. The two SO_2Cl groups are introduced at diametrical aromatic rings as was concluded from the symmetry of the ^1H NMR spectra. The ^1H NMR spectrum of **3a** exhibits a singlet at δ 7.79 for the hydrogens of the chlorosulfonylated rings and a triplet and a doublet at δ 6.40 and 6.18, respectively, for the hydrogens of the unreacted rings. Because of the symmetry there is only one AB system (δ 5.34 and 3.36) for the methylene bridge protons. Compounds **3a** and **3b** represent the first examples of calix[4]arenes having two SO_2Cl groups. These compounds are not accessible via the two-step procedure because to the best of our knowledge selective sulfonylation

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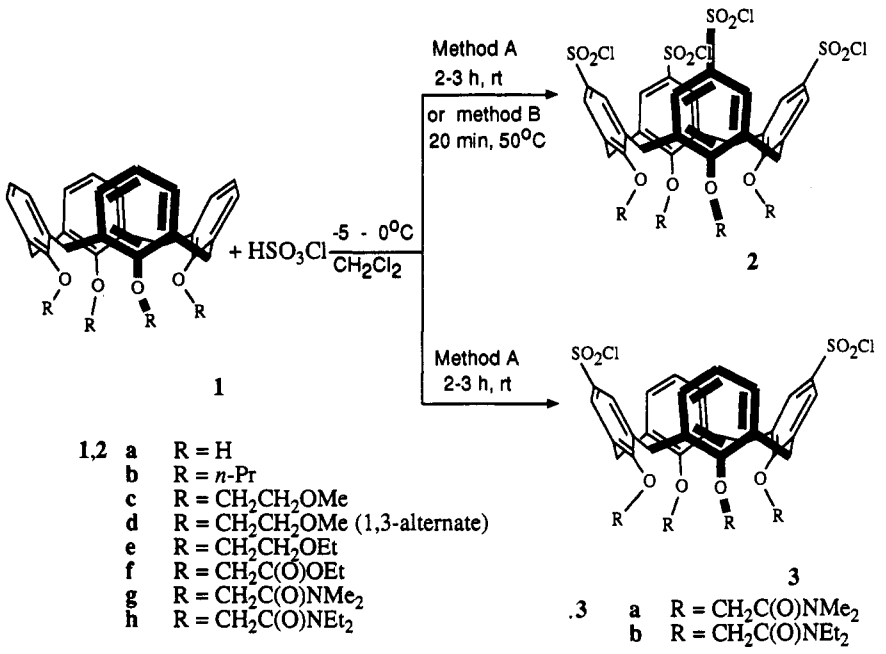
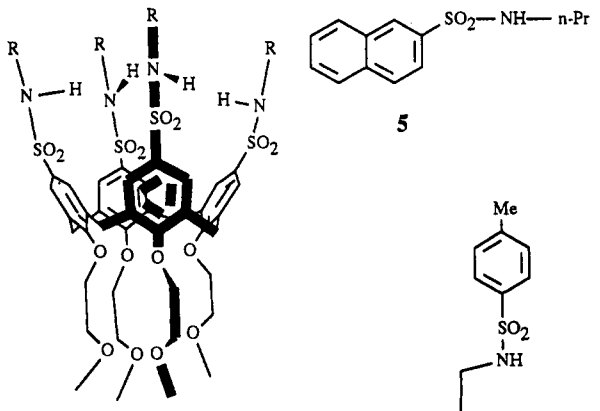
Scheme I



1,2 **a** R = H
b R = *n*-Pr
c R = CH_2CH_2OMe
d R = CH_2CH_2OMe (1,3-alternate)
e R = CH_2CH_2OEt
f R = $CH_2C(O)OEt$
g R = $CH_2C(O)NMe_2$
h R = $CH_2C(O)NEt_2$

.3 **a** R = $CH_2C(O)NMe_2$
b R = $CH_2C(O)NEt_2$

Chart I



4 **a** R = H
b R = *n*-Pr
c R = *tert*-Bu
d R = $CH_2CH_2NHC(O)Me$

5

6

of calix[4]arenes is unknown. Method B gave the tetrakis(chlorosulfonyl)calix[4]arenes **2g** and **2h** both in 61% yield.

Because TREN-derived sulfonamides form complexes with anions (vide supra),[7] these tetrakis(chlorosulfonyl)calix[4]arenes **2** might be suitable precursors for the synthesis of *hydrophobic, neutral anion receptors*. Reaction of **2c** with ammonia, *n*-propylamine, *tert*-butylamine, or *N*-acetylethylenediamine in CH_2Cl_2 for 4 h gave the corresponding calix[4]arene sulfonamides **4a–d** in yields of 64, 87, 88, and 59%, respectively. We also isolated the solid complex of **4d** with Bu_4NHSO_4, the formation of which was confirmed by a satisfactory elemental analysis. In the ^1H NMR spectrum the NH absorption has been shifted from δ 6.90 (free ligand) to δ 7.75 (complex). In the negative FAB mass spectrum of the solid complex, in addition to a peak of the free ligand, also signals of $[L + HSO_4^-]^-$ and $[L + Bu_4NHSO_4]^-$ are present. The association constants K of the 1:1 complexes of **4b–d**[22] (and of reference compounds **5** and **6**) with the tetrabutylammonium salts of $H_2PO_4^-$, HSO_4^-, Cl^-, NO_3^-, and ClO_4^- in $CDCl_3$ have been determined with ^1H NMR titration experiments and are summarized in Table I. Surprisingly in all cases a selectivity for HSO_4^- was observed. The influence of the presence of four more or less preorganized binding sites is very clear comparing the K values of **4b,c** and **4d** with those of the corresponding reference compounds **5** and **6**, respectively. For all anions **4d** shows the highest K values which may be due to the presence of four amide functions in addition to four sulfonamide moieties. However, more important is that **4d** exhibits for HSO_4^- a selectivity of about 10^2 over Cl^- and NO_3^-. Obviously the three-dimensional cavity of **4d** complexes the tetrahedral HSO_4^- better than the spherical Cl^- and the planar NO_3^-. To the best of our knowledge **4b–d** represent the first anion receptors with a selectivity for HSO_4^-.[23]

Table I. Association Constants (K, M^{-1}, $CDCl_3$) of Complexation of 4b–d, 5, and 6 with Different Anions[a]

	anions[b]				
compd	$H_2PO_4^-$	HSO_4^-	Cl^-	NO_3^-	ClO_4^-
4b	350	970	360	240	<1
4c	<10	134	72	43	<1
4d	[c]	103400	1250	513	<1
5	14	10	15	<10	16
6	262	350	330	99	84

[a] The error is <5%. [b] The counterion is Bu_4N^+. [c] Compound **4d** shows a complicated (mixed) complexation with $H_2PO_4^-$ (compare refs 7 and 32); no K value for 1:1 complexation could be determined.

Experimental Section

General. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with Me_4Si as internal standard unless stated otherwise. Fast atom bombardment (FAB) mass spectra were obtained with *m*-nitrobenzyl alcohol as a matrix.

(22) Due to the presence of broad signals in the ^1H NMR spectrum of **4a** in $CDCl_3$ the anion complexation behavior has not been studied.

(23) Examples of nonselective (hydrogen) sulfate complexation have been reported in refs 4a, 6, 7, and Smith, P. J.; Reddington, M. V.; Wilcox, C. S. *Tetrahedron Lett.* **1992**, *33*, 6085.

Table II. Yields, Melting Points, and Characteristic Spectral Data of Compounds 2a,c–h[a]

compd	yield (%)	mp (°C)	^{1}H NMR ($CDCl_3$) (δ) ArH (s, 8 H)	^{1}H NMR ($CDCl_3$) (δ) OCH_2	^{1}H NMR ($CDCl_3$) (δ) $ArCH_2Ar$	^{13}C NMR ($CDCl_3$) (δ) $ArC\text{-}SO_2$ (s)	^{13}C NMR ($CDCl_3$) (δ) $ArCH_2Ar$ (t)	FAB-MS m/z (M^+) calcd
2a[b]	52[c]	>230 dec	7.37		3.94 (s, 8 H)	138.0	30.4	817.0 (817.5)
2c	69	172–174	7.50	4.32 (t, 4 H, J = 4.4 Hz), 3.80 (t, 4 H, J = 4.4 Hz)	4.74 (d, 4 H, J = 13.5 Hz), 3.43 (d, 4 H, J = 13.5 Hz)	138.5	30.5	1015.3[d] (1015.3)
2d	54	>290 dec	7.94	4.01 (t, 4 H, J = 1.8 Hz), 3.77 (t, 4 H, J = 1.8 Hz)	3.79 (s, 8 H)	138.1	34.5	1051.0[e] (1050.9)
2e	53	212–213	7.49	4.35 (t, 4 H, J = 4.4 Hz), 3.80 (t, 4 H, J = 4.4 Hz)	4.77 (d, 4 H, J = 13.7 Hz), 3.42 (d, 4 H, J = 13.7 Hz)	138.8	31.0	1070.9[d] (1071.1)
2f	65	108–109	7.53	4.88 (s, 8 H)	5.14 (d, 4 H, J = 14.0 Hz), 3.55 (d, 4 H, J = 14.0 Hz)	139.9	31.2	1162.9 (1162.9)
2g[b]	61	208–209	7.21	5.02 (s, 8 H)	4.96 (d, 4 H, J = 13.0 Hz), 3.48 (d, 4 H, J = 13.0 Hz)	140.0	31.9	1159.0 (1158.9)
2h	61	226–228	7.50	5.15 (s, 8 H)	5.66 (d, 4 H, J = 13.7 Hz), 3.48 (d, 4 H, J = 13.7 Hz)	139.1	32.6	1234.9[d] (1235.6)

[a] All compounds gave satisfactory elemental analyses. [b] In DMSO-d_6. [c] Starting from **1b** the yield is 35%. [d] $(M - Cl)^+$. [e] $(M - H)^+$.

CH_2Cl_2 was distilled from CaH_2 and stored over molecular sieves. Calix[4]arenes **1a**,[24] **1b**,[25] **1c**,[26] **1d**,[20] **1e**,[27] and **1f**,[28] and reference compounds **5**[29] and **6**[30] were prepared according to literature procedures. All reactions were carried out under an argon atmosphere.

In the workup procedures the (combined) organic layers were washed with water (2×) and dried with $MgSO_4$, whereupon the solvent was removed under reduced pressure. The presence of solvent in the analytical samples was confirmed by ^{1}H NMR spectroscopy.

General Procedure for the Preparation of 1g,h. A mixture of calix[4]arene **1a** (4.24 g, 0.01 mol), *N,N*-dialkyl-2-chloroacetamide (0.1 mol), sodium iodide (15 g, 0.1 mol), and K_2CO_3 (13.8 g, 0.1 mol) in acetonitrile (100 mL) was refluxed for 18 h. After filtration the solvent was removed. The residue was taken up in CH_2Cl_2 (150 mL) and washed with water (3 × 400 mL). Pure compounds were obtained upon recrystallization of the crude reaction products from MeOH.

25,26,27,28-Tetrakis[(dimethylcarbamoyl)methoxy]calix[4]arene (1g): yield 78%; mp 256–258 °C; ^{1}H NMR δ 6.7–6.5 (m, 12 H), 5.11 (d, 4 H, J = 13.6 Hz), 4.84 (s, 8 H), 3.25 (d, 4 H, J = 13.6 Hz), 3.00 and 2.91 (s, 2 × 12 H); ^{13}C NMR δ 169.5 (s), 156.4 (s), 134.8 (s), 128.5 (d), 122.4 (d), 71.7 (t), 36.2 (q), 35.4 (q), 31.7 (t); MS-FAB m/z 765.4 (M^+, calcd 764.9). Anal. Calcd for $C_{44}H_{52}N_4O_8$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.28; H, 7.05; N, 7.11.

25,26,27,28-Tetrakis[(diethylcarbamoyl)methoxy]calix[4]arene (1h): yield 58%; mp 212–213 °C; ^{1}H NMR δ 6.65–6.5 (m, 12 H), 5.23 (d, 4 H, J = 13.6 Hz), 4.90 (s, 8 H), 3.4–3.25 (m, 16 H), 3.23 (d, 4 H, J = 13.6 Hz), 1.25–1.00 (m, 24 H); ^{13}C NMR δ 168.6 (s), 156.6 (s), 134.9 (s), 128.4 (d), 122.2 (d), 71.5 (t), 40.9 (t), 39.9 (t), 31.9 (t), 14.3 (q) 13.1 (q); MS-FAB m/z 877.4 (M^+, calcd 877.1). Anal. Calcd for $C_{52}H_{68}N_4O_8$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.54; H, 8.02; N, 6.12.

General Procedure for the Preparation of Bis- and Tetrakis(chlorosulfonyl)calix[4]arenes 2 and 3. To a cooled solution of calix[4]arene **1** (2 mmol) in $CHCl_3$ (25 mL) was added chlorosulfonic acid (5.6 mL, 80 mmol) at a rate to keep the temperature between 0 and 10 °C. The reaction mixture was stirred at room temperature for 2–3 h (method A) or heated at 50 °C for 20 min (method B). The reaction mixture was poured onto ice (100 g) and extracted with CH_2Cl_2 (4 × 50 mL). The crude products were recrystallized from toluene to afford pure compounds **2,3**. The yields, melting points and selected spectral data of compounds **2** are summarized in Table II.

5,17-Bis(chlorosulfonyl)-25,26,27,28-tetrakis[(dimethylcarbamoyl)methoxy]calix[4]arene (3a): yield 42%; mp 218–219 °C; ^{1}H NMR δ 7.79 (s, 4 H), 6.45–6.35 (m, 2 H), 6.2–6.15 (m, 4 H), 5.34 (s, 4 H), 4.59 (s, 4 H), 5.24 and 3.36 (d, 2 × 4 H, J = 13.8 Hz), 3.04 (s, 6 H), 2.96 (s, 12 H), 2.91 (s, 6 H); ^{13}C NMR δ 169.2 (s), 168.0 (s), 163.7 (s), 155.3 (s), 137.9 (s), 137.1 (s), 132.0 (s), 128.3 (d), 127.9 (d), 123.7 (d), 72.2 (t), 71.9 (t), 36.0 (q), 35.7 (q), 35.5 (q), 35.4 (q), 31.7 (t); MS-FAB m/z 961.3 (M^+, calcd 961.9). Anal. Calcd for $C_{44}H_{56}Cl_2N_4O_{12}S_2 \cdot 1.2CH_2Cl_2$: C, 51.03; H, 4.96; N, 5.27. Found: C, 50.98; H, 5.15; N, 5.11.

5,17-Bis(chlorosulfonyl)-25,26,27,28-tetrakis[(diethylcarbamoyl)methoxy]calix[4]arene (3b): yield 37%; mp 163–165 °C; ^{1}H NMR δ 7.79 (s, 4 H), 6.5–6.3 (m, 2 H), 6.3–6.2 (m, 2 H), 5.35 (s, 4 H), 4.68 (s, 4 H), 5.38 and 3.25 (d, 2 × 4 H, J = 13.0 Hz), 3.5–3.0 (m, 16 H), 1.3–1.0 (m, 24 H); MS-FAB m/z 1073.4 [$(M + H)^+$, calcd 1073.1]. Anal. Calcd for $C_{52}H_{66}Cl_2N_4O_{12}S_2 \cdot 1.7H_2O$: C, 56.43; H, 6.33; N, 5.07. Found: C, 56.10; H, 6.13; N, 4.83. Karl Fisher titration calcd for $2H_2O$: 2.75. Found: 2.66.

General Procedure for the Preparation of 4a–d. To a solution of **2c** (1.05 g, 1 mmol) in CH_2Cl_2 (40 mL) was added the appropriate alkylamine (10 mmol). In the case of **4a** ammonia was bubbled through the solution for 10 min. The reaction mixture was stirred at rt for 4 h and subsequently washed with 1 N HCl (2 × 50 mL) and water (3 × 50 mL). The crude reaction products were recrystallized from MeOH to give pure **4a–d**.

25,26,27,28-Tetrakis(methoxyethoxy)-5,11,17,23-tetrakis(sulfamoyl)calix[4]arene (4a): yield 64%; mp 171–173 °C; ^{1}H NMR (DMSO-d_6) δ 7.31 (s, 8 H), 6.96 (s, 8 H), 4.16 and 3.79 (t, 2 × 8 H, J = 5.0 Hz), 4.53 and 3.43 (d, 2 × 8 H, J = 13.3 Hz), 3.34 (s, 12 H); ^{13}C NMR (DMSO-d_6) δ 158.6 (s), 138.0 (s), 134.6 (s), 125.9 (d), 73.6 (t), 71.2 (t), 58.0 (q), 30.1 (t); MS-FAB m/z 973.2 (M^+; calcd 973.1). Anal. Calcd for $C_{40}H_{52}N_4O_{16}S_4 \cdot 1.5H_2O$: C, 48.04; H, 5.54; N, 5.60; S, 12.82. Found: C, 47.88; H, 5.80; N, 5.42; S, 13.01. Karl Fisher titration calcd for $1.5H_2O$: 2.70. Found: 2.66.

25,26,27,28-Tetrakis(methoxyethoxy)-5,11,17,23-tetrakis(propylsulfamoyl)calix[4]arene (4b): yield 87%; mp 191–192 °C; ^{1}H NMR δ 7.26 (s, 8 H), 4.62 and 3.30 (d, 2 × 4 H, J = 13.4 Hz), 4.84 (t, 4 H, J = 6.2 Hz), 4.21 and 3.79 (t, 2 × 8 H, J = 5.1 Hz), 3.38 (s, 12 H), 2.86 (q, 8 H, J = 6.2 Hz), 1.51 (sextet, 8 H, J = 6.2 Hz), 0.89 (t, 12 H, J = 6.2 Hz); ^{13}C NMR δ 159.1 (s), 135.2 (s), 135.1 (s), 127.2 (d), 73.8 (t), 71.6 (t), 58.6 (q), 45.1 (t), 30.7 (t), 23.3 (t) 11.1 (q); MS-FAB m/z 1141.4 (M^+; calcd 1141.5). Anal. Calcd for $C_{52}H_{76}N_4O_{16}S_4 \cdot 0.7H_2O$: C, 54.12; H, 6.76; N, 4.85. Found: C, 53.99; H, 6.75; N, 4.83. Karl Fisher titration calcd for $0.7H_2O$: 1.09. Found: 1.05.

5,11,17,23-Tetrakis[(1,1-dimethylethyl)sulfamoyl]-25,26,27,28-tetrakis(methoxyethoxy)calix[4]arene (4c): yield 88%; mp 129–130 °C; ^{1}H NMR δ 7.31 (s, 8 H), 4.73 (s, 4 H), 4.59 and 3.29 (d, 2 × 4 H, J = 13.6 Hz), 4.19 and 3.76 (t, 2 × 8 H, J = 4.6 Hz), 3.35 (s, 12 H), 1.19 (s, 36 H); ^{13}C NMR δ 159.0 (s), 138.0 (s), 134.9 (s), 127.4 (d), 73.6 (t), 71.5 (t), 58.6 (q), 54.9 (s), 30.2 (q); MS-FAB m/z 1194.5 [$(M - H)^-$, calcd 1195.2]. Anal. Calcd for

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$C_{56}H_{84}N_4O_{16}S_4 \cdot 0.7H_2O$: C, 55.58; H, 7.11; N, 4.63; S, 10.60. Found: C, 55.41; H, 7.28; N, 4.60; S, 10.53. Karl Fisher titration calcd for $0.7H_2O$: 1.04. Found: 1.02.

5,11,17,23-Tetrakis[[(2-acetylamino)ethyl]sulfamoyl]-25,26,27,28-tetrakis(methoxyethoxy)calix[4]arene (4d): yield 59%; mp 89–90 °C; ^{1}H NMR δ 7.25 (s, 8 H), 6.90 (s, 4 H), 6.30 (s, 4 H), 4.61 and 3.32 (d, 2 × 4 H, J = 13.3 Hz), 4.25-4.15 (m, 8 H), 3.8–3.75 (m, 8 H), 3.38 (s, 12 H), 3.35–3.25 (m, 8 H), 3.0–2.9 (m, 8 H), 1.99 (s, 12 H); ^{13}C NMR δ 159.4 (s), 158.9 (s), 134.8 (s), 134.6 (s), 127.0 (d), 73.7 (t), 71.5 (t), 58.5 (q), 45.1 (t), 41.9 (t), 29.9 (t), 22.9 (q); MS-FAB m/z 1313.7 (M^-, calcd 1313.6). Anal. Calcd for $C_{56}H_{80}N_8O_{20}S_4 \cdot 0.5H_2O$: C, 50.86; H, 6.17; N, 8.47; S, 9.70. Found: C, 51.07; H, 5.98; N, 8.52: S, 9.89. Karl Fisher titration calcd for $0.5H_2O$: 0.71. Found: 0.71.

Solid Complex of 4d and Bu_4NHSO_4. A mixture of **4d** (132 mg, 0.1 mmol) and Bu_4NHSO_4 (34 mg, 0.1 mmol) in $CHCl_3$ (20 mL) was stirred at rt for 18 h. The solvent was removed and the resulting solid dried: mp 45 °C; ^{1}H NMR δ 7.75 (s, 4 H), 7.37 (s, 8 H), 4.56 and 3.38 (d, 2 × 4 H, J = 13.1 Hz), 4.18 (t, 8 H, J = 5.1 Hz), 3.79 (t, 8 H, J = 5.1 Hz), 3.38 (s, 12 H), 3.4–2.9 (m, 24 H), 1.95 (s, 12 H), 1.9–1.3 (m, 16 H), 1.00 (t, 12 H, J = 7.3 Hz); MS-FAB m/z 1311.3 [(L–2 H)$^-$, calcd 1311.6], 1408.9 [(L + HSO_4^- – 2 H)$^-$, calcd 1408.7], 1650.2 [(L + $BuNHSO_4$ – 3 H)$^-$, calcd 1650.2]. Anal. Calcd for $C_{72}H_{117}N_9O_{24}S_5 \cdot 0.75CHCl_3$: C, 50.14; H, 6.76; N, 7.24. Found: C, 49.88; H, 7.07; N, 7.35.

Determination of Association Constants. The measurements were performed by ^{1}H NMR titration experiments in $CDCl_3$ at 298 K using a constant host concentration of 4 mM and a varying guest concentration of 0.3–30 mM. For each K value determination 5–10 different guest concentrations were taken. As a probe the chemical shift of the SO_2NH signal was used. The K values were calculated by nonlinear regression as described in ref 31.

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