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Introduction

In nature phosphate and sulfate binding proteins are very important receptors for the active transport systems in the cell. A very high selectivity in binding has been observed in prokaryotic, periplasmic phosphate and sulfate binding proteins, which demonstrate >106 selectivity for binding phosphate over sulfate and sulfate over phosphate, respectively. 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 or Lewis acid metal centers to accomplish anion binding. Recently we reported functionalized uranyl-containing salenates and sulfonamides derived from tris(aminoethyl)amine (TREN) that form complexes with hard anions in CH2CN with a selectivity for H2PO4−. In the present paper we report anion receptors based on chlorosulfonylated calix[4]arenes.

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

Results and Discussion

The starting calixarene tetramides 1g and 1h were obtained by reaction of 1a with the appropriate N,N-

dialkyl-2-chloroacetamidine in the presence of potassium iodide and K2CO3 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 CH2Cl2 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 tetrapropoxyxylcalix[4]arene 1b did not give the expected tetrakis(chlorosulfonyl)-calix[4]arene 2b but the tetrahydroxytetrakis(chlorosulfonyl)calix[4]arene 2a in 53% yield. Apparently under the acidic conditions, the propyl ether groups are not stable. Only a few examples of calixarenes having reactive chlorosulfonyl (SO3Cl) groups at the upper rim are known. They were prepared in two steps via sulfonylation followed by treatment with thionyl chloride, although it is known that the SO3Cl moiety can in principle be introduced in a one step like in the synthesis of chlorosulfonyl benzo-crucu ethers.

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 13C NMR spectrum the corresponding carbon absorptions are present at δ 54.5 which are both characteristic for a calix[4]arene in the 1,3-alternate conformation.

Surprisingly, treatment of calix[4]arene amides 1g and 1h (cone conformation) with chlorosulfonic acid at room temperature for 2–5 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 which results in a lower reactivity of the para positions of the corresponding aromatic rings. The two SO3Cl 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 4.2 and 1.8, 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 SO3Cl groups. These compounds are not accessible via the two-step procedure because to the best of our knowledge selective sulfonylation

(15) Very recently Kätzky et al.34 reported the partial demethylation of n-octanoniol up on reaction with chlorosulfonic acid.

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Because TREN-derived sulfonamides form complexes with anions (vide supra), these tetrakis(chlorosulfonyl)calix[4]arenes 2 might be suitable precursors for the synthesis of hydrophobic, neutral anion receptors. Reaction of 2e with ammonia, n-propylamine, tert-butylamine, or N-acetylenethylenediamine in CH2Cl2 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 Bu4NHSO4, 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 + HSO4]− and [L + Bu4NHSO4]− are present. The association constants K of the 1:1 complexes of 4b–d (and of reference compounds 5 and 6) with the tetrabutylammonium salts of H2PO4−, HSO4−, Cl−, NO3−, and ClO4− in CDCl3 have been determined with 1H NMR titration experiments and are summarised in Table I. Surprisingly in all cases a selectivity for HSO4− was observed. The influence of the presence of four more or less preorganized binding sites is very clear comparing the K values of 4b,e 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 HSO4− a selectivity of about 102 over Cl− and NO3−. Obviously the three-dimensional cavity of 4d complexes the tetrahedral HSO4− better than the spherical Cl− and the planar NO3−. To the best of our knowledge 4b–d represent the first anion receptors with a selectivity for HSO4−.

Experimental Section

General. Melting points are uncorrected. 1H and 13C NMR spectra were recorded in CDCl3 with Me4Si 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 CDCl3 the anion complexation behavior has not been studied.

(23) Examples of nonselective (hydrogen) sulfate complexation have been reported in refs 6a, 6c, 7, and Smith, E. J.; Reddington, M. V.; Wilcox, C. S. Tetrahedron Lett. 1992, 33, 6055.
Table II. Yields, Melting Points, and Characteristic Spectral Data of Compounds 2a-c-h

<table>
<thead>
<tr>
<th>compd</th>
<th>yield (%)</th>
<th>mp (°C)</th>
<th>ArH (s, 8 H)</th>
<th>OCH2</th>
<th>ArCH2Ar</th>
<th>ArSO4</th>
<th>ArCH2Ar</th>
<th>FAB-MS m/z (M+H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>52</td>
<td>&gt;320 dec</td>
<td>7.37</td>
<td>4.01 (4 H, J = 1.8 Hz)</td>
<td>3.94 (s, 4 H)</td>
<td>3.49 (s, 4 H)</td>
<td>138.0</td>
<td>30.4</td>
</tr>
<tr>
<td>2c</td>
<td>69</td>
<td>172-174</td>
<td>7.50</td>
<td>4.62 (2 H, J = 4.4 Hz), 3.80 (4 H, J = 1.8 Hz)</td>
<td>4.74 (d, 4 H, J = 13.6 Hz)</td>
<td>3.43 (d, 4 H, J = 13.6 Hz)</td>
<td>371.2</td>
<td>101.5</td>
</tr>
<tr>
<td>3d</td>
<td>54</td>
<td>&gt;290 dec</td>
<td>7.94</td>
<td>4.01 (4 H, J = 1.8 Hz)</td>
<td>3.77 (s, 4 H)</td>
<td>3.49 (s, 4 H)</td>
<td>138.1</td>
<td>34.5</td>
</tr>
<tr>
<td>2e</td>
<td>55</td>
<td>212-213</td>
<td>7.49</td>
<td>4.56 (4 H, J = 4.4 Hz)</td>
<td>3.77 (d, 4 H, J = 13.7 Hz)</td>
<td>3.42 (d, 4 H, J = 13.7 Hz)</td>
<td>138.8</td>
<td>31.0</td>
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<tr>
<td>2f</td>
<td>65</td>
<td>108-109</td>
<td>7.50</td>
<td>4.58 (s, 8 H)</td>
<td>3.80 (4 H, J = 1.8 Hz)</td>
<td>4.62 (d, 4 H, J = 14.0 Hz)</td>
<td>138.9</td>
<td>31.2</td>
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<tr>
<td>2g</td>
<td>61</td>
<td>208-209</td>
<td>7.21</td>
<td>5.02 (s, 8 H)</td>
<td>3.80 (4 H, J = 1.8 Hz)</td>
<td>4.56 (d, 4 H, J = 13.0 Hz)</td>
<td>140.0</td>
<td>31.9</td>
</tr>
<tr>
<td>2h</td>
<td>61</td>
<td>226-228</td>
<td>7.50</td>
<td>5.15 (s, 8 H)</td>
<td>3.80 (4 H, J = 1.8 Hz)</td>
<td>4.56 (d, 4 H, J = 13.0 Hz)</td>
<td>138.1</td>
<td>32.6</td>
</tr>
</tbody>
</table>

* All compounds gave satisfactory elemental analyses. In DMSO-d6. Starting from 1b the yield is 53%. * (M – Cl) *. * (M – H). 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; CHN NMR δ 7.79 (s, 4 H), 6.46–6.35 (m, 2 H), 6.2–6.15 (m, 4 H), 5.34 (s, 4 H), 4.97 (s, 4 H), 2.54 and 3.36 (d, 2 × 4 H, J = 13.6 Hz), 2.08 (s, 12 H), 2.98 (s, 12 H), 1.96 (s, 4 H), 1.90 (s, 4 H), 1.48 (s, 4 H). MS: FAB-MS m/z 916.3 (M+), 916.3 (M+). Anal. Calcd for C40H31Cl2N2O5S2: C, 49.56; H, 4.02; N, 6.07. Found: C, 49.5; H, 4.06; N, 6.08.

General Procedure for the Preparation of 1g-k. A mixture of calix[4]arene 1a (0.5 g, 2.4 mmol), N,N-diisopropylcarbodiimide (0.5 g, 2.5 mmol), sodium iodide (15 g, 0.1 mol), and K2CO3 (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 CH2Cl2 (150 mL) and washed with water (3 × 400 mL). Pure compounds were obtained upon recrystallization from the crude reaction products from MeOH.

25.26,27,28-Tetrakis[(dimethylcarbamoyl)methoxy] calix[4]arene (1g): yield 78%; mp 256–258 °C; CHN NMR δ 6.7–6.55 (m, 12 H), 5.31 (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 × 4 H, 2H, ArSO3). 13C NMR δ 168.5 (s), 157.2 (s), 150.9 (s), 150.6 (s), 148.7 (s), 141.4 (s), 139.0 (s), 138.4 (s), 128.3 (d), 122.4 (d), 71.7 (t), 36.2 (q), 35.4 (q), 31.7 (t); MS-FAB-MS m/z 766.4 (M+), calculated 764.9. Anal. Calcd for C44H39N2O9S: C, 56.02; H, 4.89; N, 5.78. Found: C, 56.0; H, 4.92; N, 5.77.

25.26,27,28-Tetrakis(diethylcarbamoyl)methoxy calix[4]arene (1h): yield 41%; mp 212–213 °C; CHN NMR δ 6.56–6.55 (m, 12 H), 5.23 (d, 4 H, J = 13.6 Hz), 4.00 (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); 13C NMR δ 156.8 (s), 154.6 (s), 153.2 (s), 128.4 (d), 122.2 (d), 71.5 (t), 40.9 (t), 38.9 (t), 31.9 (t), 14.3 (q) 13.1 (q); MS-FAB-MS m/z 774.4 (M+), calculated 773.2. Anal. Calcd for C44H39N2O9S: C, 56.0; H, 4.92; N, 5.77. Found: C, 56.1; H, 4.92; N, 5.77.

General Procedure for the Preparation of Bis- and Tris-Chlorosulfonyl calix[4]arenes 2 and 3. To a cooled solution of calix[4]arene 1 (2 mmol) in CHCL3 (25 mL) was added chlorosulfonyl 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 CH2Cl2 (4 × 50 mL). The crude products were recrystallized from toluene to afford pure


Notes
C₉H₈N₂O₆S₄•0.7H₂O: C, 55.68; 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 calcld for 0.7H₂O: 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 80–90 °C; ¹H NMR δ 7.25 (s, 8 H), 8.90 (s, 4 H), 6.30 (s, 4 H), 4.61 and 3.92 (d, 2 × 4 H, J = 13.3 Hz), 4.26–4.15 (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); ¹³C 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), 39.9 (t), 22.9 (q); MS–FAB m/z 1311.3 [L–2H]⁺, calcld 1311.6, 1408.9 [L + HSO₄⁻ – 2 H]⁺, calcld 1408.7, 1650.2 [L + BuNHSO₄ – 3 H]⁺, calcld 1650.2. Anal. Calcld for C₉H₁₃N₄O₈S₄•0.75CHCl₃: 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 ¹H NMR titration experiments in CDCl₃ 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 SO₃NH signal was used. The K values were calculated by nonlinear regression as described in ref 31.

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