Calix[4]arenes Substituted on the Narrow Rim with Malononitrile and Cobalt Bis(dicarbollide) Anion

Junmei Zhao, a Michael Bolte, b Crenguţa Dordea, a Bohumir Grüner, c Volker Böhmer a* a Abteilung Lehramt Chemie, Fachbereich Chemie, Pharmazie und Geowissenschaften, Johannes Gutenberg-Universität Mainz, Duesbergweg 10–14, 55099 Mainz, Germany Fax +49(6131)3925419; E-mail: vboehmer@mail.uni-mainz.de b Fachbereich Chemie und Pharmazeutische Wissenschaften, Institut für Anorganische Chemie, Johann Wolfgang Goethe-Universität, Max-von-Laue-Str. 7, 60438 Frankfurt/Main, Germany c Institute of Inorganic Chemistry, AS ČR, Area of Research Institutes 1001, 25068 Husinec-Řez, Czech Republic Received 26 May 2009; revised 27 July 2009

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Abstract: Nitrile groups are suitable precursors for amino functions to which various other groups can be attached. Thus, the reaction of the 1,3-bis(3-bromopropyl ether) or 1,3-bis(4-bromobutyl ether) of tert-butylcalix[4]arene with methylmalononitrile has been studied in order to attach four nitrile groups to the narrow rim. Bimacrocyclic dinitriles were formed in 70% yield with malononitrile, and tetranitriles in 85% yield with methylmalononitrile. Subsequent alkylation of the tetranitriles with cobalt dioxane–bis(dicarbollide) gave dianionic calix[4]arenes, isolated as the cesium salts in 68% and 89% yield. Two compounds were characterized by single crystal X-ray analysis.

Key words: calixarenes, boron, clusters, alkylation, nitriles

Calixarenes in general and, due to their well-defined conformations, calix[4]arenes in particular have been frequently used as platforms for the assembly of various functional groups.1 The attachment of four carbamoylmethylphosphinoxide (CMPO) groups to their wide rim 1 or narrow rim 2 (Figure 1), usually achieved by acylation of the respective tetramines, led to extractants for lanthanides and actinides with drastically increased efficiency compared to a single CMPO molecule [e.g., the technologically used (N,N-diisobutylcarbamoylmethyl)phenyloctylphosphine oxide]. The required tetramino-calix[4]arenes for the synthesis of narrow-rim CMPOs are usually obtained by reduction of cyanoalkyl ethers or by hydrazinolysis of phthalimido residues. Recently, we could show that the combination of two CMPO functions with two anionic cobalt bis(dicarbollide)(1–) (Cosan) groups (i.e., calixarenes 3) leads to a further drastic increase in the extraction ability;4,5 Am3+ is removed from a 5 × 10–8 M aqueous solution to more than 99% by a single extraction step with a 3 × 10–4 M solution of 3 (n = 4) in hexyl methyl ketone–dodecane. On the other hand, the extraction ability strongly decreases (by two to three orders of magnitude) when the number of CMPO groups in 1 is reduced from four to three.6 We therefore aimed to combine four CMPO functions with two Cosan groups in a calixarene platform. Since we excluded a calix[6]arene due to its conformational mobility, we envisaged the binding of two malononitrile units via carbon linkers7 to the distal oxygen functions of a calix[4]arene, leaving the other two hydroxy groups for the usual attachment of the anionic Cosan groups.

At a first glance, the covalent connection of malononitrile to the distal oxygen functions of a calix[4]arene might seem complicated. It requires a bifunctional linker, e.g. an α,ω-dibromoalkane, while malononitrile itself is bifunctional under C-alkylation conditions and four oxygen functions can be alkylated in the calix[4]arene (see Scheme 1); however, the 1,3-di-O-alkylation is easily possible8 with an excess of 1,4-dibromobutane in refluxing acetonitrile. Potassium carbonate as base clearly prevents further O-alkylation of 5b, which was obtained in 65% yield. Even better yields (up to 90%) were obtained for 5a with 3-bromopropanol under Mitsunobu conditions.

Unexpectedly, however, the subsequent monoklylation of malononitrile with 5a,b was more difficult. Even with a 20-fold excess, the dialkylation could not be avoided, and the bimacrocyclic 1,3-bridged calix[4]arenes 6a and 6b were readily obtained in 70% yield.9 To attach two dinitrile units to the calixarene, we therefore had to use methylmalononitrile, which cannot be dialkylated. Compounds 7a and 7b were thus prepared in about 85% yield (Scheme 1).
Two cobalt bis(dicarbollide)(1–) anions could be attached to the tetranitriles 7a and 7b by O-alkylation of the remaining two hydroxy groups of the calixarene with the cosan-dioxane derivative \([8-O(CH_2CH_2)O-1,2-C_2B_9H_{10})(1\,'2\,'-C_2B_9H_{11})-3,3\,'-Co]\). This method has already proved to be very effective for the introduction of the bulky and hydrophobic cobalt bis(dicarbollide) cluster to the narrow rim of calix[4]arenes.4,5 The respective di-anionic species 8a and 8b were formed almost exclusively as the cone-isomers, according to the NMR spectra of the crude products. Both compounds were isolated as the cesium salts in good yields (68% and 89%) after simple crystallization from dichloromethane–hexane.

Single crystals of 6a10 and 7a11 suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of 6a in acetonitrile and of 7a in ethyl acetate–chloroform. Compound 6a contains two independent molecules with slightly different shape in the asymmetric unit, which are shown in Figure 2a. An unambiguous description of the shape of a calixarene is possible using the torsion angles around the Ar–CH2 bonds,12 with alternating sign of the angles being characteristic for a molecule in the cone conformation. Easier to visualize are the inclination angles of the aromatic units with respect to the reference plane defined by the four methylene carbon atoms (Table 1). Two molecules of acetonitrile are incorporated per molecule of 6a, one of which is included in the cavity as is often found for calix[4]arenes with a (more or less regular) cone conformation. The second molecule fills gaps in the crystal lattice.

Figure 2  a) Two crystallographically different molecules of 6a with acetonitrile molecules (shown with thermal ellipsoids) included in the cavities; b) molecular conformation of 7a.
Table 1  Comparison of the Shape of 6a and 7a Using the Torsion Angles around the Ar-CH₂ Bonds and the Inclination of the Phenolic Units with Respect to the Molecular Main Plane. Defined by the Carbon Atoms C1, C2, C3, C4 of the Methylene Bridges (Oxygen Functions at Carbon Atoms C12, C22, C32, C42)

<table>
<thead>
<tr>
<th></th>
<th>6a(1)</th>
<th>6a(2)</th>
<th>7a</th>
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<tbody>
<tr>
<td>C42–C43–C1–C11</td>
<td>−87.87</td>
<td>−89.46</td>
<td>−77.60</td>
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<tr>
<td>C43–C1–C11–C12</td>
<td>101.40</td>
<td>100.05</td>
<td>113.03</td>
</tr>
<tr>
<td>C12–C13–C2–C21</td>
<td>−93.11</td>
<td>−91.26</td>
<td>−102.61</td>
</tr>
<tr>
<td>C12–C2–C21–C22</td>
<td>82.34</td>
<td>90.38</td>
<td>68.82</td>
</tr>
<tr>
<td>C22–C23–C3–C31</td>
<td>−86.46</td>
<td>−96.11</td>
<td>−75.20</td>
</tr>
<tr>
<td>C23–C3–C31–C32</td>
<td>102.70</td>
<td>96.29</td>
<td>113.74</td>
</tr>
<tr>
<td>C32–C33–C4–C41</td>
<td>−95.74</td>
<td>−92.18</td>
<td>−103.74</td>
</tr>
<tr>
<td>C33–C4–C41–C42</td>
<td>81.36</td>
<td>85.92</td>
<td>70.76</td>
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Inclination of the aromatic rings

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<tr>
<td>C11–C16</td>
<td>66.60</td>
<td>66.31</td>
<td>80.73</td>
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<tr>
<td>C12–C26</td>
<td>52.82</td>
<td>63.19</td>
<td>37.88</td>
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<tr>
<td>C31–C36</td>
<td>68.92</td>
<td>61.85</td>
<td>91.76</td>
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<tr>
<td>C41–C46</td>
<td>52.29</td>
<td>55.79</td>
<td>40.64</td>
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Figure 2b shows the molecular shape of compound 7a, which assumes a strongly pinched cone conformation, again typical for 1,3-diethers of calix[4]arenes. Both aromatic rings bearing the ether groups are ‘nearly parallel’ (interplanar angle 17.5°), while the phenolic units are strongly bent outwards (interplanar angle 101.5°). A visual inspection already reveals a more regular cone conformation for 6a in comparison to 7a. This is also expressed by the torsion angles and the inclination angles listed in Table 1.

In conclusion, we have shown that the attachment of four nitrile functions to the narrow rim of a calix[4]arene is possible by reaction of 1,3-bis(bromoalkoxy)calix[4]arenes with methylmalononitrile; the analogous reaction with malononitrile, however, leads to macroyclic 1,3-dith derivatives with two nitrile groups. The attachment of two Cosan functions to the remaining phenolic hydroxy groups was also possible. We expect that the new anionic species 8a,b will serve as useful precursors for a variety of functional ionic molecules which should be available, for instance, by reduction of the nitrile groups and subsequent acylation to introduce ligating functions such as CMPO or picolinamidex.13 These studies are currently in progress in our laboratories.

Melting points were determined on a Buchi melting point B-545 or a MEL-TEMP II apparatus and are uncorrected.1 H and 13C NMR spectra for compounds 6 and 7 were recorded on a Bruker Avance DRX-400 spectrometer at 400 and 100.6 MHz, respectively. The 1H, 1H{13B}, 1H{11Bselective}, 1H–1H COSY, 1B and 1B{1H} NMR spectra for compounds 6 were measured on a Varian Mercury Plus 400 MHz spectrometer (400 MHz for 1H, 128 MHz for 1B). Chemical shifts are referenced to the residual solvent peaks; 1B NMR signals are referenced to BF₃·OEt₂, as external standard. Mass spectra were recorded on a Waters Micromass Q-ToF Ultima 3 (for compounds 6 and 7) or on a Thermo Finnigan LCQ Fleet Ion Trap mass spectrometer (for compounds 8). All solvents were HPLC grade and were used without further purification. Column chromatography was performed on silica gel 60 (0.035–0.070 mm, Acros).

Intensity data were collected on a STOE IPDS II two-circle diffractometer with graphite–monochromated Mo Kα radiation at 173 K. The structures were solved by direct methods using the program SHELXS14 and refined against F² with full-matrix least-squares techniques using the program SHELXL.14 Hydrogen bonds formed to carbon were included at calculated positions with fixed displacement parameters. Hydrogen bonds formed to oxygen were freely refined. Two tert-butyl groups and one acetonitrile molecule in 6a are disordered over two positions.

Calix[4]arenes 6a

A soln of bis(3-bromopropyl ether) 5a (200 mg, 0.225 mmol) in anhyd THF (30 mL) was added to a freshly prepared sample of sodium malononitrile, obtained by dissolving malononitrile (297 mg, 4.5 mmol) and 1.0 equiv of NaOMe in MeOH (30 mL), followed by evaporation of the solvent. NaI (0.2 g) was added, and the mixture was stirred under N₂ at r.t. for 2 d. Then, the THF was evaporated and the residue was taken up in CHCl₃ (100 mL). The organic layer was washed with 1 M HCl (3 × 50 mL), H₂O (50 mL) and brine (50 mL), and then dried (MgSO₄). Evaporation of the solvent and purification by column chromatography (hexane–EtOAc, 4:1) afforded 6a as a white powder; yield: 127 mg (71%).

Mp 283–285 °C (dec).

1H NMR (400 MHz, CDCl₃): δ = 8.99 (s, 2 H, OH), 7.08 (s, 4 H, ArH), 7.00 (s, 4 H, ArH), 4.18 (d, J = 12.9 Hz, 4 H, ArCH₂Ar), 4.12 (t, J = 4.6 Hz, 4 H, OCH₃), 3.40 (d, J = 12.9 Hz, 4 H, ArCH₂Ar), 2.87 (m, 4 H, OCH₂CH₂), 2.47 (m, 4 H, OCH₂CH₂CH₂), 1.20 (s, 18 H, t-Bu), 1.19 (s, 18 H, t-Bu).

13C NMR (100 MHz, CDCl₃): δ = 150.7, 149.0, 148.9, 143.1, 134.3, 128.2, 126.8, 125.8, 116.3, 73.7, 34.9, 34.7, 34.3, 32.9, 31.9, 31.5, 29.7, 27.5.

MS (FD): m/z = 794.6 [M⁺].

Calix[4]arene 6b

The 1,3-bridged calix[4]arene 6b was obtained analogously, starting from bis(4-bromobutyl ether) 5b (200 mg, 0.218 mmol); yield: 126 mg (70%).

Mp >300 °C (dec).

1H NMR (400 MHz, CDCl₃): δ = 7.47 (s, 2 H, OH), 7.06 (s, 4 H, ArH), 6.78 (s, 4 H, ArH), 4.20 (d, J = 12.9 Hz, 4 H, ArCH₂Ar), 4.06 (t, J = 5.1 Hz, 4 H, OCH₂), 3.32 (d, J = 12.9 Hz, 4 H, ArCH₂Ar), 2.39 (m, 4 H, OCH₂CH₂), 2.17 (m, 4 H, OCH₂CH₂CH₂), 2.06 (m, 4 H, OCH₂CH₂CH₂CH₂), 1.28 (s, 18 H, t-Bu), 0.93 (s, 18 H, t-Bu).

13C NMR (100 MHz, CDCl₃): δ = 151.3, 150.7, 148.2, 142.5, 133.1, 127.5, 126.7, 126.7, 117.1, 76.0, 35.9, 35.4, 34.7, 34.2, 32.7, 31.9, 31.6, 30.7, 20.7.

MS (FD): m/z = 822.5 [M⁺].

Calix[4]arene 7a

1,3-Bis(4,4-dicyanopentyloxy)calix[4]arene 7a was prepared under the conditions described for 6a using methylmalononitrile instead of malononitrile. Starting from 5a (1.00 g, 1.13 mmol), pure 7a was isolated by column chromatography (hexane–EtOAc, 4:1) as a white powder; yield: 875 mg (87%).
Mp 282–284 °C.

1H NMR (400 MHz, CDCl3): δ = 7.08 (s, 4 H, ArH), 6.91 (s, 2 H, OCH2), 6.76 (s, 4 H, ArH), 4.19 (d, J = 12.9 Hz, 4 H, ArCH2Ar), 4.08 (t, J = 11.6 Hz, 3 H, OCH2), 3.34 (d, J = 12.9 Hz, 4 H, ArCH2Ar), 2.42 (m, 4 H, OCH2CH2), 2.30 (m, 4 H, OCH2CH2), 1.90 (s, 6 H, CH2CN), 1.30 (s, 18 H, t-Bu), 0.92 (s, 18 H, t-Bu).

13C NMR (100 MHz, CDCl3): δ = 151.2, 150.1, 148.4, 142.7, 133.1, 127.6, 126.8, 126.2, 117.0, 75.5, 36.5, 34.7, 34.3, 32.7, 32.3, 31.9, 31.5, 27.0, 25.5.

MS (FD): m/z = 889.3 [M+].

Calix[4]arene 7b

To obtain 1,3,5-tris(5,5-dicyanohexyloxy)calix[4]arene 7b, a solution of methylmalononitrile (435 mL, 5.44 mmol) in anhyd acetone (20 mL) was added to a suspension of K2CO3 (1.5 g, 10.9 mmol) in the same solvent (15 mL) was added by syringe. The mixture was stirred for 30 min, 5b (1.0 g, 1.09 mmol) and KI (0.5 g) were added, and the resulting mixture was stirred overnight under reflux. The solvent was evaporated and the dry residue was taken up in CHCl3 (100 mL). The organic layer was washed with 30% MeOH (2 × 5 mL) and brine (50 mL), H2O (50 mL) and brine (50 mL), and then dried (MgSO4). Evaporation of the solvent and purification by column chromatography (hexane–EtOAc, 4:1) afforded 7b as a white powder; yield: 818 mg (82%).

Mp 167–169 °C.

1H NMR (400 MHz, CDCl3): δ = 7.06 (s, 2 H, OH), 7.06 (s, 4 H, ArH), 6.76 (s, 4 H, ArH), 4.21 (d, J = 13.3 Hz, 4 H, ArCH2Ar), 3.99 (t, J = 6.1 Hz, 4 H, OCH2), 3.31 (d, J = 13.3 Hz, 4 H, ArCH2Ar), 2.17 (m, 4 H, OCH2CH2), 2.10 (m, 4 H, OCH2CH2), 2.01 (m, 4 H, OCH2CH2), 1.85 (s, 6 H, CH2CN), 1.29 (s, 18 H, t-Bu), 0.92 (s, 18 H, t-Bu).

13C NMR (100 MHz, CDCl3): δ = 151.2, 150.1, 148.2, 142.4, 133.7, 126.7, 126.1, 117.1, 76.1, 39.4, 34.7, 34.3, 32.6, 32.4, 31.9, 31.5, 29.7, 25.3, 22.6.

MS (FD): m/z = 916.1 [M+ – H].

Calix[4]arene 8a

Calix[4]arene 7a (175 mg, 0.197 mmol) was dissolved in anhyd toluene–ethylene glycol dimethyl ether (DME) (3:1, 15 mL) and deprotonated with solid 96% NaH (23 mg, 0.91 mmol). Then, a solution of cobalt dioxane–bis(dicarbollide) (370 mg, 0.90 mmol) in the same solvent (15 mL) was added by syringe and the mixture was stirred for 16 h at rt. The product was isolated as described for compound 8a and recrystallized (twice from CHCl3–hexane) to give Cs2·8a as an orange powder; yield: 780 mg (89%); HPLC purity check: 97.6%.

Mp 202–204 °C.

1H NMR (400 MHz, acetone-¢): δ = 6.93 (s, 2 H, OH), 6.93 (s, 8 H, ArH), 4.53 (d, J = 12.0 Hz, 4 H, ArCH2Ar), 4.25 (s, 8 H, cage CH4), 4.19 (t, J = 7.4 Hz, 4 H, OCH2), 4.05 (t, J = 5.4 Hz, 8 H, OCH2), 3.70 (m, 4 H, OCH2), 2.50 (m, 4 H, OCH2CH2), 1.92 (s, 4 H, CH2CN), 1.81 (m, 4 H, OCH2CH2), 1.13 (s, 36 H, t-Bu).

133.1, 127.6, 126.8, 126.2, 117.0, 75.5, 36.5, 34.7, 34.3, 32.7, 32.3, 31.9, 31.5, 29.7, 25.3, 22.6.

MS (FD): m/z = 916.1 [M+ – H].

Acknowledgment

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References


(9) A reaction of 5b with malononitrile in THF at –78 °C using LDA as base led to a complicated mixture from which the expected tetrani-trile could be isolated in 12% yield.

(10) Crystal data for 6a: C53H66N2O4⋅2MeCN, M = 877.19, monoclinic, a = 13.8422(4) Å, b = 18.3275(6) Å, c = 42.7189(11) Å, β = 97.642(2)°, V = 10741.2(5) Å³, T = 173(2) K, space group P21/c, Z = 8, µ(Mo Kα) = 0.068 mm⁻¹, 95208 reflections measured, 19962 unique reflections which were used in all calculations. The final wR(F²)[I > 2σ(I)] was 0.2685. Crystallographic data in CIF format have been deposited with the Cambridge Crystallographic Data Centre, reference no. CCDC 642222, and can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk.

(11) Crystal data for 7a: C58H72N4O4, M = 889.20, triclinic, a = 10.3770(4) Å, b = 13.3048(6) Å, c = 20.2318(9) Å, α = 92.798(3)°, β = 90.151(3)°, γ = 93.368(3)°, V = 2785.1 (2) Å³, T = 173 (2) K, space group P1, Z = 2, µ(Mo Kα) = 0.066 mm⁻¹, 77572 reflections measured, 11334 unique reflections which were used in all calculations. The final wR(F²)[I > 2σ(I)] was 0.1509. Crystallographic data in CIF format have been deposited with the Cambridge Crystallographic Data Centre, reference no. CCDC 642221.

