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Synthesis of Unique Cagelike Thiacalix[4]arene Derivatives in a 1,3-Alternate Conformation

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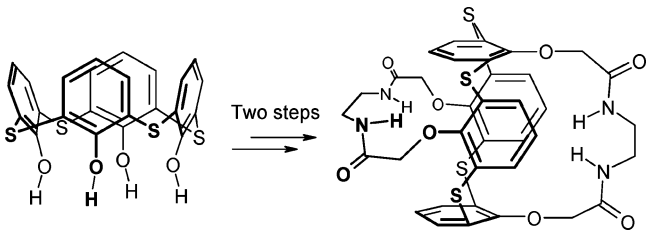

A novel type of doubly bridged thiacalix[4]arenes in the 1,3-alternate conformation has been prepared by direct aminolysis reaction of easily accessible thiacalix[4]arene tetraacetates with α,ω-diamines. Despite the high excess of diamine, both sites of a 1,3-alternate conformer can be intramolecularly bridged to form the cagelike structures in high yields. Optimum results were obtained using 1,2-ethanediamine as bridging units. X-ray analysis of the novel cagelike molecules revealed a highly preorganized array of −C(O)−NH− bonds pointing to the interior of the cavity.

Recently, thiacalix[4]arenes have become easily accessible in multigram scales using simple synthetic procedures.[1,2] Because of the presence of four sulfur atoms instead of common $-CH_2-$ bridges, the system has many novel features as compared to classical calixarenes.[3] Thiacalixarenes represent very promising building blocks and/or molecular scaffolds for the synthesis of more elaborated supramolecular systems.[4]

Recently, we described[5] the synthesis of thiacalix[4]arenes with the proximally bridged lower rim, obtained by an aminolysis reaction of thiacalix[4]arene tetraethyl esters immobilized in the cone conformation. To investigate the general applicability of this method in thiacalixarene chemistry, we also made attempts at aminolysis of the corresponding tetraethyl ester derivatives in a 1,3-alternate conformation.

In accordance with the above-mentioned results,[5] we found that the reaction of tetraacetates **1a**−**c** with an excess of 1,2-diaminoethane did not lead to the expected tetraamide **4** but instead to the formation of doubly bridged cage molecules **2** in moderate to high yield, depending on the upper rim substitution. These molecules represent one of the first examples of cagelike molecules in thiacalixarene chemistry. Similar structures representing the classical calix[4]arene analogues to structure **2a** have already been mentioned by Bitter et al.[6] However, they were obtained in low yields after a multistep synthesis starting with the corresponding diesters. As the thiacalix[4]arene tetraethyl esters in the 1,3-alternate conformation represent readily accessible molecules,[7] the simultaneous spanning of both sites using α,ω-diamine is a very convenient one-step procedure leading directly to cagelike thiacalix[4]arene derivatives in high yields.

The synthesis was accomplished according to Scheme 1. Starting thiacalix[4]arene tetraethyl esters **1a**−**c** were reacted with an excess of 1,2-ethanediamine in refluxing ethanol to give exclusively the corresponding cagelike compounds **2a**−**c** fixed in the 1,3-alternate conformation in 60%, 72%, and 28% yield, respectively. Because of their high R_f values, all of these derivatives were easily purified by column chromatography on silica gel. Interestingly, despite the use of a high excess of 1,2-ethanediamine (100 equiv), the formation of tetraamides **4** was not observed. Moreover, neither the single-bridged compounds **5** with two unreacted ethyl ester groups nor the possible byproducts **6** were isolated from the crude reaction mixtures. The use of a longer 1,3-diaminopropane bridge led to a very dramatic decrease in yield (**2b**/72% vs **3b**/2%). This indicates that the accurate length of the corresponding diamine is an essential prerequisite for the successful bridging. In other words, thiacalix[4]arene tetraacetates are suitably preorganized only for spanning with the C_2 moiety.

Structures of all of the above-mentioned doubly amide-bridged thiacalix[4]arenes in the 1,3-alternate conformation were proved by ^{1}H NMR, EA, ESI-MS, and IR spectroscopy. Figure

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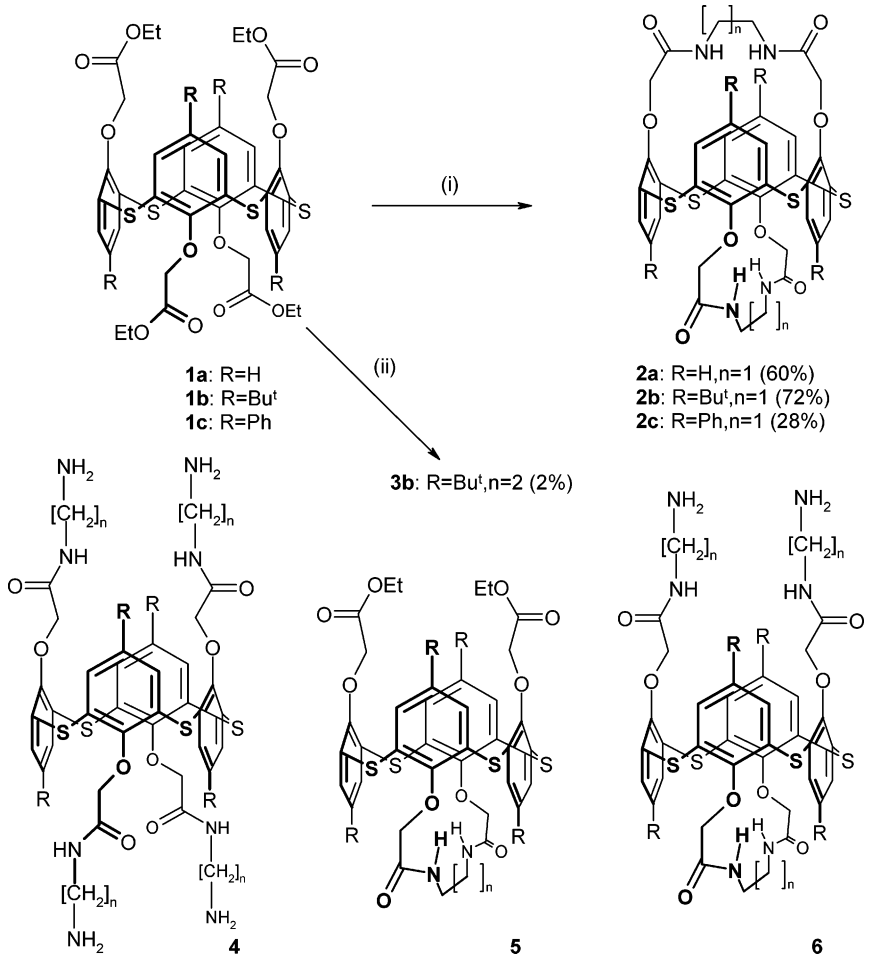
SCHEME 1[a]



[a] Reagents: (i) 1,2-Diaminoethane, EtOH/reflux. (ii) 1,3-Diaminopropane, EtOH/reflux.

1 (Supporting Information) shows the ^{1}H NMR spectrum of derivative **2a** with assignment of all signals. It is obvious that the S_4 symmetry of this molecule results in a very simple splitting pattern in the ^{1}H NMR spectra. Spanning of both distal positions on the lower rim with a symmetrical bridge does not change the symmetry of the starting compound which results in an equivalence of geminal $-O-CH_2-C(O)-$ (H_c) protons. Similarly, aromatic protons (H_a) and (H_b) in **2a** are represented by a triplet and a doublet, respectively, with a characteristic vicinal coupling constant (J = 7.7 Hz).

The final evidence for the cage structures **2a**−**c** was obtained by single-crystal X-ray crystallography. As shown in the X-ray structures (Supporting Information, Figure 2), all four −NH− bonds of both amide bridges are oriented into the cavity of thiacalix[4]arene, representing the well-preorganized system capable of possible hydrogen bonding interactions with suitable guest molecules.

In conclusion, cagelike structures based on the thiacalix[4]-arenes are easily accessible in high yields via direct aminolysis of the starting tetraesters with 1,2-diaminoethane. These compounds represent well-preorganized cavities with potential applications for the encapsulation of suitable guest molecules.

Experimental Section

Syntheses. Compounds **1a**−**c** were obtained in 40−71% yields as described in the literature.[7]

General Method for the Synthesis of Doubly Amide-Bridged Thiacalix[4]arenes in the 1,3-Alternate Conformation. An aliphatic α,ω-diamine (100 equiv) was added to the suspension of tetraacetate **1a**−**c** (0.1 g) in ethanol (20 mL), and the mixture was stirred under reflux for 72 h. The solvent was evaporated under reduced pressure, and the residue was separated by column chromatography on silica gel, using a chloroform/methanol (20:1) mixture as eluent.

Thiacalix[4]arene Derivative (1,3-Alternate) (2a). Prepared in 60% yield using 1,2-diaminoethane. Mp > 350 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.10 (m, 8H); 4.61 (s, 8H); 5.11 (bs, 4H); 7.05 (t, 4H, J = 7.7 Hz); 7.48 (d, 8H, J = 7.7 Hz). ESI MS: *m*/*z* (M^+) calcd 776; found 799 $(M + Na)^+$, 815 $(M + K)^+$. IR ($CHCl_3$): 3417 (NH), 1683 (C═O), 1535 cm^{-1}. EA calcd for $C_{36}H_{32}N_4O_8S_4$: C, 55.65; H, 4.15; N, 7.21; S, 16.51. Found: C, 55.23; H, 4.01; S, 16.24.

***p-tert*-Butylthiacalix[4]arene Derivative (1,3-Alternate) (2b).** Prepared in 72% yield using 1,2-diaminoethane. Mp > 350 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.28 (s, 36H); 3.04 (m, 8H); 4.39 (s, 8H); 5.45 (bt, 4H); 7.40 (s, 8H). ESI MS: *m*/*z* (M^+) calcd 1000; found 1023 $(M + Na)^+$. IR ($CHCl_3$): 3412 (NH), 1687 (C═O), 1533 cm^{-1}. EA calcd for $C_{52}H_{64}N_4O_8S_4$: C, 62.37; H, 6.44; N, 5.60; S, 12.81. Found: C, 62.11; H, 6.09; S, 12.66.

***p*-Phenylthiacalix[4]arene Derivative (1,3-Alternate) (2c).** Prepared in 28% yield using 1,2-diaminoethane. Mp > 350 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.60 (bs, 8H); 4.74 (s, 8H); 5.35 (bs, 4H); 7.36 (t, 4H, J = 7.1 Hz); 7.44 (t, 8H, J = 7.4 Hz); 7.55 (d, 8H, J = 7.4 Hz); 7.75 (s, 8H). ESI MS: *m*/*z* (M^+) calcd 1080; found 1103 $(M + Na)^+$, 1119 $(M + K)^+$. IR ($CHCl_3$): 3415 (NH),

1684 (C═O), 1534 cm^{-1}. EA calcd for $C_{60}H_{48}N_4O_8S_4$: C, 66.65; H, 4.47; N, 5.18; S, 11.86. Found: C, 66.31; H, 4.19; S, 11.59.

***p-tert*-Butylthiacalix[4]arene Derivative (1,3-Alternate) (3b).** Prepared in 2% yield using 1,3-diaminopropane. Mp > 350 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.28 (s, 36H); 1.64 (m, 4H); 3.10 (m, 8H); 4.33 (s, 8H); 5.47 (t, 4H, J = 5.9 Hz); 7.39 (s, 8H). ESI MS: m/z (M^+) calcd 1028; found 1051 $(M + Na)^+$. IR ($CHCl_3$): 3408 (NH), 1675 (C═O), 1528 cm^{-1}. EA calcd for $C_{54}H_{68}N_4O_8S_4$: C, 63.01; H, 6.66; N, 5.44; S, 12.46. Found: C, 62.81; H, 6.39.

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Supporting Information Available: Crystallographic data of derivatives **2a**−**c** (together with the corresponding CIF files and the X-ray structures), general experimental methods, and ^1H NMR spectrum of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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