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First synthesis of adamantylated thiacalix[4]arenes

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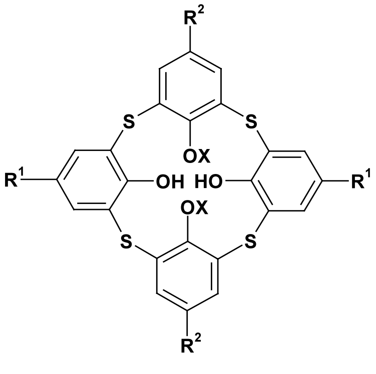
Abstract—*p*-(1-Adamantyl)thiacalix[4]arene was synthesized both by condensation of *p*-(1-adamantyl)phenol with sulfur in the presence of NaOH and by alkylation of *p*-H-thiacalix[4]arene with 1-adamantanol in trifluoroacetic acid. Using the latter method, the first thiacalix[4]arene carboxylated at the upper rim was obtained from *p*-H-thiacalix[4]arene and 3-carboxy-1-adamantanol. The X-ray structural analysis revealed that *p*-(1-adamantyl)thiacalix[4]arene adopts a cone conformation leading to an inclusion complex with chloroform under the conditions of crystallization. © 2002 Published by Elsevier Science Ltd.

Calixarenes are well known to be excellent building blocks for the design of novel host molecules and for supramolecular chemistry.[1] There is interest in the expansion of the calixarene functions through substitution of the bridging methylene groups with heteroatoms such as O, N or S. The introduction of a heteroatom as a bridge provides an additional opportunity to tune the ring size and conformational and binding properties of a macrocycle. It was recently shown[2] that heating *p*-*tert*-butylphenol with elemental sulfur under basic conditions results in the formation of *p*-*tert*-butylthiacalix[4]arene **1** (*t*-BuTC4A, Fig. 1) in 54% yield. Besides *p*-*tert*-butylphenol, *p*-(1,1,3,3-tetramethylbutyl)phenol could be converted using the same procedure into the corresponding thiacalix[4]arene **2** but in considerably lower yield.[3]

The accessibility of the parent thiacalix[4]arenes initiates a search for general methods of their derivatization. Two strategies of functionalization have been mainly studied up to now: exhaustive and partial oxidation of the sulfide bridges[4] and reactions of the lower rim hydroxyls of thiacalixarenes; exhaustive[5] and partial[6] alkylation, substitution of the phenolic OH groups with SH[7] or NH_2[8] groups. To our surprise and in contrast to classical calixarene chemistry, there are only a few examples of the upper rim derivatization of thiacalix[4]arenes. The upper rim derivatives based on the thiacalix[4]arene platform known to us are shown in Fig. 1. De-*tert*-butylation[9] and *ipso*-sulfonation[10] of *p*-*tert*-butylthiacalix[4]arene give the corresponding *p*-H-thiacalix[4]arene **3** (HTC4A) and tetrasulfonated derivative **4**. In 2001, the first report on the electrophilic substitution at the *p*-position in the thiacalixarene structure was published. Bromination of 25,27-dipropoxythiacalix[4]arene yielded the corresponding dibromo and tetrabromo derivatives **5** and **6**.[11]

Recently we have developed methods for the production of *p*-(3-R-1-adamantyl)calix[*n*]arenes (R = H, alkyl, aryl, functional groups; *n* = 4, 6, 8). It was shown that while the adamantylated octamer was formed by the direct condensation of *p*-(1-adamantyl)phenol and



1, $R^1 = R^2 = t\text{-Bu}$, X = H;
2, $R^1 = R^2$ = 1,1,3,3-tetramethylbutyl, X = H;
3, $R^1 = R^2 = H$; X = H;
4, $R^1 = R^2 = SO_3Na$; X = H;
5, $R^1 = Br$, $R^2 = H$, X = Pr;
6, $R^1 = R^2 = Br$, X = Pr

Figure 1. Upper rim derivatives based on the thiacalix[4]arene platform.

Keywords: adamantylated thiacalixarenes; synthesis; inclusion complex.

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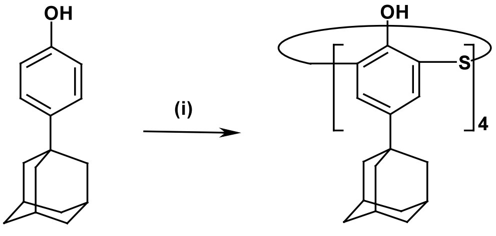
formaldehyde,[12] the adamantylated calix[4]- or -[6]arenes could be obtained only by the reaction of unsubstituted *p*-H-calix[4]- or -[6]arenes with 3-R-1-adamantanols in trifluoroacetic acid (TFA).[13]

As part of our efforts to develop new receptors for molecular or ionic recognition, we herein report on the first synthesis and structural determination of thiacalix[4]arenes adamantylated at the upper rim. The adamantyl unit was chosen as the *p*-substituent for several reasons: it is a highly lipophilic structure, that increases the solubility of a ligand in organic solvents; the adamantyl unit has several positions for the attachment of additional substituents which enables further fine tuning of the complexation properties. In the present work we have shown that *p*-(1-adamantyl)thiacalix[4]arene **7** (1-AdTC4A),[14] phenolic fragments of which are bridged by sulfur atoms, could be produced in 28% yield by direct synthesis from *p*-(1-adamantyl)phenol and elemental sulfur under the conditions described for the synthesis of *p*-*tert*-butylthiacalix[4]arene **1** (Scheme 1).

The solid state structure of **7** has been investigated by X-ray analysis.[15] Suitable crystals were obtained by slow liquid–liquid diffusion of MeOH into a chloroform solution of **7**. The X-ray study revealed the following features: (i) the thiacalixarene **7** crystallized in the orthorhombic crystal system with $Pna2_1$ as space group and the unit cell contained both compound **7** and four $CHCl_3$ molecules, one of which was localized within the cavity of the host molecule; (ii) **7** adopted a cone conformation; (iii) $CHCl_3$ substrates were found to be distorted in the crystalline phase; (iv) as in the case of *t*-BuTC4A,[9] the average distance between two adjacent oxygen atoms was 2.77 Å which may be due to the formation of intramolecular H-bonds leading to the cone conformation, although one cannot exclude a stabilizing role for the $CHCl_3$ (Fig. 2). In the case of *p*-*tert*-butylcalix[4]arene, the average distance between two adjacent oxygen atoms was ca. 2.70 Å.[1]



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Scheme 1. (i) S_8, NaOH, tetraethylene glycol dimethyl ether, Δ (28%).

A second approach towards 1-AdTC4A involved electrophilic adamantylation of HTC4A under non-oxidative acidic conditions. However, it was found that the interaction of 1-adamantanol and *p*-H-thiacalix[4]arene **3** in TFA under the conditions proposed for *p*-(1-adamantyl)calix[4]arene[13] gave a mixture of adamantylated products. The result of this reaction is apparently connected with the fact that the *p*-positions of the phenolic fragments in the thiacalixarene structure are less reactive towards electrophilic substitution than those in classical calixarenes. Exhaustive adamantylation of *p*-HTC4A was carried out by refluxing *p*-HTC4A and 1-adamantanol in TFA in the presence of a catalytic amount of $LiClO_4$ for 3 days (Scheme 2).[16] The yield of *p*-(1-adamantyl)thiacalix[4]arene was 89%, the characteristics of **7** were identical to those of the product obtained directly from *p*-(1-adamantyl)phenol. To the best of our knowledge this is the first example of the S_E-reaction for *p*-H-thiacalix[4]arene.

It seemed attractive to utilize the adamantylation reaction for the introduction of functionally modified adamantanes to the upper rim of sulfur containing macrocycles **3**. It was found that intensive refluxing of *p*-H-thiacalix[4]arene with 3-carboxy-1-adamantanol and a catalytic amount of trifluoromethanesulfonic acid in TFA gave *p*-(3-carboxy-1-adamantyl)thiacalix[4]arene **8** in 96% yield.[17] The corresponding methyl ester **9** was successfully obtained from **8**.[18] The formylation of *p*-H-thiacalix[4]arene under Duff reaction conditions (HMTA/TFA, reflux) was attempted, however, only starting material was recovered. This fact demonstrates that modification of thia-

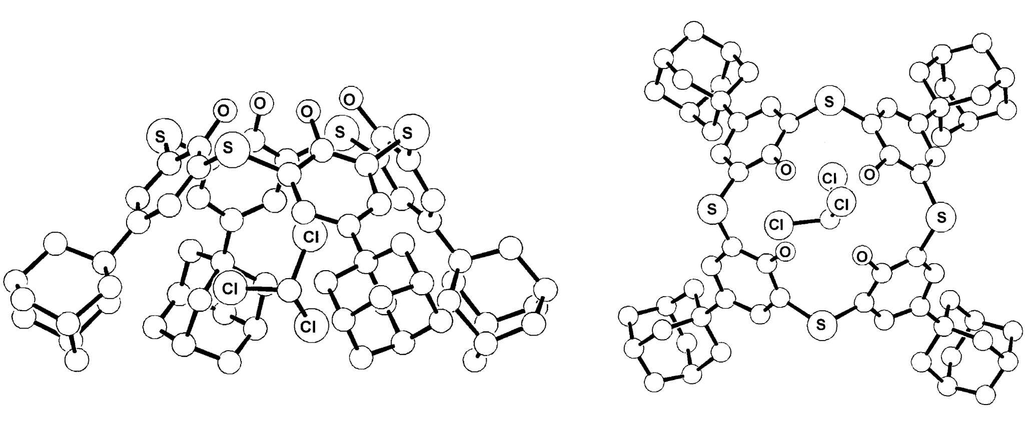
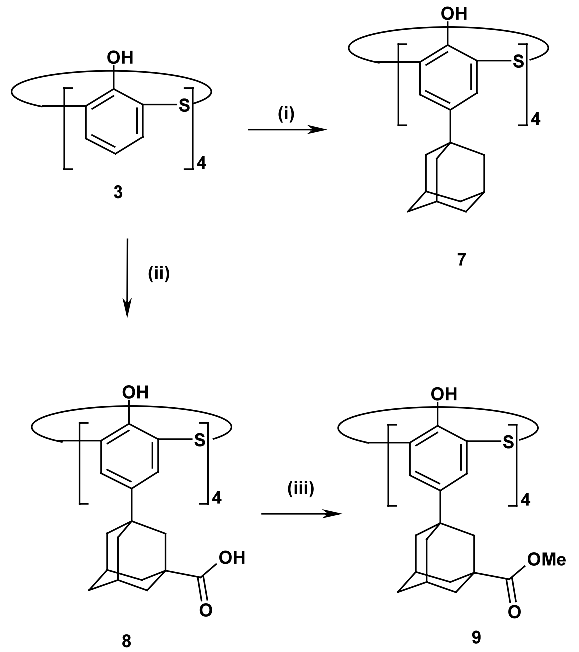


Figure 2. Lateral (left) and top (right) views of the crystal structure of the inclusion complex formed by compound **7** with $CHCl_3$. For clarity, H atoms and $CHCl_3$ molecules outside the cavity are not presented. $CHCl_3$ substrates were found to be distorted in the crystalline phase. Selected average bond distance: C–S 1.76 Å, C–O 1.38 Å.



Scheme 2. (i) 1-Adamantanol, TFA, $LiClO_4$, reflux, 72 h (89%); (ii) 3-carboxy-1-adamantanol, TFA, CF_3SO_3H, reflux, 24 h (96%); (iii) THF/MeOH/H_2SO_4, reflux, 10 h (58%).

calixarenes under electrophilic substitution conditions is difficult.

In conclusion, the syntheses of *p*-(3-R-1-adamantyl)-thiacalix[4]arenes (**7**, R = H; **8**, R = COOH) were achieved both by direct condensation of *p*-(1-adamantyl)phenol and elemental sulfur for compound **7** and by adamantylation of *p*-H-thiacalix[4]arene with 1-adamantanol or 3-carboxy-1-adamantanol in TFA for both novel thiacalixarenes. Thiacalix[4]arene **8**, bearing carboxylic groups on the upper rim has been synthesized for the first time. The X-ray structure analysis of **7** showed the inclusion of chloroform in the cavity under the conditions of crystallization. The molecules assumed a cone conformation in the solid state.

Acknowledgements

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14. A mixture of *p*-(1-adamantyl)phenol (10.5 g, 43 mmol), elemental sulfur S_8 (2.75 g, 86 mmol) and NaOH (0.89 g, 21 mmol) in tetraethylene glycol dimethyl ether (6 ml) was stirred under argon. The stirred mixture was heated gradually to 230°C over a period of 3 h and kept at this temperature for a further 3 h. The resulting dark red mixture was cooled to 110°C, diluted with toluene (10 ml) and 4 M aq. sulfuric acid solution (40 ml) followed by diethyl ether (60 ml) was stirred to give a suspension. The precipitate was collected by filtration, washed with diethyl ether, water and methanol. The crude product (3.6 g) was purified by passing a solution through SiO_2

(eluent *n*-hexane/chloroform = 4:1) and dried in vacuo (100°C, 5 h) to give an essentially pure sample of *p*-(1-adamanantyl)thiacalix[4]arene **7** (3.4 g, 28% based on *p*-(1-adamantyl)phenol) as confirmed by elemental analysis and spectroscopic data. Mp >400°C (dec.); ^{1}H ($CDCl_3$, 300 MHz, 25°C), δ (ppm): 9.60 (s, 4H, OH), 7.60 (s, 8H, Ar), 2.08 (bs, 12H, CH^{Ad}), 1.78–1.68 (m, 48H, CH_2^{Ad}); ^{13}C ($CDCl_3$, 75 MHz, 25°C), δ (ppm): 155.46, 144.86 (C^{Ar}), 135.88 (CH^{Ar}), 120.48 (C^{Ar}), 42.99 (CH_2^{Ad}), 36.46 (CH_2^{Ad}), 35.63 (C^{Ad}), 28.73 (CH^{Ad}). Found: C, 74.38; H, 7.02; S, 12.41. Calcd for $C_{64}H_{72}O_4S_4$: C, 74.12; H, 7.10; S, 12.33%.

15. X-Ray data for the 1:4 complex of **7** and chloroform: $C_{64}H_{72}O_4S_4 \cdot 4CHCl_3$, $M = 1033.54+4\times119.38$, orthorhombic, $a = 19.353(2)$, $b = 22.963(2)$, $c = 16.887(2)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 7504.6(13)$ Å^3, space group *Pna*21, $Z = 4$, $D_c = 1.336$ Mg m^{-3}, μ(Mo Kα) = 0.598 mm^{-1}. Crystal size 0.1×0.1×0.2 mm. Data were measured at 293 K. $R = 0.17$ for 2054 independent observed reflections with $[I>2\sigma(I)]$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 176273. Copies of the data can be obtain, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 12223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
16. A mixture of *p*-H-thiacalix[4]arene (124 mg, 0.25 mmol), 1-adamantanol (228 mg, 1.5 mmol) in equal volumes of TFA and dichloroethane (1.5/1.5 ml) in the presence of a catalytic amount of $LiClO_4$ was refluxed for 3 days. On completion of the reaction, the solvents were removed under reduced pressure. The resultant dark oil was treated with water, the precipitate formed was filtered. The crude product was washed with methanol (3×5 ml), hot methanol (3×5 ml), hexane (3×5 ml) and recrystallized from a $CHCl_3$/methanol mixture affording a pure sample of **7** (230 mg, 89% based on **3**).
17. *p*-(3-Carboxy-1-adamantyl)thiacalix[4]arene **8**: mp >370°C (dec.); ^{1}H (DMSO-d_6, 300 MHz, 25°C), δ (ppm): 7.63 (s, 8H, Ar), 2.12 (bs, 8H, CH^{Ad}), 1.88–1.65 (m, 48H, CH_2^{Ad}); ^{13}C (DMSO-d_6, 75 MHz, 25°C), δ (ppm): 178.57 (COOH), 155.36, 143.23 (C^{Ar}), 133.48 (bs, CH^{Ar}), 120.80 (C^{Ar}), 44.45 (CH_2^{Ad}), 41.80 (CH_2^{Ad}), 41.19 (C^{Ad}), 38.05 (CH_2^{Ad}), 36.05 (CH_2^{Ad}), 35.40 (C^{Ad}), 28.70 (CH^{Ad}). Found: C, 67.01; H, 5.76; S, 10.55. Calcd for $C_{68}H_{72}O_{12}S_4$: C, 67.52; H, 6.00; S, 10.60%.
18. A solution of **8** (180 mg, 0.15 mmol) in THF (5 ml)/MeOH (4 ml)/H_2SO_4 (0.1 ml) mixture was refluxed for 10 h. On completion of the reaction the solvents were removed under reduced pressure. The crude product was washed with methanol (4×5 ml) and was purified by passing a solution through SiO_2 (eluent dichloromethane/ethanol = 20:1) to give an essentially pure sample of *p*-(3-methoxycarbonyl-1-adamanantyl)thiacalix[4]arene **9** (110 mg, 58%) as confirmed by elemental analysis and spectroscopic data. Mp 296–297°C; ^{1}H ($CDCl_3$, 300 MHz, 25°C), δ (ppm): 9.64 (s, 4H, OH), 7.65 (s, 8H, Ar), 3.70 (s, 12H, CH_3O), 2.25 (bs, 8H, CH^{Ad}), 1.94–1.74 (m, 48H, CH_2^{Ad}); ^{13}C ($CDCl_3$, 75 MHz, 25°C), δ (ppm): 177.33 ($\mathit{C}OOCH_3$), 155.77, 143.62 (C^{Ar}), 135.88 (CH^{Ar}), 120.61 (C^{Ar}), 51.55 ($COO\mathit{C}H_3$), 44.10 (CH_2^{Ad}), 41.92 (CH_2^{Ad}), 41.64 (C^{Ad}), 37.82 (CH_2^{Ad}), 37.82 (CH_2^{Ad}), 35.97 (C^{Ad}), 28.45 (CH^{Ad}). Found: C, 68.14; H, 6.25; S, 10.04. Calcd for $C_{72}H_{80}O_{12}S_4$: C, 68.33; H, 6.37; S, 10.13.