Facile Syntheses of Cavitands with Sulfur-Containing Functional Groups

Tim Vorfalt, Herbert Plenio*
Anorganische Chemie im Zintl-Institut, TU Darmstadt, Petersenstr. 18, 64287 Darmstadt, Germany
E-mail: Plenio@tu-darmstadt.de
Received 4 July 2006; revised 8 November 2006

Abstract: The reactions of the (CH2Br)4-cavitand 1 with variable amounts of KSAc produce various (CH2Br)4–n(CH2SAc)n-cavitands (n = 0–4). Acetyl chloride and the (CH2SH)4-cavitand react to generate various (CH2SH)4–n(CH2SAc)n-cavitands (n = 0–4), which both constitute useful building blocks for hemicarcerand synthesis. Binuclear sulfur-bridged hemicarcerands are available by the reaction of CH2Br and CH2SH functional groups in the respective cavitands. The thioacetate protective group in such binuclear cavitands can be cleaved with LiAlH4 to result in the formation of the respective hemicarcerands with up to six SH groups.

Key words: cavitand, thiols, supramolecular chemistry, macrocycles

Compounds with large internal voids display a number of interesting properties such as the storage of gas molecules or the stabilization of unusual organic species, which both rely on the inclusion of guest molecules within the interior of various hosts.1 Apart from solid state compounds like zeolites2 or coordination polymers (metal organic framework structures)3 various container type molecules4 such as cavitands and carcerands5–7 calixarenes,8 cucurbiturils9,10 or cyclodextrins11,12 are known and are able to encapsulate small molecules within their interior. A historical highlight in this respect is the isolation of a room-temperature-stable cyclobutadiene trapped within a carcerand-type guest molecule by Cram et al.13 Another interesting aspect of this chemistry is the confined reaction environment offered by such container-type molecules.14,15

We are interested in hemicarcerands whose internal cavities are decorated with donor groups, to allow the endoedral coordination of metal ions, as demonstrated recently for the copper complex of a nitrogen-donor-containing hemicarcerand.16 Sulfur is the prototypical soft donor atom and displays a high affinity towards noble metal ions. In the classical Brust, Schiffrin protocol for the synthesis of monolayer protected gold clusters a large excess of thiols is required, which cap the emerging gold nanoparticles.17 It is, however, rather difficult to precisely control the size of the gold particles and many authors report on attempts to synthesize well-defined gold nanoclusters.18–24 Once such a synthesis is carried out in a spatially defined cavity, the formation of gold clusters should be subject to strict size control due to the limits of the confinement.25

A basic problem in the synthesis of such macrocycles is the large number of functional groups, which are difficult to address individually since they are spatially and electronically separated. Several approaches have been made to selectively functionalize cavitands.26 Some success has been met in the work of Gibb et al.27 or Sherburn et al.28–30 who utilize far-reaching electrostatic interactions as well as different solubilities in lithiated cavitands, obtained by selective deprotonation or Br/Li exchange. It comes as no surprise that a cavitand such as that depicted in Figure 1 is hard to modify in a selective manner as the aforementioned strategy cannot be applied. The CH2Br groups are almost 1 nm apart and there is no obvious way in which the different groups could influence each other in their reactivity.

We have recently described the functionalization of the (CH2Br)4-cavitand 1 (easily available in amounts of up to 100 g) by reaction with NaOAc, leading to the formation of a statistical mixture of the respective (CH2Br)4–n(CH2OAc)n-cavitands, which can be easily purified on a decagram scale by chromatography.16,31 We now wish to describe here the extension of this methodology to the synthesis of sulfur-rich mixed (CH2Br)4–n(CH2SAc)n-cavitands utilizing KSAc (potassium thioacetate) and...
(CH₂Br)₄₋cavitand, as well as the synthesis of (CH₂SH)₄₋₉(CH₂SAc)ₙ-cavitands by reaction of the (CH₂SH)₄₋cavitand with AcCl.

The reaction of the (CH₂Br)₄₋cavitand 1 with less than four equivalents of KSAc in various solvents yield a mixture of all possible mono-, di-, tri- and tetratosubstituted (CH₂Br)₄₋₉(CH₂SAc)ₙ-cavitands (n = 0–4) 1–5 (Scheme 1). Due to the large distance between the four functional groups it is not possible to selectively address any of the CH₂Br groups. However, when this reaction was carried out in DMA (N,N-dimethylacetamide) or acetonitrile, which both display a reasonable solubility of KSAc there is a strong preference for the formation of the tetratosubstituted product (n = 4), even when using significantly less than four equivalents of KSAc. This is probably due to the fact that the partially substituted products display better solubility than the (CH₂Br)₄₋cavitand 1 in these solvents.

In order to allow the synthesis of reasonable amounts of partially substituted cavitands (n = 1–3) the choice of the solvent is critical. We found that in order to obtain a roughly statistical mixture of the thioacetate substitution products, tetrahydrofuran is the most suitable solvent. Consequently, the reactions of various amounts of KSAc with the (CH₂Br)₄₋cavitand 1 were carried out in tetrahydrofuran over three hours to result in the desired formation of the respective substitution products (Scheme 1, Table 1). The mixture of the various substitution products could be easily separated by chromatography, since the polar thioacetate groups determine the retention properties of the respective cavitands. The fact that the (CH₂SAc)₉-cavitand is still slightly over-represented poses no problem, as this material is conveniently used for the synthesis of the (CH₂SH)₉-cavitand.

The reactions with KSAc allow the facile introduction of protected thiol functions into the cavitand framework. The thiol groups can be liberated under mild conditions either by applying ethanolic KOH or LiAlH₄. Both reactions produce the thiol in very good yields for small scale reactions; on a multi-gram scale the LiAlH₄-promoted cleavage is superior due to the mild reaction conditions employed.

The (CH₂SH)₄₋cavitand 6 obtained from the reaction of four equivalents of KSAc with the (CH₂Br)₄₋cavitand, followed by cleavage of the tetrathioacetate with LiAlH₄ is another useful building block for the synthesis of partially functionalized cavitands. For this purpose the (CH₂SH)₄₋cavitand was reacted with substoichiometric amounts of AcCl to result in the formation of the respective mixed (CH₂SH)₄₋₉(CH₂SAc)ₙ-cavitands 7–9, in which some of the thiol groups are protected as thioacetates (Scheme 1). As described for the KSAc reaction, the distribution of the products was statistical while the overall yield of all products was almost quantitative. By applying the appropriate stoichiometry the desired mono-, di-, or tri-substituted cavitand could be synthesized in up to 35% yield. Howev-

**Scheme 1** Synthesis of the (CH₂Br)₄₋₉(CH₂SAc)ₙ-cavitands (n = 1–4) and (CH₂SH)₄₋₉(CH₂SAc)ₙ-cavitands (n = 1–4). Reagents and conditions: a) n KSAc, THF; b) 4 KSAc, THF, ii. LiAlH₄; c) MeCOCl, DABCO, THF.
In order to obtain useful amounts of polyfunctional sulfur-containing biscavitands, the procedure needed to be improved. With this in mind, the two complementary cavitands $(\text{CH}_2\text{Br})_4(\text{CH}_2\text{SAc})_4$-cavitand 4 and $(\text{CH}_2\text{SH})_4(\text{CH}_2\text{SAc})_4$-cavitand 9 were reacted in various solvent/base mixtures. Among these, CH$_2$Cl$_2$/DABCO turned out to be the best combination, resulting in the formation of the binuclear cavitand 13 in respectable 63% yield. The cleavage of the six thioacetate protective groups led to the formation of the biscavitand 14 with six thiol groups in excellent 86% yield (Scheme 3).

In conclusion, we have developed facile synthetic procedures for the synthesis of sulfur-rich cavitands with mixed substituents; either with a variable number of electrophiles in the $(\text{CH}_2\text{Br})_4(\text{CH}_2\text{SAc})_4$-cavitand series, synthesized in the reaction of KSAc with the $(\text{CH}_2\text{Br})_4$-cavitand 4.

**Scheme 2** Reagents and conditions: a) 3 FcCH$_2$SH, DABCO, CH$_2$Cl$_2$; b) i. KOH, EtOH → 11, 61% ii. 4, DABCO, CH$_2$Cl$_2$, 13%.
cavitand or with variable numbers of nucleophiles in the (CH2SH)4–n(CH2SAc)n-cavitand series obtained from (CH2Br)4-cavitand and acetyl chloride. The sulfur protective groups can be removed almost quantitatively with LiAlH4 to generate the free thiol function. Both series of cavitands 2–5 and 7–10, constitute useful building blocks for the synthesis of hemicarcerands. Preliminary experiments show that biscavitands with up to six SH groups are accessible. It will be the subject of future work to demonstrate that high nuclearity or even polymeric cavitands can be obtained using the building blocks described here.

Commercially available solvents and reagents were purified according to literature procedures. The (CH2Br)4-cavitand was prepared according to published procedures.31 KSAc p.a. was dried (120 °C/0.1 Torr) prior to use. Column chromatography was done on silica gel MN60 (63–200 μm) and TLC on Merck plates coated with silica gel 60, F254. NMR Spectroscopy: Spectra were recorded at 300 K with a Bruker DRX 500 (1H NMR 500 MHz, 13C NMR 125.75 MHz) or a Bruker AC 200 (1H NMR 200 MHz) spectrometer. 1H NMR spectra were referenced to residual protonated impurities in the solvent and 13C NMR to the solvent signals: CDCl3 [δ(H) 7.26, δ(C) 77.0]. Mass Spectra: ESI-MS on a Bruker Esquire-LC. Elemental analyses were difficult to obtain, since the solvent history of the synthesis is very difficult to remove from cavitand-type molecules.

(CH2Br)4(CH2SAc)0-Cavitands 2, 3a, 3b, 4, 5
(CH2Br)4-cavitand 1 (10 g, 9.28 mmol, 1 equiv) was dissolved in THF (20 mL) and KSAc (2.11 g, 18.56 mmol, 2 equiv) was added. After stirring the mixture for 3 h, the volatiles were removed in vacuo. The remaining solid was dissolved in CH2Cl2 (40 mL); silica gel (20 g) was added and the solvent carefully removed in vacuo. The adsorbed product was purified by chromatography on silica gel (initially cyclohexane–EtOAc, 8:1). For the elution of the various products the polarity of the eluent was gradually increased: (CH2Br)4-, (CH2Br)3(CH2SAc)1- and (CH2Br)2(CH2SAc)2-cavitands, cyclohexane–EtOAc (8:1); (CH2Br)(CH2SAc)1- and (CH2SAc)4-cavitands, cyclohexane–EtOAc (4:1). The amount of product corresponded to a combined yield of 85%. For typical yields for the individual products depending on the equivalents of KSAc per (CH2Br)4-cavitand, see Table 1.

| Scheme 3 | Reagents and conditions: a) DABCO, CH2Cl2 → 13, 63% ; b) LiAlH4, THF, 86%.

54% overall yield
Syntheses of Cavitands with Sulfur-Containing Functional Groups

Anal. Calcd for \( \text{C}_52\text{H}_58\text{Br}_2\text{O}_{10}\text{S}_2 \) (1066.95): C, 58.54; H, 5.48. Found: C, 58.39; H, 5.72.

\( \text{ArC} = \text{ArH} \), 5.91 (d, \( \text{OC} \), 4.48–4.43 (m, 8 H, OCH\( \text{OH} \) and ArCH\( \text{Br} \)), 3.86 (s, 4 H, ArCH\( \text{S} \)), 2.25 (s, 6 H, ArCH\( \text{SCH}_2\text{CH}_3 \)), 2.20–2.21 (m, 8 H, CH\( \text{CH}_2\text{CH}_3 \)), 1.34–1.24 (m, 8 H, CH\( \text{CH}_2\text{CH}_2\text{CH}_3 \)), 0.94 (t, \( J = 7.6 \text{ Hz} \), 12 H, \( \text{CH}\left(\text{CH}_3\right)_2\text{CH}_3 \)).

\( \text{ArC} = \text{ArH} \), 136.9, 123.5, 122.2, 118.5, 114.4, 98.2, 35.5, 31.0, 29.2, 25.9, 22.5, 22.0, 19.8, 13.08.

Anal. Calcd for \( \text{C}_52\text{H}_58\text{Br}_2\text{O}_{10}\text{S}_2 \) (1066.95): C, 58.54; H, 5.49. Found: C, 58.39; H, 5.72.

\( \text{CH}\left(\text{CH}_2\text{SH}\right)\text{Cl}_2\text{PPh}_3 \text{Cavitand} 7 \)

\( \text{ArC} = \text{ArH} \), 136.9, 123.5, 122.2, 118.5, 114.4, 98.2, 35.5, 31.0, 29.2, 25.9, 22.5, 22.0, 19.8, 13.08.

Anal. Calcd for \( \text{C}_52\text{H}_58\text{Br}_2\text{O}_{10}\text{S}_2 \) (1066.95): C, 58.54; H, 5.49. Found: C, 58.39; H, 5.72.

\( \text{CH}_2\text{Br}_2\text{S}_2\text{Ac} \text{Cavitand} 3b \)

\( \text{ArC} = \text{ArH} \), 5.91 (d, OCH\( \text{OH} \)), 4.48–4.43 (m, 8 H, OCH\( \text{OH} \) and ArCH\( \text{Br} \)), 3.86 (s, 4 H, ArCH\( \text{S} \)), 2.25 (s, 6 H, ArCH\( \text{SCH}_2\text{CH}_3 \)), 2.20–2.21 (m, 8 H, CH\( \text{CH}_2\text{CH}_3 \)), 1.34–1.24 (m, 8 H, CH\( \text{CH}_2\text{CH}_2\text{CH}_3 \)), 0.94 (t, \( J = 7.6 \text{ Hz} \), 12 H, \( \text{CH}\left(\text{CH}_3\right)_2\text{CH}_3 \)).

\( \text{ArC} = \text{ArH} \), 136.9, 123.5, 122.2, 118.5, 114.4, 98.2, 35.5, 31.0, 29.2, 25.9, 22.5, 22.0, 19.8, 13.08.

Anal. Calcd for \( \text{C}_52\text{H}_58\text{Br}_2\text{O}_{10}\text{S}_2 \) (1066.95): C, 58.54; H, 5.49. Found: C, 58.39; H, 5.72.

\( \text{CH}_2\text{Br}_2\text{S}_2\text{Ac} \text{Cavitand} 4 \)

\( \text{CH}_2\text{Br}_2\text{S}_2\text{Ac} \text{Cavitand} 5 \)

Same procedure as for the mixed cavitands was used, but 5 equivalents of K\( \text{S} \)\( \text{Ac} \) were applied per mole of \( \text{CH}_2\text{Br}_2\text{S}_2\text{Ac} \)-cavitand; chromatography: cyclohexane–EtOAc (1:1); yield: 95%.
1.27 (m, 8 H, CH(CH_2)_3CH(CH_3)). 1.08–0.96 (m, 12 H, CH(CH_3)_2CH(CH_3)).


(CH_2SH)_3(CH_2SCF_2)_2(Cavitand)_11

To a suspension of (CH_2Br)_1(CH_2SAc)_3-cavitand 10 (150 mg, 0.98 mmol) in EtOH (8 mL), was added KOH (100 mg). The mixture was stirred for 16 h. Silica gel (3 g) was added to the mixture and the volatiles were carefully removed. Chromatographic purification with cyclohexane–EtOAc (4:1) afforded 12; yield: 20 mg (13%); R_f = 0.46 (cyclohexane–EtOAc:4:1).

1H NMR (500 MHz, CDCl_3): δ = 7.10–6.97 (m, 8 H, ArH), 5.88 (m, J = 7.2 Hz, 2 H, OCH(OH)), 5.68–5.54 (m, 6 H, OCH(OH)), 4.80–4.67 (m, 8 H, ArCH=O), 4.36 (m, J = 7.2 Hz, 2 H, OCH(OH)), 4.31 (m, J = 7.2 Hz, 2 H, OCH(OH)), 4.25 (m, J = 7.2 Hz, 2 H, OCH(OH)), 4.22–4.17 (m, 6 H, OCH(OH) and CH=O), 4.16–4.10 (m, 16 H, CH=C=O), 3.70–3.44 (m, 22 H, CH=CH and CH=C=O and CH=CH), 2.56–2.30 (m, 16 H, CH=CH(CH_2CH_3)), 1.40–1.30 (m, 16 H, CH=CH(CH_2CH_3)), 1.06–0.96 (m, 24 H, CH(CH_3)_2CH(CH_3)).

MS (ESI, positive): m/z = 2487.8 [12 + Na^+], 2465.3 [12 + H^+].

MS (ESI, negative): m/z = 2500.3 [12 + Cl^–], 2543.7 [12 + Br^-].

Anal. Calcd for C_83H_88Fe_3O_9S_4: C, 65.35; H, 5.81. Found: C, 64.79; H, 6.16.

(CH_3CH_2)_3(CH_2SCF_2)_2(CH_2SAc)_2(Cavitand)_13

To a solution of (CH_2Br)_3(CH_2SAc)_2-cavitand 4 (72 mg, 0.06 mmol) with (CH_2SH)_3(CH_2SCF_2)_2-cavitand 11 (90 mg, 0.04 mmol, 1 equiv) in THF (8 mL), was added LiAlH_4 (20 mg, 0.52 mmol, 13 equiv). After stirring for 3 h at rt., aq 2 M HCl (2 mL) was added carefully to destroy excess of LiAlH_4, followed by CH_2Cl_2 (10 mL). The phase were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried (MgSO_4) and evaporation in vacuo to afford (CH_2SH)_3(CH_2SCF_2)_2(CH_2SAc)_2-cavitand 13 as a colorless powder; yield: 60 mg (86%).

1H NMR (500 MHz, CDCl_3): δ = 7.14–7.03 (m, 8 H, ArH), 5.95 (d, J = 7.0 Hz, 4 H, OCH(OH)), 5.69 (d, J = 7.0 Hz, 4 H, OCH(OH)), 4.81–4.71 (m, 8 H, ArCH=O), 4.48 (d, J = 7.0 Hz, 4 H, OCH(OH)), 4.35 (d, J = 7.0 Hz, 4 H, OCH(OH)), 3.61–3.53 (m, 16 H, ArCH=O and ArCH=C=O and ArCH=CH), 2.27–2.15 (m, 12 H, CH=C=O and CH=C=O and CH=C=O), 1.91–1.82 (m, 6 H, ArCH=O), 1.43–1.33 (m, 16 H, CH=C=O and CH=C=O and CH=C=O), 1.07–0.98 (m, 24 H, CH=C=O and CH=C=O and CH=C=O).

C NMR (125.75 MHz, CDCl_3): δ = 152.2, 151.8, 148.4, 137.0, 126.1, 118.3, 98.8, 35.5, 32.1, 31.1, 27.0, 19.9, 19.8, 17.0, 13.2, 13.1.

ESI-MS (positive): m/z = 2172.4 [M – H^+].


ESI-MS (negative): m/z = 20755.5 [M + Ba^2+], 2031.5 [M + Cl^-] for C_{106}H_{132}O_{27}S_7.

Acknowledgment

This work was supported by the Deutsche Forschungsgemeinschaft.

References