Thioderivatives of Resorcin[4]arene and Pyrogallol[4]arene: Are thiols tolerated in the self-assembly process?

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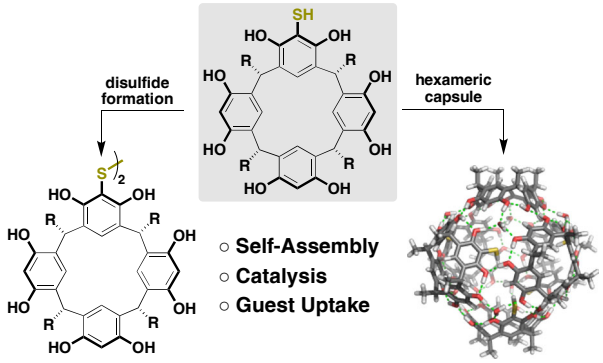
Supporting Information Placeholder



ABSTRACT: Three novel thiol bearing resorcin[4]arene and pyrogallol[4]arene derivatives were synthesized. Their properties were studied with regards to self-assembly, disulfide chemistry, and Brønsted acid catalysis. This work demonstrates that (1) one aromatic thiol on the resorcin[4]arene framework is tolerated in the self-assembly process to a hexameric hydrogen bond-based capsule, (2) thio-derivatized resorcin[4]arene analogs can be covalently linked through disulfides, and (3) the increased acidity of aromatic thio-substituent is not sufficient to replace HCl as co-catalyst for capsule catalyzed terpene cyclizations.

Macrocycles constitute a large proportion of molecules investigated in supramolecular chemistry.[1] Phenolic macrocycles of the calix[4]arene family, in particular, have proven to be highly functional and versatile bowl-shaped building blocks.[2] Calix[4]arene and its sister molecules resorcin[4]arene (**RS**) and pyrogallol[4]arene (**PG**) (Figure 1a) are obtained via simple one-step procedures and are even commercially available. They feature a conformationally restricted and easily derivatizable framework.[3] Both **RS** and **PG** are capable of self-assembly in apolar solvents, forming hexameric capsules **I** and **II** through hydrogen bonds.[4] These supramolecular assemblies are capable of guest uptake[5] and in the case of **RS,** the structure's interior serves as an enzyme-like catalytic pocket for numerous reactions.[6]

Sulfur-containing macrocycles have been of interest since the early days of supramolecular chemistry, starting with thioether-bridged carcerands reported by Cram in the early 1980s (Figure 1b).[7] Subsequently, several covalently linked thioether, and disulfide-containing carcerands and hemicarcerands with remarkable guest uptake capabilities have been reported.[8] In particular, the reversibility of disulfide chemistry is of interest as it provides access to defined thermodynamically favored structures through dynamic covalent chemistry (DCvC).[9] Besides these covalently linked sulfur-containing supramolecular containers also some non-covalently assembled structures have been reported.[10] To this point, the application of sulfur in hydrogen bonded systems has been limited to thiourea motifs, in which the thione serves as hydrogen bond acceptor in the self-assembly of a dimeric capsule (Figure 1b).[11]

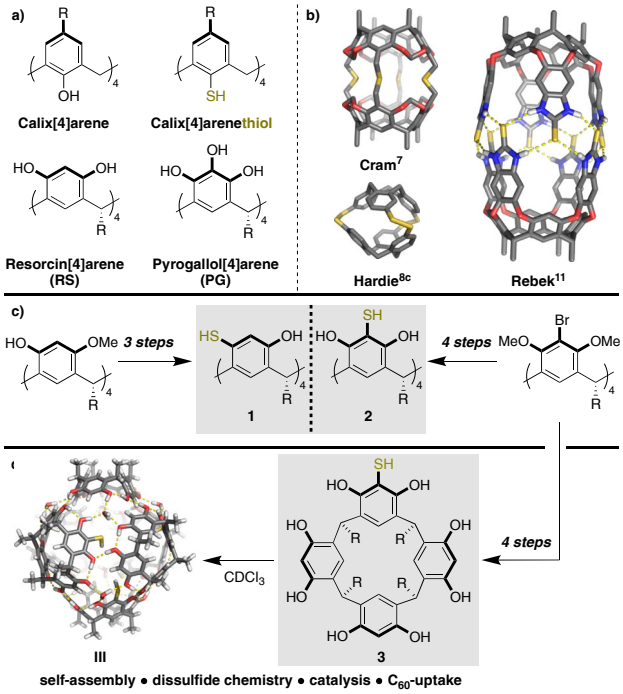


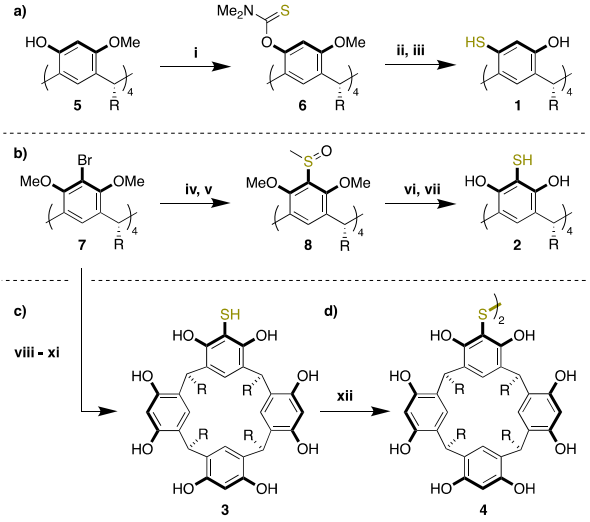
Figure 1. (a) Calix[4]arene family. (b) Selected sulfur-containing supramolecular structures. (c) New tetrathiol calix[4]arenes **1** and **2**. (d) Monothiolresorcin[4]arene **3** capable of self-assembly, disulfide chemistry, catalysis, and C_{60}-fullerene and ammonium salt uptake.

Phenol-bearing calix[4]arenes have been thoroughly investigated and some thiol derivatives have been synthesized and utilized to generate supramolecular structures.[12] However, no sulfur analogs bearing both free phenols and thiols have been reported to our knowledge. In this work, we aimed to synthesize thiol derivatives of **RS** and **PG** in order to address the following three questions: (1) Are thiol-derivatives of **RS** and **PG** able to self-assemble to supramolecular capsules, despite the steric demands of the sulfur atoms? (2) Is it possible to covalently link thiol-containing hydrogen bond-based capsules via oxidative disulfide formation? (3) Is the increased acidity of thiol-containing capsules sufficient to catalyze terpene cyclizations, which presently require HCl as an acidic co-catalyst?[6a, 13]

To answer these questions, three novel thiol derivatives were proposed, two of which are tetrathiol analogs of **RS** and **PG,** labeled **1** and **2** respectively (Figure 1c). Our previous studies on the resorcin[4]arene framework demonstrated that the number of substituents strongly affects the properties of the corresponding macrocycle.[13b] Therefore, an additional monothiol-**RS** derivative **3** was investigated (Figure 1d), in order to minimize potential disruptions of the hydrogen bond network due to the size of the large sulfur atom. We herein report the synthesis and characterization of these three novel macrocycles **1**-**3**.

Most members of the calix[4]arene family can be obtained through electrophilic aromatic substitution of the respective phenols with aldehydes.[14] However, due to the high nucleophilicity of the respective thiol building blocks, direct cyclizations of the corresponding mercaptophenols are unsuccessful. Therefore, an alternative route towards macrocycles **1**-**3** is required. For the synthesis of **1** (Scheme 1a), readily available tetramethoxy resorcin[4]arene **5**[15] was used as the starting material. In the first step, **5** is converted into tetra-*O*-thiocarbamate **6**. The applied conditions were adapted from related reactions on the resorcin[4]arene framework[16] and optimized. Through the application of high-temperature microwave conditions,[17] **6** is converted into the corresponding tetra-*S*-thiocarbamate via Newman-Kwart rearrangement. Removal of the methyl protecting groups with boron tribromide and subsequent reduction of the *S*-thiocarbamate using modified conditions for related molecules[12e, 18] yields tetrathiol **1** in 16% overall yield over three steps.

Scheme 1. Synthesis[a] of thioderivatives of RS and PG. (a,b) Synthesis of tetrathiols **1** and **2**. (c) Synthesis of monothiol **3**. (d) Synthesis of disulfide **3**. R = $C_{11}H_{23}$.



[a]Reagents and conditions: i) C(S)ClNMe$_2$, Cs_2CO_3, acetone, 77%; ii) DMA, MW, 300 °C, then BBr_3, DCM, 72% over two steps; iii) $LiAlH_4$, THF, 29%; iv) *n*BuLi, S_2Me_2, THF, 74%; v) *m*CPBA, DCM, 97%; vi) 2,6-lutedine, TFAA, DCM, then NEt_3, MeOH, 38%; vii) BBr_3, DCM, 91%; viii) *n*BuLi, S_2Me_2, THF, then *n*BuLi, MeOH, 42%; ix) *m*CPBA, DCM, 98%; x) 2,6-lutedine, TFAA, DCM, then NEt_3, MeOH, 92%, xi) BBr_3, DCM, 96%; xii) DMSO-d_6, $CDCl_3$, 100%.

For the synthesis of **2** (Scheme 1b) a different approach for the aryl thiol introduction was chosen, as a suitably protected counterpart to **5** is not readily available. The protected and tetrabrominated compound **7**[19] was identified as an appropriate starting material. **7** enables the construction of carbon-sulfur bonds through bromolithium exchange, followed by quenching with dimethyl disulfide.[20] The resulting methyl thioether is oxidized to the corresponding sulfoxide **8** with *m*CPBA.[18] Avoiding the

use of superstochiometric amounts of *m*CPBA in addition to the application of low reaction temperatures proved to be crucial for preventing overoxidation to the sulfone. A Pummerer rearrangement and subsequent removal of the methyl group protecting groups with boron tribromide yielded **2** in 25% overall yield over four steps. A similar synthetic route was followed for the monothiol macrocycle **3** (Scheme 1c). Following the installation of a single *S*-methyl moiety, and removal of the remaining bromo substituents, the sequence paralleled the one developed for **2**, delivering **RS**-derivative **3** in 36% overall yield over four steps. The macrocycles **1**-**3** were fully characterized by ESI-HRMS, NMR- and IR-spectroscopy.

With all three thiol-bearing macrocycles at hand, we started investigating their properties. No evidence for self-assembly was obtained by NMR spectroscopy for **1** and **2** (Supporting Information (SI), Chapter 2.5.2). However, the formation of the hexameric assembly **III** in $CDCl_3$ was observed for monothiol **3** as confirmed by DOSY-NMR (Figure 2; SI, Figure S12). These findings seem to affirm our assumptions regarding the disruption of the hydrogen bond network with an increasing number of thiols due to the size of the sulfur atom. According to the ^{1}H NMR spectra in $CDCl_3$, the thiol moieties of compounds **1** and **2** do not participate in hydrogen bonding with neighboring phenols (SI, Figure S9), indicating that they function mainly as bulky groups impeding the self-assembly process to molecular capsules.

Next, we investigated the potential of **1** and **2** to generate defined structures via disulfide bond formation. Reaction conditions applied to related systems[8c] showed either no conversion or lead to oligomerization into undefined product mixtures. However, monothiol **3** was efficiently dimerized via the literature-known mild oxidant DMSO (Scheme 1d).[21] The formation of disulfide **4** was confirmed by HRMS and NMR data, in particular DOSY-NMR (SI, Chapter 2.5). DOSY-NMR measurements have been established as a reliable tool for the size determination of supramolecular capsules.[22] In order to verify the disulfide formation for **4**, $CDCl_3$/DMSO 1:1, a polar solvent mixture that prevents self-assembly via hydrogen bonds, was chosen. A smaller diffusion value *D* was observed for **4** as compared to its precursor **3** and the monomeric benchmark **RS** (SI, Table S1), providing strong evidence for the formation of dimeric species. The studies concerning the disulfide formation indicated that the investigated thiol macrocycles require irreversible oxidative conditions for disulfide formation, which prevented the formation of disulfide bridged capsules via DCvC.

Next, the self-assembling properties of the only defined disulfide product, disulfide **4**, were investigated by means of DOSY-NMR measurements in the apolar solvent $CDCl_3$. The diffusion value observed indicates the formation of a trimeric capsule **IV** of similar dimensions as the systems **I**-**III** (Figure 2; SI, Figure S13, Chapter 3).

Solvent \ Compound	1	2	3/III	4/IV[c]	RS/I	PG/II
$CDCl_3$/DMSO-d_6 (1:1) D [$\cdot 10^{-5}$ cm^{2}s^{-1}]	-[a]	-[a]	0.16	0.12	0.16	-[b]
$CDCl_3$ D [$\cdot 10^{-5}$ cm^{2}s^{-1}]	0.40	-[b]	0.23	0.24	0.24	0.24

Figure 2. Diffusion values *D* for macrocycles (20 mM) and assemblies. [a]Rapid oligomerization. [b]Macrocycle barely soluble in given NMR-solvent. [c]Dimeric species measured at 10 mM.

With capsules **III** and **IV** at hand, they were investigated concerning their guest uptake capabilities. Both assemblies encapsulate alkyl ammonium salts such as TBAB (SI, Chapter 4). This was expected as both assemblies possess similar hydrogen bond networks as **I**, capable of anion stabilization.[23] However, two observation came as a surprise. Firstly, both **III** and **IV** showed a fast guest exchange for the alkyl ammonium salt on the ^{1}H-NMR timescale and secondly, **III** was able to encapsulate C_{60}-fullerene (SI, Figure S29). The ability to encapsulate fullerenes is unexpected since **I**, **II**, and **IV** are incapable to function as hosts for this type of guest (SI, Figures S30-32). To our knowledge, no hydrogen bonded capsule has been reported to encapsulate both alkylammonium salts and fullerenes before.[13b, 24] The fast guest exchange on the ^{1}H-NMR time scale for alkyl ammonium salts is likely a result of the decreased stability of capsules **III** and **IV** as compared to **I** and **II**. To quantify the stability of the assemblies and gain insight into the strength of their hydrogen bond network, DOSY-NMR titrations with MeOD were performed.[25] These studies demonstrated that both **III** and **IV** are considerably less stable than their relatives **I** and **II**, as they disassemble at much lower methanol concentrations (Figure 3a; SI, Chapter 5). We attribute these findings to the presence of the sterically demanding sulfur atoms disrupting the hydrogen bond network in both **III** and **IV**. According to computational analysis, the bulky thiols of assembly **III** do not participate in the hydrogen bonding, and the disulfide bridges present in **IV** add additional constraints to the supramolecular structure (SI, Chapter 3).

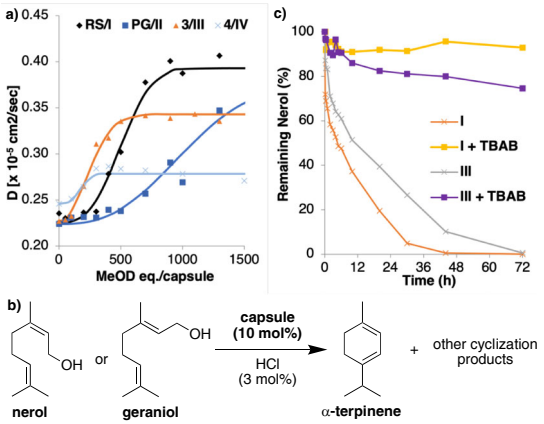


Figure 3. (a) Stability of capsules **I**-**IV** towards the protic solvent MeOD as characterized by the change in the diffusion value *D* upon titration. (b) HCl-co-catalyzed supramolecular

terpene cyclization of nerol and geraniol. (c) Nerol conversion by **I** and **III** and controls blocked by TBAB.

Finally, we tried to answer the third question posed in the introduction: Is the increased acidity of a thiol-bearing capsule (SI, Chapter 6) enough to enable terpene cyclizations (Figure 3b) without the need for HCl as co-catalyst? Capsule **III** is the only suitable assembly identified in this study to answer this question, as assembly **IV** does not contain free thiols. Test reactions with nerol and geraniol demonstrated no significant conversion, while geranyl acetate suffered from a nucleophilic attack by **3**'s thiol, leading to alkylation and subsequent disassembly of **III** (SI, Figure S38). Therefore, we conclude that the increased acidity of **III** is not sufficient to catalyze terpene cyclizations on its own. Next, we investigated potential differences in the terpene cyclization with HCl as a co-catalyst in direct comparison to **I** (Figure 3c). A very similar product distribution for the cyclization of nerol and geraniol was obtained for **I** and **III** (SI, Chapter 7). The reactions with **III** proceeded slower and showed a more significant background reaction when the capsules were blocked by the strongly binding alkylammonium guest TBAB. The slower reaction and the stronger background conversion might be a result of the decreased stability of **III** compared to **I** (Figure 3a).

In summary, we have demonstrated the applicability of two distinct methods to install thiols on the resorcin[4]arene framework. These protocols allowed us to synthesize three novel thiol-analogs of resorcin[4]arene and pyrogallol[4]arene, investigate the influence of free thiols on their properties, and compare them to **RS** and **PG**. We found that: (1) Thiol-derivatives of **RS** can self-assemble into a hexameric capsule as long as the amount of thiols is kept to a minimum. (2) Disulfide formation with thiol-derivatized resorcin[4]arenes is possible but requires irreversible oxidative conditions. Thus, it is limited to monothiol macrocycles in order to prevent oligomerization, and is not suited for DCvC. The dimeric disulfide **4** obtained under mild oxidative conditions from **3** forms a trimeric capsule **IV** of similar size as capsules **I**-**III**, as confirmed by DOSY-NMR studies. (3) The increased acidity introduced by the six thiols of **III** is not sufficient to catalyze terpene cyclizations on its own. Additionally, it was found that capsule **III** displays unusual guest uptake properties by being able to encapsulate both alkylammonium salts and C_{60}-fullerenes. Overall, these studies clarified the consequences of introducing thiols into hydrogen bond-based molecular capsules, and contributed to the understanding of the catalytically active resorcin[4]arene capsule that has attracted growing interest over the last years.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, computational models, and NMR spectra and HRMS data of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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