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Homoselenacalix[*n*]arenes

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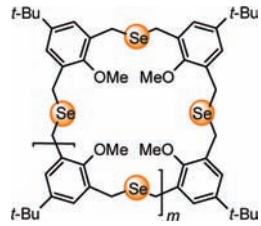
ABSTRACT



A novel family of homoselenacalix[*n*]arenes ($n = 3-8$), with bridging CH_2SeCH_2 groups connecting the aryl subunits, has been synthesized via two different approaches employing nucleophilic Se species. The macrocycles are adequately characterized, including single-crystal X-ray structures for the homoselenacalix[4]- and homoselenacalix[6]arene homologues. The combined features of a calixarene-like macrocyclic scaffold and the presence of multiple selenium atoms create appealing (biomimetic) supramolecular opportunities.

Over the past 3 decades, the design and synthesis of a variety of calixarene macrocycles has emerged as an essential part of supramolecular chemistry, providing high versatility in forming three-dimensional cavities which can selectively form host−guest complexes with neutral molecules or ions.[1] Besides the extensively explored classical carbon-bridged calix[*n*]arenes, several other families of "calixarenoid" macrorings with particular properties have been developed and the chemistry of some of these calixarene-like metacyclophanes has been rejuvenated in recent years. Among those, heteracalixarenes, in which the traditional methylene linkages between the aromatic units are replaced by heteroatoms (e.g., S, NR or O),[2] and homoheteracalixarenes, calixarene analogues in which one or more methylene units are expanded to CH_2XCH_2 groups (X = O, NR or S),[3−6] are particularly attractive since they introduce heteroatoms which might provide additional binding sites.

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The presence of additional methylene units (and possibly heteroatoms) in homocalixarenes results in an enlarged cavity size as well as conformational flexibility, features that might be advantageous for binding guests in an induced-fit fashion.[3−6] Within the subgroup of homoheteracalixarenes, the oxygenated analogues have been studied most intensively.[3,4] Different combinations and permutations of CH_2 and CH_2OCH_2 groups have afforded various macrocyclic homooxacalixarene frameworks. Hexahomotrioxacalixarenes, the most available symmetrical homologues within this family, have been applied as efficient synthetic hosts for both metal and organic (quaternary ammonium) ions, and fullerenes,[3,4] while an oxovanadium complex has recently been shown to be a superior olefin polymerization catalyst.[4h] The synthesis and host−guest properties of homoaza- and homothiacalixarenes have also been explored, although to a lesser extent.[5,6] However, to date, there have been no reports of an extension of (homo)heteracalixarene chemistry to the corresponding third or fourth-row "isologues" of the chalcogen series.[7]

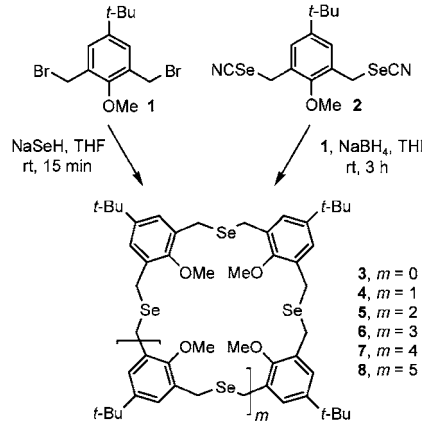
Organoselenium compounds are of great interest from a biological and pharmaceutical point of view. Inspired by the importance of natural selenoproteins, synthetic organoselenium derivatives have been designed as glutathione peroxidase (GPx) mimics and antithyroid drugs, and applied for cancer prevention, inflammation protection, immune responses, and photodynamic tumor therapy.[8,9] A number of macrocycles containing selenium atoms within the ring system have been synthesized over the years.[10] The complexation chemistry of selenoethers as versatile σ-donor ligands for transition metals and their charge-transfer complexation with electron acceptors are well-established. The easy (reversible) conversion of selenides to selenoxides and selenones enables Se-based macrocycles to bind different guest molecules in its different oxidation states.

From the above, it is evident that (homo)calixarene macrocycles containing Se atoms are attractive target molecules. Herein, we report convenient and versatile synthetic procedures toward hitherto unknown homoselenacalix[*n*]arenes ($n = 3-8$).[7]

Synthetic strategies toward homothiacalixarenes usually involve substitution reactions of 1,3-bis(mercaptomethyl)-benzene nucleophiles on 1,3-bis(bromomethyl)benzene derivatives.[6] Unfortunately, selenols are not as easy to prepare and handle as the corresponding thiols, and readily oxidize to diselenides. The required selenium bisnucleophiles can, however, in situ be generated from bis(bromomethyl)benzenes and sodium hydroselenide (NaSeH) or, alternatively, 1,3-bis(selenocyanato)benzene derivatives can be used.

Our first trial toward the formation of homoselenacalixarenes involved reaction of 1,3-bis(bromomethyl)benzene and NaSeH (1:1 ratio) in THF under high dilution conditions. Analysis of the crude reaction mixture by electrospray mass spectrometry (ESI-MS) pointed toward the formation of macrocycles containing 2−10 dimethyleneselena links, but poor solubility hampered efficient purification of the homologues. For this reason, another monomer enforcing favorable solubility to the macrocycles, 1,3-bis(bromomethyl)-5-*tert*-butyl-2-methoxybenzene (**1**), was envisaged. Moreover, this substitution pattern allows direct comparison with related (homo)calixarenes and might enable modification of the lower rim at a later stage. Dropwise addition of 1 equiv of NaSeH in ethanol (freshly prepared by reaction of a 1:2 molar ratio of Se powder and $NaBH_4$ suspended in ethanol) into a flask containing 1 equiv of **1** in THF at room temperature over 15 min resulted in the formation of a (kinetic) mixture of homoselenacalix[*n*]arenes ($n = 3-7$) in 86% total yield with a 37:20:14:8:7 product ratio of **3**−**7**, respectively (Scheme 1). The rest of the reaction mixture consisted of polymeric material (and possibly higher cyclooligomers). All homoselenacalixarenes **3**−**7** show good solubility in a variety

Scheme 1. Synthetic Pathways toward Homoselenacalix[*n*]arenes **3**−**8**



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of (medium polarity) organic solvents such as CH_2Cl_2, ethyl acetate, and THF. The calixarenes were separated by column chromatography (silica) and the macrocycle size was easily deduced by ESI-MS. An extension of the reaction time over a longer period has the advantage of increasing the yield of homoselenacalix[4]arene **4** (~45%, ~30% **3**), but at the same time the reaction is troubled by the oxidation of a small amount of NaSeH to sodium selenide (Na_2Se_2), which in turn results in the insertion of diselenide bridges, rendering this approach less attractive. The use of an excess of NaSeH has no profound influence on the calixarene ratio. The addition of NaSeH at once into a solution of dibromide **1** increased the content of polymer formation.

A more selective synthesis of *p-tert*-butyloctahomotetraselenacalix[4]arene tetramethylether **4**[11] could be achieved through a [2 + 2] reductive coupling protocol starting from dibromide **1** and bisselenocyanate **2** (Scheme 1), easily prepared by reaction of **1** and KSeCN. An excess of $NaBH_4$ (3 equiv), suppressing diselenide formation, was added dropwise to a mixture of **1** and **2** (1:1 ratio) in THF using high dilution conditions, affording homoselenacalix[4]arene **4** in 67% yield and homoselenacalix[6]arene **6** in 18% yield, while additionally affording homoselenacalix[8]arene **8** (9% yield). When the reaction was repeated with a larger quantity and higher concentration of reactants (5 mmol **1** and **2**, ~10 mM in THF), even larger macrocycles ($n = 10, 12, 14$) were obtained, but these could not efficiently be separated chromatographically. Homoselenacalix[4]arene **4** could alternatively be purified by selective crystallization from a $CHCl_3$-pentane solvent mixture. Additional advantages of the [2 + 2] cyclocondensation are the absence of odd-numbered calixarenes, simplifying purification, and the opportunity to prepare asymmetrical homoselenacalixarenes.

Homoselenacalix[*n*]arenes **3**−**8** were completely characterized by NMR spectroscopy (^{1}H, ^{13}C and ^{77}Se) and ESI-MS. The ^{1}H NMR spectra of all calixarenes are easily interpreted and show only singlet signals. The absence of coupling for the geminal protons of the methylene groups (due to diastereotopicity) indicates conformational flexibility in solution.[3−6] Except for the *tert*-butyl groups, all other protons show a distinct chemical shift depending on the macrocycle size. The protons of the intraannular methoxy substituents are shifted upfield considerably with respect to the acyclic precursors and this effect is most pronounced for homoselenacalix[4]arene **4**. This indicates that a conformation in which the protons of the methoxy groups face the rings of neighboring aromatic units is likely more populated in this case. Hence, analysis of the ^{1}H NMR spectrum of the crude reaction mixture can provide a reliable quantitative insight on the respective calixarenes produced (via integration of the methoxy signals). The chemical shift differences for the aromatic and methylene protons are much smaller. Variable temperature ^{1}H NMR spectra of **4** give additional information on the conformational behavior. No signal splitting was observed for temperatures down to −60 °C while further shielding of the methoxy protons, ranging from δ 3.22 ppm at room temperature to 2.95 ppm at −60 °C, was noticed.[3−6] The ^{77}Se NMR spectra for **3**−**8** contain only one signal arising from the bridging Se atoms, confirming the uniformity of all selenium atoms. A minor downfield ^{77}Se chemical shift is observed with increasing cavity size.

To confirm the structure and analyze the conformations of the synthesized macrocycles in the solid state, single crystals of **4** and **6** were grown.[12] The solid-state conformations determined for these homoselenacalix[*n*]arenes differ from the structures reported for analogous homooxa and homoaza derivatives (Figure 1).[4,5] Homoselenacalix[4]arene

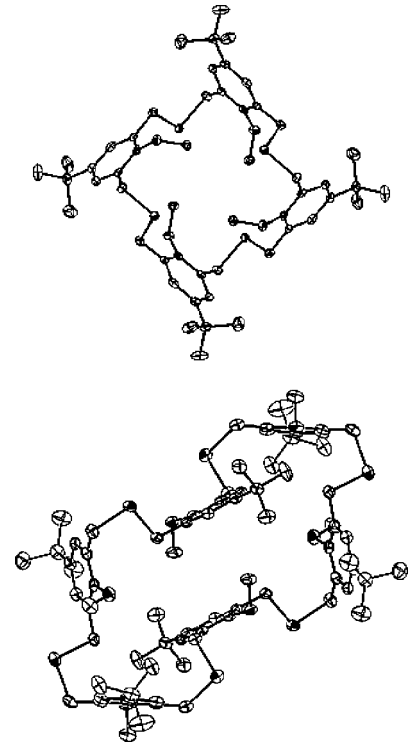


Figure 1. ORTEP representations of homoselenacalix[*n*]arenes **4** (top) and **6** (bottom), determined by X-ray crystallography (top view). Thermal ellipsoids are set at 50% probability.[13]

4 adopts a heavily twisted (distorted) 1,3-alternate conformation with 4-fold symmetry, with the bridging Se atoms oriented inside the cavity. Two crystallographic independent homoselenacalix[4]arene entities, with similar structural features, can be distinguished in the crystal structure. The methoxy groups on the intraannular rim are directed inward, properly arranged so as to minimize steric hindrance. Two of the methoxy hydrogens show weak hydrogen interactions with neighboring Se atoms, while the third hydrogen atom is involved in a weak CH−π interaction with a phenyl ring. The latter interaction seems to correspond well with the

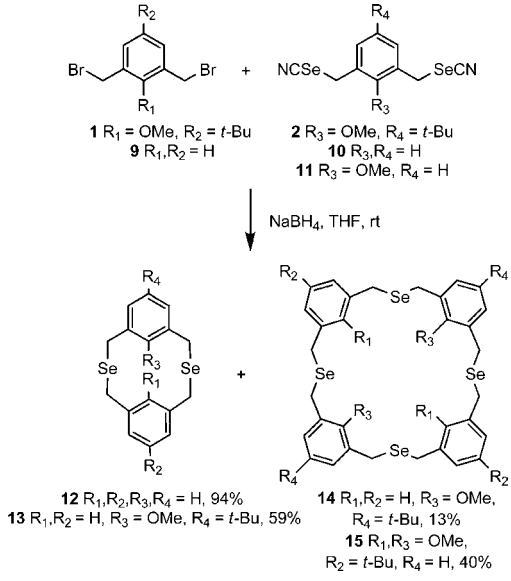
(11) Alternative denotations: tetraselena[3.3.3.3]calixarene or 2,11,20,29-tetraselena[3.3.3.3]metacyclophane.[3−6]

(12) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as suppl. publ. no. CCDC-729034 and CCDC-729035. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223−336033 or e-mail: deposit@ccdc.cam.ac.uk).

observed shielding effect in the ^{1}H NMR spectrum. On the other hand, a 1,3,5-alternate conformation is observed for the expanded homoselenacalix[6]arene **6**. The bridging Se atoms are directed outside the cavity and facing phenyl rings are oriented antiparallel. The methoxy substituents are partly included in the cavity and partly directed outward. The two self-included methoxy groups show weak CH$-\pi$ interactions with the opposing phenyl rings, while two of the outward directed methoxy groups show weak hydrogen interactions with Se.

To vary the substitution pattern of the homoselenacalixarenes, substituent-free (at the 2- and 5-position) precursors **9** and **10** were initially combined under reductive conditions (Scheme 2). However, [1 + 1] coupling product **12** was

Scheme 2. Exploration of the Selenacyclophane Size



obtained almost quantitatively (94%). Hence, we decided to perform a preliminary study on the effect of intra- and extraannular substituents on the macrocyclization outcome. Reaction of 5-*tert*-butyl-2-methoxy-bisselenocyanate **2** and **9** under identical conditions gave again the dimeric diselena[3.3]metacyclophane (**13**, 59%) as the main compound, together with 13% of homoselenacalix[4]arene **14**. This indicates that the absence of an interior methoxy group favors [1 + 1] cyclocondensation. In contrast, the coupling reaction between **1** and bisselenocyanate **11** (lacking the *tert*-butyl moiety) under similar reaction conditions afforded homoselenacalix[4]arene **15** (40%) as the major product (Scheme 2). No diselena[3.3]cyclophane product was detected in this reaction (as for cyclocondensation of **1** and **2**). The above observations indicate that the methoxy group on the inner rim is not only a useful diagnostic tool to determine the ring size by NMR and enables postmacrocyclization modifications, but also plays a crucial role for the selective formation of the cyclic tetramers.

In summary, a series of homoselenacalix[*n*]arenes of different ring size ($n = 3-8$), containing bridging dimethyleneselena units connecting the aryl parts, has been synthesized and the macrocycles were completely characterized, including X-ray structures for the calix[4]- and calix[6]arene homologues. Se-bridged calixarene macrocycles not only represent an addition to the expanding field of organoselenium chemistry, but can evolve into an important family of potential receptor molecules in which the Se atoms impose specific complexation patterns and provide an additional probe to monitor interactions (via ^{77}Se NMR). Further elaboration of the synthetic chemistry of (homo)selenacalixarenes and their supramolecular applications are currently actively being pursued within our group.

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Supporting Information Available: Experimental procedures and data, NMR (^{1}H, ^{13}C, ^{77}Se) spectra of the novel macrocycles and precursors, and additional information regarding the X-ray structures of **4** and **6**. X-ray data for **4** and **6** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) H atoms, disorder (*t*-Bu in **6**) and incorporated solvent ($CHCl_3$ in **4**) are omitted for clarity.