Synthetic Protocols towards Selenacalix[3]triazines

Joice Thomas,[a] Wim Van Rossom,[a] Kristof Van Hecke,[b,c] Luc Van Meervelt,[b] Mario Smet,[a] Wim Dehaen*[a] Wouter Maes*[a,d]

[a] Molecular Design and Synthesis, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium
Fax +32(16)327990; E-mail: wim.dehaen@chem.kuleuven.be

[b] Biomolecular Architecture, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium

[c] Department of Inorganic and Physical Chemistry, Ghent University, Krijgslaan 281, Building S3, 9000 Ghent, Belgium

[d] Design & Synthesis of Organic Semiconductors (DSOS), Institute for Materials Research (IMO-IMOMEC), Hasselt University, Universitaire Campus, Agoralaan 1 – Building D, 3590 Diepenbeek, Belgium
E-mail: wouter.maes@uhasselt.be

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Abstract: Selenium-bridged heteracalixarenes were synthesized by convenient one-pot S_NAr reactions starting from variously 2-substituted 4,6-dichloro-1,3,5-triazine building blocks. Reactions of these precursors with sodium hydroselenide afforded the selenacalix[3]triazines as the only macrocyclic products. Yields of the cyclotrimers were significantly increased by optimization of the macrocyclization conditions, the optimum parameters being dependent on the triazine functionalization pattern. X-ray diffraction studies allowed unambiguous identification of the structures and comparison with the solid-state features of analogous heteracalixarenes.

Key words: (hetera)calixarenes, macrocycles, selenium, 1,3,5-triazines, substituent effects

Calixarenes have extensively been studied as efficient (scaffolds towards) artificial receptors in molecular recognition chemistry.[1] A possible structural modification of the calixarene skeleton involves replacement of the methylene bridges between the aromatic units by heteroatoms. Such substitutions have resulted in the emergence of a novel subclass within the calixarene family, known as 'heteracalixarenes' (mostly S, NR, and O).[2–6] The presence of heteroatoms instead of the usual CH_2 bridges makes heteracalixarenes appealing macrocycles with many features that are not present in the chemistry of classical calixarenes. The heteroatom bridges provide an additional opportunity to tune the ring size, conformation, and binding properties, with the possibility of a wider range of noncovalent interactions and recognition events (via the lone pairs with donor ability on the heteroatoms).

Among these heteracalixarenes, the sulfur analogues have been studied most due to their straightforward synthetic accessibility through condensation of phenols with elemental sulfur.[3a–d,4] They are widely recognized as receptor molecules for small organic compounds and heavy metals, and their coordination complexes with transition metals have been explored as catalytically active surfaces. On the other hand, the analysis of published data in recent years clearly indicates a renewed interest in the synthesis and applications of aza- and oxacalixarenes.[3e–i] Several azacalixarene cyclooligomers have been explored as powerful hosts towards the binding of fullerenes (C_{60} and C_{70}) and some derivatives were also studied for their selective adsorption of CO_2 in the solid state.[5] The field of oxacalix[*n*]arenes has recently witnessed a fast growth as an increasing amount of work was devoted to their synthesis and conformational studies.[6] There have also been a few reports on silicon- and germanium-linked calixarenes, as well as related structures bridging heteroaromatic subunits.[3a]

Following the discovery of selenoenzymes, organoselenium chemistry has received considerable interest, aiming at potential applications in biochemistry, organic synthesis (as reagents or intermediates), heavy atom versions of oligonucleotides and proteins for crystallographic studies, the synthesis of semiconducting materials, and ligand chemistry.[7,8] Many organo-Se compounds have been analyzed as biological mimics capable to stimulate the antioxidant function of glutathione peroxidase (GPx).[8] The chemistry of macrocyclic ligands containing Se atoms is of great interest because they are generally better σ-donor ligands than their corresponding O and S counterparts.[9] The large size of Se leads to an increased cavity size and imposes significant differences on the electronic and conformational features of the selenamacrocycles, resulting in an interesting coordination behavior that is quite different from its lighter congeners. One of the additional advantages of Se-based macrocycles is the possibility to monitor host–guest interactions by the shift in the ^{77}Se NMR resonance.

The peculiar features of Se and the projected difference in physical properties of the heteracalixarene subclass compared to classical calixarenes encouraged us to design and synthesize calixarenoid macrocycles containing bridging Se atoms as attractive target molecules. We have previously reported on the synthesis of a series of homoselenacalix[*n*]arenes (with CH_2SeCH_2 linkages) of varying ring size (n = 3–8) by two different approaches, either via a [2+2] reductive coupling protocol or by applying sodium hydroselenide (NaSeH) to generate (in situ) a Se bisnucleophile.[10] The first method provided a high yield and se-

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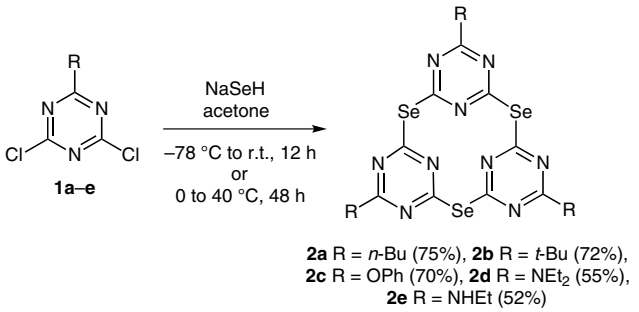
lectivity for the tetrameric cyclic oligomers, whereas the second approach resulted in a mixture of macrocycles of different ring size (with somewhat higher selectivity for the homoselenacalix[3]arenes). On the other hand, our group has wide experience in the preparation of oxygen-bridged calix[*n*]arenes through nucleophilic aromatic substitution (S_NAr) reactions on halogenated pyrimidine building blocks.[11] With this background in organoselenium and heteracalixarene chemistry, we envisaged the synthesis and supramolecular studies of unknown selenacalix[*n*]arenes (with direct Ar–Se–Ar bonds) – missing links within the heteracalixarene series – by S_NAr reactions on activated hetarenes.[12]

The envisaged protocol towards the synthesis of selenacalixarenes involved the S_NAr reaction of in situ generated NaSeH with electrophilic halogenated heterocycles. In the initial attempts, 4,6-dichloropyrimidine or 2,6-dichloropyrazine were combined with NaSeH under different conditions (temperature, solvent, concentration, NaSeH preparation; see below). This approach did, however, not yield any desired macrocyclic compounds. A somewhat more encouraging result was obtained for the reaction of 2,6-dichloropyridine and NaSeH at an elevated temperature (130 °C for 24 h in DMSO). The formation of a selenacalix[3]pyridine cyclooligomer was observed by electrospray ionization-mass spectrometry (ESI-MS). The low reactivity of the electrophilic pyridine species, the rather harsh reaction conditions, and major difficulties in isolating and purifying the desired selenacalix[3]pyridine were, however, crucial drawbacks. Hence the focus was directed towards 2-substituted 4,6-dichloro-1,3,5-triazine building blocks, whose highly electron-deficient nature imposes excellent reactivity in S_NAr reactions.[3g,6a,b,d–h,13] For this purpose, several 4,6-dichlorotriazine building blocks **1a**–**e**, easily available by the possibility of controlled sequential substitution on cyanuric chloride, were synthesized (Scheme 1).



Scheme 1 One-pot synthetic pathway towards selenacalix[3]triazines **2a**–**e**

In the first trial towards the synthesis of selenacalix[*n*]arenes employing triazine building blocks, NaSeH (freshly prepared by reaction of a 1:2 molar ratio of Se powder and $NaBH_4$ suspended in ethanol) was added to a solution of 2-butyl-4,6-dichloro-1,3,5-triazine (**1a**) in THF at 0 °C (and the reaction was continued at r.t. overnight), resulting in the formation of a moderately soluble yellow colored crude product mixture. Analysis of a sample by ESI-MS revealed the formation of calix[3]arene **2a** (*m*/*z* = 643.2). No ESI-MS traces of other linear or cyclic oligomers could be observed. Purification by column chromatography (silica gel) yielded selenacalix[3]triazine **2a** in a very poor yield (4%). A thorough search for the optimum conditions to obtain a maximum amount of macrocycle **2a** was hence conducted (Table 1).

Table 1 Optimization of the Yield of Selenacalix[3]triazine **2a**

Entry	Solvent	NaSeH[a]	Temp (°C)	**2a** (%)[b]
1	THF[c]	EtOH	0 to r.t.	4
2	THF[d]	EtOH	0 to r.t.	9
3	THF[d]	EtOH	–78 to r.t.	16
4	THF[d]	H_2O	–78 to r.t.	32
5	THF[d]	H_2O[e]	–78 to r.t.	23
6	CH_2Cl_2[d]	H_2O	0 to r.t.	35
7	CH_2Cl_2[d]	EtOH	0 to r.t.	22
8	acetone[d]	H_2O	–78 to r.t.	60
9	acetone[f]	H_2O	–78 to r.t.	75
10	acetone[d]	EtOH	–78 to r.t.	20
11	acetone[d]	H_2O[e]	–78 to r.t.	48

[a] NaSeH: 1 equiv in 4 mL of solvent.
[b] Yields for the isolated analytically pure compounds.
[c] Concentration of triazine precursor **1a** (before NaSeH addition): 24 mM.
[d] Concentration of triazine precursor **1a** (before NaSeH addition): 6.9 mM.
[e] NaSeH: 1.2 equiv in 4 mL of H_2O.
[f] Concentration of triazine precursor **1a** (before NaSeH addition): 3.4 mM.

Performing the reaction under high dilution conditions resulted in an increase in the yield of **2a** to 9% (Table 1, entry 2). In an attempt to limit the formation of colored noneluting side products, NaSeH was added at –78 °C (entry 3), decreasing the amount of side products and increasing the yield to 16%. An encouraging result was then obtained by changing the solvent for the preparation of NaSeH from ethanol to water (entry 4). The amount of colored side products was further reduced and the yield was doubled (32%) as compared to the NaSeH/EtOH combination. Increasing the ratio of NaSeH to 1.2 equivalents slightly decreased the yield of **2a** (entry 5). The cyclooligomerization reaction was also performed in CH_2Cl_2 (entries 6,7). Although decomposition of the triazine precursor was limited under these two-phase conditions, the reactivity was also strongly reduced. Even after 4 days the conversion was still not complete and the maximum isolated yield of calix[3]arene **2a** was 35%. An increase in the ratio of NaSeH or an elevated temperature (35 °C) did not considerably affect the obtained yield. A breakthrough was finally achieved by using acetone as the

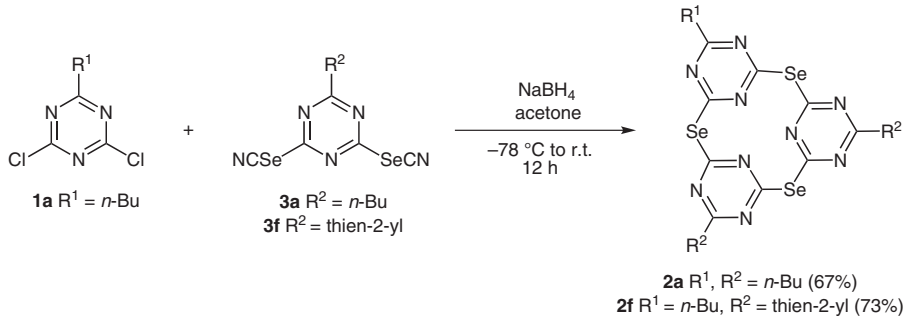
reaction solvent with an increase in the overall yield of **2a** to 60% (entry 8). Only a slight yellow coloration was observed when NaSeH in water was added to triazine precursor **1a** at –78 °C. The decomposition was almost absent when the amount of acetone was doubled (resulting in a concentration decrease from 6.9 to 3.4 mM), affording cyclotrimer **2a** in 75% yield (entry 9). A significant reduction in the yield was observed upon repeating the reaction as reported above but using NaSeH in ethanol (entry 10). Changing the ratio of the reagents (1.2 equiv of NaSeH in H_2O) again caused a drop in the obtained yield of **2a** (entry 11). Hence, by carefully optimizing the S_NAr conditions the yield for selenacalix[3]triazine **2a** was increased spectacularly from 4% to 75%. It is important to note that in this case the cyclic trimer[14] is essentially the only (major) product formed and it can easily and efficiently be isolated in pure form by simple precipitation of the macrocycle directly from the reaction mixture in water.

To vary the substitution pattern of the selenacalix[3]triazine macrocycle, a few (proof-of-principle) functional groups were introduced at the stage of the triazine building blocks (prior to macrocyclization). The substituted 4,6-dichlorotriazines **1b**–**e** were then reacted with NaSeH under the conditions as optimized for **2a** (Scheme 1). The S_NAr reaction of 2-*tert*-butyl-4,6-dichloro-1,3,5-triazine (**1b**) and NaSeH resulted in the analogous selenacalix[3]triazine **2b** in an overall yield of 72%. Once again, purification could simply be achieved by precipitation from the reaction mixture (acetone) in water. Through introduction of a phenoxy group on the dichlorotriazine precursor, the corresponding trimeric cyclooligomer **2c** was also prepared in a similarly high yield (70%). Since the electrophilicity of the triazine moiety is reduced by the introduction of the phenoxy group, the above reaction was carried out at a higher concentration of precursor **1c** (11.7 mM). When the reaction was repeated with larger reagent quantities and at a higher concentration (1.0 g **1c**, 20.7 mM), the analytically pure macrocycle **2c** was precipitated from acetone–water in 56% yield. Once more none of the larger cyclooligomers was observed in the crude mixture (as evidenced by ESI-MS). Under the same reaction conditions as described above for cyclotrimer **2c**, the reaction of 4,6-dichloro-*N*,*N*-diethyl-1,3,5-triazin-2-amine (**1d**) with NaSeH resulted in an unsatisfactory yield of 4% of selenacalix[3]arene **2d** (after chromatographic purification). An appreciable amount of unreacted starting material remained in the reaction mixture, even after 48 hours of reaction, which may be attributed to the further increase in electron density in the triazine precursor. A larger amount of **2d** was obtained (39%) by using a small excess of NaSeH (1.2 equiv) in ethanol and avoiding too high dilution (20.5 mM in acetone). However, the reaction mixture still contained quite some remaining precursor **1d** and some polymeric material was observed as well. When the reaction was performed using NaSeH (1.05 equiv in water) in acetone (18.1 mM **1d**) at 40 °C over a period of two days, most of the starting material was consumed and the degree of polymer formation was considerably reduced. The pure product **2d** was obtained in 55% yield by precipitation in water followed by crystallization of the precipitate in MeCN–CH_2Cl_2 (3:2) (to purify the macrocycle from oligomeric open chain structures). Similar observations were made for the synthesis of selenacalix[3]arene **2e** (isolated yield of 52% by precipitation from acetone–water). Attempts to synthesize selenacalix[*n*]arenes starting from 2-aryltriazine precursors were hampered by the poor solubility of the desired macrocycles. Several aromatic substituents such as 2-thienyl, *p*-methoxyphenyl and *p*-tolyl groups were introduced on the triazine heterocycle and the resulting 4,6-dichlorotriazine derivatives were reacted with NaSeH. The formation of the corresponding selenacalix[3]triazines was confirmed by ESI-MS. However, the rather insoluble nature of the products severely hampered efficient purification and characterization.

All selenacalix[3]triazines **2a**–**e** showed good solubility in a variety of organic solvents (e.g., CH_2Cl_2) and the macrocycles were completely characterized by NMR spectroscopy (^1H, ^{13}C, and ^{77}Se) and (high resolution) mass spectrometry. The ^1H NMR spectra of dichlorotriazines **1a**–**e** and the corresponding selenacalixarenes **2a**–**e** showed only marginal differences, which complicated ^1H NMR analysis. On the other hand, the ^{13}C NMR spectra gave a clear shift for the carbon atoms linked to Se (as compared to the C–Cl bonds in the acyclic precursors). The ^{77}Se NMR spectra for **2a**–**e** contained only one signal arising from the bridging Se atoms, confirming the uniformity of all selenium bridges (see Supporting Information).

In an attempt to synthesize a selenacalix[4]triazine macrocycle, a [2+2] reductive fragment coupling protocol was performed starting from 2-butyl-4,6-dichlorotriazine (**1a**) and diselenocyanate **3a** (Scheme 2). The latter was synthesized by the reaction of **1a** and KSeCN. Remarkably, this approach induced significant scrambling and selenacalix[3]triazine **2a** was still the major product (67% isolated yield). Surprisingly, no trace of the targeted selenacalix[4]triazine (or other cyclic homologues) could be observed. In general, the lack of evidence for the formation of cyclic tetramers or other (larger) cyclic structures in any of the procedures points to a reversible macrocyclization reaction. A dynamic process of ring opening and (re)cyclization favors selective formation of the thermodynamically most stable products, in this case apparently the selenacalix[3]triazines.[15] Heteracalix[3]arenes, the smallest possible cyclooligomers within the series, have previously been obtained for the S- and N-bridged macrocycles, but have never been observed for oxacalixarenes, for which the cyclotetramers are the thermodynamically favored species.[3,6,14]

Using two different triazine building blocks, we also succeeded in synthesizing an asymmetrically substituted selenacalix[3]triazine. Combination of thienyl-substituted diselenocyanate **3f** with triazine building block **1a** in a 1:1 ratio under reductive coupling conditions afforded asymmetrical selenacalix[3]triazine **2f** in 73% yield. Addition-



Scheme 2 One-pot synthetic pathway towards selenacalix[3]triazines **2a**,**f**

ally, the selenacalix[3]triazine analogue with two *n*-butyl and one 2-thienyl substituent was formed in a small amount. The [2+2] approach thus allowed the introduction of aromatic substituents on the selenacalixarene framework, since the remaining alkyl group guarantees reasonable solubility. The ^{77}Se NMR spectrum of **2f** contains two signals with a 1:2 intensity arising from the two types of Se atoms bridging the different aromatic constituents.

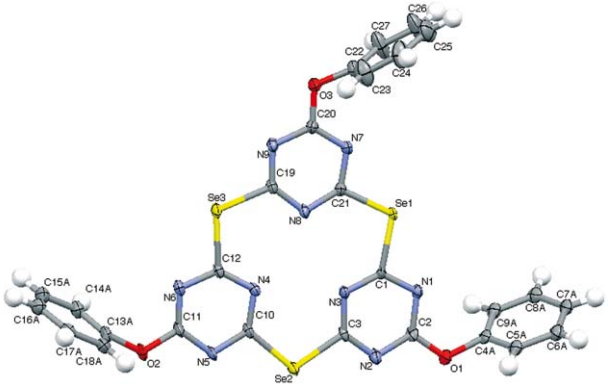


Figure 1 ORTEP representation (with atom labeling scheme) of selenacalix[3]triazine **2c** as determined by X-ray crystallography. Thermal ellipsoids are shown at the 50% probability level. For clarity, the disordered phenoxy groups are not shown.

To confirm the structures and to elucidate the conformations of the synthesized macrocycles in the solid state, single crystals of some of the selenacalix[3]triazines were grown.[16] The solid-state conformations determined for these cyclotrimers are similar to the approximately disk-shaped structure reported for the analogous thiacalix[3]triazine derivative (R = *t*-Bu).[14c,17] Selenacalix[3]triazine **2c** (R = OPh) adopts an almost planar conformation (Figure 1), that is, the triazine rings are tilted 1.8(2)°, 2.2(2)°, and 2.3(2)° to the plane through the bridging Se atoms (compared to 3.4°, 16.3°, and 32.1° for the thiacalix[3]triazine[14c]). Two phenoxy groups are found disordered on the macrocyclic framework. The three triazine units are not related by any crystallographic symmetry and the C–Se bond lengths vary within the range of 1.899(5) to 1.936(4) Å. Short intramolecular con-

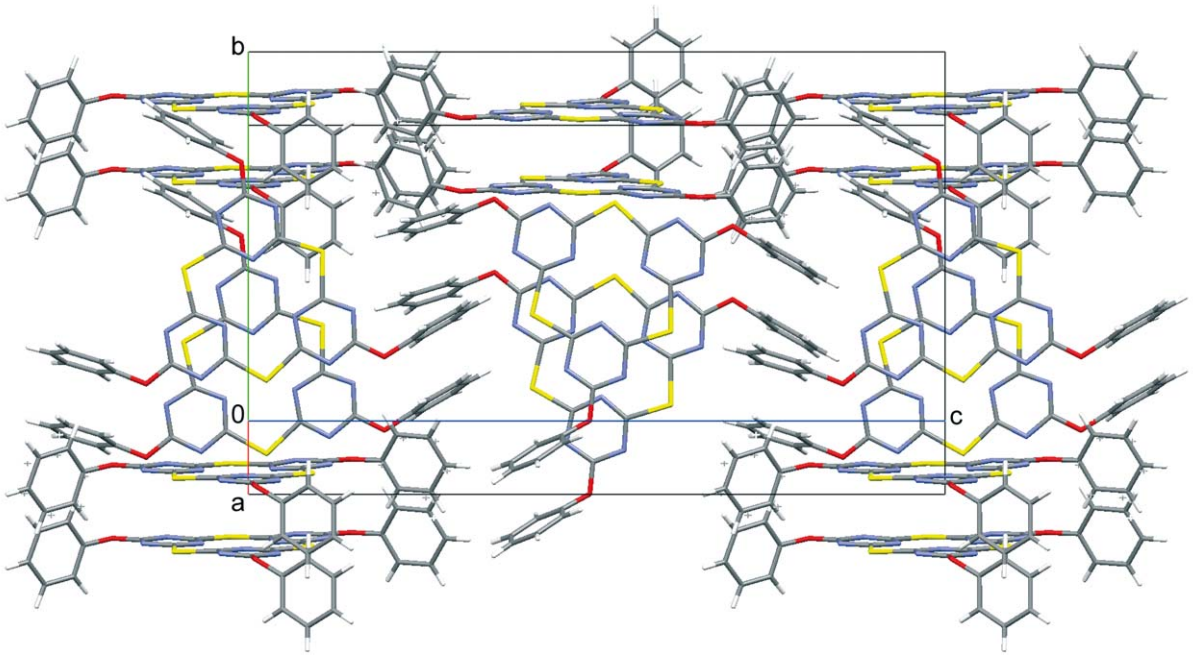


Figure 2 Packing of the crystal structure of selenacalix[3]triazine **2c**, indicating the stacking of two Se atoms and one O atom on the triazine rings of a second symmetry-equivalent molecule

tacts (within their van der Waals radius) are observed between the interior nitrogen atoms, with distances of 2.881(6), 2.938(6), and 2.879(6) Å, respectively (2.73–2.79 Å for the thiacalix[3]triazine congener[14c]). In the packing, the macrocycles are stacked on top of each other, that is, two selenium atoms and one phenoxy oxygen atom are stacked on the triazine rings of a second symmetry-equivalent molecule [distances between Se and O atoms and ring centroids are 3.441(2), 3.455(2) and 3.456(5) Å, respectively; Figure 2].[8e,18] CH–π and π–π ring-ring interactions are observed between the triazine rings of symmetry-equivalent molecules, as also described for the thiacalix[3]triazine,[14c] as well as between the phenoxy substituents [distances between the centroids in the range of 4.303(3)–5.974(4) Å].

In conclusion, selenacalix[3]triazine macrocycles were synthesized selectively in high yields by carefully optimized one-pot S_NAr reactions on *m*-dichlorinated triazine heterocycles. Different functionalities on the triazine building blocks were proven to be compatible with the applied S_NAr conditions, allowing the preparation of a number of substituted selenacalix[3]triazines, including an asymmetrically substituted derivative. The optimum (dilution) conditions were dependent on the electronic nature of the appended groups. The choice of substituents is somewhat limited to moieties engendering sufficient solubility to the macrocycles. A major advantage of the reported synthetic method is the easiness of purification simply by precipitating the selenacalix[3]arene cyclooligomer from the reaction mixture (acetone) in water. All macrocycles were completely characterized, including solid-state structures for two derivatives.

NMR spectra were acquired on commercial instruments (Bruker Avance 300 MHz or Bruker AMX 400 MHz) and chemical shifts (δ) are reported in parts per million (ppm) referenced to TMS (^{1}H) or the internal (NMR) solvent signals (^{13}C).[19] *J* values are given in Hz. The ^{77}Se NMR spectra were recorded using Ph_2Se_2 in $CDCl_3$ as an external reference (δ_{Se} = 463).[20] Mass spectra were run using a HP5989A apparatus (CI, 70 eV ionization energy) with Apollo 300 data system or a Thermo Finnigan LCQ Advantage apparatus (ESI). Exact mass measurements were acquired on a Kratos MS50TC instrument (performed in the EI mode at a resolution of 10 000) or a Bruker Daltonics Apex2 FT-ICR instrument (performed in the ESI mode at a resolution of 60 000). Both the calculated and experimental masses reported refer to the 100% intensity peak of the isotopic distribution. Melting points (not corrected) were determined using a Reichert Thermovar apparatus. For column chromatography 70–230 mesh silica gel 60 (E. Merck) was used as the stationary phase. Chemicals received from commercial sources were used without further purification. Reaction solvents (THF, EtOH, and acetone) were used as received from commercial sources.

Triazine Building Blocks

2-Butyl-4,6-dichloro-1,3,5-triazine (1a)

n-BuMgBr (56 mL, 1 M in THF) was added dropwise to a cold (0 °C) solution of cyanuric chloride (10.0 g, 54.3 mmol) in anhyd THF (100 mL) over a period of 5 min. The temperature was gradually increased to r.t. and stirring was continued for another 5 h. The reaction was quenched by careful addition of aq NH_4Cl (100 mL). CH_2Cl_2 (200 mL) was added, the organic layer was separated and washed with distilled H_2O (100 mL), dried ($MgSO_4$), filtered, and evaporated to dryness to afford the crude product. Purification by column chromatography (silica gel, eluent CH_2Cl_2–heptane, 4:1) afforded triazine derivative **1a** (9.0 g, 80%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.91 (t, *J* = 7.7 Hz, 2 H), 1.81 (q, *J* = 7.7 Hz, 2 H), 1.42 (s, *J* = 7.4 Hz, 2 H), 0.96 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.4, 171.8, 38.5 (CH_2), 29.6 (CH_2), 22.5 (CH_2), 13.8 (CH_3).

MS (ESI+): *m*/*z* = 206 [MH^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_7H_9Cl_2N_3$: 205.0174; found: 205.0159.

2-*tert*-Butyl-4,6-dichloro-1,3,5-triazine (1b)

This compound was prepared according to the procedure reported by Hintermann et al.[21] Material identity and purity were confirmed by MS, ^{1}H, and ^{13}C NMR analyses.

2,4-Dichloro-6-phenoxy-1,3,5-triazine (1c)

This compound was prepared according to the procedure reported by Götz et al.[22] Material identity and purity were confirmed by MS, ^{1}H, and ^{13}C NMR analyses.

4,6-Dichloro-*N*,*N*-diethyl-1,3,5-triazin-2-amine (1d)

This compound was prepared according to the procedure reported by Hermon et al.[23] Material identity and purity were confirmed by MS, ^{1}H, and ^{13}C NMR analyses.

4,6-Dichloro-*N*-ethyl-1,3,5-triazin-2-amine (1e)

This compound was prepared according to the procedure reported by Bruun et al.[24] Material identity and purity were confirmed by MS, ^{1}H, and ^{13}C NMR analyses.

2,4-Dichloro-6-(thien-2-yl)-1,3,5-triazine (1f)

To a solution of cyanuric chloride (1.00 g, 5.42 mmol) in anhyd THF (20 mL) at 0 °C was added a solution of 2-thienylmagnesium bromide (6.52 mL, 1 M in THF) dropwise over 5 min. The temperature was gradually increased to r.t. and stirring was continued for another 5 h. The reaction was quenched by careful addition of aq NH_4Cl (20 mL), and CH_2Cl_2 (50 mL) was subsequently added. The organic solution was washed with distilled H_2O (20 mL), dried ($MgSO_4$), filtered, and evaporated to dryness to afford the crude product mixture. Purification by column chromatography (silica gel, eluent CH_2Cl_2–heptane, 80:20) afforded the product as a slightly yellow solid (1.02 g, 81%); mp 105–106 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 2.8 Hz, 1 H), 7.87 (d, *J* = 4.0 Hz, 1 H), 7.26–7.22 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7 (CCl), 170.3, 138.1, 136.3 (CH), 135.2 (CH), 129.4 (CH).

MS (CI): *m*/*z* = 231 [MH^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_7H_3Cl_2N_3S$: 230.9425; found: 230.9431.

Selenacalix[3]triazines

NaSeH; Safety Precautions

The most convenient procedure to prepare NaSeH involves reduction of Se with $NaBH_4$. It allows a rapid and easy preparation of NaSeH without the necessity of generating dangerously toxic H_2Se. NaSeH is an unstable compound and decomposes in moist air with the formation of polyselenides and precipitation of Se. It should be used directly as prepared (in a fume hood) in solution or suspension without isolation.[25]

4,6,10,12,16,18,19,20,21-Nonaaza-5,11,17-tributyl-2,8,14-triselenacalix[3]arene (2a)

Dichlorotriazine precursor **1a** (0.100 g, 0.48 mmol) was dissolved in acetone (140 mL) and the solution was degassed by purging with argon for 10 min. A solution of NaSeH (0.48 mmol, 1 equiv) in distilled H_2O (4 mL) was freshly prepared according to a reported

procedure[26] and added dropwise by syringe into the flask containing **1a** at –78 °C. The temperature was gradually increased to r.t. over 1 h. After stirring the resulting mixture for another 12 h, the reaction mixture was added to H_2O (40 mL), and the precipitate formed was collected by filtration and dried under vacuum to afford the analytically pure product **2a** (0.078 g, 75%) as an off-white solid; mp 73–74 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.77 (t, *J* = 7.7 Hz, 6 H), 1.77 (q, *J* = 7.6 Hz, 6 H), 1.40 (s, *J* = 7.4 Hz, 6 H), 0.95 (t, *J* = 7.3 Hz, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.2, 178.0, 38.1 (CH_2), 29.8 (CH_2), 22.5 (CH_2), 13.9 (CH_3).

^{77}Se NMR (76.3 MHz, $CDCl_3$): δ = 559.

MS (ESI+): *m*/*z* = 643.2 $[M + H]^+$.

FTMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{27}N_9Se_3$ + Na: 665.9793; found: 665.9784.

4,6,10,12,16,18,19,20,21-Nonaaza-5,11,17-tri-*tert*-butyl-2,8,14-triselenacalix[3]arene (2b)

The dichlorotriazine precursor **1b** (0.100 g, 0.48 mmol) was dissolved in acetone (140 mL) and the solution was degassed by purging with argon for 10 min. A solution of NaSeH (0.48 mmol, 1 equiv) in distilled H_2O (4 mL) was freshly prepared according to a reported procedure[26] and added dropwise by syringe into the flask containing **1b** at –78 °C. The temperature was gradually increased to r.t. over 1 h. After stirring the resulting mixture for another 12 h, the reaction mixture was added to H_2O (40 mL), and the precipitate formed was collected by filtration and dried under vacuum to afford the analytically pure product **2b** as an off-white solid (0.075 g, 72%); mp 176–177 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 27 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.0, 179.0, 39.6, 28.7 (CH_3).

^{77}Se NMR (76.3 MHz, $CDCl_3$): δ = 562.

MS (ESI+): *m*/*z* = 643.5 $[M + H]^+$.

FTMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{27}N_9Se_3$ + Na: 665.9793; found: 665.9790.

4,6,10,12,16,18,19,20,21-Nonaaza-5,11,17-triphenoxy-2,8,14-triselenacalix[3]arene (2c)

Dichlorotriazine precursor **1c** (0.200 g, 0.82 mmol) was dissolved in acetone (70 mL) and the solution was degassed by purging with argon for 10 min. A solution of NaSeH (0.82 mmol, 1 equiv) in distilled water (4 mL) was freshly prepared according to a reported procedure[26] and added dropwise by syringe into the flask containing **1c** at –78 °C. The temperature was gradually increased to r.t. over 1 h. After stirring the resulting mixture for another 12 h, H_2O (70 mL) was added, and the precipitate formed was collected by filtration and dried under vacuum to afford the analytically pure product **2c** (0.145 g, 70%) as an off-white solid; mp 222–223 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (t, *J* = 7.8 Hz, 6 H), 7.33–7.26 (m, 3 H), 7.15 (d, *J* = 8.5 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.9, 166.8, 151.3, 129.9 (CH), 126.7 (CH), 121.3 (CH).

^{77}Se NMR (76.3 MHz, $CDCl_3$): δ = 577.

MS (ESI+): *m*/*z* = 751.5 $[M + H]^+$.

FTMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{15}N_9O_3Se_3$ + Na: 773.8703; found: 773.8704.

4,6,10,12,16,18,19,20,21-Nonaaza-5,11,17-tris(*N*,*N*-diethylamino)-2,8,14-triselenacalix[3]arene (2d)

Dichlorotriazine precursor **1d** (0.200 g, 0.90 mmol) was dissolved in acetone (50 mL) and the solution was degassed by purging with argon for 10 min. A solution of NaSeH (0.98 mmol, 1.05 equiv) in distilled H_2O (3 mL) was freshly prepared according to a reported procedure[26] and added dropwise by syringe into the flask containing **1d** at 0 °C. The temperature was gradually increased to 40 °C and stirring was continued for 2 days. The reaction mixture was cooled to r.t., H_2O (50 mL) was added, and the resulting precipitate was collected by filtration and dried under vacuum to afford crude product **2d** (0.150 g, 72%) as an off-white solid; mp 175–176 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.60–3.48 (m, 12 H), 1.15 (t, *J* = 6.8 Hz, 18 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.4, 160.2, 41.7 (CH_2), 12.8 (CH_3).

^{77}Se NMR (76.3 MHz, $CDCl_3$): δ = 549.

MS (ESI+): *m*/*z* = 688.2 $[M + H]^+$.

FTMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{30}N_{12}Se_3$: 688.0228; found: 688.0330.

UV/Vis (MeCN): λ_{max} (log ε) = 259 nm (4.50).

4,6,10,12,16,18,19,20,21-Nonaaza-5,11,17-tris(*N*-ethylamino)-2,8,14-triselenacalix[3]arene (2e)

The dichlorotriazine precursor **1e** (0.200 g, 1.03 mmol) was dissolved in acetone (50 mL) and the solution was degassed by purging with argon for 10 min. A solution of NaSeH (1.08 mmol, 1.05 equiv) in distilled H_2O (3 mL) was freshly prepared according to a reported procedure[26] and added dropwise by syringe into the flask containing **1e** at 0 °C. The temperature was gradually increased to 40 °C and stirring was continued for 2 days. The reaction mixture was cooled to r.t., H_2O (50 mL) was added, and the resulting precipitate was collected by filtration and dried under vacuum to afford analytically pure product **2e** (0.110 g, 52%) as an off-white solid; mp 197–198 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.59 (br t, *J* = 4.1 Hz, 3 H), 3.45 (t, *J* = 4.9 Hz, 6 H), 1.21 (t, *J* = 5.3 Hz, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.8, 161.8, 36.1 (CH_2), 14.7 (CH_3).

^{77}Se NMR (76.3 MHz, $CDCl_3$): δ = 549.

MS (ESI+): *m*/*z* = 603.6 $[MH^+]$.

FTMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{18}N_{12}Se_3$ + Na: 626.9179; found: 626.9174.

Diselenocyanates

2-Butyl-4,6-diselenocyanato-1,3,5-triazine (3a)

To a solution of **1a** (0.100 g, 0.48 mmol) in degassed THF (6 mL) at 0 °C was added a solution of KSeCN (0.244 g, 1.7 mmol) in THF (10 mL) dropwise over 5 min. The temperature was gradually increased to 40 °C and stirring was continued for 2 days. EtOAc (20 mL) was subsequently added and the organic solution was washed with distilled H_2O (20 mL), dried ($MgSO_4$), filtered, and evaporated to dryness to afford the crude product. Purification by column chromatography (silica gel, eluent: CH_2Cl_2) afforded **3a** as a slightly yellow oil (0.056 g, 12%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.88 (t, *J* = 7.6 Hz, 2 H), 1.87–1.73 (m, 2 H), 1.50–1.33 (m, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.3, 176.4, 97.6 (CN), 38.3 (CH_2), 29.2 (CH_2), 22.4 (CH_2), 13.8 (CH_3).

^{77}Se NMR (76.3 MHz, $CDCl_3$): δ = 436.

MS (CI): *m*/*z* = 346 $[MH^+]$.

FTMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_9H_9N_5Se_2$ + Na: 369.9083; found: 369.9078.

2,4-Diselenocyanato-6-(thien-2-yl)-1,3,5-triazine (3f)

To a solution of **1f** (0.400 g, 1.72 mmol) in degassed THF (6 mL) at 0 °C was added a solution of KSeCN (0.868 g, 6.02 mmol) in THF (10 mL) dropwise over 5 min and the resulting mixture was stirred at r.t. for 2 days. EtOAc (20 mL) was subsequently added and the organic solution was washed with distilled H_2O (20 mL), dried

($MgSO_4$), filtered, and evaporated to dryness to afford the crude product mixture. Purification by column chromatography (silica gel, eluent CH_2Cl_2–heptane 90:10) afforded **3f** as a slightly yellow solid (0.270 g, 42%); mp 142–143 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (dd, *J* = 4.0, 1.1 Hz, 1 H), 7.81 (dd, *J* = 4.9, 1.1 Hz, 1 H), 7.26–7.20 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.0, 166.9, 137.6, 137.4 (CH), 136.2 (CH), 129.7 (CH), 97.8 (CN).

^{77}Se NMR (76.3 MHz, $CDCl_3$): δ = 439.

MS (CI): *m*/*z* = 373 [MH^+].

FTMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_9H_3N_5SSe_2$ + Na: 395.8332; found: 395.8330.

[2+2] Cyclooligomerization

4,6,10,12,16,18,19,20,21-Nonaaza-5,11,17-tributyl-2,8,14-triselenacalix[3]arene (2a)

A solution of $NaBH_4$ (8 mg, 0.202 mmol) in distilled H_2O (3 mL) was added dropwise to a stirred mixture of diselenocyanate **3a** (35 mg, 0.101 mmol) and triazine **1a** (21 mg, 0.101 mmol) in degassed acetone (30 mL) at –78 °C. The temperature was gradually increased to r.t. over 1 h and stirring was continued for another 6 h. CH_2Cl_2 (20 mL) was subsequently added and the organic solution was washed with distilled H_2O (20 mL), dried ($MgSO_4$), filtered, and evaporated to dryness to afford the crude product mixture. Purification by column chromatography (silica gel, eluent: CH_2Cl_2–heptane–EtOAc, 45.5:45.5:9) afforded **2a** as a slightly yellow solid (22 mg, 67%).

4,6,10,12,16,18,19,20,21-Nonaaza-5,11-dibutyl-2,8,14-triselena-17-(thien-2-yl)calix[3]arene (2f)

A solution of $NaBH_4$ (10 mg, 0.268 mmol) in distilled H_2O (3 mL) was added dropwise to a stirred mixture of triazine **1a** (27 mg, 0.134 mmol) and diselenocyanate **3f** (50 mg, 0.134 mmol) in degassed acetone (30 mL) at –78 °C. The temperature was gradually increased to r.t. over 1 h and stirring was continued for another 6 h. CH_2Cl_2 (20 mL) was subsequently added and the organic solution was washed with distilled H_2O (20 mL), dried ($MgSO_4$), filtered, and evaporated to dryness to afford the crude product mixture. Purification by column chromatography (silica gel, eluent: CH_2Cl_2–heptane–EtOAc, 45.5:45.5:9) afforded **2f** as a slightly yellow solid (34 mg, 73%), which could not perfectly be purified by standard column chromatography; mp 204–205 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 3.8 Hz, 2 H), 7.70 (d, *J* = 4.9 Hz, 2 H), 7.20 (t, *J* = 4.4 Hz, 2 H), 2.78 (t, *J* = 7.7 Hz, 2 H), 1.80–1.73 (m, 2 H), 1.45–1.34 (m, 2 H), 0.96 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.4, 177.9, 164.8, 138.9, 134.7 (CH), 134.0 (CH), 129.0 (CH), 38.2 (CH_2), 29.8 (CH_2), 22.5 (CH_2), 13.9 (CH_3).

^{77}Se NMR (76.3 MHz, $CDCl_3$): δ = 564, 561.

MS (ESI+): *m*/*z* = 695.9 [MH^+].

FTMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{15}N_9S_2Se_3$ + Na: 719.8280; found: 719.8283.

Crystal Structure Determination

For the structure of compound **2c**, X-ray intensity data were collected on a SMART 6000 diffractometer equipped with a CCD detector using CuKα radiation (λ = 1.54178 Å), and using φ and ω scans. The images were interpreted and integrated with the program SAINT from Bruker.[27] The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using the SHELXTL program package.[28] Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms.

Crystal data for **2c**: $C_{27}H_{15}N_9O_3Se_3$, *M* = 750.36, crystallization by vapor diffusion of pentane into a $CHCl_3$ solution of **2c**, orthorhombic, $P2_12_12_1$ (No. 19), *a* = 4.7517(3), *b* = 19.3543(13), *c* = 28.3517(16) Å, *V* = 2607.4(3) Å^3, *T* = 100(2) K, *Z* = 4, ρ_{calc} = 1.911 g cm^{-3}, μ(CuKα) = 5.585 mm^{-1}, *F*(000) = 1464, crystal size 0.3 × 0.15 × 0.1 mm, 4793 independent reflections (R_{int} = 0.0699). Final *R* = 0.0491 for 4453 reflections with $I > 2\sigma(I)$ and *wR2* = 0.1293 for all data.

CH–π ring interactions were found between C(8A)–H(8A), C(15B)–H(15B), C(17B)–H(17B) and aromatic rings C4B–C9B (2.97 Å between the H atom and the ring centroid), C22–C27 (2.87 Å), and C4A–C9A (2.67 Å), respectively. Phenoxy rings O1/C4–C9 and O2/C13–C18 were found disordered and could be modeled in two positions with occupancies of 0.51 and 0.49, respectively. Therefore, 1,2- and 1,3-distances were restrained to be equal with those of phenoxy ring O3/C22–C27.[29]

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are ^{1}H, ^{13}C and ^{77}Se NMR spectra for the triazine precursors and selenacalix[3]triazines, and FTMS (ESI+) isotopic patterns for selenacalix[3]triazines **2a** and **2f**.

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