Oxacalix[*n*](het)arenes

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Oxacalix[*n*]arenes, reassessed members of the calixarene family in which the traditional methylene bridges are replaced by oxygen atoms, have emerged as a promising class of macrocycles in recent years. This *tutorial review* summarizes the synthetic progress made in the field during the last few years and aims to stimulate its current evolution from a merely synthetic to a more applied branch of macro- and supramolecular chemistry.

1. Introduction

Calix[*n*]arenes are [1$_n$]metacyclophanes that are easily synthesized on a multi-gram scale, traditionally by cyclooligomerization of a *p*-substituted phenol derivative and formaldehyde (*e.g.*, *p-tert*-butylcalix[4]arene **1**), and they can be readily functionalized at both the *endo*- (lower rim) and *exo*-positions (upper rim) of the central annulus.[1] Calixarenes are considered as the third generation of synthetic receptors (in addition to crown ethers and cyclodextrins). Due to their high level of preorganization and well understood conformational preferences, they have been widely used as molecular platforms and host molecules in diverse domains of supramolecular chemistry. Besides the largely explored 'classical' carbon-bridged calix[*n*]arenes, several other families of related 'calixarenoid' macrocycles have emerged during the last few decades. 'Heterocalixarenes' (*e.g.*, calixpyrroles, calixfurans), a venerable family of calixarenes incorporating heteroaromatic arene units in the calixarene framework, have attracted particular interest for their peculiar supramolecular receptor properties.[2] On the other hand, 'heteracalixarenes', in which the methylene linkages between the aromatic units are replaced by heteroatoms, are less prevalent, although they inherently possess different properties (*e.g.*, size, conformational preferences, host–guest properties) that might expand the scope of classical calixarene chemistry considerably.[3] Thiacalixarenes (*e.g.*, **2**) have been studied extensively, mainly due to their synthetic availability from phenols and elemental sulfur,[4] while both the aza- and oxacalixarene analogues have been underexposed. Recent publications of novel synthetic procedures towards both types of heteroatom-bridged calixarenes have, however, created a renewed interest in these attractive macrocycles.

Oxacalixarenes are oxygen-bridged heteracalixarenes of general structure **3** (for the cyclic tetramer or oxacalix[4]arene) and they may be regarded as fully aromatic crown ethers. The well-established nomenclature, numbering, and rules for carbon-bridged calixarenes have been retained for oxacalixarenes (as for other heteracalixarenes). Oxacalixarenes have already been prepared in 1966, but up until a few years ago it has been very quiet in this field. More recently, a number of groups have reinvestigated synthetic nucleophilic aromatic substitution (S_NAr)

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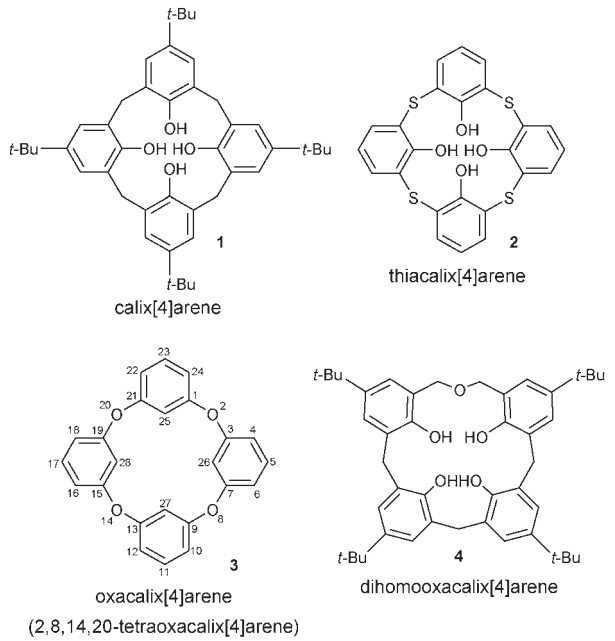
Wim Dehaen was born in Kortrijk, Belgium. He obtained his PhD in 1988 under the guidance of Prof. G. L'abbé on a study concerning the rearrangements of 5-diazoalkyl-1,2,3-triazole derivatives. After postdoctoral stays in Israel (1988–1990), Denmark (3 months in 1990), the UK (3 months in 1994) and Belgium (1990–1998) he was appointed associated professor at the KU Leuven (Belgium) in 1998, becoming a full professor at the same university in 2004. Up to 2008, over 250 publications have appeared in international journals about his work on heterocyclic and supramolecular chemistry.

protocols towards oxacalix[*n*]arenes. As a result, a large variety of novel functionalized oxacalix[*n*]arenes (usually oxacalix[4]arenes) have now become accessible, including oxacalixheteroaromatics, in which the particularities of both the families of hetero- and heteracalixarenes may be combined. At this moment, the focus has been mainly on the synthetic exploration and functionalization of oxacalix[4]arenes, but, as more elaborated macrocycles are emerging, the study of their properties and (supramolecular) applications will certainly attract the attention of many scientists in the near future.



In this tutorial review we will summarize the origin, recent growth, present status and future directions of oxacalixarene chemistry. Oxacyclophane analogues with *ortho*- and/or *para*-linked arene units within their macrocyclic structure, strictly speaking, do not belong to the precisely defined subclass of oxacalixarenes (as oxa[1_n]metacyclophanes) and will hence not be covered in this review. Homooxacalixarenes (*e.g.*, **4**), oxygenated homologues of classical calixarenes that are formed as side products during their synthesis or by directed methodologies,[1] and 'mixed' heteracalixarenes, in which different sorts of heteroatoms constitute the bridging moieties (*e.g.*, diazadioxacalix[4]arenes), will not be discussed either.

2. Historical background

The first oxacalixarene macrocycle appearing in the literature was synthesized by Sommer and Staab in 1966.[5] They investigated the formation of cyclic poly(aryl ether)s by reaction of resorcinol (**5**) and a dihalogen component activated for S_NAr by the introduction of *ortho*/*para*-nitro groups, 1,5-dichloro-2,4-dinitrobenzene (**6**). When both products were reacted in equimolar amounts in DMF at 85–90 °C for 12 h, in the presence of K_2CO_3 base, the (high-melting) cyclic tetramer **7** was obtained in a single step in 13% yield (Fig. 1). Hydrogenation and

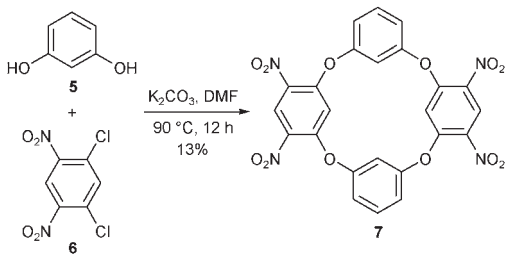


Fig. 1 Original oxacalix[4]arene synthesis by Sommer and Staab.[5]

subsequent reductive deamination afforded the unsubstituted 'parent' oxacalix[4]arene **3** (7%).

In 1974, Lehmann studied the synthesis of tetrameric macrocyclic aromatic ethers derived from dihydroxybenzenes and 1,5-difluoro-2,4-dinitrobenzene (the carbon–fluorine bond being more reactive towards S_NAr).[6] He was able to improve the yield of oxacalix[4]arene **7** to 46% (Et_3N base, 20 min reflux in DMF, followed by precipitation of the product). Structural proof was provided by both mass and ^1H NMR spectroscopy. NMR studies, hindered by the low solubility (attributed to strong crystal-state forces) of **7** in NMR solvents, permitted partial conformational analysis. A large conformational mobility was assumed for the oxacalix[4]arene, while the relatively high-field shift of the internal protons was attributed to a shielding effect of the neighbouring aromatic rings.

In the same year, Gilbert reinvestigated the synthesis of analogous macrocyclic tetraarylethers by reacting 1,5-dichloro-2,4-dinitrobenzene (**6**) with numerous (2-, 4-, or 5-) halogenated or alkylated resorcinol derivatives.[7] His modified synthetic procedure (2 h at 150 °C in DMF with $NaHCO_3$ base) was faster and provided higher yields (60–95%) of the cyclic tetramers (*e.g.*, 60% for **7**), which could be purified by recrystallization. The use of the difluoro analogue or high-dilution conditions was proven to be unnecessary. The macrocyclization was found to be fairly sensitive to structural factors, since several of the investigated building blocks failed to yield cyclic compounds. Electrophilic substitution reactions (nitration, bromination, and sulfonation) allowed the post-macrocyclization introduction of several functional moieties on the oxacalixarene scaffold. Gilbert later on patented some of his octanitro macrocyclic compounds as explosives characterized by a good thermal stability.[8]

In 1976, Bottino and co-workers reported the synthesis and characterization of several S- and O-bridged macrocycles.[9] Both resorcinol and 4,6-dichlororesorcinol were reacted with 1,5-dichloro-2,4-dinitrobenzene (**6**) under dilute conditions (DMF, KOH base, reflux, 2 h) to afford oxacalix[4]arenes in 25–28% yield. The oxygen-bridged macrocycles were found to be more soluble than the sulfur-bridged ones.

In general, initial efforts to prepare oxacalixarenes, which were in fact not yet recognized as 'calixarenes' at that time, were limited to nitrated dihalobenzenes as the electrophilic reaction partner and they all suffered from some kind of drawback, *e.g.*, modest yields, high reaction temperatures and/or extended reaction times and low solubility (depending on the substitution pattern), causing a limited availability. For

these reasons, oxacalixarenes have been virtually absent from the literature for 25 years. Only quite recently, initiated by the progress achieved for the thiacalixarene analogues and a wider general attraction of calixarenes and their appealing supramolecular properties, a renewed interest in these oxygen-bridged cyclooligomers has emerged.

3. The new era of oxacalixarene chemistry

The present revival of oxacalixarenes has been initiated by the contributions of several research groups (especially the groups of Chambers, Wang and Katz) who have (re)investigated the synthesis and conformational behaviour of novel oxacalix[4]arene macrocycles, considerably expanding the synthetic scope, and providing a springboard for other groups entering the field. Most recent routes towards oxacalixarenes still use the old-fashioned but very versatile and flexible S_NAr procedures, although an Ullmann-type coupling strategy has been described as well. The heteracalixarene framework can be constructed either directly from a one-step condensation of an electrophilic and a nucleophilic building block, or the oxacalix[4]arene can be prepared through a fragment-coupling strategy. Besides oxacalix[4]arenes, larger oxacalix[*n*]arenes (n = 6, 8, 10 or 12) have also been reported recently. Heteroaromatic electrophilic components have been used in similar S_NAr-based macrocyclizations, furnishing different subclasses of oxacalix[*n*]hetarenes.

3.1 Oxacalix[4]arenes

The wide potential of S_NAr-based routes towards a wealth of structurally diverse oxacalix[4]arenes was recognized by Katz and co-workers in 2005.[10] They envisaged that the introduction of suitable substituents on the resorcinol component (*e.g.*, alkyl or ester moieties) could result in tetranitrooxacalix[4]arene derivatives with an enhanced solubility. The S_NAr conditions were optimized and reactions of 1,5-difluoro-2,4-dinitrobenzene (**8**) and (substituted) 1,3-dihydroxybenzenes **9** could now be conducted at ambient temperature in DMSO using (finely ground) K_2CO_3 base, affording very high yields (mostly above 85%) of diversely functionalized oxacalix[4]arenes in one single step within a very short time (15 min) (Fig. 2). This extremely simple, high-yielding procedure does not require inconvenient high-dilution conditions and was proven to be tolerant to diverse functionalities on the nucleophilic building block, notably hydroxyl-substitution, affording both upper and lower rim (partially) hydroxyl-substituted oxacalix[4]arenes **10**, which can be regarded as true analogues of the traditional carbon-bridged calixarenes. The astonishingly high yield for the cyclic tetramer and the virtual absence of larger oxacalix[*n*]arenes and acyclic oligomers prompted the authors to suggest that the oxacalix[4]arene may be the thermodynamic product from a reversible dynamic process of ring opening and cyclization (dynamic covalent chemistry[11]).

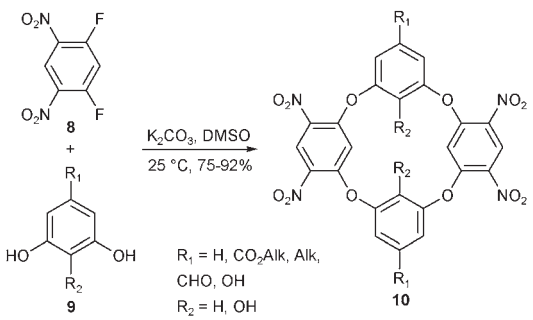


Fig. 2 One-step synthesis of functionalized oxacalix[4]arenes **10** (Katz *et al.*[10]).

Since reaction of phloroglucinol and 1,5-difluoro-2,4-dinitrobenzene (**8**) afforded the *exo*-annular bishydroxyl-substituted oxacalix[4]arene **10** (R_1 = OH, R_2 = H) in 90% yield, the ability to create a bicyclic structure using the available nucleophilic moieties was recognized. Moreover, the observed (solid-state) 1,3-*alternate* conformation places the phenol moieties in close proximity (see later). Hence, on changing the reaction conditions to a 2 : 3 ratio of phloroglucinol and **8**, and using Et_3N as a base and an elevated temperature (80 °C), Katz and co-workers were able to synthesize a bicyclooxacalix[4]arene through a one-step protocol in 58% yield, without high-dilution techniques.[12]

The lower rim hydroxyl-functionalized oxacalix[4]arene **10** (R_1 = H, R_2 = OH) was applied by Bitter *et al.* for the synthesis of oxacalix[4]crown ethers.[13] O-Alkylation reactions were successful with mono- and bifunctional agents under basic conditions (K_2CO_3, MeCN, 12 h at 80 °C), but were found to result in extensive ring cleavage, affording large amounts of polymeric side products and diminishing the yield. A one-pot procedure (oxacalix[4]arene formation and O-alkylation with oligo(ethylene glycol) ditosylates) furnished the desired oxacalix[4]crown ethers in higher yields.

Vicente and co-workers applied the S_NAr conditions optimized by Katz for the synthesis of an oxacalix[4]arene **11** carrying two cofacial porphyrin chromophores (in 91% yield), simply by using 5-(3,5-dihydroxyphenyl)-10,15,20-triphenylporphyrin as the nucleophilic component (Fig. 3).[14] Recently, the same group has optimized the synthesis of asymmetrical oxacalix[4]arene porphyrins with potential hydrogen-bond functionalities, mimicking natural heme systems, through a '3 + 1' fragment-coupling synthesis.[15] Variously functionalized linear triaryl precursors **13a–d** were easily obtained on a multi-gram scale (in 75–85% yield) from 5-substituted 1,3-dihydroxybenzenes **12a–d** and 1,5-difluoro-2,4-dinitrobenzene (**8**) in a 1 : 3 ratio in acetone at rt with K_2CO_3 base (Fig. 4). Cyclization was then performed with the previously

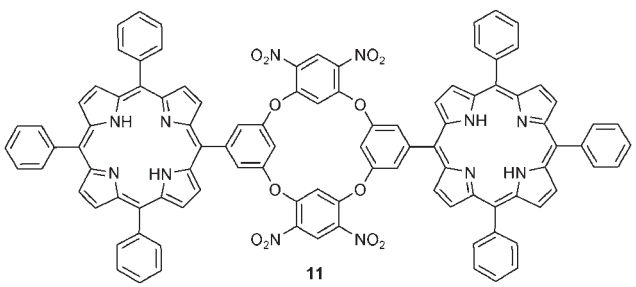


Fig. 3 Oxacalix[4]arene-locked bis-porphyrin **11** (Vicente *et al.*[14]).

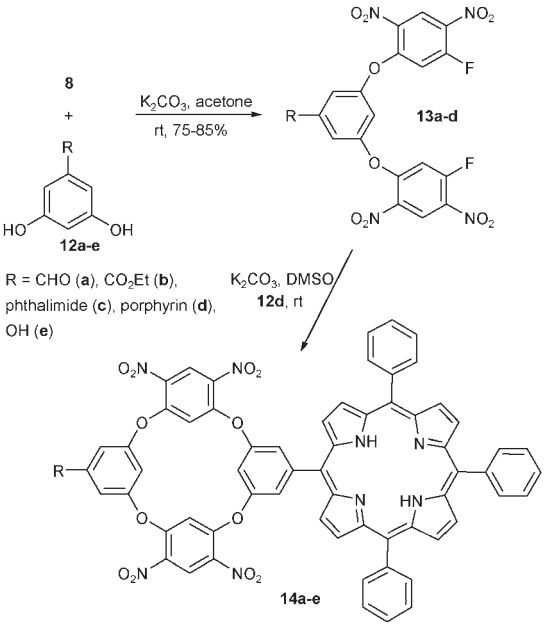


Fig. 4 Fragment-coupling synthesis of functionalized oxacalix[4]arene–porphyrin conjugates **14a–e** (Vicente *et al.*[15]).

described bis-phenolic AB_3-porphyrin **12d** at rt in DMSO with K_2CO_3 base, affording the cyclic tetramers **14a–c** in over 80% yield. On treatment of trimer **13d** (R = porphyrin) with resorcinol derivatives **12a–c,e**, scrambling was observed, resulting in formation of the symmetrical oxacalix[4]arene-bisporphyrin **14d** as the major product. Acid hydrolysis of ester-functionalized oxacalix[4]arene **14b** easily afforded the carboxyl-functionalized conjugate. A porphyrin with two opposing *meso*-oxacalix[4]arene groups has also been prepared using a similar procedure, and the photophysical properties of all porphyrin-oxacalix[4]arene conjugates were studied.

Zhang and Chen have synthesized oxacalix[4]arenes with an enlarged cavity based on a triptycene derivative as the nucleophilic reaction partner.[16] Upon reaction of 2,7-dihydroxytriptycene,

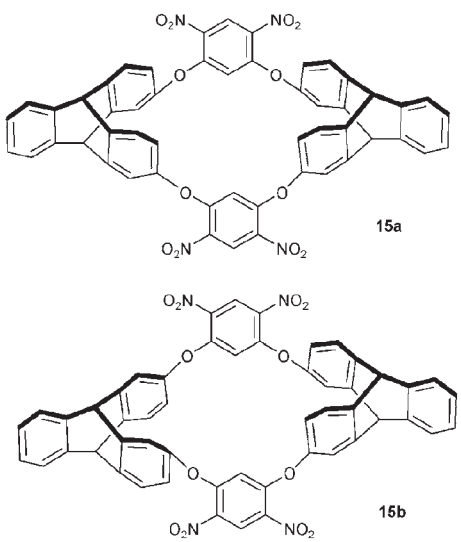


Fig. 5 Triptycene-based oxacalix[4]arene isomers **15a,b** (Zhang and Chen[16]).

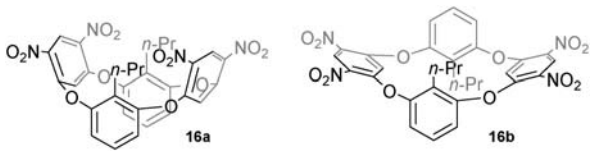


Fig. 6 *syn* and *anti* Oxacalix[4]arene conformers **16a,b** (Konishi *et al.*[17]).

which possesses two possible linking modes, and **8** (under standard Katz conditions: K_2CO_3, DMSO, rt, 1 h), two oxacalix[4]arene isomers **15a,b** were isolated as a pair of diastereomers (in 22 and 15% yield, respectively, Fig. 5).

Konishi *et al*. recently performed an investigation of kinetic and thermodynamic reaction conditions for the synthesis of oxacalixarenes.[17] For this purpose, they designed an oxacalix[4]-arene bearing intra-annular n-propyl groups on the resorcinol building block. Since the bulky propyl chain is unable to pass through the central annulus of the oxacalix[4]-arene, two conformational isomers **16a,b** could be formed (Fig. 6), the ratio depending on the reaction conditions. S_NAr of **8** and 2-propylresorcinol, activated with Et_3N base, in acetonitrile (at reflux) afforded a mixture of *syn* and *anti* conformers **16a,b** of the oxacalix[4]arene, along with the oxacalix[6]arene analogue (separated by GPC), with a kinetically controlled product distribution. On the other hand, the same reaction with an excess of CsF in DMF at 100 °C afforded the thermodynamically favoured *syn* oxacalix[4]arene isomer **16a** as the main product (in up to 89% yield), as a result of the reversibility of the cyclization process under these conditions (*via* an *ipso*-attack of the fluoride anion). Moreover, the kinetic product mixture could be converted into the (most stable) *syn* oxacalix[4]arene conformer **16a** on subjecting the mixture to the thermodynamic reaction conditions.

In a follow-up paper, the same authors reported the synthesis of novel asymmetrical ABAC-type oxacalix[4]arenes and their CsF-catalyzed disproportionation.[18] The previously established kinetic conditions (Et_3N, MeCN) were used to obtain a linear ABA-trimer (3 : 1 molar ratio of **8** : **5**, 71%), which was then cyclized with another 2-substituted resorcinol component C under similar conditions (1 : 1 molar ratio, 69–78%). An attempt to prepare the linear trimer using CsF in DMF resulted in selective formation of the oxacalix[4]arene as the predominant, thermodynamically most stable product. When CsF was added to an ABAC-type oxacalix[4]arene (bearing a propyl group on the resorcinol unit) in DMSO solution at 80 °C, a gradual decrease of the amount of ABAC was observed (by ^1H NMR), with a simultaneous build-up of both symmetrical ABAB and ACAC cyclic tetramers (due to reversible macrocyclization). Depending on the applied ABAC-type oxacalix[4]arene, non-selective ether bond scission was observed under thermodynamic conditions, resulting in a complex mixture of (predominantly non-cyclic) oligomers.

Besides the usually applied S_NAr strategy, an Ullmann coupling procedure towards oxacalixarenes has recently been developed by You *et al.*[19] The *N*,*N*-dimethylglycine promoted Ullmann coupling of resorcinol (**5**) and 3,5-dibromo-4-nitrotoluene (**17**), in dilute solution, afforded oxacalix[4]arene **18** in yields up to 37% (Fig. 7). The method could also be applied

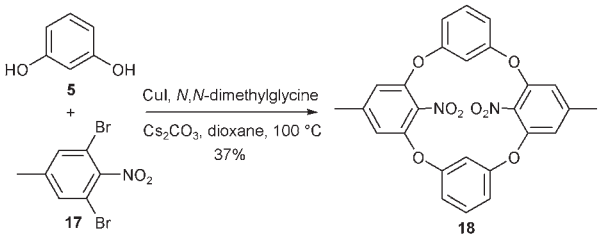


Fig. 7 Ullmann coupling reaction towards oxacalix[4]arene **18** (You *et al.*[19]).

for 2,7-dihydroxynaphthalene (21%). Hydrogenation of the nitro groups could easily be achieved (H_2, 10% Pd/C (5%), DMF: 90% yield), offering numerous post-macrocyclization pathways using the intra-annular amino groups.

Some multicyclic macrostructures containing oxacalixarene units have been prepared starting from resorcinarene templates.[20] These types of structures fall, however, beyond the scope of this review.

3.2 Oxacalix[4]hetarenes

Until recently, the synthesis of heteracalixarene macrocycles by S_NAr processes involving heteroaromatic moieties has been an uncommon way to expand structural diversity. Most oxacalix[4]arenes have been obtained from a 1,5-dihalo-2,4-dinitrobenzene electrophilic building block. The extension to electron deficient heteroaromatic systems is quite logical, though, since several of these systems are particularly attractive because of their high reactivity in S_NAr reactions. Moreover, the additional heteroatoms can impose novel supramolecular features on the oxacalixarene skeleton, *e.g.*, increased substrate recognition. The oxacalix[4]hetarenes synthesized so far can easily be classified according to the embedded (aza)heteroaromatic rings.

3.2.1 Oxacalix[2]arene[2]pyridines. Chambers and coworkers have studied the synthesis of novel polyhalogenated macrocycles, including tetraoxa-bridged heteracalix[2]arene[2]pyridines, starting from polyfluoropyridine derivatives and using a stepwise fragment-coupling approach.[21–23] A large excess (10 equiv.) of perfluoro-4-isopropylpyridine (**20**) was combined with the bis-trimethylsilyl derivative of orcinol (**19**) under desilylating conditions to obtain a linear trimer **21** in good yield (Fig. 8). Cyclization of **21** with a second equivalent of **19** under similar conditions afforded oxacalix[4]arene **22** in 33% yield (after column chromatographic purification). Similar results were obtained with 4-methoxy-2,3,5,6-tetrafluoropyridine.[21,23]

When Katz *et al*. studied the synthesis of bicyclooxacalix[4]arenes, they also investigated some 2,6-dihalogenated pyridines as electrophilic building blocks.[12] Efficient bicyclooxacalixhetarene formation was observed starting from 2,6-dichloro-3-nitropyridine and 2,6-dichloro-(4-ethyl)-pyridine-3,5-dicarbonitrile in DMSO at rt using Cs_2CO_3 base (80–95% yield), while an increased reaction temperature of 120 °C was required for the less reactive 2,3,5,6-tetrachloropyridine (45% yield). Based on these results, a novel study towards oxacalix[4]hetarenes incorporating various azaheteroaromatic moieties was conducted.[24] In these oxacalix[2]arene[2]hetarenes, the appended substituents as well as the nitrogen

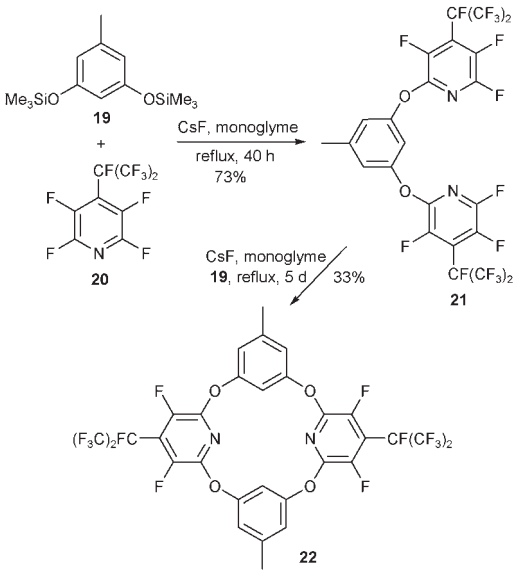


Fig. 8 Stepwise strategy towards oxacalix[2]arene[2]pyridine **22** (Chambers *et al.*[21–23]).

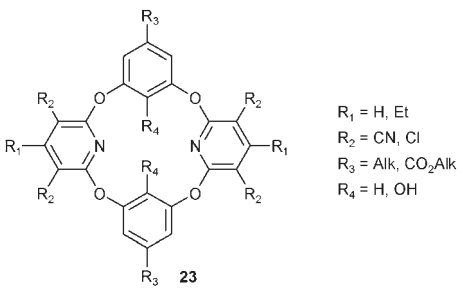


Fig. 9 Oxacalix[2]arene[2]pyridines (Katz *et al.*[24]).

atoms on the azaheterocycles can be advantageously used for various supramolecular applications. Among the novel oxacalix[4]arenes, functionalized oxacalix[2]arene[2]pyridines **23** were synthesized using the previously established conditions (Cs_2CO_3, DMSO, variable reaction temperature) in remarkably high yields (70–95%) as a result of thermodynamic product control (Fig. 9). The thermodynamic reversibility of the macrocyclization process was studied by resubjecting an oxacalix[2]arene[2]pyridine to the S_NAr conditions, together with an extra amount of the nucleophilic building block (2 equiv.). Within 10 min, the cyclic tetramer was completely absent from the reaction mixture and was majorly converted to a linear trimer, reflecting the applied 2 : 1 molar ratio, while addition of a similar amount of the electrophilic component caused macrocycle reformation.

Zhang and Chen applied the conditions optimized by Katz *et al*. to prepare triptycene-based oxacalix[2]arene[2]pyridine isomers.[16]

3.2.2 Oxacalix[2]arene[2]triazines. One of the first groups to recognize the efficiency of using electron deficient heterocycles for the synthesis of heteroatom-bridged calix[2]arene[2]hetarenes is the group headed by Wang. In 2004, they described a convenient two-step '3 + 1' fragment-coupling strategy towards

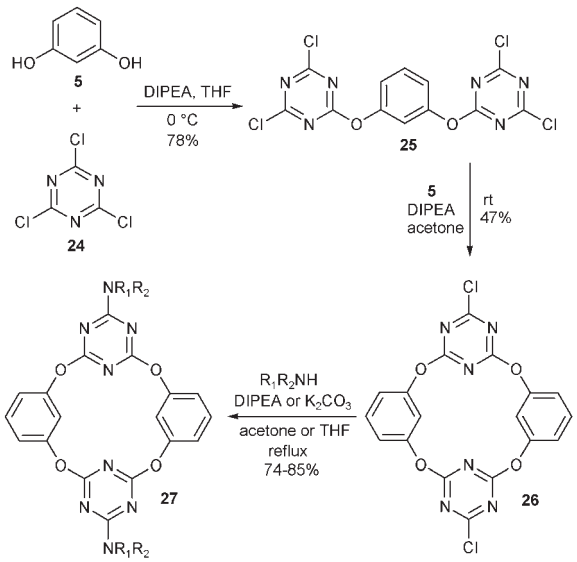


Fig. 10 '3 + 1' Fragment-coupling synthesis and functionalization of oxacalix[2]arene[2]triazines (Wang *et al.*[25,26]).

heteracalix[2]arene[2]triazines.[25] Reaction of resorcinol (**5**) and 2 equivalents of (highly reactive) cyanuric chloride (**24**) in THF at 0 °C using diisopropylethylamine (DIPEA) as a base afforded trimer **25** in 78% yield (Fig. 10). Cyclization of the (isolated and purified) trimer with a second equivalent of **5** under high-dilution conditions in acetone at rt resulted in the desired oxacalix[4]arene **26** in 47% yield. Similar results could be obtained with *m*-phenylenediamine or 3-aminophenol bis-nucleophiles. Various attempts to prepare oxacalix[2]-arene[2]triazine **26** in one step by reacting resorcinol and cyanuric chloride (1 : 1 ratio) gave a maximum yield of only 11%. The stepwise approach, which could be applied on a multi-gram scale, hence seems to be advantageous.

Oxacalix[2]arene[2]triazines can serve as ideal scaffolds for the construction of functional heteracalixarenes since the remaining free chlorine groups at the upper rim can easily be substituted by nucleophiles, *e.g.*, amines containing chelating pyridine groups (*e.g.*, **27**, Fig. 10).[26]

In 2007, the same group reported the stepwise synthesis of an oxacalix[2]arene[2]triazine using methyl-4-benzyloxy-3, 5-dihydroxybenzoate as the nucleophilic reaction partner.[27] Deprotection of the benzyl groups using a large excess of $AlCl_3$ in toluene resulted in simultaneous introduction of *p*-tolyl groups on the triazine moieties. Reaction of methyl-4-benzyloxy-3,5-dihydroxybenzoate and 2,4-dichloro-6-*p*-tolyl-1,3,5-triazine by a fragment-coupling approach afforded the desired oxacalix[2]arene[2]triazine as a mixture of two conformational isomers, a thermodynamically favoured 1,3-*alternate* and a kinetically favoured flattened partial cone conformer, stable due to steric effects, their ratio depending on the applied macrocyclization conditions. Treatment of the kinetic product with K_2CO_3 resulted in rapid and complete conversion to the thermodynamic conformer, probably by cleavage and reformation of the diarylether linkages. Similar results were obtained by introducing bulky *tert*-butyl groups on both reaction partners.

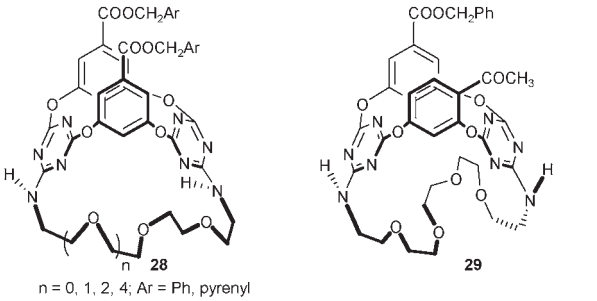


Fig. 11 Oxacalix[2]arene[2]triazine azacrowns (Wang *et al.*[28,29]).

Recently, Wang and co-workers synthesized upper rim 1,3-*alternate* oxacalix[4]arene azacrowns **28** through condensation of diamine-terminated oligo(ethylene glycol) linkers with a dichlorinated oxacalix[2]arene[2]triazine (Fig. 11).[28] The calixcrown formation could be favoured by reducing the conformational flexibility of the oxacalix[4]arene scaffold *via* the introduction of bulky benzyloxycarbonyl groups. Due to conjugation of the amine substituents to the triazine rings and, as a result, two possible orientations of the oligo(ethylene glycol) linker, the azacrowns were (mostly) obtained as a mixture of *syn* and *anti* isomeric forms (only the *syn* isomer **28** is shown in Fig. 11). The ratio of the isomers depends on the length of the azacrown chain, the *syn* isomer being preferred for shorter linkages to relieve the steric strain, and could be roughly estimated from the ^{1}H NMR spectra.

Using a similar stepwise synthetic approach based on two different nucleophilic building blocks (2,4-dihydroxyacetophenone and a 3,5-dihydroxybenzamide or -benzoate), asymmetrically substituted oxacalix[2]arene[2]triazines have been synthesized.[29] Macrocyclic condensation with a diamine-terminated oligo(ethylene glycol) linker (n = 2) afforded (a racemic mixture of) inherently chiral oxacalix[2]arene[2]-triazine *anti*-azacrown isomers in a very high yield (*e.g.*, **29**, Fig. 11). The azacrown bridging moiety is required to prevent conformational interconversion of the isomers. An identical strategy using a chiral nucleophilic building block afforded chiral oxacalix[4]arenes, and, after condensation with a diamine linker, the final chiral oxacalixcrowns as a pair of diastereomers (showing two sets of resonance signals in their NMR spectra). Chromatographic separation of the diastereomers has, however, not been achieved to date.

Zhang and Chen also applied cyanuric chloride as an electrophile towards triptycene-based oxacalix[4]arenes, either by a direct or a fragment-coupling strategy (using similar conditions).[16]

3.2.3 Oxacalix[2]arene[2]pyrimidines. Within their study of dichlorinated azaheterocycles as electrophilic building blocks for the construction of oxacalix[4]hetarenes, Katz *et al.* also described the synthesis of oxacalix[2]arene[2]pyrimidines.[24] When 4,6-dichloropyrimidine and orcinol were combined in DMSO with Cs_2CO_3 base at 50 °C, the oxacalix[4]arene was isolated in a disappointing 12% yield, together with a number of larger cyclooligomers and polymeric material. However, when the same reagents were mixed at 120 °C, the pursued oxacalix[2]arene[2]pyrimidine could be isolated in an excellent 91% yield.

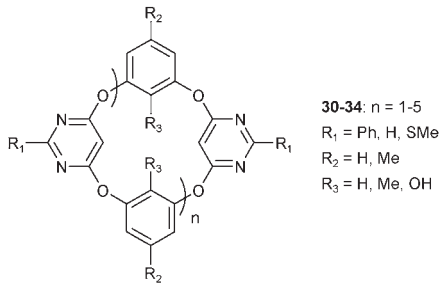


Fig. 12 Oxacalix[*m*]arene[*m*]pyrimidines (*m* = 2–6) (Dehaen *et al.*[30]).

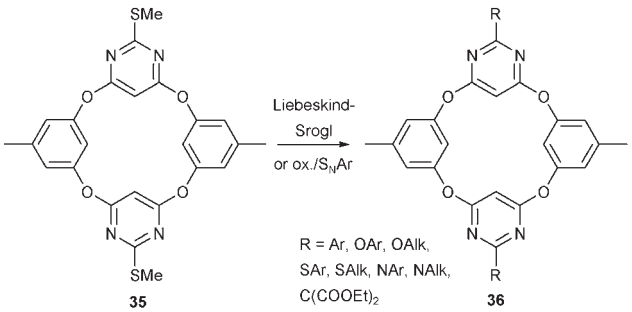


Fig. 13 Post-macrocyclization modification of the oxacalix[2]arene[2]-pyrimidine skeleton (Dehaen *et al.*[31]).

Almost simultaneous with this work, oxacalix[*m*]arene[*m*]-pyrimidines **30–34** (*m* = 2–6) were synthesized within our group by S_NAr reactions of *meta*-dihydroxybenzenes and 4,6-dihalopyrimidine building blocks (Fig. 12).[30] Depending on the S_NAr conditions, either a mixture of oxacalix[*n*]arenes, ranging from the oxacalix[4]- up to the oxacalix[12]arene, could be prepared or the oxacalix[4]arene could be obtained selectively in over 80% yield (optimum conditions: DMF, K_2CO_3, 18C6, 70 °C, 24 h). The electrophilic (pyrimidine) and the nucleophilic components could both be varied, allowing the preparation of functionalized oxacalix[4]hetarenes.

The ease of elaboration of the substitution pattern makes oxacalix[*m*]arene[*m*]pyrimidines versatile and unique platforms for the exploration of various supramolecular applications of oxacalixarenes. Diversely functionalized oxacalix[2]arene[2]pyrimidines have been synthesized starting from a bis(methylsulfanyl)-substituted oxacalix[4]arene **35** by two efficient post-macrocyclization pathways (Fig. 13).[31] Functionalized aryl groups were introduced on the pyrimidine building block *via* Liebeskind–Srogl cross-coupling reactions, while a variety of O-, S-, N-, and C-nucleophiles were inserted on the calixarene skeleton by S_NAr reactions on the (oxidized) bis(methylsulfonyl)oxacalix[4]arene analogue.

3.2.4 Miscellaneous oxacalixheteroaromatics. In 2006, Katz and co-workers employed 2,6-dichloropyrazine as an electrophilic building block in the synthesis of oxacalixhetarenes and they observed that the product distribution varied strongly with the reaction temperature, as was observed for oxacalix[2]arene[2]pyrimidines.[24]

The same group more recently reported the first examples of oxacalix[4]arenes incorporating 1,8-naphthyridines.[32] An

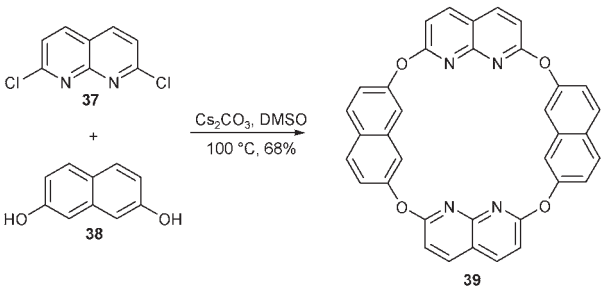


Fig. 14 Synthesis of oxacalix[2]naphthalene[2]naphthyridine **39** (Katz *et al.*[32]).

oxacalix[4]hetarene **39** with an increased cavity size could, for instance, be synthesized out of 2,7-dichloro-1,8-naphthyridine (**37**) and 2,7-dihydroxynaphthalene (**38**) as S_NAr reaction partners (Fig. 14). As observed before, higher temperatures favoured formation of the oxacalix[4]arene (100 °C: 68% yield).

3.3 Larger oxacalix[*n*]arenes (*n* = 6–12)

Large fully aromatic crown ethers have scatteringly been described in the past, but none of these systems actually corresponded to a real (completely *meta–meta*-linked) oxacalix[*n*]arene (*n* > 4) framework. However, more recently, numerous research groups are reporting the presence of large 'expanded' oxacalix[*n*]arenes (mostly *n* = 6) in their reaction mixtures obtained after S_NAr.[14,17,24,28,30] The yields of the enlarged oxa-bridged cyclooligomers, which are not always easy to purify, heavily depend on the employed reaction conditions. Kinetically controlled reactions often give a mixture of cyclooligomers in varying yields. On the other hand, the thermodynamically favoured oxacalix[4]arene is usually obtained rather selectively in a high yield under more thermodynamic conditions (*e.g.*, a higher reaction temperature or other solvent/base combinations). Within our group, it was for instance observed that a mixture of oxacalix[*m*]arene[*m*]-pyrimidines (*m* = 2–6) could be obtained starting from orcinol and 4,6-dichloro-2-phenylpyrimidine under non-equilibrating conditions (Fig. 12).[30] Chromatographic separation of the obtained mixture afforded pure oxacalix[8]arene

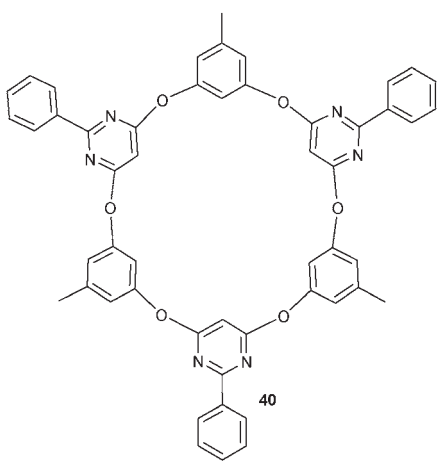


Fig. 15 Oxacalix[3]arene[3]pyrimidine **40** (Dehaen *et al.*[30]).

(10%), oxacalix[10]arene (8%), oxacalix[6]arene **40** (8%) (Fig. 15), oxacalix[12]arene (8%), and oxacalix[4]arene (30%), respectively.

One of the current challenges within the oxacalixarene field involves the selective synthesis of large oxacalix[*n*]arenes, preferably by straightforward S_NAr procedures, in order to enable them to develop from rare examples into useful molecular probes for selective recognition studies.

You and co-workers also observed the formation of an oxacalix[6]arene in 25% yield through Ullmann coupling of 1,3-difluoro-2-nitrobenzene and resorcinol in dilute pyridine solution.[19]

A totally different approach to large oxacalixarene macrocycles was reported by Gibb *et al.*[20c] They demonstrated that functionalized oxacalix[8]arenes, even asymmetrically substituted ones, are easily accessible by removal of the resorcinarene template from their cavitand structures.

4. Conformational analysis

Conformational analysis of oxacalix[4]arenes has been facilitated by the recent widespread availability of X-ray diffraction techniques. Oxacalix[4]arenes have generally been found to adopt a (distorted) 1,3-*alternate* conformation in the solid state (Fig. 16), regardless of the substitution pattern, probably due to the lack of hydrogen bonding groups stabilizing (partial) cone conformations. This was observed for regular oxacalix[4]arenes,[10,14,17] bicyclooxacalix[4]arenes[12] (all-1,3-*alternate*) as well as oxacalix[4]hetarenes.[16,22,24–32]

From comparison of the bond lengths, it is noticed that the bridging O-atoms mainly conjugate into the electrophilic (het)arenes. In many cases, the nucleophilic component rings are eclipsing and nearly parallel, while the electrophilic aromatic rings approach planarity or are oriented to maintain conjugation to the bridging O-atoms.

Both the groups of Konishi and Wang recently noticed that the introduction of sterically bulky groups, which are unable to rotate through the central annulus, can result in the formation of two stable oxacalix[4]arene conformers: a regular thermodynamically favoured 1,3-*alternate* ('boat') and a kinetically controlled flattened partial cone ('chair') conformer (Fig. 6).[17,27]

The conformational behaviour of oxacalix[4]arenes in solution has been investigated by variable-temperature NMR experiments.[10,17,22,25] In all cases, only one set of sharp resonance signals has been observed, even at very low temperatures. This may indicate either a single conformation or a very rapid conformational interconversion on the NMR time scale. Based on the characteristic upfield shifts for the interior protons on the electrophilic components of oxacalix[4]arenes, attributed to (partial) orientation of these protons in the anisotropic shielding cone of the adjacent aromatic groups, it has often been presumed that the preferred conformation in solution resembles the solid-state 1,3-*alternate* conformation.

A particular case is formed by the triptycene-based oxacalix[4]-hetarene diastereomers reported by Zhang and Chen.[16] The *cis* isomers adopt the general 'boat-like' 1,3-*alternate* conformation. For the *trans*-oxacalix[2]triptycene[2]pyridine isomer a 'chair-like' conformation was observed, while a dynamic conversion between both possible conformations was proposed for the *trans*-oxacalix[2]triptycene[2]triazine diastereomer, based on variable-temperature NMR measurements. The oxacalix[4]-hetarenes containing upper rim chlorine atoms were found to assemble into tubular structures and porous solid-state networks, with an important contribution from chlorine bonding.

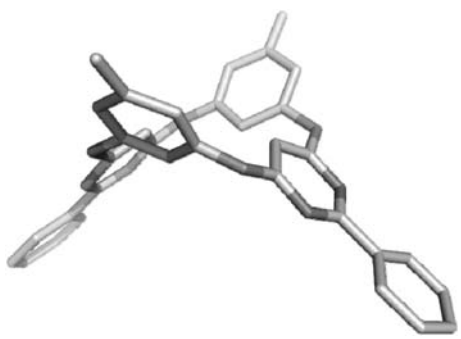


Fig. 16 Single crystal structure of an oxacalix[2]arene[2]pyrimidine (see Fig. 12: R_1 = Ph, R_2 = Me, R_3 = H).[30]

5. Molecular recognition

Although traditional calixarenes have widely been used as versatile receptor molecules in various host–guest systems, either by molecular encapsulation of a guest in the calixarene cavity or by providing an ideal scaffold for the introduction of precisely oriented complexing moieties, oxacalixarenes have only scarcely been investigated as (frameworks for) molecular receptor molecules. As more sophisticated oxacalix[*n*]arenes are entering the field, their application in host–guest chemistry will emerge as a major challenge for research groups involved in supramolecular chemistry.

Chambers and co-workers analyzed the ability of their polyfluorinated oxacalix[2]arene[2]pyridine **22** (Fig. 8) to complex either cations or anions by ESI-MS, and they observed negatively charged complex ions for halide anions, while no coordination with metal cations was noticed under these conditions.[21,22] The same oxacalix[4]hetarene macrocycle was also found to be useful for the extraction of sodium picrate from an aqueous phase into dichloromethane solution.[22]

Bitter *et al.* also studied cation extractions with their oxacalix[4]crown ligands using biphasic chloroform–aqueous alkali picrate systems.[13] In contrast to similar (thia)calix[4]-arene derivatives, no appreciable cation extractability could be observed for the oxacalixcrowns, which was attributed to the lack of π–cation interactions of the adjacent electron-poor 1,3-*alternate* aromatic rings. The complexation of the oxacalixcrown-6 host with benzylammonium perchlorate was also investigated by ^{1}H NMR titrations, and a limited contribution of π–π contact between the host and guest aromatic systems was observed (as indicated by the very poor shifts of the aromatic protons).

Oxacalix[2]arene[2]triazines **27** with appended chelating pyridine bidentate ligands (Fig. 10) were investigated by Wang *et al.* for metal ion complexation *via* UV-Vis

spectrophotometric titrations and were found to form 1 : 1 complexes with Cu^{2+} ions selectively (in a MeCN–water mixture).[26] In the same group, oxacalix[4]arene azacrowns **28** (Fig. 11) were investigated as supramolecular host molecules.[28] Oxacalixazacrowns carrying fluorescent pyrene labels were studied by ^{1}H NMR and fluorescence titrations, indicating a change in the cavity in response to fluoride anions, assigned to a contraction of the triazine units due to deprotonation of an NH group. Surprisingly, no interaction of the azacrowns with (metal) cations could be observed.

Katz and co-workers recently reported preliminary molecular recognition measurements using oxacalix[2]naphthalene[2]naphthyridine **39** (Fig. 14).[32] It was envisaged that the increased cavity size (π–π interactions) and hydrogen bonding potential (due to the internal nitrogen atoms) of this novel molecular tweezer should enhance the binding of neutral guests and impose substrate selectivity. Relatively weak 1 : 1 complexation (K_a = 45 M^{-1}) with *o*-salicylic acid was observed by ^{1}H NMR spectroscopic titrations.

The potential of bicyclooxacalix[4]arenes, analogous to the macrocycles described by Katz *et al.* but consisting of 1,3,5-triazine units as trivalent bridging moieties,[12] as versatile cages for anions has been analyzed theoretically.[33] DFT calculations indicate that such bicyclic molecules can bind fluoride anions, both in the gas phase as well as solution, *via* strong CH···F^- hydrogen bonds and additional π–F^- interactions with the electron deficient triazine moieties, while the cage is too small to accommodate chlorine anions. However, experimental proof has not been provided yet.

Shimizu and co-workers studied the encapsulation of electrochemically active guest molecules by oxacalix[4]arene **10** (Fig. 2: R_1 = OH, R_2 = H).[34] The oxacalixarene host was shown to possess host–guest interactions for both the ferrocene/ferrocenium and cobaltocenium/cobaltocene redox couple, with modest association constants, and a remarkable thermodynamic preference for the positively charged over the neutral guest species was observed (an 85-fold enhancement for the ferrocene/ferrocenium couple), attributed to π–cation interactions with the electron-rich hydroxyl-substituted aromatic rings. Cyclic voltammetric measurements showed a large negative shift (−114 mV) of the half-wave potential ($E_{1/2}$) for the one-electron oxidation of ferrocene in the presence of 8 equivalents of the host oxacalixarene. For the cobaltocenium guest, complexation could also be detected by ^{1}H NMR spectroscopy.

6. Perspectives

Although the oxacalixarene field has seen a remarkable increase of attention during the last few years, and a lot of (mainly synthetic) progress has already been made, many opportunities and challenges still remain unexplored. From a synthetic point of view, one of the major challenges involves a more thorough understanding of the factors that determine the kinetic *versus* thermodynamic reaction profile observed in S_NAr-based macrocyclizations, and, related to that, a ring size selective synthesis of larger oxacalix[*n*]arenes ($n > 4$). Further investigations towards novel, more sophisticated functional oxacalix[*n*](het)arenes are also required to fully elucidate and exploit the potential of these macrocycles in a number of promising supramolecular applications, which have only just started to be explored.

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