Heterocalixaromatics, new generation macrocyclic host molecules in supramolecular chemistry†

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Heterocalixaromatics, the heteroatom bridged calix(hetero)arenes, have been emerging as new generation macrocyclic host molecules in supramolecular chemistry recently. Being different from the conventional calixarenes in which the aromatic rings are linked by methylene units, heterocalixaromatics assemble various aromatic rings by different heteroatoms. Owning to the intrinsic nature of heteroatoms that can adopt different electronic configurations to form various degrees of conjugation with their neighboring aromatic rings, heterocalixaromatics exhibit unique structural features and versatile recognition properties in comparison to conventional calixarenes. This feature article highlights recent advances in the synthesis, functionalization, structure and molecular recognition of nitrogen- and/or oxygen-bridged calixaromatics, with a primary focus on our own work.

Introduction

The design and synthesis of new and functional macrocyclic host molecules have always been one of the driving forces to promote the major advances in supramolecular chemistry. This has been manifested by well known examples such as crown ethers,[1] cryptands,[2] spherands[3] and cyclodexitrin derivatives.[4] More recent examples include calixarenes,[5] calixresorcarenes,[6] calixpyrroles,[7] cucurbiturils[8] and others.[9] Because of their easy availability, unique conformational and cavity structures, and versatile molecular recognition properties, calixarenes have attracted tremendous attention for several decades and calixarene chemistry has become an indispensable part of supramolecular science.[10]

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† This article is dedicated to Professor Zhi-Tang Huang on the occasion of his 80th birthday.

Along with the rapid development of macrocyclic host guest chemistry, recent years witness a fast growing interest in heteroatom-bridged calix(hetero)arenes, or simply, heterocalixaromatics.[11,12] In fact, the first nitrogen (NH)-bridged calix[4]arene[13] and oxygen-bridged calix[4]arenes[14] may date back to the 1960s. In the following 40 years, however, they had not attracted attention from organic chemistry community, most probably owing to the obstacles of synthesis. For example, the first oxacalix[4]arene was obtained in only 13% yield from the direct condensation reaction between 1,3-dichloro-4,6-dinitrobenzene and resorcinol,[14] while the reaction between 1,3-dibromobenzene and 1,3-diaminobenzene gave hardly any isolable amount of azacalix[4]arene.[13,15] In 1997, Miyano and co-workers[16] reported the convenient and practical synthesis of thiacalix[4]arene in 54% yield by heating a mixture of *p-tert*-butylphenol and elemental sulfur in tetraglyme in the presence of sodium hydroxide as a catalyst. In 2004, we established a highly efficient stepwise fragment coupling method for the synthesis of various nitrogen- and/or oxygen-bridged calixaromatics.[17,18] Katz's group reported in 2005 an improved one-pot

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synthesis of oxacalixaromatics in very good yields.[19] It has since then opened a new avenue for the study of supramolecular chemistry based on heterocalixaromatics. Being different from the conventional calixarenes in which the aromatic rings are linked by methylene units, heterocalixaromatics assemble aromatic rings by heteroatoms. Since the heteroatoms such as nitrogen have different electronic and steric nature from carbon, introduction of heteroatoms into the bridging positions of calixarenes has resulted in a fundamentally new class of macrocyclic host molecules. The distinct features of diverse heterocalixaromatics, as revealed by recent studies, include the interesting structures and molecular recognition properties that are regulated by the bridging heteroatoms. This feature article will highlight recent advances in the synthesis, functionalization, structure and molecular recognition of nitrogen and/or oxygen bridged calixaromatics, with a primary focus on our own work. The chemistry of thiacalixarenes is not included because it has been reviewed very recently.[20]

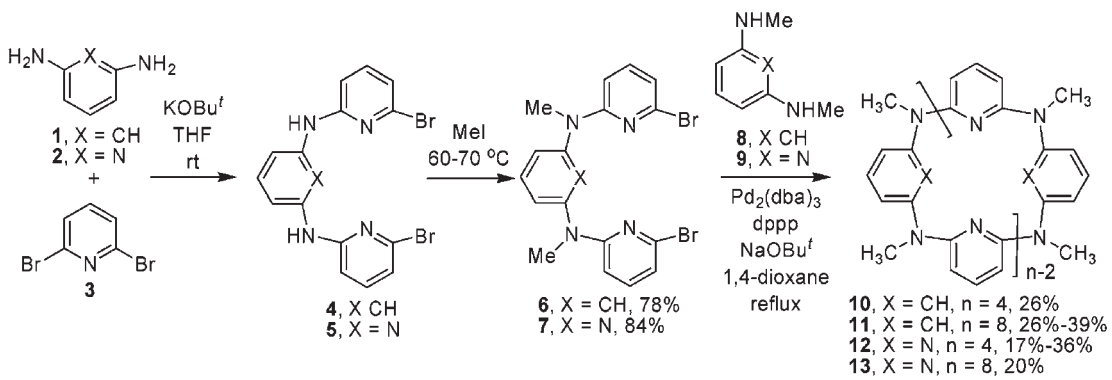
Synthesis

Retrosynthetically, heterocalixaromatics might be prepared by several methods. In order to establish a general and diversity-orientated method for the synthesis of both symmetric and non-symmetric heterocalixaromatics macrocycles, we decided to explore the stepwise fragment coupling approach using readily available starting materials. One of our first synthetic targets was azacalix[2]arene[2]pyridine.[17] We found that, in the presence of an excess amount of KOBu^t, 1,3-phenylenediamine **1** underwent efficient two directional nucleophilic aromatic substitution (S_NAr) reaction with two equivalents of 2,6-dibromopyridine **3** to afford *N*,*N*′-bis(6′-bromopyrid-2′-yl)-1,3-phenylenediamine **4** in almost a quantitative yield. Upon the treatment with methyl iodide and KOBu^t, **4** was converted into a linear fragment **6**. The linear fragment **6** can be prepared conveniently in a one-pot reaction fashion in good yield without isolation of **4**. As we expected, the formation of macrocyclic azacalix[2]arene[2]pyridine from the reaction of **6** with *N*,*N*′-dimethyl-1,3-phenylenediamine **8** was not trivial. After screening various reaction conditions, we found that the $Pd_2(dba)_3$-catalyzed macrocyclic cross coupling reaction between **6** and **8** using 1,3-bis(diphenylphosphino)propane (dppp) as a bidentate phosphine ligand yielded the desired azacalix[2]arene[2]pyridine **10**. Interestingly, in addition to **10**, a larger macrocyclic ring homolog azacalix[4]arene[4]pyridine **11**, that was derived from two pieces of trimer **6** and two equivalents of diamine **8**, was also isolated. The combined yield of **10** and **11** was around 45%. At different reaction temperatures such as 110 and 80 °C, **10** and **11** have been selectively obtained in yields up to 26 and 39%, respectively[17,21] (Scheme 1).

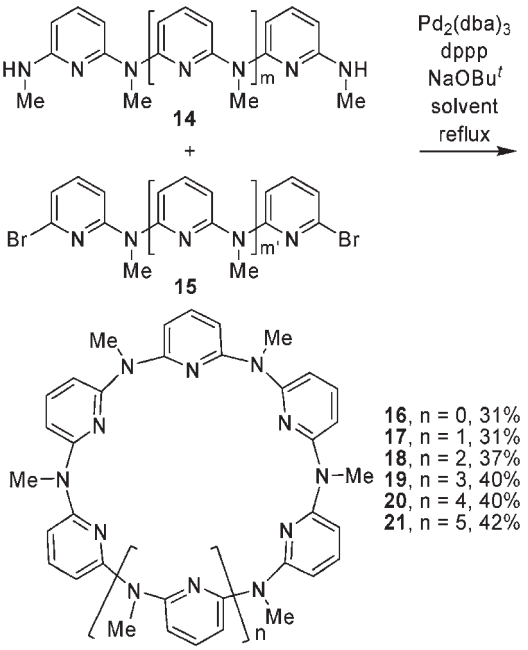
Applying the same fragment coupling strategy, we have synthesized azacalix[4]pyridine **12** and azacalix[8]pyridine **13** from 2,6-diaminopyridine **2** and 2,6-dibromopyridine **3**.[21] Under optimized macrocyclic cross coupling conditions, the $Pd_2(dba)_3$/dppp-catalyzed reaction of the linear trimer **7** with 2,6-bis(methylamino)pyridine **9** produced azacalix[4]pyridine **12** and azacalix[8]pyridine **13** selectively in yields up to 36 and 20%, respectively (Scheme 1).

The fragment coupling approach works equally well for the construction of other different macrocyclic ring-sized azacalix[*n*]pyridines that contain both odd and even numbers of pyridine units.[22,23] For example, while the reaction between **14** ($m = 0$) and **15** ($m' = 1$) (2 + 3) led to the formation of both azacalix[5]pyridine **16** and azacalix[10]pyridine **21**,[22] the fragment coupling between α,ω-diaminated linear oligomers **14** ($m = 3, 4$) and α,ω-dibrominated linear oligomers **15** ($m' = 3, 4, 5$) afforded larger macrocyclic azacalix[*n*]pyridines ($n = 6$–9) **17**–**20** in yields of 31–40%[23] (Scheme 2). It is worth noting that all linear oligomers **14** and **15** are readily prepared, without using any expensive reagents and catalysts, in large scale and in excellent yields from commercially available 2,6-dibromopyridine and methylamine.[22,23]

To construct diverse heterocalixaromatics composed of other heteroatoms and other aromatic rings, and also to test the generality of the macrocyclic fragment coupling strategy, we systematically explored the synthesis of heterocalixtriazine derivatives.[18] Triazine is a valuable unit in molecular recognition and assembly. Triazine-containing molecules such as melamine derivatives, for example, have been used as both hydrogen bond donor and acceptor to bind a number of guest molecules including carbohydrates, cyanuric acid and uracil derivatives through multiple hydrogen bonding interactions.[24–32] Cyanuric chloride, a cheap and commodity chemical widely used in pharmaceutical and agrochemical industries, exhibits high reactivity toward nucleophilic reagents. Most notably, three chloro substituents of cyanuric chloride are replaced consecutively by same or different



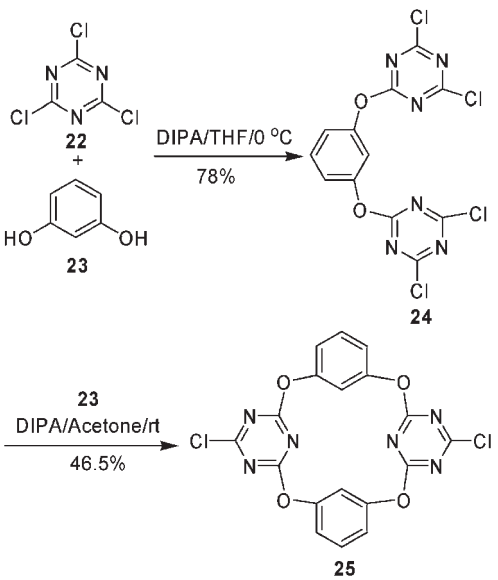
Scheme 1 Fragment coupling approach to azacalix[*m*]arene[*n*]pyridines.



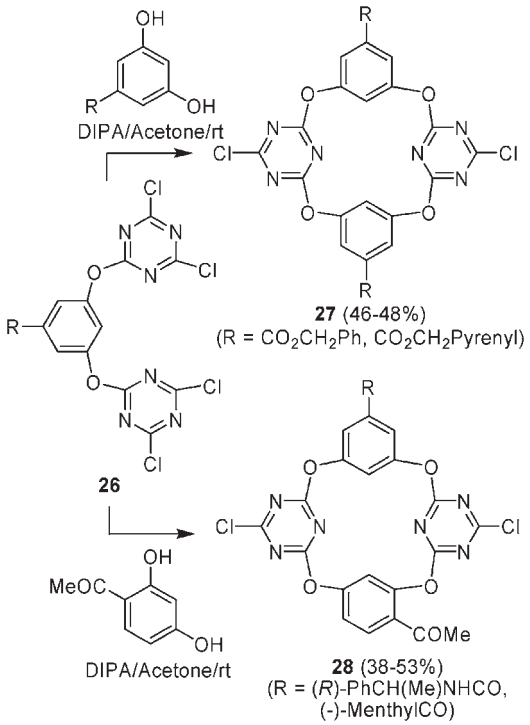
Scheme 2 Macrocyclic cross coupling reaction for the synthesis of azacalix[*n*]pyridines (n = 5–10) **16–21**.

nucleophiles in a controlled manner at different temperatures. It appears as a unique building block in the construction of heterocalixaromatics. We found the reaction between cyanuric acid **22** and resorcinol **23** proceeded very smoothly at 0 °C in the presence of diisopropylethylamine (DIPEA) as an acid scavenger to yield linear trimer **24**. To our delight, at room temperature, macrocyclic aromatic nucleophilic substitution of **24** with resorcinol **23** took place very efficiently in acetone to form desired oxacalix[2]arene[2]triazine **25** in 46.5% yield[18] (Scheme 3).

The fragment coupling protocol appears general and applicable to the synthesis of not only symmetrically substituted oxacalix[2]arene[2]triazine derivatives but also non-symmetrically



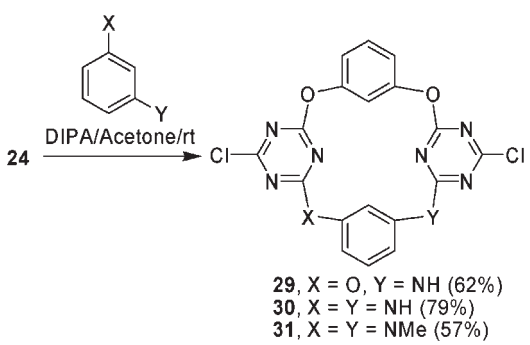
Scheme 3 Synthesis of oxacalix[2]arene[2]triazine **25**.



Scheme 4 Synthesis of symmetrically and nonsymmetrically substituted oxacalix[2]arene[2]triazine derivatives.

substituted ones as well. Illustrated in Scheme 4, for example, are the synthesis of both symmetric and non-symmetric functionalized oxacalix[2]arene[2]triazine derivatives **27**[33] and **28**, respectively.[34] When linear trimers **26**, which are derived from 3,5-dihydroxybenzoic acid esters and cyanuric chloride, undergoes macrocyclic coupling reaction with 2, 4-dihydroxyacetophenone, non-symmetrically substituted oxacalix[2]arene[2]triazines **28** are obtained in 38–53% yield.[34]

One of the most appealing advantages of fragment coupling approach is the convenient and straightforward introduction of different heteroatoms and substituents into the bridging positions of heterocalixaromatics at will. Being a reactive linear trimer, fragment **24** is able to undergo macrocyclic coupling reaction with other dinucleophilic reactants. The use of 3-aminophenol, 1,3-diaminobenzene and 1,3-bis(mentylamino)benzene thus leads to the formation of azatrioxa-, diazadioxa- and *N*,*N*′-dimethyldiazadioxa-calix[2]arene[2]triazine compounds **29–31** in yields ranging from 57 to 79%[18] (Scheme 5).



Scheme 5 Synthesis of oxygen/nitrogen-bridged calix[2]arene[2]-triazines.

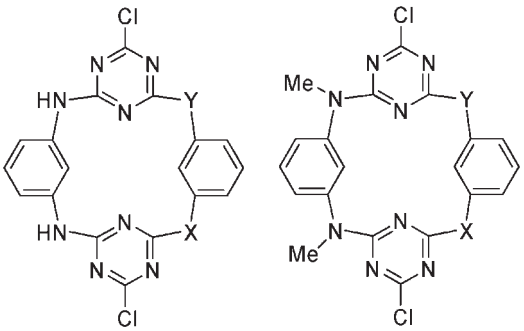


Fig. 1 Structures of aza/oxacalix[2]arene[2]triazines prepared by the macrocyclic fragment coupling approach.

The generality and the advantage of macrocyclic fragment coupling method in synthesis have been further reflected in the preparation of aza/oxacalixa[2]arene[2]triazines that have different combinations of oxygen, nitrogen and substituted nitrogen linkages. Shown in Fig. 1 are some examples of oxatriaza- (**32**), *N*,*N*′-dimethylated oxatriaza- (**35**), tetraaza- (**33**) and partially or fully methylated tetraaza-calix[2]arene[2]-triazines **34** and **36** prepared utilizing fragment coupling method from 1,3-diaminobenzene, 1,3-bis(methylamino)benzene and 3-aminophenol.[18] Among the heterocalix[2]arene[2]-triazines synthesized, compounds **29**, **32** and **35** are actually non-symmetric macrocycles because of the different bridging heteroatom linkages. These macrocycles are hardly accessible by other synthetic methods. It is worth addressing that, for the construction of diverse heterocalix[2]arene[2]triazines, the stepwise fragment coupling approach is a dream synthetic method. It does not need any expensive and toxic chemical reagents and catalysts, and it is completely metal free. The reactions proceed under very mild conditions and afford high chemical yields. Moreover, the synthesis is easily scaled up, and all aza/oxacalix[2]arene[2]triazines are obtainable in several tens of grams in laboratory.[18]

The macrocyclic fragment coupling strategy has been successfully applied for the synthesis of other heterocalixaromatics. For example, Tsue and co-workers have recently reported the synthesis of azacalix[4]arene **37**[35] (Fig. 2) and its larger macrocyclic azacalix[8]arene analog **38**[36] from 1,

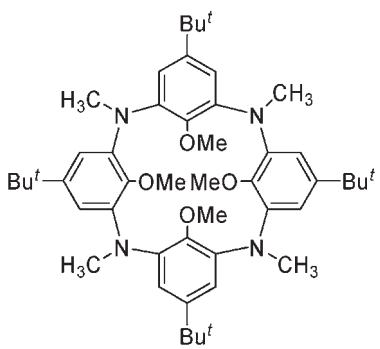
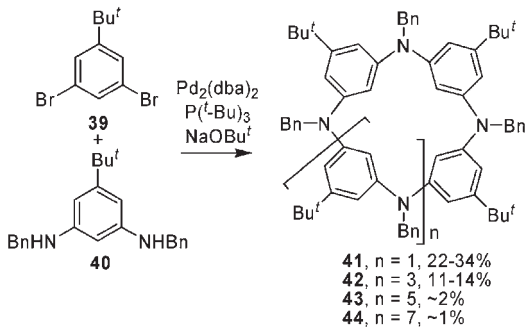


Fig. 2 Azacalix[4]arene **37** obtained from a stepwise synthetic method.

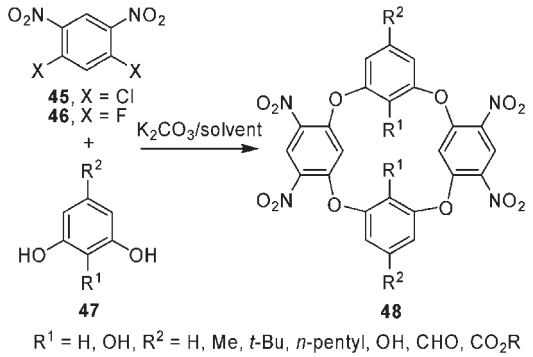


Scheme 6 Condensation between 1,3-dibromo-5-*tert*-butylbenzene **39** and 1,3-bis(benzylamino)benzene **40**.

3-dibromo- and 1,3-diaminobenzene derivatives *via* the stepwise fragment coupling reactions.

For the synthesis of symmetrically substituted azacalixaromatics, both direct condensation reaction of aromatic diamines with 1,3-dihalogenated aromatic substrates and direct self-condensation of *m*-halogenated aromatic amines have been investigated.[15,37–41] In contrast to the stepwise fragment coupling protocol, both approaches lead to the formation of a mixture of macrocyclic and linear oligomers. In most cases, the azacalix[*n*]aromatics products are isolated in low yields. For example, in the presence of $Pd_2(dba)_3$ and P(*t*-Bu)$_3$, reaction between 2,6-bis(methylamino)pyridine **9** and 2,6-dibromopyridine **3** forms a mixture of azacalix[4]pyridine and azacalix[6]pyridine in 1.5 and 10.1% yield, respectively.[38] $PdCl_2[P(o\text{-tolyl})_3]_2$-catalyzed self-condensation of 3-bromo-*N*-methylaniline yields a mixture of azacalix[*n*]arenes (n = 3–8), and the chemical yield of each macrocycle does not exceed 13%.[37] Slightly improved chemical yields have been observed for the direct condensation of aromatic amines or diamines bearing *N*-aryl or *N*-benzyl substituent(s).[15,39–41] Cross coupling reaction between 1,3-dibromo-5-*tert*-butylbenzene **39** and 1,3-bis(benzylamino)benzene **40** produces a mixture of azacalix[*n*]arenes **41–44** (n = 4, 6, 8, 10) in yields ranging from around 1% for azacalix[10]arene **44** to 22–34% for azacalix[4]arene **41**[41] (Scheme 6). The beneficial effect of the *N*-aryl or *N*-benzyl group on the formation of macrocyclic ring products is probably due to their steric influence leading to the conformation of oligomeric precursors more favorable for intramolecular macrocyclization.

While the direct condensation reaction method does not give satisfactory results for the synthesis of azacalixaromatics regarding the selectivity and chemical yield, one-pot reaction approach has been developed with great success for the production of oxygen bridged calixaromatics. Historically, the first oxygen-bridged calixarene compound was synthesized in 1966 by Sommer and Staab[14] who performed the direct aromatic nucleophilic substitution (S_NAr) reaction of 1, 3-dichloro-4,6-dinitrobenzene **45** with resorcinol **47** (R^1 = R^2 = H) in the presence of K_2CO_3 in DMF. The chemical yield was, however, only 13%. Using a more reactive reactant, 1,3-difluoro-4,6-dinitrobenzene **46**, Lehmann[42] in 1974 improved the chemical yield to 46%. Recently, one-pot synthesis of oxacalixaromatics was investigated by Katz's group.[19] They reported that when finely ground anhydrous K_2CO_2 was used as a base and DMSO as the solvent, a number of



Scheme 7 One-pot synthesis of oxacalix[4]arenes.

resorcinol derivatives **47** can react very efficiently with 1, 3-difluoro-4,6-dinitrobenzene **46** at room temperature to afford oxacalix[4]arenes **48** in yields of 75–92%. The reaction tolerates a range of functional groups including hydroxy, ester and aldehyde (Scheme 7). The straightforward synthesis has later been extended to the preparation of oxacalix[2]arene[2]-pyridine **49** (R^1 = H, OH, R^2 = CO_2Me, CO_2Et, *t*-Bu, R^3 = CN, Cl),[43] oxacalix[2]arene[2]pyrimidine **50** (R^1 = Me, *n*-pentyl, CO_2Me, R^2 = H; R^1 = Me, R^2 = Ph, SMe),[43,44] and oxacalix[2]arene[2]pyrazine **51** (R = Me, *n*-pentyl, CO_2Me)[43] (Fig. 3) in high yields when the corresponding activated 2,6-dichloropyridine, 2,6-dichloropyridine and 4, 6-dichloropyrimidine were applied, respectively. Very recently, oxacalixaromatics of an expanded cavity has been reported.[45,46] Katz's group successfully employed one-pot condensation reaction between 2,7-dichloro-1,8-naphthyridine and 2,7-dihydroxynaphthalene to prepare oxacalix[2]naphthalene[2]naphthyridine **52**[45] (Fig. 3). The high selectivity and high efficiency for the formation of cyclotetramers in these macrocyclic condensation reactions have been shown to be the result of thermodynamic product control.[43]

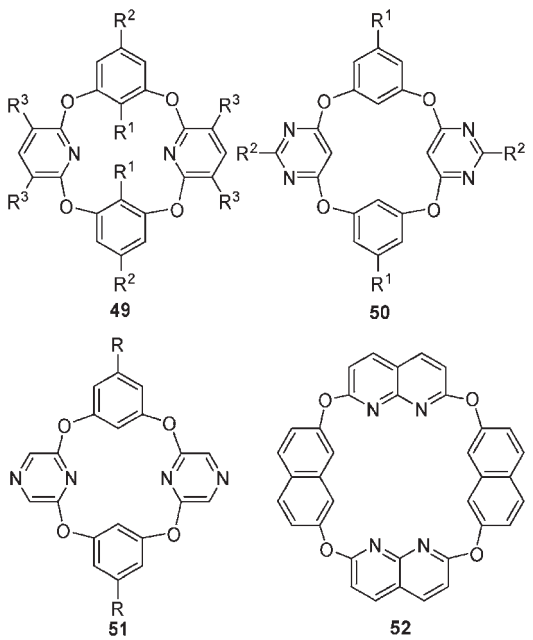
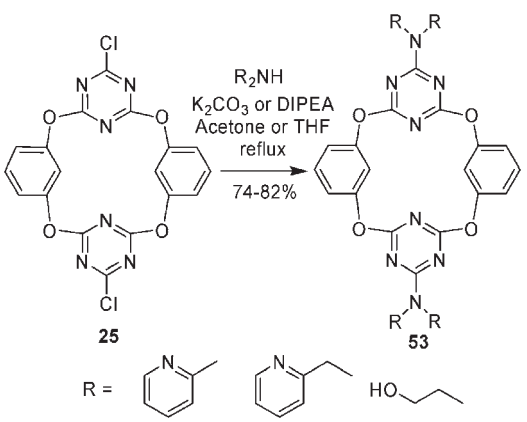


Fig. 3 Oxacalixaromatics prepared from direct condensation between resorcinol and activated *meta*-dihalogenated heteroarene derivatives.

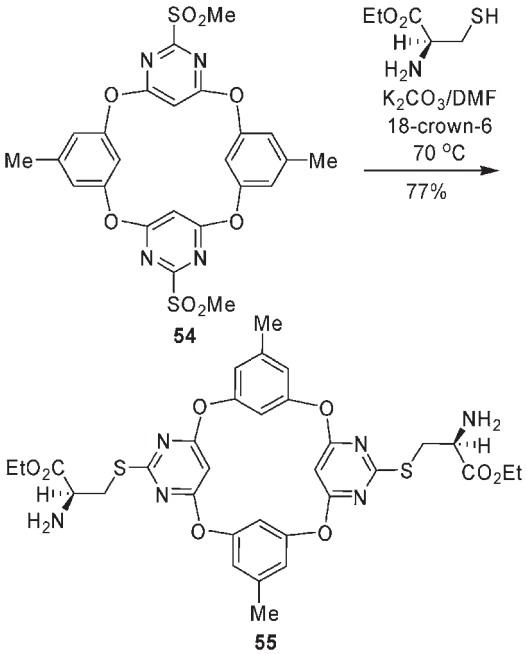
Functionalization

Functionalized heterocalixaromatics, macrocycles containing functional groups for molecular recognition and molecular self-assembly, are obtained by two methods. As depicted in Schemes 4 and 7 and in Fig. 3, functionalized heterocalixaromatics **27**,[33] **28**,[34] **48–51**[43,44] and others[47–49] were synthesized employing functionalized aromatic dinucleophile and dielectrophile reactants. The other method for the construction of heterocalixaromatics bearing desired functional groups at desired positions is based on chemical modifications of the parent macrocyclic rings. This method is especially important and useful when the parent heterocalixaromatics contain some handles, reactive and transformable groups, for chemical manipulations. Heterocalix[2]arne[2]triazines **25** and **27–36**, derived from cyanuric chloride, provide a unique platform for further chemical modifications and functionalizations because the chloro substituent on the triazine ring is readily substituted by a number of nucleophilic reagents. For example, aromatic nucleophilic substitution reaction of chloro of **25** by functionalized amines and alcohols leads to the formation of heterocalix[2]arene[2]triazines **53** armed with useful chelation moieties such as pyridin-2-yl, pyridin-2-ylmethyl and hydroxy groups[50] (Scheme 8). Post-macrocylization functionalizations of heterocalixaromatics have also been reported recently by Dehaen and co-workers[51] By reacting two L-cysteine esters with bis(methylsulfonyl)-substituted oxacalix[2]arene[2]pyrimidine **54**, which was prepared from the reaction between 3,5-dihydroxytoluene and 4,6-dichloro-2-(methylthio)pyrimidine followed by the oxidation of sulfide into sulfone using *m*-CPBA as an oxidant,[44,51] they synthesized a chiral oxacalix[2]arene[2]pyrimidine derivative **55** in 77% yield (Scheme 9).

Higher level molecular architectures have also been constructed on the basis of dichloro-substituted oxacalix[2]-arene[2]triazines. Treatment of **27** with diamines **56** of a long polyether chain in the presence of K_2CO_3 gives rise to oxacalix[2]arene[2]triazine aza-crowns **57**.[33,34] The longer the polyether chain, the higher the chemical yield. It is interesting to point out that, because of the formation of conjugation of amino groups with triazine rings, the oxacalix[2]arene[2]-triaizne azacrowns exists in a mixture of *syn*- and *anti*-isomeric forms in solution. The ratio of the *syn*-isomer **57a** to the

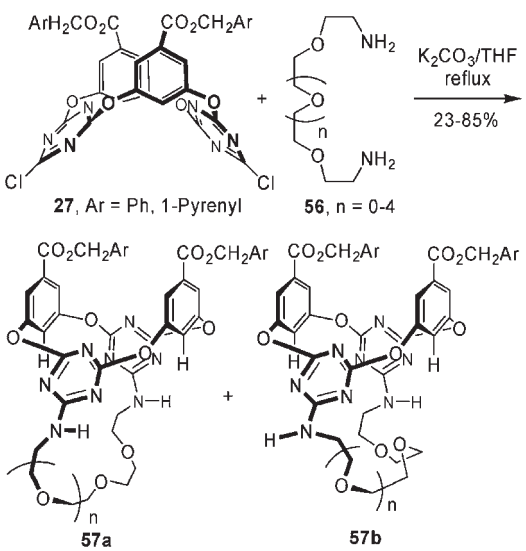


Scheme 8 Functionalization of oxacalix[2]arene[2]triazine.

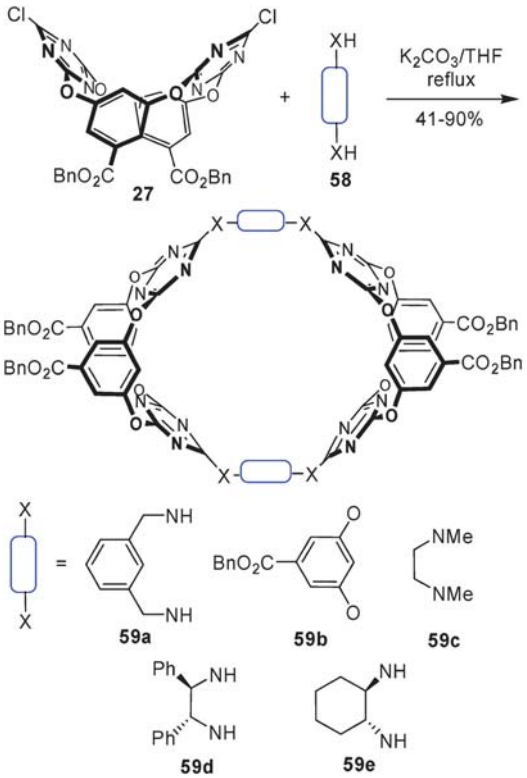


Scheme 9 Synthesis of a chiral oxacalix[2]arene[2]pyrimidine.

anti-isomer **57b**, as determined by ^{1}H NMR spectroscopy, ranges from 0 : 1 to 2.2: 1[33] (Scheme 10). When dinucleophiles that have a short spacer between two nucleophilic sites such as 1,3-bis(aminomethyl)benzene, resorcinol, *N*,*N*′-dimthylethylenediamine are used in the reaction, no oxacalixcrowns or oxacalixazacrowns are obtained. Instead, molecular cages **59a**, **59b**, **59c** result in good to excellent yields (Scheme 11). Chiral molecular cages **59d** and **59e** are readily available from enantiopure (1*R*,2*R*)-1,2-diphenylethylenediamine and (1*R*,2*R*)-1,2-cyclohexanediamine starting materials, respectively[52] (Scheme 11). The high efficiency of the formation of oxacalixazacrowns and molecular cages is most probably attributable to the preorganization of oxacalix[2]arene[2]triazines in a stable 1,3-alternate conformation under the reaction conditions.

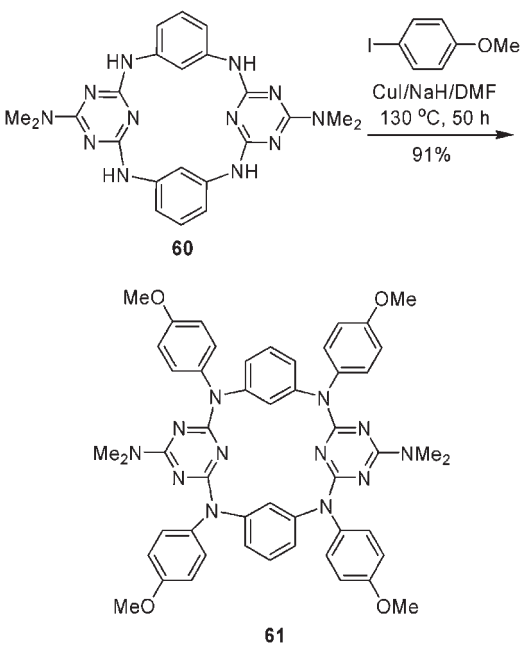


Scheme 10 Synthesis of oxacalixazacrowns.



Scheme 11 Construction of bis(oxacalix[2]arene[2]triazine) molecular cages.

In addition to the chemical modifications on the aromatic rings, one of the advantages of nitrogen (NH)-bridged calixaromatics, in comparison to the conventional calixarenes, is their facile functionalization in the bridging positions. This has been demonstrated by the example of *N*-arylation of aza(NH)-calix[2]arene[2]triazine. Under the Ullmann reaction

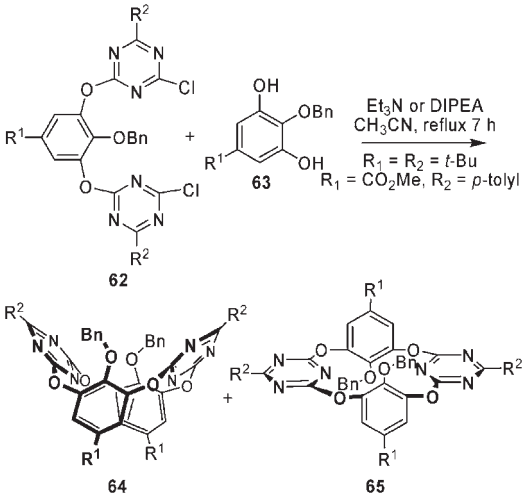


Scheme 12 Functionalization on the bridging nitrogen atoms of azacalix[2]arene[2]triazine.

conditions, aza(NH)calix[2]arene[2]triazine **60** undergoes exhaustive cross coupling reaction with 4-methoxyphenyl iodide to afford product **61** in excellent yield[53] (Scheme 12).

Structure

Introduction of heteroatoms into the bridging positions of the calixaromatics has resulted in heterocalixaromatics of intriguing structural characteristics. Being different from conventional calix[4]arenes that can form mainly four different types of conformations, heterocalix[4]aromatics obtained so far give only two stable conformational structures, namely, 1,3-alternate and the flattened partial cone conformations. This is most probably because of the lack of the intramolecular hydrogen-bond network that exists in calix[4]arenes derived from phenol derivatives. In most cases, heterocalix[4]aromatics adopt a 1,3-alternate conformation.[17–19,43–45,53] Only when heterocalix[4]aromatics contain large substituents at lower rim are flattened partial cone conformation observed.[54,55] For example, from the macrocyclic fragment coupling reaction between **62** and **63**, the flattened partial cone conformers **65** are isolated as kinetically controlled products in low yields, in addition to the formation of 1,3-alternate conformers **64** (Scheme 13). The flattened partial cone conformers **65** are very stable in the solid state and in solution phase even at an elevated temperature, since the bulky groups such as *p*-tolyl, *tert*-butyl and benzyloxy prohibit the free rotation of the benzene and triazine rings around the *meta–meta* axes or through the annulus. Interestingly, however, upon the treatment with K_2CO_3 in refluxing acetonitrile, the flattened partial cone conformers **64** transform completely into the thermodynamically more stable 1,3-alternate conformational products **65**. The mechanism of the



Scheme 13 Formation of 1,3-alternate and the flattened partial cone conformers.

conformational transformation remains intriguing. It has been suggested that the conformational transformation proceeds most likely through ether bond scission.[55]

Careful scrutiny of the 1,3-alternate conformation of the heterocalix[4]aromatics reveals that heteroatoms such as nitrogen and oxygen adopt sp^2 electronic configuration, and form conjugation with one of their neighboring aromatic rings.[17–19,21] Therefore the cavity of heterocalix[4]aromatics cab be viewed as being resultant from a cyclic array of two pieces of planar conjugated aromatic segments and two isolated aromatic ring in a 1,3-alternate fashion (Fig. 4). As illustrated in Fig. 4, for example, azacalix[4]pyridine **12**[21] adopts a 1,3-alternate conformation with C_{2v} symmetry.

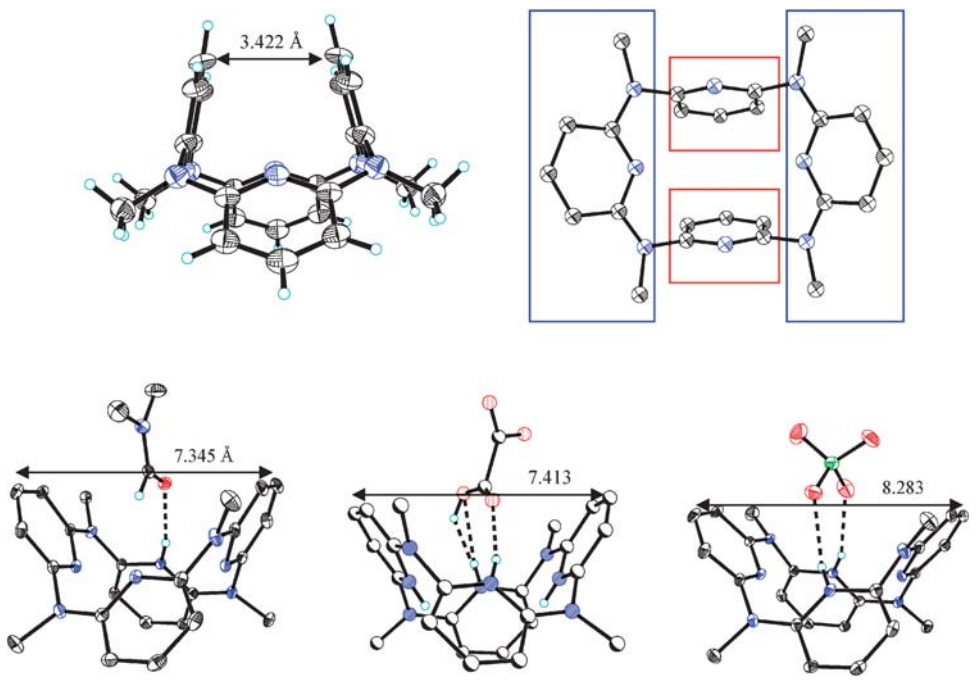
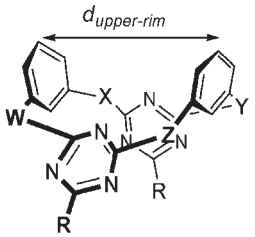


Fig. 4 Conformational structures of azacalix[4]pyridine (side view, upper left and top view, upper right) and its complexes with DMF (**12**·$HClO_4$·DMF) (down left), with oxalic acid (**12**·$HO_2CO_2H·H_2O$) (down middle), and with perchloric acid (**12**·$HClO_4$) (down right). Anion species are not shown for clarity.

Table 1 Effect of the bridging heteroatoms on the cavity size



Entry	W	X	Y	Z	R	$d_{upper\text{-}rim}$/Å	Ref.
1	O	O	O	O	Cl	5.011	18
2	O	O	O	N–H	Cl	6.533	18
3	O	O	N–H	N–H	Cl	7.979	18
4	O	O	N–Me	N–Me	Cl	5.175	18
5	O	N–H	N–Me	N–Me	Cl	5.559	18
6	N–H	N–H	N–H	N–H	Cl	7.392	18
7	N–H	N–H	N–Me	N–Me	Cl	7.393	18
8	N–H	N–H	N–Bn	N–Bn	Cl	6.993	53
9	N–Me	N–Me	N–Me	N–Me	Cl	6.046	18
10	N–Bn	N–Bn	N–Bn	N–Bn	Cl	4.269	53
11	N–Bn	N–Bn	N–Bn	N–Bn	Cl	4.031	53
12	N–PMP	N–PMP	N–PMP	N–PMP	NMe_2	3.514	53

[a] PMP, *p*-methoxyphenyl.

Two isolated pyridine rings are face-to-face parallel with the two conjugated pyridine rings are nearly edge-to-edge orientated. Very interestingly and remarkably, owning to the intrinsic nature of nitrogen atom that can form sp^2 and sp^3 electronic configurations and can form different degrees of conjugation with its adjacent aromatic rings, azacalix[4]-pyridine self-regulates its conformation and cavity structure in order to best fit the guest species. This has been clearly exemplified by that, when interacted with acids, azacalix[4]-pyridine changes its 1,3-alternate conformation with C_{2v} symmetry into a distorted 1,3-alternate conformation with approximate S_4 symmetry. The cavity size, which is defined by the distance ($d_{upper\text{-}rim}$) between two upper-rim carbon atoms of pyridine rings, varies from 7.345 to 8.283 Å in the complexes[21] (Fig. 4).

In the case of heterocalix[2]arene[2]triazines, the combination of heteroatoms and the substituents on the bridging nitrogen atoms plays an important role in determining the cavity or cleft size of the macrocycles.[18,53] Summarized in Table 1 are the distances between two upper-rim carbon atoms of two face-to-face allied benzene rings (d_{upper}). The distances vary dramatically from 3.514 to 7.979 Å. In general, the replacement of oxygen atoms by nitrogen atoms in the bridging positions leads to the increase of the distance (entries 1–3, Table 1) because of the stronger tendency of nitrogen to undergo conjugation. Due to the steric effect, introduction of more and larger substituents on the bridging nitrogen atoms results in the decrease of the cleft size of azacalix[2]arene[2]-triazines (entries 6–12, Table 1). The regulation of the cavity size by the combination of heteroatoms in the linking positions of calixaromatics really offers the opportunity for the rational design of synthetic receptors in supramolecular chemistry.

Molecular recognition

The size-tunable cavity, multiple binding sites and the functionalizations at will render heterocalixaromatics unique macrocyclic host molecules in the study of molecular recognition. Oxacalix[2]arene[2]triazines functionalized with two 2, 2′-bi(pyridinyl)amino and bis(2-pyridinemethyl)amino groups **53** have been shown by us to selectively bind Cu^{2+} ion, forming the 1 : 1 complexes with the bonding constants log $K_{1:1}$ of 4.43 and 4.09, respectively.[50] The upper-rim 1,3-alternate oxacalix[2]arene[2]triazine azacrowns **57** is able to interact fluoride with good selectivity.[33]

We have extensively explored applications of azacalixpyridine macrocycles in the recognition of metal cations,[56] neutral molecules[57] and fullerenes.[17,21–23] Being a multi-nitrogen containing macrocycle, azacalix[4]pyridine **12** exhibits intriguing binding ability toward metal cations. As determined by fluorescence titration measurement, azacalix[4]pyridine forms a 1 : 1 complex with Zn^{2+} ion, giving a binding constant log $K_{1:1}$ of 5.97, in correspondence to a dissociation constant K_d of 1.07 μM. Very interestingly, the interaction of the host molecule with Zn^{2+} guest leads to a great enhancement of fluorescence emission, due to the rigidification and coplanarity of the host macrocyclic ring when complexing with the Zn^{2+} ion guest. More significantly, the fluorescence sensing is highly selective toward Zn^{2+}, no fluorescence intensity being observed in the presence of many other metal cations except for Cu^{2+} ion. However, since Cu^{2+} ion exists at very low concentrations in biological samples, it has marginal effect on the application of azacalix[4]pyridine in sensing Zn^{2+} ion in biological systems.[56]

Azacalix[4]pyridine **12** is a also versatile receptor for hydrogen bond donors. By means of ^1H NMR titration, we have found that azacalix[4]pyridine **12** forms 1 : 1 complexes with monool and diol guests selectively.[57] While the binding constants for most monools and diols tested are below 270 M^{-1}, strong complexation with resorcinol is evidenced by a large

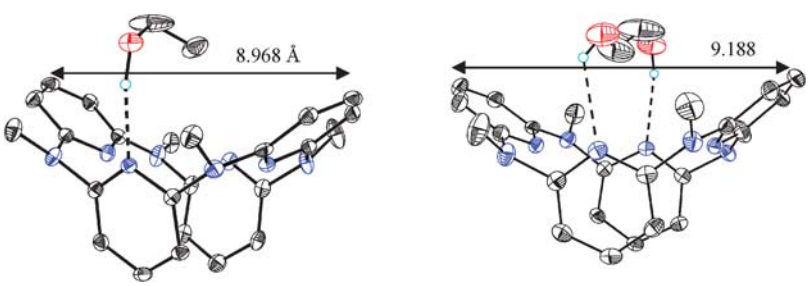


Fig. 5 X-Ray crystal structures of the complexes between azacalix[4]pyridine **12** with ethanol (left) and with ethylene glycol (right).

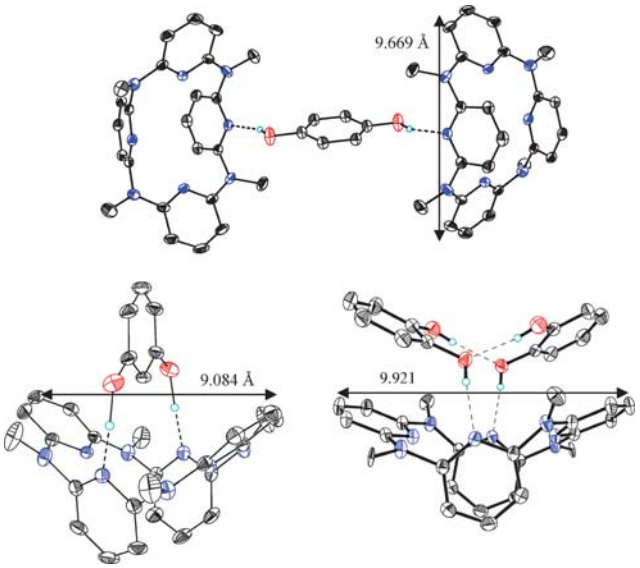


Fig. 6 X-Ray crystal structures of the complexes of azacalix[4]-pyridine **12** with hydroquinone (upper), resorcinol (down left) and catechol (down right).

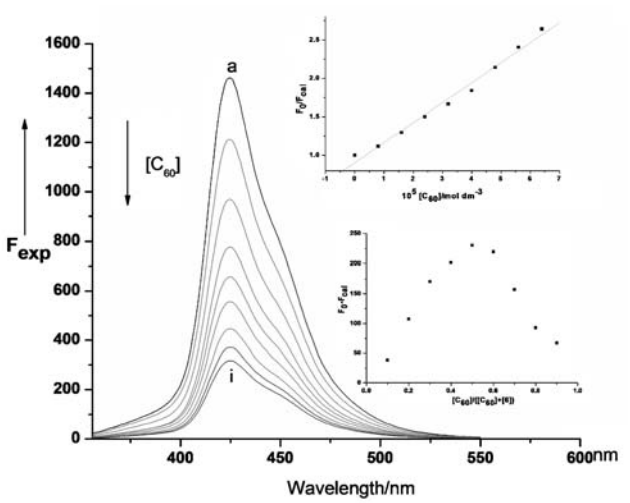


Fig. 7 Emission spectra (λ_{ex} = 336 nm) of azacalix[5]pyridine **16** (3.2×10^{-6} mol dm^{-3}) in the presence of C_{60} in toluene at 25 °C. The concentrations of C_{60} for curves a–i (from top to bottom) are 0, 0.799, 1.60, 2.40, 3.20, 4.00, 4.80, 5.59, 6.39 ($\times 10^{-5}$ mol dm^{-3}). Insets: The upper inset is the variation of fluorescence intensity F_0/F_{cal} of **16** with increasing C_{60} concentration. The lower inset is the Job plot for the **16**·C_{60} complex in toluene solution ([**16**] + [C_{60}] = 6.4×10^{-6} mol dm^{-3}).

binding constant ($K_{1:1}$ = 6000 M^{-1}). The high selectivity has been used to differentiate 1,3-dihydroxybenzene from other aromatic diols in solution using ^{1}H NMR spectroscopy.

In the solid state, azacalix[4]pyridine **12** is able to form various guest-dependent host–guest complexes with both aliphatic and aromatic monools and diols (Fig. 5 and 6). X-Ray single-crystal structures show azacalix[4]pyridine **12** gives 1 : 1 molecular sandwich complexes with ethanol, ethylene glycol (Fig. 5), and resorcinol (Fig. 6). In addition to intermolecular hydrogen-bonding effect, C–H$\cdots\pi$ interaction is also evidenced by the short distance between methylene hydrogen atom of alcohol guests and the plane of pyridine ring of the host. Complexation of azacalix[4]pyridine **12** with catechol and hydroquinone, however, gives rise to the formation of a 1 : 2 butterfly-layered complex and a 2 : 1 capsule-like complex (Fig. 6), respectively. While intermolecular hydrogen bonds are the driving force for the formations of molecular capsule and molecular sandwich structures, a network of hydrogen bonding among host and two guest molecules along with the $\pi\cdots\pi$ interaction between host and guest molecules provide energy to stabilize the butterfly-layered complex. It is very important to address that although azacalix[4]pyridine still adopts a 1,3-alternate or a slightly twisted 1,3-alternate conformation in all the complexes, the bond lengths and bond angles of bridging nitrogen atoms vary slightly, leading to various finely tuned clefts. The upper-rim distance between two edge-to-edge positioned pyridine rings in all complexes ranges from 8.989 to 9.921 Å, in sharp contrast to that of the host **12** (3.422 Å, Fig. 4) without including any guest species. This also indicates convincingly that the azacalix[4]pyridine **12** is a intelligent macrocyclic host. It can self-regulate its conformation through the adjustment of conjugation of bridging nitrogen atoms with their linking pyridine rings to yield a cavity for the most efficient interaction with the guest species.

Large macrocyclic azacalix[*n*]pyridines (*n* = 5–10) are powerful host molecules able to interact with fullerenes C_{60} and C_{70}.[21–23] Depicted in Fig. 7 is the example of fluorescence titration of azacalix[5]pyridine **16** by C_{60}. We have found that, in all cases, the fluorescence intensity of host molecules **16–21** are quenched consistently with increasing concentration of fullerene C_{60} or C_{70}. The Job plot studies indicated 1 : 1 complexation of macrocyclic hosts with C_{60} and C_{70} in toluene. Based on a well established method,[58] the fluorescence intensity F_{exp} is calibrated to F_{calc}, and calculation from the plots of F_o/F_{calc} *vs.* the concentration of fullerene C_{60} gives the association constants ($K_{1:1}$) of 2.6×10^4 to 6.6×10^4 M^{-1} for C_{60} and 6.2×10^4 to 1.3×10^5 M^{-1} for C_{70}.[21–23] In the case of azacalix[4]arene[4]pyridine **11**, the complexation with C_{60} and C_{70} in toluene affords binding constants $K_{1:1}$ up to 7.1×10^4 and 1.4×10^5 M^{-1}, respectively. Remarkably, the process of host–guest interaction between azacalix[4]arene[4]pyridine **11** and C_{60} can be easily monitored by naked-eye observation of color change from characteristic red–purple to yellow brown in toluene.[17] Azacalix[*n*]pyridine (*n* = 5–10) macrocycles represent the strongest mono-macrocyclic receptors to interact with fullerenes C_{60} and C_{70}.[17,21–23]

Conclusions and outlook

Heterocalixaromatics, the heteroatom bridged calix(hetero)arenes, have been emerging as new-generation macrocyclic host molecules in supramolecular chemistry. With the advent of powerful synthetic methods, including the stepwise macrocyclic fragment coupling strategy and the direct macrocyclic condensation reaction approach, and of efficient post-macrocyclization functionalizations, a large number of diverse heterocalixaromatics are now readily available from commodity *meta*-substituted aromatic dinucleophiles and dielectrophiles. Owning to the intrinsic electronic nature of heteroatoms such as nitrogen that can adopt different electronic configurations

to form various degrees of conjugation with their adjacent aromatic rings, heterocalixaromatics exhibit unique structure and molecular recognition properties. Most notably, heterocalixaromatics are able to self-regulate their conformational and cavity structures to achieve maximum or the most efficient interactions with the guest species.

Compared with the most well known macrocyclic host molecules such as crown ethers, cyclodextrins and calixarenes, *etc*. the chemistry of heterocalixaromatics is still in its infancy. To be explored are the efficient synthesis of novel and functional heterocalixaromatics, the generation and control of other stable conformational structures, the construction of more sophisticated heterocalixaromatic-based high level molecular architectures, and the mechanisms, especially the dynamic process of conformational changes of heterocalixaromatics in molecular recognition. Applications of heterocalixaromatics in self-assembly and supramolecular catalysis are also expected in not-too-distant future.

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