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Nitrogen and Oxygen Bridged Calixaromatics: Synthesis, Structure, Functionalization, and Molecular Recognition

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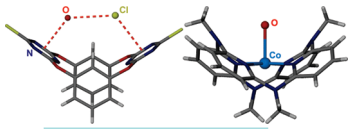

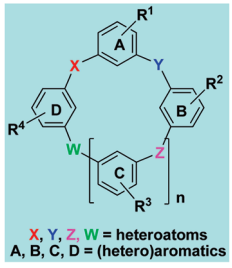

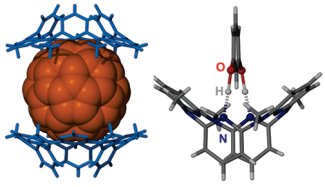

Pedersen, Lehn, and Cram established supramolecular chemistry through their pioneering work with crown ethers, cryptands, and spherands. Since then, the hallmark of supramolecular science has been an increasing sophistication in the design and construction of macrocyclic molecules, as manifested in cyclodextrin derivatives, calixarenes, resorcinarenes, cyclotriveratrylenes, cucurbiturils, calixpyrroles, cyclophanes, and many other examples. Indeed, macrocyclic compounds provide unique models for the study of noncovalent molecular interactions. They also constitute building blocks for constructing high-level molecular and supramolecular architectures and fabricating molecular devices and advanced materials.

As a postgraduate in the Huang laboratory in the late 1980s, I became interested in the calix[*n*]arenes because of their unique conformational structures and versatile complexation properties. The notion of introducing heteroatoms, and particularly nitrogen, into the bridging position of conventional calixarenes was particularly intriguing. Nitrogen, unlike methylene, can adopt either an sp^2 or sp^3 electronic configuration, providing different conjugation systems with adjacent aromatic rings. Consequently, depending on the configuration and conjugation, a range of C–N bond lengths and C–N–C bond angles is possible. The conformation and cavity size in heteroatom-bridged calixarenes might thus be tuned through the bridging heteroatoms and the number of aromatic rings. Furthermore, because heteroatom linkages significantly affect the electron density and distribution on aromatic rings, the electronic features of macrocyclic cavities might be regulated by heteroatoms. Given the essentially limitless combinations possible, only synthetic hurdles would prevent access to numerous diverse heteracalixaromatics.

We began a systematic study on nitrogen- and oxygen-bridged calixarenes in 2000, years later than originally envisioned. Before this study, very few heteracalixaromatics had been reported, owing to the formidable synthetic challenges involved. Apart from thiacalixarene, the synthesis of nitrogen- and oxygen-bridged calixarenes appeared very difficult. But since our first publications in 2004, we have been delighted to see the rapid and tremendous development of the supramolecular chemistry of this new generation of macrocycles.

In this Account, I summarize the synthesis of N- and O-bridged calixaromatics and their regiospecific functionalization on the rims and bridging positions, focusing on the fragment coupling approach and contributions from our laboratory. I describe the construction of molecular cages based on heteracalixaromatics and discuss the effect of both bridging heteroatoms and substituents on macrocyclic conformations and cavity sizes. Molecular recognition of neutral organic molecules and charged guest species is also demonstrated.

The easy accessibility, rich molecular diversity, unique conformation, and cavity tunability of heteracalixaromatics make them invaluable macrocycles for research in supramolecular chemistry. New heteracalixaromatics, with well-defined conformations and cavity properties, will provide powerful tools for probing noncovalent interactions, leading to the development of new molecular sensing and imaging systems. Multicomponent molecular self-assembly of heteracalixaromatics as functional modules with metals, metal clusters, or charge-neutral species should result in multidimensional solid and soft materials with diverse applications. The profitable incorporation of heteracalixaromatics into molecular devices can also be anticipated in the future. Moreover, the construction of enantiopure, inherently chiral heteracalixaromatics should provide important applications in chiral recognition and asymmetric catalysis.

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1. Introduction

Owing to the pioneering work of Pedersen, Lehn, and Cram, the study of crown ethers, cryptands, and spherands resulted in the establishment of supramolecular chemistry. The sophistication of the design and construction of ingenious macrocyclic molecules has ever since been one of the driving forces to promote the major advances of supramolecular science. This has been manifested by the examples of cyclodextrin derivatives, calixarenes, resorcinarenes, cyclotriveratrylenes, cucurbiturils, calixpyrroles, various cyclophanes, etc.[1] Indeed, macrocyclic compounds have been providing unique models in the study of noncovalent molecular interactions, and they have been serving as building blocks in the construction of high-level molecular and supramolecular architectures and in the fabrication of molecular devices and advanced materials.

When I worked as a postgraduate student in the later 1980s with Professor Zhi-Tang Huang,[2] a renowned chemist for his work in heterocyclic chemistry, calixarenes, and heat-resistant polymers, I became interested in calix[*n*]arenes because of their unique conformational structures and versatile complexation properties.[3] As an organic chemist trained in heterocyclic chemistry through the study of the structure and reactions of heterocyclic 1,1-enediamines,[4] I was fascinated by the idea of introducing heteroatoms, particularly nitrogen, into the bridging positions of conventional calixarenes. Being different from the methylene linkage, nitrogen can adopt sp^2 and sp^3 electronic configurations. Either an sp^2 or sp^3 hybrid nitrogen atom can form, in various degrees, different conjugation systems with its adjacent aromatic rings, giving resultantly different $C_{Ar}-N$ bond lengths and $C_{Ar}-N-C_{Ar}$ bond angles. The conformation and cavity of the heteroatom-bridged calixarenes might thus be *fine-tuned* by the bridging heteroatoms, in addition to *coarse-tuning* by varying the number of aromatic rings. Furthermore, since heteroatom linkages affect significantly the electron density and distribution on aromatic rings, the electronic feature of macrocyclic cavities might be regulated by heteroatoms. Moreover, as combinations of heteroatoms and (hetero)aromatic rings are almost limitless, numerous diverse heteracalixaromatics would be possible, provided that synthetic methods are available.

Our systematic study on nitrogen- and oxygen-bridged calixarenes started in 2000, many years later than we proposed. Very few heteracalixaromatics were known, however, prior to our study because of formidable synthetic challenges.[5] Except thiacalixarene, which was prepared in good yield by Miyano[6] in 1997 from heating a mixture of *p-tert*-butylphenol, sulfur, and NaOH in tetraglyme at 230 °C, the synthesis of nitrogen- and oxygen-bridged calixarenes appeared difficult.[5] For example, condensation of resorcinol with 1,3-dichlorobenzene gives oxacalix[4]arene in 13% yield,[7] while the Pd-catalyzed amination of 3-bromo-*N*-methylaniline leads to a mixture of azacalix[*n*]arenes ($n = 4-10$) with the highest chemical yield of azacalix[4]arene not exceeding 13%.[8] To our delight, since our first publications in 2004,[9,10] there has been a very rapid and tremendous development of the supramolecular chemistry of this new generation of macrocyclic molecules.[11−13] In this Account, I will summarize our endeavors on the study of the synthesis, structure, and functionalization of diverse nitrogen- and oxygen-bridged calixaromatics. Applications of heteracalixaromatics in molecular recognition toward charged and neutral organic guests will be demonstrated.

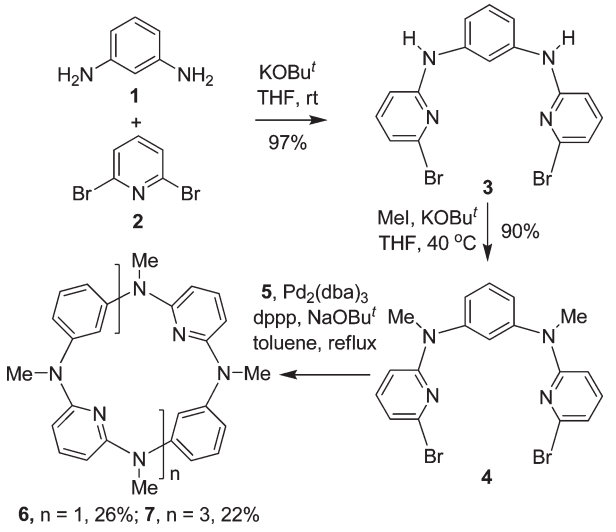
2. Synthesis of Parent Heteracalixaromatics

In order to establish efficient and diversity-oriented synthetic methodology, we explored the fragment coupling approaches starting from readily available aromatic dielectrophiles and dinucleophiles. To endow the parent macrocycles with functions, we were particularly interested in heteracalixaromatics that contain heteroaromatic rings including pyridine, pyrimidine, and triazine.

We initiated our study with the synthesis of azacalix[*m*]arene[*n*]pyridines.[9] As delineated in Scheme 1, benzene-1,3-diamine **1** undergoes efficient two-directional nucleophilic aromatic substitution reaction (S_NAr) with 2,6-dibromopyridine **2** to give a linear trimer **3**. Treatment of **3** with methyl iodide produces intermediate **4**. While the S_NAr reaction between **4** and aromatic diamines is not effective, palladium-catalyzed cross-coupling reaction of **4** with N^1,N^3-dimethylbenzene-1,3-diamine **5** in refluxing toluene affords azacalix[2]arene[2]pyridine **6** in 26% yield. In addition to [3 + 1] double aryl amination of **4** with **5**, a larger macrocyclic ring homologue, azacalix[4]arene[4]pyridine **7**, is also produced in 22% from the multiple [3 + 1 + 3 + 1] cross-coupling reactions of **4** with **5**. Azacalix[4]arene-[4]pyridine **7** is synthesized selectively in an improved yield of 39.5% when reaction is performed at 80 °C in 1,4-dioxane.[9]

Based on fragment coupling approach, we have prepared a number of homologous azacalix[*n*]pyridines **8**−**14** ($n = 4-10$).[14−16] Following the same procedures depicted in Scheme 1, employment of 2,6-diaminopyridine and

SCHEME 1



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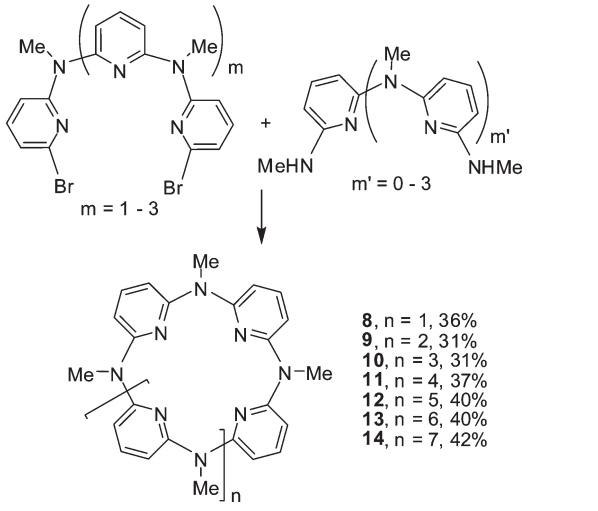

2,6-bis(methylamino)pyridine instead of **1** and **5**, respectively, leads to the formation of azacalix[4]pyridine **8** and azacalix[8]pyridine **11** in a total yield up to 53%. Under optimized conditions, [3 + 1] fragment coupling reaction gives selectively azacalix[4]pyridine **8** in 36% yield.[14] Macrocyclic [$m + m'$] fragment cross-coupling reactions between dielectrophilic and dinucleophilic linear fragments, which are easily obtained from iterative S_NAr reactions between 2,6-dibromopyridine **2** and 2,6-diaminopyridine derivatives, furnish the synthesis of azacalixpyridines in 31−42% isolated yields[15,16] (Scheme 2).

Palladium-catalyzed cross-coupling reaction was found not effective for the direct synthesis of NH-bridged calixpyridines, useful scaffolds for N-functionalization (*vide infra*). To circumvent the problem, *N*-allyl groups were used as protecting groups prior to macrocyclic ring formation. Scheme 3 illustrates the successful [1 + 3] and [2 + 2] fragment coupling reactions for the synthesis of calix[4]pyridines bearing one to four allyl groups on the bridging positions. Cleavage of *N*-allyl groups affords $(NH)_m(NMe)_{4-m}$-bridged calix[4]pyridines (Scheme 3).[17] *N*-Boc-protected linear trimers **25** and **26** also undergo Pd-catalyzed double cross-coupling reactions with benzene-1,3-diamine **1** to produce macrocyclic products **27** and **28** in 30% and 57% yields, respectively. Hydrolysis gives NH-bridged calix[*m*]arene-[*n*]pyridine products **29** ($m = 1$, $n = 3$) and **30** ($m = n = 2$) (Scheme 4).[18]

Fragment coupling approach works excellently for the construction of heteroatom-bridged calix[2]arene-[2]triazines.[10] Taking advantage of the differentiated reactivity of the three chloro substituents on cyanuric chloride, we first prepared trimer **33** from the S_NAr reaction of resorcinol **31** with cyanuric chloride **32** at 0 °C in the presence of diisopropylethylamine (DIPEA) as an acid scavenger. Subsequent S_NAr reaction of **33** with resorcinol **31** at room temperature gave tetraoxacalix[2]arene[2]triazine **34** in 46.5%. Analogous S_NAr reaction with *m*-aminophenol, benzene-1,3-diamine, and N^1,N^3-dimethylbenzene-1,3-diamine produced the corresponding heteracalix[2]arene-[2]triazines **35**, **36**, and **37** in 57%−79% yields (Scheme 5). Combination of aromatic dinucleophiles in the first and second steps led to symmetric and unsymmetric heteracalix-[2]arene[2]triazines **38**−**40** (Scheme 6). It is worth addressing that the fragment coupling approach is ideal for the synthesis of heteracalix[2]arene[2]triazines. First, it enables the construction of diverse heteroatom-linked calixaromatics simply employing different combinations of reactants. In addition, all reactions proceed under very mild conditions and require no expensive and toxic catalysts and reagents. Furthermore, synthesis is easily executed with high efficiency and good chemical yields. Last but not least, all reactions are scalable, allowing large scale preparation of heteracalix[2]arene[2]triazines in the laboratory.

Theoretically, the fragment coupling approach can be applied to synthesize unlimited heteracalixaromatics that combine diverse heteroatoms and (hetero)aromatic rings. Many heteracalixaromatics have been prepared indeed using this protocol.[11−13,19−27] Recently, we[28] have extended the fragment coupling approach to the synthesis of azacalix[4]pyrimidines **44** by means of consecutive S_NAr reactions starting from 4,6-diaminopyrimidines **41** and 4,6-dichloropyrimidine **42** (Scheme 7). It should be noted that direct reaction between **41** and **42** is

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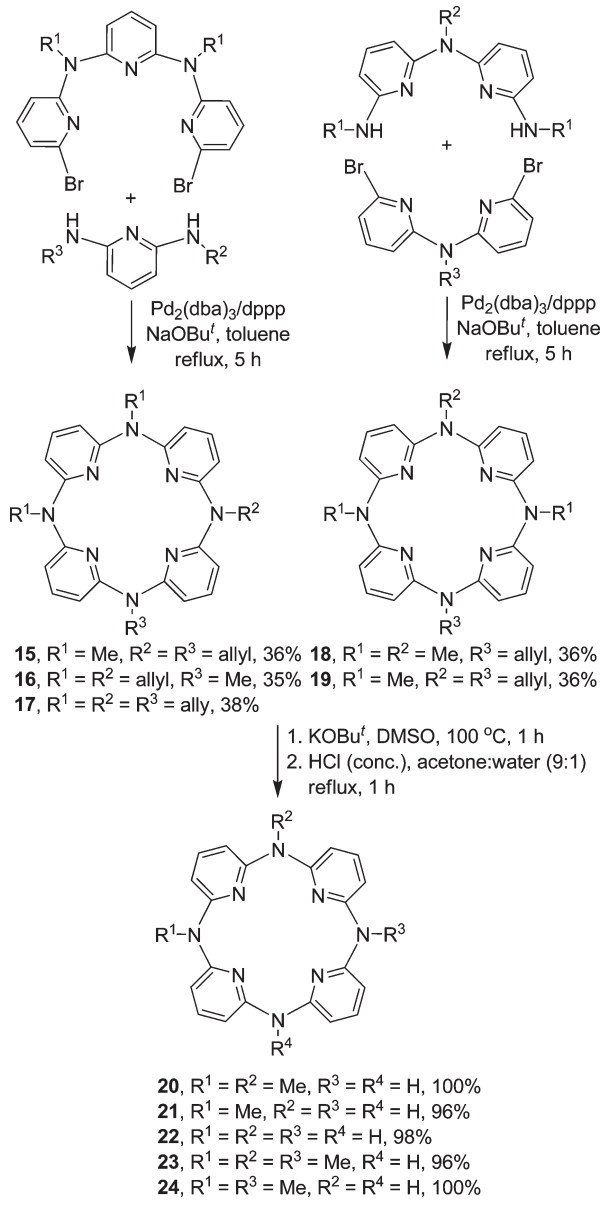
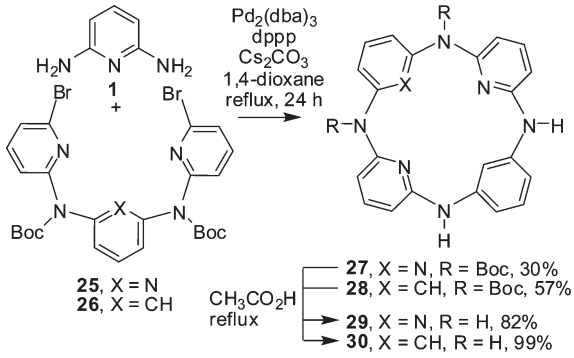


only effected for the synthesis of symmetric azacalix[4]pyrimidines **44a**–**d** with much lower chemical yields,[28] although the one-pot method has been reported to work effectively for some other symmetric heteracalixaromatics.[11–13,29]

3. Structure of Heteracalixaromatics

In contrast to conventional calix[4]arenes that occur in four major different conformations,[3] a dominant majority of heteracalixaromatics form 1,3-alternate conformations in the solid state. Close scrutiny of the bond lengths and bond angles of the 1,3-alternate conformation of heteracalixaromatics reveals that all bridging nitrogen and oxygen atoms adopt sp^2

SCHEME 4



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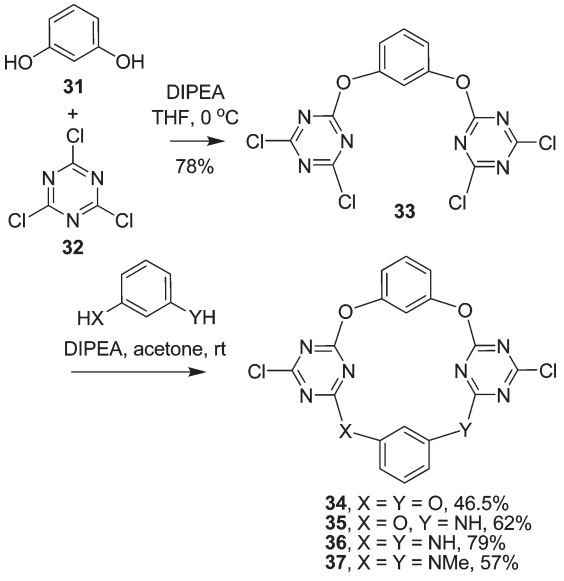

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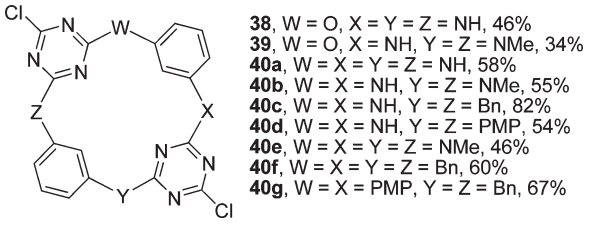


electronic configuration. However, they form various conjugation systems with their adjacent aromatic rings depending on the nature of aromatic rings and of the substituent on the bridging atoms. Importantly, it is the formation of different conjugations that dictate the fine-tuning of macrocyclic conformation and of the cavity size.

Azacalix[4]pyridine **8**,[14] for example, gives a highly symmetric 1,3-alternate conformation with C_{2v} symmetry. Two

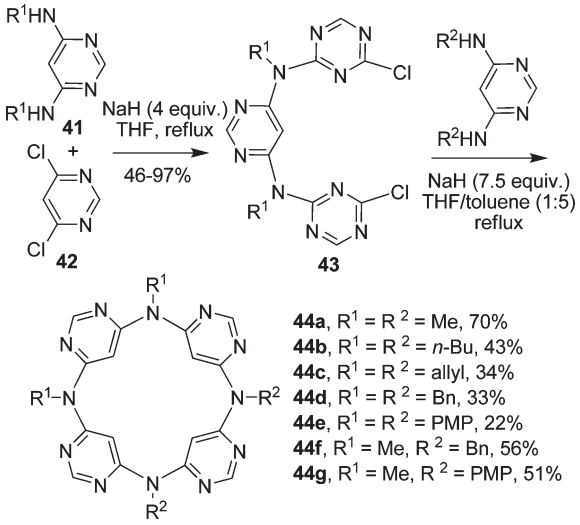
conjugated 2,6-diaminopyridine rings tend to be edge-to-edge orientated with upper rim distance of 9.063 Å, while two isolated pyridine rings are face-to-face eclipsed with the upper rim distance of 3.422 Å. The cavity of azacalix[4]pyridine results from a cyclic array of two pieces of larger and of smaller planar segments in a 1,3-alternate fashion (Figure 1). In the case of $(NH)_m(NMe)_{4-m}$-bridged calix[4]pyridines **20**–**24**, interplay between bridging units and pyridine rings results in varied conjugated fragments, affording twisted 1,3-alternate conformations of varied cavity size in the solid state.[17]

Upon treatment with acids, azacalix[4]pyridine **8** is mono-, di-, and triprotonated to form complexes with DMF, ClO_4^-, and $HOOCCO_2^-$ species[14] (Figure 2). It is noteworthy that the macrocycle adopts a distorted 1,3-alternate conformation with approximate S_4 symmetry. The cavity size, which is defined by the distance between two upper-rim carbon atoms of pyridine rings, varies greatly from 7.345 to 8.213 Å depending on the guest species included. From the supramolecular chemistry viewpoint, it is the guest species that induces the change of host molecular structure. Nevertheless, it is because of the intrinsic nature of the nitrogen atom to form different hybrid states and various degrees of conjugation with its neighboring aromatic rings that azacalix[4]pyridine self-regulates its conformation and fine-tunes its cavity to achieve the strongest interactions with guest species.[14]

All heteracalix[2]arene[2]triazines **34**–**40** give 1,3-alternate conformations in the crystalline state.[10,30] Two triazine rings, each in conjugation with two bridging heteroatoms, have a propensity to orientate in an edge-to-edge manner, while two isolated benzene rings tend to be face-to-face parallel. Controlled by the combination of heteroatoms and the substitutions on the bridging nitrogen atoms, the macrocyclic cavity size, the distance between upper rim carbons of two benzene rings ($d_{\text{upper rim (B)}}$), varies dramatically from 7.98 to 3.51 Å (Figure 3). For example, cavity size increases from tetraoxa- (**34**, 5.01 Å) to azatrioxa- (**35**, 6.53 Å) and diazadioxa- (**36**, 7.98 Å) bridged calix[2]arene[2]triazines. In the cases of tetraazacalix[2]arene[2]triazines **40a**–**40g**, introduction of more and larger substituents leads to gradual decreases of cavity size from 7.39 (**40a**) to 4.03 Å (**40g**),[10,30] with an extreme example of tetra(*p*-methoxyphenylaza)-linked calix[2]arene[2]triazine that gives the shortest upper rim distance as 3.51 Å.[30]

The dominant occurrence of 1,3-alternate conformation of heteracalix[4]aromatics is ascribed to the lack of an

SCHEME 7



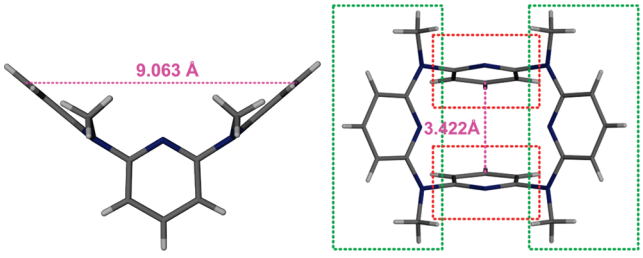


FIGURE 1

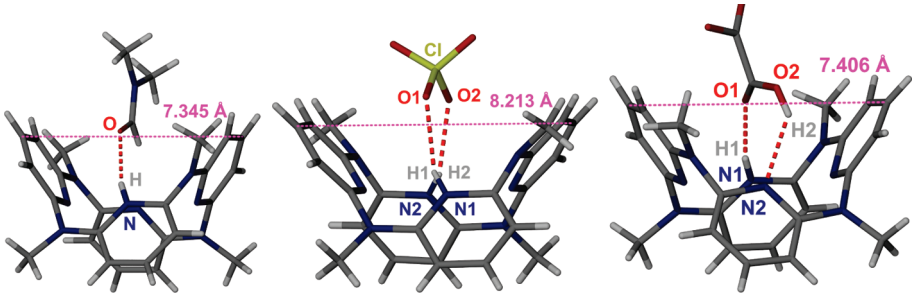


FIGURE 2

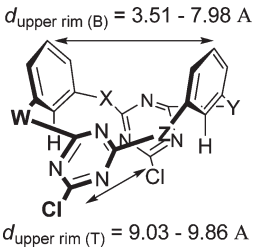


FIGURE 3

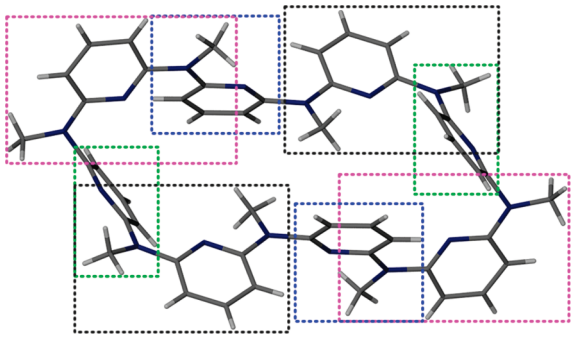
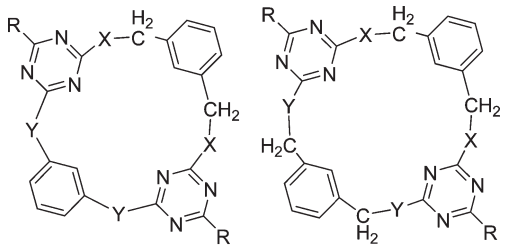


FIGURE 4

SCHEME 8



intramolecular circular hydrogen-bonding network that exists in conventional calix[4]arenes.[3] The outcomes of our recent study[31] on homo heteracalix[2]arene[2]triazines **45** and **46** (Scheme 8) have suggested that the preference of heteracalix[4]aromatics to forming 1,3-alternate confirmation is most probably due to the dipole−dipole interactions among aromatic rings. The presence of methylene segments in homo heteracalix[2]arene[2]triazines **45** and **46** reduces the dipole−dipole repulsion between the neighboring benzene and triazine rings, leading therefore to different 1,2-alternate and partial cone structures other than 1,3-alternate conformers.

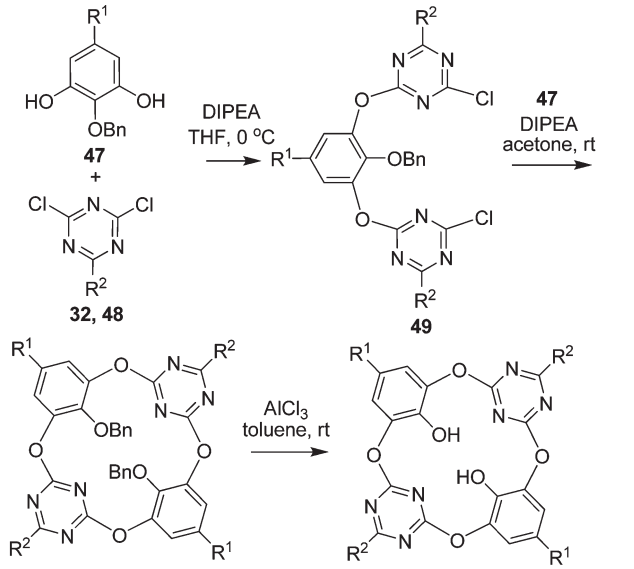
The X-ray crystal structures of larger homologous heteracalixaromatics such as azacalix[*n*]pyridines (*n* = 5−8, 10),[14−16,32] azacalix[4]arene[4]pyridine,[9] oxacalix[3]arene[3]triazine,[33] and dioxatriazacalix[2]arene[3]pyridine[34] have been obtained. Interestingly, heteracalix[8]-[17] and heteracalix[10]pyridines[18] give the parallelogram structure with aromatic rings being alternately aligned, while azacalix[4]arene[4]pyridine adopts a 1,2,3-partial cone.[9] Heteracalixaromatics bearing odd numbers of aromatic rings, on the other hand, give heavily distorted alternate conformations in the solid state.[15,16,34] The capability of bridging nitrogen in forming diverse conjugations with aromatic rings is explicitly illustrated in the X-ray structure of azacalix[8]pyridine (Figure 4), which shows at least four different conjugation systems of the nitrogen atoms with their connecting pyridine rings.[14]

In solution, heteracalixaromatics may not retain conformational structures observed in the solid state. As indicated clearly by the ^{1}H and ^{13}C NMR spectra, which show, respectively, one set of proton and carbon signals, heteracalixaromatics are very fluxional and the interconversions among different conformations take place rapidly relative to the NMR time scale. In addition to the fluxional conformers, however, heteracalix[2]arene[2]triazines bearing large substituents on the rims and bridging positions may adopt stable symmetric 1,3-alternate conformation.[30,33,35−38] This is not only supported, though nonexclusively, by the spectroscopic data, it is evidenced indirectly by the reaction of heteracalix[2]arene[2]triazines in the construction of high-level molecular architectures[36−38] (*vide infra*). The shape-persistence of the substituted 1,3-alternate heteracalix[2]arene[2]triazines is most likely the result of the steric effect imposed by the large substituents, which prohibits the free rotation of aromatic rings around the *meta*−*meta* axes or through the annulus.

4. Functionalization of Heteracalixaromatics

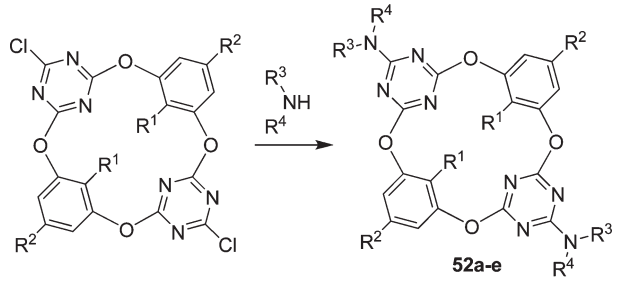
The fragment coupling approach provides a straightforward method for the preparation of functionalized heteracalixaromatics when appropriate functionalized fragments are utilized. As aforementioned in the synthesis of NH-bridged calix[4]pyridines, use of N-allylated 2,6-diaminopyridine reactants gives rise to azacalix[4]pyridines **15**−**19** functionalized with allyl groups on the bridging positions.[17] Shown in Scheme 9 is the synthesis of heteracalixaromatics with functional groups on the upper and lower rims employing pyrogallol and gallic acid derivatives **47** as building units. $AlCl_3$-mediated O-deprotection in toluene produces effectively the dihydroxylated oxacalix[2]arene[2]triazines **51**. O-Debenzylation reaction of **50a** (R^2 = Cl) results in the spontaneous arylation of triazine with toluene.[33]

SCHEME 9



50a, $R^1 = CO_2Me$, R^2 = Cl, 43%
50b, $R^1 = CO_2Me$, R^2 = *p*-tolyl, 92%
50c, $R^1 = R^2$ = *t*-Bu, 82%
51a, $R^1 = CO_2Me$, R^2 = *p*-tolyl, 75%
51b, $R^1 = R^2$ = *t*-Bu, 91%

SCHEME 10

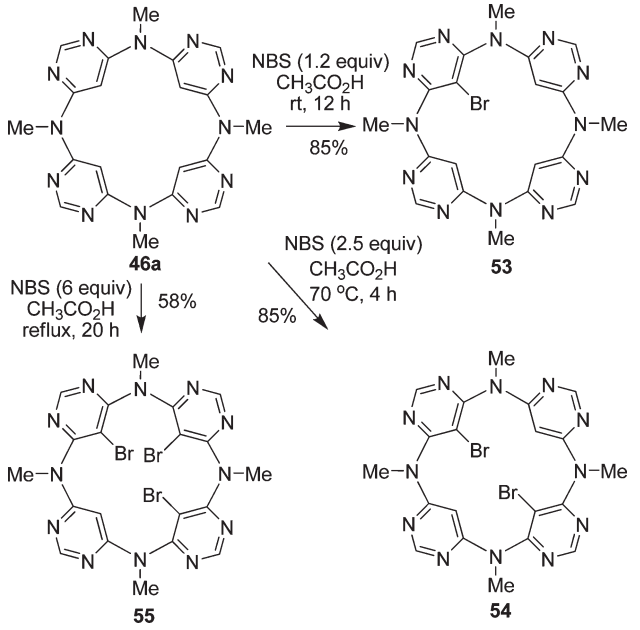


52a, $R^1 = R^2$ = H, $R^3 = R^4 = CH_2CH_2OH$, 82%
52b, $R^1 = R^2$ = H, $R^3 = R^4$ = Pyridin-2-yl, 81%
52c, $R^1 = R^2$ = H, $R^3 = R^4$ = Pyridin-2-ylmethy, 74%
52d, $R^1 = R^2 = R^3$ = H, R^4 = 1-Naphthyl, 74%
52e, R^1 = BnO, $R^2 = CO_2Me$, $R^3 = R^4$ = *n*-Bu, 86%

Postmacrocyclization modifications constitute important methods to obtain functionalized heteracalixaromatics. Taking advantage of the reactivity of chlorotriazine in **34**–**40** toward nucleophiles, we have synthesized a variety of functionalized heteracalix[2]arene[2]triazines. Some examples are shown in Scheme 10.[10,16,39]

To generate halogenated heteracalixaromatics, valuable precursors for further functionalizations, we have studied the bromination reaction of azacalixpyrimidines. Because of the electronic effect of the bridging nitrogen, bromination reaction occurs exclusively on the lower rim positions. Pleasingly, selective mono-, di-, and tribromination reactions were achieved conveniently by simply varying the ratio of

SCHEME 11



azacalix[4]pyrimidine over brominating reagent NBS and controlling the reaction temperature[28] (Scheme 11). Intriguingly, when azacalix[2]arene[2]pyridine **30** was treated with $CuBr_2$ in THF at ambient temperature, bromination reaction occurred specifically on the pyridine ring rather than the benzene ring. The preference of electrophilic reaction on the pyridine moiety was further exemplified by the deuteration reaction of **30** with CF_3CO_2D, which produced **57** as the sole product[18] (Scheme 12). The higher reactivity of the pyridine ring in comparison to the benzene ring is the result of the formation of conjugation of bridging nitrogen atoms with pyridine ring rather than the benzene ring.[14,18]

To install the functionality regiospecifically on the lower rim of azacalixaromatics, we[40] explored the aryl C–H activation of azacalix[1]arene[3]pyridine **58** (Scheme 13). Under aerobic conditions, reaction of **58** with $Cu(ClO_4)_2 \cdot 6H_2O$ (1.5 equiv) proceeds efficiently at room temperature to yield quantitatively a well-characterized Ar–Cu(III) complex **59**. The formation of **59** is most probably derived from the disproportionation of [**58**–$Cu(ClO_4)_2$] complex with free Cu(II). The Cu(I) generated might undergo auto-oxidation with air to regenerate the Cu(II) species under aerobic conditions. Stabilized by the formation of square-planar coordination by the inherent pyridine rings, Ar–Cu(III) intermediate **59** is however very reactive in acetonitrile. Treatment of **59** with tetraethylammonium halides affords halogenated products **60a**–**c** in 90–99% yields, while interaction with sodium thiocyanate, potassium cyanide, and sodium

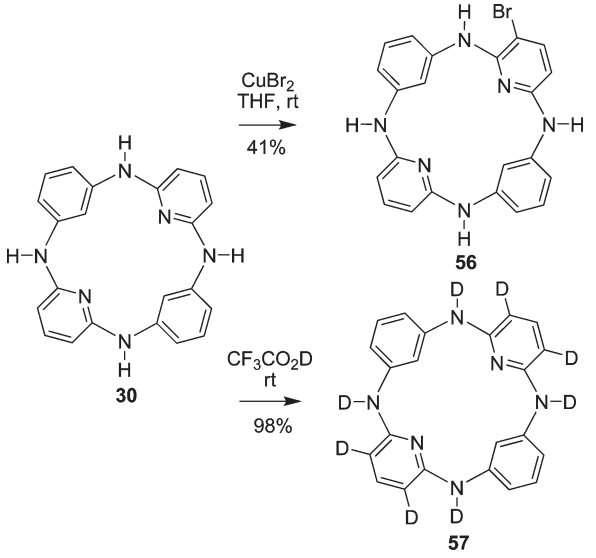
carboxylate allows the facile introduction of SCN (**60d**), CN (**60e**), OCOR (**60f**–**h**) groups, respectively. Saponification of ester **60h** gives hydroxylated azacalix[1]arene[3]pyridine **60i**.

One of the salient advantages of heteracalixaromatics over conventional calixarenes is the convenient and straightforward functionalizations on the bridging positions, because NH bridges provide unique handles for chemical manipulations. Demonstrated in Scheme 14 are the exhaustive allylation and arylation for efficient synthesis of *N*-allyl and *N*-*p*-methoxyphenyl (PMP) substituted azacalixaromatics **61**[18] and **62**.[30]

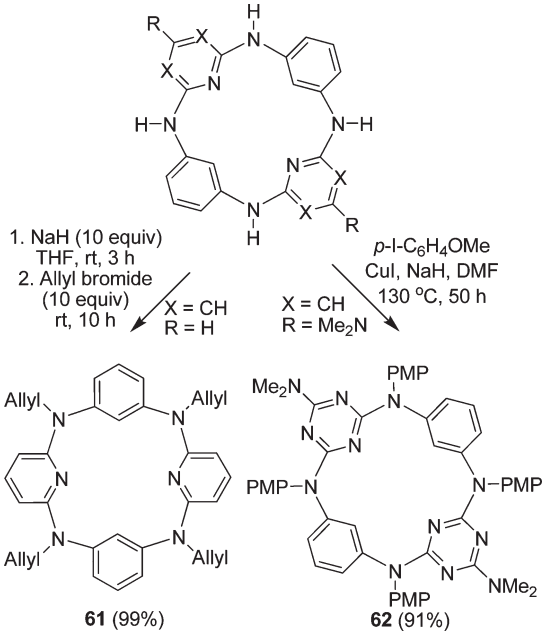
5. Construction of Sophisticated Molecular Architectures

Because of versatile reactivity, heteracalixaromatics can serve as the building blocks in the construction of sophisticated molecular architectures. By means of S_NAr reaction of dichloro-substituted oxacalix[2]arene[2]triazines **63** with diamines derived from oligomeric ethylene glycols, we[36,37] have synthesized calixazacrowns **64** that exist as a pair of *syn*- and *anti*-isomers in solution due to the formation of conjugation between amino groups and triazine rings (Scheme 15). When benzyl 3,5-dihydroxy-

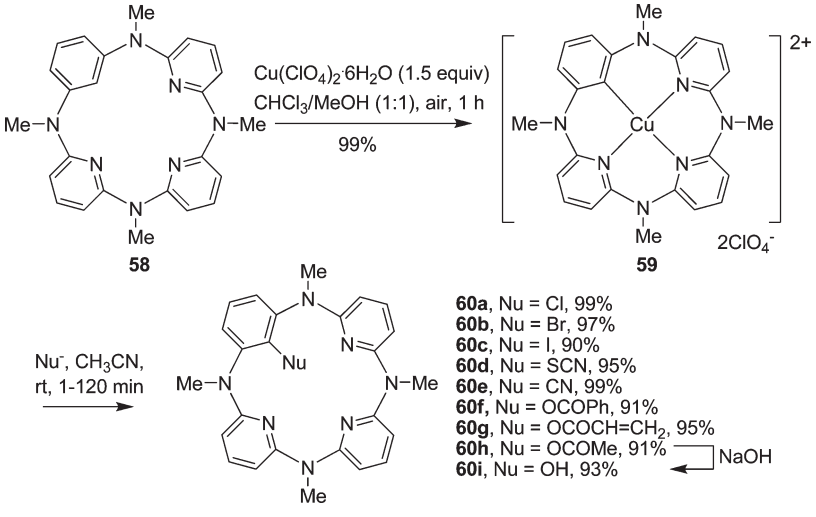
SCHEME 12



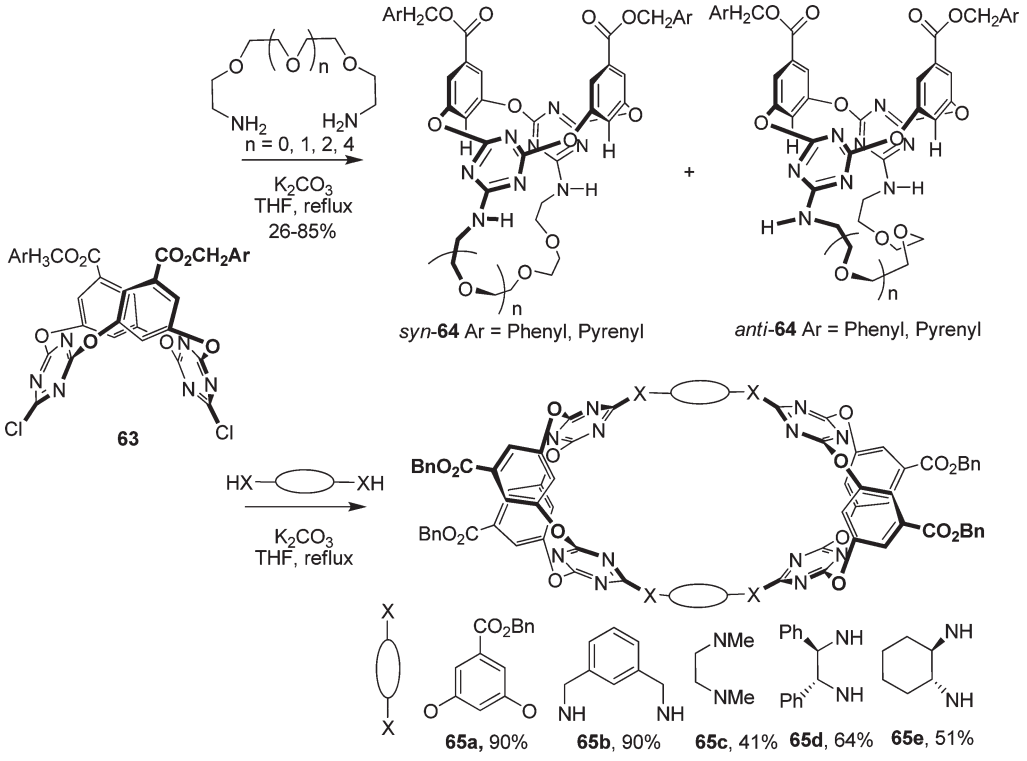
SCHEME 14



SCHEME 13



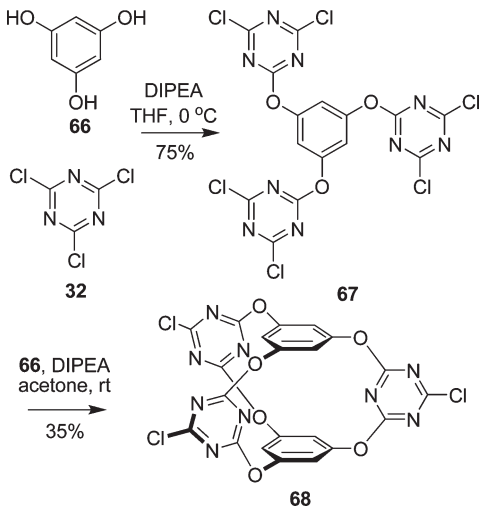
SCHEME 15



benzoate and diamines bearing a short spacer were employed, instead of 1 + 1 reaction between two reactants to give small cage molecules, bis-oxacalix[2]arene[2]triazines **65** of different large cavities were produced in good to excellent yields from a 2 + 2 reaction fashion. Chiral cages **65d** and **65e**[38] were readily constructed from enantiopure 1*R*,2*R*-1,2-diphenylethylenediamine and 1*R*,2*R*-1,2-cyclohexanediamine (Scheme 15).

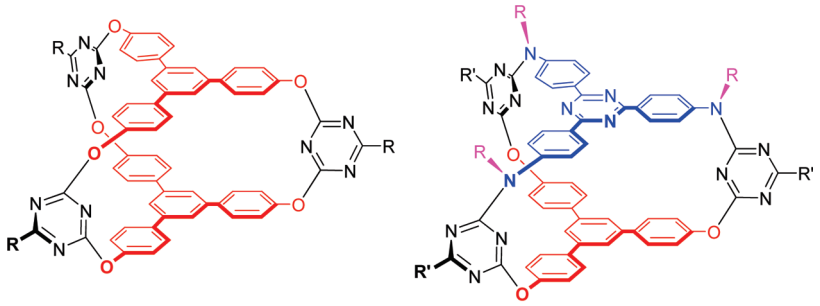
Exclusive formation of bis-oxacalix[2]arene[2]triazine compound **65a** between the reaction of **63** and benzyl 3,5-dihydroxybenzoate implies that oxacalix[2]arene-[2]triazine remains in solution in the shape-persistent 1,3-alternate conformation with two triazine rings being edge-to-edge positioned (*vide supra*). This suggests, on the other hand, that two benzene rings of **63** might be in proximity as observed in the solid state. It led us to attempt the synthesis of oxygen-bridged bicyclocalix[2]arene[2]triazine **68**. As depicted in Scheme 16, the desired molecule **68** was constructed successfully from phloroglucinol **66** and cyanuric chloride via the intermediate **67**. Evidenced by X-ray structure, bicyclooxacalix[2]arene[2]triazine **68** forms a triangular prism cage with D_{3h} symmetry.[41] Following the same strategy, use of 1,3,5-tri(*p*-hydroxyphenyl)-benzene or a combination 2,4,6-tri(*p*-aminophenyl)triazine and 1,3,5-tri(*p*-hydroxyphenyl)benzene gives rise to,

SCHEME 16



respectively, larger triangular prisms **69a** and **70a** of different aromatic interiors.[42] S_NAr reaction of chlorotriazine moieties of **69a** and **70a** with functionalized amines affords prisms **69b**–**e** and **70b**–**c** with functionalities on the peripheral edge positions. Triangular prisms functionalized on the vertex nitrogen positions such as compounds **71a** and **71b** have also been constructed using 2,4,6-tri(*p*-aminophenyl)-triazine and 2,4,6-tri[(*p*-allylamino)phenyl]triazine as one of the building bases[42] (Scheme 17).

SCHEME 17



69a, R = Cl, 38%
69b, R = Me_2N, 79%
69c, R = Et_2N, 76%
69d, R = $N(CH_2CH_2OH)_2$, 61%
69e, R = pyridin-2-yl, 64%

70a, R = *n*-Bu, R' = Cl, 41%
70b, R = *n*-Bu, R' = $N(CH_2CH_2OH)_2$, 65%
70c, R = *n*-Bu, R' = pyridin-2-ylmethyl, 70%
71a, R = H, R' = *n*-BuO, 36%
71b, R = allyl, R' = *n*-BuO, 34%

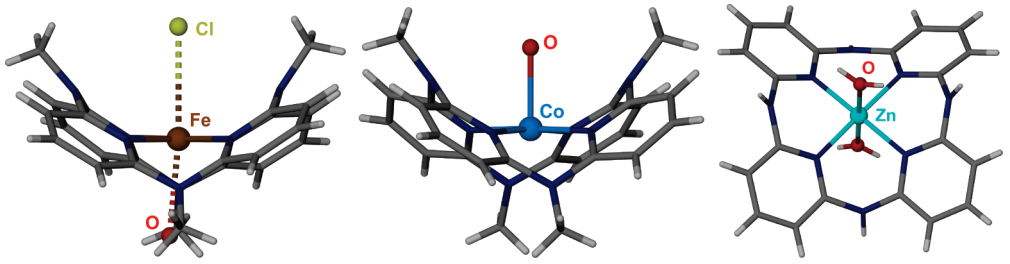


FIGURE 5

6. Molecular Recognition and Assembly

To exploit applications of heteracalixaromatics in supramolecular chemistry, our endeavors in the past years have concentrated on their molecular recognition properties. We have demonstrated that heteracalixaromatics are a class of powerful and versatile host molecules in complexing neutral organic molecules and charged guest species.

6.1. Complexation with Metal Cations. Being macrocycles featuring multiple binding sites, azacalix[4]pyridines act expectedly as hosts to recognize metal ions. While exhibiting no affinity toward alkali and alkaline earth metal cations, azacalix[4]pyridine **8** forms 1:1 complexes selectively with transition and heavy metal ions including Cr^{3+}, Fe^{2+}, Co^{2+}, Cu^{2+}, Zn^{2+}, Ag^{+}, Hg^{2+}, Pb^{2+}, and Pd^{2+} in a mixture of water and acetonitrile, giving binding constants (log $K_{1:1}$) ranging from 2.7 to 8.2.[43] Interestingly, the interaction of azacalix[4]pyridine **8** with Zn^{2+} leads to about 3-fold enhancement of fluorescence intensity of the host.[44] Further screening for Zn^{2+}-sensing molecules has led to the discovery of $(NH)_2(NMe)_2$-brdiged azacalix[4]pyridine **20**, which shows more than 13-fold enhancement of fluorescence intensity when it forms 1:1 complex with Zn^{2+} ion.[17] Remarkably, the presence of other metal ions does not interfere with the complexation with Zn^{2+}, rendering macrocyclic host **20** a candidate for the development of Zn^{2+}-specific fluorescence sensors. It is important to note that, as revealed by X-ray crystal structures (Figure 5), all azacalix[4]pyridines change their 1,3-alternate conformation drastically into the saddle conformation with four pyridine nitrogen atoms being organized into a square planar tetradentate ligand to complex metal ions.[17,43] In contrast to azacalix[4]pyridines that have convergent binding sites on the smaller rim, azacalix[4]pyrimidines contain multiple divergent binding sites on the larger rim. The coordination self-assembly of azacalix[4]pyrimidine **44a** with cubane-like copper halides (Cu_4X_4), for example, produces coordination networks of different topologies.[45]

6.2. Inclusion of Neutral Organic Molecules. Azacalix[4]pyridine **8** also behaves as a versatile hydrogen bond receptor to recognize a number of alcohols and aliphatic and aromatic diols.[46] Interestingly, depending on the structure of guest species, host–guest complexes of different stoichiometries were obtained. Interaction with ethanol, ethylene glycol, 1,3-dihydroxypropane, and resorcinol gives 1:1 inclusion complexes in the solid state. However, host–guest interaction with catechol and hydroquinone leads, respectively, to 1:2 and 2:1 complexes. As shown by the X-ray crystal structures, complexes are stabilized mainly by the

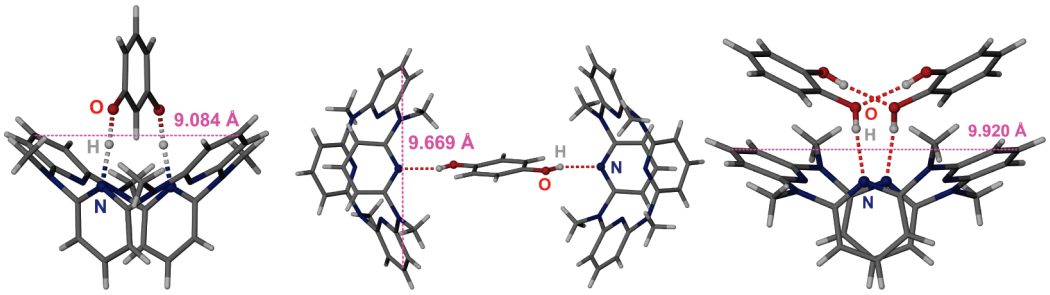


FIGURE 6

formation of intermolecular hydrogen bonds, in addition to weak C−H/π and π/π interactions between host and guest. Directionality of hydrogen bonding dictates the formation of sandwich-type (Figure 6a), molecular capsule-like (Figure 6b), and butterfly-layered (Figure 6c) complexes. It is noteworthy that although azacalix[4]pyridine adopts a similar 1,3-alternate conformation, the bond lengths and bond angles of bridging nitrogen atoms vary slightly to give different fine-tuned cavities in which upper rim distances range from 9.084 to 9.920 Å (Figure 6). By means of ^{1}H NMR titration, we observed that azacalix[4]pyridine displays high selectivity in the recognition of alcohols and diols in solution. The association constant for the azacalix[4]pyridine−resorcinol complex is 6000 M^{-1}, whereas the macrocyclic host associates weakly with all other guest species investigated with association constants ($K_{a(1:1)}$) smaller than 270 M^{-1}. The NOESY spectroscopy suggests that the structure of azacalix[4]pyridine−resorcinol complex at 198 K in solution is similar to that in the crystalline state. Based on variable-temperature ^{1}H NMR spectroscopic analysis, the strong binding of azacalix[4]pyridine toward resorcinol is both enthalpy and, particularly, entropy favored. The high selectivity has been applied to differentiate resorcinol from other diols easily using ^{1}H NMR spectroscopy.[46]

Bearing two hydroxyl groups in a V-shaped cleft, oxacalix[2]arene[2]triazine **50c** acts as a hydrogen bond donor to interact with 2,2′-dipyridine, 4,4′-bipyrdine, and 1,10-phenanthroline.[33] Evidenced by the formation of intermolecular hydrogen bonds on the basis of ^{1}H NMR titration study, macrocycle **51b** complexes with each guest in a 1:1 manner in solution, but their association constants are small, ranging from 37.7 to 213 M^{-1}. Surprisingly, host−guest complexes with a 2:2 stiochiometry were observed in all cases in the solid state. As illustrated in Figure 7, two host molecules, which adopt 1,3-alternate conformation, are aligned head-to-head to form a giant cavity in which

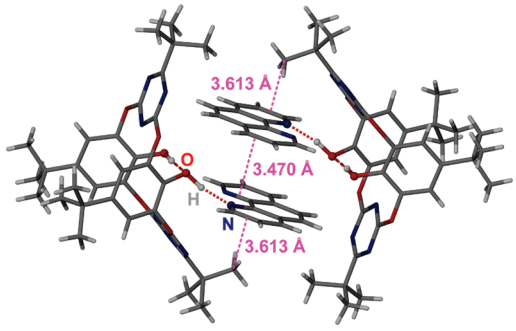


FIGURE 7

two guest molecules are included mainly through intermolecular hydrogen bond interactions. Other weak noncovalent bond interactions as such CH/π, π/π, and lone-pair-electron/π interactions may also contribute to the stabilization of host−guest complexes.[33]

Observation of a giant oval-shaped cavity of azacalix[4]arene[4]pyridine **7** led us to exploit its application in supramolecular fullerene chemistry. Astonishingly, interaction of C_{60} with azacalix[4]arene[4]pyridine **7** resulted in a color change of C_{60} solution in toluene from characteristic red-purple to light brown. Fluorescence titration study gave a binding constant of 70680 ± 2060 M^{-1} for the 1:1 complex between azacalix[4]arene[4]pyridine and C_{60} in toluene.[9] Our follow-up studies[14−16] have shown that azacalix[*n*]pyridines bearing five or more aromatic rings are powerful macrocyclic receptors to form 1:1 complex with fullerenes C_{60} and C_{70} in toluene. The binding constants are in the range of 2.60×10^4 to 7.1×10^4 M^{-1} and 6.24×10^4 to 1.37×10^5 M^{-1}, respectively. To the best of our knowledge, they represent the strongest monomacrocyclic hosts in complexation with C_{60} and C_{70}. As indicated by the binding constants, azacalixpyridine macrocycles, in general, interact more strongly with C_{70} than with C_{60}, albeit the selectivity is not high.[9,14−16] To gain insight into the mechanism of interaction, we have succeeded, after spending enormous

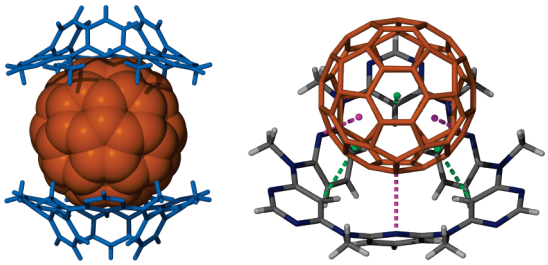


FIGURE 8

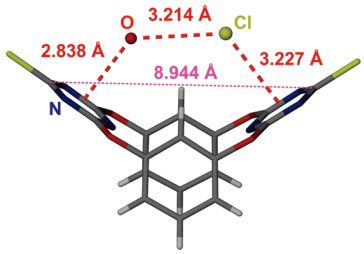
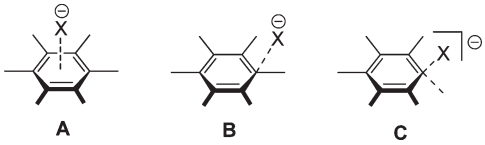


FIGURE 9

SCHEME 18



effort, in obtaining the X-ray single-crystal structure of C_{60}–azacalix[3]pyridine[3]pyrimidine complex very recently.[47] In the solid state, C_{60} is encapsulated by two interdigitated 1,3,5-alternate azacalix[3]pyridine[3]pyrimidine macrocycles. As indicated by the distances between carbon atom of pyrimidine at lower-rim position and the plain of and the centroid of the six-membered ring of C_{60}, and the distance of pyridine nitrogen atom to the centroid of the five-membered ring of C_{60}, which are shorter than the sum of van der Waals radius, there are strong and multiple π/π interactions between azacalix[3]pyridine[3]pyrimidine and C_{60} (Figure 8). Moreover, as evidenced by the distance of methyl group on the bridging nitrogen to C_{60}, six methyl groups, which constitute a rim of a concave cavity, form weak C–H/π interactions with C_{60}. Apparently, the multiple noncovalent interactions between sterically fitted concave and convex π surfaces provide the driving force for the formation of a complex between heteracalixaromatics and fullerenes. It should be emphasized that the electron-donating effect of bridging nitrogen atoms increases the electron density of aromatic rings, which enhances their affinity to π-electron-deficient fullerenes.

6.3. Interactions with Anion Species. Intrigued by the theoretical proposals that anions and electron-deficient aromatic rings attract mutually by the formation of anion–π (A), weak σ (B), and strong σ (C) interaction motifs[48] (Scheme 18), we[49] have conducted a study on the interactions of oxacalix[2]arene[2]triazines with halides because the charge-neutral macrocycles provide a unique electron-deficient cleft formed by two triazine rings. As evidenced by spectrophotometric titration experiments, dichloro-substituted oxacalix[2]arene[2]triazine **34** shows high affinity toward fluoride and chloride in acetonitrile, giving binding constants ($K_{1:1}$) over 4000 M^{-1}. When chloro substituents were reduced, the resulting host associates weakly with fluoride with $K_{1:1}$ of 68 M^{-1}. No interaction was found between halides and dimethylamino-substituted oxacalix[2]arene[2]triazine. The substituent effect is in agreement with DFT calculations, which indicate clearly an increase of electron density on triazine ring when an electron-withdrawing chloro substituent is replaced by an electron-donating dimethylamino group. To our delight, complexes between **34** and tetraethylammonium chloride and bromide gave single crystals, and X-ray structures provided solid evidence for chloride–π and bromide–π interactions. In the case of host–chloride complex (Figure 9), for example, the distances of chloride to the plane and to the centriod of one of the triazine rings are nearly the same, being 3.218–3.247 Å and 3.227–3.249 Å, respectively, shorter than the sums of van der Waals radii. No hydrogen bonding of halide with arene C–H halide was observed. Interestingly, both complexes include one water molecule in the cavity. The water molecule, which is hydrogen bonded with halide, forms a lone-pair-electron/π interaction with the other triazine ring because the distance of water oxygen to the triazine centroid is 2.833–2.849 Å. It is also worth noting that the upper rim distance between two triazine rings in the host–halide–water ternary complexes is approximately 8.9 Å, while the corresponding distance for the parent macrocycle is about 9.5 Å, indicative of the self-fine-tuning character of oxacalix[2]arene[2]triazine.

To probe other noncovalent interactions between the halide and aromatic system, we have devised a conformationally rigid bicyclooxacalix[2]arene[2]triazine cage molecule **68** (Scheme 16).[41] The isothermal titration calorimetry measurements indicate weak 1:1 association between cage and fluoride, chloride, and bromide in acetonitrile, with the association constant being 361, 146, and 95 M^{-1}, respectively. Complexation of **68** with tetraethylammonium

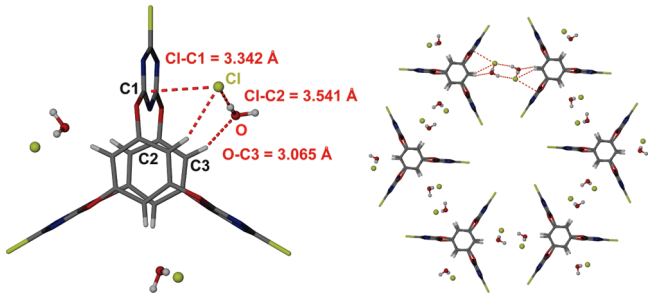


FIGURE 10

chloride forms a weak σ-interaction motif between halide and the triazine ring in the solid state. The X-ray crystal structure in Figure 10 shows that in each V-shaped electron-deficient cleft of bicyclooxacalix[2]arene[2]triazine was included a pair of hydrogen-bonded chloride and water. Being completely different from the ternary complex shown in Figure 9, however, chloride is located just above the carbon atom of the triazine ring with a chloride−carbon distance of 3.342 Å. The chloride also forms a hydrogen bond with the arene C−H of one of the benzene moieties, giving a C_{Ar}−H···Cl^- distance of 3.541 Å. The included water molecule, on the other hand, is also hydrogen bonded to C−H of the other benzene ring. Directed by the hydrogen bonding of paired chloride and water in each cleft with other pairs of chloride ions and water molecules included in the neighboring hosts, an infinite two-dimensional honeycomb-like assembly is yielded (Figure 10).

7. Conclusion and Perspective

In this Account, I have focused on the fragment coupling approach for the synthesis of diverse heteroatom-bridged calixaromatics and their selective functionalizations on rims and bridging positions. The structures of heteracalixaromatics have been discussed with the emphasis on the effect of the bridging heteroatoms and the substituents on the fine-tuning of conformations and cavities. I have also demonstrated preliminary applications of heteracalixaromatics in molecular recognition toward neutral organic molecules and charged species through various noncovalent bond interactions.

The easy accessibility, rich molecular diversity, unique conformation, and cavity tunability would render heteracalixaromatics a new generation of invaluable macrocycles in the study of supramolecular chemistry. We can expect, for example, that the fabricated heteracalixaromatics with defined conformation and cavity would provide powerful tools to probe the essence of noncovalent bond interactions, leading to the development of new molecular sensing and imaging systems. Multicomponent molecular self-assembly of heteracalixaromatics as functional modules with metals, metal clusters, or charge-neutral species would result in multidimensional solid and soft materials that may find wide applications in gas storage and in supramolecular catalysis. The exploration of heteracalixaromatics in molecular machines and devices can also be anticipated in future. Last but not least, construction of enantiopure inherently chiral heteracalixaromatics and their applications in chiral recognition and in asymmetric catalysis is an important and interesting direction that will surely attract great attention.

BIOGRAPHICAL INFORMATION

Professor Mei-Xiang Wang is a Professor of Organic Chemistry at Department of Chemistry, Tsinghua University, in Beijing. He worked at the Institute of Chemistry, Chinese Academy of Sciences, before 2009. His research interests are supramolecular chemistry of novel and functional macrocyclic molecules, enantioselective biocatalysis and biotransformations, and organic reactions and their applications in the synthesis of natural and bioactive products.

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FOOTNOTES

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