

## Review Article

# Lower-Rim Substituted Calixarenes and Their Applications

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This review discusses in detail “calixarenes” since their discovery as by-products of the phenol formaldehyde bakelites till the present scenario wherein calixarene has assumed a new dimension in the field of supramolecular chemistry. Extensive literature exists for calixarenes; but herein we have tried to concentrate on the different lower-rim modified calixarenes with their potential applications. An attempt has also been made to critically evaluate the synthesis procedures for different lower-rim substituted calixarenes.

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## 1. INTRODUCTION

Molecules react chemically in specific and selective ways to form the basis of the living world. Taking cue from this, chemists have shifted their focus from molecular chemistry (chemistry of covalent bonds) to supramolecular chemistry (chemistry of noncovalent interactions) with the supramolecular architecture being constructed either through self-assembly of subunits or by selective host-guest interactions. In self-assembly, particles assemble into atoms, atoms assemble into molecules, and these molecules react with one another to reassemble into new molecules. The molecules assemble with themselves and with other molecules via intermolecular noncovalent bonds to form supramolecular arrays or assemblies [1]. The structural integrity of the final architecture is preserved by noncovalent interactions. The most effective example of self-assembly occurring in living systems is virus, the mechanism of which has been studied in detail. Inspired by the nature's ways of constructing and functioning, the synthetic chemists had the most logical choice of creating supramolecular assemblies via self-assembly. Before the accidental discovery of crown ethers [2] by Pedersen, the word supramolecule was not commonly used; but along with cyclodextrins [3] the crown ethers were also included as another example of host-guest interactions. Later came the discovery of calixarenes [4], which became the third generation of supramolecules. All coexist under the title of supramolecules as well as host-guest chemistry.

Since there is no clear demarcation between host-guest and supramolecule, it is indeed not always possible to differentiate the two, however, molecular recognition is a cornerstone of both these facts. Since the attention is on molecules having molecular cavities which will act as building blocks for the compounds to mimic natural molecular recognition processes, calix[*n*]arenes serve as a good example of study in supramolecular chemistry. As already mentioned above, calixarenes are a widely recognized and researched topic in supramolecular chemistry. There were and there are still a good number of research groups whose work has already generated hundreds of original journal articles, extensive literature reviews [5–9] and monographs [10].

### 1.1. Calixarenes: their origin and synthesis

In 1872, Adolf von Baeyer heated aqueous formaldehyde with phenol to give a hard resinous product. Three decades later, in 1905–1909, Leo Baekland devised a process and he marketed the strong resin obtained from phenol-formaldehyde, under the name Bakelite. Alois Zinke, a new entrant in this field explored the different possibilities of reacting various *p*-alkyl phenols with aqueous formaldehyde and sodium hydroxide, and assigned the products of the treatment as cyclic tetrameric structures calling them “mehrkernmethylenephenolverbindungen.” These compounds were classed as [1,*n*]metacyclophanes (where *n* is the number of benzene rings) (Figure 1).

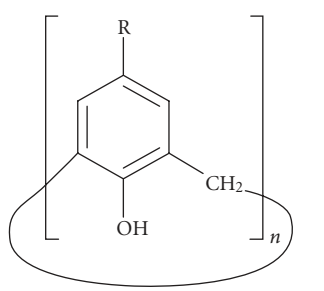


FIGURE 1: [14]metacyclophane or calix[4]arene.



FIGURE 2: Calix crater.

Although worked upon by many, the credit of naming this class goes to C. D. Gutsche who perceives a similarity between the shapes of these cyclic tetramers and a type of Greek vase known as calix crater (Figure 2); they suggested the compound to be called “Calixarenes.”

Calixarenes are a class of cyclooligomers formed after phenol-formaldehyde condensation, with defined upper and lower rims and a central annulus (Figure 3).

Thus originated a category of compounds derived from *p*-tert-butyl phenol and it was designated as *p*-tert-butyl calix[*n*]arene. After Zinke reported that *p*-methyl, *p*-tert-butyl, *p*-amyl, *p*-octyl, *p*-cyclo-hexyl, *p*-benzyl (Figure 4), and *p*-phenyl phenol condense with formaldehyde to yield high melting materials, all of which the group assumed to be cyclic tetramers, it was later extensively characterized by Kammerer and the interpretation was subsequently invalidated.

The same group modified the 10-step procedure of synthesizing calixarene from *p*-cresol of Hayes and Hunter (Figure 5).

Due to the presence of their preformed cavities, the calixarenes are able to act as host molecules. Due to such structural elaboration, the calixarenes lend themselves well to many applications. This “crater” or “basket” plays a very important role in shaping the entire architecture of calixarene for its function in host-guest chemistry, since this theory is highly interdependent on two terms: “shape” and “functionality.” One of the most interesting and fascinating aspects of calixarenes lies in the fact that they can assume different forms due to the flexibility in the rotation of Ar-CH<sub>2</sub>-Ar

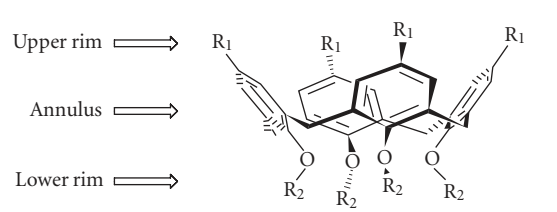


FIGURE 3: Division of calix[4]arene (applicable to all the calixarenes).

bonds, and hence came into existence the “cone,” “partial cone,” “1,2-alternate,” and “1,3-alternate” conformations (Figure 6), which were earlier suggested by Cornforth and later designated by Gutsche [10]. Calix[6]arenes can exist in eight different “up-down” conformations like calix[4]arenes[5], wherein cone conformation is the most stable conformation amongst all the forms of calix[*n*]arenes.

A series of books and reviews have been published which discuss in length the calixarenes and its substituted derivatives being used for the recognition of cation, anion neutral molecules, and organic moieties [1–10]. The literature survey reveals that plenty of work has been done in synthesizing upper-rim modified calixarenes. Comparatively less work has been done at the lower rim of calixarenes. The focus of modifying the calixarenes was much concentrated on the upper rim, due to the easy removal of *t*-butyl group that facilitated different substituted calixarenes [4, 10] with many applications.

## 2. STRUCTURAL MODIFICATIONS

### 2.1. Upper-rim modification of calix[*n*]arenes and their potential applications

Easy removal of the *t*-butyl group facilitates in the formation of diverse ranges of upper-rim functionalized calix[*n*]arenes. One of the most common features observed in almost every research work is the extended application of calixarene for the study of metal calixarene complexation behavior. Different substituents tend to influence the complexation behavior of the entire calixarene architecture. The bithiophene groups substituted at the upper rim gave rise to a host-guest complex of tungsten oxo calixarene complex [11]. Interaction of 4-sulfonic calix[*n*]arenes with niclosamide was investigated, which is a relatively new work in calixarenes-drug chemistry. The 4-sulfonic calix[8]arenes improved the solubility of the niclosamide the most, compared to -[4]arenes and -[6]arenes. The complex formed could be due to hydrogen bonding, hydrophobic bonding, and also possibly due to the electron donor-acceptor interactions [12] (Figure 7).

Another 4-sulfonic calix[*n*]arene interaction with neutral molecule like furosemide has been observed. The molecular size of 4-sulfonic calix[6]arene influenced the increase in the solubility of the furosemide the most with the presence of noncovalent interaction behavior [13]. Naphthalimido group introduced at the upper rim of calixarenes in varying

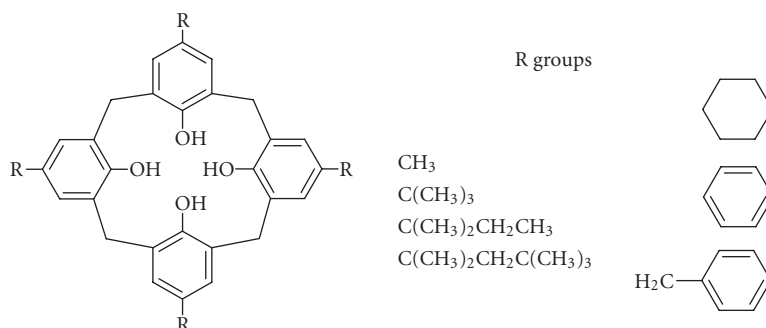


FIGURE 4: Parent calix[4]arene with different alkyl substituents on the upper rim.

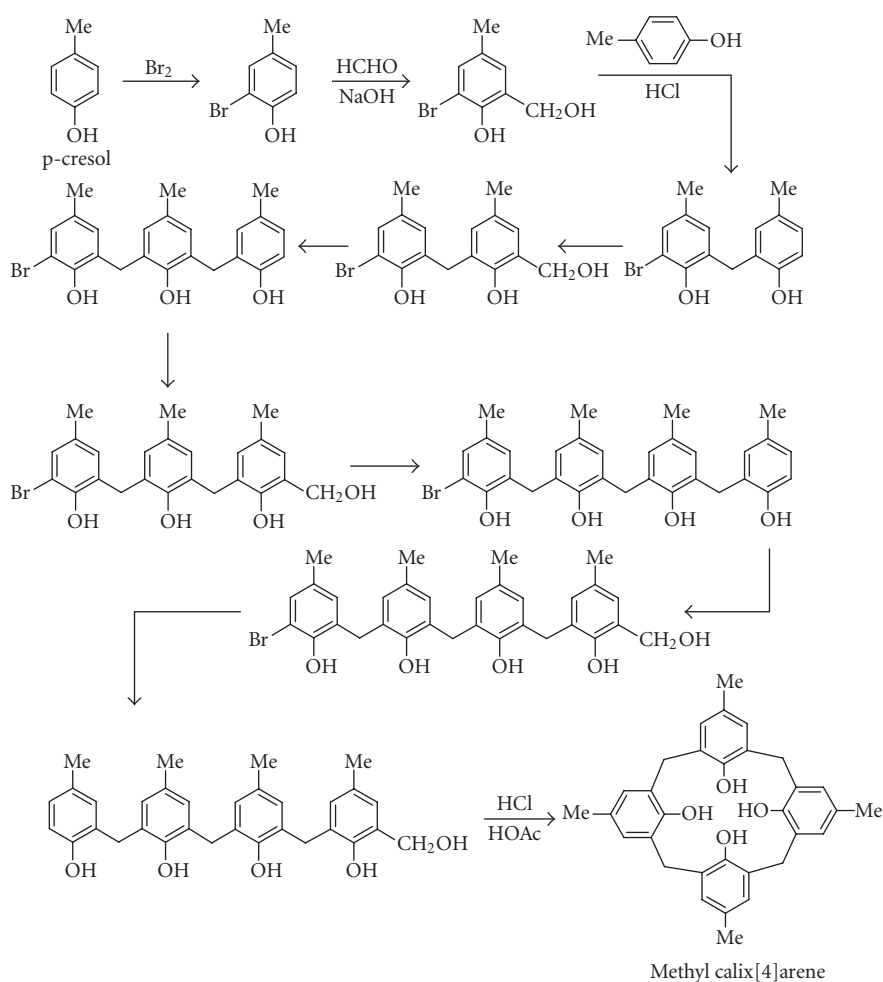


FIGURE 5: Ten-step synthesis of methylcalix[4]arene by Hayes and Hunter.

proportions and a molecular capsule of two calixarenes is formed via perylene-bisimide spacer, the compound is used for UV and fluorescence studies [14]. An Rh–Rh unit formed an intermolecular link between two calix[4]arenes macrocycles and served as a ligand for transition metal catalysts [15] (Figure 8).

Two pyridyl groups were linked via amide linkage at the upper rim and the calix[4]arene bispyridyl amides forming complexes with aromatic and alkyl dicarboxylic acids [16]. Diphenyl phosphino groups were attached at the upper rim of calix[4]arenes forming an organometallic ruthenium complex [17]. 4-hydroxybenzyl groups introduced at

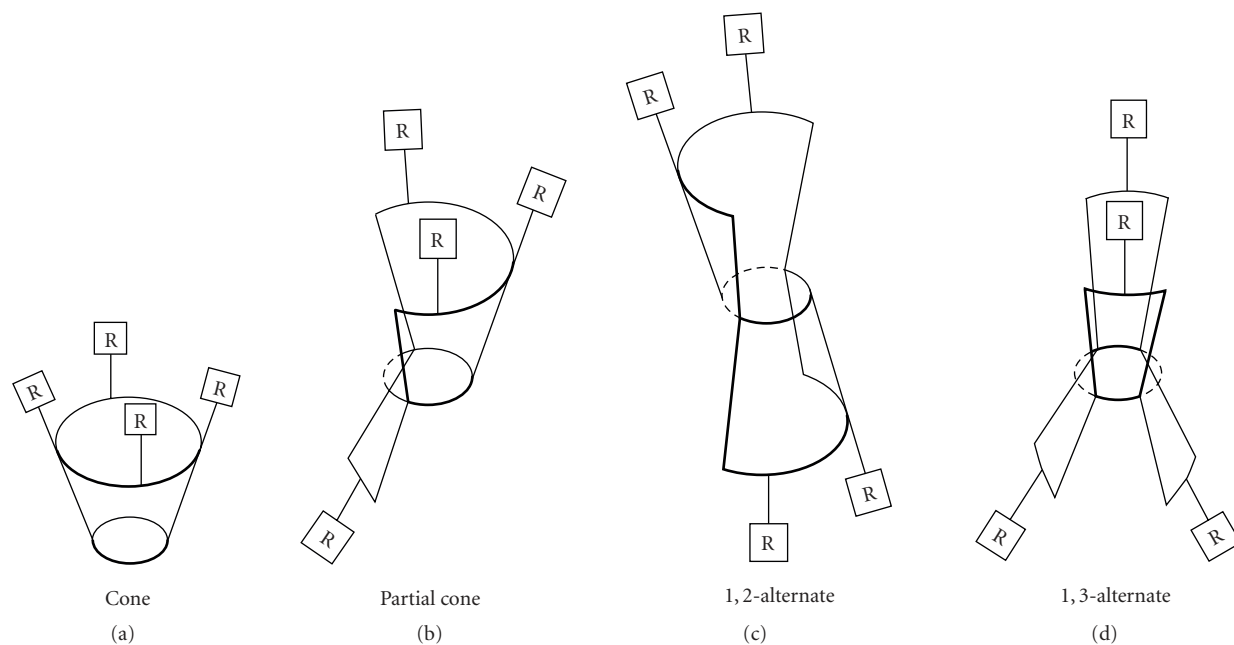


FIGURE 6: Conformers of calix[4]arenes.

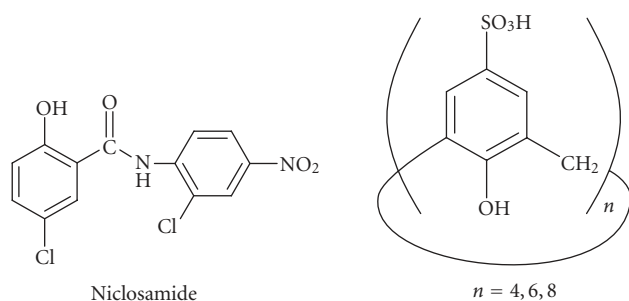
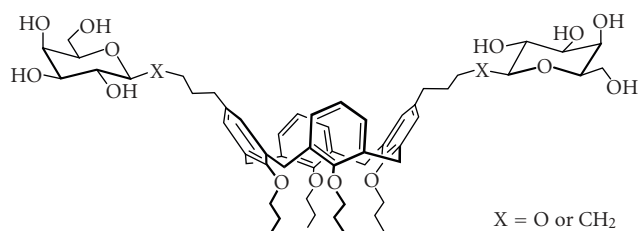
FIGURE 7: Molecular structure of niclosamide and 4-sulphanotocalix[ $n$ ]arenes.

FIGURE 9: Calix[4]arene O- and C-Glycoconjugates.

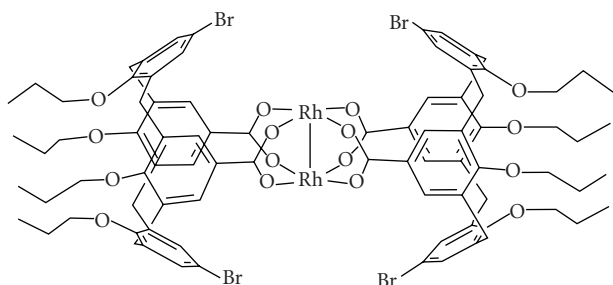


FIGURE 8: Bis(calix[4]arene) dirhodium complex.

the upper rim of the calix[4]arene acted as anion binding groups [18]. Studies have revealed that the complexation of transition metals, like heavy metals, is most certainly favored

by the incorporation of “softer” donor atoms such as nitrogen (as the amine), sulfur or phosphorus. A recent study of thiazolazo groups introduced at all the four positions of calix[4]arene was used to study for its recognition of heavy metal ions [19, 20]. Calix-O-glycosides were synthesized by multiple glycosylations of upper rim of calix[4]arene polyols [21]. These calyx sugars were successfully prepared by stereo selectively substituting at the upper rim with glycol (Figure 9).

Heterocyclmethanamines attached at the upper rim of calix[4]arene (Figure 10) acted as a potential ligand for synthetic modeling of multinuclear metalloenzymes [22].

Semicarbazone was attached at two positions of the upper rim of calix[4]arene and fixed on a resin and studied for its sorption and separation studies of La(III), Ce(III), Th(IV), and U(VI) [23]. Isocyanide groups introduced at the upper rim of calix[4]arene was studied for its complexation with gold [24]. Adamantyl group introduced at the upper rim of calix[4]arenes gave rise to adamantyl calixarene [25].

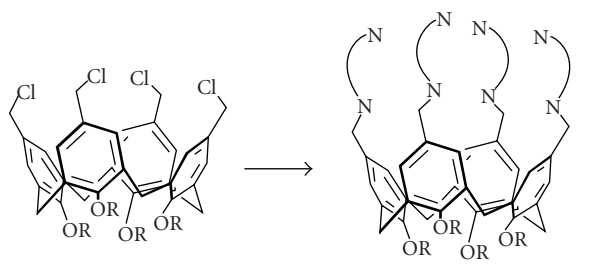


FIGURE 10: Calix[4]arenes linked to multiple bidentate N-donors.

## 2.2. Lower-rim modification of calix[*n*]arenes

The lower rim of calixarenes is less subjected to modification, but the applications of calixarenes substituted at the lower rim are far greater than substituted at the upper rim. Due to the expansion of the cavity after substitution, the lower rim can facilitate the complexation with bigger moieties like heavy metals and also organic molecules. The research put forth over here shows that after the structural modification of calix[*n*]arene, easy encapsulation of drugs, organic molecules as well as heavy metals is observed. Hence the phenolic hydroxyl groups at the lower rim of the calixarenes represent an excellent reactive function for the introduction of groups, which modify the shape, and the complexing properties of these molecules. Preliminary work on the lower rim of calixarenes has been started with alkylation and acylation reactions, which have been reviewed extensively in books [1, 9, 10] and review articles [5–8]. Different lower-rim modifications can be done as follows.

### 2.2.1. Esterification

Esterification reactions on the lower rim of calix[*n*]arene have been the earliest reported work. The acylation and aroylation generally involve all the OH groups, a minor change in reaction conditions can change the outcome of the reaction. An excess or less amount of aroylating/acylating agent, the equivalents of reactants, the base, the solvent all contribute to the conformation of calix[*n*]arene (where  $n = 4/6$ ). The main focus of aroylation has been with benzoyl chloride, *p*-nitro benzoyl chloride and 3,5-di nitro benzoyl chloride; although a number of other reagents are used for the synthesis of calixarene esters. Calixarene glycine ester acetamides have been synthesized from acetyl chlorides and glycine ethyl ester [26]. Esterification has also been reported for calix[8]arene where reaction of *p*-tert-butylcalix[8]arene with di-ethyl dibromomalonate gave the tetra ester derivative with a cone conformation [27]. O-acylated derivative of octa-tert-butyl calix[8]arene was prepared in high yields, by treating with dimethylacetamide in presence of acetic anhydride to give 95.4% octa-O-acetyl-octa(tert-butyl)calix[8]arene [28]. O-substituted calix[8]arenes were also prepared using allyl bromide in presence of potassium hydroxide and polyethylene glycol di-ether in toluene to give its corresponding derivative [29].

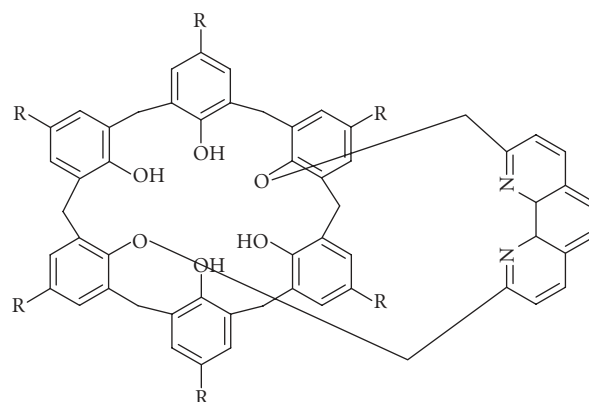


FIGURE 11: Calix[6]arene bridged by a 1,10-phenanthroline.

### 2.2.2. Etherification

Alkylation has been studied in considerable detail in calix[4]arene series, and methods have been devised for preparing the mono, 1,2-di, 1,3-di, tri, and tetra ethers. Monoethers can be prepared in moderate-to-good yields by direct alkylation using an alkylating agent with sodium hydride as the base in toluene solution [30], barium hydroxide as the base in DMF solution [30] or 1.2 equivalent of a weak base and an excess of alkylating agent RX was used, where R includes methyl, ethyl, allyl or ethoxy carbonylmethyl [31]. Monobenylation of 1,3-*p*-dinitrocalix[4]arene, with aluminum trichloride as the catalyst yielded its respective derivatives, the aroylation occurring preferentially on the aryl residues not containing the *p*-nitro groups [32]. It is observed that distal dialkylation leading to 1,3-diethers is generally much more easily achieved than proximal dialkylation leading to 1,2-diethers. Under conditions similar to those leading to monoethers, but with an excess of the alkylating agent, 1,3-diethers were produced, often in very high yields; as, for example, 1,10-phenanthroline was used as a spacer to link intramolecularly and this derivative of -calix[6]arene was found to complex with Cu [33] (Figure 11).

Trimethylation of the parent calix[4]arene was accomplished with dimethylsulphate in DMF in the presence of BaO · Ba(OH)<sub>2</sub> [10]. Higher yields of triether, however, can be obtained when the starting material is already partially alkylated. Another approach to the triether as well as the mono- and diethers involved protection-deprotection sequences [30]. Tetraalkylation of calix[4]arenes is generally carried out with an excess of the alkylating agent in the presence of the strong-base sodium hydride, although in some instances the much weaker-base potassium carbonate is also used.

The first instance of alkylation of the sulfide bridge was achieved by the cycloalkylation of *p*-tert-butylcalix[4]arene and *p*-tert-butylthiacalix[4]arene with various aliphatic glycols. This intrabridging of the calix[4]arene afforded 1,2- and 1,3-bridged calixarenes with O, S-cyclization, which caused the formation of sulfonium phenoxide betaines as shown in [34] (Figure 12).

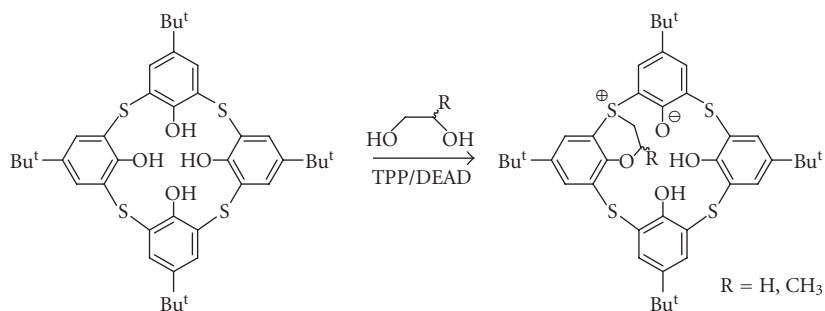


FIGURE 12: Bridged calix[4]arenes.

New borono alkoxy calix[4]arenes were synthesized by alkylation, allylation, and hydroboration and this significantly gave rise to boronoalkoxy calix[4]arenes with 1,3-bridged structure which could coordinate significantly with monosaccharides [35]. *p*-tert-butylcalix[4]arene was reacted with *p*- and *m*-benzyl bromides in the presence of alkali metal carbonates, and silylation of these derivatives gave their respective derivatives [36]. A series of six calix[4]arene derivatives bearing allyl groups and/or benzyl groups have been functionalized at the phenolic oxygen atoms [37]. *p*-tert-butylcalix[4]arene diamides were synthesized in a stepwise method where it was first reacted with ethylbromoacetate, then the hydrolysis was followed by the conversion to acid chloride and amidation [38].

Regioselective synthesis of monoalkylethers of *p*-tert-butyl calix[6]arene in good yield was achieved with a variety of electrophiles using 2,2 equivalent, of potassium carbonate as base in acetonitrile under ultrasonic irradiation at ambient temperature [39]. The first example of selectively functionalized calix[7]arenes has been obtained by weak-base promoted O-alkylation or O-benzylation of *p*-tert-butylcalix[7]arene. Mono, 1,3- and 1,4-disubstituted calix[7]arenes have been obtained in workable yields, while the 1,2,4,6-tetra substitution was achieved with surprisingly high selectivity by 50–88% yield by using potassium carbonate as the base [40] (Figure 13).

The calix[8]arenes present an interesting case where in addition to the fully O-substituted calix[8]arenes, which was obtained by treatment with strong bases and a large excess of derivatizing agent [41], twenty eight partially alkylated calix[8]arenes were also obtained. Neri and coworkers have reported the first success in selective lower-rim substitution and provided details for the preparation of 1,3,4,6-tetra-O-arylmethyl ether of tert-butyl-calix[8]arene obtainable in yields of 20–41% using potassium carbonate as the base [42]. The direct methylation was studied in considerable detail, and procedures were worked out for generating some of the partially methylated compounds in isolable yields [43].

Alkylation with aryl methyl halides containing heteroatoms provided still another route for the introduction of functional groups onto the lower rim [44]. Methylthioethoxy and pyridyl 2 methyl oxy groups were introduced at the lower

rim of calix[4]arene to give rise to bis derivatives of both types 1 and 2 [45] (Figure 14).

Polysiloxane derivatives of calix[4]arene were prepared in presence of chloroplatinic acid [46]. Proximal O,O' capped calix[4]arenes with a disiloxane bridge is synthesized using cesium carbonate as the base in THF, also providing an alternative of desilylation and thereafter alkylation using benzyl bromide with potassium tert-butoxide as a base to give rise to unsymmetrical calix[4]arenes [47]. An ether-amide linkage was synthesized using 2-diethylcarbamoylmethoxyethoxy group at the lower rim of *t*-butyl-calix[4]arene [48] (Figure 15).

Calix[4]arene containing pyridinyl moiety was synthesized forming a tetraether derivative [49]. Selective 2,2'-bipyridine units at 1,3 position and two benzyl units at 2,5 positions at the lower rim of calix[4]arene was prepared [50] as in (Figure 16).

A new family of calix[4]arene was prepared by the incorporation of 2,2'-bithiazole units [51]. Water soluble calix[4]arene incorporating both sulfonate groups at its upper rim and 2,2'-bipyridine groups at its lower rim was also prepared [52]. Etherification in 1,3-alternate conformation was carried out on calix[4]arene using R = 2-MeOC<sub>6</sub>H<sub>4</sub>OCH<sub>2</sub>CH<sub>2</sub> with considerable good yields [53].

Schiff-base derivatives were synthesized using the amino ethoxy derivatives of calix[4]arene with the aromatic aldehydes in high yields [54]. Copolyethers and polyurethanes containing lower- and upper-rim calix[4]arene units in the fixed cone conformation were prepared by reacting the bisphenol with the distal calix[4]arene diols [55].

### 2.2.3. Bridged calix[n]arenes

The first synthesized lower-rim 1,3 ring bridged calixarene is the calix[4]arene crown [56] in early 1980s and now represented by dozens of examples [1, 6, 9]. The parent calixcrowns as well as their dimethyl ethers retain some conformational flexibility and can exist in cone, partial cone, and 1,3-alternate conformations, but ethers with larger groups such as isopropyl and benzyl have fixed cone conformations. There is also the report of the dialkylation of calix[4]arene capped by diamide bridges which gave rise

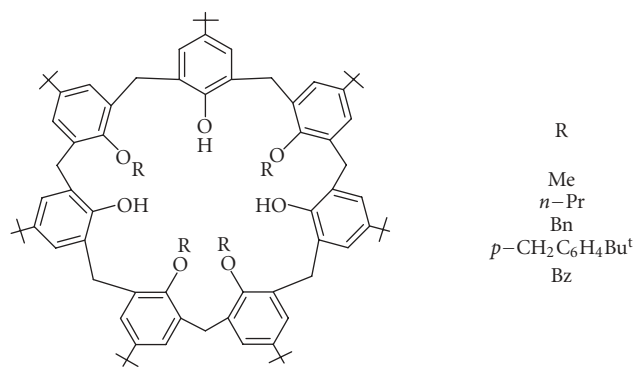


FIGURE 13: Selectively functionalized calix[7]arenes.

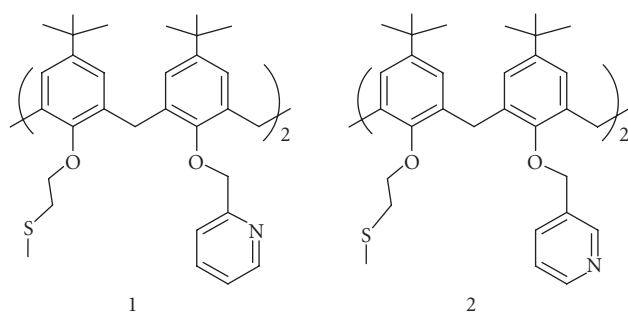
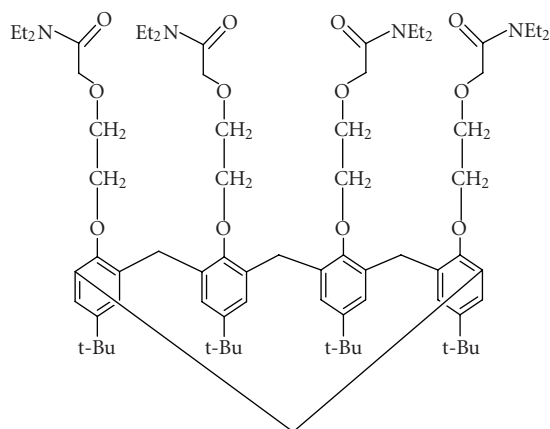


FIGURE 14: Lower-rim calix[4]arene derivatives with mixed pendent arms.

FIGURE 15: 2-diethylcarbamoylmethoxyethoxy substituted *t*-butyl-calix[4]arene.

to fully substituted compounds of 1,3-alternate conformation. The diesters were then cyclized with diamines to afford doubly capped derivatives [57]. Other crown ether-type bridges have been synthesized [54] like the aza crowns [58], the bipyridyls [58], and a variety of aza crown-type structures. Another type of 1,3-bridged calix[4]arene including those with a double bond in the bridge have been prepared by the ruthenium-catalyzed coupling of the 1,3-bisbutenyl ether [59]. Only a few examples of calixcrowns of

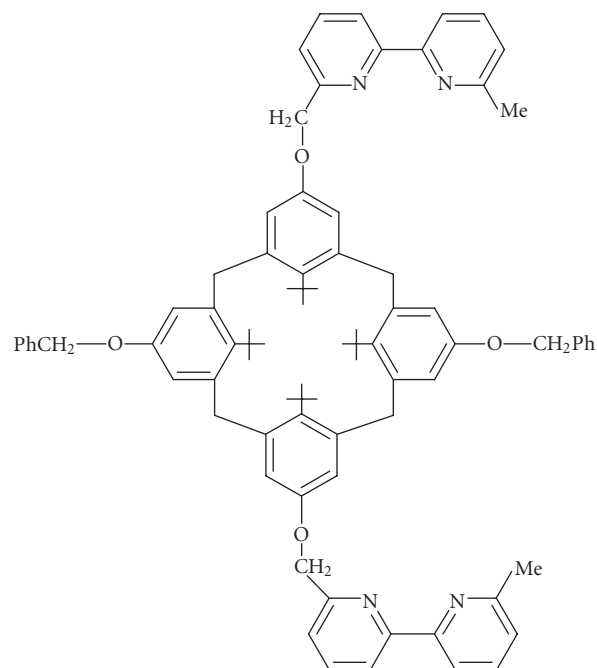


FIGURE 16: Calix[4]arene-based bipyridine podand.

the larger calixarenes have been reported. New borono alkoxy calix[4]arenes were synthesized by alkylation, allylation, hydroboration, and significantly gave rise to boronoalkoxy-calix[4]arenes with 1,3-bridged structure which could coordinate significantly with monosaccharides [60]. Calix[4]arene dibenzo crown ether has been prepared in 1,3-alternate conformation using  $R = C1-C40$  *n*-alkyl chains [61].

Azo benzene derivatized crown *p*-*tert*-butyl calix[4]arene was synthesized in a stepwise method and a 1,3-bridged structure was formed [62]. Crown ethers derived from bicyclocalix[4]arenes in which the opposite phenolic units are connected by a poly oxyethylene bridge at the lower rim and a 2,6-di methylene-4-nitrophenol bridge at the upper rim were reported [63]. These derivatives were found to be potential ligands for the complexation of potassium and cesium. Calix[4]arene derivative containing pyridyl methoxy group at its lower rim has been synthesized using potassium carbonate and sodium iodide [64]. The spanning of *t*-Bu-calix[5]arene has been accomplished with tetraethyleneyethoxy and pentaethylenoxy chains joining the 1,3 rings and with hexaethylenoxy chains joining the 1,3 rings [65]. Tri-O-substituted 1,3-bridged calix[5]arene-crown-6ethers bearing alkyl, arylalkyl, alkoxyalkyl, and alkoxy carbonylmethyl residues were attached at the lower rim of the calix[5]arene with cone conformations although they possess a bulky structure [66] (Figure 17).

The first  $C_{3v}$ -symmetrical calix[6](aza)crown has been obtained in five-step synthesis procedure to give a cone conformation and prevent a ring inversion [67] (Figure 18). Diester intrabridging of *p*-*tert*-butyl calix[8]arene was afforded

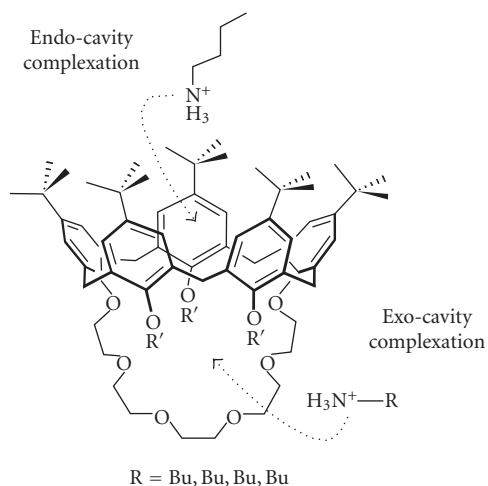


FIGURE 17: 1,3-bridged calix[5]arene crown-6 ethers.

using spanner adipoyl chloride in the presence of sodium hydride as the base and hence yielded singly and doubly intrabridged esters; xantheno calix[8]arenes were also obtained in the course of the rearrangement of the intermediate product [68].

Examples of porphyrins quadruply attached to the lower rim of calixarene have been reported [69]. *p*-tert-butyl calix[4]arenes with diester bridge spanning the 1,3-distal positions on the lower rim were prepared by cyclocondensation of polyethylene glycol bis bromo acetates with tert-butylcalix[4]arene [70] (Figure 19).

One of the few lower-rim-spanned calix[5]arenes that has been reported is the 1,3-di-ester obtained in low yield from *p*-tert-butyl calix[5]arene and *o*-phthaloyl chloride [71] but considerable attention has been devoted to bridge the lower rim of calix[6]arenes with spanners other than polyethyleneoxy. An *m*-xylene bridged calix[6]arene has been synthesized with the other positions being functionalized by methoxy groups [72]. It has been observed that for big spanners, the calix[6]arene is conformationally inflexible and retains its cone structure.

Calix[8]arenes have been quadruply-spanned by a durylene moiety to give a structure that has fixed pseudopleated loop conformation [70], a potential moiety for the complexation of different metal ions [73]. Biscrowned calix[8]arenes were synthesized by alkylating *p*-tert-butylcalix[8]arene or calix-[8]monocrowns with diethylene glycol tosylate [74] (Figure 20) triethylene glycol ditosylate, in the presence of various bases where 22 possible isomers were isolated in varying yields.

Bis-calixarenes connected by four tetraalkyltetra(tosyl-oxyethoxy) groups have been reported called as calixtubes, in high yields in 71% yield. These molecules proved highly selective for complexation of potassium over other I-group cations and barium [75] (Figure 21). Calix[4]crown diacylamides with two acetaminoanthraquinone units at the lower rim have been reported [76].

### 3. APPLICATIONS

The spurt in the increase of literature regarding calixarenes in the last 25 years can be ascribed to the growing interest in introducing different functional groups via different synthetic procedures. But also the major factor that has contributed for the proliferation of these research papers is the tailor-made structure of calixarenes for its use as complexing agents, for it is this possibility and its potential that has brought for calixarenes this recognition that they enjoy today. The use of these modified calixarenes as sensors for metal ion, organic/neutral molecules, and drugs recognition has brought calixarenes to limelight. They have become a wonder molecule in the hands of a chemist. This wonder molecule has its roots in host-guest chemistry.

During the molecular evolution of biological system, the highly selective complexation process between the host and the guest must have played a central role; this attribute of biological life was mimicked in synthetic chemistry which later came to be known as the host-guest chemistry. A molecular complex is composed of at least one host and one guest components. The host is an organic molecule or ion whose binding sites converge. The guest is an organic molecule or ion or metal ion whose binding sites diverge [77]. The complexes of the host-guest chemistry are held together in unique structural relationship by forces other than those of covalent nature. They can be pole-pole, pole-dipole or dipole-dipole variety, more specifically, the components of complex are bound together by hydrogen bond, by ion-pair, by  $\pi$ - $\pi$  stacking interactions, and by van-der Waals forces [78, 79]. There are a number of ways by which the complexation phenomena could be studied. In addition to the powerful spectrophotometric methods now available, most often NMR and/or UV-Vis spectrometry and various other techniques like mass spectrometry are also being used [80]. The precise structures of complexes are most directly obtained by X-ray crystallography, and the reasonable assumption is generally made that the solid structure architecture is similar to the solution state. The ability in terms of sensitivity and the selectivity of the calixarene as a host to discriminate among a group of guests makes it a special class of subject in supramolecular chemistry.

#### 3.1. Lower-rim esters

Much more effective than the simple ethers, the esters have been extensively studied. The earliest to be studied among this family of compounds were esters for which it was determined, using phase transfer extraction measurements, that the cyclic tetramers, pentamers, and hexamers extract all of the alkali cations, the cyclic tetramer works best with  $\text{Na}^+$ , the cyclic pentamer better with  $\text{K}^+$ ,  $\text{Rb}^+$ , and  $\text{Cs}^+$ , and the cyclic hexamer best with  $\text{Rb}^+$  and  $\text{Cs}^+$  but very poorly with  $\text{Na}^+$ , and the cyclic heptamer and octamer are quite ineffective [81].

McKervey, Diamond, and Svehla continued to publish on the use of calixarenes esters as electrochemical sensors. The calix[4]arene tetra ethyl ester synthesized by this group



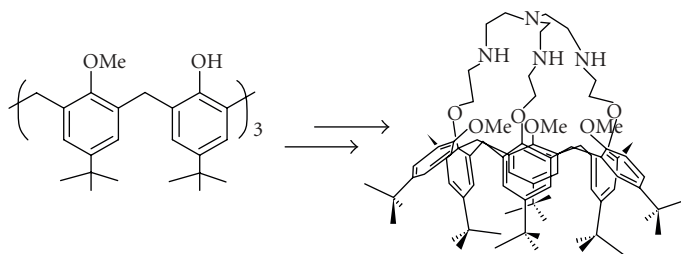
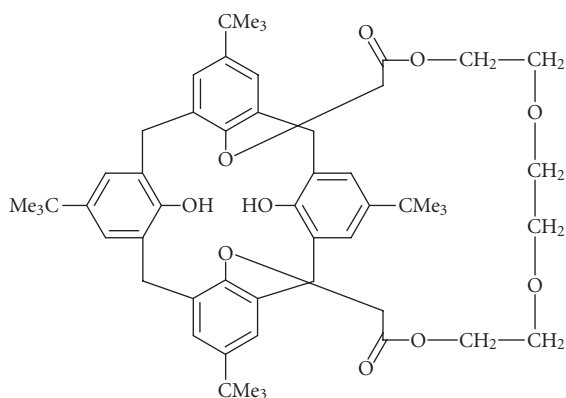
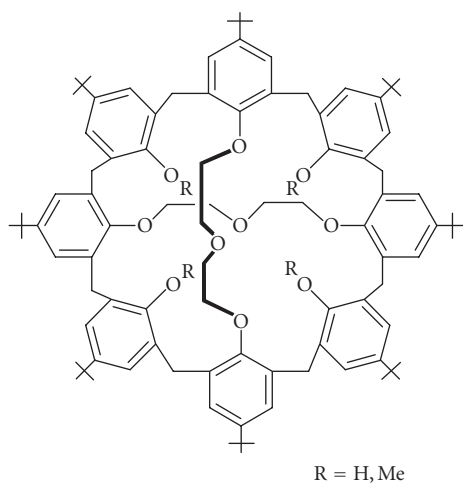
FIGURE 18: First  $C_{3v}$ -symmetrical calix[6](aza)crown.

FIGURE 19: Lower-rim functionalized acetate derivative of calix[4]arene.

FIGURE 20:  $D_{2d}$ -symmetrical 1,5-3,7-calix[8]bis-crown-3 derivatives.

continues to be commercially available as sodium selective electrode and is commonly used in hospitals for measuring sodium in blood. This group has also showed the calixarenes could produce electrodes selective for potassium and cesium [6]. Ester derivatives, the synthesis of which can be achieved smoothly, binds amines, with a preference for shorter amines [82].

The ligand discriminates according to guest hydrophobicity and shows selectivity for phenylalanine and tyrosine esters over glycine, alanine and 4-aminobutyric acid, with the interaction primarily taking place due to tripodal hydrogen bonding. Ammonium and alkylammonium ions can be sensed by calixarenes where diquinone is part of the macrocycle together with ligating sites such as ester or amide for hydrogen bonding [83, 84].

### 3.2. Lower-rim ethers, ketones, amides, and carboxylic acids

Lower-rim ethers and their counterparts, ketones, amides, and carboxylic acids have good complexing properties. The earliest examples of lower-rim-substituted calixarenes investigated for their complexation properties are the ethyleneoxy compounds [85, 86] which show only a modest degree of cation binding agency. As it is the case for crown ethers, calixarenes with oxygen donor atoms turned out to be suitable for selectively binding alkali ions. The ligands are more hydrophobic compared with crown ethers and the membranes therefore are more stable. Nitrophenol or azophenol moieties on calix[4]arenes equipped with additional ester groups [87] transform the Li/Na selectivity in organic solutions into a bathochromic shift from 350 to 425 nm with the help of an auxiliary base to support the deprotonation. The calixarene with a nitrophenylazophenyl group is rather versatile. It not only detects lithium ions in the presence of weak base, but also in turn detects weak bases such as volatile amines when  $Li^+$  is already present in the membrane [88, 89] (Figure 22).

Ketones have complexing features [90] similar to those of the esters previously described. Stability constant measurements and extraction data indicate that the cyclic tetrameric ketones are better than their ester analogs for the extraction of  $Li^+$  and also for  $Rb^+$  and  $Cs^+$ . The ketone has a broader range of extraction capability than its cyclic tetramer and hexamer counterparts but shows little selectivity among the cations.

Amides were first prepared and studied by Ungaro et al. [91] and subsequently in considerable detail by Mckervey et al. [6, 92] and Beer et al. [93–96] (Figure 23). As against the ethers, esters, and ketones, the amides very effectively complex alkaline earth cations [91]. In extraction studies the cyclic tetramers are shown to prefer  $Eu^{+3}$  over  $Pr^{+3}$  and  $Yb^{+3}$ ,

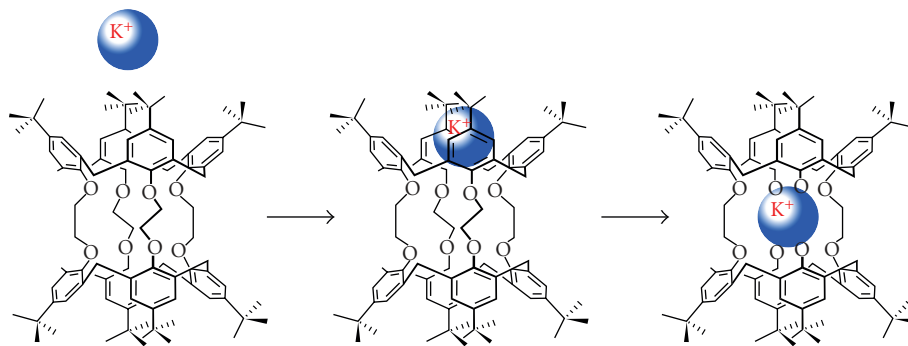


FIGURE 21: Calix[4]tubes.

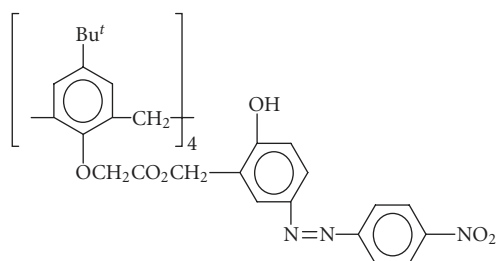


FIGURE 22: Chromogenic nitrophenylazophenol calix[4]arene.

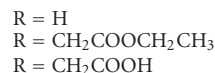
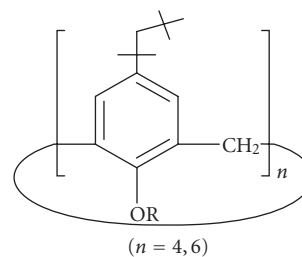


FIGURE 24: Calixarene esters for complexation with rare earths.

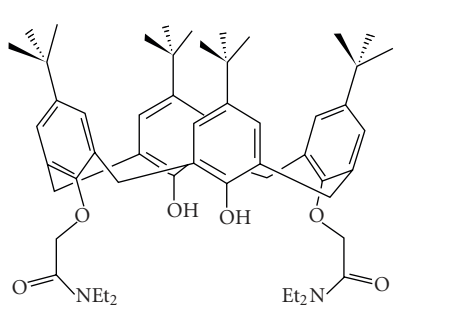


FIGURE 23: 1,3-bis(diethyl amide)-substituted calix[4]arene.

with Eu<sup>3+</sup> the cyclic hexamers being better than the cyclic tetramers showing the highest extraction effectiveness [97].

Trivalent cations are also effectively bound by the amides [98] like Pr<sup>3+</sup>, Eu<sup>3+</sup>, and Yb<sup>3+</sup>. The amides prove to be superior to the esters and ketones for complexing Ag<sup>+</sup> [91] and within the amide series the cyclic pentamer is an especially strong complexing agent. The larger Tl<sup>+</sup> cation forms weaker complexes than Ag<sup>+</sup>. Among the ester, acid, or amide groups anchored to calixarenes, the latter turned out to form most stable complexes with alkaline earth due to the high carbonyl group polarity [99].

With phosphine oxide groups appended to the lower rim, in good Ca<sup>2+</sup>/Na<sup>+</sup> selectivity and membrane durability is achieved in ISEs. Expanding the calix[*n*]arene cavity from *n* = 4 over 5 to 6 changes the Sr/Na selectivity of the amide

derivatives from 0.09 to 2.8 to 760 in extraction which further improves with alkyl ether instead of *t*-butyl groups in 4-position of the phenyl groups [100]. Amide derivatives of calixarenes have also been used for Sr<sup>2+</sup> separation in synergistic mixtures with hydrophobic anion [98, 101] which should work in ISE membranes as well.

Carboxylic acids differ from the esters, ketones, and amides in having ionizable groups. The carboxylic acids are all more effective complexing agents for alkali cations than the corresponding esters, ketones, and amides. Although the calixarene carboxylic acids form complexes with some of the alkali metal cations, [102] the fact that they have an even greater capacity for alkaline earth cations was first realized in the mid 1980s [86] and subsequently studied in some detail. The acids form stronger complexes with lanthanide cations like Pr<sup>3+</sup>, Eu<sup>3+</sup>, and Yb<sup>3+</sup> than with alkali and alkaline earth cations. The calix[4]arene dicarboxylic acid and calix[6]arene ester are useful for the extraction of the rare earths [103, 104] (Figure 24).

Some of the carboxylic acids have proved to be highly effective complexation agents for the uranyl cation [105]. The analogous *p*-tert-butylcalix[5]arene and -[6]arenes are somewhat less effective uranophiles, but the corresponding hydroxamic acids (*n* = 6) is even better and also competes with CO<sub>3</sub><sup>2-</sup> ions [106–108].

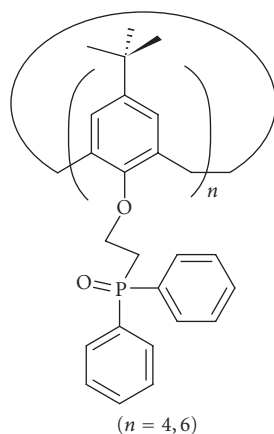


FIGURE 25: Phosphine oxide derivatives of calix[6]arene.

### 3.3. Lower-rim nitrogen, sulfur, and phosphorus containing groups

The McKerverey group introduced tetrameric calixarenes where nitrogen and sulfur were used in the coordination center and they were found to be selective for soft heavy metal ions such as silver [6]. Electrodes based on the hexamer derivative of the phosphine oxide series of derivatives were found to have excellent selectivity for lead ions [6] (Figure 25).

Thioester groups in calix[4]arenes lower the selectivity over sodium ions to some extent due to their carbonyl oxygens. Thiocarbamoyl groups or dithiocarbamoyl groups attached to the calixarene skeleton (Figures 26(a) and 26(b)) provide selectivity for  $\text{Ag}^+$ ,  $\text{Pd}^{2+}$ ,  $\text{Hg}^{2+}$  and other soft metal ions over hard ones [109, 110].

A class of hosts forms only weak complexes with the alkali and alkaline earth cations but forms strong complexes with  $\text{Ag}^+$ ,  $\text{Pb}^{2+}$ , and  $\text{Cd}^{2+}$  being the thioamides [110]. The cyclic pentamer is particularly effective for the extraction of  $\text{Cd}^{2+}$  and the cyclic hexamer shows a high affinity towards  $\text{Ag}^+/\text{Cu}^{2+}$  and  $\text{Ag}^+/\text{Pb}^{2+}$  selectivities. Calixarenes binding sites at the sulfur atoms have the potential for forming ditopic bimetallic complexes. There is some evidence that this has been accomplished with  $\text{Ag}^+$  and  $\text{Na}^+$  for the compound in which  $n = 6$  although the same compound excludes the  $\text{Na}^+$  ion [111]. Calixarenes containing diphenylphosphoryl acetamide moieties on the upper rim [112] and lower rim [113], respectively, are highly efficient extractants for  $\text{Eu}^{3+}$ ,  $\text{Th}^{3+}$ ,  $\text{Np}^{3+}$ ,  $\text{Pu}^{3+}$ , and  $\text{Am}^{3+}$ . The N,N-dimethyl dithiocarbamoyl ethyl ether is an effective extractant [114, 115] for  $\text{Pd}^{2+}$  and other heavy metals.

### 3.4. Lower-rim bridged calixarenes

Crowned calixarenes called calixcrowns, carrying bridging polyethylenoxy moieties on the lower rim and being first prepared by Ungaro et al. [56] in 1983, have proved to be very effective cation-complexing agents. They are characterized

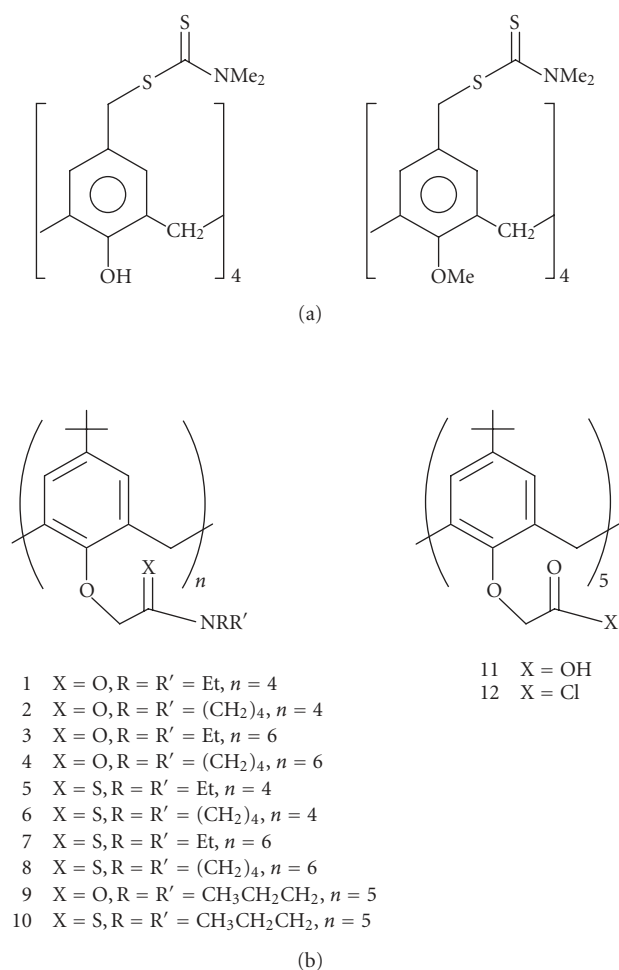


FIGURE 26: (a) Thia calix[n]arenes; (b) thia calix[n]arenes

by a high degree of molecular preorganization and therefore achieve even higher selectivity, especially among alkali ions. In contrast to the esters, ketones, and amides, which are selective for  $\text{Na}^+$ , the calixcrowns show a preference for the larger cations. Several calixcrown dialkyl ethers have been studied [28, 68]. The crown moiety and the calixarene restrict each other's molecular flexibility leading to a better discrimination by ion size. The ligand [116] with a narrow cavity for maximum Na/K selectivity, which when mixed with fluorephore makes an optode, can be miniaturized for intracellular measurements.

An alternate conformation, but with azacrown-5 moieties and its monocrown relatives, shows  $\text{K}^+$  selectivity in transport as well as in ISEs which translates into an optical signal with the help of the nitrophenol chromophoric group [117–119] (Figure 27).

Attaching benzo or naphtho groups to the crown moiety increases the Cs/Na selectivity. The Cs/K selectivity on the other hand improves to over 4000 after removal of the two phenolic oxygens outside the crown cavity [120]. Doubly crowned calix[4]arene such as (Figure 28) avoid the need for

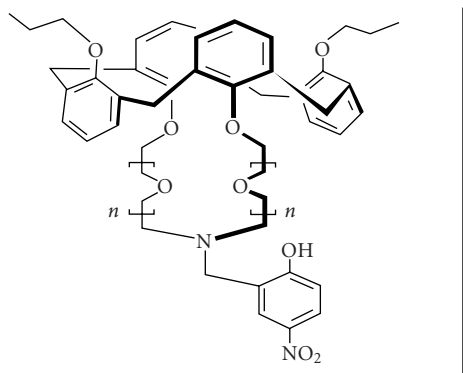


FIGURE 27: Calix[4]azacrown ethers in the 1,3-alternate conformation.

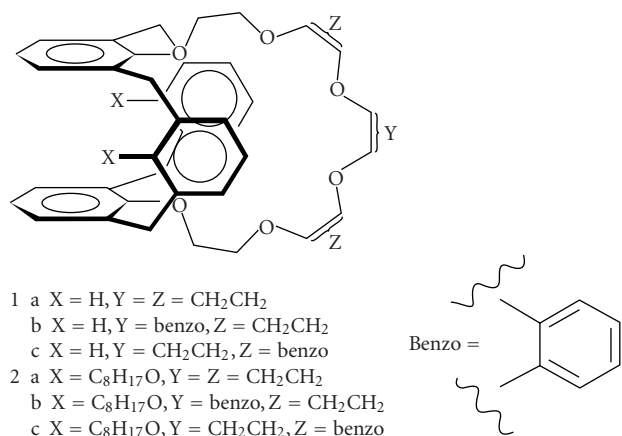


FIGURE 28: Doubly crowned calix[4]arene.

protective groups during synthesis and can bind two metal ions in one molecule.

#### 4. CONCLUDING REMARKS

Since last few decades calix[*n*]arenes ( $n = 4-8$ ), like cyclodextrins and crown ethers, have played an important role as host for ions, neutral molecules, and organic guests. The first part of the review mentions in detail the “calixarenes,” their origin, and the different modifications that are possible within this molecule. The calixarene molecule due to its reactive positions at the upper rim (removal of alkyl group) and the lower rim (removal of hydroxyl group) can be functionalized with identical or different binding groups. The few examples discussed here demonstrate the unlimited possibilities that exist for molecules like calixarenes for modifications. Their modified potential applications have been discussed towards the second half of the article, which range from their use as selective sensors for different analytical applications and medical diagnostics to their use in decontamination of wastewater, construction of electrodes, and membranes for transportation.

#### ACKNOWLEDGMENTS

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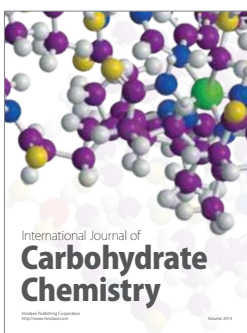
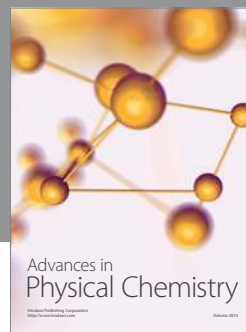
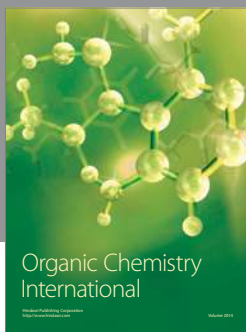
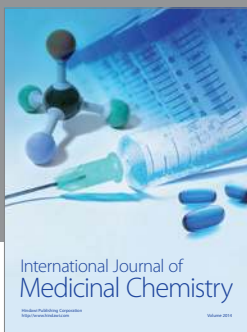
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