Functionalization reactions of calixarenes

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Abstract
In this review examples of functionalization reactions of calixarenes are presented with those involving the wide rim being presented first, followed by those involving the narrow rim, and then by reactions involving functionalization of both rims. The application possibilities of the obtained compounds are also described.

Keywords: Calixarenes, chirality, conformation, functionalization, narrow rim, wide rim

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1. Introduction
Calixarenes are widely studied due to their interesting properties, including the fact that they are valuable receptors besides cyclodextrins, and cucurbiturils. An advantageous feature of calixarenes is their easy availability. Functionalization of calixarenes at their wide and at their narrow rims, permits the synthesis of a variety of derivatives having desired properties and is the topic of the present review.

The large number of publications dealing with calixarenes is a reflection of their various applications. Calixarenes are receptors for neutral and charged species, they form complexes
with metal ions,\textsuperscript{21-23} and are promising for environment protection due to their ability to extract cesium and lanthanides from radioactive waste.\textsuperscript{24,25} They are of interest for the design of sensor,\textsuperscript{26-28} and catalysts,\textsuperscript{29,30} and are useful in chiral recognition,\textsuperscript{31,32} as well, polymers,\textsuperscript{33-35} and supramolecular structures,\textsuperscript{36-38} containing calixarenes exist. It is worth noting that calixarenes may be applied in the design of metal-organic nanotubes,\textsuperscript{39,40} vesicles,\textsuperscript{41} and nanoparticles.\textsuperscript{42} Attention should be paid also to capped calixarenes,\textsuperscript{43} and calixtubes,\textsuperscript{44} along with their complexation properties.

Compounds related to calixarenes include resorcinarenes\textsuperscript{45-47} bearing two hydroxyl groups on the phenyl moieties able to form cavitands\textsuperscript{48,49} which are precursors of capsules.\textsuperscript{50} An interesting class are the pyrogallolarenes built from pyrogallol units\textsuperscript{51} which are components of metal-organic nanocapsules.\textsuperscript{52}

Related to calixarenes also are the calixcrowns,\textsuperscript{53,54} which are calixarenes bearing crown ether units; calixquinones,\textsuperscript{55,56} containing one or two quinone units instead of phenol moieties of calixarenes; calixpyrroles,\textsuperscript{57-59} built from pyrrole units, and calixphyrins,\textsuperscript{60,61} formed by the reduction of porphyrins. Pillarenes,\textsuperscript{62-64} in which benzene rings are linked by para, and not by meta positions as in calixarenes should also be included. A special group are the thia, oxa and azacalixarenes, in which the linking methylene groups of calixarenes are formally replaced by sulfur,\textsuperscript{65-67} oxygen,\textsuperscript{68-70} or nitrogen,\textsuperscript{71-73} atoms, respectively.

This contribution is a continuation of our previous works concerning calixarenes,\textsuperscript{74} their complexes with metal ions,\textsuperscript{75,76} covalently and noncovalently bound calixarene assemblies,\textsuperscript{77} and cavitands,\textsuperscript{78} forming dimeric,\textsuperscript{79} as well as trimeric and hexameric\textsuperscript{80} capsules. Since the amount of reports dealing with calixarenes is enormous, only selected examples are described in this review. The text consists of three chapters; two of them concern functionalization of the wide and the narrow rims of calixarenes, and in the third chapter the functionalization of both rims is presented.

\section*{2. Functionalization of the wide rim of calixarenes}

Many calixarenes functionalized at the wide rim are known,\textsuperscript{81-86} It should be noted that functionalization of the wide rim is more difficult than of the narrow rim. Functionalization of the wide rim requires protection of the narrow rim hydroxyl groups and also removal of the \textit{t}-butyl groups from the wide rim. Some selected examples of functionalizations of calixarene at the wide rim are shown below.

In a study of calixarene monophosphines as supramolecular receptors, reactions leading to 1-4 have been performed.\textsuperscript{87} The synthesis of calixarene monophosphines 1 and 2 begins with the nickel-catalyzed reactions of dibromocalixarene 5 and of tetrabromocalixarene 6 with Ph\textsubscript{2}POEt affording calixarene phosphine oxides 7 and 8, which were reduced with PhSiH\textsubscript{3} to give 1 and 2, respectively.
Scheme 1

The synthesis of 3 and 4 involves the Suzuki-Miyaura coupling of 7 and 8 with p-tolylboronic acid yielding 9 and 10, which upon reduction afford 3 and 4.

Scheme 2
It was found that compounds 1-4 form with [RuCl₂(p-cymene)]₂ inclusion complexes; the complexation of 1 and 3 leads to [RuCl₂(p-cymene)L] complexes 11 (L=1) and 12 (L=3).

Scheme 3

In continuation of the above experiments concerning calixarene monophosphines, compounds 13-17 have been synthesized for use in preparation of Suzuki-Miyaura cross-coupling catalysts.¹⁸ Thus, bromocalixarene 18 was alkylated in the presence of sodium hydride to afford 19-22 which, upon halogen-lithium exchange, followed by reaction with Ph₂PCl yielded 13-16. Debenzylation of 14 using AlCl₃ gave 17.

Scheme 4
In order to investigate the coordination ability of phosphines 13-17, the reaction of 14 with [PdCl$_2$(cod)] leading to trans-23 and cis-24 was performed. It was found that 23 upon treatment with CDCl$_3$ undergoes isomerization into 24.

Scheme 5

The reaction of 14 with [Pd(o-C$_6$H$_4$NMe$_2$)Cl]$_2$ affords complex 25 which was treated with AgBF$_4$ in THF to give the complex 26; recrystallization of 26 performed by slow diffusion of hexane into a commercial undried dichloromethane solution of 26 yields the aquo complex 27.

cod = 1,5-cyclooctadiene
Scheme 6

For the study of Suzuki-Miyaura cross-coupling reactions, the catalysts were generated in situ by mixing the respective monophosphines from among 13-17 with the palladium precursor. In these experiments, bromobenzene, 2-3-and 4-bromotoluene, 2-and 4-bromoanisole, 1-bromonaphthalene and 2-bromo-6-methoxynaphthalene served as aryl bromides, while [Pd(OAc)\textsubscript{2}], [Pd(dba)\textsubscript{2}] and [PdCl\textsubscript{2}(cod)]\textsubscript{2} were used as the palladium precursors; NaH, NaOH, KOH, K\textsubscript{2}CO\textsubscript{3}, Cs\textsubscript{2}CO\textsubscript{3} and CsF were used as the bases.

Scheme 7

It was found that combining each of the monophosphines 13-17 with [Pd(OAc)\textsubscript{2}] and NaH in dioxane, yielded a highly efficient catalytic system for the Suzuki-Miyaura cross-coupling of aryl bromides with phenylboronic acid. Notably also, these catalysts remained stable for several days.\textsuperscript{88}
In order to study phosphorylation which occurs in biochemical processes, the phosphatase inhibitory properties of compounds 28 and 29 have been investigated. In these experiments it was found that the introduction of methylenebisphosphonic acid 28 onto calix[4]arene 30 to form compounds such as 33 and 34, results in the efficient inhibition of alkaline phosphatase whereas this inhibition of 28 itself is only very low. For these phosphatase inhibitory studies, calixarenes 33 and 34 containing one and two units of 28, respectively, were synthesized via the reactions of calixarene aldehydes 31 and 32.

Scheme 8

Treatment of calixarenes 31 and 32 with sodium diethylphosphite generated in situ from diethylhydrogenphosphite and sodium in dioxane afforded esters 35 and 36 which were then converted to the corresponding acids 33 and 34 by reaction with Me$_3$SiBr followed by methanol.

Scheme 9
The phosphatase inhibitory activities of 28, 29, 33, 34 and 36 which were found to decrease in the order 34 > 33 > 29 > 28 were examined in the hydrolysis reactions of p-nitrophenylphosphate catalyzed by calf intestine alkaline phosphatase. The esterified calixarene 36 showed no inhibitory activity and therefore one may conclude that the free phosphonyl groups are responsible for the inhibitory properties of 28, 29, 33 and 34. The activity of these compounds as phosphatase inhibitors likely results from their coordination to the metal (Zn$^{2+}$ and Mg$^{2+}$) ions in the enzyme active site.

Properties of a photolabile calixarene bearing an internal sensitizer have been examined. Considering the fact that α-hydroxyalkyldithianes are known to undergo photofragmentation in the presence of an electron transfer sensitizer, such as benzophenone, the synthesis of calixarene 37 bearing two photocleavable dithianylhydroxymethyl groups and two benzophenonecarboxylate groups was performed. It was found that 37 indeed undergoes a photoinduced fragmentation.

Scheme 10

The synthesis of 37 begins with the reaction of dialdehyde 38 with lithiated dithiane 39 to afford compound 40. Benzophenone-4-carboxylic acid was used as the tethered internal sensitizer and it was coupled to 40 via its chloride 41 formed by treatment with oxalyl chloride. The coupling of 40 with 41 in the presence of triethylamine yielded the mono and disubstituted products 42 and 37, respectively.

For the photochemical study, 37 was irradiated with a medium pressure mercury lamp; the process was monitored by $^1$H NMR and confirmed the ability of 37 to self-sensitized photofragmentation.

In a study of calixarenes with ferrocenyl redox-active units, calixarenes 43 and 44 bearing ferrocenyl units were synthesized for investigation of their electrochemical properties. The synthesis involves the reaction of calixarene dialdehyde 45 with 4-ferrocenylaniline, affording the
Schiff base 43, which upon reduction, yields calixarene 44. It was found that 43 and 44 electrochemically recognize La$^{3+}$, Ce$^{3+}$, Pb$^{2+}$ and Cu$^{2+}$ ions and the study of the extraction properties toward metal ions showed selectivity of 44 for Cu$^{2+}$, Fe$^{3+}$, Pb$^{2+}$ and Cd$^{2+}$ ions over Co$^{2+}$ and Ni$^{2+}$.

Scheme 11

Scheme 12
Redox-active anion sensors have also been widely investigated and the use of ferrocene units in these species should be noted. It has been established that anion sensors adsorbed on surfaces in SAMs are advantageous since they are robust and portable, and moreover, the preorganization of receptors onto a surface enhances the thermodynamic driving force associated with receptor/analyte binding. With these considerations in mind, the disulfide-functionalized calixarenes bearing ferrocene units, 46-48 were synthesized for construction of SAM redox-active anion sensors adsorbed on gold surfaces.93

The synthesis of 46 and 47 started with the reaction of tetraaminocalixarene 49 with BOC anhydride affording 50a and 50b which upon treatment with ferroceneacid chloride, give 51 and 52, respectively. Their deprotection by TFA leads to 53 and 54 which react with thiocytic acid in the presence of the carbodiimide coupling reagent, EDC, yielding 46 and 47, respectively.

Scheme 13
In order to obtain 48 bearing the ferrocene unit linked by the urea moiety to the calixarene platform, the reaction of calixarene 50b with isocyanatoferrocene leading to calixarene 55 was performed. Deprotection of 55 afforded 56, which upon treatment with thiocitic acid and EDC, yielded 48.

Scheme 14
The anion sensing properties of 46-48 were studied using chloride, benzoate, dihydrogen phosphate and perrhenate anions. The cathodic shifts of the respective ferrocene/ferrocenium redox couple, resulting from the anion binding, were measured. It was established that SAMs of 48 adsorbed onto a gold electrode, selectively recognized perrhenate anions in aqueous solution in the presence of equimolar amount of dihydrogen phosphate, and are thus promising for the design of electrochemical anion sensors.\textsuperscript{93}

Surfactant triscarboxycalixarenes 57a-k bearing \( n \)-alkyl chains with 1-12 carbon atoms have been synthesized with the aim of investigating their self-assembly properties.\textsuperscript{94} The synthesis begins with the treatment of calixarenes 58a-k with methyl iodide to form quaternary ammonium salts which, upon reaction with sodium cyanide yield tris(cyanomethyl)calixarenes 59a-k. The hydrolysis of 59a-k with alcoholic potassium hydroxide affords triscarboxycalixarenes 57a-k, all of which were found to form typical micelles in aqueous media at biologically relevant pH 6 and pH 8 values.

Scheme 15
A convenient method of regioselective functionalization of calix[8]arenes at the wide rim of aromatic rings 1 and 5 has been reported. This functionalization was performed using a protection-deprotection procedure, the protected derivatives were the xylylene-bridged calix[8]arenes 61a and 61b, synthesized by the reaction of p-t-butylcalix[8]arene 60 with m- and p-bis(bromomethyl)benzenes, respectively. Hexamethylation of calixarenes 61a,b with methyl iodide afforded 62a,b and hexapropylation with n-propyl iodide afforded 63a,b. The removal of the xylylene bridge from 62a,b and 63a,b was achieved by hydrogenolysis (H₂, Pd/C) to give hexasubstituted calix[8]arenes 64 and 65 having two free hydroxyl groups on rings 1 and 5.

It was found that upon treatment with nitric acid, 64 and 65 undergo selective ipso-nitration of rings 1 and 5 to afford 1,5-dinitrocalix[8]arenes 66 and 67, respectively. Calixarene 67 was exhaustively propylated to give 68, which upon reduction with H₂/Raney Ni yielded the corresponding diamino-derivative 69, whose amino groups can undergo further reactions. The selective de-t-butylation of 64 and 65 using AlCl₃ in the presence of toluene or phenol gave de-t-butylated calix[8]arenes 70 and 71.
Upon oxidation with $\text{Ti(OCOCF}_3)_3$ in the presence of trifluoroacetic acid, calixarenes $64$ and $65$ afforded 1,5-calix[8]diquinones $72$ and $73$ which when subjected to reduction with $\text{NaBH}_4$ gave 1,5-calix[8]dihydroquinones $74$ and $75$.

The above methodology enables access to calix[8]arenes selectively substituted at the wide rim of aromatic rings 1 and 5 and as a result, calix[8]arenes containing nitro, amino, quinone and hydroquinone functionalities can be easily synthesized.\textsuperscript{95}
3. Functionalization of the narrow rim of calixarenes

Some examples of functionalization of the calixarene narrow rim, selected from a large number of such processes,\textsuperscript{96-101} are presented. For the functionalization of calixarene narrow rim using Pd-catalyzed Sonogashira coupling reactions, the bis-triflate calixarene 76 and alkynes 77a-d have been employed.\textsuperscript{102} The reaction of 76 with trimethylsilylacetylene 77a affords monoalkynylcalixarenes 78 and 79 along with derivatives 80 and 81, the formation of 79-81 containing iodine atoms, which were obtained via direct metal-assisted substitution by a halide was rather unexpected. It was also observed that calixarene 79 treated with phenylacetylene 77d yields dialkynylcalixarene 82.

![Scheme 20](image-url)
Reactions of 76 with alkynes 77b and 77c afforded monoalkynylcalixarenes 83 and 84, respectively, however the dialkynyl products were not formed. On the other hand, the reaction of 76 with 77d yielded both expected monoalkynyl and dialkynylcalixarenes 85 and 86, respectively.

Scheme 21

The homocoupling of monoethynylcalixarene 87 leading to bis-calixarene 88 has also been achieved. For this purpose 78 was treated with tetrabutylammonium fluoride (TBAF) to remove the
TMS group, the formed 87, upon reaction with CuI in the presence of DBU, afforded the rigid narrow-rim-bridged bis-calixarene 88.\(^\text{102}\)

It is well-known that the narrow-rim \(O\)-alkylation of calix[4]arenes with alkyl halides proceeds favorably at the distal hydroxyl groups. This behavior results from a circular intramolecular hydrogen bonding in the monoalkylated intermediate and has been extensively studied.

However, the dialkylation at proximal hydroxyl groups, which is very important for the design of synthetic receptors, has been less intensively investigated. A convenient method for such syntheses is to “cap” two proximal hydroxyls with a disiloxane bridge as in 89. In these alkylation reactions, organohalides such as BuI or BrCH\(_2\)COOEt were used and \(t\)-BuOK, K\(_2\)CO\(_3\) or Cs\(_2\)CO\(_3\) served as bases. The reactions of capped 89 with the organohalides in the presence of a base afforded syn and anti products 90 and 91, respectively, which upon subsequent desilylation with TBAF, gave the corresponding syn and anti proximally-dialkylated products. The syn/anti ratio of these dialkylation products depends on the alkyl halide and the base used. Dialkylation of calixarene 89 in the presence of \(t\)-BuOK gives syn product exclusively, as did the use of K\(_2\)CO\(_3\), however the use of Cs\(_2\)CO\(_3\) strongly shifts the stereoselectivity toward the anti product.\(^\text{103}\)

\[ \text{Scheme 23} \]

In the experiments the reaction of 92 with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in the presence of imidazole afforded disiloxane bridged 89. The treatment of 89 with the organohalides MeI, BrCH\(_2\)COOEt or PhCH\(_2\)Br yielded 1,2-alt 93 a-c which upon desilylation by TBAF gave \(O,O'\)-dialkylated 1,2-alt calixarenes 94a-c.\(^\text{104}\)

However, it was found that the treatment of 89 with methyl iodide under changed conditions may give monomethylated product 95. The reaction of the remaining hydroxyl group of 95 with benzyl bromide completed the alkylation yielding 1,2-alt 96 which upon deprotection with TBAF afforded 1,2-alt 97. It is noteworthy that compounds of the type of 96 and 97 are inherently chiral due to the presence of two differently substituted adjacent aromatic rings.\(^\text{104}\) All of these reactions proceeded smoothly and with excellent yields.
Scheme 24

Scheme 25
In recent years, fluorescent molecular sensors for the detection of environmentally important heavy metals, such as copper,\textsuperscript{105,106} and mercury,\textsuperscript{107,108} have received increasing interest. To this aim, calixarenes 98-103 bearing attached dansyl groups have been synthesised and investigated for their use as fluorescent sensors for metal ions.\textsuperscript{109} Their syntheses involve the treatment of the appropriate calixarenes with dansyl chloride and sodium hydride, in THF. In this way calixarenes 104-106 were converted into 98-100, respectively.

Scheme 26

Scheme 27
Similar reaction of calixarene 107 affords the mixture of cone 101a and paco 101b, which could be separated by column chromatography. Using the same procedure, calixarenes 108 and 109 yielded 102 and 103, respectively.
The crystal structures of dansylated calixarenes, namely the unsolvated 101b, and two solvated species 98•CH₂(OH)CN and 99•3CH₃CN have been described, in the crystal structure of 101b, the calixarene is in a paco conformation, while in the solvates of 98 and 99 the calixarenes are fixed in cone conformations. Fluorescence measurements have shown that calixarenes 98-102 selectively recognize Cu²⁺ ions; moreover, 101a may be used for simultaneous determination of Cu²⁺ and Hg²⁺ ions.¹⁰⁹

The direct alkylation of calixarene 92 with substituted benzaldehydes 110a,b has been reported. The reaction of 92 with 110a affords the mono- and dialdehydes 111a and 112a, respectively. However, in the case of 110b the dialdehyde 112b was obtained as the sole product.¹¹⁰

![Scheme 30](image)

Scheme 30

The introduction of aldehyde groups into calixarenes can enable further functionalization reactions. Thus, the condensation of 111a and 112a,b with S-methyl- and S-benzyl-dithiocarbazates affords the sulfur-containing Schiff bases, from 111a two products 113a,b were obtained, while the reaction of 112a,b yielded four products 114a-d.¹¹⁰ It is noteworthy that syntheses of mono-functionalized calixarenes,¹¹¹ such as 111a and 113a,b are not as common as those leading to fully functionalized species.
In order to investigate the reactivity of the aldehyde groups of calixarene 115, it was submitted to reactions with hydrazine hydrate and with diaminomaleonitrile affording 116 and 117, with salicylaldehyde hydrazone and 2-pyridinaldehyde hydrazone, compounds 118 and 119 were formed, respectively. All reactions proceed at room temperature, the \(^1\)H NMR data indicate that the products are in cone conformations. In all cases it was found that the pendant arms of the compounds do not adopt a face-to-face structure but are bent away from each other.
Scheme 33

For a study using calixarenes as receptors for the colorimetric detection of fluoride ions, compounds 120-123 were synthesized. It should be noted that due to its high electronegativity and small size, fluoride ion can form strong hydrogen bonds at low concentrations, and is a sufficiently strong base to promote deprotonation at higher concentrations. The synthesis of the receptors commenced with the treatment of calixarene 124 with p-hydroxybenzaldehyde and p-hydroxyacetophenone, leading to 125a and 125b, respectively. Reaction of 125a with p-nitrophenylhydrazine and 2,4-dinitrophenylhydrazine affords calixarenes 120 and 121, while 125b with the same reagents yields 122 and 123.114

It was found that 120 selectively recognizes F$^-$ ions; among H$_2$PO$_4^-$, AcO$^-$ and F$^-$ ions, the solution color changes from yellow to purple only with F$^-$ ions, whereas with 121 the color also changes with H$_2$PO$_4^-$ and AcO$^-$ ions. The observation that the limiting value in the absorption maximum of 120 was achieved at four F$^-$ equivalents instead of only two equivalents was unexpected. This behavior is explained by the fact that addition of one F$^-$ equivalent results in the hydrogen bonding with the NH protons in 120 and formation of a 1:1 complex, 120 • F$^-$. Upon addition of a second F$^-$ equivalent, the complex 120 • 2F$^-$ is formed, and further addition of F$^-$
equivalents causes deprotonation of the NH groups. The above studies are promising for further design of colorimetric sensors of fluoride ions.\textsuperscript{114}

\textbf{Scheme 34}

In a study of calixarenes containing tethered drug moieties, calixarene \textbf{126} substituted by nalidixic acid, a quinolone antibiotic, has been synthesized; for this purpose calixarene \textbf{92} was treated with bromopropyl ester of nalidixic acid \textbf{127}.\textsuperscript{115}
All six possible conformational isomers of the proximally para-disubstituted calixarene 128 were selectively synthesized and isolated; they are one cone, two paco, two 1,2-alt and one 1,3-alt conformers. It was established that the two paco 128b* and 128c*, one 1,2-alt 128e* and one 1,3-alt 128f* conformers are inherently chiral.\textsuperscript{116}

(in the structures of 128a-f the disubstituted rings are darkened)

Scheme 36
The above compounds were synthesized by propylation of calixarenes 129, 130, 131* and 132* in the presence of a base. The role of the base in this process is very important: e.g. for 129 the use of NaH leads preferentially to cone 128a, whereas in the presence of Cs₂CO₃ and t-BuOK, conformers paco 128b* and 1,2-alt 128d, respectively, are obtained.

Scheme 37

Calixarenes 128b*, 128c*, 128e* and 128f* are promising precursors for the design of synthetic receptors capable of chiral discrimination, since bromine atoms may be readily replaced by other substituents.

The tannin-like calixarene 133a, bearing two gallate units was synthesized along with calixarenes 133b and 133c. Gallic acid is present in the plant tannin in form of condensed
compounds, e.g. with glucose or quinic acid, tannins have biological properties and are able to bind proteins and metal ions.

Scheme 38

The synthesis of 133a begins with the reaction of calixarene 92 with 3,4,5-triacetoxybenzoyl chloride affording 134 which, upon deacetylation with hydrazine monohydrate, yields the desired product. Calixarenes 133b and 133c were obtained by a similar procedure.

Scheme 39

The 1H NMR spectra show that calixarenes 133a-c are in cone conformations and have C2 symmetry. The galloyl groups in 133a are situated near to each other, allowing an unusual nonbonding close contact, the OH-π interaction between the hydroxyl group and the aromatic ring of the galloyl unit is therefore possible.

The reactions of easily-accessible calixarene phosphoric esters 135-138 with bromotrimethylsilane, followed by methanol, have been reported to yield water soluble calixarene phosphoric acids 139-142.11
The reactions of chiral calixarene 143, leading to inherently chiral calixarenes 144-146 have also been reported. These begin with the acylation of 143 by benzoyl chloride affording calixarene 144, bromination of 143 and 144 with NBS yields calixarenes 145 and 146, respectively. Calixarenes 143-146 react with bromotrimethylsilane forming trimethylsilyl esters 147-150 which, without isolation, were treated with methanol to give inherently chiral calixarene phosphoric acids 151–154, formed as racemic mixtures of two enantiomers, similarly to 143-146.

Scheme 41
Reactions of 151–154 with L-(-)-α-phenylethylamine (PEA) afford weakly dissociated diastereomeric salts 155–158, respectively, which could be easily separated into diastereomers by RP HPLC on Separon SGX 18 or Partisil 5 ODS 3 achiral columns. Other chiral amines may also be used besides L-PEA. \[^{118}\]

Due to their conformational flexibility the chemistry of large calix[n]arenes (n = 6,8) has been less investigated than that of calix[4]arenes. It should be pointed out that large calixarenes have
some advantages since they may serve as receptors for bulky guest molecules and as enzyme mimics. Considering the many applications of calixarenes, as well as the potentially valuable properties of calix[n]arenes ($n=6,8$), synthetic methods for preparation of water-soluble large calixarenes functionalized at the narrow rim have been reported,\textsuperscript{119} using calixarenes 159-161 as starting materials.

![Scheme 44](image)

**Scheme 44**

Two types of reagents were chosen: *bromoalkanenitriles and oligo(ethylene glycol)* derivatives, in both cases, calixarenes which can be further functionalized are obtained. Moreover, the reactions with oligo(ethylene glycol) derivatives afford hydrophilic calixarenes. A simple synthetic procedure involves the use of 4-bromobutynitrile, 7-bromoheptanenitrile as well as activated tri, hexa- and dodeca(ethylene glycol) derivatives.

*In reactions with bromoalkanenitriles* the full alkylation of 159-161 performed with bromobutynitrile in the presence of K$_2$CO$_3$ yielded 162-164, and reaction of 160 with bromoheptanenitrile yielded 165.

![Scheme 45](image)

**Scheme 45**
In reactions with oligo(ethylene glycol) derivatives, the monoalkylation of 160 with 3,6,9-trioxadecyl mesylate, carried out in the presence of sodium hydride afforded 166.

Scheme 46

Partial alkylation of 160 and 161 with Br(CH$_2$CH$_2$O)$_3$Me gave rise to 167 and 168, while the partial alkylation of 159–161 using Br(CH$_2$CH$_2$O)$_6$THP afforded 169–171, respectively.

THP = 3,4-dihydro-2H-pyrane (protecting agent)

Scheme 47
In order to obtain fully alkylated products, second alkylations of 167 and 168 with Br(CH₂CH₂O)₃Me and of 169-171 with Br(CH₂CH₂O)₆THP afforded 172, 173, and 174-176, respectively.

Scheme 48

The above syntheses of calix[6]arenes and calix[8]arenes functionalized at the narrow rim extend the possibilities of their applications by introduction of various, e.g. solubilizing or fluorescent groups, which could be promising for the design of biological models or molecular sensors.¹¹⁹

A large class of calixarenes bridged by crown ethers i.e. calixcrowns, exists,¹²⁰,¹²¹ and these are efficient acceptors of metal ions. A related class of compounds are the calixaza-crowns,¹²²-¹²⁴ which also show complexing properties.

The synthesis of an interesting spirobiscalixazacrown 177 has been reported. Its structure consists of two calixazacrown moieties connected by a spiro-carbon atom, for comparison purposes calixazacrown 178, i.e. half-part of 177 was also synthesized. Both 177 and 178 were obtained by the reaction of calixarene 179 with appropriate diamino derivatives 180 and 181, respectively, and were investigated for their complexing properties.¹²⁵
Scheme 49

It was observed that 177 forms 1:2 complexes, 177•M₂, with Ag⁺, Zn²⁺ and Fe²⁺ ions, whereas 178 affords 1:1 178•M complexes. In the 177•M₂ complexes, one metal ion is situated in each cavity. The complexation of 177 with metal ions proceeds slower than complexation of 178 since the next metal ion enters the second cavity of 177 with more difficulty than does the first.
4. Functionalization of both rims of calixarenes

Many functionalization reactions of calixarenes at both rims are known,\textsuperscript{126-131} and some examples are described below. In a study of calixarene chromogenic chemosensors for both cations and anions,\textsuperscript{132} and with the aim to construct molecular logic gates,\textsuperscript{133,134} calixarene 182 recognizing Ca\textsuperscript{2+} and I\textsuperscript{−} ions has been synthesized.\textsuperscript{135} The process involves the treatment of dipropargylcalixarene 183 with p-nitroaniline and NaNO\textsubscript{2} affording calixarene 184 containing azo groups which upon click reaction with azide 185 yields calixarene 182.

\begin{center}
\includegraphics[width=0.9\textwidth]{scheme_50.png}
\end{center}

**Scheme 50**

Calixarene 182 has triazole units as metal-ligating groups responsible for recognition of Ca\textsuperscript{2+}, Pb\textsuperscript{2+} and Ba\textsuperscript{2+} ions, while its phenol hydroxyl groups are responsible for binding of F\textsuperscript{−}, AcO\textsuperscript{−} and H\textsubscript{2}PO\textsubscript{4}\textsuperscript{−} anions. The color changes resulting from the presence of azo groups are distinct and may be detected by naked eye. The UV/Vis spectral behavior of 182 toward Ca\textsuperscript{2+} and F\textsuperscript{−} ions enables the construction of a dual output molecular switch, as an INHIBIT logic gate with a YES logic function; the system is operated by inputs of Ca\textsuperscript{2+} and F\textsuperscript{−} ions. The above experiments are promising for design of miniaturized molecular level devices.

Synthesis of 1,3-\textit{alt} calixarenes bearing imidazolyl (186–188) and pyrazolyl (189–191) units has been performed for design of the directional 2D coordination network.\textsuperscript{136,137} In this process the starting calixarene 192 containing mesitylene rings was chloromethylated to give derivative 193 which reacted with sodium imidazolate and pyrazolate affording compounds 186 and 189, respectively.
Compounds 186 and 189 upon Suzuki coupling with boronic esters 194 and 195 bearing p-methylthiophenyl and pyridyl groups, respectively, performed with the use of Pd(PPh₃)₄ as a catalyst, yielded in the case of 186 compounds 187 and 188, and in the case of 189 compounds 190 and 191.

Scheme 52
The structural investigation has shown that 186 affords crystalline discrete metallamacrobicycles in the presence of metal halides MX$_2$ (M = Co, Zn, Cu, Hg; X = Cl or Br), whereas 189 forms infinite 1D coordination networks with CoX$_2$ (X = Cl or Br) and with ZnCl$_2$. It was found however that the acentric 191 bearing two pyrazolyl and two pyridyl groups forms the desired directional 2D coordination network with ZnCl$_2$.

The water soluble calixarenes 196a,b having deep cavities were synthesized with the aim to investigate their inclusion complexation with pyridines and with aromatic cations. The synthesis begins with the reduction of calixarenes 197a,b with BH$_3$•THF complex affording 198a,b which upon treatment with ethyl bromoacetate yield esters 199a,b. The subsequent hydrolysis of 199a,b leads to 196a,b as potassium salts, bearing eight and twelve potassium carboxylate units, respectively.

Scheme 53

It is noteworthy that 196a and 196b are both water soluble and highly stable, calixarene 196a has a hydrophobic, and 196b a hydrophilic cavity. It was found that 196a,b form 1:1 inclusion complexes with pyridines 200, 201 and aromatic cations 202–206. The 196b•203 complex showed the highest binding constant.

Comparing complexing properties of 196a and 196b, it was found that 196a binds 200 and 201 more strongly than 196b does, whereas 196b binds 202–206 more strongly than 196a does. Comparing properties of guests it was observed that 196a binds more strongly with 200 and 201 than with 202–206. The affinity of 202 and 203 as guests of 196a and of 196b is higher for 203 than for 202, this fact showing that the presence of the methyl group in the ring of 203 enhances its binding strength. All of the above experiments were performed in aqueous medium and therefore they are of interest for investigation of biological processes.
Pyridines and aromatic cations used as guest molecules of 196a,b

Scheme 54

It is known that chiral, especially inherently chiral calixarenes are able to include enantiomers of chiral guest molecules, this property being of a great value, e.g. in the design of chiral advanced materials, in the preparation of enantioselective sensors and in asymmetric synthesis. In this aspect both enantiomers of inherently chiral calixarene carboxylic acids 207a and 207b with ABCD substitution patterns have been prepared.139

Calixarene 208 was reacted with (R+)-N-(α-phenylethyl)bromoacetamide affording calixarene 209 and benzylation of one its hydroxyl groups leads to the mixture of paco diastereomers 210a and 210b. Diastereotopicity of 210a and 210b results both from the presence of the chiral carbon atom of phenylethylamide group and of the ABCD asymmetrical substitution of the calixarene macrocycle. Diastereomers 210a and 210b were separated by column chromatography and regioselectively brominated with NBS to give monobromocalixarenes 211a and 211b. The phenylethylamide and benzoyl groups of 211a and 211b were removed by treatment with KOH in ethanol/water medium affording chiral cone carboxylic acids 207a and 207b which are promising for the chiral recognition of organic compounds.

In the study of calixarene self-organized solids, the calixarenequinhydrone charge-transfer complex 212 has been synthesized140 For this purpose, dimethoxycalixarene 213 was oxidized with thallium (III) trifluoroacetate to give calixarediquinone 214 which, upon reduction with sodium borohydride, yielded calixarededihydroquinone 215.
Scheme 55
The direct synthesis of 212 by mixing calixarenediquinone 214 and calixarenedihydroquinone 215 was impossible due to the lack of solubility of 215. Therefore, 212 was prepared by partial reduction of 214 with NaH, leading to formation of the sodium salt of 212. It was observed that 212 shows solvatochromism in the visible region and this result is promising for use of quinhydrone type calixarenes in the design of sensors.

The electrophilic ipso-nitration reactions of calix[6]arene 216 bearing three methylimidazolyl groups in alternate ring positions have been performed. It was observed that the reaction of 216 with fuming nitric acid and glacial acetic acid at room temperature in CH₂Cl₂ leads to partial ipso-nitration, affording tris-nitrated product. However, the reaction of 216 with concentrated sulfuric acid at 60 °C leads to ipso-sulfonation of all benzene rings, affording hexa-sulfonated compound 218.

Scheme 56

Scheme 57
In order to understand why the nitration proceeds only on the anisole rings in preference to imidazolyl-substituted rings, the nitration was performed on calix[6]arenes bearing other than methylimidazolyl groups, for this purpose, calixarenes 219a-c containing amino groups and 220 containing i-butyl groups have been used. Calixarenes 219a,b were obtained by known procedures, \(^{142}\) calixarenes 219c and 220 were synthesized from 219d by treatment with 3-(N,N-dimethylamino)propylchloride and i-butyl iodide, respectively.

Scheme 58

Calixarenes 219a-c and 220 were nitrated as in the case of 216, it was observed that 219a-c afforded the tris-nitrated products 221a-c, whereas from 220 the hexa-nitrated product 222 has been obtained.

Scheme 59

\[
\begin{align*}
\text{R} & \\
\text{a} & \text{CH}_2\text{CH}_2\text{NH}_2 \\
\text{b} & \text{CH}_2\text{CH}_2\text{NMe}_2 \\
\text{c} & \text{CH}_2\text{CH}_2\text{CH}_2\text{NMe}_2 \\
\text{d} & \text{H} \\
\end{align*}
\]
The crucial role of the substituent R may be explained by the presence of a protonable site in this group. Calixarene 216 containing methylimidazolyl groups as well as calixarenes 219a-c containing arms with primary and tertiary amino groups, are protonated under the strongly acid nitration conditions. These protonated amino groups form hydrogen bonds with the phenolic oxygen atoms of calixarene, therefore the whole aromatic ring has lower electron density, i.e. is deactivated toward electrophilic attack of nitronium ion NO$_2^+$+. As a result, in 219a-c, the nitration proceeds only on the anisole rings and not on the rings containing amino groups. However, in 220, where the amino groups are absent, such deactivation does not exist and therefore the nitration affords hexa-nitrated product 222.

Scheme 60

It should be pointed out that the studied selective ipso-nitration of calix[6]arenes allows the direct introduction of three nitro groups in alternate rings, therefore the disymmetrization of the wide rim is possible. This selectivity depends on the nature of the substituents on the phenolic rings of the calixarenes. Facile reduction of the nitro groups leading to amino groups opens further synthetic perspectives for selectively functionalized calix[6]arenes.$^{141}$

With the consideration of usefulness of amino groups, 1,3-alt calix[4]arenes bearing four or eight amino groups have been synthesized.$^{143}$

In order to obtain tetraaminocalixarenes the following reactions were performed. The reaction of calixarene 92 with N-bromopropylphthalimide affords 223 which with bromopropynitrile gives 224, this compound can be also obtained from 92 by treatment with bromopropynitrile yielding 925, subsequently reacted with N-bromopropylphthalimide. Cleavage of 224 with hydrazine in ethanol proceeds without reduction of the nitrile groups to give 226, this compound was acetylated affording 227 which upon reduction yielded 228.
Scheme 61

The $O$-allylation of 229 with allyl bromide gives rise to 230 which by simultaneous reduction of nitro groups and hydrogenation of C = C double bonds affords diaminocalixarene 231. The protection of amino groups of 231 by phthalimide units leads to 232, which was submitted to ipso-nitration yielding dinitrocalixarene 233. The treatment of compound 233 with hydrazine in ethanol by cleavage of the phthalimide groups gives 234, and catalytic hydrogenation of the nitro groups affords 235.
Scheme 62

Investigation of the partial protection of 236 by Boc has shown that the reaction with two Boc anhydride equivalents leads to mono- and diprotected calixarenes 237 and 238, while the use of three Boc anhydride equivalents affords tri- and tetraprotected 239 and 240, respectively.
Scheme 63

Scheme 64
Calixarene 223 was ipso-nitrated to give 241 which, with allyl bromide yields 242, which in turn, is catalytically reduced to 243. Compound 242 treated with hydrazine in EtOH affords 244 in which the nitro groups are retained, however, when this reaction proceeds in the presence of Pd/C catalyst it leads to tetraaminocalixarene 245.

In order to obtain octaaminocalixarenes, the following reactions were performed. Calixarene 92 was treated with N-bromopropylphthalimide to give 246 which upon ipso-nitration yields 247. The catalytic reduction of the nitro groups of 247 affords 248, while reaction of 247 with hydrazine in EtOH results in the cleavage of the phthalimido groups affording 249. Reaction of 247 with hydrazine in EtOH in the presence of Pd/C causes simultaneous cleavage of the phthalimido groups and reduction of the nitro groups leading to the octaaminocalixarene 250. The presence of amino groups in calixarenes is of a great importance for their further reactions.143

Scheme 65

Due to their redox properties, porphyrins are important components in crucial biological electron-transport systems such as respiration and photosynthesis. Porphyrins have high electronic excitation energy, allowing light/electricity conversion and are thus promising for their use in solar
cells. It has been reported that anionic calixarene 251 may form noncovalent assemblies with free base or metallated (M = Cu$^{2+}$, Zn$^{2+}$, Au$^{3+}$) cationic porphyrins A.

Scheme 66

The titration of 251 with aliquots of porphyrins A initially forms the central core, i.e. 251•A serving as a template for complexing further porphyrin units. The subsequent addition of two equivalents of porphyrin A leads to formation of the assembly 251•A$_3$ in which the added A molecules are situated above and below the central core plane (i.e. before and behind the top view plane), the next two A molecules afford 251•A$_5$ assembly, and addition of further two A molecules leads to 251•A$_7$ assembly.

Scheme 67
Porphyrrins used may be different and the core porphyrin may be metallated or not; the sequence and stoichiometry of formed assemblies depend on the order of addition and number of used porphyrin equivalents. The above assemblies with desired porphyrin sequences are promising for construction of molecular devices.

As a continuation of the above investigations, the noncovalent assemblies of octacationic biscalixarene 252 with tetraanionic copper porphyrin B have been synthesized, the templating agent 252 is water soluble and has cavities oriented in a divergent fashion.

Scheme 68

Scheme 69
The synthesis of 252 begins by the treatment of calixarene 253 with 1,6-hexanediyl ditosylate affording 254 which reacts with paraformaldehyde and HCl in dioxane to give 255. The amination of 255 with Me₃N yields bis-calixarene 252.

During the UV/Vis titration, the aqueous solution of 252 was treated stepwise with B aliquots. Initially the central core 252₄•B is formed, which upon addition of four B equivalents affords the 252₄•B₅ assembly. The subsequent treatment of 252₄•B₅ with two B equivalents yields the 3D 252₄•B₇ assembly, (i.e. 252₄•B₅ in which two added B equivalents are situated below and above the central core), whereas the treatment of 252₄•B₅ with twelve 252 equivalents leads to the 2D assembly 252₁₆•B₅. It is noteworthy that in experiments the different porphyrins may be used.

![Scheme 70](image-url)
5. Conclusion

The rapid development of research area of calixarenes observed today, results in a large amount of reports. One may believe that examples shown in the present review, albeit only selected, could provide some information connected with functionalization of these compounds. It is noteworthy that the properties of obtained functionalized calixarenes strongly depend on their structure.

Many works deal with calixarene complexes,\(^{150-153}\) among them complexes with metal ions,\(^{152,153}\) are of a great importance so for recovery as well as for removal of toxic metals from industrial sewages. Having in view the ecological safety one should also point out studies concerning the nuclear waste management.\(^{153}\)

The works aiming to use calixarenes for construction of systems adsorbing gases such as hydrogen,\(^{154}\) or methane,\(^{155}\) are of interest in the field of energetics, and the development of these investigations is expected. A growing attention is paid today to a wide range of sensors,\(^{156,157}\) as well as to removal of undesired compounds from industrial waste,\(^{158-160}\) this research area being strongly connected with the environment protection.

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7. References

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