Part I

General Characteristics of Calixarenes
1

Reactivity of Calixarenes

Numerous reactions of calixarenes have been reported [1–14]; some examples of these are described here. To improve the properties of calixarenes, functionalization of the narrow [15–17] as well as of the wide rim is carried out [18–20]. In the first part, functionalization of the narrow rim of calixarenes is described, followed by functionalization of the wide rim. Then some examples of calixarene bridging are presented.

1.1

Functionalization of the Narrow Rim

A series of calixarenes bearing azo chromophores on the narrow rim were synthesized using two routes. The first one was a direct reaction of calixarenes 1a–c with 4-chloroacetoaminoazobenzene 2 in the presence of K₂CO₃ and KI. In the second, indirect approach calixarenes reacted with ethyl chloroacetate affording esters 3 hydrolyzed to give acids 4, which were treated with thionyl chloride, followed by p-aminoazobenzenes ArNH₂. Both procedures led to the formation of calixarenes 5 containing azo chromophores [21].

Copyright © 2009 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 978-3-527-32263-3
Reactivity of Calixarenes

In order to introduce the ferrocenyl unit into calixarenes, the reaction of 1a–c with ethyl chloroacetate affording esters 3 was performed. These compounds reacted with hydrazine to give hydrazides 6, which upon treatment with ferrocenecarboxaldehyde yielded derivatives 7 [22].

The reaction of calix[6]arene 8a with (+)-camphor-10-sulfonyl chloride RCl 9 affords either the mono-O-sulfonylated product 8b or the hexa-O-sulfonylated product 8c, depending on the stoichiometry [23]. This rather unexpected result, i.e. the absence of di- to pentasubstituted products, is due to the structure of 8b in which the camphor-sulfonyl unit covers the narrow rim of calixarene, thus forming a steric hindrance for substitution of the second hydroxyl group.

However, if the second hydroxyl group is sulfonylated, the two substituents repulse one another; therefore, other hydroxyl groups are exposed to reaction with excess sulfonyl chloride to give 8c.

It was established that 1,3,5-trimethoxy-t-butylcalix[6]arene 10 reacts with phenylpyridines 11 and 12 and with fluorenylpyridine 13 to give calix[6]arenes 14, 15, and 16 respectively, functionalized at alternate rings on the narrow rim [24]. The $^1$H NMR measurements show that 14–16 exist predominantly in the $C_{3v}$ cone conformation and have unusually deep cavities.
1.1 Functionalization of the Narrow Rim
The restriction of the conformational flexibility of calix[6]arenes may be achieved by using the Ritter reaction. This procedure involves the reaction of calix[6]arenes bearing one, three, and six cyanomethoxy groups on the narrow rim i.e. 17, 18, and 19 respectively, with tertiary alcohols [25]. Functionalization of 17 and 18 with 1-adamantanol 20a (R=H) or 3-substituted 1-adamantanol 20b (R=CH₂COOH) yielded monoamides 21a,b and triamides 22a,b respectively, existing in rigid cone conformations.
The reaction of 19a–c bearing six cyanomethoxy groups showed an unexpected regioselectivity, since with adamantanol or t-butyl alcohol they afford tetramides 23, adopting a flattened 1,2,3-alt conformation. This result, i.e. the selective functionalization of the narrow rim of calixarenes bearing exhaustively modified hydroxyl groups is rather surprising, because usually selective reactions occur in calixarenes with free hydroxyl groups.
1. Reactivity of Calixarenes

1.2 Functionalization of the Wide Rim

In order to obtain anion binding derivatives of calixarenes, syntheses of poly-Lewis-acid-based calixarenes have been studied. For this purpose, calix[4]arene 1a was subjected to the removal of the \( \text{t-butyl} \) groups, followed by \( \text{O-methylation} \) to give 24; its bromination afforded tetrabromocalix[4]arene 25. The reaction of 25 with \( \text{t-butyllithium} \) gave the tetralithium salt, which without isolation was silylated with chlorotrimethylsilane affording tetrakis-silylated derivative 26 and the trisilylated derivative 27 [26]. However, the use of boron electrophiles after lithiation, e.g. boron trifluoride or boron trichloride instead of \( \text{Me}_3\text{SiCl} \), resulted in only partial boronation.

![Chemical structure of calixarenes 1a, 24, 25, 26, and 27]

In the next experiment, calix[8]arene 1c was used. The removal of \( \text{t-butyl} \) groups from 1c afforded 28a, which was methylated to give 28b. The subsequent bromination yielded 29, which was lithiated, forming the octalithium salt; this without isolation was treated with \( \text{Me}_3\text{SiCl} \), yielding 30. It was shown that only partial silylation occurs, since only disilylated compound 30 was obtained [26].

Tetraiodocalixarene 31 was subjected to the Wurtz–Fittig reaction with the use of \( \text{Na/Me}_3\text{SiCl} \) in 1,2-dimethoxyethane (DME), affording the mixture of tetrakis- and tris-silylated calixarenes cone 32 and flattened cone 33, separated by chromatography. However, the reaction of tetrabromocalixarene 34 with \( \text{Na/Me}_3\text{SiCl} \) in toluene gave 35, both C-silylated and O-silylated, which upon hydrolysis yielded tetrakis-silylated calixarene 36 [27].
It should be noted that the above Wurtz–Fittig reactions are promising, since such large-scale processes are safer, cheaper, and easier to perform than those using t-butyllithium.
Reactivity of Calixarenes

A series of calix[4]arenes with azo moieties containing four, three, two, and one free phenol groups, as well as those without free phenol groups, have been investigated in view of their conformational properties. Calixarenes with azo moieties, containing one to four free phenol groups were synthesized either by coupling calixarenes with corresponding diazonium salts or by reaction of calixarene diquinones with nitros substituted phenylhydrazines [28].

The coupling of calixarene 37a with diazonium salt 38 [29] affords azosubstituted calixarenes containing four free phenol groups 39; similarly, reactions of 40 with 38 and 41 yield azosubstituted calixarenes containing three phenol groups 42. Similar reactions of calixarenes 43 with 38, 41, or 44 afford 45 containing two phenol groups. An alternative procedure, i.e. oxidation of 46 with ClO\textsubscript{2} leading to calix[4]arene diquinones 47, subsequently treated with 4-nitro- and 2,4-dinitrophenylhydrazine, also gives rise to azosubstituted calixarenes containing two phenol groups 48. The coupling of calixarenes 49 with diazonium salts 38 or 41 yields calixarenes 50a,b, containing only one free phenol group.
1.2 Functionalization of the Wide Rim

\[
\begin{align*}
\text{DMF / MeOH} + \text{O}_2N & \rightarrow \text{R}_1O \text{R}_3O \text{R}_3OH \\
\text{ClO}_2 + \text{H}_2\text{SO}_4 & \rightarrow \text{R}_1 \text{R}_2 \text{R}_3 \text{N}_2\text{Cl}^-
\end{align*}
\]
Acetylation and benzoylation of calixarenes bearing azo moieties were carried out for investigation of conformational changes that occur during these processes. In the study of calixarenes with four phenol groups, it was found that acetylation of cone 39a affords 1,3-alt 51, and benzoylation of 39b gives rise to paco 52. Acetylation of tetrasubstituted 39e containing four phenol groups yields 1,3-alt 53 and acetylation of 42a,b with three phenol groups leads to paco 54a,b. Acetylation of 48a–d containing two phenol groups affords calixarenes 1,3-alt 55.
1.2 Functionalization of the Wide Rim

Ac₂O / pyridine

39e

1,3-alt 53

Ac₂O / pyridine

R

42

a A

b N

Paco 54

R

a A

b N

Ac₂O / pyridine

R

48

a COPh H

b CH₂Ph H

c COPh NO₂

d CH₂Ph NO₂

1,3-alt 55

a COPh H

b CH₂Ph H

c COPh NO₂

d CH₂Ph NO₂
The conformational flexibility of calixarenes is usually explained by the presence of intramolecular hydrogen bonds, which is related to the number of free phenol groups. Accordingly, calixarenes containing four phenol groups $39a$–$e$ exist as cone conformers.

It could be expected that the conformational properties will be influenced by the decrease in the number of phenolic groups. However, it was shown that $42a,b$ containing three phenol groups and $45a$–$g$ containing two phenol groups also exist as cone conformers. One should note that calixarenes with two phenol groups, obtained by an alternate route via calix[4]arene diquinones $47a,b$ present in their cone and paco conformations being in equilibrium with each other, afford $48a$–$d$ as cone conformers. The results of single-crystal X-ray diffraction analysis of $50a,b$ containing one phenol group indicate that they are present in a flattened cone conformation [28].

An efficient synthesis of oligothiophene-substituted calix[4]arenes was performed. The process begins with the stabilization of the cone conformation of cone $37a$, which involves the alkylation of calix[4]arene with bromopropane or bromodecane, followed by bromination with N-bromosuccinimide (NBS). The tetrabromoderivative $56$ obtained was submitted to palladium-catalyzed Kumada cross coupling with thiophenylmagnesium bromide, prepared in situ, in the presence of PdCl$_2$(dpdf) to give tetrasubstituted calixarene $57$. The bromination of $57$ with NBS yielded $58$, which, upon cross-coupling with thiophenylmagnesium bromide, afforded bisthiophenylcalixarene $59$. By repetition of such a sequence of bromination with NBS and cross-coupling reactions, tris(thienyl)- and tetra(thienyl)calixarenes $60$ and $61$ were obtained respectively [30]. The electrochemical and optical properties of synthesized oligothiophene-substituted calix[4]arenes $59$–$61$ were determined. It should be noted that they show high thermal stability ($T_d > 400$ °C).
The heteroarylation of calix[4]arene 37a at the wide rim was performed in a one-step procedure as an example of the direct C–C coupling of calixarene with electron-poor 1,2,4-triazinone 62 via the SN1 methodology. The reaction can be performed in trifluoroacetic acid (TFA) in the presence of acylating agents, such as acetic or trifluoroacetic anhydrides. Treatment of 62 with acetic or trifluoroacetic anhydride in TFA yields a protonated form of 2-acyl-1,2,4-triazinone. The process is accompanied by the rearrangement of the N(2)-acyl derivatives to those bearing the acyl group at the N(1) atom, adjacent to the reaction center [31].

Organic anhydrides acylate hydroxyl groups of calixarene 37a and change its conformation from cone into 1,3-alternate. The nature of the acylating agent influences the stereochemistry of the reaction of 37a with 62. Thus, in the presence of Ac₂O, the 1,3-alt calixarene 63 is formed, whereas reaction with (CF₃CO)₂O and the subsequent recrystallization from MeOH gives, via the 1,3-alt intermediate 64, the cone calixarene 65. It is noteworthy that 63 and 65 effectively transport La³⁺ ions.
Reactivity of Calixarenes
The glycoside cluster effect exists in the carbohydrate–protein interaction, an important process in intercellular communication and in the adhesion of bacteria and viruses to the cell surface. For a better understanding of this effect, the glycocluster assemblies on calix[4]arene scaffold were synthesized.

The 1,2,3-triazole linkers have been formed via click chemistry, i.e. the copper (I)-catalyzed Huisgen 1,3-dipolar cycloaddition of azides to alkynes [32]. Calixarenes 66 and 67 bearing azido units, as well as calixarene 68 containing ethynyl groups, were used as starting materials. The reaction of 66 and 67 with ethynyl glycoside 69 afforded glycoclusters 70 and 71. The reaction of 68 with azidomethylglucoside 72 yielded glycocluster 73. It should be noted that the formation of 1,4-disubstituted triazole rings resulted in very high yield [33].
Cholic acid is being used as a building block for the construction of conformationally controllable foldamers [34] and nonfoldamers [35]. It was established that calixarene 74 can reversibly switch between a micelle-like conformation (with the hydrophilic faces of cholates pointing outward) in polar environments and a reversed-micelle-like conformation in nonpolar environments [36]. As a result of the conformational change, 74 can act as a tunable supramolecular host to bind polar guests in nonpolar solvents and nonpolar guests in polar solvents.

The amphiphilic calixarene 75 containing cholate units linked by azobenzene spacers was synthesized. It was sensitive both to solvent changes (due to cholate units) and ultraviolet (UV) irradiation (due to azobenzene units). In nonpolar solvents, 75 turns its polar faces inward to bind polar guests, e.g. sugar derivatives. In polar solvents, 75 turns its nonpolar faces inward to bind hydrophobic guests, e.g. pyrene. Calixarene 75 can also respond to UV irradiation, resulting in the trans – cis isomerization of azobenzene units; it should be noted that the response toward both kinds of solvents and UV light is fully reversible [37].

Many calixarenes bearing azobenzene units on the wide rim are known [38]. The synthesis of 75 begins with the diazotization of calixarene 76 followed by coupling with phenol to give calixarene 77, which upon reaction with brominated cholate 78 affords 75.

In the study of guest-binding properties of 75, it was observed that, in 5% CD$_3$OD/CCl$_4$, i.e. a mostly nonpolar mixture, 75 binds phenyl β-D-glucopyranoside 79. The binding of polar guests in a nonpolar mixture shows that 75 can adopt reversed-micelle-like conformations similar to that of 74.
1.2 Functionalization of the Wide Rim

\[ R = n-C_6H_{13} \]

1. NaNO₂ / HCl
2. Phenol / pyridine
It was found that pyrene 80 is a suitable guest for the micelle-like conformer. In methanol, 74 and 75 bind with pyrene through the hydrophobic faces of cholates, supporting the formation of micelle-like conformations in polar solvents. The above experiments combining the solvent-induced conformational changes and photoisomerization of 75 show their dual responsive properties.

The palladium-catalyzed Buchwald–Hartwig procedure was used for the synthesis of cyclenylcalixarenes [39]. Monobromo- and dibromocalixarenes 81 and 82 reacted with threefold Boc-protected cyclen 83b in the presence of catalytic amount of Pd(OAc)$_2$ and tris(t-butyl)phosphine affording mono- and biscyclenylcalixarenes 84 and 85 respectively. It should be mentioned that cyclen 83a was Boc-protected to give 83b in order to avoid the connection of more calixarene units on its molecule. The Boc-protective groups were removed from 84 and 85 in the presence of TFA to give N-protonated mono- and biscyclenylcalixarenes 86 and 87. They were basified with a basic anion exchanger affording mono- and biscyclenylcalixarenes 88 and 89, which upon treatment with Zn(ClO$_4$)$_2$·6H$_2$O yielded metallated compounds 90 and 91 [39].
1.2 Functionalization of the Wide Rim
In order to investigate the influence of conformation of starting materials on the Buchwald–Hartwig process, cone dibromocalixarene 92 was alkylated with 1-iodopropane in tetrahydrofuran (THF) using Me$_3$SiOK as a base to give 1,3-alt 93, which was treated with 83b. This reaction afforded mono- and biscyclenylcalixarenes 94 and 95, both as 1,3-alt conformers.

It is worth noting that the 1,3-alt tetrabromocalixarene 96 does not form calixarene containing four cyclen units, but the reaction of 96 with 83b leads to 1,3-alt monocyclenylcalixarene 97. This fact results from the increased steric hindrance of the 1,3-alt system, since the presence of one bulky tri(Boc)cyclen unit at the wide rim of calixarene molecule causes the outstretching of two of its neighboring propoxy groups. As a consequence, two bromine atoms present at the narrow rim are located closer to each other, making their substitution impossible. This
behavior resembles a complexation-induced negative allostERIC effect observed in some 1,3-alt calixarenes. It should be noted that calixarene 90 shows binding affinity to chloride, acetate, and benzoate anions, forming 1:1 complexes with them.

1.3 Functionalization of Both Rims

Calixarenes bearing isoxazole or isoxazoline substituents undergo Mo(CO)$_6$-mediated opening of the heterocyclic ring to give calixarene derivatives containing $\alpha$, $\beta$-unsaturated $\beta$-aminoketone or $\beta$-hydroxyketone units respectively [40, 41].

Calixarenes 98 bearing isoxazole units at the narrow rim afford compounds 99. Calixarenes 100 and 101 bearing isoxazoline units at the narrow rim yield products 102 and 103 respectively; in the former case also, the cleaved calixarene 37a is obtained. Calixarenes 104a–c bearing isoxazoline moiety at the wide rim undergo a similar reaction, leading to 105a–c. The $^1$H NMR results have shown the cone conformation for all calixarenes studied.
By investigating models of metalloenzymes, it was found that calixarene 106 treated with imidazole 107 affords derivative 108 containing three imidazolyl arms at the narrow rim, which mimics the coordination core encountered in enzymes. Upon binding a transition-metal ion, such calixarenes are constrained to a cone conformation, thus mimicking the enzyme funnel that controls the access to the metal center [42].

In the search for supramolecular models of metalloenzyme sites, the replacement of t-butyl groups by electrophilic substituents has been performed on the basis of an example of ipso-chlorosulfonylation [42]. When aromatic rings were O-substituted by a protonable imidazole units, they became deactivated toward an electrophilic attack, and therefore the anisole rings could be selectively ipso-chlorosulfonylated under mild conditions at room temperature. The regioselectivity was controlled by the presence of protonable imidazole units at the narrow rim. The process is selective and highly efficient.
It was established that treatment of 108 with chlorosulfonic acid at room temperature leads to the formation of the intermediate 109, which upon hydrolysis yields the sulfonate derivative 110, and gives sulfonamide derivatives 111a–d with amines. The reactions of 109 were performed with NH₃, NHMe₂, and t-butyldimethylsilyl (TBDMS)-protected diethanolamine; in the latter case, the deprotection with TFA was necessary to obtain 111d [42]. The above reactions of 108 are useful for the synthesis of calixarenes selectively functionalized at the wide rim, and cause water solubilization of obtained products.
Reactivity of Calixarenes

When reaction of 108 with chlorosulfonyl acid is carried out at a higher temperature (reflux of CH₂Cl₂), perchlorosulfonylation, leading to hexachlorosulfonyl calixarene 112, takes place. Similarly, hydrolysis of 112 affords the hexaanion 113, and reaction with TBDMS-protected diethanolamine leads to 114a, deprotected to 114b.

It should be noted that hexaanion 113 cannot be constrained to the desired cone conformation due to the strong repulsion at the wide rim. In order to avoid perchlorosulfonation, in the synthesis of 110 and 111 only three benzene rings were sulfonated by carrying out the reaction at room temperature.

The reaction of 108 with HNO₃ in the presence of AcOH yields the product of ipso-nitration 115. This process may be combined with chlorosulfonylation of 115, leading to the ipso-chlorosulfonylation product 116. Hydrolysis of 116 afforded tris-sulfonate derivative 117, and the reaction of 116 with NHMe₂ and TBDMS-protected diethanolamine gave tris-sulfonamides 118 [42].
1.3 Functionalization of Both Rims

SnCl₂ / EtOH

HNO₃ / AcOH

DCM

PhCH₂Cl

or

n-C₄H₉Br

or

BrCH₂COOEt

OH

HO

OH

HO

OH

NO₂

NH₂H₂N

RO

OR

HO

OH

O₂N

N

N

Me

COOH

OH

RO

OR

HO

OH

NH

RO

HN

OR

HO

N

N

Me

O

N

N

Me

OMe

O

N

Me

Cl

−

R

a

CH₂Ph

b

n-C₄H₉

c

CH₂COOEt

R

a

CH₂Ph

b

n-C₄H₉

c

CH₂COOEt

R

DMT-MM

R

a

CH₂Ph

b

n-C₄H₉

c

CH₂COOEt

DMT-MM
Reactivity of Calixarenes

The functionalization of narrow and wide rims of calixarene 1a has been performed. Reaction of 1a with benzyl chloride, 1-bromobutane, or ethyl bromoacetate affords calixarenes 119, substituted on the narrow rim, which upon nitration yield dinitro calixarenes 120.

Reduction of 120 with SnCl₂ leads to the formation of diaminocalixarenes 121. These compounds were treated with 2,2’-bipyridine 122 in the presence of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) as condensing agent to give calixarenes 123 substituted on the wide rim [43].

1.4 Bridging of Calixarenes

In the study of photochemical reactions of calixarenes [44, 45], the photochemical cycloisomerizations of calixarenes containing phenylethynyl groups have been investigated. Calixarenes 124 serve as an example. they undergo photochemical cycloisomerization to give 125. It was found that the attempted second photochemical reaction, which should have led to 126a,b, did not occur; instead 127a,b was formed [46]. One should mention that molecular mechanics modeling has shown that 126a,b are highly strained.

It was observed that the presence of hydroxyl groups in starting compounds is necessary for the above photocyclization/rearrangement reactions. This was confirmed by the fact that the photoirradiation of 124c,d containing O-propyl groups instead of hydroxyl groups did not result in the formation of desired products.

The above reactions are assisted by the templating effect of the calixarene scaffold; their mechanism is proposed. It should be noted that these reactions are rare examples of intramolecular cyclizations of calixarenes containing alkynyl groups.
1.4 Bridging of Calixarenes

[Chemical equations and diagrams]
Reactivity of Calixarenes

Calixarene 1a reacts with bis(tosylethoxy)benzenes 128 to give intramolecularly bridged calixcrowns 129a,b, and intermolecularly bridged biscalixcrown 130. Calixcrowns 129a and 129b of 1:1 stoichiometry are formed from ortho and meta isomers of 128, while 130 of 2:2 stoichiometry is obtained from the para isomer of 128 [47].

The bridging of calixarenes bearing allyl substituents on narrow or wide rims has been reported. This process occurs by 1,3-dipolar cycloaddition reactions, with benzodinitrile oxides 131 serving as bis-1,3-dipoles; benzodinitrile oxides are formed in situ from benzodihydroximoyl chlorides e.g. 132 [48].

In the study of diallylcalixarenes, it was observed that the reaction of 133 with isophthalaldinitrile oxide (in the form of 132) affords calixarene 134 bridged at the narrow rim; a similar reaction of 135 with 132 yields calixarene 136, bridged at the wide rim. When 135 reacted with terephthalaldinitrile oxide (in the form of 137), the diastereomers 138 and 139 were obtained.
1.4 Bridging of Calixarenes
1.4 Bridging of Calixarenes

1. t-BuLi / THF
2. (Allyl)Me₂SiCl / Et₃N

TBAF / THF
By investigating monoallylcalixarenes, it was found that the reaction of 140 bearing the allyl group at the wide rim with terephthalaldinitrile oxide 137 did not give the expected biscalixarene 141; instead the asymmetric calixarene 142 bearing isoxazoline and oxime moiety was formed.

However, the reaction of 140 with thiophene-2,5-dinitrile oxide (in the form of 143) afforded the desired biscalixarene 144 along with isoxazoline-oxime compound 145. The reaction of monoallylcalixarene 146, bearing the allyl group at the narrow rim yielded biscalixarene 147, as expected.

Bridging of allyldimethylsilylated calixarenes, which leads to the formation of a Si–O–Si siloxane link, was investigated [49]. The reaction of 148 with t-BuLi, followed by (allyl)Me₂SiCl, afforded calixarene 149 bearing two allyldimethylsilyl groups; 149 upon treatment with tetrabutylammonium fluoride (TBAF) in THF yielded bridged calixarene 150. Calixarene 151 containing four allyldimethylsilyl groups afforded the bridged compound 152 via a similar reaction with TBAF. Both bridged products 150 and 152 have the flattened cone conformation.

The reaction of calixarene 153 with TBAF gave rise to bridged compounds 154 obtained as a mixture of cone and paco conformers. Removal of benzyl groups by hydrogenation in the presence of Pd/C yielded dihydroxycalixarenes 155, also as a mixture of cone and paco conformers. This result was unexpected because usually the presence of hydroxyl groups, allowing the hydrogen bonding, favors the formation of the cone conformer exclusively; in this case, however, presumably the presence of the siloxane bridge increased the barrier of the conformational change. Both cone and paco 155 were separated by chromatography [49].
1.4 Bridging of Calixarenes

![Diagram showing the bridging of calixarenes]

Cone 155 + Paco 155

$\text{Ph} \quad \text{Ph}$

$\text{Me}_2\text{Si} \quad \text{Me}_2\text{Si}$

$\text{O} \quad \text{O}$

$\text{MeO} \quad \text{MeO}$

$\text{H}_2\text{Pd} / \text{C}$

$\text{TBAF} / \text{THF}$

$\text{R} = \text{C}_6\text{H}_5\text{Ph}$
1.5 Other Reactions of Calixarenes

Contrary to many modifications of narrow and wide rims of calixarenes, the monofunctionalization of four methylene bridges of calixarenes is rather rare [50]; the following reactions of 156a,b may serve as examples. For this purpose, calixarenes 156a,b were brominated with NBS to give 156c,d, respectively, which were used as starting materials for functionalization.

The solvolysis of 156d in trifluoroethanol (TFE) under SN1 conditions yielded calixarene 156e containing four trifluoroethyl groups. In order to obtain the tetraethoxy-substituted product 156f, the solvolysis of 156d in EtOH/TFE (1:1) mixture was carried out. The reaction of 156d with NaN₃ in TFE leads to 156g of paco conformation. The above reactions gave rise to products containing C–O bonds in the case of TFE and EtOH, and C–N bonds in the case of azide [51].

In order to synthesize products with C–C bonds, the solvolytic Friedel–Crafts reaction of 156c with 2-methylfuran was performed in TFE using 1,2-butylenoxide as a scavenger of HBr; calixarene 157 was obtained as the sole product. The X-ray analysis results have shown its pinched cone conformation with all furanyl substituents situated at equatorial positions of the macrocycle and the furanyl oxygen atoms pointing toward the narrow rim [51].
1.5 Other Reactions of Calixarenes

- Concentrated HCl / benzene
- NaOH / TEBA
- Acetone
- Concentrated HCl / benzene
Synthesis of biscalixarenes joined tail to tail via ether linkages was carried out. Biscalixarenes have interesting recognition abilities; they are promising in the design of redox active chromophores, ditopic receptors, and ion selective electrodes [52]. The acid-catalyzed condensation of \( p \)-cresol with formaldehyde leads to calix[6]arene 158 in a single step. The reaction of 158 with bis(2-chloroethyl)ether in the presence of NaOH and triethylbenzylammonium chloride (TEBA) as a phase-transfer catalyst (PTC) affords biscalix[6]arene 159.

In order to obtain other biscalixarenes, 158 was treated with bromoacetic acid to give calixarene 160, which reacted with bis(2-chloroethyl)ether in the presence of NaOH and TEBA, yielding biscalix[6]arene 161a. The reaction of 161a with thionyl chloride gives rise to 161b, which upon condensation with N-phenylhydroxylamine affords biscalixarene 161c bearing hydroxamic acid moieties.

In the above syntheses, a phase-transfer catalyst was used; a large amount of solvents and a longer reaction time would have been required without the use of the catalyst [52].