Calixarenes containing modified *meso* bridges

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**Abstract**

In the first part of this review calixradialenes and homocalixarenes are described showing their syntheses and application possibilities. The second part concerns the use of compounds related to spirodienonecalixarenes in the synthesis of wide rim functionalized calixarenes.

**Keywords:** Calixradialenes, homocalixarenes, ketocalixarenes

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**1. Introduction**

Calixarenes and their derivatives are cage macrocycles important as scaffolds upon which receptors of organic compounds and metal ions have been designed. They are intensively studied due to the wide range of their applications, e.g. they form inclusion complexes useful in various fields,¹ form calixarene capsules,² are promising as chiral NMR solvating agents,³ form gold⁴...
and silver\textsuperscript{5} nanoparticles, are useful as catalysts\textsuperscript{6} and as liquid crystals,\textsuperscript{7} serve for design of sensors\textsuperscript{8-10} and are promising as therapeutic agents.\textsuperscript{11,12}

Calixarenes belong to the family of cage macrocycles, including besides them cyclodextrins,\textsuperscript{13-15} cucurbiturils\textsuperscript{16,17} and pillararenes.\textsuperscript{18} All macrocycles of this family are useful in the field of supramolecular chemistry for formation of inclusion complexes\textsuperscript{1,19-21} and rotaxanes in which they serve as rings.\textsuperscript{22-25}

One should note also heterocalixarenes, \textit{i.e.} thia-, aza- and homooxa-calixarenes containing S, N and O heteroatoms in their structures,\textsuperscript{26-28} They have recently attracted considerable attention due to their easy accessibility and versatile receptor properties. Related to calixarenes are resorcinarenes and pyrogallolarenes, which recently are being intensively studied.\textsuperscript{29,30}

Attention should be paid also to pillararenes, a new class of cage macrocycles interesting for their receptor properties,\textsuperscript{31} reactivity\textsuperscript{32} and promising therapeutic applications,\textsuperscript{33,34} as well as the formation of rotaxanes,\textsuperscript{35} supramolecular polymers,\textsuperscript{36} gold nanoparticles,\textsuperscript{37} artificial transmembrane channels,\textsuperscript{38} vesicles\textsuperscript{39} and liquid crystals.\textsuperscript{40}

The present paper is a continuation of our earlier review on calixarenes functionalized at meso positions,\textsuperscript{41} as well as of other papers dealing with rotaxanes containing calixarene macrocycles as rings,\textsuperscript{22} functionalized calixarenes,\textsuperscript{42} covalently and noncovalently bound assemblies of calixarenes\textsuperscript{43} and calixarene complexes with metal ions;\textsuperscript{44,45} calixarenes and resorcinarenes were described in ref. 30.

Calixarenes containing modified meso bridges\textsuperscript{46-48} are synthesized \textit{via} substitution of methylene bridges\textsuperscript{49-52} or \textit{via} their oxidation to keto groups;\textsuperscript{53,54} they have not been as intensively studied as calixarenes functionalized at wide\textsuperscript{55,56} or narrow\textsuperscript{57,58} rims. Therefore it seems of interest to describe several selected examples of this class of compounds, showing their possible applications.

In the present review, calixradialenes which are new species promising as synthons for reactions performed at meso positions, will be presented first. Homocalixarenes will then also be briefly described; these compounds deserve an attention due to their receptor properties.

In the previous paper on meso functionalized calixarenes\textsuperscript{41} we showed the oxidation of $p$-$t$-butylcalix[4]arene into bist(spirodieneone)calix[4]arene. In this review compounds related to spirodieneone calixarenes will be described as synthons of wide-rim functionalized calixarenes obtained by the acid-mediated bist(spirodieneone) route and by a silver-mediated $p$-bromodieneone route.

Calixarenes containing modified meso bridges may be considered as a supplement to numerous reports dealing with functionalized calixarenes, especially those functionalized at their wide rims.

2. Calixradialenes

Calixradialenes are calixarene derivatives with exocyclic double bonds. The name calixradialenes is connected with their formal similarity to radialenes, in which double bonds
radiate from the centre of the macrocycle. Structures of [6]radialene and calix[n]radialene are shown in Scheme 1.

Calixradialenes are obtained from ketocalixarenes by reaction with MeLi followed by water elimination.\(^{59}\) Treatment of ketocalix[4]arene 1 containing two keto groups at adjacent *meso* positions with MeLi, and subsequent elimination of water, affords calixradialene 2 with two exocyclic double bonds at adjacent *meso* positions. (Scheme 1)

![Scheme 1](image)

Similar reactions of ketocalix[n]arenes 3-5 (n=4-6) lead to the respective calix[n]radialenes 6-8 (n=4-6). We describe first the syntheses (Scheme 2) of the ketocalix[n]arenes 3-5.

Ketocalix[4]arene 3 was synthesized previously from \(p\)-t-butylcalix[4]arene tetraacetate by \(\text{CrO}_3\) oxidation followed by hydrolysis of the acetate groups and methylation of the hydroxy groups.\(^{60}\) It may be also obtained from calixarene 9 by perbromination with NBS in wet CHCl\(_3\) under UV irradiation; the formed octabromo intermediate 10 (not isolated) upon hydrolysis affords 3.\(^{61}\) Ketocalix[n]arenes 4 and 5 (n = 5 and 6, respectively) have been synthesized from bromocalixarenes 11 and 12 which upon hydrolysis afforded hydroxy derivatives 13 and 14. Subsequent oxidation by \(\text{CrO}_3\) gave 4 and 5.\(^{59}\) The ketocalix[n]arenes 3-5 (n = 4-6) upon reaction with MeLi, followed by water elimination yielded calix[n]radialenes 6-8 (n = 4-6) with
exocyclic double bonds in all \textit{meso} positions.\textsuperscript{59} Calixradialenes are promising as synthons for reactions performed at the \textit{meso} positions of calixarenes.

\begin{equation}
\text{NBS} / \text{wet CHCl}_3 \quad 500 \text{ W}
\end{equation}

\begin{equation}
\text{CaCO}_3 \quad \text{H}_2\text{O/THF}
\end{equation}

\begin{equation}
\text{CrO}_3 \quad \text{AcOH/Ac}_2\text{O}
\end{equation}

\begin{equation}
\text{MeLi} \quad \text{H/CHCl}_3
\end{equation}

**Scheme 2**

3. Homocalixarenes

Homocalixarenes, \textit{i.e.} calixarenes in which some of the methylene groups in \textit{meso} positions are replaced by more extended bridges, are interesting for their large receptor cavities. The size of the homocalixarenes may be tuned by programming the number of methylene groups which are situated between the aromatic rings.

First the homocalixarenes with ethylene bridges instead of methylene ones will be presented. Then homocalixarenes with all bridges at \textit{meso} positions greater than one carbon atom, here referred to as all-homocalixarenes will be described.
3.1. Homocalixarenes with ethylene bridges at meso positions

An example of a synthesis of homocalixarene with ethylene bridges at the meso positions is that of the condensation of 2-hydroxyphenylethanones 15a or 15b with paraformaldehyde under basic conditions. The reaction of 15a afforded two homocalixarenes, 16a and 17, which were separated by column chromatography. In the case of KOH, RbOH and CsOH, 16a is the major product, while in the presence of LiOH or NaOH, 17 prevails. The reaction of 15b performed in the presence of CsOH affords homocalixarene 16b as the sole product, which without isolation, was treated with ethyl bromoacetate to give homocalixarene 18.

![Scheme 3](image)

Scheme 3
The syntheses are simple, and the obtained homocalixarenes have roomy cavities, allowing the inclusion of large guest molecules. This fact is promising for their use in supramolecular chemistry. Another example of a homocalixarene is 19, obtained from diphenylmethane dialdehyde 20 using aluminum powder and sodium hydroxide. Compound 19 has proven useful as a synthon for further reactions. (Scheme 3)

3.2. All-homocalixarenes
A synthesis of all-homocalixarenes, i.e. homocalixarenes having all bridges greater than one carbon atom, involves the reaction of biscarbene complexes 21 or 22 with diyne 23, affording homocalix[3]arene 24 and homocalix[4]arene 25, respectively. The syntheses proceed by triple annulation which forms two aromatic rings and one macrocyclic ring. The above procedure enables control over the cavity size and over the symmetry of the whole molecule. (Scheme 4)
4. Compounds Related to Spirodienonecalixarenes Serving as Synthons

Among reactions of bis(spirodienone)calix[4]arene and related compounds, an important example is the functionalization of the wide rim of a calixarene. Two main approaches are described below: the acid-mediated bis(spirodienone) route, and the silver-mediated $p$-bromodienone route.

4.1. Wide rim-functionalized calixarenes obtained by acid-mediated bis(spirodienone) route

The parent calixarene 26 upon mild oxidation with trimethylphenylammonium tribromide 27 affords bis(spirodienone)calix[4]arene 28. The subsequent acid-mediated reaction of 28 with alcohols leads to functionalization of a calixarene wide rim, affording mono- and di-alkoxycalix[4]arenes 29 and 30; this procedure overcomes the need for prior protection of the narrow rim hydroxyl groups. Reactions were performed in the presence of $p$-toluenesulfonic acid ($p$-TSA).66

As a trial, alcohols a-g were used with 28. Methanol a and propargyl alcohol g yielded two products, i.e. mono- and di-alkoxy-calixarenes, whereas other alcohols afford only monoalkoxy-calixarenes. (Scheme 5)
The value of this method should be emphasized, since functionalization of the wide rim of calixarenes is more difficult than that of a narrow rim. It is noteworthy that the above direct substitution of the wide rim of calixarene via bis(spirodieneone)calixarene 28 proceeds by an efficient and mild procedure. The obtained mono- and di-methoxycalixarenes 29a and 30a may serve for the synthesis of calix[4]mono- and diquinones which are difficult to achieve using any other route. For this purpose, 29a and 30a were treated with BBr3. The resulting demethylation yielded 31 and 32 containing one and two 1,4-dihydroxybenzene rings, respectively.

Oxidation of 29a and 31 with cerium(IV) ammonium nitrate (CAN) affords calix[4]monoquinone 33, and oxidation of 30a leads to the formation of calix[4]diquinone 34. (Scheme 6)

Scheme 6
For similar functionalization of the wide rim of calixarenes via a bis(spirodienone) route phenols and thiols were also used. The reaction of 28 with phenols affords mono- and diaryloxy-calixarenes 35 and 36, respectively, whereas in the case of thiols only monosubstituted products 37 were obtained.67 (Scheme 7)

![Diagram of functionalization](image)

R = 4-Me, 4-OMe, 4-Br, 4-I, 2-I

**Scheme 7**

### 4.2. Wide-rim functionalized calixarenes obtained by silver-mediated \( p \)-bromodienone route

A related approach to calixarene wide-rim functionalization, referred to as a \( p \)-bromodienone route, involves the procedure often used for preparation of spirodienone-calixarenes, *i.e.* the treatment of the appropriate calixarene, *e.g.* 38 with trimethylphenylammonium tribromide 27 in the presence of a base. This reaction yields a mixture of the *exo* and *endo* stereoisomers of \( p \)-bromodienone-calixarenes 39a and 39b. The *exo* isomer 39a reacts with a methanolic solution of AgClO₄ to give \( p \)-methoxycalixarene 40. It was observed that this reaction leading to 40 proceeds also when using the mixture of stereoisomers 39a and 39b without the isolation step.68 The procedure involves the silver-mediated formation of aryloxenium cation A,69 which, upon reaction with methanol forms intermediate B, undergoing rearomatization into 40. In this functionalization of the wide rim, the alcohols a-g were used.

It is noteworthy that the obtained products may undergo modification of the introduced nucleophile, *e.g.* 40e was propylated to give 41 which upon hydrogenolysis afforded calixarene 42 containing a single hydroxyl group on the wide rim, which is difficult to achieve by any other approach.70 (Scheme 8)
In a similar way, calixarenes containing two distal \( p \)-bromodienone moieties were formed. For this purpose, dipropoxycalixarene 43 was treated with 27 to give a mixture of stereoisomers 44a,b,c. The reaction of this mixture with methanol or benzyl alcohol in the presence of AgClO\(_4\) affords corresponding calixarenes 45 or 46 containing two rings substituted at the wide rim by methoxy- or benzyloxy groups, respectively. (Scheme 9)

One should note that the above procedure, \( i.e. \) the \( p \)-bromodienone route, is a convenient method for wide rim functionalization of calixarenes using the easily accessible \( p \)-bromodienonecalixarenes.68
The $p$-bromodienone route serves also for substitution of para- and meta- positions of calixarene rings by aromatic moieties. The aromatics used in this process should be sufficiently activated. It was observed that less reactive substrates yield mainly C-O para-substituted products, while more activated substrates mainly afford the inherently chiral C-C meta-substituted compounds. As an example, the mixture of exo/endo stereoisomers of 39, obtained as
above, reacted with AgClO₄ and nucleophile ArOH 47 in 1,2-dimethoxyethane in the presence of Na₂CO₃ to give calixarene 48 and calixarenes 49 as a racemic mixture.⁷¹ (Scheme 10)

Scheme 10

The mechanism proposed for the synthesis involves the silver-mediated initial formation of the aryloxenium cation A, which upon reaction with the nucleophile forms the intermediate C. Intermediate C reacts by two routes: the de-t-butylation and the dienone-phenol rearrangement. The de-t-butylation of C yields the rearomatized para-substituted calixarene 48. The dienone-phenol rearrangement of C however, (involving the 1,2-migration of the nucleophilic moiety), affords the meta-substituted calixarene 49. Compound 49 is inherently chiral and is obtained as a racemic mixture. (Scheme 10).
For investigation two compounds were chosen as nucleophiles, namely, as less activated substrates substituted phenols 50a-d, and as a more activated substrate 2,6-dimethylphenol 51. As expected, the less activated substrates 50a–d afforded only para-substituted products, while the more activated 51 yielded only meta-substituted products as a racemic mixture.

The above reactions lead to deep calixarenes, and the use of highly activated aromatic substrates enables formation of inherently chiral calixarenes which are promising in enantio-discrimination.71

5. Conclusions

In view of the rapid progress in calixarene chemistry,72-74 as well as in that of cyclodextrins75-77 and cucurbiturils,78-80 promising for various applications, it seemed of interest to add the above described examples of calixarenes with modified meso bridges and the procedures leading to the synthesis of wide rim functionalized calixarenes; one may hope that they will to some extent enlarge knowledge in the calixarene area.

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**Authors’ Biographies**

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![Wanda Sliwa](image1)

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