

## Calixarenes Enhanced as Dendrimers. A Mini Review

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**Abstract:** This mini review focuses on the synthesis of hyperbranched and dendrimers made of calix[4]arenes and thiacalix[4]arenes taken from literature. At the same time it places our investigations of calixdendrimers within the context of extant literature.

**Keywords:** Calix[4]arenes, thiacalix[4]arenes, dendrimers.

### INTRODUCTION

Over the two past decades, dendrimers and hyperbranched molecules have attracted considerable attention because of the special properties determined by their repetitively structured architecture. Intensive studies have been performed of their use as new functional materials in nanotechnology, with both biochemical and medical applications in view [1]. The preparation of such branched structures demands the use of particular building blocks with the appropriate stereochemistry and multiple, equivalent reaction centres. Calixarenes [2], with their multiple sites for functionalisation on a conformationally restricted, macrocyclic scaffold, are obvious substrates for such modular syntheses. Their chemistry is well-established and has engendered extensive research not only because of their capacity for forming complexes with a variety of guests, both charged and neutral, but also because of their ease of functionalisation, enabling their use in the construction of sophisticated derivatives such as calixcrowns [3,4], calixcryptands [4] and calixspherands [5,6]. Particular interest also attends the construction of molecules containing two or more calixarene units and which can be used to form hyperbranched species [7].

The first work reporting the use of calixarenes to build dendrimers has been published in 1995 by Lhotak and Shinkai [8]. A series of oligo-calixarenes linked through the phenolic oxygen with the help of aliphatic chains (lower rim-lower rim connections). Monobromoalkyl derivatives **1** ( $n = 2, 3$  and  $6$ ) of *O*-tripropyl-substituted calix[4]arene were used as starting molecules. Reactions of **1** with suitable differently substituted calixarenes gave double-, triple- and penta-calixarenes (see Chart 1).

All the calix[4]arenes were shown to be in cone conformation. These oligo-calixarenes were claimed to represent the first step towards calixarene-based dendrimers.

Due to the number of possible complexation sites, the only evident result obtained by <sup>1</sup>H-NMR, is that these multi-calixarenes can bind metal cations (Na<sup>+</sup> and Li<sup>+</sup> as perchlorates in CDCl<sub>3</sub>:CD<sub>3</sub>CN = 4:1 v/v) up to the number of calix[4]arene units in the molecule.

In 1998, Mogck *et al.* [9] reported the synthesis of covalently linked multi-calixarenes. Mono *ipso*-nitration of *p*-*tert*-butylcalix[4]arene tetraethers and subsequent reduction provided an easy access to *p*-monoamino calix[4]arenes. Reactions with various di- and triacid chlorides lead to double- and triple-calix[4]arenes (Chart 2).

When similar reactions were with tetraacid chlorides derived from calix[4]arenes in the cone or in the 1,3-alternate conformations penta-calix[4]arenes are obtained which can be regarded as the first generation of calix[4]arene-based dendrimers (Chart 3).

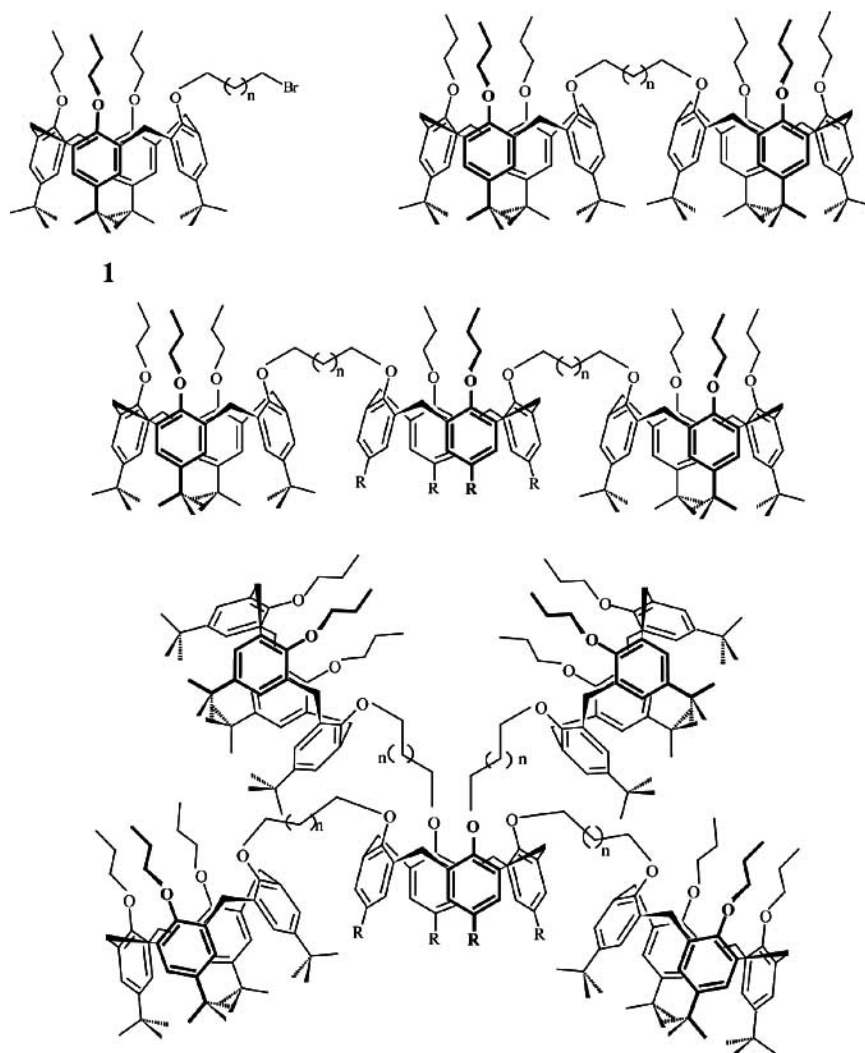
Penta-calix[4]arene **2** (Y = -CH<sub>2</sub>COOC<sub>2</sub>H<sub>5</sub>) was used to complex NaSCN in CDCl<sub>3</sub>. Complexation of four Na<sup>+</sup> in the four tetra ester cavities was demonstrated by observing the retained S<sub>4</sub>-symmetry of the ligand after complexation. Addition of free ligand leads to a spectrum corresponding to a superimposition of the complex and the free ligand leading to the conclusion of no-cation-exchange.

In 2002, Szemes *et al.* [10] reported the synthesis of calix[4]arene-based dendrimers containing up to seven calix[4]arene moieties (see 5 of Chart 4).

The construction takes advantage of the selective 1,3-*O*-dialkylation of calix[4]arene and subsequent dinitro derivative formation. The linkage of the calix[4]arenes is made after reduction of the nitro functions (see calixarene **3** in Chart 4) which are reacted with acyl chloride precursors. Tricalix[4]arene **4** forms strong complexes with La<sup>3+</sup>, Gd<sup>3+</sup> and Lu<sup>3+</sup> evidenced by UV-Vis titrations.

In 2003, Xu *et al.* [11] described a modular strategy towards macromolecules which combines diverse peptide synthesis with functionalized calixarene chemistry. The design of certain calix[4]arene amino acids were used to construct multivalent entities such as calix-peptide-

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**Chart 1.**

dendrimers. The first generation of two calix[4]arene peptide dendrimers **6** is given in Chart 5.

Complexation  $^1\text{H-NMR}$  studies were investigated with  $\text{NaClO}_4$  in  $\text{CDCl}_3$ . In both cases  $\text{Na}^+$  complexes were observed with a localisation of the cation close to the carbonyl functions. Apparently  $\text{Na}^+$  cation disrupted the intramolecular  $\text{C}=\text{O}\cdots\cdots\text{H-N}$  hydrogen bonding present in the free ligand at the lower rim upon complexation.

In 2004, Stany *et al.* [12] reported the synthesis of thiacalix[4]arenes in the cone or 1,3-alternate conformations bearing two or four carboxylic functions on the lower rim which were reacted as acyl chloride with para amino calix[4]arenes to give the corresponding penta calixarenes with retention of configuration (see Chart 6). The 1,3-alternate conformer was observed to be less reactive due to steric hindrance allowing the obtention of tricalix[4]arene **7** possessing inherent chirality.

The same year, Appelhans and co-workers [13] used similar thiacalix[4]arenes in the 1,3-alternate conformation possessing carboxylic acid functions for the design of dendritic cores with amino surface groups (Chart 7). Because of the steric hindrance it was added a phenyl spacer leading to the formation of novel thiacalixarenes bearing protected lysine groups.

These compounds were claimed to be the first example of thiacalix[4]arene derivatives potentially useful as dendritic cores for subsequent branching derivatization.

Recently, Bu *et al.* [14] reported the synthesis of the second generation of a dendrimer based on calixcrown by the convergent pathway (Chart 8).

Wang *et al.* [15] synthesized calix[4]arenes substituted at the narrow or wide rim by eight carbamoylmethylphosphine oxide (CMPO) functions in a dendritic manner.

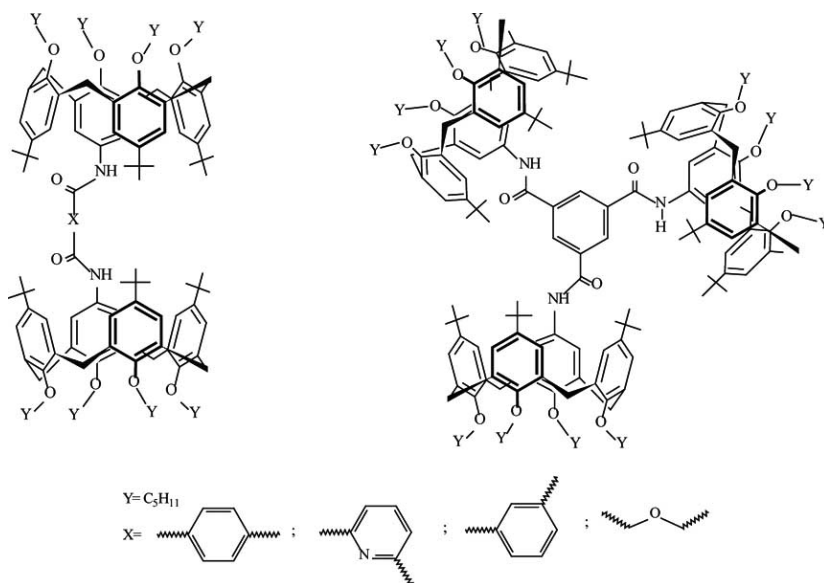


Chart 2.

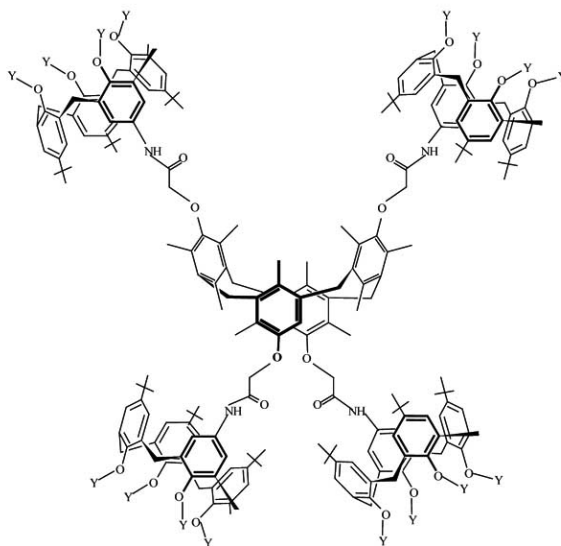
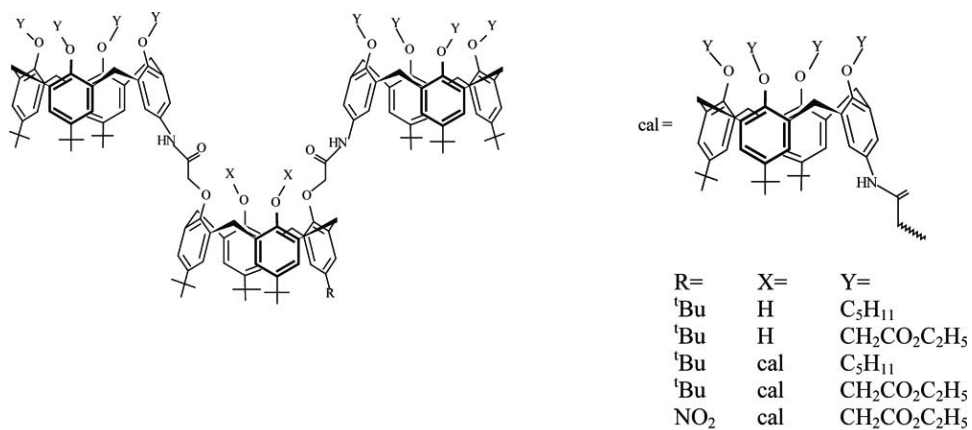


Chart 3.

Extractions of Eu<sup>3+</sup> and Am<sup>3+</sup> were carried out from water to *o*-nitrophenylhexyl ether. <sup>1</sup>H-NMR relaxivity titrations

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for wide rim octa-CMPO derivatives revealed the formation of solvent-free 1:2 ligand/metal complex, while the wide rim

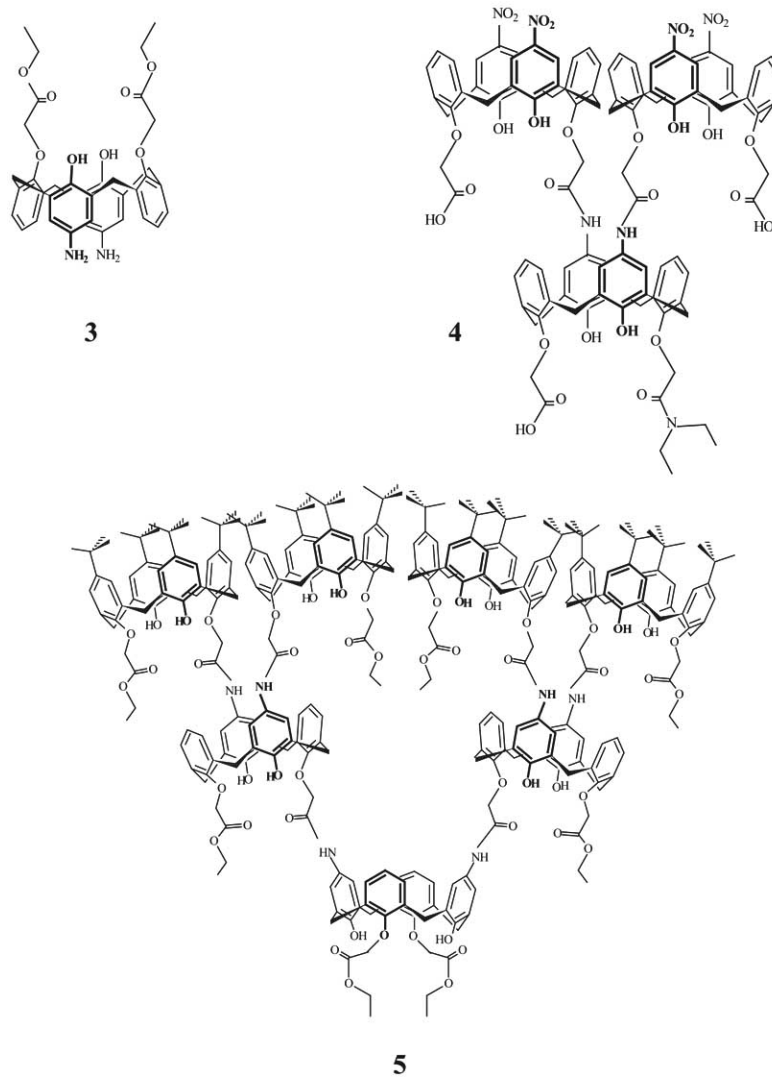


Chart 4.

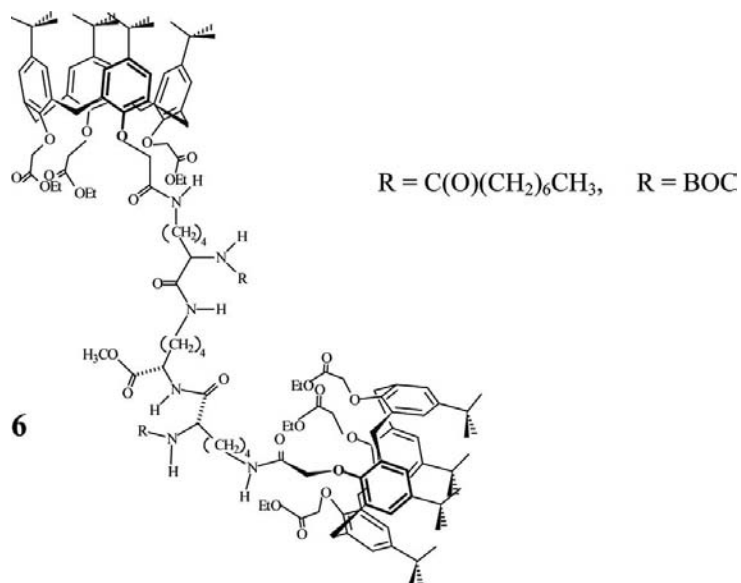


Chart 5.

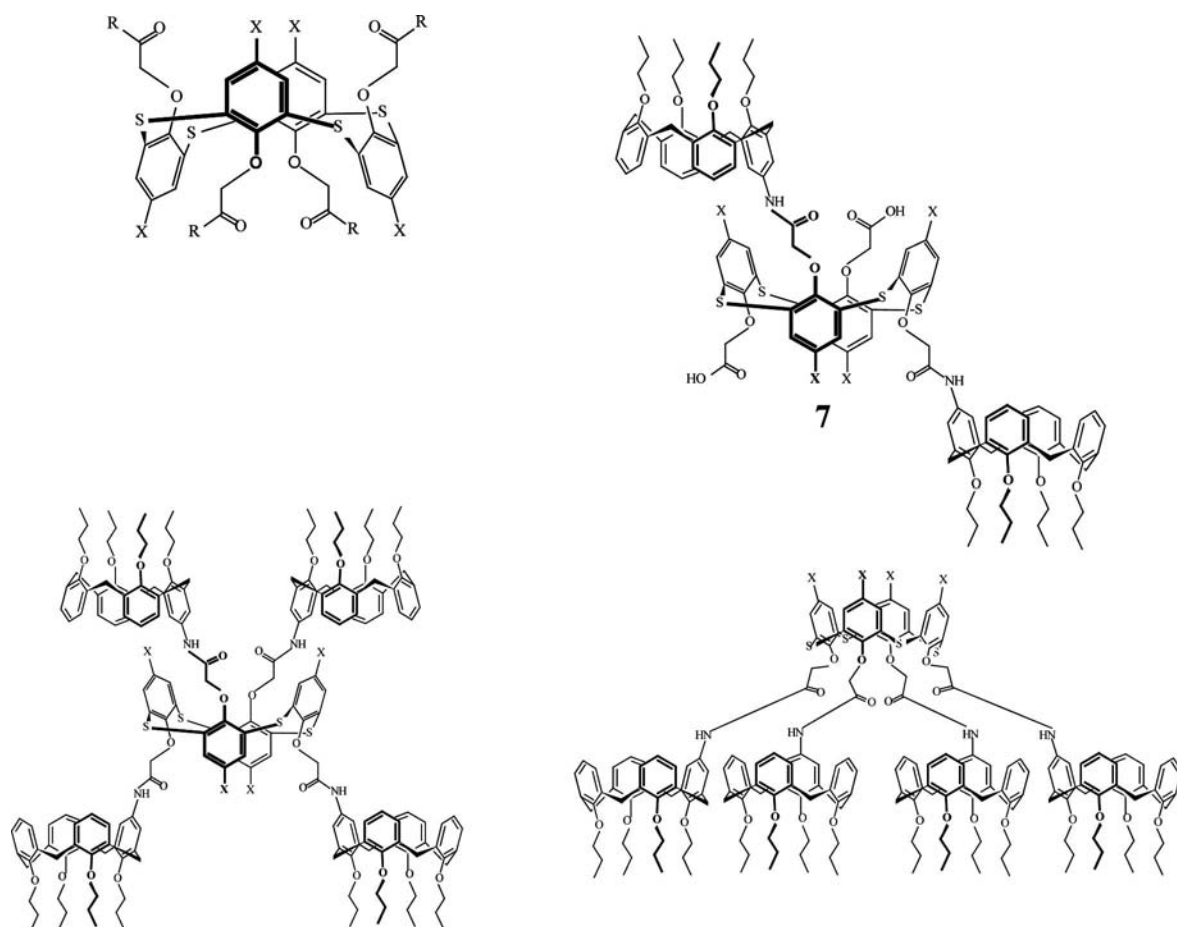


Chart 6.

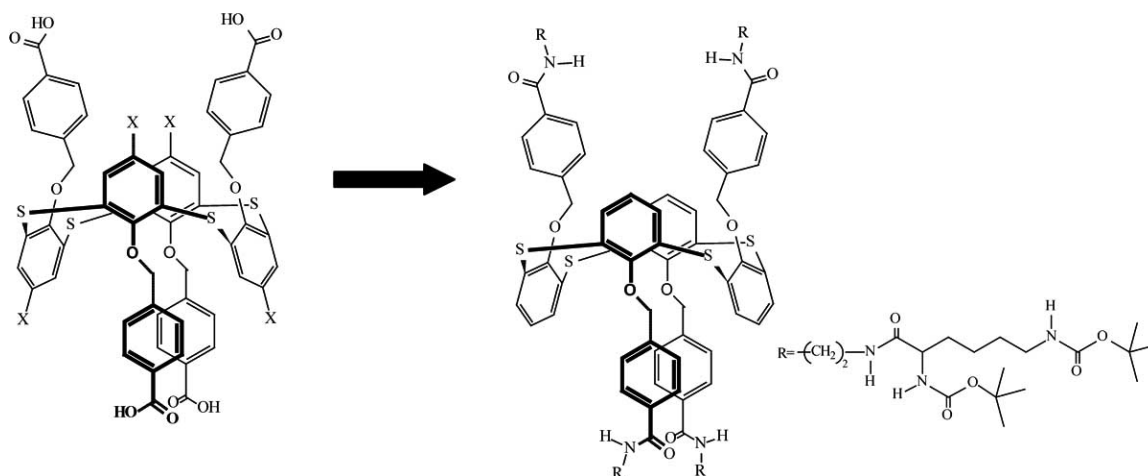


Chart 7.

tetra-CMPO formed oligomers complexes under similar conditions.

Concerning our research in this field, we have synthesized a diamido calix[4]arene **8** derivative from 'tren' and monocarboxymethylcalix[4]arene which is used for the preparation of a variety of hyperbranched molecules by reaction with chosen methyl ester compounds (Chart 10). Due to its 'classical' Y dendron shape two calixarenes are added in one time allowing the generation of dendrimers [16].

More particularly, tricalix[4]arene **9**, corresponding to the first generation of dendrimer of calixarenes, was useful to achieve the synthesis of the second generation through the 1,3-selective di-*O*-functionalisation of the calix[4]arene units (Scheme 1) [17].

In a same manner related hyten-tricalix **10** was synthesized [18] by reacting monocarboxymethylcalix[4]arene with a readily-prepared hydroxyl derivative of 'tren',  $\text{HOCH}_2\text{C}(\text{CH}_2\text{SCH}_2\text{CH}_2\text{NH}_2)_3$  = 'hyten'.

This lead to the formation of a dendrimer with a core containing 6 hetero atoms N3S3 while tricalix **9** contains

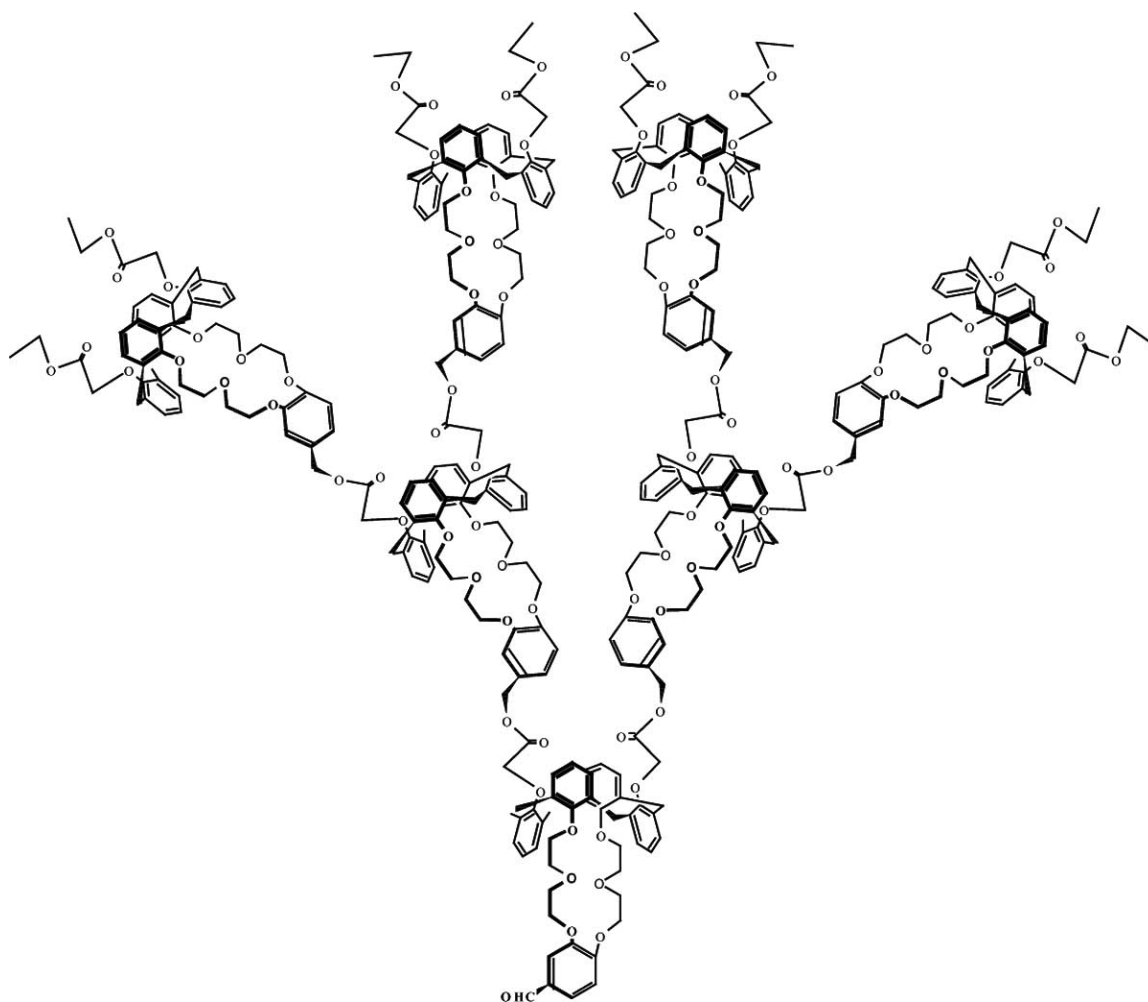


Chart 8.

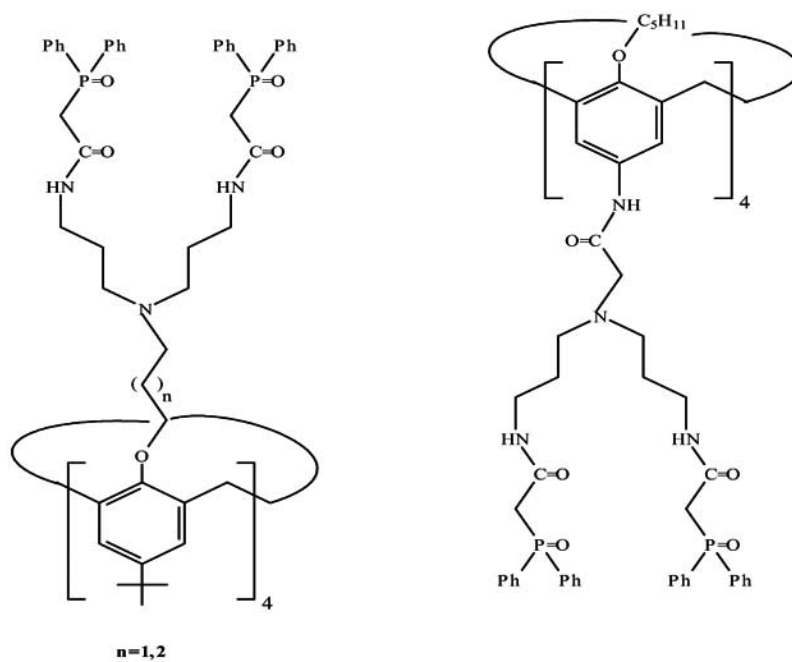


Chart 9.

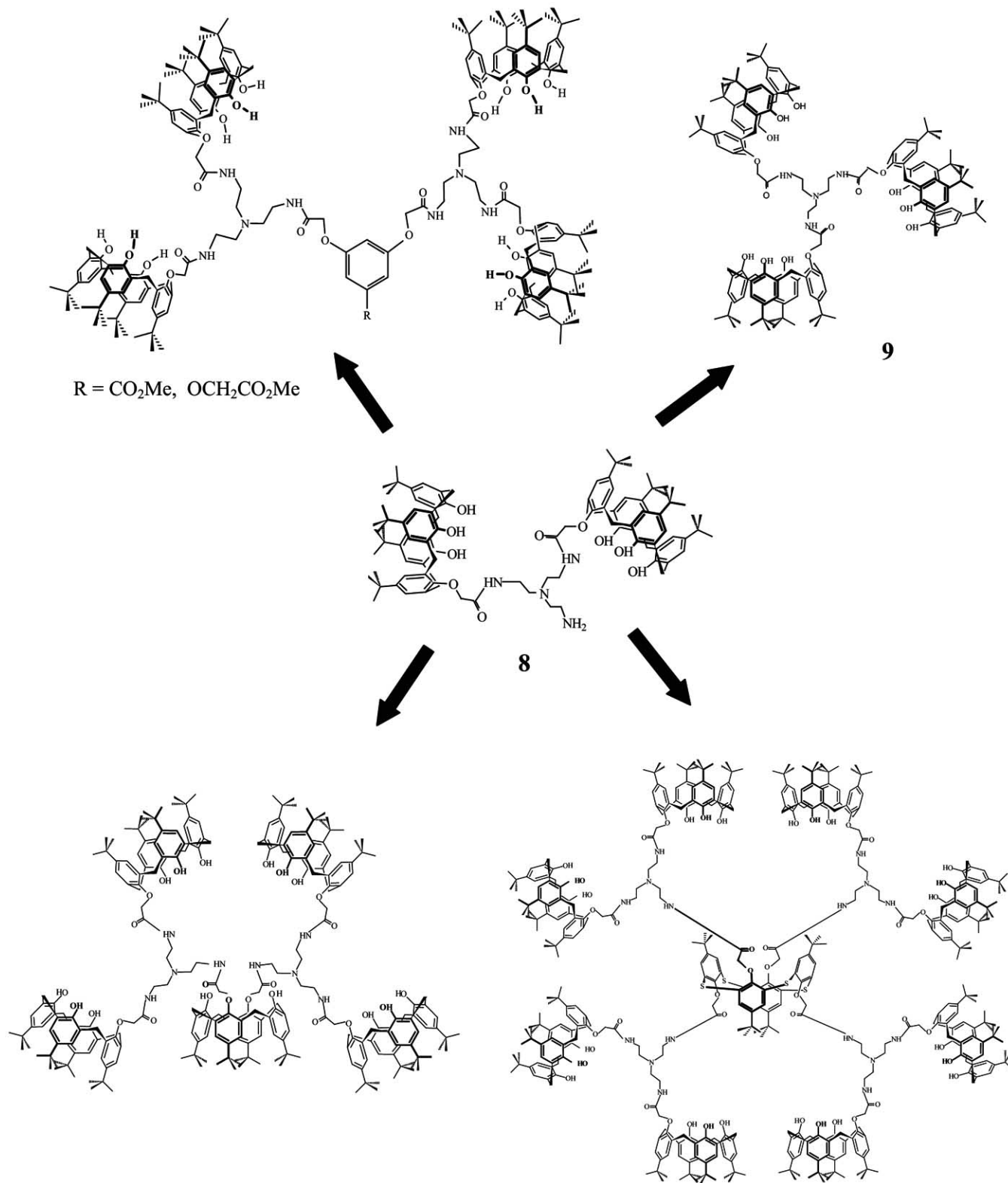
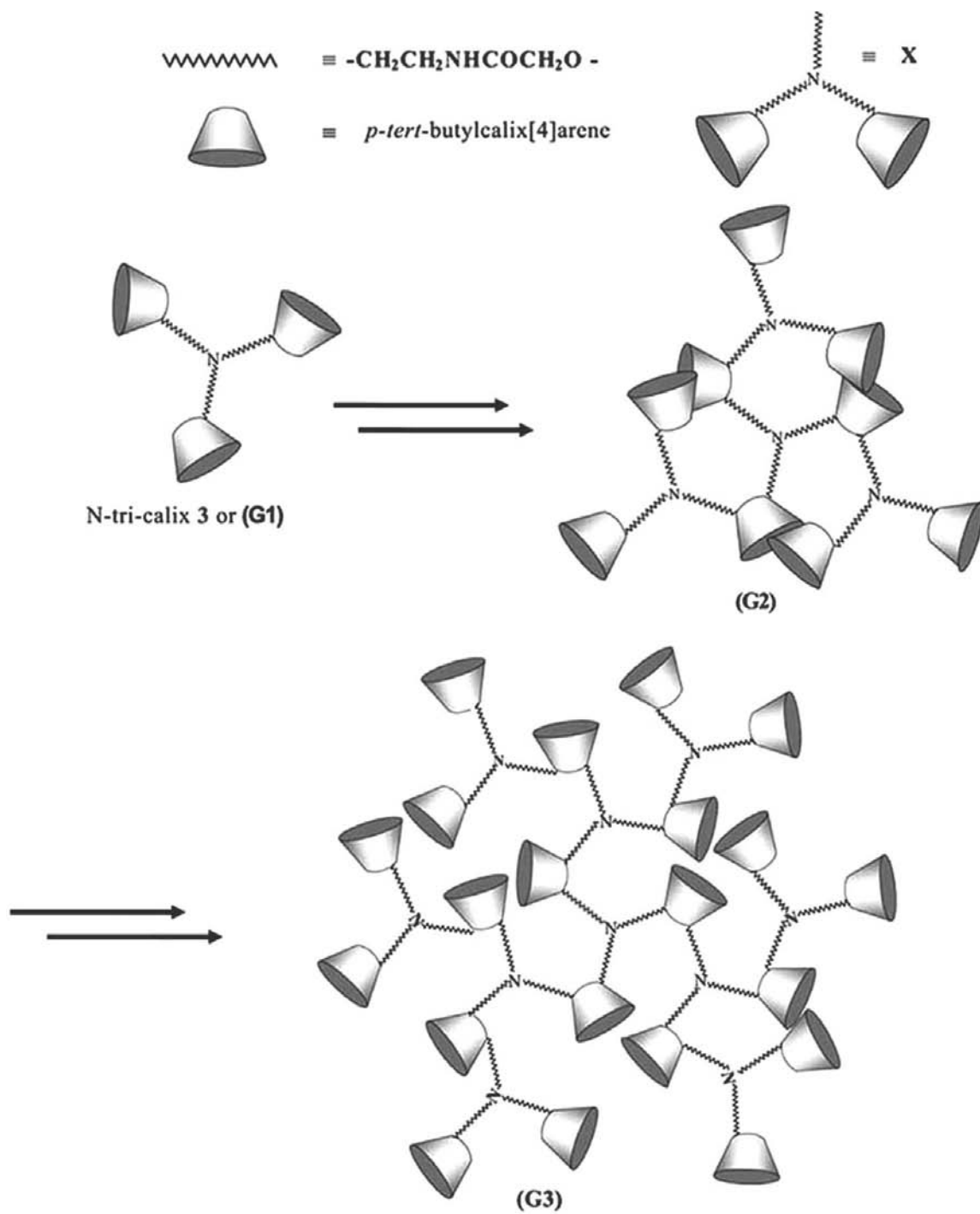


Chart 10.

only 4 N atoms. At the same time it was isolated hyten-dicalix-SCH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub> **11** (Chart 11).

These molecules, designed as dendrimer precursors, retain a core capable of acting as a multidentate ligand for metal ions. Studies of complex formation with Zn(II) and

Co(III) by these **9-11** showed that indeed there is preferential binding to the core (rather than the phenolic sites of the calixarene units), suggesting new mechanisms for the control of the structure and stereochemistry of dendrimer species [18].

**Scheme 1.** Modular approach of (G2) and (G3) from (G1).



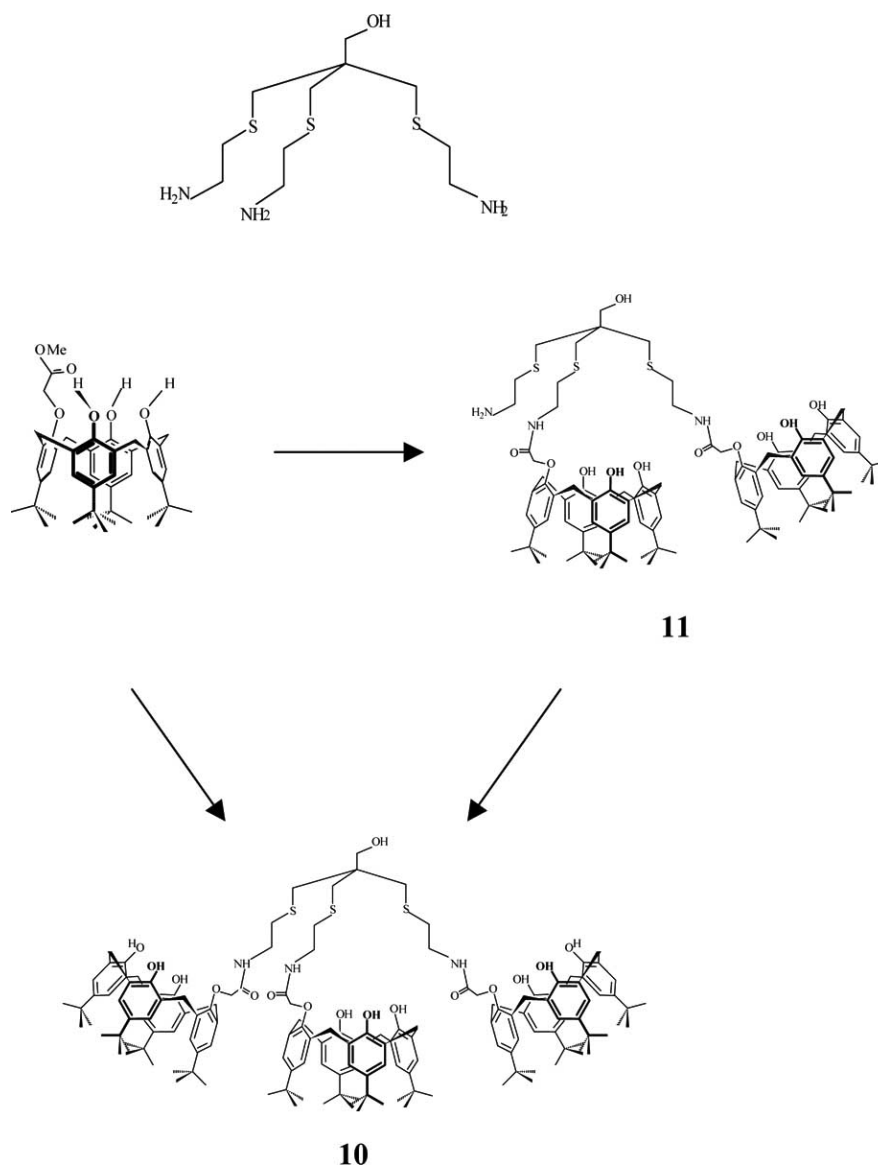


Chart 11.

To conclude, this mini review pointed out the new interest of chemists in introducing calixarenes in dendrimers chemistry. In many areas, calixarene and dendrimer chemistry have real and important applications [1, 2] and the meeting of both fields approaching true maturity may lead to a new field of applications. In a more general point of view calixarenes chemists show interest for new research fields into nanosciences and nanotechnologies. Calixarenes are already involved in microcapsules, molecular machinery, molecular reactors, protein sensing, nanotubes, nanoparticles, rotaxanes and catenands and they can be seen by STM techniques.

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