

Calixarenes enhanced as dendrimers. A mini review

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ABSTRACT

This mini review focuses on the construction of dendrimers from calix[4]arene and thia calix[4]arenes.

Dendrimers (greek *dendron* = tree) and hyperbranched molecules represent a novel class of structurally controlled macromolecules derived from branches-upon-branches structural motif.¹ ce to many practical or industrial situations.

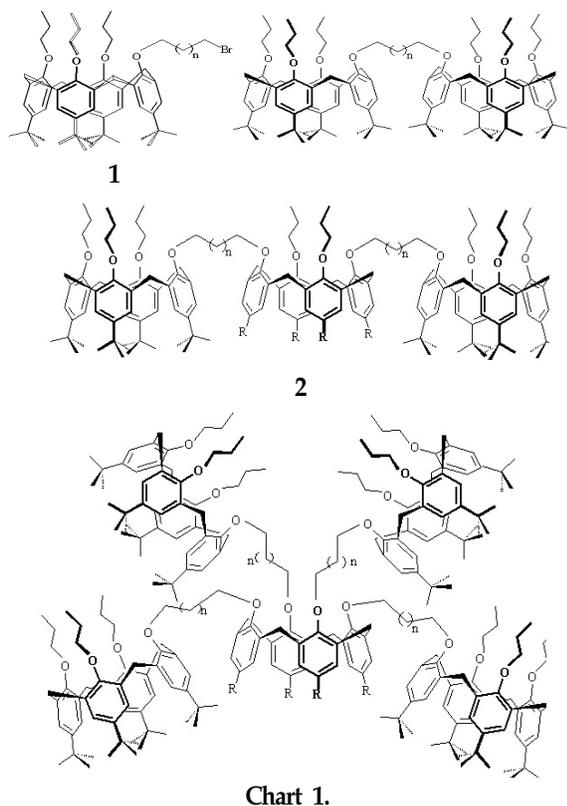
Unlike collections of small molecules which might require supramolecular assembly to deliver function, dendrimers can simply use internal dynamics to arrange multiple and interconnected components in ways that minimize free energy and afford specific function. Such intramolecular reorganizations may lead to shape and volume changes, the creation of internal microenvironments, the cooperative organization of the surface or inner functionalities, the concentration or exclusion of substrate from the molecular "cavity" of dendrimers, or the formation of defined multimolecular assemblies. Shape and volumes are depending on the *ingredients* used for constructing dendrimers. Due to their versatility calixarenes² have been chosen as molecular bricks for constructing various hyperbranched molecules and dendrimers. Calixarenes are one of the most developed macrocyclic compounds in supramolecular sciences and the combination of dendrimers concepts and calixarene chemistry is awaited for giving rise to an important class of new calixarenes enhanced as dendrimers benefiting

of both properties. Calixarenes are macrocyclic compounds containing cavities of molecular-sized dimensions. They consist of phenolic units arranged in cyclic arrays by the linking with methylene bridges *ortho* to the phenol function. They are prepared from cheap chemicals by very simple reactions. Due to their supramolecular properties (they have both a hydrophobic and a hydrophilic cavities) and easy chemical modifications (they are chemically modified in almost unlimited manner) calixarenes have engendered extensive research because of their capacity for forming complexes with a variety of guests and because of their selective functionalizations extending their use in the construction of large architectures such such as calixcrowns,^{3,4} calixcryptands⁴ and calixspherands,^{5,6} calixcavitands⁷ and calixcarcerands.⁷ They are involved in a wide range of research fields (inclusion science, host-guest chemistry, molecular recognition, highly selective agents for cesium recovery, separation reagents, pollution control, membranes for electronic devices, bioactive as antimicrobial activity, biomimetic catalysis, radiotherapy, coordination chemistry related to catalysis, nanocomposite construction based on calixarene aggregates, molecular wires, molecular liquid crystals, analytical applications as molecular probes).²

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

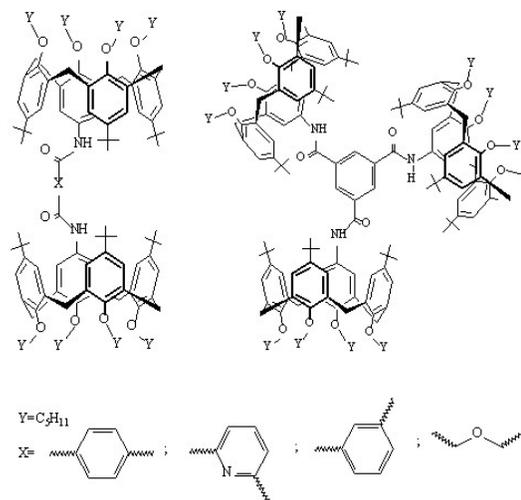
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rim-lower rim connections). Monobromoalkyl derivatives **1** ($n = 2, 3$ and 6) of *O*-tripropyl-substituted calix[4]arene were used as starting molecules. Reactions of **1** with suitable differently substituted calixarenes gave double-, triple- and 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 $^1\text{H-NMR}$, is that these multi-calixarenes can bind metal cations (Na^+ and Li^+ as perchlorates in $\text{CDCl}_3:\text{CD}_3\text{CN} = 4:1$ 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*-butyl calix[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).

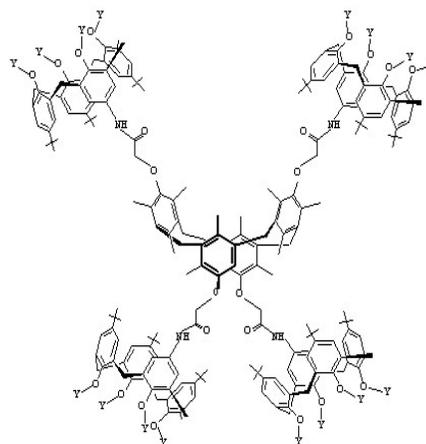
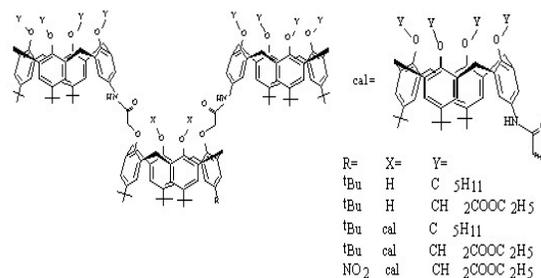
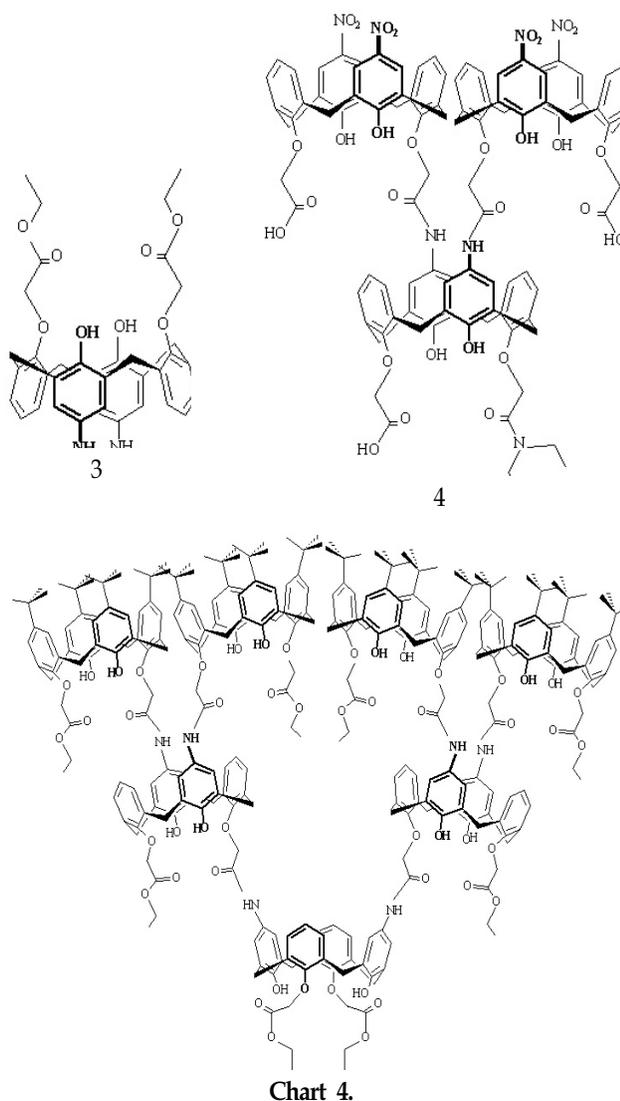


Chart 3.

Penta-calix[4]arene **2** ($Y = -CH_2COOC_2H_5$) was used to complex NaSCN in $CDCl_3$. Complexation of four Na^+ in the four tetra ester cavities was demonstrated by observing the retained S_4 -symmetry of the ligand after complexation. Addition of free ligand lead to a spectrum corresponding to a superimposition of the complex and the free ligand leading to the conclusion of no-cation-exchange.

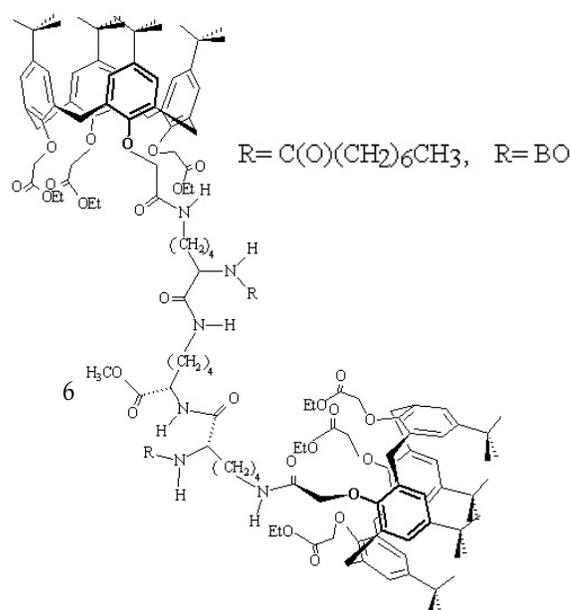
In 2002, Szemes *et al.*¹⁰ reported the synthesis of calix[4]arene-based dendrimers containing up to seven calix[4]arene moieties (see Chart 4).



The construction takes advantage of the selective 1,3-O-di-alkylation of calix[4]arene and subsequent dinitro derivative

formation. The linkage of the calix[4]arenes is made after hydrogenation of the nitro functions (see calixarene **3** in chart 4) which are reacted with acyl chloride precursors. Tricalix[4]arene **4** form strong complexes with La^{3+} , Gd^{3+} and Lu^{3+} 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-dendrimers. The first generation of two calix[4]arene peptide dendrimers **6** is given Chart 5.



Complexation 1H -NMR studies were investigated with $NaClO_4$ in $CDCl_3$. In both cases Na^+ complexes were observed with a localisation of the cation close to the carbonyl functions. Apparently Na^+ cation disrupted the intramolecular $C=O \cdots H-N$ hydrogen bonding present in the free ligand at the lower rim upon complexation.

In 2004, Stany *et al.*¹² reported the synthesis of thiaca-lix[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

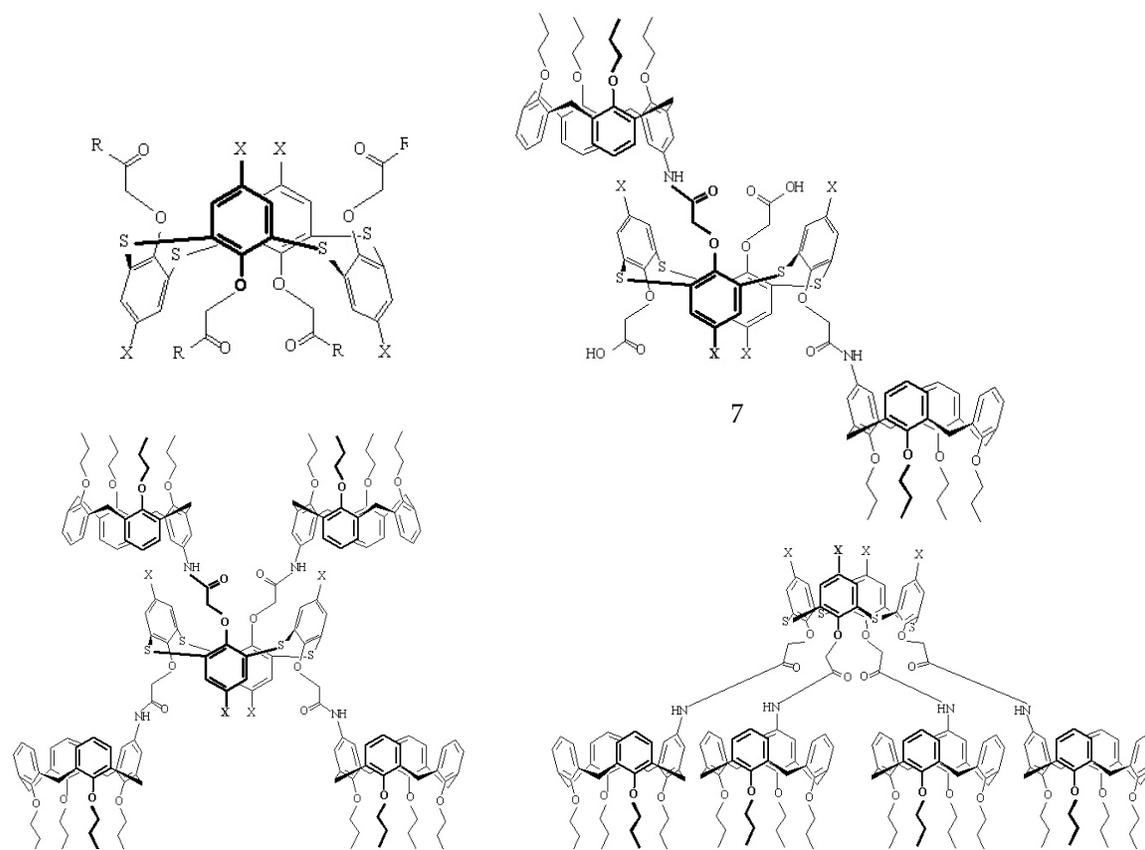


Chart 6.

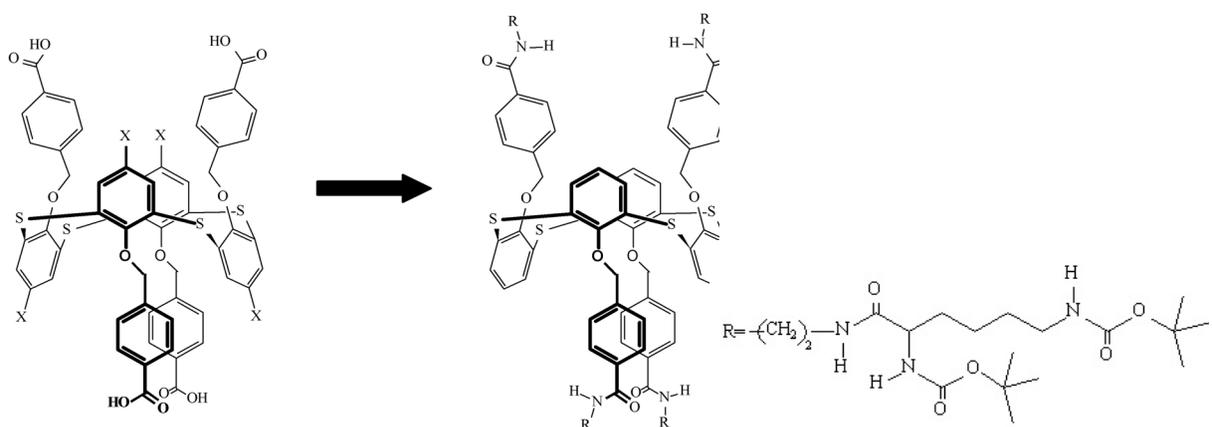


Chart 7.

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-workers¹³ used similar thiacalix[4]arenes in the 1,3-alternate conformation possess-

ing 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.

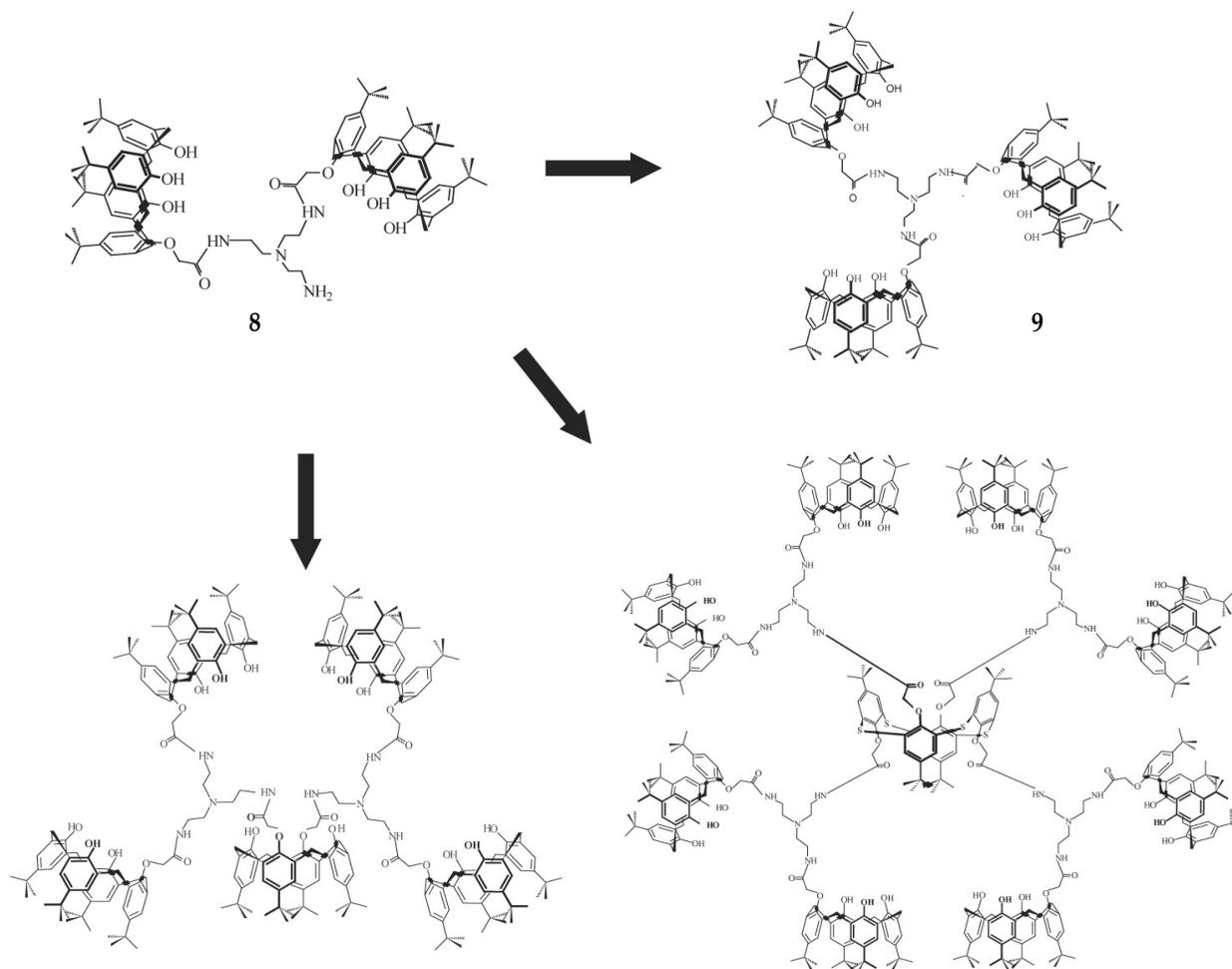


Chart 8.

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

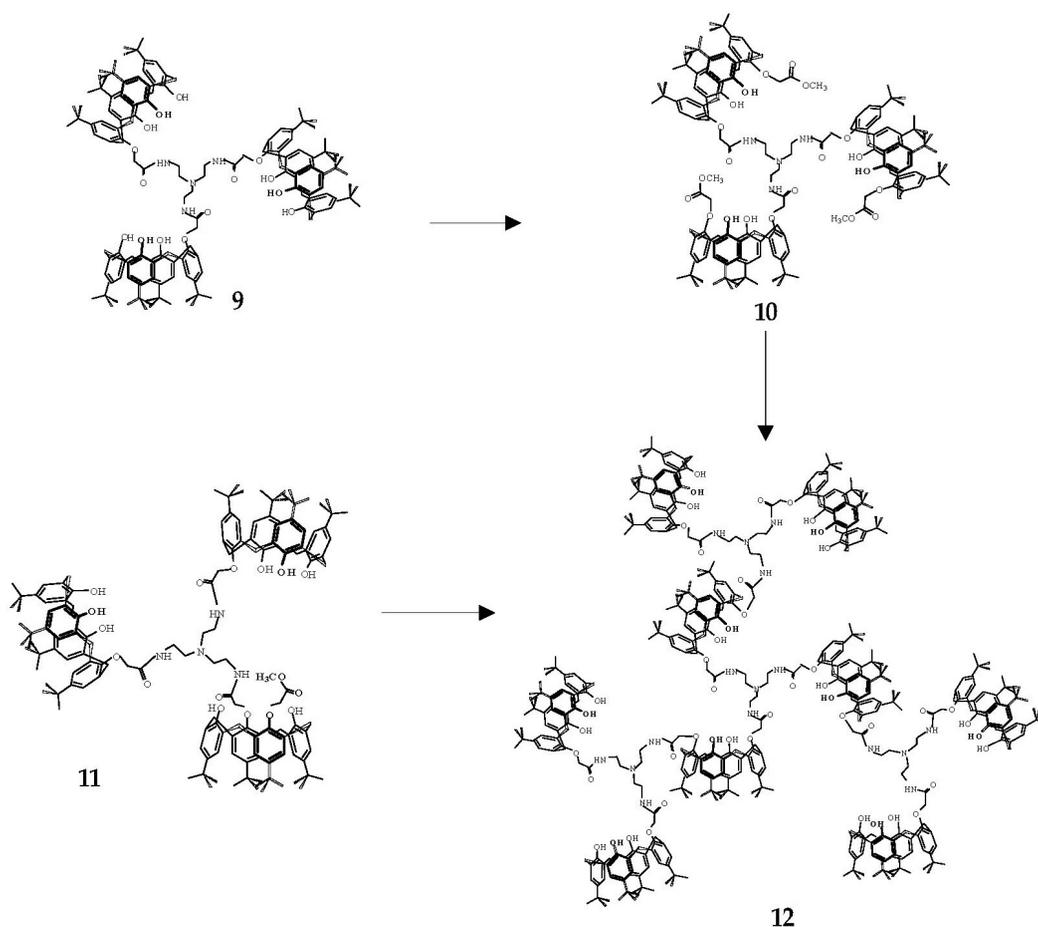
Lastly, Cheriaa *et al.*¹⁴ synthesized a diamido calix[4]arene **8** derivative from 'tren' and monocarboxymethylcalix[4]arene which is used for the preparation of a variety of hyperbranched molecules by reaction with chosen methyl ester compounds (Chart 8). Due to its 'classical' Y dendron shape two calixarenes are added in one time allowing the generation of dendrimers.

More particularly, tricalix[4]arene **9**, corresponding to the first generation of dendrimer of calixarenes, was useful to achieve the divergent (*via 10*, the trimethyl ester of **9**) and convergent (*via 11*, monomethyl ester of **9**) synthesis of the second generation of the calix-dendrimer **12** through the 1,3-

selective di-O-functionalisation of the calix[4]arene units.¹⁵

Investigations were conducted with various calixarene-dendrimers of the extraction of solid zinc picrate into CDCl_3 . The cations were observed to be localized in the 'tren' residue clearly demonstrating metal ion coordination may offer a means of controlling the orientation of pendent groups from a coordinating core as in the present molecules. More over the possibility of generating dendrimers with organized different sets of coordinating sites may offer the possibility of preparing material presenting different metal ions arranged in ordered arrays as shown in figure 2.

To conclude this mini review pointed out the new interest of chemists in introducing calixarene chemistry into nanosciences and more particularly into dendrimers chemistry. In many areas, calixarene and dendrimer chemistries have real



Scheme 1. Obtention of the second generation of calix-dendrimer 12 by divergent (via 10) and convergent (via 11) synthesis.

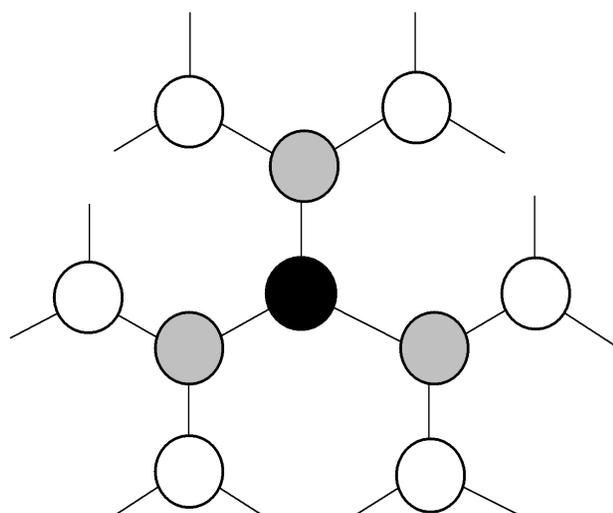


Fig 2. Three different metal cations arranged in an ordered arrays of a dendrimer.

and important applications^{1,2} and the meeting of both fields approaching true maturity has to lead to a new field of applications. For example among the potential applications one could be the development of biopharmaceutical properties of calixarenes¹⁶ *via* dendrimer chemistry.

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(Received Sep 29, 2004; Accepted Dec 24, 2004)