Review Article

Calixarene-Based Dendrimers. A Timely Review

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Abstract

This timely review focuses on the synthesis of dendrimers from calix[4]arenes and thiacalix[4]arenes. Some interesting features of these calix-dendrimers are given.

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 **1–4**.

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}H-NMR, is that these multicalixarenes can bind metal cations (Na$^+$ and Li$^+$ as perchlorates in CDCl$_3$: CD$_3$ CN = 4:1 v/v) up to the number of calix[4]arene units in the molecule.
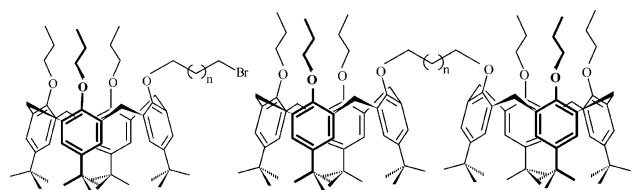
In 1997, Nagasaki and co-workers [9] synthesized photochromic dendrimers **5** which involve a 1,3-alternate conformer of a calix[4]arene as a core and azobenzene units as branches. The typical photo-switching of the azobenzene units was maintained in the interior of the dendrimers allowing the regulation of the particle sizes leading to potential developments of drug delivery systems.

In 1998, Mogck *et al.* [10] 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]arenas **6** and **7**.

When similar reactions were done with tetraacid chlorides derived from calix[4]arenes in the cone or in the 1,3-alternate conformations penta-calix[4]arenes **8** and **9** were obtained which can be regarded as the first generation of calix[4]arene-based dendrimers.
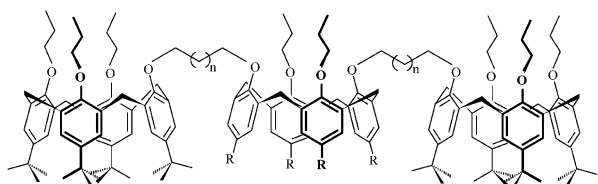
Penta-calix[4]arene **9** (Y = –CH$_2$CO$_2$C$_2$H$_5$) was used to complex NaSCN in CDCl$_3$. Complexation of four Na$^+$ in the four tetra ester cavities was demonstrated by observing the retained S$_4$-symmetry of the ligand after complexation. Addition of free ligand lead to a spectrum corresponding to a superimposition of the complex and the free ligand leading to the conclusion of no-cation-exchange.

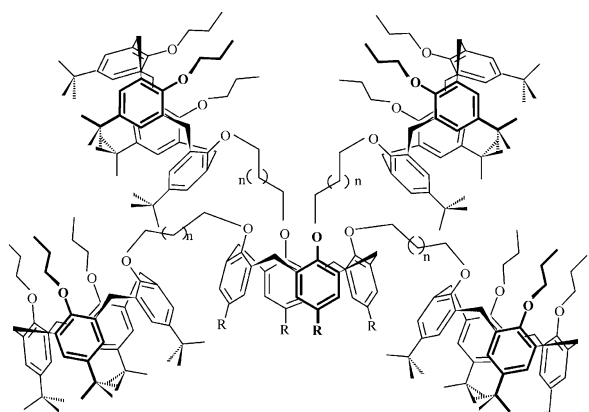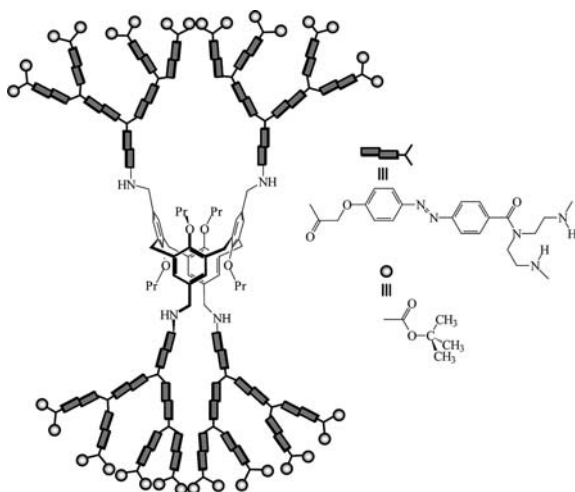* Author for correspondence: E-mail: bakloutilassaad@yahoo.fr

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6   **7**

$Y = C_5H_{11}$

$X =$

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cal =

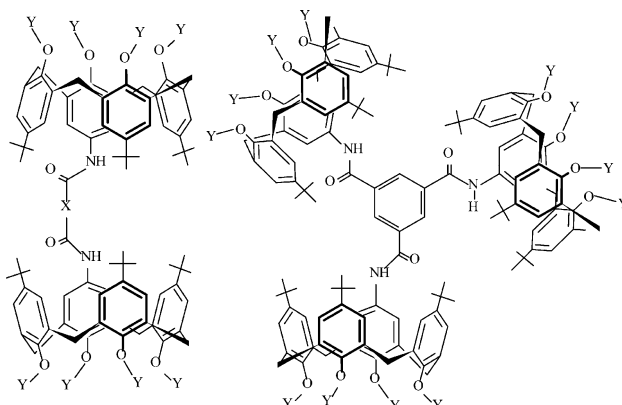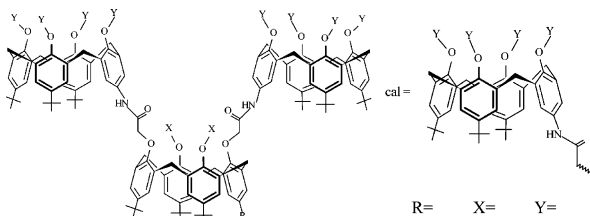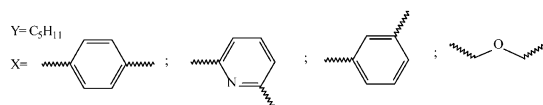| R=	X=	Y=
^tBu	H	C_5H_{11}
^tBu	H	$CH_2CO_2C_2H_5$
^tBu	cal	C_5H_{11}
^tBu	cal	$CH_2CO_2C_2H_5$
NO_2	cal	$CH_2CO_2C_2H_5$

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In 1999, Roy and Kim [11] described the first synthesis of a dendrimeric water-soluble, *p-tent*-butyl calix[4]arene **10** with sugar residues at its periphery. Lectin binding properties were observed. The lipophlic part of **10** provides the driving force for stable assembly and/or adhesion of a calixarene monolayer surface while the hydrophilic carbohydrates mimic the saccharide rich surface of cells. Lectin binding ability allows to envisage the preparation of materials directly adsorbed onto lipophilic surface of polystyrene microtiter plates which should be useful in bioanalytical devices.
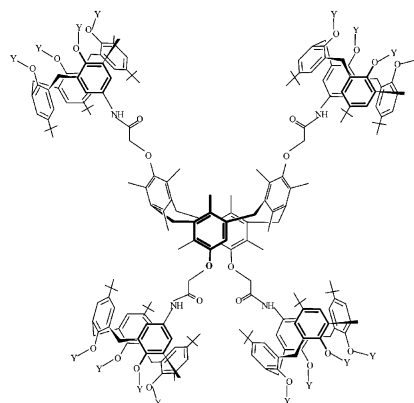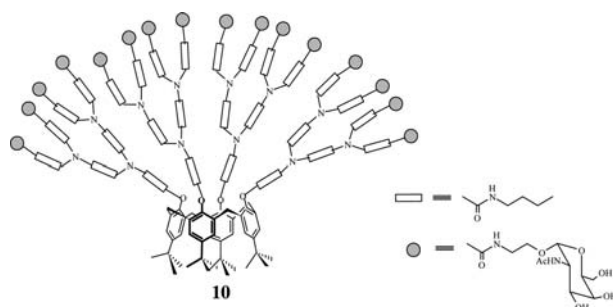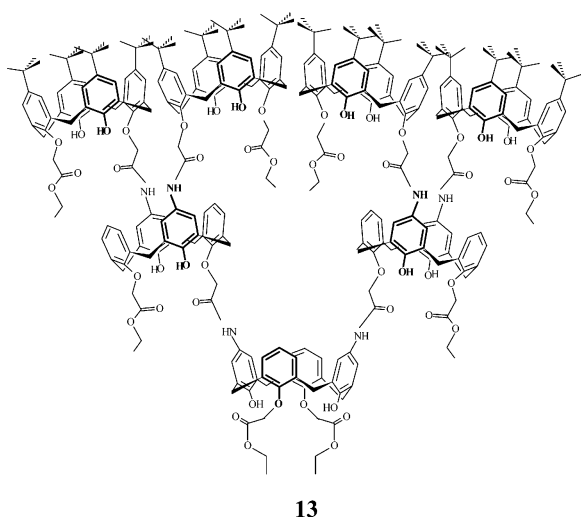

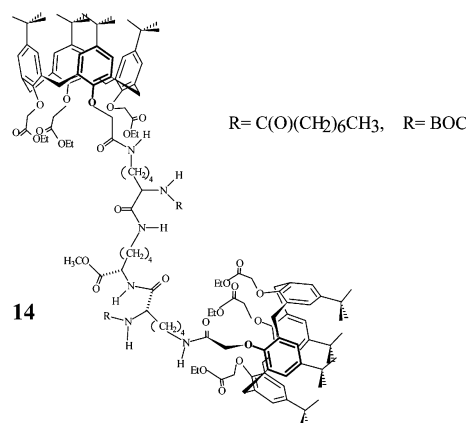**10**

11 **12**

R= C(O)(CH₂)₆CH₃,   R= BOC

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In 2002, Szemes *et al.* [12] reported the synthesis of calix[4]arene-based dendrimers, **12** and **13**, containing up to seven calix[4]arene moieties.

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 hydrogenation of the nitro functions (see calixarene **11**) which are reacted with acyl chloride precursors. Tricalix[4]arene **12** forms strong complexes with La^{3+}, Gd^{3+} and Lu^{3+} evidenced by UV–Vis titrations.

In 2003, Xu *et al.* [13] 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 **14** have been described.

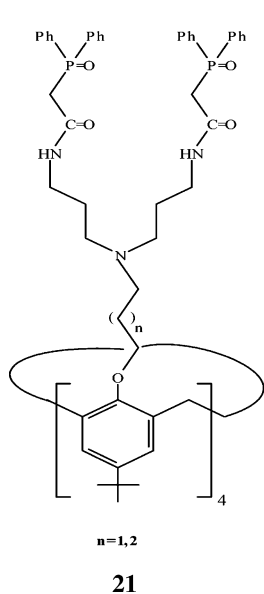Complexation ^{1}H-NMR studies were investigated with NaClO$_4$ in CDCl$_3$. In both cases Na$^+$ complexes were observed with a localisation of the cation close to the carbonyl functions. Apparently Na$^+$ cation disrupted the intramolecular C=O ...H–N hydrogen

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n=1,2

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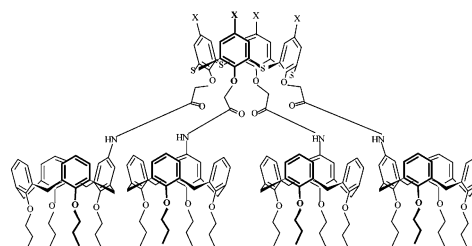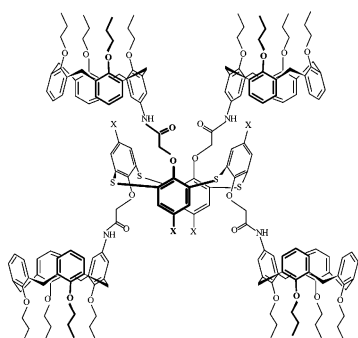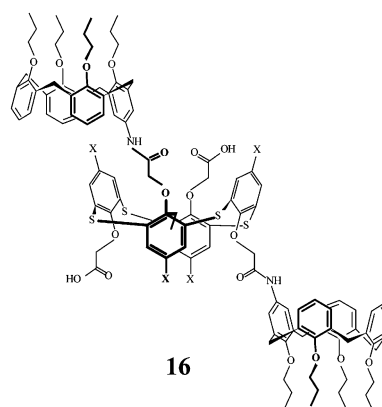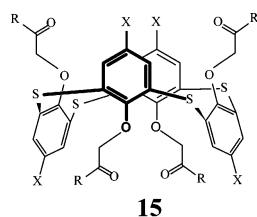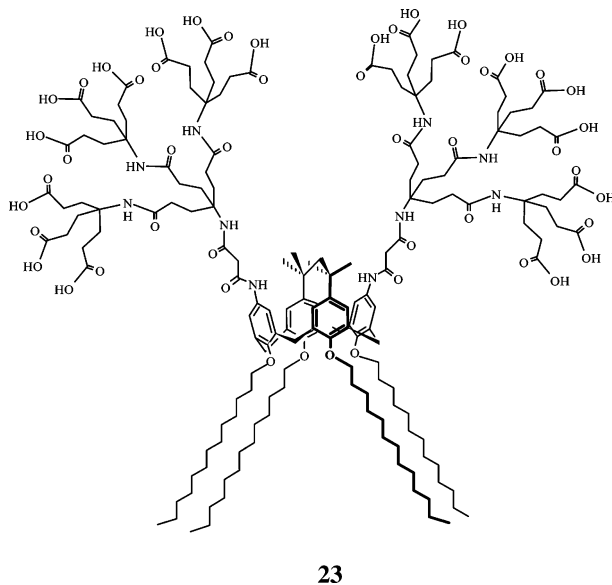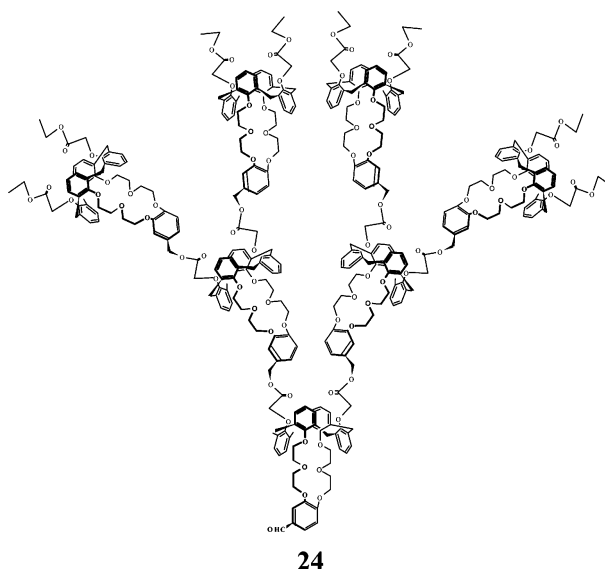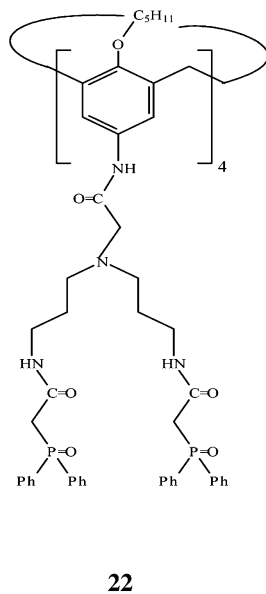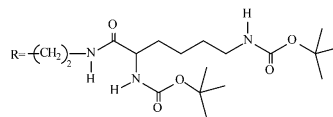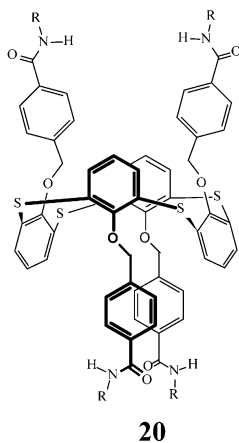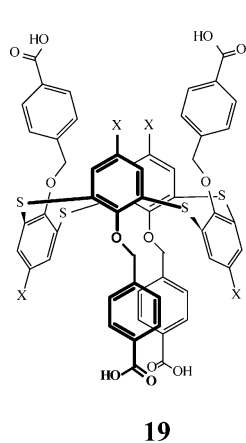
bonding present in the free ligand at the lower rim upon complexation.

In 2004, Štastný *et al.* [14] reported the synthesis of thiacalix[4]arenes in the cone or 1,3-alternate confor-

mations bearing two or four carboxylic functions on the lower rim which were reacted as acyl chloride with para amino calix[4]arenes. The 1,3-alternate conformer **15** was observed to be less reactive due to steric hindrance allowing the obtention of tricalix[4]arene **16** possessing inherent chirality. The cone conformer lead to the corresponding penta calixarenes **17** and **18** with retention of configuration.

The same year, Appelhans and co-workers [15] used similar thiacalix[4]arenes **19** in the 1,3-alternate conformation possessing carboxylic acid functions for the design of dendritic cores with amino surface groups. Because of the steric hindrance it was added a phenyl spacer leading to the formation of novel thiacalixarenes **20** bearing protected lysine groups.

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

Wang *et al.* [16] synthetized calix[4]arenes **21** and **22** substituted at the narrow or wide rim by eight carbamoylmethyl-phosphine oxide (CMPO) functions in a

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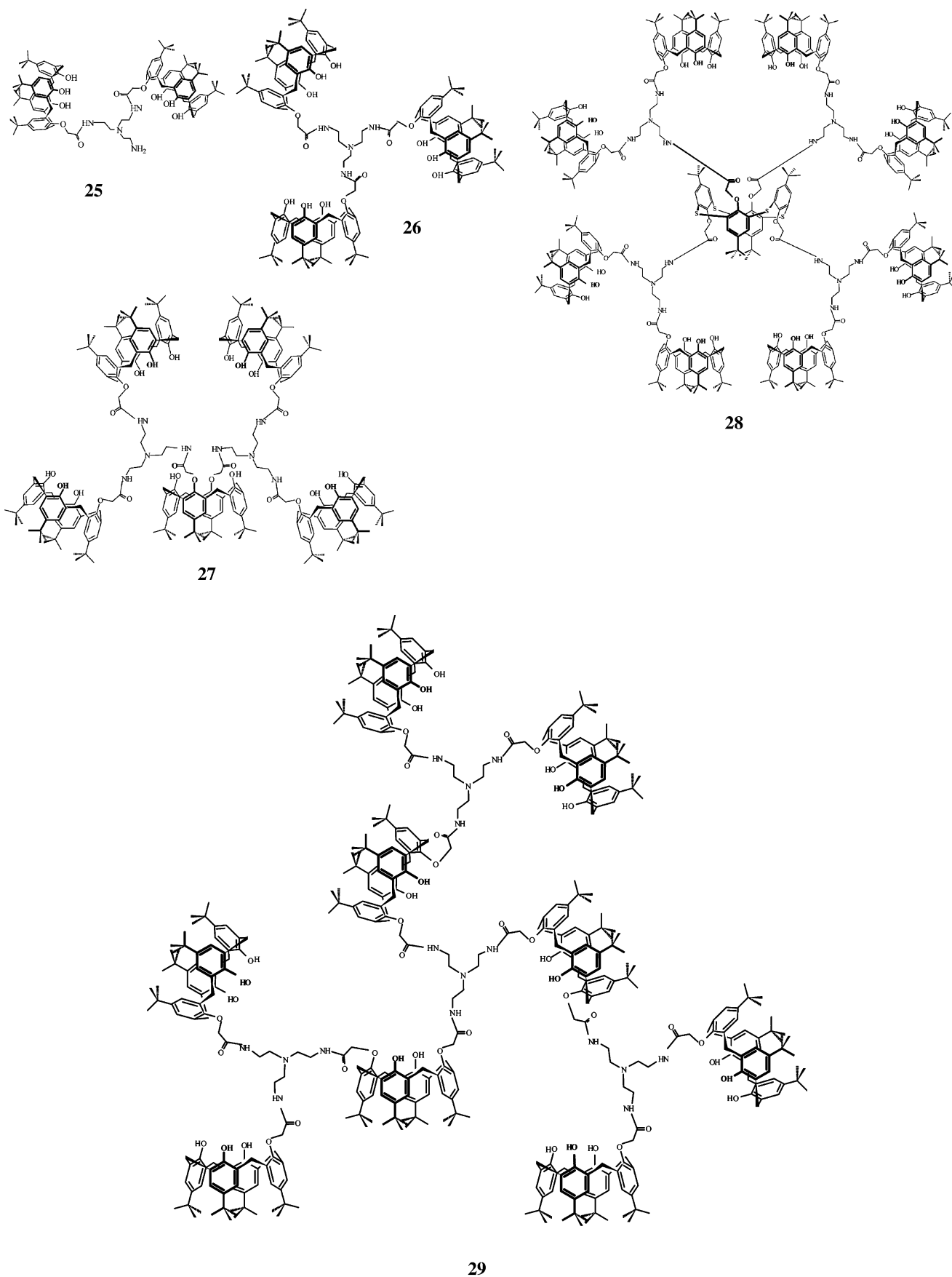
dendritic manner. Extractions of Eu^{3+} and Am^{3+} were carried out from water to *o*-nitrophenylhexyl ether. ^{1}H-NMR relaxivity titrations for wide rim octa-CMPO derivatives revealed the formation of solvent-free 1:2 ligand/metal complex, while the wide rim tetra-CMPO formed oligomers complexes under similar conditions.
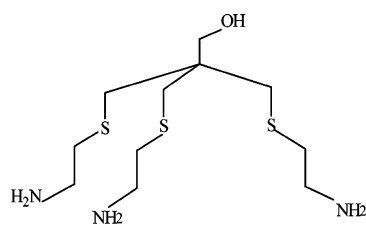
Similarly, related hyten-tricalix **33** was synthetized [21] by reacting monocarboxymethylcalix[4]arene **31** with a readily-prepared hydroxyl derivative of 'ten', $HOCH_2C(CH_2SCH_2CH_2NH_2)_3$ = 'hyten' **30**. This lead to the formation of a denrimer with a core containing 6 hetero atoms N3S3 while tricalix **26** contains only 4 N atoms. At the same time it was isolated hyten-dicalix-$SCH_2CH_2NH_2$ **32**.

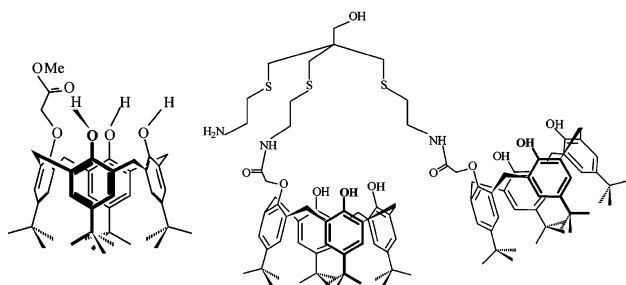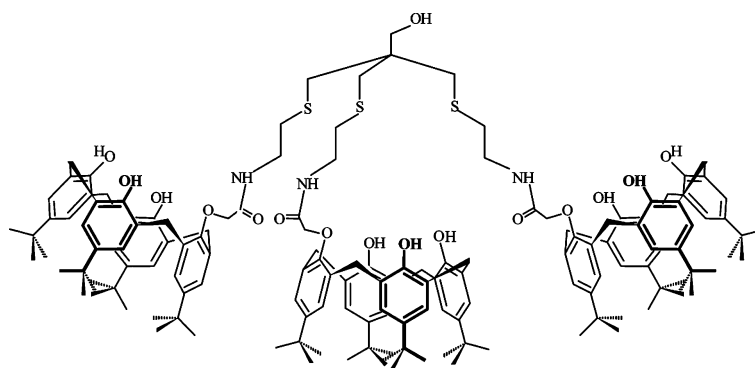These molecules, designed as dendrimer precursors, retain a core capable of acting as a multidentate ligand for metal ions. Studies of complex formation with Zn(II) and Co(III) by these **26**, **32**, **33** showed that indeed there is preferential binding to the core (rather than the phenolic sites of the calixarene units), suggesting new mechanisms for the control of the structure and stereochemistry of dendrimer species [21].

To conclude, this timely review pointed out the new interest of chemists in introducing calixarenes in dendrimers chemistry. In many areas, calixarene and dendrimer chemistries 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.

Acknowledgements

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Kellermann *et al.* [17] have synthesized amphiphilic dendro-calixarene **23** that assembles into complete uniform and structurally persistent micelles formed by the arrangement of seven molecules maintained together by hydrogen bonding. The specific target of these micelles is their use of as vehicles for the delivery of apolar molecules.

Recently, Bu *et al.* [18] reported the synthesis of the second generation of a dendrimer **24** based on calixcrown by the convergent pathway. Potential uses in cesium removal from nuclear wasted waters can be envisioned.

Concerning our laboratory research, Cheriaa *et al.* [19] synthetized a diamidocalix[4]arene **25** derivative from 'tren' and monocarboxymethylcalix[4]arene which is used for the preparation of a variety of hyperbranched molecules by reaction with chosen methylester compounds. Due to its 'classical' Y dendron shape two calixarenes are added in one time allowing the generation of dendrimers.

More particularly, tricalix[4]arene **26**, 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 **27–29** [20].

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