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A New Approach to Dendrimers made from *p*-*tert*-Butyl Calix[4]arenes*

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A new family of hyperbranched molecules and dendrimers has been constructed from a diamide–dicalix derivative prepared from monocarbomethoxymethyl *p*-*tert*-butyl calix[4]arene and tris(2-aminoethyl)amine ('tren') via amide-formation reactions. The selective 1,3-di-*O*-functionalization of *p*-*tert*-butyl calix[4]arene moieties allows the synthesis of first- (G1) and second-generation (G2) calix-dendrimers. Replacement of the quadridentate amine by a trithia-ether-triamine-mono-ol, 'hyten', again results in acylation of the amino groups, but with the generation of a central cavity with different complexing properties.

Keywords: Calixarenes; Hyperbranched molecules; Dendrimers; Convergent and divergent synthesis

INTRODUCTION

Dendrimers (Greek *dendron* = tree) and *hyperbranched molecules* represent a novel class of conformationally restricted macromolecules displaying a "branches-upon-branches" structural motif [1–26]. Dendrimers are well defined, highly branched macromolecules with a bonding structure that radiates from a central core (Fig. 1) and are synthesized through stepwise, repetitive reaction sequences that guarantee polymers which are monodisperse. Each step generates a shell, so that, depending on the shell which is outermost, dendrimers are described as being of the first, second, third etc.... generations (G1, G2, G3, ...). The synthetic procedures developed for dendrimer preparation permit nearly complete control over the critical molecular design parameters, such as size, shape surface/interior chemistry, flexibility and topology.

They are two ways to build a dendrimer. The "divergent" dendritic construction results from the sequential monomer (branching unit) addition beginning from an initial core and proceeding outward toward the macromolecular surface. To a respective core representing the zeroth generation (G0) and possessing reactive sites a generation of monomeric building blocks is covalently connected to give the first generation (G1). Building blocks can be added according to the reactive centers on the surface (end groups) of (G1) to give (G2) etc. The "convergent" mode of dendritic construction is another strategy whereby branched polymeric arms (dendrons) are synthesized from "outside-in". Then the covalently linkage to the initial core gives the various generations.

The repetitive branching sequence in a dendrimer creates a novel architecture. Exceptional features of the dendritic architecture include a high degree of structural symmetry, an internal density gradient passing through a minimum and a well defined number of terminal groups with functionality that differs from that of the interior. In combination, these features make of dendrimers molecules ideal for the development of functional nanoscale materials in which their unique properties (electronic, optical, opto-electronic, magnetic, chemical, supramolecular, or biological) are exploited. Recent developments include stimuli responsive polymers [6], pseudo-stationary phases [18], colloidal and liquid crystals of self-assembled hyperbranched molecules [5], host-guest systems [6] as delivery vehicles for medical uses [23], gene transfection [8], drug delivery [26], catalysis

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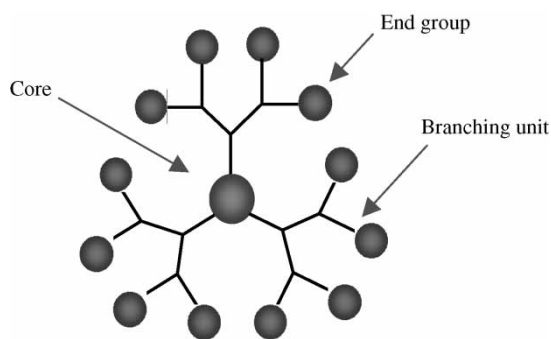


FIGURE 1

[17], contrasts agents for visualizing in magnetic resonance imaging [8], Langmuir–Blodgett films [6], light harvesting [19], luminescent hosts [5], sensors arrays [9], non linear optics, rheology modification [8], nanoscale science and nanotechnology [1–26].

Unlike collections of small molecules which might require supramolecular assembly to deliver function, dendrimers may do this by simple internal rearrangements. These can lead to shape and volume changes, the creation of internal microenvironments, the cooperative organization of surface or inner functionalities, substrate concentration in or exclusion from the molecular “cavity” of dendrimers, or the formation of defined multimolecular assemblies. Shape and volume are dendrimer properties which depend on the components used in their construction and thus, due to their versatility, we have chosen *calixarenes* as molecular bricks for constructing various hyperbranched molecules and dendrimers.

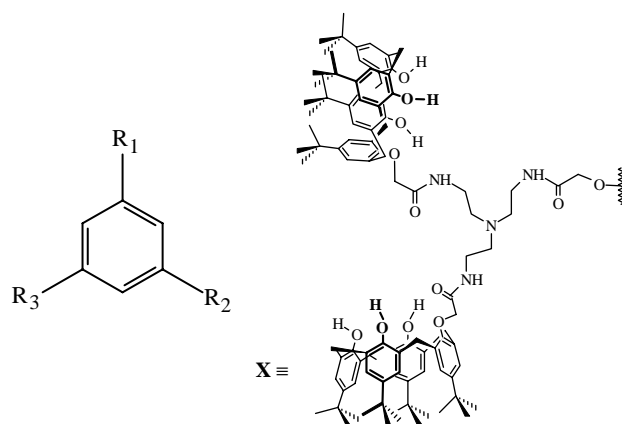
Calixarenes (Greek *calix* = calice) are macrocyclic compounds containing cavities of molecular-sized dimensions [27–36]. They consist of phenolic units arranged in cyclic arrays by the formation of methylene bridges *ortho* to the phenol function. Calixarenes have engendered extensive research both because of their capacity for forming complexes with a variety of guests and because of the ease of their selective functionalization, extending their use to the construction of large architectures such as calixcrowns, calixcryptands, calixspherands, calixcavitands, calixcarcerands, calixcatenates etc. They have been the basis of research in many fields such as those of inclusion science, host-guest and general supramolecular chemistry and have found a wide range of applications, such as in highly selective agents for cesium recovery, separation reagents in resource recovery and pollution control, sensors and catalysts, biocides and pharmaceuticals and in various nanocomposites. Thus, given their prominence as one of the most widely-exploited macrocyclic compounds in supramolecular science, calixarenes must be considered to provide entities of exceptional promise for incorporation within dendritic structures to generate new materials.

PREPARATION OF HYPERBRANCHED CALIX-BASED MOLECULES

The report, in 1991 [37], of water-soluble “sylvanols” obtained by amide formation between calixarene carboxylates and tris(hydroxymethyl)amine, may be considered the first of a hyperbranched calixarene. Various following studies [38–48] were based upon the use of calixarene units as both the core and branches of dendrimer-like molecules, though progress towards true dendrimer structures has been slow.

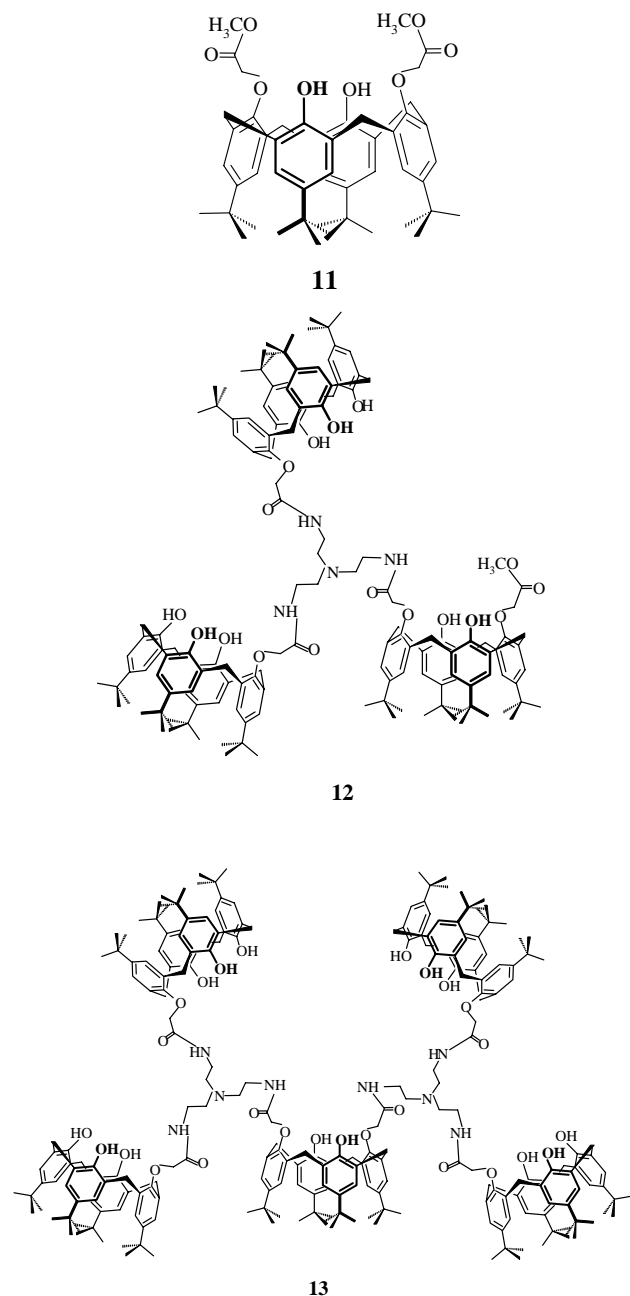
We started our work on calix-dendrimers in 2004 [49]. They are constructed through modular synthesis *via* the formation of amido bonds and taking advantage of the selective 1,3-di-*O*-alkylation of *p*-*tert*-butyl calix[4]arenes. As shown in Scheme 1, the synthesis of our calix-dendrimers begins by the reaction of *p*-*tert*-butyl calix[4]arene with bromomethylacetate in basic conditions to give the monocarboxymethyl *p*-*tert*-butyl calix[4]arene **1** [49]. A crystal structure determination showed **1** to adopt the *cone* conformation in the solid state [50]. ¹H NMR spectroscopy indicates this conformation to be preserved in solution for **1** and for all its derivatives presently described. Amide formation by reaction of **1** with tris(2-aminoethyl)amine (‘tren’) readily provides both *N*-dicalix-CH₂CH₂NH₂ **2** and *N*-tricalix **3**.

Isolated **2** converted to **3** by extended reaction with **1**. It is a valuable “dendron” for the formation of a variety of other hyperbranched calixarene derivatives. Thus, reaction of **2** with can be trimethyl ester phenyl-derivatives **4** and **5** gives the different possible mono-, di- and tri-substituted hyperbranched products **6–10** [49].



- 4** R₁ = -CO₂CH₃; R₂ = R₃ = -OCH₂CO₂CH₃
5 R₁ = R₂ = R₃ = -OCH₂CO₂CH₃
6 R₁ = -CO₂CH₃; R₂ = -OCH₂CO₂CH₃; R₃ = X
7 R₁ = -CO₂CH₃; R₂ = R₃ = X
8 R₁ = R₂ = -OCH₂CO₂CH₃; R₃ = X
9 R₁ = -OCH₂CO₂CH₃; R₂ = R₃ = X
10 R₁ = R₂ = R₃ = X

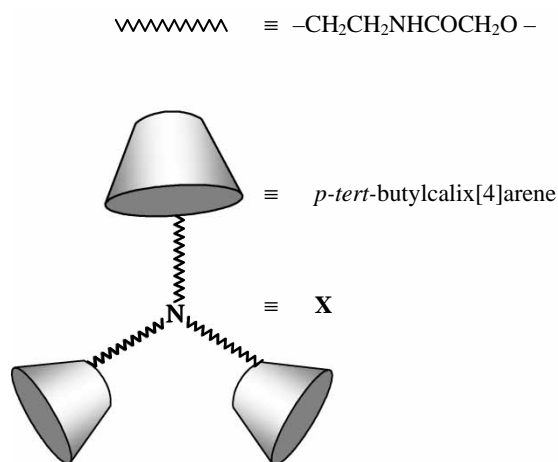
2 also reacts with 1,3-bis(methoxycarbonyl methoxy)-*p*-*tert*-butylcalix[4]arene **11** to give the mono- and di-substituted products **12** and **13**.



It is important to note that the difference in the rates of the stepwise amide-formation reactions of the dicarboxylate ester species is sufficient for the monosubstituted compounds to be readily isolated. The residual ester group can then be used in different molecular constructions [51,52].

ELABORATION OF CALIX-DENDRIMERS

To simplify representation of the large molecular structures involved for calix-dendrimers, we have used the following symbols:



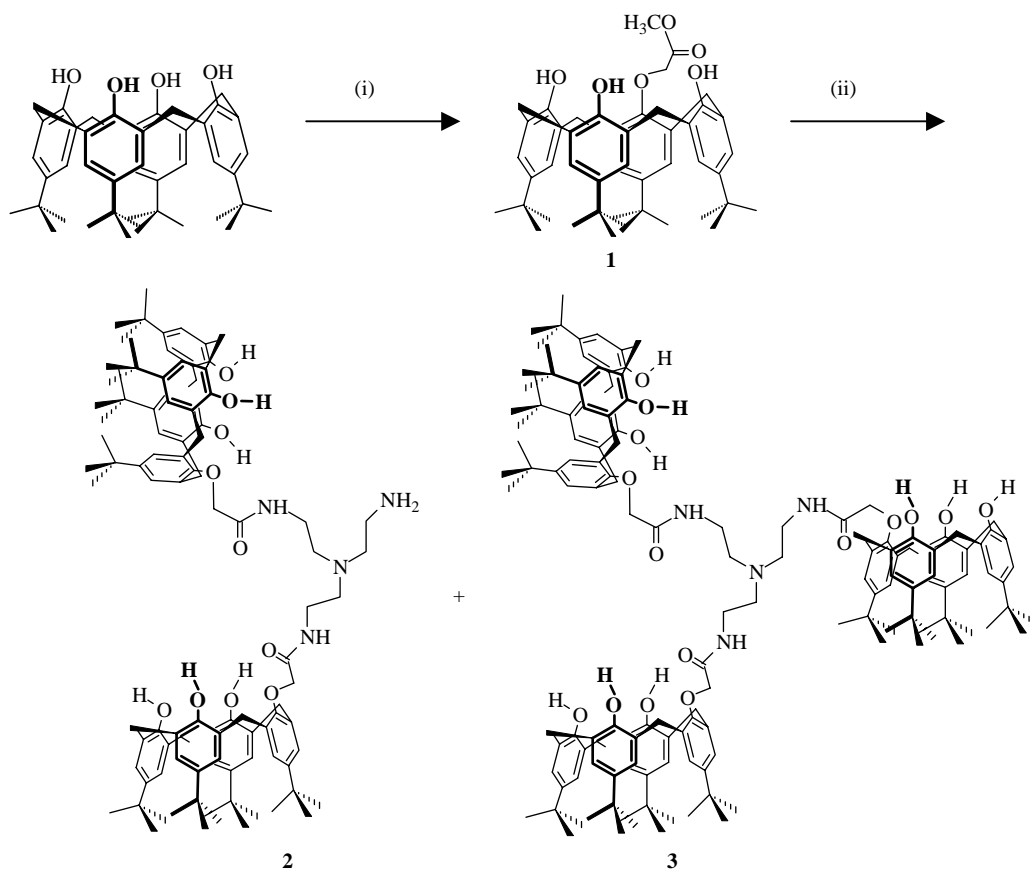
In these terms, the extension of the first-generation (**G1**) dendrimer **3** to the second- (**G2**) and third- (**G3**) generation species can be shown as in Scheme 2. The actual synthesis of the **G2** molecule **14** can be achieved by both “convergent” and “divergent” procedures, depending on the choice of precursors, as illustrated in Schemes 3 and 4, respectively.

The convergent approach to (**G2**) takes advantage of the isolation of **12**, which is in fact a derivative of *N*-tri-calix **3** with one methoxycarbonylmethoxy function. As shown in Scheme 3, this monomethyl ester reacts with ‘tren’ to yield the (**G2**) calix-dendrimer **14**. The molecular formula of **14** is $\text{C}_{444}\text{H}_{576}\text{O}_{48}\text{N}_{16}$ with MW = 6905.45, MALDI-TOF mass spectrometry enabling ready detection of the species 14H^+ , $m/z = 6906.54$.

The divergent synthesis is depicted in Scheme 4. *N*-tri-calix **3** reacts with methyl bromoacetate in basic conditions to yield the *N*-tri-calix tris(methyl ester) derivative **15** in which the $-\text{OCH}_2\text{CO}_2\text{CH}_3$ functions are symmetrically distributed, one of each being in the distal position to the amide-bearing substituent on each calixarene unit. Reaction of **15** with *N*-dicalix- $\text{CH}_2\text{CH}_2\text{NH}_2$ **2** gives the (**G2**) calix-dendrimer **14**. Once again, a partially substituted species **16**, with one residual ester group and thus being another potential dendron, is readily isolated.

CHANGING THE INITIAL CORE

Replacement of ‘tren’ by ‘hyten’, $\text{HOCH}_2\text{C}(\text{CH}_2\text{SCH}_2\text{CH}_2\text{NH}_2)_3$, leads to related hyperbranched molecules **17** and **18** by its reaction with monocarboxymethylcalix[4]arene **1**. This leads to the formation of a hyperbranched molecules with a core, possibly suitable as a multidentate ligand for metal-ion binding, based on a trithiaether-triamide rather than

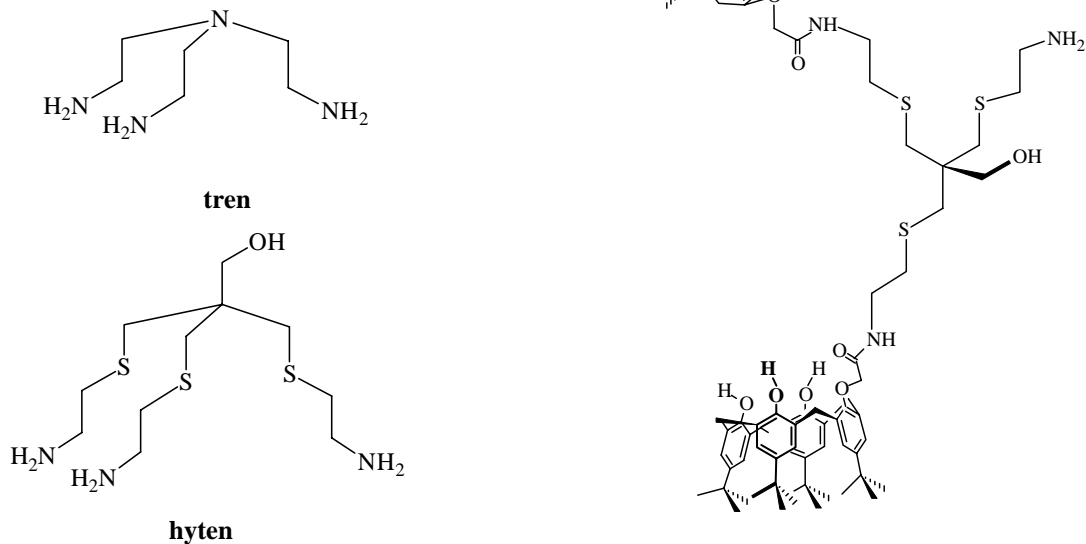


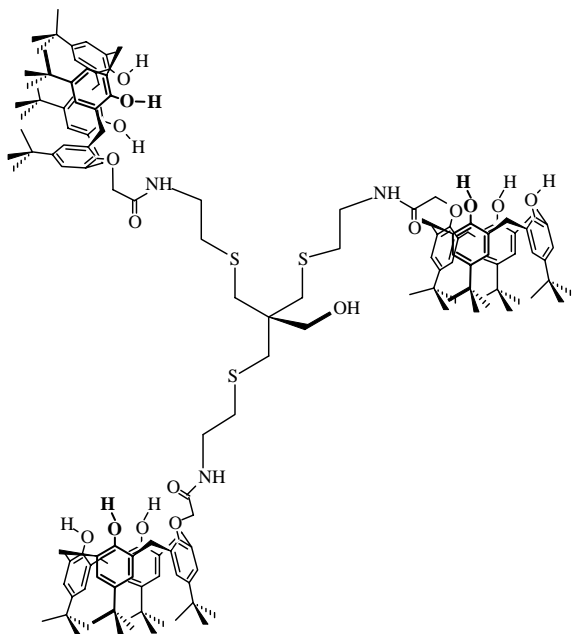
(i) $\text{BrCH}_2\text{CO}_2\text{CH}_3$, K_2CO_3 , acetone, reflux 24h, 28 %.

(ii) $\text{N}(\text{CH}_2\text{CH}_2\text{NH}_2)_3$, toluene:methanol (v/v), reflux 6d, 21 % of 2 and 13 % of 3.

SCHEME 1 Synthesis of 1, 2 and 3.

an amine–triamide unit. Studies of complex formation with $\text{Zn}(\text{II})$ and $\text{Co}(\text{III})$ have shown 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.

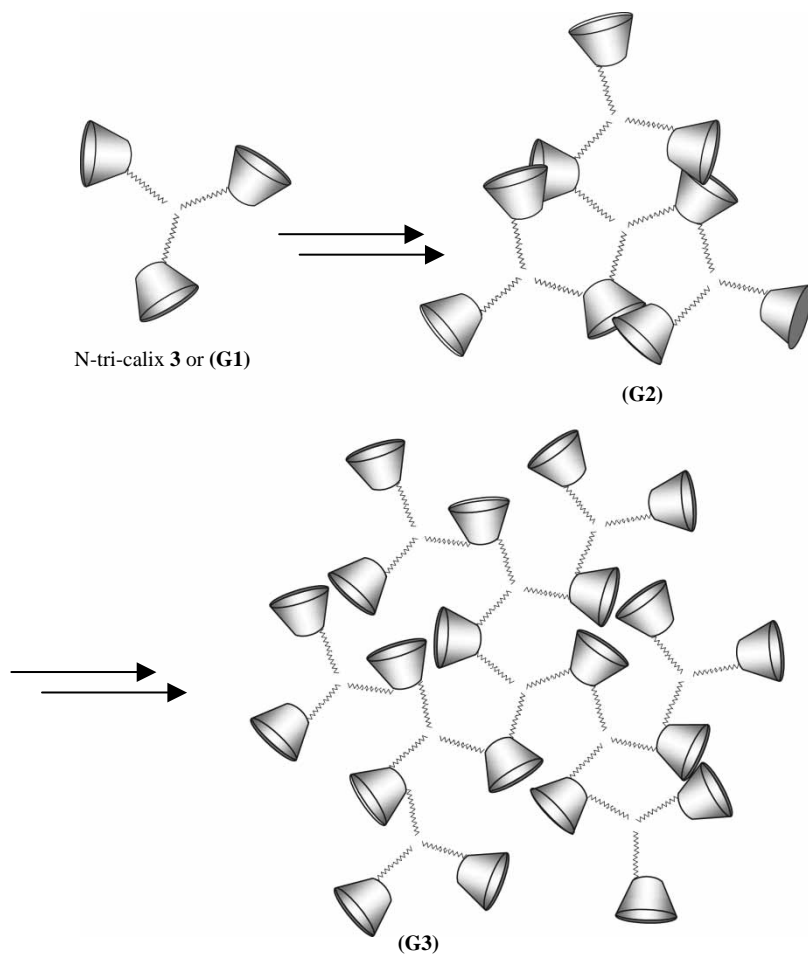




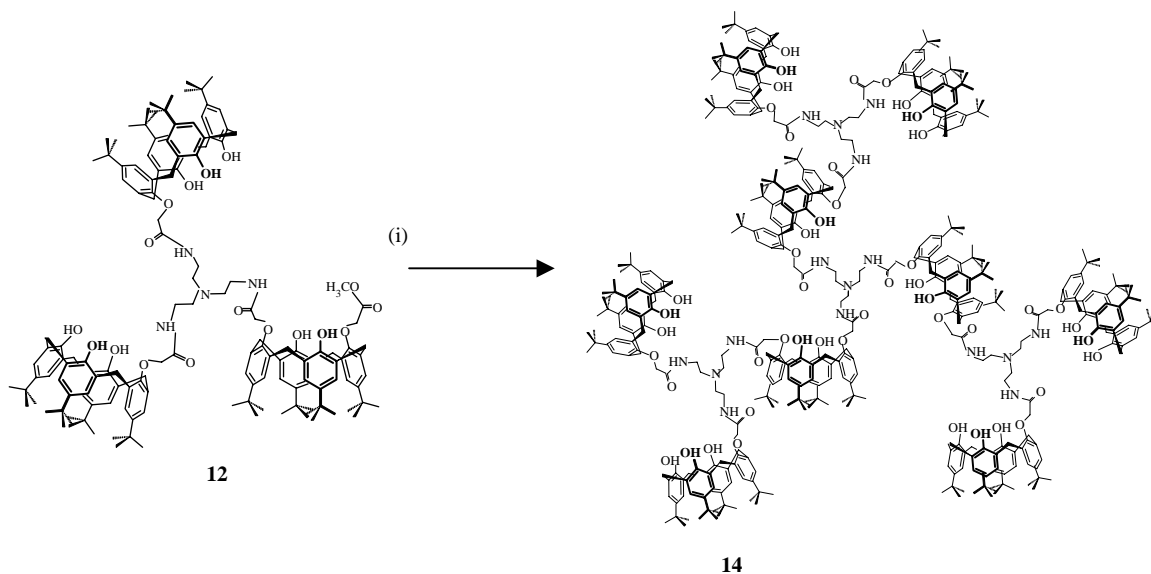
CONCLUSION AND PERSPECTIVES

The use of amide formation by reaction of polyamines with polyester calixarene derivatives enables the facile isolation not only of calix-dendrimers but also of dendrons suitable for the elaborations of higher dendrimers and various hyperbranched molecules. The presence of a core derived from the polyamine provides a site for metal ion binding and thus potentially for the use of complexation as a means of control of the form of the dendrimer. Current work is directed towards: (a) the synthesis of the (G3) calix-dendrimer by convergent (from **16**) and divergent (from **14**) syntheses; (b) the construction of mixed or hetero-dendrimeric structures of the (G2) type containing branches derived from 'tren' and 'hyten' to lead to dendrimers incorporating multiple cavities suitable for the binding of transition metal ions.

Other kinds of cores can be chosen in the large panel of polyamines and polyaminoalcohols found in literature [53].



SCHEME 2 Modular approach to (G2) and (G3) from (G1).



(i) $\text{N}(\text{CH}_2\text{CH}_2\text{NH}_2)_3$, toluene:methanol (v/v), reflux 10d, 13 %.

Scheme 3 Convergent synthesis of the (G2) calix-dendrimer 14.

Acknowledgements

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