Synthesis of Calix dendrimers

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Dedicated to Professor Alain Krief on his 65th anniversary

Abstract

The present paper is a timely review of a work developed in the laboratory and dealing with the chemistry of dendrimers. The main originality of these dendrimers is that they contain only calix[4]arene units by taking advantage of their 1,3-selective dialkylation. The linking of the calixarenes is made by amidation reaction with tri primary amines serving as branches.

Keywords: Calixarenes, dendrimers, 1,3-selective dialkylation, amidation, zinc complexation

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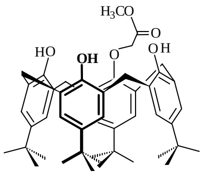
Most of the research of the *Laboratoire de Conception Moléculaire* in Strasbourg, France, is devoted to fundamental research and industrial applications of calixarenes as supramolecular tools. The present paper is a timely review of a part of the work developed in the laboratory and dealing with the chemistry of dendrimers.

Dendrimers (Greek *dendron* = tree) are macromolecules, synthesized step-by-step by repetitive chemical reactions. The constituents radiate in branching form from a central core, creating a sphere of chemical groups that can be tailored according to requirements.[1] 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**....). They are two ways to prepare a dendrimer. The 'divergent' one results from sequential monomer branching beginning from a core and proceeding outward toward the macromolecular surface. The 'convergent' mode is another strategy whereby branched polymeric arms (dendrons) are synthetized from "outside-in". Shape and volume are dendrimer properties which depend on the components used. We have chosen *calixarenes* as molecular elements for preparing hyperbranched molecules and dendrimers. *Calixarenes* (Greek *calix* = calice) are macrocycles consisting of phenolic units arranged in cyclic arrays by the formation of methylene bridges *ortho* to the phenol function. They are the object of 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 calixcrowns, calixcryptands, calixspherands, calixcavitands, calixcarcerands, calixcatenates etc.[2] Given their prominence as one of the most widely-exploited macrocycles in supramolecular science, calixarenes must be considered to provide entities of exceptional promise for incorporation within dendritic structures to generate new materials. This new family of molecules has been termed ‘calix dendrimers’ and has been the subject of review articles mainly describing their synthesis with some complexation studies. In the major cases the calix dendrimers are constructed with calix units but in such a way it is not possible to grow the next generations.[3]

We reported our first calix dendrimers in 2004.[4] They are constructed *via* the formation of amido bonds and taking advantage of the selective 1,3-di-O-alkylation of *p*-*tert*-butyl calix[4]arenes. The synthesis begins by the reaction of *p*-*tert*-butyl calix[4]arene with $BrCH_2CO_2Me$ in basic conditions to give the monomethyl ester *p*-*tert*-butyl calix[4]arene (**1**).[4] A crystal structure determination showed **1** to adopt the *cone* conformation in the solid state.[5] ^1H NMR spectroscopy indicates this conformation to be preserved in solution for **1** and for all the derivatives presently described. Amide formation by reaction of **1** with tris(2-aminoethyl)amine (‘tren’) readily provides both N-dicalix-$CH_2CH_2NH_2$ (**2**) and N-tri-calix **3**. **2** can be converted to **3** by extended reaction with **1**. A crystal structure determination showed that both calixarene units of **2** adopt the cone conformation. In a general manner the calixarenes moieties were observed by ^1H NMR to be in cone conformation for all the calix-dendrimers described in this paper.



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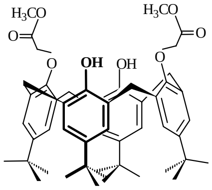

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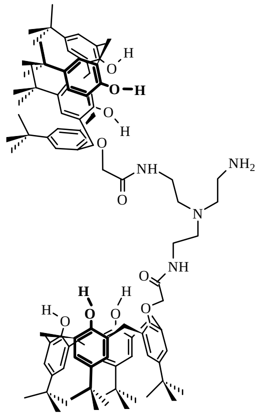

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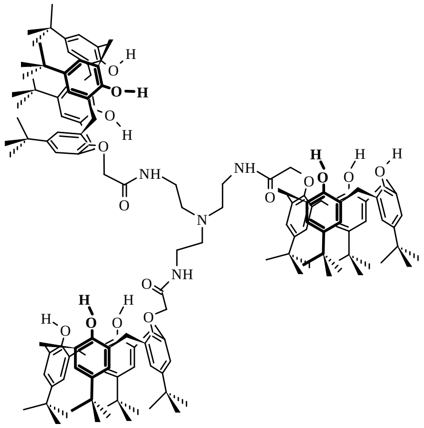

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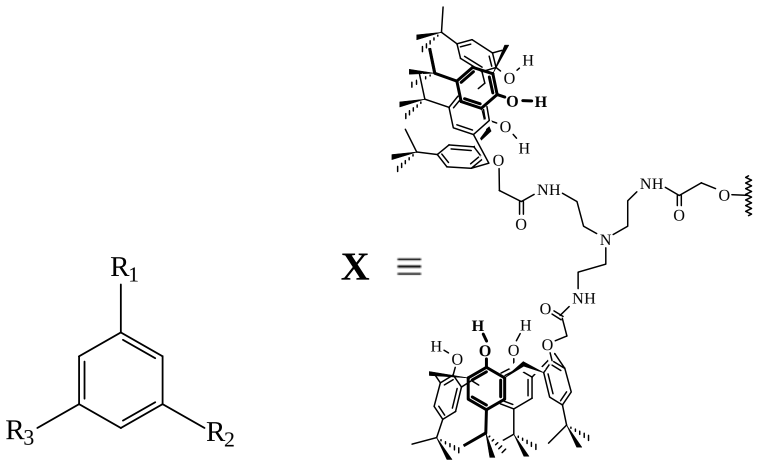
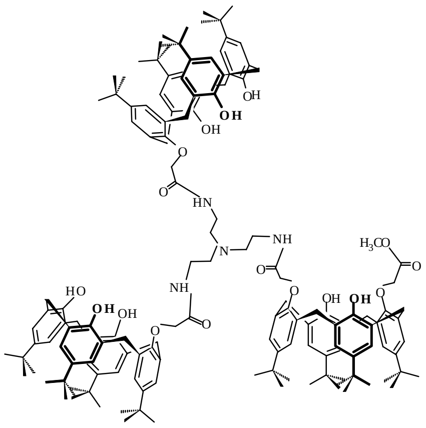
Compound **2** is a valuable "dendron", bearing a reactive NH_2 function and reaction with methyl ester compounds **5** and **6** gave hyperbranched calixarene derivatives with a benzene core **8-10**.[3]



4 $R_1 = -CO_2CH_3$; $R_2 = R_3 = -OCH_2CO_2CH_3$
5 $R_1 = R_2 = R_3 = -OCH_2CO_2CH_3$
6 $R_1 = -CO_2CH_3$; $R_2 = -OCH_2CO_2CH_3$; $R_3 =$ **X**
7 $R_1 = -CO_2CH_3$; $R_2 = R_3 =$ **X**
8 $R_1 = R_2 = -OCH_2CO_2CH_3$; $R_3 =$ **X**
9 $R_1 = -OCH_2CO_2CH_3$; $R_2 = R_3 =$ **X**
10 $R_1 = R_2 = R_3 =$ **X**

Subsequently, we constructed hyperbranched molecules involving only calix[4]arenes. The reaction of **2** with *cone*-1,3-dimethyl ester (**11**) gave the mono- and di-substituted products **12** and **13**.



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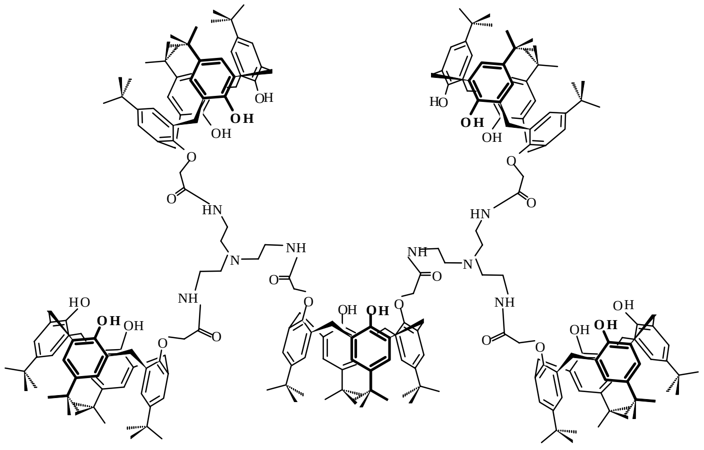

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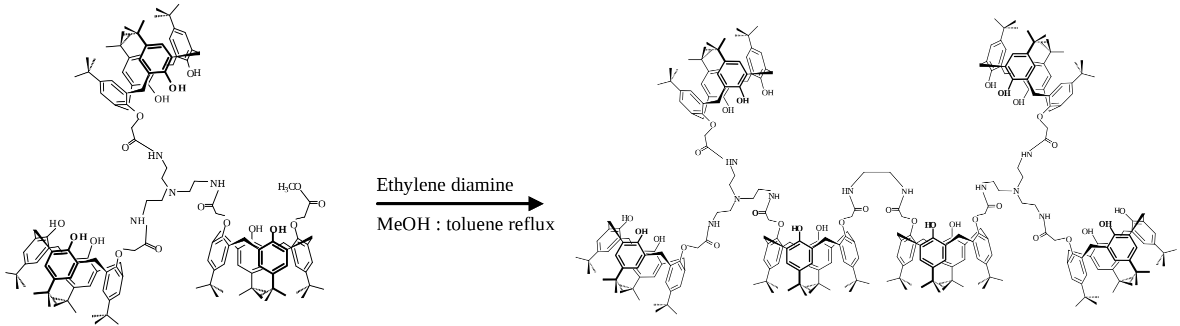
The residual methyl ester group of **12** (considered as a “dendron” but different from **2**) can then be used in diverse molecular constructions. For example, **12** was reacted with ethylene diamine or $NH_2CH_2CH_2NH_2$ (Scheme 1) to give hexacalix **14** which can be seen as two N-tri-calix **3** attached one to the other by a 1,3-diethylene diamido link [6]. The molecular formula of **14** is $C_{294}H_{380}O_{32}N_{10}$ with a calculated molecular weight of MW = 4566.3. It was found *m/z* = 4565.74 with the MALDI-TOF techniques. This construction corresponds to a ‘convergent’ synthesis.



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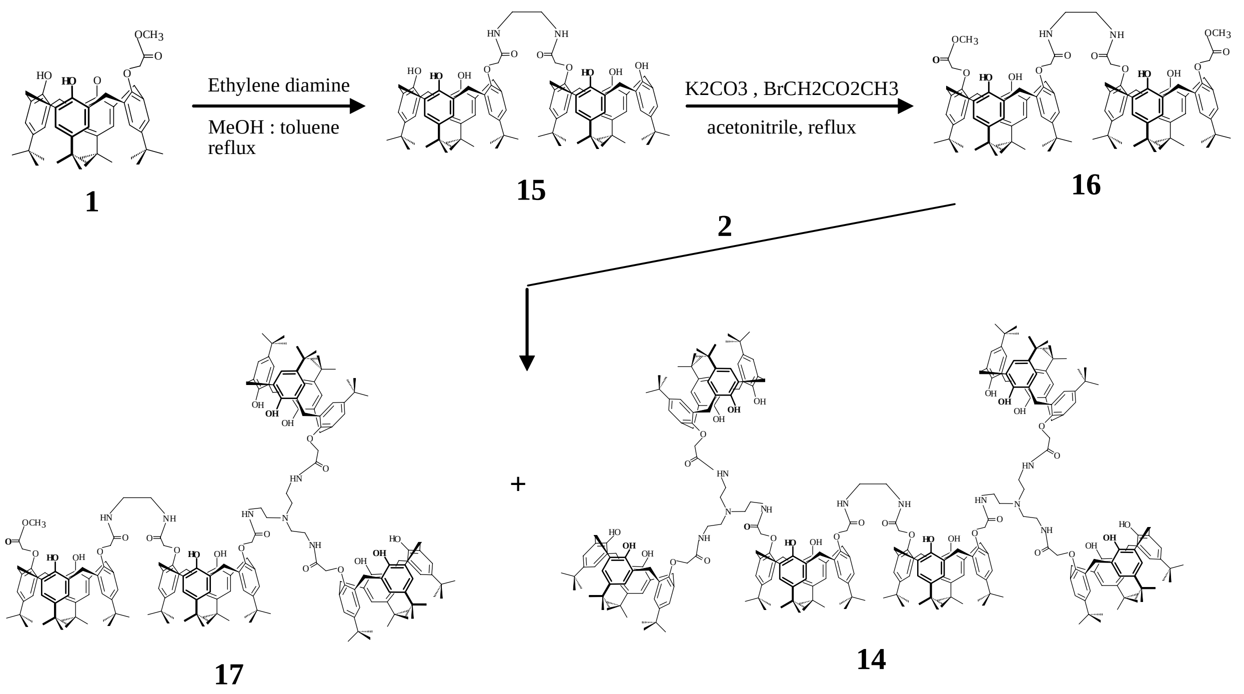
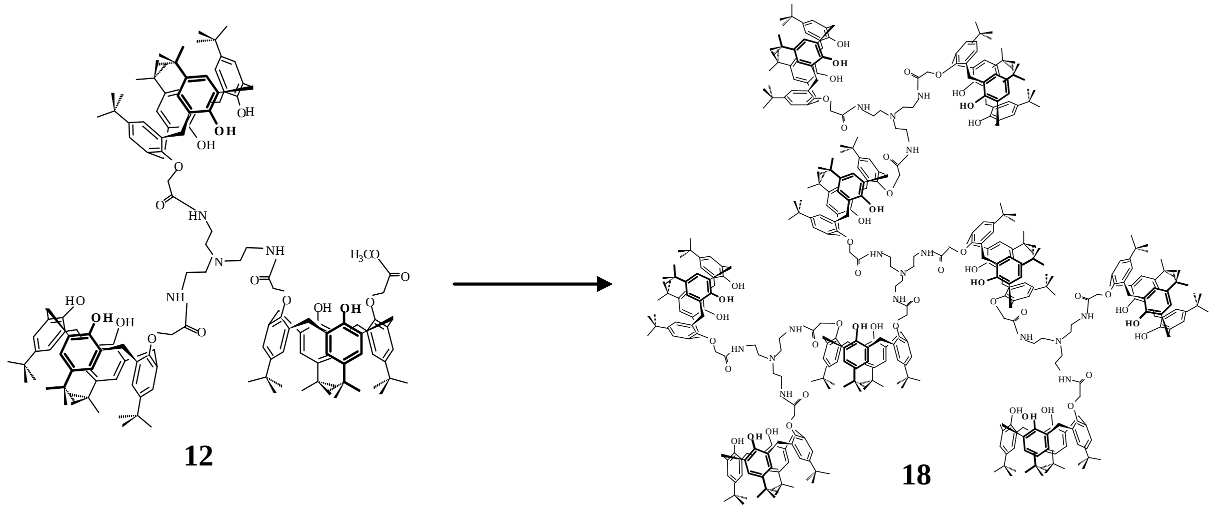
Scheme 1. Preparation of **14**.

Compound **14** was also obtained according to Scheme 2 by the so-called ‘divergent’ synthesis. **1** was reacted with ethylene diamine to produce **15** which was further selectively di-alkylated on ‘opposite’ positions into di-methyl ester **16**. The reaction of **16** with **2** produced **14** and **17**.



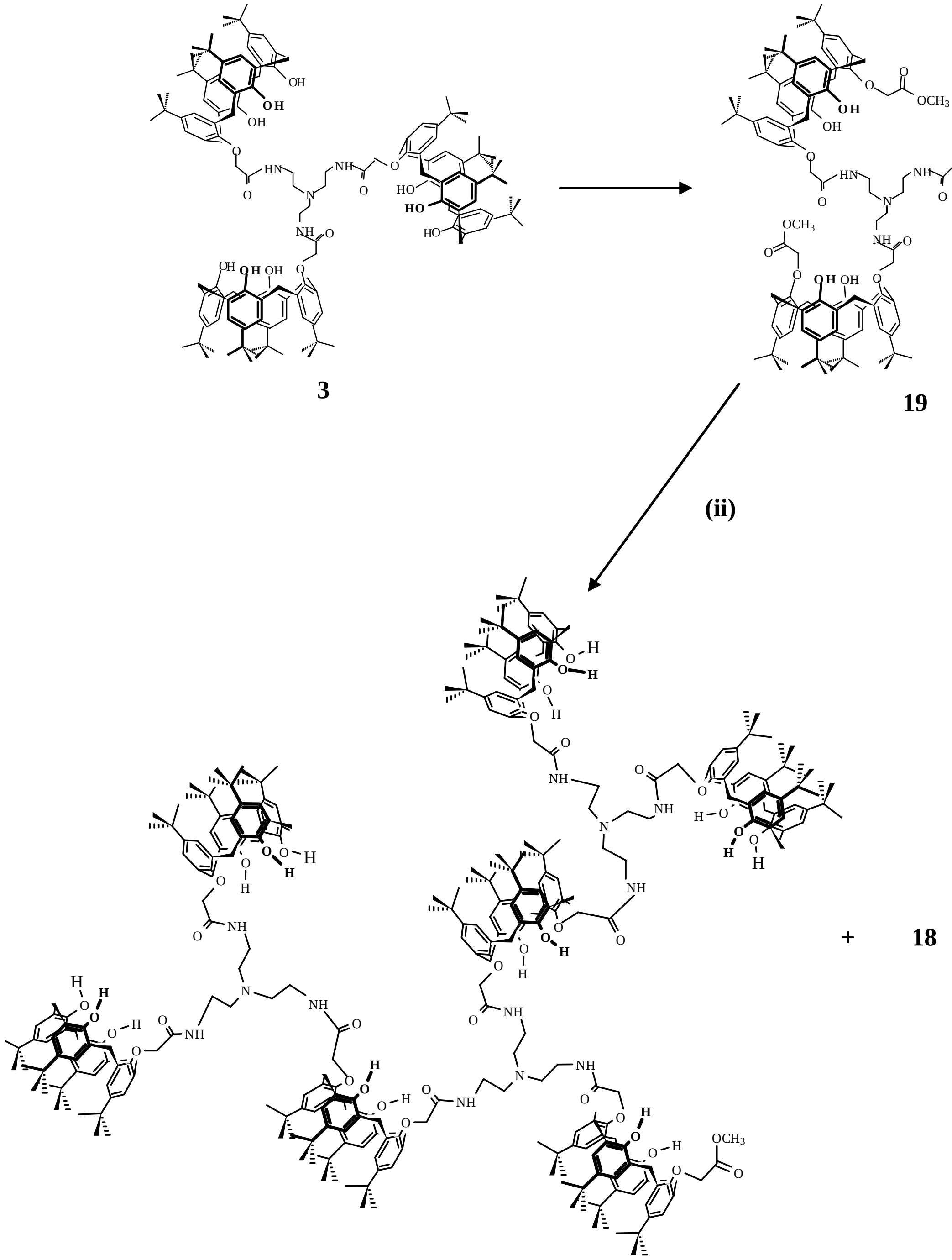
Scheme 2. Preparation of **15-17**.

A very similar approach, nonacalix **18** (considered as **G2**) was prepared by using tripodal $N(CH_2CH_2NH_2)_3$ or 'tren' as a 'link and core' couple. As shown in scheme 3, **12** was reacted with 'tren' to yield the calix dendrimer **18**. The molecular formula of **18** is $C_{444}H_{576}O_{48}N_{16}$ with MW = 6905.45, MALDI-TOF mass spectrometry enabling ready detection of the species **18**H^+, *m/z* = 6906.54.[6]



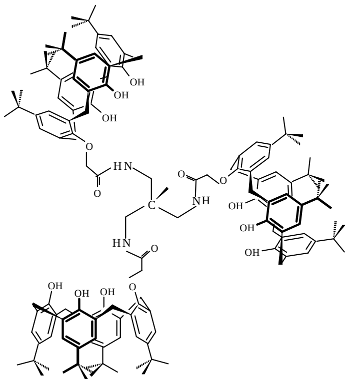
Scheme 3. Convergent synthesis of the **G2** calix-dendrimer **18**.

The ‘divergent’ synthesis of **18** is depicted in Scheme 4. **3** was alkylated into N-tri-calix tri methyl ester **19** in which the methyl ester functions are distal to the amide-bearing substituent on each calixarene unit. Reaction of **19** with **2** gives the calix dendrimer **18**. Heptacalix was isolated at the same time.



Scheme 4. Divergent synthesis of **G2** of calix-dendrimer **18**.

The ‘tren’ was chosen not only because the construction of a dendrimer needs a Y-shaped molecule but also because it leads to the formation of hyperbranched molecules with a core and focal centers, suitable as a multidentate ligand for metal-ion binding. Replacement of ‘tren’ by ‘tame’[7], ‘hyten’[7] and ‘sen’[8] leads to related molecules **21-23**.



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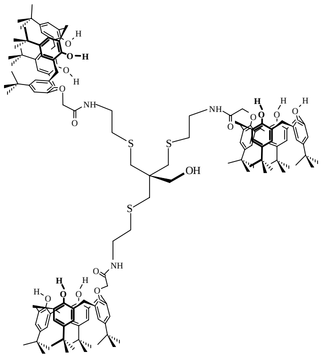

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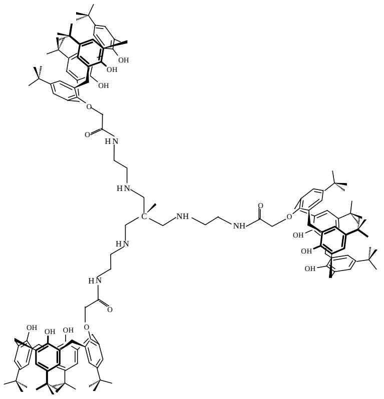

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Studies of complex formation with Zn(II) have shown that indeed there is preferential binding to the core except for **22** in which Zn(II) was located on the phenolic sites of the calix units, suggesting new mechanisms for the control of the structure and stereochemistry of dendrimer species.

Perspectives

One of the main areas to be investigated in the near future will be to prepare the **G3** of calix-dendrimer constructed from calix[4]arene and tren as branches. The second work will be to prepare mixed calix-dendrimers constructed from calix[4]arene and different tripodal polyamines. The selective complexation at the level of the different tripodal centers may lead to the formation of supramolecular structures in which the metals are precisely organized in ordered manner. The isolation of di-calix with remaining NH_2 functions able to chelate cation opens the way of synthesizing metallocalix-dendrimers.

More generally one can assume the use of both the complexation properties of the tripodal centers and the chemical properties (functionalization and complexation) of calixarenes to create molecular systems capable of action such as light harvesting.

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