

Novel calixarene-based hyperbranched molecules with N-multidentate chelating sites

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ABSTRACT

Two novel calixarene-based hyperbranched molecules with N-multidentate chelating sites have been prepared. Complexation studies have been carried out to evidence coordination at the N-multidentate sites.

Key words : dendrimers, dendrons, calixarenes

The special properties of dendrimers and hyperbranched molecules come from their very peculiar molecular structures (1). The chemical structures of these large molecules are accurately defined because they are prepared by established reactions and chosen pathways (1). Dendrimers are monodisperse and consistent in size and form with regular branched three-dimensional architectures composed of a central core, branches, and end groups. The preparation of such branched structures requires the use of particular building blocks with the appropriate stereochemistry and multiple, equivalent reaction centres. Calixarenes (2), with their multiple sites for functionalization on a conformationally restricted, macrocyclic scaffold, are attractive 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

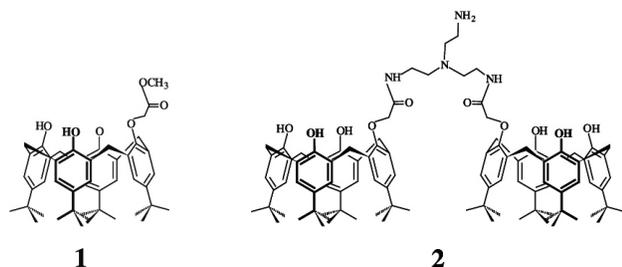
ease of functionalization, enabling their use in the construction of sophisticated derivatives such as calixcrowns (3), calixcryptands (4) and calixspherands (5).

We recently published a mini-review (6) focusing on the construction of dendrimers from calix[4]arenes and/or thiacalix[4]arenes in which we pointed out that the combination of dendrimer and calixarene chemistries could potentially lead to some interesting applications. Although the chemistry of so-called 'calix-dendrimers' is at the present time mainly restricted to the description of synthetic strategies, one can see that these molecules are constructed from a wide diversity of molecular segments interconnecting the calix[4]arenes units in cone and/or 1,3-alternate conformation. The molecular segments are often functionalized and offer additional supramolecular properties (molecular interactions and supramolecular construction) to those of the calixarenes. For instance, Mogck *et al.* (7) reported a penta-calix[4]arene corresponding to a dendrimer with a 1,3-alternate calix[4]mesitylene as a core and four calix[4]arene bearing four ethyl ester functions as end groups. This penta-calix[4]arene was shown to complex four Na⁺ cations through

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the four end group-calixarenes. More recently, Bu *et al.* (8) reported the synthesis of a nona-calixarene as the second generation of a dendrimer based on a calixcrown in the 1,3-alternate conformation by the convergent pathway. Potential uses in cesium complexation and subsequent applications in nuclear waste treatment can be envisioned.

We previously published the synthesis of a series of hyperbranched molecules and dendrimers based on calix[4]arenes (9-11). The molecular segments are multidentate ligands of type N4 (derived from 'tren')^{9,10} or N3S3 (derived from 'ten') (11). Complexation of transition metals (Zn²⁺ and Co³⁺) occurred in the multidentate region rather than in the phenolic sites of the calixarene units. More particularly, the dendrimers derived from 'tren' were constructed by taking advantage of the preparation of the N-dicalix **2** derived from 'tren' and monocarboxymethylcalix[4]arene **1** (9, 10).



The present paper reports on two recent results. First, we report on the crystalline structure of **2** which shows the cone conformation of the calix[4]arene units. Second we describe the preparation of the tetra-calix[4]arene **5** and hexa-calix[4]arene **6** from **1** and **2** as new members of the family. Compound **6** presents several N-chelating centres and preliminary complexation studies are reported for selected metals.

Crystal structure of $2 \cdot (\text{CH}_3)_2\text{CO} \cdot \text{CH}_2\text{Cl}_2 \cdot 3\text{CH}_3\text{OH} \cdot 2\text{H}_2\text{O}$

The crystal structure of the bis-calixarene **2** is represented in Fig 1 (12).

The two calixarene moieties are in cone conformation, the dihedral angles between the four aromatic rings and the mean plane defined by the four oxygen atoms (r.m.s. deviations 0.11 and 0.13 Å for the two moieties) are 71.75 (9), 61.87 (10), 60.13

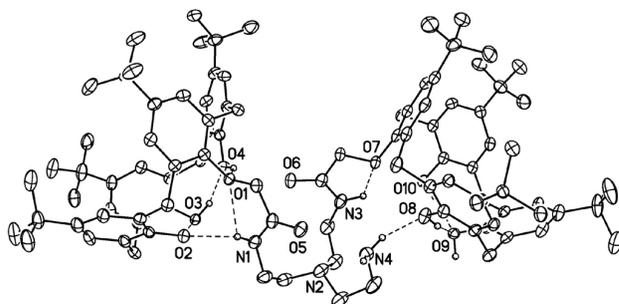


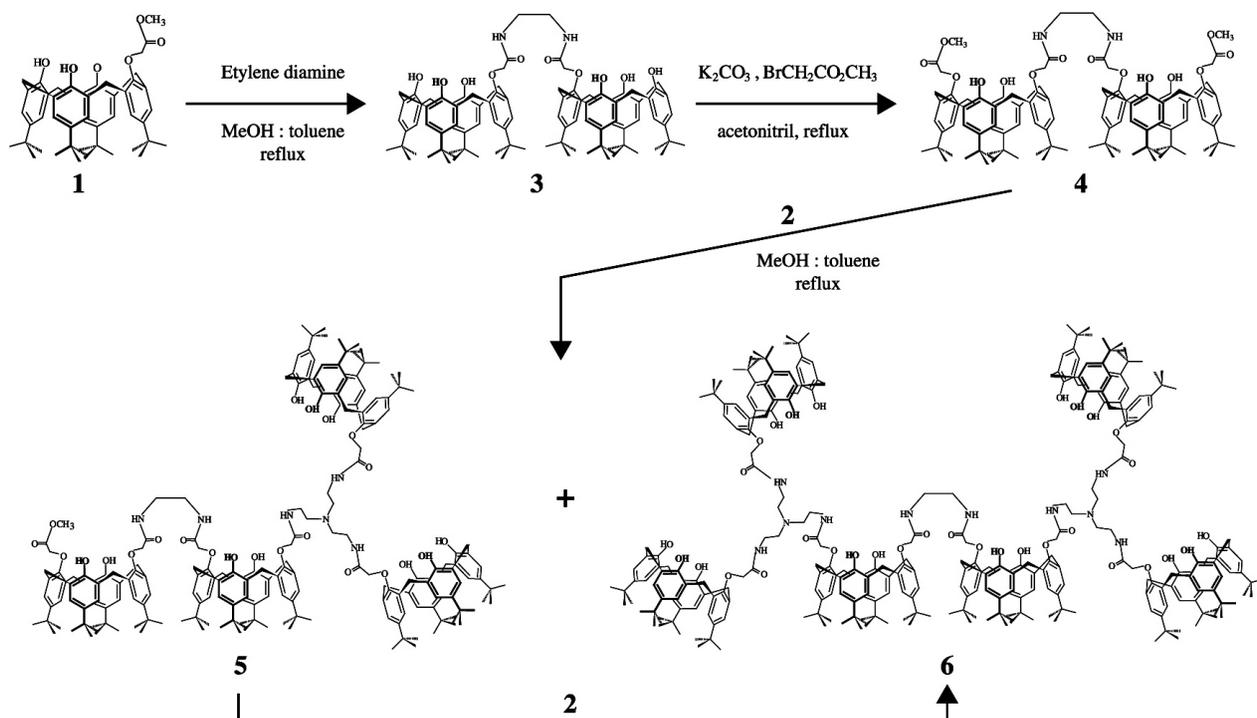
Fig 1. View of the structure of compound **2**. Hydrogen atoms not involved in hydrogen bonds are omitted. Hydrogen bonds are shown as dashed lines. Only one position of the disordered *tert*-butyl group was represented. Displacement ellipsoids are drawn at the 30% probability level.

(11), 32.06 (11)° for the first unit and 78.14 (9), 42.67 (9), 56.89 (7), 45.61 (9)° for the second unit. The conformations of the two units are thus slightly different, but the ring bearing the *O*-substituent (corresponding to atoms O1 and O7) is the more tilted with respect to the mean plane in both cases. The angle between the two O₄ mean planes is 81.08 (7)°. The chain connecting the two calixarene units and the side chain attached to it adopt an extremely irregular conformation, held by eleven hydrogen bonds, nine being intra- and two intermolecular (the latter involving a water molecule and a carboxy group in a neighbouring bis-calixarene molecule). In the first unit, the four phenolic oxygen atoms are hydrogen bonded one to the other by their three protons, whereas, in the second unit, three of them only are hydrogen bonded together, one of the protons being diverted towards a water molecule. The secondary ammonium groups are involved either in a bifurcated hydrogen bond with two phenolic oxygen atoms (N1) or in a simple hydrogen bond with the oxygen atom bearing the chain (N3). The primary ammonium group (N4) is hydrogen bonded to a phenolic oxygen of the same molecule and a carboxy group of a neighbouring unit.

Synthesis of **5** and **6**.

The synthesis of **5** and **6** is given in Scheme 1.

Monocarboxymethylcalix[4]arene **1** was reacted with 3 equivs of ethylene diamine (amidation reaction) in a 1:1 mixture of CH₃OH/toluene at reflux for 48 h to afford pure

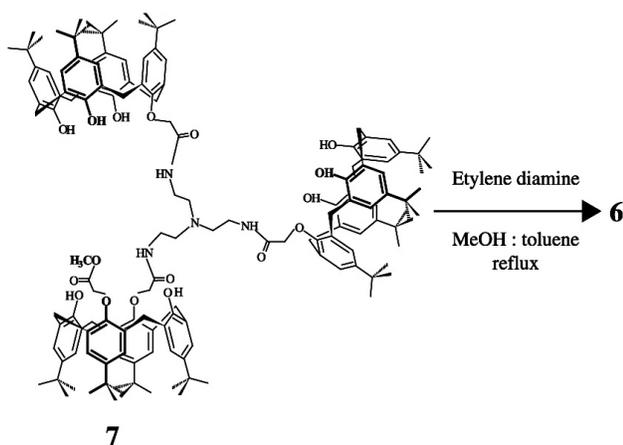


Scheme 1. Preparation of 5 and 6

dicalix **3** in 34% yield after chromatography on SiO_2 column with 95/5 CH_2Cl_2 /acetone as eluent (17). The formation of the amide functions was deduced from the ^1H NMR spectrum of **3** displaying a triplet at 9.32 ppm with $J = 6.0$ Hz for the CONH protons. The two calix[4] units have the cone conformation, as shown by the presence of two characteristic AB systems at 3.38 and 4.16 ppm ($J = 13.5$ Hz) and 3.39 and 4.27 ppm ($J = 14.0$ Hz) for the ArCH_2Ar protons of the macrocycle (18). The cone conformation is probably maintained by H-bonds between the phenolic OH appearing as singlets at 10.10 ppm and 9.44 ppm in an integration ratio equal to 1:2 (18). Dicalix **3** was subsequently reacted with 3 equivs of $\text{BrCH}_2\text{CO}_2\text{CH}_3$ in the presence of 2 equivs of K_2CO_3 in acetonitrile with a reflux of 24 h. After neutralization, the crude residue was precipitated with methanol to give dicalix dimethylester **4** in 54% yield. The 1,3-di-O-alkylation was deduced from the symmetry of **4**, as shown by the presence of only one singlet at 3.79 ppm for the OCH_3 , one singlet at 4.40 ppm for the $\text{ArOCH}_2\text{CO}_2\text{CH}_3$, the ArCH_2Ar protons displaying two AB systems at 3.23 and 4.10 ppm ($J = 13.0$ Hz) and at 3.33 and 4.32 ppm ($J = 13.5$ Hz). The final step to tetra-calix **5** and hexa-calix **6** was achieved by amidation of dica-

lix dimethyl ester **4** by 4 equivs of N-dicalix **2** in a 1:1 mixture of CH_3OH /toluene and a reflux of 7d. The solvents were evaporated under reduced pressure and the crude residue was chromatographed on a column (SiO_2 ; 95/5 CH_2Cl_2 /acetone). Tetra-calix **5** (0.043 g; 23%) was eluted first ($R_f = 0.65$) and obtained as a transparent paste; then, hexa-calix **6** (0.020 g; 8%) was isolated ($R_f = 0.59$) also as a transparent oil. The formation of tetra- or hexa-calix products was evidenced by MALDI-TOF mass spectrometry. **5** presented a single peak at $m/z = 3073.76$ for a calculated molecular weight $\text{MW} = 3074.21$ and **6** showed a molecular peak at $m/z = 4565.74$ for a calculated molecular weight $\text{MW} = 4566.3$. Because **6** is more symmetrical than **5** its ^1H NMR spectrum was first interpreted. Three types of CONH protons were found as three triplets at 8.03 ppm ($J = 5.5$ Hz) for the dicalix unit (2 protons), 8.87 ppm ($J = 5.5$ Hz) for the N-dicalix unit (4 protons), 8.98 ppm ($J = 5.5$ Hz) for the dicalix unit (2 protons). Three singlets at 4.29, 4.43 and 4.58 ppm were attributed to the $\text{ArOCH}_2\text{NHCO}$ -dicalix (4 protons), $\text{ArOCH}_2\text{NHCO}$ -dicalix (4 protons) and $\text{ArOCH}_2\text{NHCO}$ -N-dicalix (8 protons). Concerning the ArCH_2Ar one could distinguish two broad AB systems at 3.24 and 4.10 ppm ($J = 13.5$ Hz)

for the ArCH_2Ar -dicalix (8 protons) and 3.35 and 4.22 ppm ($J = 13.0$ Hz) for the ArCH_2Ar -N-dicalix (16 protons). The loss of a symmetry plane in **5** leads to a more complicated ^1H NMR spectrum. However, four broad triplets are found at 9.24 ppm ($J = 6.0$ Hz), 8.98 ppm ($J = 6.0$ Hz), 8.91 ppm ($J = 5.5$ Hz) and 8.67 ppm ($J = 5.5$ Hz) for the NH -dicalix (3 protons) and NH -N-dicalix (2 protons). The presence of the unreacted methyl ester function is shown by a singlet at 4.68 ppm for the two protons of $\text{ArOCH}_2\text{CO}_2\text{CH}_3$ and the singlet at 3.79 ppm for the three protons of OCH_3 . The characteristic AB systems of ArCH_2Ar were detected as multiplets 3.29 to 4.40 ppm and 4.20 to 4.33 ppm. As a confirmation, **6** was also prepared by different pathways: **5** was reacted with 2 equivs of N-dicalix **2** in amidation conditions with a reflux of 5 days to give **6** in 35% yield; or either the already published N-tricalix monomethyl ester **7** (**9**) was reacted with ~ 0.5 equiv. of ethylene diamine in amidation conditions with reflux of 8 days (see scheme 2) to give **6** in similar yield (20).



Scheme 2. Preparation of **6** from **7**.

Preliminary investigations were conducted on the extraction of solid zinc(II) picrate hydrate into CDCl_3 solutions (10^{-3} M) by the linear dendrimer **6** until the ^1H NMR spectra of the resultant solutions remained unchanged (one day). The 2:1 (metal:ligand) stoichiometry of the complex was deduced from the integration ratio between the singlet of the picrate at 8.52 ppm and the aromatic protons of **6**. The spectrum of $\mathbf{6} \cdot \mathbf{2}(\text{ZnPic}_2)$ was broadened and the different signal patterns could not be interpreted. Ligand **6** presents three potential Zn(II)-coordination sites which are delineated by the amide

functions. This broadening can originate from the metal-coordinating sites exchange and/or a mixture of different arrangements of trinuclear complexes.

Further work is in progress to elucidate these findings by investigation of complexation of various cations in other solvents.

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- (12) The data were collected at 100(2) K on a Nonius Kappa-CCD area detector diffractometer using graphite-monochromated Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$). The crystal was introduced in a glass capillary with a protecting "Paratone-N" oil (Hampton Research) coating. The unit cell parameters were determined from ten frames, then refined on all data. The data (ϕ - and w -scans) (13) were processed with HKL2000 (14). The structure was solved by direct methods with SHELXS-97 and subsequent Fourier-difference synthesis and refined by full-matrix least-squares on F^2 with SHELXL-97 (15). No absorption correction was done. The solvent molecules are very badly resolved and some of them are seemingly highly disordered. Two methanol and two water molecules were refined with 0.5 occupancy factors so that the displacement parameters retain acceptable values (methanol) or because they are too close to one another (water oxygen atoms O17 and O18). One *tert*-butyl group is rotationally disordered over two positions which were refined with occupancy parameters constrained to sum to unity. All non-hydrogen atoms were refined with anisotropic displacement parameters, with restraints for some atoms in the disordered group and solvent molecules. The hydrogen atoms bound to phenolic oxygen atoms and nitrogen atoms were found on a Fourier-difference map. Those bound to methanol and water oxygen atoms were not found, nor introduced. The other hydrogen atoms were introduced at calculated positions and all were treated as riding atoms with an isotropic displacement parameter equal to 1.2 (OH, NH, CH, CH₂) or 1.5 (CH₃) times that of the parent atom. The molecular plot was drawn with SHELXTL (16). Crystal data for **2** · (CH₃)₂CO · CH₂Cl₂ · 3CH₃OH · 2H₂O: C₁₀₅H₁₅₄C₁₂N₄O₁₆, $M = 1799.22$, monoclinic, space group $C2/c$, $a = 39.072(2)$, $b = 29.3895(15)$, $c = 26.1623(12) \text{ \AA}$, $\beta = 130.363(2)^\circ$, $V = 22891(2) \text{ \AA}^3$, $Z = 8$. Refinement of 1255 parameters on 21485 independent reflections out of 262315 measured reflections ($R_{int} = 0.065$) led to $R_1 = 0.092$, $wR_2 = 0.260$ and $S = 1.048$. CCDC reference number 602714
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- (17) **General:** Uncorrected melting points (Mps), Buchi 500. ¹H-NMR, Bruker SY 200 (δ in ppm from TMS, J in Hz). Matrix-assisted laser desorption/ionization time of flight (MALDI TOF) mass spectra were recorded on a Voager DE-STR from PerSeptive Biosystems Inc. All the reactions were run under a nitrogen atmosphere. SiO₂ (Geduran 1.11567) was used for column chromatography. TLC plates for R_f's were from Merck (Silica 60, F₂₅₄-0.5 mm, Art 5744). All reagents and solvents were commercial and used without further purification. Preparation of dicalix **3**: Monocarboxymethylcalix[4]arene **1** (9) (1.942 g, 2.69 mmol), NH₂CH₂CH₂NH₂ (0.053 g, 0.89 mmol) and a 1:1 mixture of CH₃OH/toluene (20 ml) were refluxed for 48 h. The solvents were evaporated under reduced pressure. The residue was purified by chromatography on a column (SiO₂; 95/5 CH₂Cl₂/acetone) to give dicalix **3** (0.434 g; 34%) as a white solid. Mp = 142-143 °C. ¹H NMR (CDCl₃):

10.1 (s, 2H, OH), 9.44 (s, 4H, OH), 9.32 (broad t, 2H, $J = 6.0$ Hz, NH), 7.05 (d, 4H, $J = 2.5$ Hz, ArH), 7.04 (s, 4H, ArH), 7.03 (s, 4H, ArH), 6.98 (d, 4H, $J = 2.5$ Hz, ArH), 4.60 (s, 4H, ArOCH₂CONH-dicalix), 4.27 (d, 4H, $J = 14.0$ Hz, AB system, ArCH₂Ar), 4.16 (d, 4H, $J = 13.5$ Hz, A'B' system, ArCH₂Ar), 3.92 (broad s, 4H, CH₂-NH), 3.39 (d, 4H, $J = 14.0$ Hz, AB system, ArCH₂Ar), 3.38 (d, 4H, $J = 14.13$ Hz, A'B' system, ArCH₂Ar), 1.22 (s, 36H, *tert*-butyl), 1.21 (s, 18H, *tert*-butyl), 1.17 (s, 18H, *tert*-butyl). Molecular weight calcd for C₉₄H₁₂₀O₁₀N₂: MW = 1437.99. Found $m/z = 1459.75$ (3 + Na)⁺. Preparation of dicalix dimethyl ester **4**: Dicalix **3** (0.407 g; 0.27 mmol), K₂CO₃ (0.037 g; 0.27 mmol), BrCH₂CO₂CH₃ (0.123 g; 0.81 mmol) and acetonitrile (25 ml) were refluxed for 24 h. After evaporation of the solvents under reduced pressure the crude residue was dissolved in CH₂Cl₂ and 1N HCl-water and the organic layer was dried over sodium sulphate. After filtration, dicalix dimethyl ester **4** was precipitated pure as a white powder (0.231 g; 54%) with methanol during the evaporation of CH₂Cl₂. Mp 161-164 °C. ¹H NMR (CDCl₃): 8.64 (broad t, 2H, $J = 4.5$ Hz, NH), 7.03 (d, 4H, $J = 5.5$ Hz, ArH), 7.02 (d, 4H, $J = 5.5$ Hz, ArH), 6.82 (s, 4H, ArH), 6.79 (s, 4H, ArH), 4.71 (s, 4H, ArOCH₂CONH-dicalix), 4.40 (s, 4H, ArOCH₂CO₂CH₃), 4.32 (d, 4H, $J = 13.5$ Hz, AB system, ArCH₂Ar), 4.10 (d, 4H, $J = 13.0$ Hz, A'B' system, ArCH₂Ar), 3.86 (broad s, 4H, CH₂-NH), 3.79 (s, 6H, OCH₃), 3.33 (d, 4H, $J = 13.5$ Hz, AB system, ArCH₂Ar), 3.23 (d, 4H, $J = 13.0$ Hz, A'B' system, ArCH₂Ar), 1.28 (s, 36H, *tert*-butyl), 0.97 (s, 18H, *tert*-butyl), 0.96 (s, 18H, *tert*-butyl). Preparation of tetracalix **5** and hexacalix **6**: Dicalix dimethyl ester **4** (0.092 g; 0.057 mmol), N-dicalix **2** (0.350 g; 0.23 mmol) and a 1:1 mixture of CH₃OH/toluene (4 ml) were refluxed for 7 days. The solvents were evaporated under reduced pressure. The crude residue was chromatographed on a column (SiO₂; 95/5 CH₂Cl₂/acetone). Tetracalix **5** (0.043 g; 23%) was eluted first ($R_f = 0.64$) and obtained as a colorless paste. Then, hexacalix **6** (0.020g; 8%) was isolated ($R_f = 0.59$) also as a colorless oil. Data of **5**: ¹H NMR (CDCl₃): 9.24 (broad t, 1H, $J = 6.0$ Hz, NH-dicalix), 8.98 (broad t, 1H, $J = 6.0$ Hz, NH-dicalix), 8.91 (broad t, 2H, $J = 5.5$ Hz, NH-N-dicalix), 8.67 (broad t, 1H, $J = 5.5$ Hz, NH-dicalix), 7.00-7.06 (m,

22H, ArH), 6.93-6.97 (m, 8H, ArH), 6.86 (s, 2H, ArH), 4.68 (s, 2H, ArOCH₂CO₂CH₃), 4.63 (s, 2H, ArOCH₂CONH-dicalix), 4.60 (s, 4H, ArOCH₂CONH-N-dicalix), 4.58 (s, 2H, ArOCH₂CONH-N-dicalix), 4.54 (s, 2H, ArOCH₂CONH-dicalix), 4.20-4.33 (m, 16H, ArCH₂Ar), 3.86 (broad s, 2H, CH₂-NH), 3.79 (s, 3H, OCH₃), 3.72 (broad s, 2H, CH₂-NH₂), 3.68 (broad s, 2H, CH₂-tren), 3.68 (m, 4H, CH₂-tren), 3.29-4.40 (m, 16H, ArCH₂Ar), 3.07 (broad s, 2H, CH₂-tren), 2.98-3.03 (m, 4H, CH₂-tren), 1.31 (s, 18H, *tert*-butyl), 1.25 (broad s, 18H, *tert*-butyl), 1.23 (broad s, 27H, *tert*-butyl), 1.21 (broad s, 54H, *tert*-butyl), 1.16 (broad s, 27H, *tert*-butyl). Molecular weight calcd for C₁₉₇H₂₅₄O₂₃N₆: MW = 3074.21. Found MALDI-TOF: $m/z = 3075.02$. Data of **6**: ¹H NMR (CDCl₃): 8.98 (broad t, 2H, $J = 5.5$ Hz, NH), 8.87 (broad t, 4H, $J = 5.5$ Hz, NH), 8.03 (broad t, 2H, $J = 5.5$ Hz, NH), 7.01-7.04 (m, 32H, ArH), 6.93-6.95 (m, 8H, ArH), 6.89 (s, 4H, ArH), 6.87 (s, 4H, ArH), protons), 4.58 (s, 8H, ArOCH₂NHCO-N-dicalix), 4.43 (s, 4H, ArOCH₂NHCO-dicalix), 4.29 (s, 4H, ArOCH₂NHCO-dicalix), 4.22 (broad d, 16H, $J = 13.0$ Hz, AB system, ArCH₂Ar-N-dicalix), 4.10 (broad d, 8H, $J = 13.5$ Hz, A'B' system, ArCH₂Ar-dicalix), 3.68 (broad s, 4H, CH₂-NH), 3.48-3.54 (m, 12H, CH₂-tren), 3.35 (broad d, 16H, $J = 13.0$ Hz, AB system, ArCH₂Ar-N-dicalix), 3.24 (broad d, 8H, $J = 13.5$ Hz, A'B' system, ArCH₂Ar-dicalix), 2.89-3.02 (m, 12H, CH₂-tren), 1.24 (broad s, 36H, *tert*-butyl), 1.23 (broad s, 36H, *tert*-butyl), 1.20 (broad s, 72H, *tert*-butyl), 1.16 (broad s, 36H, *tert*-butyl), 0.95 (broad s, 36H, *tert*-butyl). Molecular weight calcd for C₂₉₄H₃₈₀O₃₂N₁₀: MW = 4566.3. Found MALDI-TOF: $m/z = 4565.74$. Preparation of **6** from **5**: Tetracalix **5** (0.031 g; 0.009 mmol), **2** (0.029g; 0.019 mmol) and a 1:1 mixture of CH₃OH/toluene (4 ml) were refluxed for 5 days. After evaporation of the solvents under reduced pressure the residue was chromatographed on a column (SiO₂; 95:5 CH₂Cl₂/acetone) to yield hexacalix **6** (0.025 g; 5%). Preparation of **6** from **7**: N-tricalix *monomethyl ester* **7** (0.281g; 0.12 mmol), ethylene diamine (0.004 g; 0.06 mmol) and a 1:1 mixture of CH₃OH/toluene (1 ml) were refluxed for 8 days. After evaporation of the solvents under reduced pressure the residue was chromatographed on a column (SiO₂; 95:5 CH₂Cl₂/acetone) to yield hexacalix **6** (0.034 g; 6%)

- (18) In a general manner, the *cone conformation* has been identified for all species described in this paper from the AB and A'B' systems and the coupling constants observed for the diastereotopic methylene protons which are very similar to those of the genuine cone conformation of monocarboxymethylcalix[4]arene **1** as determined by X-ray diffraction (19)
- (19) Ben Othman A, Cheriaa N, Abidi R, Vicens J, Thuéry P (2004) *Acta Cryst* **C60**, 859
- (20) This reaction can be considered as the construction of a dendrimer by a convergent synthesis as depicted in ref. 10

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