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Calixarene-based dendrimers. Second generation of a calix[4]-dendrimer with a 'tren' as core

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Abstract—Hyperbranched calix[4] (**4**) and calix[4]-dendrimer (**5**) as a second generation (G2) of calixdendrimers have been synthesized by divergent and convergent synthesis via amidation reactions.

Dendrimers and hyperbranched molecules have attracted considerable attention because of the special properties determined by their repetitively structured architecture.[1] 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 centers. Calixarenes,[2] with their multiple sites used in *selective* functionalization 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 functionalization, 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 and dendritic-like structures.[7] The first paper introducing calix[4]arenes as potential building blocks for dendrimers has been published in 1995 by Lhotak and Shinkai[8] followed by several publications dealing with the elaboration of various so-called calixdendrimers made up of calix[4] and/or thiacalix[4] units.[9–13] However, no synthesis with repetitive motives of (thia)calix[4]arenes has been published up to now. In this letter we report the synthesis of second generation (G2) calix[4]-dendrimer **5** by divergent and convergent synthesis.

In a previous publication we have described the synthesis of Y-shaped diamido N-dicalix-$CH_2CH_2NH_2$ **(1)** derived from *tris*(2-aminoethyl)amine or 'tren' and *mono* methoxycarbonylcalix[4]arene providing a starting material useful for the preparation of a variety of hyperbranched molecules by further amidation reactions with chosen methyl ester compounds.[14] Among them, we reported the synthesis of N-tricalix **2**. The *divergent synthesis* of calix[4]-dendrimer **5** takes advantage of the selective 1,3-di-O-alkylation of calix[4]arenes. Thus, according to Scheme 1, N-tricalix **2** was selectively transformed into N-tricalix *trimethyl ester* **3** by refluxing **2** with 4 equiv of $BrCH_2CO_2CH_3$ in the presence of 1.5 equiv of K_2CO_3 in acetonitrile for 24 h. Compound **3** was obtained in pure form as a white solid by chromatography on SiO_2 with CH_2Cl_2 as eluent in 37% yield. Then, **3** was reacted with 6 equiv of N-dicalix-$CH_2CH_2NH_2$ **(1)** in a refluxing mixture of 1:1 methanol–toluene for 8 d. Chromatography of the residue on SiO_2 with a 9:1 mixture of CH_2Cl_2–acetone afforded pure hyperbranched calix[4] (**4**) (formation of two new amido functions) as a colorless oil in 11%. When reaction time was 12 d, a similar work-up procedure gave calix[4]-dendrimer **5** in 5% yield. In a separate experiment **4** which still contains one reactive methyl ester function was refluxed with **1** in a 1:1 mixture of methanol/toluene for 3 d and calix[4]-dendrimer **(5)**

Keywords: Calixarenes; Dendrimers; Second generation; Amido functions.

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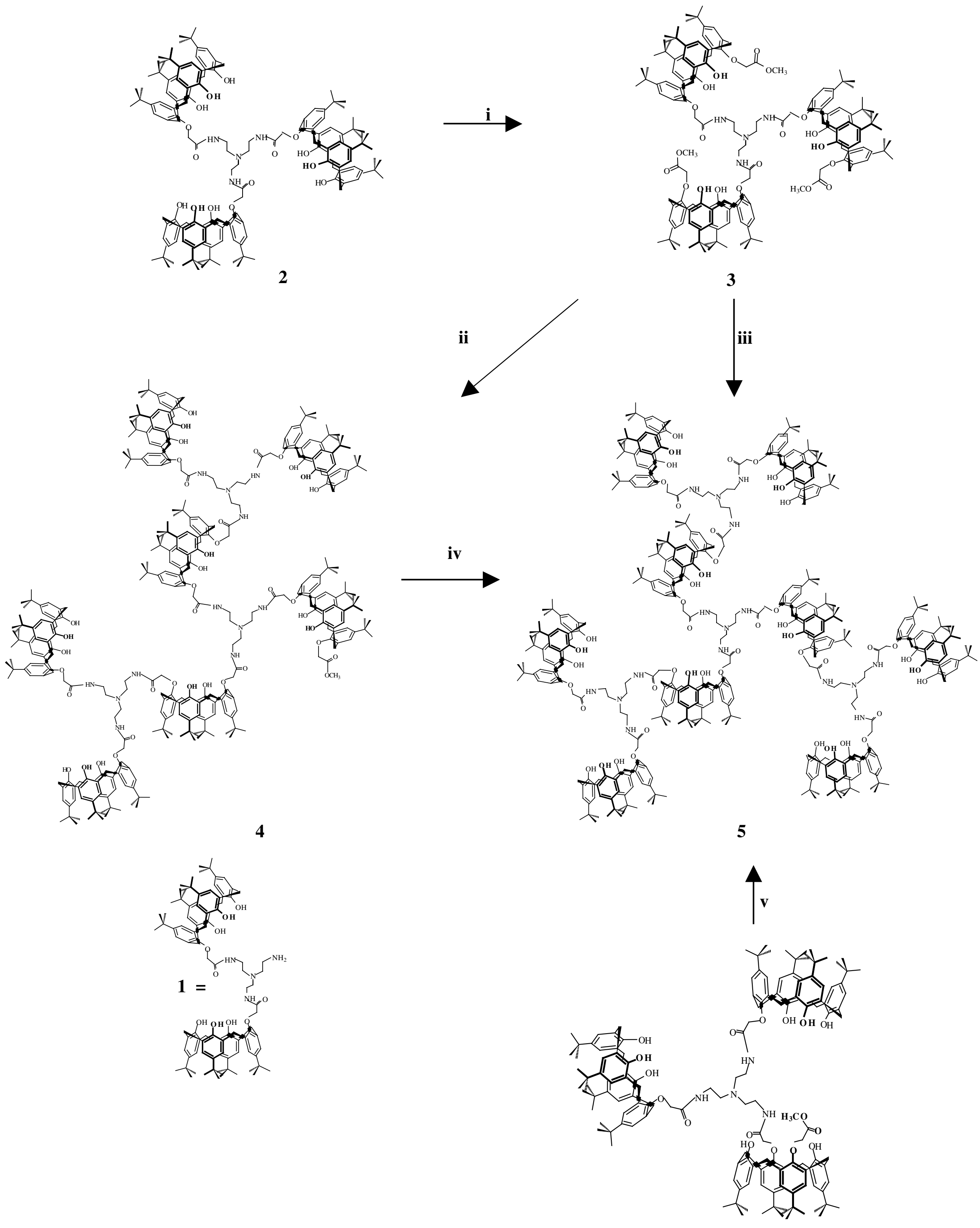
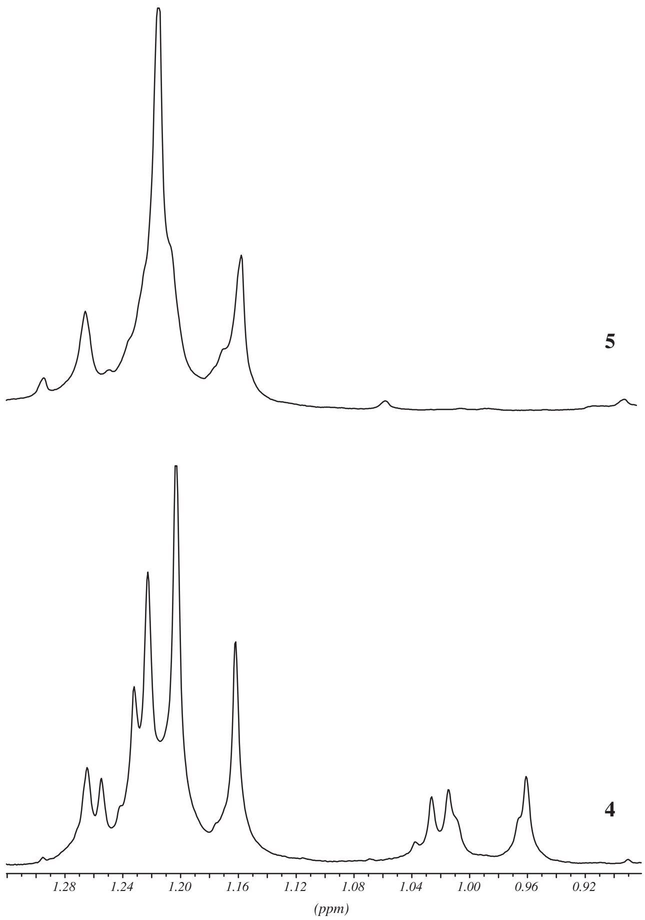


Scheme 1. Synthesis of (**4**) and (**5**). Reagents and conditions: (i) $BrCH_2CO_2CH_3$, K_2CO_3, acetonitrile; (ii) **1**, methanol–toluene, reflux, 8 days; (iii) **1**, methanol–toluene, reflux, 12 days; (iv) **1**, methanol–toluene, reflux, 3 days; (v) 'tren', methanol–toluene, 15 days.

was isolated in 74% yield. For the *convergent synthesis*, N-tricalix *monomethyl ester* **6**, isolated in a previous work,[14] was reacted with 0.25 equiv of tren in similar conditions by refluxing for 15 d. Calix[4]-dendrimer (**5**) was isolated in 8% yield.

N-tricalix *trimethyl ester* **3**, hyperbranched calix[4] **(4)** and calix[4]-dendrimer (**5**) were characterized by ^{1}H NMR technique and mass spectrometry.[15] All the calix[4]arene moieties were observed to be in the cone conformation due to the presence of characteristic AB



Scheme 2. ^{1}H NMR spectra of the *p-tert*-butyl region of **4** and **5**.

system in the ^{1}H NMR spectra matching those observed for the mono methyl ester of *p-tert*-butyl calix[4]arene which are known to adopt the cone conformation, at least in the solid state.[16] A broadening of the signals of the ^{1}H NMR spectra was observed with the increase of the dendrimer generation. Interestingly, the gain of symmetry from **4** to **5** was seen in the *p-tert*-butyl region of their ^{1}H NMR spectra in which the 9 singlets ascribed for **4** are reduced to 3 singlets in **5** (see Scheme 2).

In the present letter, we have shown the construction by divergent and convergent procedures of calixdendrimers consisting of *p-tert*-butyl calix[4]arenes linked by tren-Y-segments via amido functions. Future work will be devoted to (a) the growing of next generation (G3), (b) construction of mixed calixdendrimers in which the core and the Y-segments are of different nature, and as a consequence (c) the complexation of different metals in the calixdendrimers.

Acknowledgements

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15. **General**: Uncorrected melting points (Mps), Büchi 500. ^{1}H NMR, Bruker SY 200 (δ in ppm from tms, J in Hz). Matrix-Assisted Laser Desorption/Ionization-Time Of Flight (MALDI-TOF) mass spectra, Biflex Bruker. All the reactions were run under nitrogen atmosphere. SiO_2 (Geduran 1.11567) was used for column chromatography. TLC plates for R_f's were from Merck (Silica 60, F_{254}-0.5 mm, Art 5744). All reagents and solvents were commercial and used without further purification. N-dicalix-$CH_2CH_2NH_2$ (**1**), N-tricalix **2** and N-tricalix *monomethyl ester* **6** were prepared as published.[14] Preparation of N-tricalix trimethylester **3**: N-tricalix **2** (0.251 g, 0.113 mmol), K_2CO_3 (0.023 g, 0.169 mmol) and acetonitrile (10 mL) were stirred at rt for 1 h. $BrCH_2CO_2CH_3$ (0.069 g, 0.451 mmol) was added and the reaction mixture

was refluxed for 24 h. The solvents were removed under reduced pressure and the residue was treated with dichloromethane, water and 1 M HCl–H_2O until pH ~ 4. The organic layer was dried over Na_2SO_4. After filtration and removal of the solvents, the residue was purified by column chromatography (SiO_2–CH_2Cl_2) to yield **3** (0.105 g, 37%) as a white solid. Mp 197–198 °C. R_f = 0.71 (8:2 CH_2Cl_2–acetone). ^{1}H NMR ($CDCl_3$): 8.53 (t, J = 6.2 Hz, 3H, N*H* amide), 7.29 (s, 6H, O*H*), 7.03–7.01 (m, 12H, Ar*H*), 7.03 (broad s, 12H, Ar*H*), 4.64 (s, 6H, ArOC*H*$_2$CONH), 4.64 (s, 6H, ArOC*H*$_2$CO$_2$Me), 4.29 (d, J = 13.1 Hz, 6H, AB system, ArC*H*$_2$Ar), 4.16 (d, J = 13.1 Hz, 6H, A′B′ system, ArC*H*$_2$Ar), 3.81 (s, 9H, OC*H*$_3$), 3.68 (q, J = 6.2 Hz, 6H, C*H*$_2$-tren), 3.32 (d, J = 13.1 Hz, 6H, AB system, ArC*H*$_2$Ar), 3.28 (d, J = 13.1 Hz, 6H, A′B′ system, ArC*H*$_2$Ar), 3.18 (t, J = 6.2 Hz, 6H, C*H*$_2$-tren), 1.26 (s, 54H, *tert*-butyl), 0.94 (s, 54H, *tert*-butyl). Molecular weight calcd for $C_{153}H_{198}O_{21}N_4$: MW = 2429.27. MALDI-TOF: Found *m*/*z* = 2428.11. Preparation of hyperbranched calix[4] (**4**). N-dicalix-$CH_2CH_2NH_2$ **(1)** (0.188 g, 0.12 mmol) and **3** (0.05 g, 0.02 mmol) and a 1:1 mixture of methanol–toluene (4 mL) were refluxed for 8 d. The solvents were evaporated under reduced pressure. The residue was dissolved in dichloromethane and washed with water. The organic layer was dried over Na_2SO_4. After filtration and evaporation, the residue was purified by chromatography on a column (SiO_2: 9:1 CH_2Cl_2–acetone) to yield **4** (0.020 g, 19%) as colorless oil. R_f = 0.35 (8:2 CH_2Cl_2–acetone). ^{1}H NMR ($CDCl_3$): 8.96 (bs, 2H, N*H* amide), 8.81 (bs, 3H, N*H* amide), 8.50 (bs, 1H, N*H* amide), 7.94 (bs, 3H, N*H* amide), 7.08 (s, 12H, Ar*H*), 7.01 (s, 20H, Ar*H*), 6.94 (d, J = 3.2 Hz, 12H, Ar*H*), 6.85 (d, J = 1.8 Hz, 6H, Ar*H*), 6.79 (bs, 6H, Ar*H*), 4.62–4.42 (m, 20H, ArOC*H*$_2$), 4.31–4.06 (m, 28H, ArC*H*$_2$Ar), 4.29 (s, 3H, OC*H*$_3$), 3.65 (bs, 6H, C*H*$_2$-tren), 3.65 (bs, 12H, C*H*$_2$-tren), 3.34–3.31 (m, 28H, ArC*H*$_2$Ar), 2.92 (bs, 12H, C*H*$_2$-tren), 2.81 (bs, 6H, C*H*$_2$-tren), 1.26 (s, 18H, *tert*-butyl), 1.25 (s, 18H, *tert*-butyl), 1.23 (s, 18H, *tert*-butyl), 1.22 (s, 36H, *tert*-butyl), 1.20 (s, 54H, *tert*-butyl), 1.16 (s, 36H, *tert*-butyl), 1.02 (s, 18H, *tert*-butyl), 1.01 (s, 18H, *tert*-butyl), 0.96 (s, 36H, *tert*-butyl). Molecular weight calcd for $C_{347}H_{450}O_{39}N_{16}$: MW = 5413.45. MALDI-TOF: Found *m*/*z* = 5414.56. Preparation of calix[4]-dendrimer (5) from **1** and **3**: N-dicalix-$CH_2CH_2NH_2$ **(1)** (0.188 g, 0.12 mmol) and N-tricalix *trimethylester* **3** (0.05 g, 0.02 mmol) and a 1:1 mixture of methanol–toluene (3 mL) were refluxed for 12 d. The solvents were evaporated under reduced pressure. The residue was dissolved in dichloromethane and washed with water. The organic layer was dried over Na_2SO_4. After filtration and evaporation, the residue was purified by chromatography on a column (SiO_2: 9:1 CH_2Cl_2–acetone) to yield calix[4]dendrimer (**5**) (0.011 g, 8%) as a colorless oil. R_f = 0.57 (8 :2 CH_2Cl_2–acetone). ^{1}H NMR ($CDCl_3$):10.17 (bs, 3H, N*H* amide), 9.45 (bs, 6H, N*H* amide), 8.98 (bs, 3H, N*H* amide), 7.05–6.96 (m, 72H, Ar*H*), 4.73 (s, 12H, ArOC*H*$_2$), 4.57 (bs, 12H, ArOC*H*$_2$), 4.39–4.09 (m, 36H, ArC*H*$_2$Ar), 3.65 (bt, 24H, C*H*$_2$-tren), 3.49 (bs, 24H, C*H*$_2$-tren), 3.38 (d, 18H, J = 12.0 Hz, AB System, ArC*H*$_2$Ar), 3.34 (d, 18H, J = 12.0 Hz, A′B′ System, ArC*H*$_2$Ar), 1.26 (s, 72H, *tert*-butyl), 1.22 (s, 180H, *tert*-butyl), 1.14 (s, 72H, *tert*-butyl). Molecular weight calcd for $C_{444}H_{576}O_{48}N_{16}$: MW = 6905.45. MALDI-TOF: Found *m*/*z* = 6906.54. Preparation of calix[4]-dendrimer (5) from **6**: N-tricalix *monomethyl ester* **6** (0.14 g, 0.061 mmol) and 'tren' (0.002 g,0.0015 mmol) and a 1:1 mixture of methanol–toluene (3 mL) were refluxed for 10 d. The solvents were evaporated under reduced pressure. The residue was dissolved in dichloromethane and washed with water. The organic layer was dried over Na_2SO_4. After filtration and evaporation, the residue was purified by chromatography on a column (SiO_2: 9:1 CH_2Cl_2–acetone) to yield dendrimer **5** (0.013 g, 13%).

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