Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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To cite this Article Mahouachi, Mouna , Kim, Yang , Lee, Sang Ho , Abidi, Rym , Harrowfield, Jack and Vicens, Jacques(2005) 'Calixarene-based Hyperbranched Molecules with an N,S-Multidentate Ligand Core', Supramolecular Chemistry, 17: 4, 323 — 330
To link to this Article: DOI: 10.1080/10610270500114681
URL: http://dx.doi.org/10.1080/10610270500114681

Supramolecular Chemistry, June 2005 Vol. 17 (4), pp. 323–330

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Calixarene-based Hyperbranched Molecules with an N,S-Multidentate Ligand Core

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Received (in Southampton, UK) 28 January 2005; Accepted 3 March 2005

Reactions between a tripodal trithiaether-triamine and the monomethoxycarbonylmethyl ether of *p-tert*-butylcalix[4]arene led to the ready isolation of both di- and triamides, namely di- and tricalixaryl derivatives of the tripod. 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 new ligands show that indeed there is preferential binding to the core (rather than to the phenolic sites of the calixarene units), suggesting new mechanisms for the control of the structure and stereochemistry of dendrimer species.

Keywords: Calixarenes; Dendrimers; Multidentate ligand

INTRODUCTION

Dendrimers and hyperbranched molecules have attracted considerable attention because of their special properties determined by their repetitively structured architecture [1–6]. Numerous studies have been carried out regarding their use as new functional materials in nanotechnology, with both biochemical and medical applications in view [1–6]. The preparation of such branched structures demands the use of particular building blocks with the appropriate stereochemistry and multiple, equivalent reaction centres. Calixarenes [7–11], 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 [12,13], calixcryptands [13] and calixspherands [14,15].

Particular interest has also been given to the construction of molecules containing two or more calixarene units that can be used to form hyperbranched and dendritic-like structures [16]. In 1995, Lhotak and Shinkai [17] built a series of oligocalixarenes linked through the phenolic oxygen by aliphatic chains (lower rim–lower rim connections). All the calix[4]arenes were shown to be in the cone conformation. Because of the large number of possible complexation sites, analysis of metal ion binding by these multicalixarenes is complicated but it certainly appears that they may bind as many alkali-metal cations as there are calixarene units [17]. In 1998, Mogck *et al.* [18] reported the synthesis of double and triple calix[4]arenes by reacting *p*-monoaminocalix[4]arenes with various di- and triacid chlorides. Similar reactions with tetraacid chlorides derived from calix[4]arenes in the cone or in the 1,3-alternate conformations gave pentacalix[4]arenes, regarded as the first generation of calix[4]arene-based dendrimers [18]. In 2002, Szemes *et al.* [19] reported calix[4]arene-based dendrimers 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 to give amine sites suitable for acylation.

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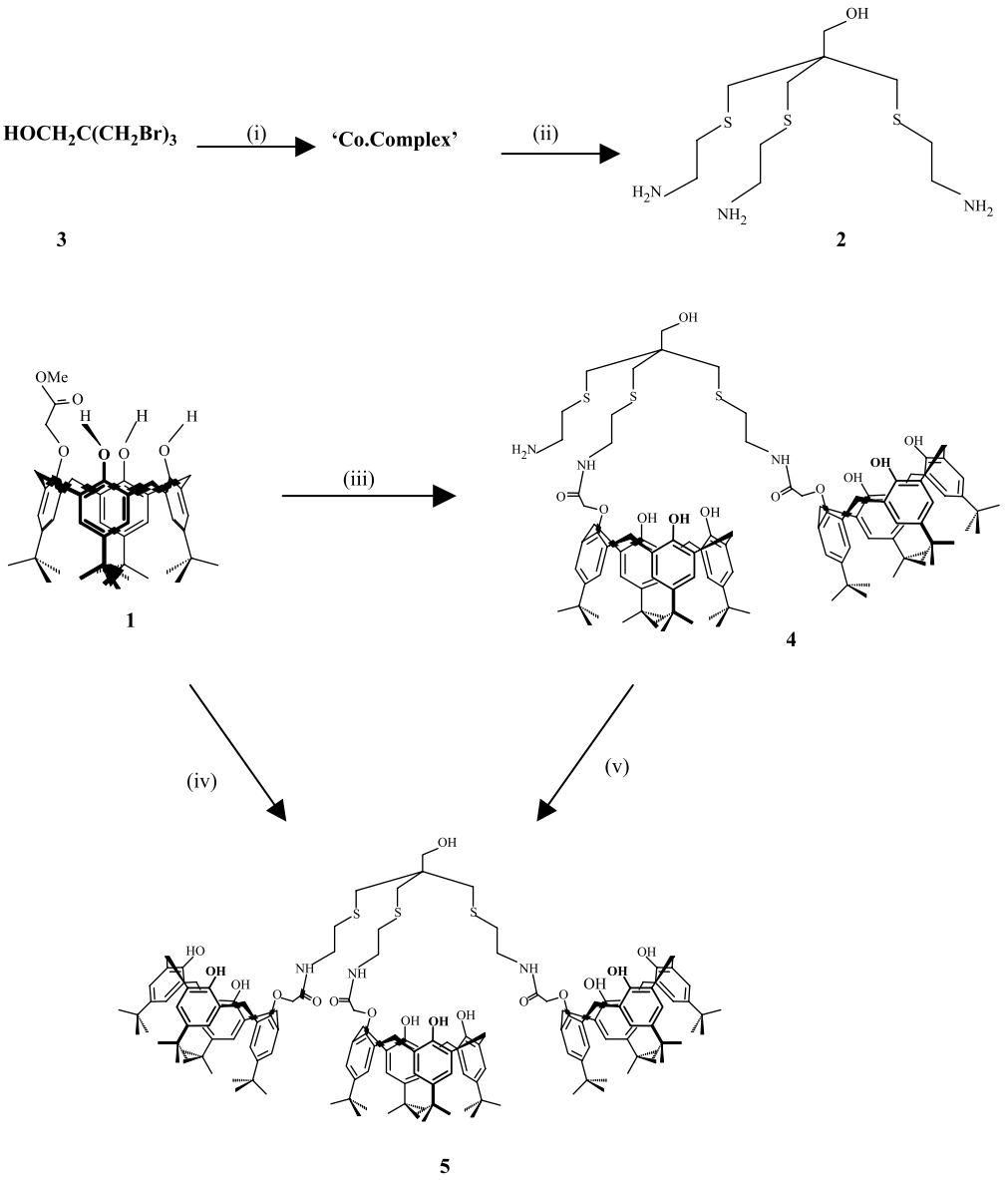
ISSN 1061-0278 print/ISSN 1029-0478 online © 2005 Taylor & Francis Group Ltd
DOI: 10.1080/10610270500114681



(i) 2-aminoethanethiol, NaOEt, EtOH;
(ii) Formation, chromatographic purification of and final ligand release from the Co(III) complex.
(iii) **2**, 1:1 methanol-toluene, reflux, 1d;
(iv) **2**, 1:1 methanol-toluene, reflux, 8d;
(v) **1**, 1:1 methanol-toluene, reflux, 6d.

SCHEME 1 Synthesis of **2**, **4** and **5**. (i) 2-Aminoethanethiol, NaOEt, EtOH; (ii) formation and chromatographic purification of, and final ligand release from, the Co(III) complex; (iii) **2**, 1:1 methanol–toluene, reflux, 1 day; (iv) **2**, 1:1 methanol–toluene, reflux, 8 days; (v) **1**, 1:1 methanol–toluene, reflux, 6 days.

Strong complexes with La^{3+}, Gd^{3+} and Lu^{3+} were detected by UV–Vis titrations. In 2003, Xu *et al.* [20] described a modular strategy combining peptide synthesis with functionalized calixarene chemistry. The design of calix[4]arene amino acids enabled the construction of the first generation of two calix[4]-arene peptide dendrimers. Na^{+} complexes were observed, with localization of the cation close to the carbonyl functions. In 2004, Stastny *et al.* [21] reported the synthesis of thiacalix[4]arenes in the cone or 1,3-alternate conformations bearing two or four carboxylic functions on the lower rim that were reacted as the acyl chlorides with *p*-amino calix[4]arenes to give the corresponding tri- and pentacalixarenes [21]. Similarly, Appelhans *et al.* [22] used thiacalix[4]arenes in the 1,3-alternate conformation possessing carboxylic acid functions for the design of dendritic cores with amino surface groups. These compounds were claimed to be the first examples of thiacalix[4]arene

derivatives potentially useful as dendritic cores for subsequent branching derivatization.

In a previous publication we described the synthesis of a Y-shaped diamido calix[4]arene deriving from $N(CH_2CH_2NH_2)_3$ ('tren') and monomethoxycarbonylmethylcalix[4]arene **1**, which was used for the preparation of a variety of hyperbranched molecules by further amidation reactions with chosen methyl ester compounds [23]. Investigations were conducted with various calixarene-dendrimers of the extraction of solid zinc picrate into $CDCl_3$. The cations were observed to be localized in the 'tren' residue, clearly demonstrating that metal ion coordination might offer a means of controlling the orientation of pendent groups from a coordinating core, as in the present molecules.

While a 'tren' residue offers a potentially quadridentate site for metal ion binding [24], this renders it unable to occupy all coordination sites about most common metal cations, and a site of higher denticity, with a varied array of donor atoms, is thus attractive as a dendrimer core open to more subtle and possibly more restrictive forms of metal ion control. The well-known ligands 'sen', $CH_3C(CH_2NHCH_2CH_2NH_2)_3$ [25,26], and 'ten', $CH_3C(CH_2SCH_2CH_2NH_2)_3$ [27], for example, can occupy all coordination sites about an octahedral metal ion centre, forming, at least in the case of Co(III) [25,27], stable chiral species, while they still both resemble 'tren' in providing tripodal arrays of primary amino centres suitable for acylation. The second of these ligands contains only primary amino centres, indicating that its acylation reactions should be the simpler to investigate, and we report here the characterization of the reactions of a readily-prepared hydroxy derivative of 'ten', $HOCH_2C(CH_2SCH_2CH_2NH_2)_3$ = 'hyten' (**2**), with the monomethoxycarbonylmethyl derivative of *p-tert*-butylcalix[4]arene, **1**.

RESULTS AND DISCUSSION

According to Scheme 1, the synthesis of 'hyten' (**2**) was achieved through a somewhat more direct (though similar) route to that of 'ten', in which pentaerythritol tribromide (**3**) was reacted with the sodium salt of cysteamine (2-aminoethanethiol) in ethanol at reflux. The crude reaction product was purified by formation and chromatographic separation of its Co(III) complexes [28], the pure ligand being first isolated as its hydrochloride after reduction and acid treatment of the cobalt complex. By reaction with hydroxide-form anion exchange resin, this was converted to an aqueous solution of the free aminothiaether, from which **2** was obtained as a viscous oil by vacuum distillation. The reaction between **1** and **2** proceeds in a stepwise fashion, with the rates for consecutive steps differing sufficiently to allow ready isolation of the diacyl compound **4** and the triacyl compound **5** by simple variation of the reaction period. Thus, reaction between **1** and **2** in a 5:1 molar ratio in 1:1 methanol/toluene at reflux for 24 h provided, after chromatography, pure hytendicalix **4** in 21% yield as a yellow solid. When the reaction period was extended to 8 days, hytentricalix **5** was obtained in 36% yield. Compound **5** was also obtained by reacting **4** and **1** in a 1:2 molar ratio in similar conditions for 6 days' reflux in a 15% yield. Compounds **4** and **5** were fully characterized by ^{1}H NMR spectroscopy, mass spectrometry and elemental analysis. The cone conformation of the calixes was confirmed in both cases. For **4**, the ^{1}H NMR spectrum showed two AB systems at 4.27 and 3.49 ppm with $J = 13.5$ Hz and 4.22 and 3.48 ppm with $J = 13.5$ Hz for the ArCH_2Ar of the calixarene ring. Similarly, the spectrum of **5** showed two AB systems at 4.27 and 3.48 ppm with $J = 13.9$ Hz and 4.20 and 3.46 ppm with $J = 13.2$ Hz (see for example the correlations patterns shown in Fig. 1 for **5**). These data closely match those for the two AB systems at 4.47 and 3.49 ppm ($J = 13.2$ Hz) and 4.30 and 3.42 ppm ($J = 13.5$ Hz) of the monoester **1**, known to adopt the cone conformation, at least in the solid state [29]. The amide NH resonances appear as a triplet at 9.43 ppm with $J = 5.7$ Hz for **4**, while a triplet was observed at 9.22 ppm with $J = 5.6$ Hz for **5**. In **4**, possibly because of exchange broadening due to the presence of one basic amino group, neither the phenolic OH nor the amine NH proton resonances were detected. By contrast, in **5**, two phenol hydroxyl resonances were observed at δ 10.10 ppm and 9.42 ppm in the intensity ratio 1:2 (see also the correlated sequence CON*H*CH_2CH_2 in Fig. 1).

Although, in the case of hyten itself [27], coordination of a metal ion can involve the formation of three, five-membered N,S-chelate rings, it would be anticipated for acyl derivatives of hyten that coordination at the amide sites [30] would involve the oxygen rather than the nitrogen centres, leading to larger, seven-membered S,O-chelate rings and thus to possibly less stable complex species. Coordination through five-membered S,N-chelate rings would, however, be possible by deprotonation of the amide, a reaction facilitated by a high charge on the metal ion [30]. For such reasons, we conducted preliminary assessments of the metal ion binding abilities of the new ligands **4** and **5** by examining the binding of Zn(II) and of Co(III) under various conditions designed to ensure binding to the donor atoms of the core and not to those of the calixarene units, which usually only become good metal ion binding sites once deprotonated [7–11]. The percentage of extraction (E%), from water to dichloromethane, of Zn(II) and of Co(III) as their picrate salts was determined to be 15.3% and 15.4%, respectively, for **4** and 6.5% and 4.6%, respectively, for **5**. This was a preliminary indication that the NH_2

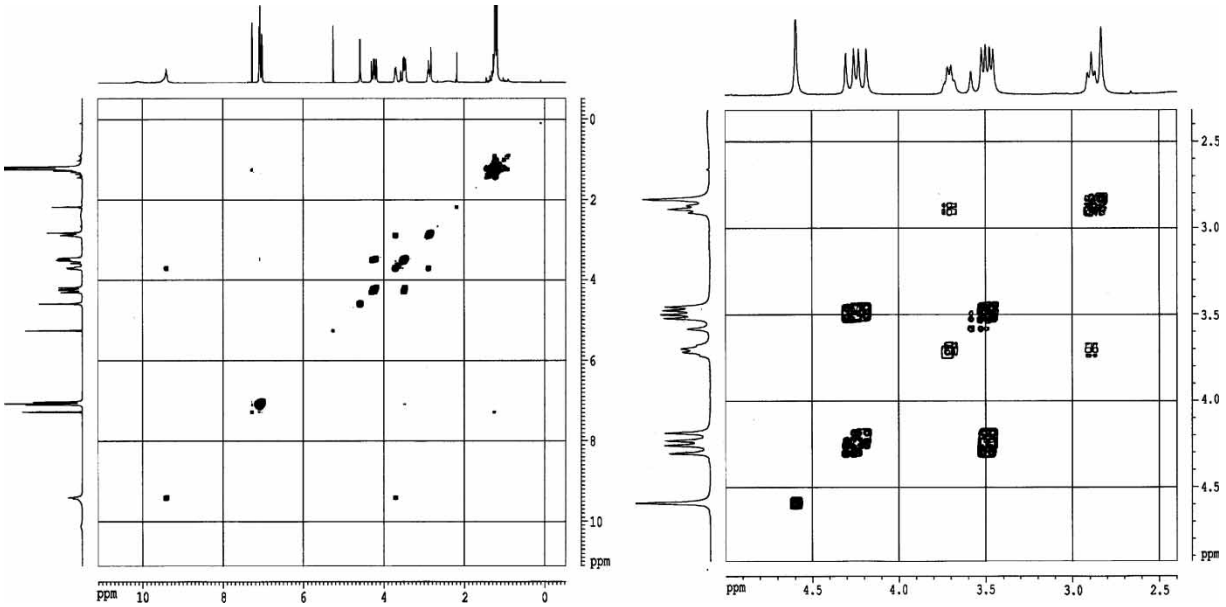


FIGURE 1 2D ^{1}H NMR spectrum of **5** in $CDCl_3$: (left) complete spectrum; (right) from 2.25 to 5.00 ppm.

function is involved in the complexation by increasing the percentage of extraction. The free amino group of **4** would be expected to bind well to both Zn(II) and Co(III), one of the consequences of this being that it would no longer serve to catalyse exchange of the phenolic protons and thus it is particularly significant that the (slow) reaction of solid zinc picrate with a deuterated chloroform solution of **4** leads to a solution for which two phenolic proton resonances (as in free **5**) can be detected (see Fig. 2, the ^{1}H NMR spectrum of **5** has been given for visualizing the phenolic protons).

This is also true for the solution produced by the reaction between $[Co(en)_2(dmso)_2]^{3+}$ (en = ethane-1,2-diamine; dmso = dimethylsulfoxide) [31] and **4** in $CH_3CN/CHCl_3$. It was intended that this reaction would lead to the replacement of the two dmso ligands of the reactant complex by the $-SCH_2CH_2NH_2$ chelate arm of **4** and the yellow/orange colour of the product is certainly consistent with the replacement of both dmso ligands, as is the fact that the product of this reaction is completely soluble in dichloromethane, a solvent in which the reactant complex is completely insoluble. The success of this reaction implies that it should be possible to obtain a chiral $[Co(hyten\text{-}dicalix)_3]^{3+}$ species, the facial isomer of which should be susceptible to a capping reaction, leading to a hexacalix species suitable as a dendrimer core, and interestingly one that might be obtained in an optically active form. In the case of ligand **5**, reaction with an equimolar quantity of hydrated zinc(II) picrate produced, as for ligand **4**, major changes in the NMR spectrum compared to that of the free ligand (in $CDCl_3$ solutions). An attempt was made to prepare the Co(III) complex of **5** by oxidation of a 1:1 mixture of **5** and $[Co(en)_2(dmso)_2](ClO_4)_2$ [32] in $CH_3CN/CHCl_3$ containing NEt_3 to deprotonate the amide centres but, although a deep brown colour developed in the solution, its evaporation resulted in decolorization and deposition of a very small quantity of insoluble brown material along with what appeared to be oxidized ligand (sulfoxide?). While this synthesis requires further investigation, it appears that the desired Co(III) species is not stable. The ^{1}H NMR spectrum of the 1:1 mixture of **5** and hydrated zinc(II) picrate showed a pattern very similar to **5** and we deduced the zinc cation to be incorporated, in keeping with the symmetry of **5**. The most strongly shifted signals were those of N*H*, ArOC*H*$_2$, SC*H*$_2$CH$_2$ and C*H*$_2$S, with $\Delta\delta$ values equal to 1.04, 0.31, 0.10 and 0.10 ppm, respectively, indicating that zinc interacts strongly with the carbonyl of the amido functions and in a weaker manner with the sulfur atoms.

EXPERIMENTAL

Melting points were determined on a Buchi 500 electrothermal apparatus in sealed capillaries under nitrogen. ^{1}H NMR spectra were recorded on a Bruker SY 200 spectrometer (^{1}H at 300 MHz). The 2D COSY spectrum was measured on a Bruker Avance 300 instrument (^{1}H at 300 MHz). Chemical shifts δ are expressed in ppm from TMS as internal standard. Coupling constants J are given in Hz. FAB(+) mass spectra were recorded on a ZAB HF VG-Analytique. Elemental analyses were provided by the Service de Microanalyse of the Institut de Chimie de Strasbourg. All the reactions were run under a nitrogen atmosphere. SiO_2 (Geduran 1.11567) was used for column

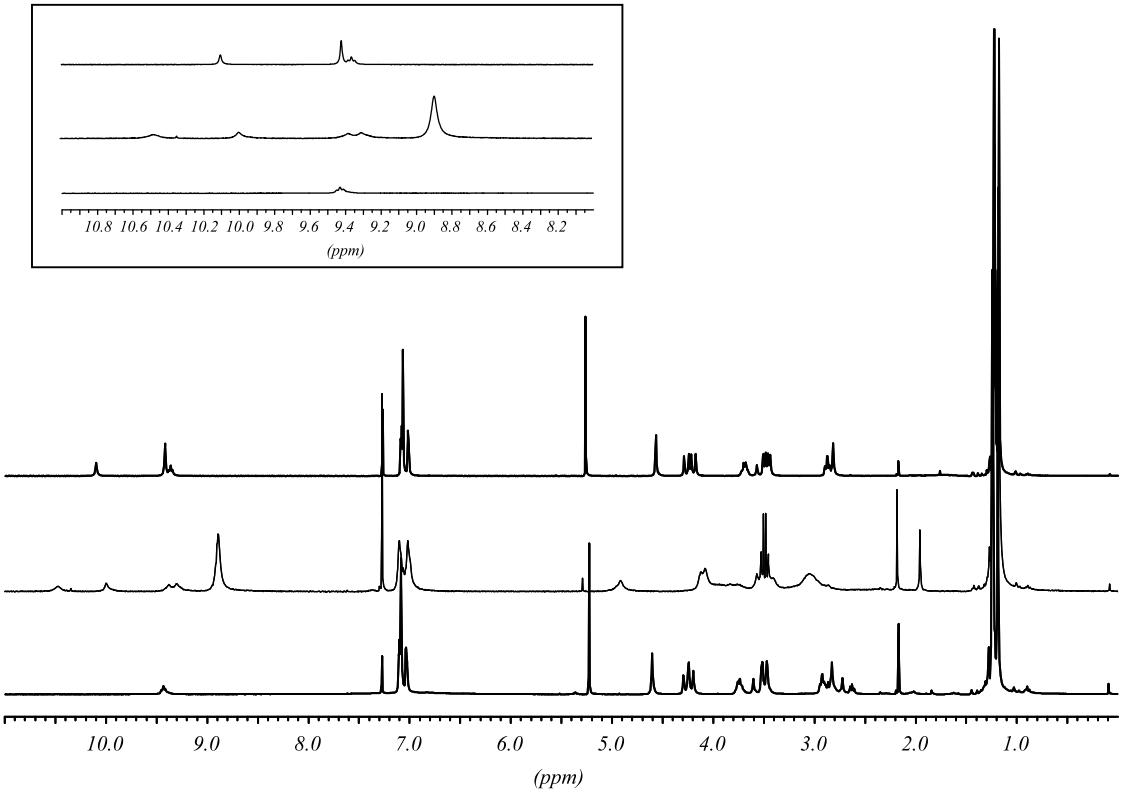


FIGURE 2 ^{1}H NMR spectra of free **4** (lower), Zn(II) complex of **4** (middle) and free **5** (upper) in $CDCl_3$.

chromatography. All reagents and solvents were available commercially and were used without further purification. We present here an improved synthesis of the known monomethoxycarbonylmethyl derivative [23], **1**, of *p-tert*-butylcalix[4]arene.

Preparation of 3-(2-Aminoethylsulfanyl)-2,2-bis (2-aminoethylsulfanylmethyl)-propan-1-ol or Triamino-trisulfur (N_3S_3) or Hyten, 2

Sodium metal (0.805 g, 34.5 mmol) was dissolved in absolute ethanol (150 mL) in a round-bottomed flask protected with a $CaCl_2$ drying tube. 2-Aminoethanethiol (2.756 g, 34.5 mmol) was added and full deprotonation ensured by heating the mixture at reflux (under N_2) for 30 min. After cooling, pentaerythritol tribromide **3** (3.045 g, 11.5 mmol) was added and the mixture heated at reflux for a further 60 min, by which time precipitation of NaBr seemed to have ceased. The mixture was cooled, filtered and the solvent removed by distillation under reduced pressure (*ca*. 20 mmHg), leaving a viscous, yellow oil. This was dissolved in methanol (200 mL) and $CoCl_2{\cdot}6H_2O$ (2.861 g, 12.2 mmol) and acetic acid (0.719 g, 12.5 mmol) were added. A stream of air was bubbled through the resulting solution for 3 h. The solvent was evaporated off and the brown residue was dissolved in 0.1 M HCl (200 mL). This solution was passed through a column (4 × 50 cm) of Dowex 50W × 2 cation exchange resin, which was washed with water (500 mL) and then 0.5 M HCl (500 mL) after absorption of the complex cations. The desired complex of ligand **2** was removed as the major orange band produced by elution with 2 M HCl. Evaporation of the eluate and recrystallization of the residue from the minimum volume of hot 0.1 M HCl provided $[Co(hyten)]Cl_3$ (4.083 g, 71%). To obtain the free ligand, $[Co(hyten)]Cl_3$ (2.182 g) was dissolved in water (50 mL), mixed with excess Zn powder (10.000 g) and stirred as 3 M HCl (100 mL) was added gradually. Once the solution had become essentially colourless, it was filtered to remove unreacted Zn, the filtrate then being diluted to 1.5 L with water and passed through Dowex 50W × 2 to absorb the protonated **2**. To remove Co(II) and Zn(II), the column was eluted with 1 M HCl (500 mL), and the amine was then eluted by the passage of 2 M HCl. The solution of protonated amine was evaporated to dryness, the residue dissolved in water (100 mL) and this solution passed through a column of hydroxide-form Dowex 1 × 8 anion exchange resin to provide an aqueous solution of the free amine. The water was removed by distillation under reduced pressure to give a residue (1.28 g) of **2** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 2H, CH_2OH), 3.42 (s, 1H, O*H*), 2.89 (t, 6H, $J = 6.4$ Hz, N—CH_2—CH_2), 2.65 (s, 6H, —CH_2CH_2—S), 2.64 (t, 6H, $J = 6.4$ Hz, CCH_2S), 2.01 (br s, 6H, NH_2). Anal. Calcd for $C_{11}H_{27}ON_3S_3$(%): C, 42.14; H, 8.68. Found: C, 42.28; H, 8.89.

Preparation of Monomethyl Ester 1

p-tert-Butyl calix[4]arene (6.280 g, 9.67 mmol), K_2CO_3 (0.782 g, 5.11 mmol) and acetonitrile (270 mL) were stirred at room temperature for 1 h. $BrCH_2CO_2CH_3$ (3.608 g, 23.6 mmol) was added and the reaction mixture was heated at reflux for 20 h. The solvents were removed under reduced pressure and the residue was treated with dichloromethane and 1 M HCl 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 **1** (3.270 g, 47%) as a white solid, mp 147–148°C (lit. 148–149°C) [29]. ^{1}H NMR ($CDCl_3$, δ in ppm from TMS): 10.24 (s, 1H, O*H*), 9.26 (s, 2H, O*H*), 7.12 (s, 2H, Ar*H*), 7.08 (s, 4H, Ar*H*), 7.01 (s, 2H, Ar*H*), 4.93 (s, 4H, ArOCH_2), 4.47 (d, 2H, J = 13.2 Hz, AB system, ArCH_2Ar), 4.30 (d, 2H, J = 13.5 Hz, A′B′ system, ArCH_2Ar), 3.95 (s, 3H, OCH_3), 3.49 (d, 2H, J = 13.2 Hz, AB system, ArCH_2Ar), 3.42 (d, 2H, J = 13.5 Hz, A′B′ system, ArCH_2Ar), 1.26 (s, 9H, *tert*-butyl), 1.06 (s, 18H, *tert*-butyl), 0.93 (s, 9H, *tert*-butyl).

Preparation of Hyten-dicalix 4

Monomethyl ester **1** (4.060 g, 5.54 mmol) and N_3S_3 (**2**) (0.575 g, 1.84 mmol) in a 1:1 mixture of methanol:toluene (40 mL) were heated at reflux for 1 day. The solvents were evaporated under reduced pressure. The residue was purified by chromatography on a column (SiO_2; 1:1 CH_2Cl_2—acetone) to yield hyten-dicalix **4** (1.010 g, 21%) as a yellow solid, mp 138–140°C. ^{1}H NMR ($CDCl_3$)δ 9.43 (t, 2H, J = 5.7 Hz, N*H* amide), 7.10 (d, J = 2.1 Hz, 4H, Ar*H*), 7.08 (s, 8H, Ar*H*), 7.03 (d, J = 2.1 Hz, 4H, Ar*H*), 4.60 (s, 4H, ArOCH_2),4.27 (d, 4H, J = 13.5 Hz, AB system, ArCH_2Ar), 4.22 (d, 4H, J = 13.5 Hz, A′B′ system, ArCH_2Ar), 3.74 (q, 4H, J = 5.7 Hz, CH_2CH_2NH), 3.60 (br s, 2H, CH_2OH), 3.49 (d, 4H, J = 13.5 Hz, AB system, ArCH_2Ar), 3.48 (d, 4H, J = 13.5 Hz, A′B′ system, ArCH_2Ar), 2.92 (t, 4H, J = 6.2 Hz, S—CH_2—CH_2), 3.86 (q, 2H, J = 5.7 Hz, $CH_2CH_2NH_2$), 2.82 (s, 4H, —CH_2—S), 2.72 (s, 2H, —CH_2—S), 2.62 (t, 2H, J = 6.2 Hz, S—CH_2—CH_2), 2.17 (s, 1H, O*H*), 1.24 (s, 18H, *tert*-butyl), 1.23 (s, 36H, *tert*-butyl), 1.19 (s, 18H, *tert*-butyl); ^{13}C NMR ($CDCl_3$) δ 168.5, 149.0, 148.8, 146.9, 144.1, 143.7, 132.8, 132.7, 128.2, 127.4, 127.1, 126.9, 126.1, 125.9, 44.8, 38.5, 36.0, 34.3, 34.1, 33.9, 33.2, 32.9, 32.2, 31.5, 31.4, 31.1, 30.9; IR (KBr) ν_{max}(cm^{-1}): 3330 (N—H), 1672 (C═O). Anal. Calcd for $C_{103}H_{139}O_{11}N_3S_3{\cdot}2CH_3OH$ (%): C, 71.84; H, 8.44. Found: C, 71.61; H, 8.49. Calcd MW = 1689.4. Found FAB(+): m/z = 1689.5.

Preparation of Hyten-tricalix 5

Monomethyl ester **1** (3.820 g, 5.28 mmol) and N_3S_3 (**2**) (0.304 g, 1.08 mmol) in a 1:1 mixture of methanol: toluene (8 mL) were heated at reflux for 8 days. The solvents were evaporated under reduced pressure. The residue was purified by chromatography on a column (SiO_2; 9:1 CH_2Cl_2—acetone) to yield hyten-tricalix **5** (1.505 g, 36%) as a white solid, mp 178–180°C. ^{1}H NMR ($CDCl_3$) δ 10.10 (br s, 3H, OH), 9.42 (br s, 6H, OH), 9.22 (t, 3H, J = 5.6 Hz, N*H* amide), 7.09 (d, J = 2.3 Hz, 6H, Ar*H*), 7.07 (s, 6H, Ar*H*), 7.02 (d, J = 2.3 Hz, 6H, Ar*H*), 4.57 (s, 6H, ArOCH_2), 4.27 (d, 6H, J = 13.9 Hz, AB system, ArCH_2Ar), 4.20 (d, 6H, J = 13.2 Hz, A′B′ system, ArCH_2Ar), 3.69 (q, 6H, J = 5.6 Hz, CH_2CH_2NH), 3.57 (br s, 2H, CH_2OH), 3.48 (d, 6H, J = 13.9 Hz, AB system, ArCH_2Ar), 3.46 (d, 6H, J = 13.2 Hz, A′B′ system, ArCH_2Ar), 2.88 (t, 6H, J = 6.2 Hz, S—CH_2—CH_2), 2.82 (s, 6H, —CH_2—S), 2.17 (s, 1H, O*H*), 1.23 (s, 27H, *tert*-butyl), 1.22 (s, 54H, *tert*-butyl), 1.18 (s, 27H, *tert*-butyl); ^{13}C NMR ($CDCl_3$) δ 168.3, 149.0, 148.9, 148.0, 146.9, 144.0, 143.7, 132.8, 128.2, 127.4, 127.1, 126.9, 126.1, 125.9, 53.3, 44.9, 38.6, 36.1, 34.3, 34.1, 33.9, 33.2, 32.9, 32.2, 31.5, 31.4, 31.1, 30.8, 29.7; IR (KBr) ν_{max}(cm^{-1}): 3330 (N—H), 1679 (C═O). Anal. Calcd for $C_{149}H_{195}O_{16}N_3S_3{\cdot}CH_3OH{\cdot}CH_2Cl_2$(%): C, 72.62; H, 8.11. Found: C, 72.44; H, 8.24. Calcd MW = 2378.4. Found FAB(+): m/z = 2378.8.

Extraction Measurements

The extraction of Zn(II) and Co(III) by **4** and **5** was carried out according to Pedersen [33] as their picrate salts. Some 5 mL of an aqueous solution of metal picrates (2.5×10^{-4} M) and 5 mL of a dichloromethane solution of the ligands **4** and **5** (2.5×10^{-4} M) were shaken together vigorously for 2 min. The mixture was then stirred magnetically in a thermostated bath at 20°C. After complete separation, the two phases were analysed by UV—Vis absorption. The absorbances at 355 nm were used to calculate the percentage of extraction (E%) from equation:

$$E\% = 100 \times (A_0 - A)/A$$

where A is the absorbance of the water phase in the presence of the ligand and A_0 is the absorbance without the ligand.

Complexation Investigations

Zinc(II) Complexation

Solutions of the ligands **4** and **5** in chloroform were mixed with acetonitrile solutions of equimolar quantities of $Zn(Pic)_2{\cdot}6H_2O$, the solvent volumes being comparable to achieve a homogeneous solution. To ensure equilibration, the solutions were allowed to stand at room temperature for 12 h, then evaporated to dryness. The residues were dried under high vacuum (10^{-3} mmHg) before being dissolved in $CDCl_3$ to record their NMR spectra. ^{1}H NMR ($CDCl_3$) of a 1:1 mixture of $Zn(Pic)_2{\cdot}6H_2O$ and **4**: δ 10.47 (broad s, 2H, N*H* amide), 9.99 (broad s,

2H, OH), 9.37 (broad s, 4H, O*H*), 9.30 (broad s, 2H, NH_2), 8.89 (s, broad s, 4H, Pic), 7.10 (d, $J = 2.2$ Hz, 4H, Ar*H*), 7.06 (s, 8H, Ar*H*), 7.02 (d, $J = 2.2$ Hz, 4H, Ar*H*), 4.91 (s, 4H, ArOCH_2), 4.12–4.08 (m, 8H, ArCH_2Ar), 3.83 (q, 4H, $J = 5.9$ Hz, CH_2CH_2NH), 3.52-3.41 (m, 10H, CH_2OH, ArCH_2Ar), 3.05–2.86 (m, 14H, S—CH_2—CH_2, $CH_2CH_2NH_2$, CH_2—S, CH_2—CH_2), 2.18 (s, 1H, O*H*), 1.24 (s, 18H, *tert*-butyl), 1.21 (s, 36H, *tert*-butyl), 1.18 (s, 18H, *tert*-butyl). ^{1}H NMR ($CDCl_3$) of a 1:1 mixture of $Zn(Pic)_2{\cdot}6H_2O$ and **5**: δ 10.26 (broad s, 3H, N*H* amide), 10.06 (br s, 3H, OH), 9.37 (br s, 6H, OH), 8.83 (broad s, 4H, Pic), 7.10 (d, $J = 2.4$ Hz, 6H, Ar*H*), 7.09 (s, 6H, Ar*H*), 7.04 (s, 6H, Ar*H*), 7.02 (d, $J = 2.4$ Hz, 6H, Ar*H*), 4.88 (s, 6H, ArOCH_2), 4.17 (d, 6H, $J =$ 13.7 Hz, AB system, ArCH_2Ar), 4.15 (d, 6H, $J =$ 13.1 Hz, A′B′ system, ArCH_2Ar), 3.69 (q, 6H, $J =$ 5.6 Hz, CH_2CH_2NH), 3.55 (br s, 2H, CH_2OH), 3.54 (d, 6H, $J = 13.7$ Hz, AB system, ArCH_2Ar), 3.44 (d, 6H, $J = 13.1$ Hz, A′B′ system, ArCH_2Ar), 2.98 (broad s, 12H, S—CH_2—CH_2, CH_2—S), 2.18 (s, 1H, O*H*), 1.22 (s, 81H, *tert*-butyl), 1.18 (s, 27H, *tert*-butyl).

Co(III) Complexation

A solution of $[Co(en)_2(dmso)_2](ClO_4)_2$ [32] in CH_3CN was mixed with a solution of an equimolar amount of **4** in CH_2Cl_2, the violet colour due to the reactant complex rapidly turning to yellow–orange. After 10 min, the solution was evaporated to dryness (CAUTION: perchlorate) and the yellow-orange residue dried under vacuum (10^{-3} mmHg). It was then dissolved in $CDCl_3$ to record the NMR spectrum. ^{1}H NMR ($CDCl_3$) Co complex of **4**: δ 10.14 (broad s, 2H, N*H* amide), 9.59 (broad s, 2H, O*H*), 9.44 (s, 4H, O*H*), 9.41 (broad s, 2H, NH_2), 7.09 (d, $J = 2.2$ Hz, 4H, Ar*H*), 7.07 (s, 8H, Ar*H*), 7.01 (d, $J = 2.2$ Hz, 4H, Ar*H*), 4.63 (s, 4H, ArOCH_2), 4. 24 (d, 4H, $J = 13.5$ Hz, AB system, ArCH_2Ar), 4.20 (d, 4H, $J = 13.5$ Hz, A′B′ system, ArCH_2Ar), 3.73–3.67 (m, 6H, CH_2CH_2NH, OHCH_2), 3.50 (d, 4H, $J =$ 13.5 Hz, AB system, ArCH_2Ar), 3.48 (d, 4H, $J =$ 13.5 Hz, A′B′ system, ArCH_2Ar), 2.90 (broad s, 6H, S—CH_2—CH_2, $CH_2CH_2NH_2$), 2.64 (broad s, 8H, CH_2—S, S—CH_2—CH_2), 2.17 (s, 1H, O*H*), 1.23 (s, 18H, *tert*-butyl), 1.22 (s, 36H, *tert*-butyl), 1.18 (s, 18H, *tert*-butyl).

CONCLUSIONS

We have demonstrated the ready synthesis of two new hyperbranched molecules, **4** and **5**, based on a core that is potentially a sexidentate-N_3S_3 ligand. Both molecules seem to incorporate transition metal ions within this core, although this may be achieved in different ways, suggesting different applications of metal ion binding in dendrimer formation. Future work will be directed towards (a) the synthesis of various hyperbranched molecules using **4**, (b) growing next generations by taking advantage of the 1,3-selective di-*O*-functionalization of calixarenes from **5** (these dendrimers could be *homogeneous* with all same branches or *heterogeneous* with different branches), (c) the preparation of dendrimers with different shapes and sizes by using CH_2OH as the reactive functional group, (d) the preparation of metallodendrimers, and (e) investigating their potential use as drug delivery vehicles and/or contrast agents for visualization in NMR imaging [3,34,35].

Acknowledgements

MM thanks the Centre Culturel Français in Tunisia for financial support.

References

[1] Newkome, G. R.; Moorefield, C. N.; Vögtle, F. In *Dendrimers and Dendrons*; VCH: Weinheim, Germany, 2001.
[2] Newkome, G. R.; Moorefield, C. N.; Vögtle, F. In *Dendritic Molecules*; VCH: Weinheim, Germany, 1996.
[3] Fréchet, J. M., Tomalia, D. A., Eds; *Dendrimers and Other Dendritic Polymers*; Wiley: London, 2001.
[4] Smith, D. K., Ed.; *Recent Developments in Dendrimer Chemistry, Tetrahedron Symposium in Print*, 2003; 59, p 3787.
[5] Astruc, D., Ed.; *Dendrimers and Nanosciences, Comptes Rendus de Chimie*; Elsevier: France, 2003.
[6] Tomalia, D. A. *Aldrichim. Acta* **2004**, *37*, 39.
[7] Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds; *Calixarenes 2001*; Kluwer: Dordrecht, 2001.
[8] Mandolini, L., Ungaro, R., Eds.; *Calixarenes in Action*; Imperial College: London, 2000.
[9] Gutsche, C. D. In *Calixarenes Revisited*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry, Royal Society of Chemistry: London, 1998.
[10] Vicens, J., Böhmer, V., Eds.; *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Kluwer: Dordrecht, 1991.
[11] Gutsche, C. D. In *Calixarenes*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry, No. 1, Royal Society of Chemistry: London, 1989.
[12] Casnati, A.; Ungaro, R.; Asfari, Z.; Vicens, J. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001; Chapter 20.
[13] Pulpoka, B.; Ruangpomvisuti, V.; Asfari, Z.; Vicens, J. In *Cyclophane Chemistry for the 21st Century*; Takemura, H., Ed.; Research Signpost: Kerala, India, 2002; Chapter 3.
[14] Reinhoudt, D. N.; Dijkstra, P. J.; In't Veld, P. J.; Bugge, K. E.; Harkema, S.; Ungaro, R.; Ghidini, E. *J. Am. Chem. Soc.* **1987**, *109*, 4761.
[15] Groenen, L. C.; Brunink, J. A. J.; Iwema-Bakkler, W. I.; Harkema, S.; Wijmenga, S. S.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1899.
[16] Saadioui, M.; Böhmer, V. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001; Chapter 7.
[17] Lhotak, P.; Shinkai, S. *Tetrahedron* **1995**, *51*, 7681.
[18] Mogck, O.; Parzuchowski, P.; Nissinen, M.; Böhmer, V.; Rokicki, G.; Rissanen, K. *Tetrahedron* **1998**, *54*, 10053.
[19] Szemes, F.; Drew, M. G. B.; Beer, P. D. *Chem. Commun.* **2002**, 1228.
[20] Xu, H.; Kinsel, G. R.; Zhang, J.; Li, M.; Rudkevich, D. M. *Tetrahedron* **2003**, *59*, 583.
[21] Stastny, V.; Stibor, I.; Dvorakova, H.; Lhotak, P. *Tetrahedron* **2004**, *60*, 3383.
[22] Appelhans, D.; Stastny, V.; Komber, H.; Voigt, D.; Voit, B.; Lhotak, P.; Stibor, I. *Tetrahedron Lett.* **2004**, *45*, 7145.
[23] Cheriaa, N.; Abidi, R.; Vicens, J. *Tetrahedron Lett.* **2004**, *45*, 7795.

[24] A broad review of the coordination properties of polyamines may be found in:House, D. A. In *Comprehensive Coordination Chemistry*; Wilkinson, G., McCleverty, J. A., Gillard, R. D., Eds.; Pergamon Press: Oxford, 1985; 2, Chapter 13, p 23.
[25] Sarneski, J. L.; Urbach, F. L. *J. Am. Chem. Soc.* **1971**, *93*, 884.
[26] Harrowfield, J. M.; Jang, G. H.; Kim, Y.; Thuéry, P.; Vicens, J. *J. Chem. Soc., Dalton Trans*. **2002**, 1241 and references therein.
[27] Gahan, L. R.; Hambley, T. W.; Sargeson, A. M.; Snow, M. R. *Inorg. Chem.* **1982**, *21*, 2699.
[28] Studies of the coordination chemistry of **2**, including crystal structure determinations of its complexes, will be reported in detail elsewhere.
[29] Ben Othman, A.; Cheriaa, N.; Abidi, R.; Vicens, J.; Thuéry, P. *Acta Cryst.* **2004**, *C60*, 859.
[30] Angus, P. M.; Jackson, W. G.; Sargeson, A. M. *Inorg. Chem.* **1993**, *32*, 5285.
[31] Lantzke, I. R.; Watts, D. W. *Aust. J. Chem.* **1967**, *20*, 35.
[32] Chan, E. J.; Cox, B. G.; Harrowfield, J. M.; Ogden, M. I.; Skelton, B. W.; White, A. H *Inorg. Chim. Acta* **2004**, *357*, 2365 and references therein.
[33] Pedersen, C. J. *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **1968**, *27*, 1305.
[34] Polyethyleneglycol-surface PAMAM-dendrimers are used for encapsulation and release of molecule drugs, see Aldrich Catalogue number Z51, 403–9.
[35] Bioorganic and biomimetic chemistry and medicinal applications of calixarenes are found in: Sansone, F.; Segura, M.; Ungaro, R. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001; Chapter 27.