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Synthesis of Fréchet-type Tetramethylated Resorcarene Dendrimers

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Abstract

Tetramethylated resorcarenes are good core molecules for the synthesis of Fréchet-type dendrimers. Fréchet-type dendron bromides were synthesised on a gram scale, and were easily attached under phase-transfer conditions to the tetramethylated resorcarene core to obtain pure products in high yields.

Introduction

Resorcarenes have been widely used as starting material for the synthesis of various types of host molecules [1], and studies of their chemical properties and molecular recognition properties have also been reported [2]. Dendrimers are polymers with a well-defined, highly branched molecular architecture, which is characterised by a central multifunctional core, from which one or more shells of branching units extend towards terminating peripheral monomers [3]. Dendrimers can be prepared by the divergent or the convergent method. The former method starts from a central core molecule and proceeds radially outward [4]. In contrast, the latter approach builds the dendrimer from the periphery towards the central core [5]. In this study, the convergent method was used to synthesise the dendritic wedges (see Scheme 3).

Resorcarenes and calixarenes are attractive candidates for multifunctional cores in dendritic molecules, because these macrocyclic phenols have numerous sites for attaching dendritic wedges. Several research groups have used the phenolic OH functions of calixarenes and resorcarenes as core molecules for the synthesis of dendrimers [6]. This approach is of particular interest, because the dendrons are not equally distributed in space due to the bowl-shaped geometry of the resorcarene, but rather extend to the open side of the bowl and may thus change its host–guest properties.

In our earlier studies, we attached Fréchet-type dendron amines to the 2-position of each resorcarene ring through Mannich reaction with rather high yields [7]. We now aim at exploring other possibilities to use resorcarenes as core molecules in dendrimers, and for this purpose we chose tetramethylated resorcarenes [8] as new core molecules (Scheme 1). As described below, Fréchet-type dendrons bearing benzylic bromides at their focal points can be easily attached to the resorcarene core with high yields under phase-transfer conditions.

Experimental section

General

^{1}H and ^{13}C, HMQC, HMBC, and variable temperature NMR spectra were measured with Bruker Avance DRX 500 (500 MHz for ^{1}H and 126 MHz for ^{13}C) spectrometer in $CDCl_3$ solution. ESI mass spectra were recorded on a Micromass LCT ESI-TOF instrument equipped with a Z geometry electrospray ion source. The samples were introduced into the source as CH_2Cl_2:CH_3CN (2:1) solutions of the dendrimer and ca. 4–5 equivalents of CsCl at flow rates of 34 μL/min. A constant spray and highest intensities were achieved with a capillary voltage of 4700 V at a source temperature of 80 °C and a desolvation temperature of 120 °C. Other selected source parameters were as follows: Sample cone voltage: ca. 180 V, extraction cone voltage: 2 V, flow of cone gas: 10 L/h, flow of desolvation gas: 150–200 L/h. Multiple scans (50–200) were recorded and averaged for each spectrum in order to improve the signal-to-noise ratio. The third generation dendrimer has a molecular weight outside the available mass range. All attempts to incorporate a doubly charged cation failed, and no signal was observed at half the molecular

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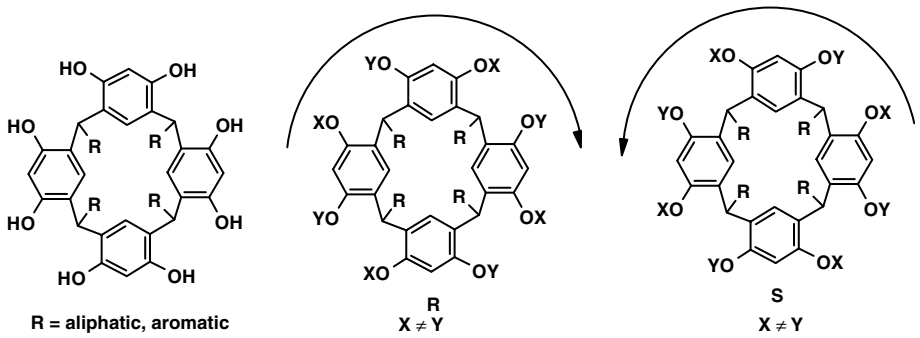


Scheme 1. Molecular structure of resorcarene, and the two enantiomers of the inherently chiral substituted resorcarene (tetrasubstituted Y = H).

mass of the corresponding salt adducts. Melting points were measured with Mettler Toledo FP62 apparatus and are uncorrected. Elemental analyses were performed on Vario EL III apparatus.

Materials

All starting materials were commercially available unless otherwise stated and used as such. Dichloromethane and acetone were distilled over P_2O_5 and stored over molecular sieves before use. Tetramethylated resorcarenes (**3**) [8] and Fréchet dendron wedges (**4**) [5] were prepared according to literature.

*Tetramethylated resorcarene (**3a**)*

Prepared from 3-methoxyphenol (1.77 mL, 0.016 mol) and propanal (1.17 mL, 0.016 mol) in dry CH_2Cl_2 (80 mL) with $BF_3 \cdot Et_2O$ (4.05 mL, 0.032 mol) to give **3a** as white solid (1.1 g, 42%). ^{1}H NMR δ 0.88 (t, J = 7.2, 12H, CH_3), 2.16 (m, 8H, CH_2), 3.83 (s, 12H, O−CH_3), 4.14 (t, J = 7.8, 4H, CH), 6.35 (s, 4H, Ar−H), 7.21 (s, 4H, Ar−H), 7.49 (s, 4H, OH). ^{13}C NMR δ 12.55, 26.97, 35.19, 55.88, 100.06, 123.59, 124.49, 153.08, 153.74. MS (ESI-TOF) m/z 679.25 $[M + Na]^+$. Anal. Calcd. for $C_{40}H_{48}O_8 \cdot 0.2H_2O$: C, 72.75; H, 7.38. Found C, 72.71; H, 7.37. m.p. > 300 °C.

*Tetramethylated resorcarene (**3b**)*

Prepared from 3-methoxyphenol (1.77 mL, 0.016 mol) and hexanal (1.99 mL, 0.016 mol) in dry CH_2Cl_2 (80 mL) with $BF_3 \cdot Et_2O$ (4.05 mL, 0.032 mol) to give **3b** as white solid (1.4 g, 42%). ^{1}H NMR δ 0.87 (t, J = 6.7, 12H, CH_3), 1.25 (m, 24H, CH_2), 2.14 (m, 8H, CH_2), 3.83 (s, 12H, O−CH_3), 4.24 (t, J = 7.7, 4H, CH), 6.35 (s, 4H, Ar−H), 7.22 (s, 4H, Ar−H), 7.49 (s, 4H, OH). ^{13}C NMR δ 14.01, 22.68, 27.76, 31.96, 33.14, 33.97, 55.87, 100.02, 123.67, 124.64, 124.75, 152.96, 152.62. MS (ESI-TOF) m/z 847.40 $[M + Na]^+$. Anal. Calcd. for $C_{52}H_{72}O_8 \cdot 2H_2O$: C, 72.53; H, 8.90. Found C, 72.60; H, 8.66. m.p. 233 °C.

*Tetramethylated resorcarene (**3c**)*

Prepared from 3-methoxyphenol (1.77 mL, 0.016 mol) and dodecanal (1.99 mL, 0.016 mol) in dry CH_2Cl_2 (80 mL) with $BF_3 \cdot Et_2O$ (4.05 mL, 0.032 mol) to give **3c** as white solid (2.1 g, 45%). ^{1}H NMR δ 0.85 (t, J = 6.7, 12H, CH_3), 1.25 (m, 72H, CH_2), 2.16 (m, 8H, CH_2), 3.82 (s, 12H, O−CH_3), 4.22 (t, J = 7.8, 4H, CH), 6.35 (s, 4H, Ar−H), 7.20 (s, 4H, Ar−H), 7.51 (s, 4H, OH). ^{13}C NMR δ 10.49, 14.01, 14.08, 22.68, 22.97, 23.77, 28.07, 28.93, 29.39, 29.70, 29.73, 29.75, 30.38, 31.93, 33.06, 33.99, 38.78, 100.01, 123.70, 124.61, 124.72, 128.79, 130.84, 132.49, 152.97, 153.62, 167.71. MS (ESI-TOF) m/z 1221.02 $[M + (CH_3)_3NH]^+$. Anal. Calcd. for $C_{76}H_{120}O_8$: C, 78.57; H, 10.41. Found C, 78.15; H, 10.44. m.p. 125.0 °C.

*General procedure for the preparation of Fréchet-type tetramethylated resorcarene dendrimers (**5**–**8**)*

Tetramethylated resorcarene **3** was dissolved in dry acetone under nitrogen. K_2CO_3 and [18]crown-6 were added. The mixture was stirred for a while, and finally the corresponding dendron bromide **4** was added. The mixture was kept at 60 °C for 48 h [G-0]/90 h [G-1]/110 h [G-2]/120 h [G-3]. The crude product was chromatographically purified (CH_2Cl_2:EtAc). In some cases, recrystallisation (**5**: MeOH:CH_2Cl_2, **7b**: MeOH, **8**: MeOH:CH_2Cl_2) was helpful.

*Tetramethylated C2-resorcarene dendrimer (**5**)*

Prepared from **3a** (0.10 g, 0.15 mmol), **4a** (0.10 g, 0.63 mmol), [18]crown-6 (0.001 g, 0.05 mmol) and K_2CO_3 (0.11 g, 0.80 mmol) in acetone (20 mL). The product was purified by column chromatography (CH_2Cl_2:EtAc 9:1) to give **5** as white crystalline solid (0.12 g, 81%). Crystallisation from dichloromethane–methanol provided crystals suitable for X-ray analysis. ^{1}H-NMR δ 0.96 (t, J = 7.2, 12H, CH_2CH_3), 1.92 (m, 8H, CH_2CH_3), 3.40 (s, 12H, OCH_3) 4.51 (t, J = 7.5, 4H, Ar_2CHR), 4.70 (d, J = 11.2, 4H, OCH_2Ph), 4.94 (d, J = 11.4, 4H, OCH_2Ph), 6.37 (s, 4H, ArH), 6.73 (s, 4H, ArH), 7.28 (m, 20H, PhH). ^{13}C NMR δ 12.87, 27.48, 37.52, 55.46, 71.02, 97.76, 126.23, 126.42, 127.34, 127.45, 128.21, 137.89, 155.24, 155.74, 168.65. MS (ESI-TOF) m/z 1055.29 $[M + K]^+$. Anal. Calcd for $C_{68}H_{72}O_8$: C, 80.29; H, 7.08. Found C, 79.86; H, 7.07. m.p. 196 °C.

*Tetramethylated C2-resorcarene dendrimer (**6a**)*

Prepared from **3a** (0.27 g, 0.41 mmol), **4b** (0.70 g, 1.8 mmol), [18]crown-6 (0.04 g, 0.15 mmol) and K_2CO_3 (0.28 g, 2.0 mmol) in acetone (55 mL). The product was purified by column chromatography (CH_2Cl_2:EtAc 30:1) to give **6a** as colourless needles (0.74 g, 97%). ^{1}H NMR δ 0.92 (t, J = 7.0, 12H, CH_3), 1.92 (m, 8H, CH_2), 3.42 (s, 12H, CH_3), 4.53–4.73 (m, 12H, CH_3, O–CH_2–Ph), 5.01 (m, 16H, O–CH_2–Ph), 6.33 (s, 4H, Ar–H), 6.54 (m, 12H, Ph–H), 6.73 (s, 4H, Ar–H), 7.29 (m, 40H, Ph–H). ^{13}C NMR δ 12.90, 27.50, 37.46, 55.65, 70.06, 71.09, 98.43, 101.09, 106.31, 126.27, 126.62, 127.46, 127.92, 136.92, 140.39, 155.17, 155.82, 159.93. MS (ESI-TOF) m/z 1998.65 $[M + Cs]^+$. Anal. Calcd. for $C_{124}H_{120}O_{16}\cdot 1H_2O$: C, 79.04; H, 6.52. Found C, 78.72; H, 6.26. m.p. 59 °C.

*Tetramethylated C5-resorcarene dendrimer (**6b**)*

Prepared from **3b** (0.33 g, 0.40 mmol), **4b** (0.70 g, 1.8 mmol), [18]crown-6 (0.04 g, 0.15 mmol) and K_2CO_3 (0.28 g, 2.0 mmol) in acetone (55 mL). The product was purified by column chromatography (CH_2Cl_2:EtAc 60:1) to give **6b** as colourless needles (0.74 g, 89%). ^{1}H NMR δ 0.82 (t, J = 7.0 12H, CH_3), 1.22 (m, 24H, CH_2), 1.86 (m, 8H, CH_2), 3.14 (s, 12H, CH_3), 4.42–4.76 (m, 12H, CH, O–CH_2–Ph), 4.95 (m, 16H, O–CH_2–Ph), 6.33 (s, 4H, Ar–H), 6.53 (m, 12H, Ph–H), 6.71 (s, 4H, Ar–H), 7.28 (m, 40H, Ph–H). ^{13}C NMR δ 14.12, 22.66, 28.05, 32.25, 34.60, 35.87, 55.68, 70.06, 71.14, 98.51, 101.02, 106.39, 108.20, 126.30, 126.78, 127.49, 128.08, 136.79, 140.38, 155.07, 155.72, 159.93. MS (ESI-TOF) m/z 2167.25 $[M + Cs]^+$. Anal. Calcd. for $C_{136}H_{144}O_{16}\cdot 2H_2O$: C, 78.89; H, 7.21. Found C, 79.01; H, 6.79. m.p. 50 °C.

*Tetramethylated C11-resorcarene dendrimer (**6c**)*

Prepared from **3c** (0.47 g, 0.41 mmol), **4b** (0.70 g, 1.8 mmol), [18]crown-6 (0.04 g, 0.15 mmol) and K_2CO_3 (0.28 g, 2.0 mmol) in acetone (70 mL). The product was purified by column chromatography (CH_2Cl_2:EtAc 50:1) to give **6c** as colourless oil (0.96 g, 99%). ^{1}H NMR δ 0.87 (t, J = 7.0 12H, CH_3), 1.17 (m, 72H, CH_2), 1.87 (m, 8H, CH_2), 3.42 (s, 12H, CH_3), 4.41–4.90 (m, 12H, CH, O–CH_2–Ph), 5.00 (m, 16H, O–CH_2–Ph), 6.33 (s, 4H, Ar–H), 6.53 (m, 12H, Ph–H), 6.69 (s, 4H, Ar–H), 7.28 (m, 40H, Ph–H). ^{13}C NMR δ 14.08, 22.67, 28.42, 29.37, 29.70, 29.79, 29.90, 30.15, 31.92, 34.64, 35.90, 55.68, 70.06, 71.14, 98.51, 101.53, 106.35, 126.32, 127.49, 127.93, 128.06, 128.54, 136.94, 140.39, 155.07, 155.73, 159.93, 160.10. MS (ESI-TOF) m/z 2503.81 $[M + Cs]^+$.

*Tetramethylated C2-resorcarene dendrimer (**7a**)*

Prepared from **3a** (0.15 g, 0.23 mmol), **4c** (0.95 g, 1.2 mmol), [18]crown-6 (0.025 g, 0.095 mmol) and K_2CO_3 (0.16 g, 1.2 mmol) in acetone (55 mL). The product was purified by column chromatography (CH_2Cl_2:EtAc 70:1) to give **7a** as colourless needles (0.82 g, quantative). ^{1}H NMR δ 0.92 (m, 12H, CH_3), 1.91 (m, 8H, CH_2), 3.43 (s, 12H, CH_3), 4.41–5.02 (m, 60H, CH, O–CH_2–Ph), 6.38 (s, 4H, Ar–H), 6.51 (m, 16H, Ar–H, Ph–H), 7.26 (m, 80H, Ph–H). ^{13}C NMR δ 14.31, 27.34, 37.51, 55.71, 69.87, 70.14, 101.53, 106.34, 127.51, 127.93, 128.52, 128.57, 136.78, 139.37, 159.80, 160.19. MS (ESI-TOF) m/z 3696.89 $[M + Cs]^+$. Anal. Calcd for $C_{236}H_{216}O_{32}\cdot 1H_2O$: C, 79.13; H, 6.13. Found C, 79.53; H, 6.11. m.p. 57 °C.

*Tetramethylated C5-resorcarene dendrimer (**7b**)*

Prepared from **3b** (0.19 g, 0.24 mmol), **4c** (0.95 g, 1.2 mmol), [18]crown-6 (0.025 g, 0.095 mmol) and K_2CO_3 (0.16 g, 1.2 mmol) in acetone (55 mL). The product was purified by column chromatography (CH_2Cl_2:EtAc 50:1) and recrystallised from methanol to give **7b** as colourless needles (0.86 g, quantative). ^{1}H NMR δ 0.76 (t, J = 7.0, 12H, CH_3), 1.22 (m, 24H, CH_2), 1.90 (m, 8H, CH_2), 3.44 (S, 12h, O–CH_3), 4.62 (m, 4H, CH), 4.85 (m, 56H, O–CH_2–Ph), 6.38 (m, 36H, Ar–H, Ph–H), 7.26 (m, 84H, Ar–H, Ph–H). ^{13}C NMR δ 14.12, 22.64, 28.11, 32.26, 34.55, 36.04, 55.67, 69.89, 70.05, 101.15, 106.42, 126.28, 127.50, 127.98, 136.78, 139.06, 139.36, 140.23, 155.75, 159.80, 159.97, 160.14. MS (ESI-TOF) m/z 3865.08 $[M + Cs]^+$. Anal. Calcd for $C_{248}H_{240}O_{32}\cdot 4H_2O$: C 78.29; H, 6.57. Found C, 77.95; H, 6.09. m.p. 54 °C.

*Tetramethylated C11-resorcarene dendrimer (**7c**)*

Prepared from **3c** (0.27 g, 0.24 mmol), **4c** (0.95 g, 1.2 mmol), [18]crown-6 (0.025 g, 0.095 mmol) and K_2CO_3 (0.16 g, 1.2 mmol) in acetone (55 mL). The product was purified by column chromatography (CH_2Cl_2:EtAc 50:1) to give **7c** as colourless oil (0.94 g, quantative). ^{1}H NMR δ 0.85 (t, J = 7.0, 12H, CH_3), 1.17 (m, 72H, CH_2), 1.91 (m, 8H, CH_2), 3.45 (s, 12H, O–CH_3), 4.62 (t, J = 7.0, 4H, CH), 4.76 (m, 48H, O–CH_2–Ph), 6.39 (s, 4H, Ar–H), 6.51 (m, 48H, Ph–H), 7.28 (m, 84H, Ar–H, Ph–H). ^{13}C NMR δ 14.07, 22.65, 28.49, 29.36, 29.70, 29.78, 29.90, 30.20, 69.88, 70.04, 70.13, 71.15, 101.52, 106.38, 126.30, 127.49, 127.91, 128.51, 136.78, 139.06, 139.37, 140.24, 155.09, 155.75, 159.80, 160.14. MS (ESI-TOF) m/z 4202.38 $[M + Cs]^+$.

*Tetramethylated C2-resorcarene dendrimer (**8**)*

Prepared from **3c** (0.10 g, 0.14 mmol), **4d** (1.2 g, 0.72 mmol), [18]crown-6 (0.015 g, 0.057 mmol) and K_2CO_3 (0.10 g, 0.72 mmol) in acetone (60 mL). The product was purified by column chromatography (CH_2Cl_2:EtAc 50:1) and recrystallised from methanol–CH_2Cl_2 mixture to give **8** as colourless needles (0.95 g, quantative). ^{1}H NMR δ 0.88 (t, J = 7.3, 12H,

CH_3), 1.88 (m, 8H, CH_2), 3.38 (s, 12H, O−CH_3), 4.38 (t, J = 7.4, 4H,CH), 4.70−5.03 (m, 120H, O−CH_2−Ph), 6.35−6.62 (m, 84H, Ph−H), 7.23−7.39 (m, 164H, Ar−H, Ph−H). ^{13}C NMR δ 13.00, 29.68, 55.65, 69.89, 69.99, 101.53, 101.62, 106.31, 106.39, 127.50, 127.52, 127.65, 127.89, 127.97, 128.49, 128.55, 136.78, 139.21, 139.35, 159.79, 159.98, 160.04, 160.10, 160.18. Anal. Calcd for $C_{460}H_{408}O_{64}\cdot 4H_2O$: C, 78.56; H, 5.96. Found C, 78.18; H, 5.69. m.p. 59 °C.

X-ray data collection and crystal structure determinations

X-ray data for all complexes were collected on a Nonius Kappa CCD diffractometer using graphite-monochromatised MoK_α radiation and temperature of 173.0 K. Structure solutions were performed by SHELXS-97 and refined on F^2 by full-matrix least-squares techniques (SHELXL-97) [9]. Hydrogen atoms were calculated to their idealised positions and refined as riding atoms (temperature factor 1.2 or 1.5 times C temperature factor). Methyl carbon C43 in **3b** is disordered over two positions (site occupation factors 0.502:0.498). Six carbons of one of the C11 chains of **3c** were refined isotropically with fixed bond lengths and temperature factors since no other reasonable model for the disorder of the chain could be built. Crystallographic details are presented in Table 1. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-256240, 256241 and 280272. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)123−336033 or e-mail: deposit@ccdc.cam.ac.uk).

Results and discussion

The reaction of monomethylated resorcinol **2** with 1 equiv. of selected aldehyde in the presence of 2 equiv. of $BF_3\cdot Et_2O$ in anhydrous dichloromethane gave the C_4-symmetric chiral tetramethylated resorcarenes **3** with reasonable yields (42% for **3a** and **3b**, and 45% for **3c**) (Scheme 2) [8].

The mass spectra confirmed that the desired products were obtained. Signals were observed at 679.25 for [**3a** + Na^+], 847.40 for [**3b** + Na^+], 1221.02 for [**3c** + Me_3NH^+], and 1183.93 for [**3c** + Na^+]. The ^{1}H NMR spectra provide clear evidence for tetramethylated resorcarenes with C_4-symmetry, as there was one set of signals for the alkyl chains, one signal for the methoxy groups, one signal for the bridging methines and two signals for the aromatic protons. Evidence for racemic mixtures of tetramethylated resorcarenes **3** comes from the ^{1}H NMR spectra in the presence of the chiral shift reagent europium tris[3-(heptafluoropropylhydroxy methylene)-(+)-camphorate]. Adding this reagent to the samples resulted in a doubling of the phenolic, aromatic, and alkyl chain signals each with 1:1 integrations.

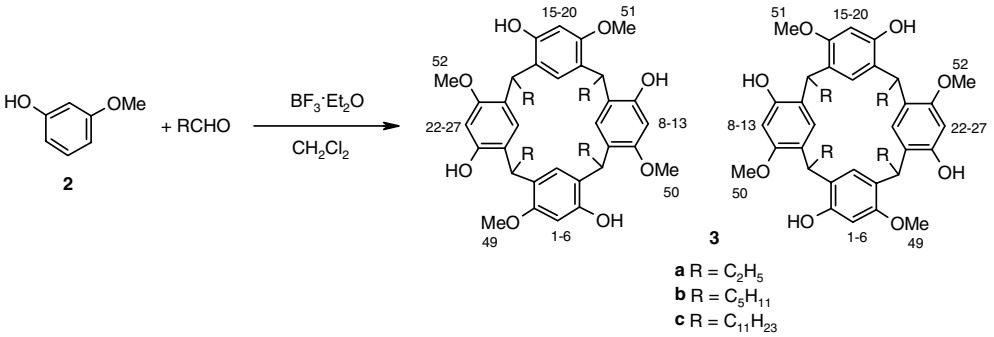
Suitable crystals for single crystal X-ray determination of the solid-state structures of **3b** and **3c** were obtained from ethanol solutions, while several attempts to obtain high-quality crystals and data sets from **3a** failed. Resorcarene **3b** crystallises as bands of mutually included pairs of molecules in an asymmetric unit (Figure 1). The two molecules in the pairs are enantiomers, i.e. the direction of the rotation of the methoxy groups is right-handed in one of the molecules and left-handed in the other one.

The mutual inclusion of methoxy groups in the next neighbour's cavity is due to the favourable C-H···π interactions of the methoxy group with the aromatic

Table 1. Crystallographic data for resorcarenes **3b**, **3c** and **5**

	3b	**3c**	**5**
Formula	$2C_{52}H_{72}O_8$	$C_{76}H_{120}O_8$	$2C_{68}H_{72}O_8$
Formula weight	825.10	1161.72	1017.26
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)	P-1 (No. 2)
Crystal colour	Colourless	Colourless	Colourless
a/Å	12.2425(5)	11.4872(2)	13.4989(4)
b/Å	36.6729(9)	51.453(1)	17.6339(6)
c/Å	21.7305(9)	12.9436(2)	24.3822(7)
α/°	90	90	82.992(1)
β/°	102.021(1)	111.699(1)	76.138(2)
γ/°	90	90	82.026(2)
V/Å^3	9542.4(6)	7108.2(2)	5556.5(3)
Z	4	4	4
μ/mm^{-1}	0.076	0.068	0.078
Refl collected/unique/R_{int}	23364/13455/0.072	42775/13683/0.075	35343/18356/0.102
Final R indices[a]	0.072/0.167	0.080/0.199	0.055/0.102
GOF	0.981	1.021	0.868

[a]($I > 2\sigma I$).



Scheme 2. Synthesis and relevant crystallographic numbering of tetramethylated resorcarenes.

cavity of the nearby host, the closest distances being C51···Ct(C1B–C6B) = 3.36 Å, C51···Ct(C22B–C27B) = 4.05 Å and C52B···Ct(C15–C20) = 4.33 Å. In addition, a hydrogen bond between two hydroxyl groups of the facing resorcarenes (O27···O27B = 2.820 (4) Å) stabilise the inclusion. The methoxy groups of the two opposing hosts, however, do not occupy the whole cavity, but there is enough room for yet another methoxy group of another adjacent host. Continuous chains of self-included hosts are thus formed (Figure 1, right). The closest CH_3···aromatic centroid distances in this case are C49···Ct(C8B–C13B)* = 4.11 Å, C50B*···Ct(C4–C6) = 3.81 Å, C50B···Ct(C8–C13) = 3.40 Å. The self-included chains are further connected to a framework of chains by weak methoxy-hydroxyl CH_3···O hydrogen bonds of 2.99–3.38 Å and the C5 alkyl chains govern the packing into hydrophobic and hydrophilic layers.

Resorcarene **3c** crystallises with one molecule in an asymmetric unit, but due to the centrosymmetric space group both right- and left-handed enantiomeric forms are present. Again, self-inclusion through C–H···π interactions between the methoxy groups and the aromatic cavity is observed (C51···Ct(C1–C6)* = 3.98 Å, C51···Ct(C8–C13)* = 3.45 Å and C49···Ct(C15–20)** = 4.39 Å), and self-included chains similar to **3b** are formed (Figure 2). In the crystal packing, hydrophobic interactions of the long lower rim C11 alkyl chains play a governing role creating clear hydrophobic and hydrophilic regions in the crystal.

Both **3b** and **3c** adopt, as expected, a slightly pinched crown conformation stabilised by the hydrogen bonds from unsubstituted hydroxyl group to methoxy oxygen. In **3b**, however, the stabilisation of the conformation of both resorcinarenes in an asymmetric unit is due to three intramolecular hydrogen bonds (2.780(4)–2.828(4) Å), and remaining hydrogen bonds are intermolecular bonds to adjacent hosts. In **3c**, the cyclic seam of intramolecular hydrogen bonds is complete, i.e. all four hydroxyl groups form conformation-stabilising H-bonds of 2.789(4)–2.982(4) Å to adjacent methoxy groups.

The Fréchet dendron wedges **4b**–**d** ([G-1]-Br, [G-2]-Br, and [G-3]-Br) (Scheme 3) were prepared according to Fréchet's procedures [5] and characterised by means of NMR, mass spectrometry and elemental analysis.

Under phase-transfer conditions, Fréchet-type dendron bromides can be easily attached with high yields (Scheme 3) to the tetramethyl resorcarene core in acetone solution in the presence of **3**, [G-x]-Br (**4**), K_2CO_3,

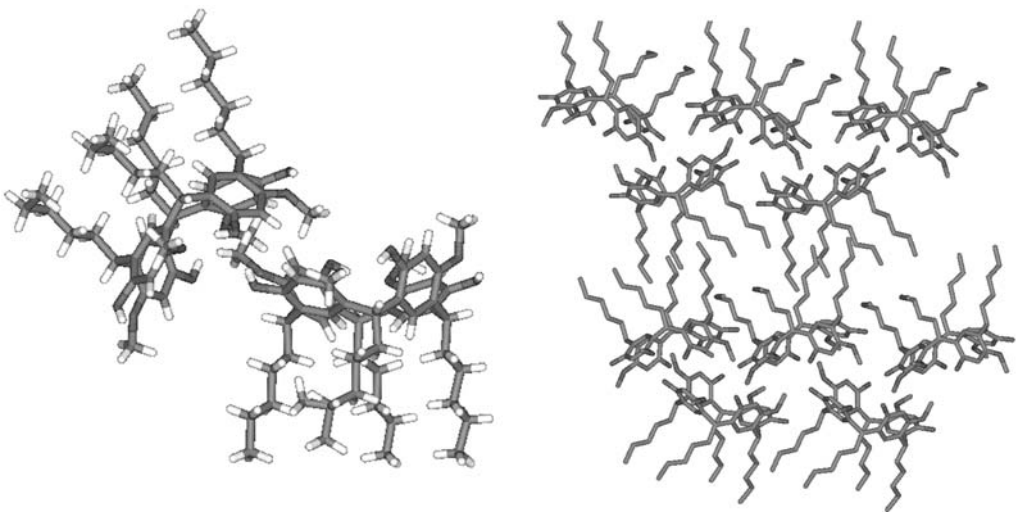


Figure 1. Crystal structure of resorcarene **3b**, asymmetric unit (left) and crystal packing (right). Resorcarene molecules form self-included pairs, in which the methoxy groups occupy the cavity of the adjacent host. Hydrogens are omitted from the crystal packing view for clarity.

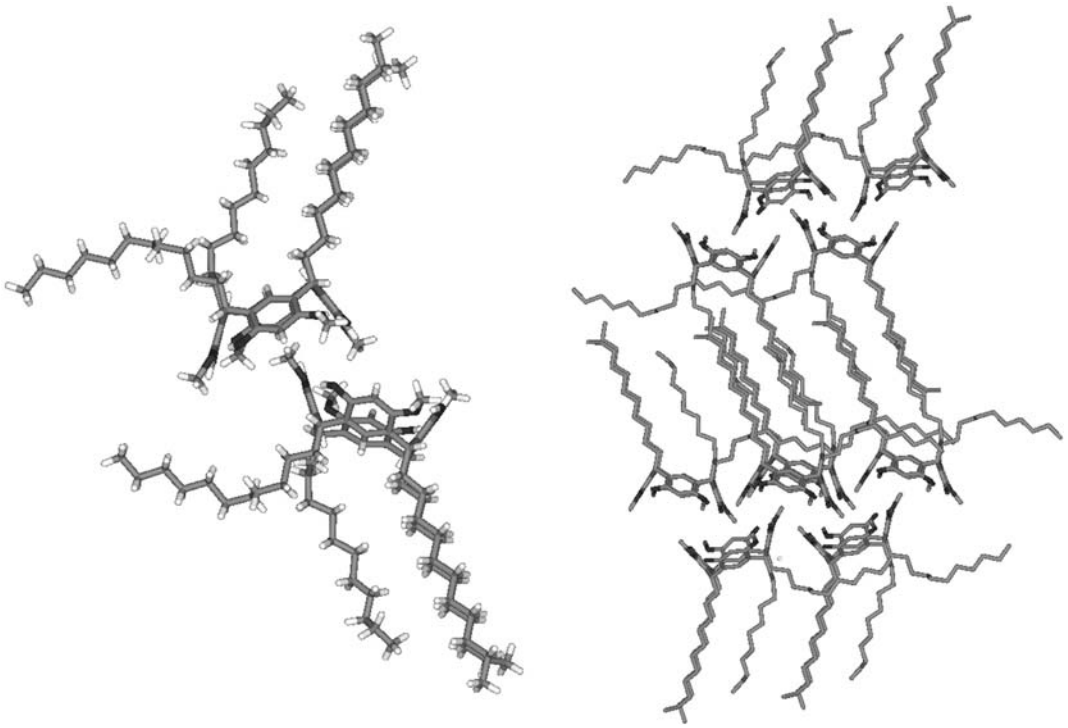
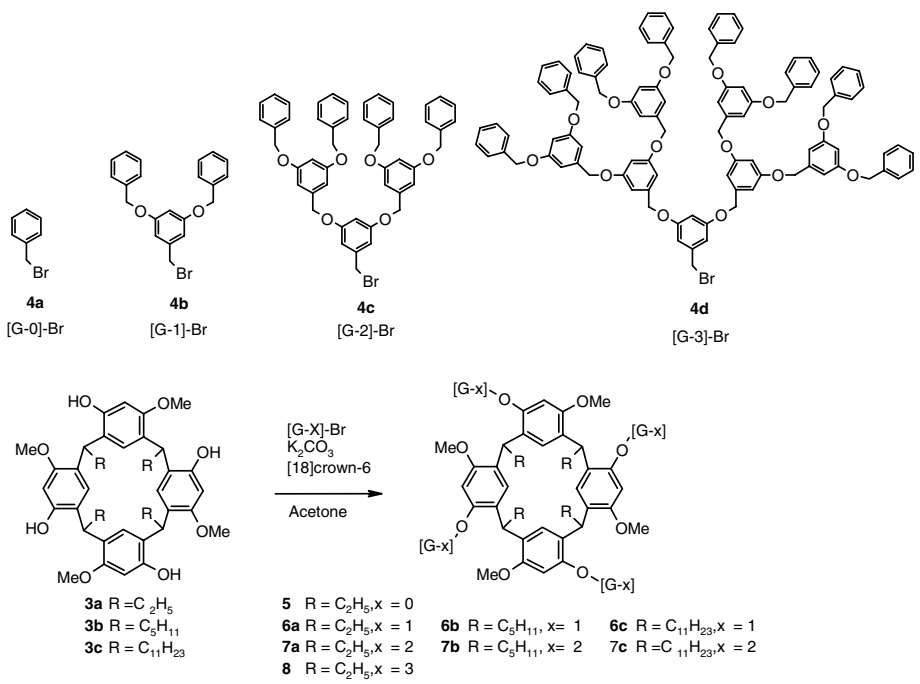


Figure 2. Resorcarene **3c** also forms self-included assemblies in the solid state (left). The crystal packing is governed by the self-inclusion of methoxy groups as well as the hydrophobic interactions between the long C11 alkyl chains (right). Hydrogen atoms are omitted for clarity from crystal packing view.

and [18]crown-6 mediating the solid–liquid phase transfer of the potassium carbonate into the organic solvent. All the products were purified by column chromatography. Yields of zero and first generation dendrimers varied from 81% to nearly quantitative, and with the second and third generations all the yields were quantitative. The only exception was **3c** with the third generation dendron **4d**, which gave only small yields of a hard-to-purify product (see Figure 3).

After substitution of the four free hydroxyl groups, no stabilising hydrogen bonds for the crown conformation exist. Therefore the conformation of the dendrimers has changed from crown to boat conformation, as seen in NMR spectra and the X-ray crystal structure



Scheme 3. Fréchet-type dendronbromides **4a**–**d** and the synthesis of tetramethylated resorcarene dendrimers **5**–**8**.

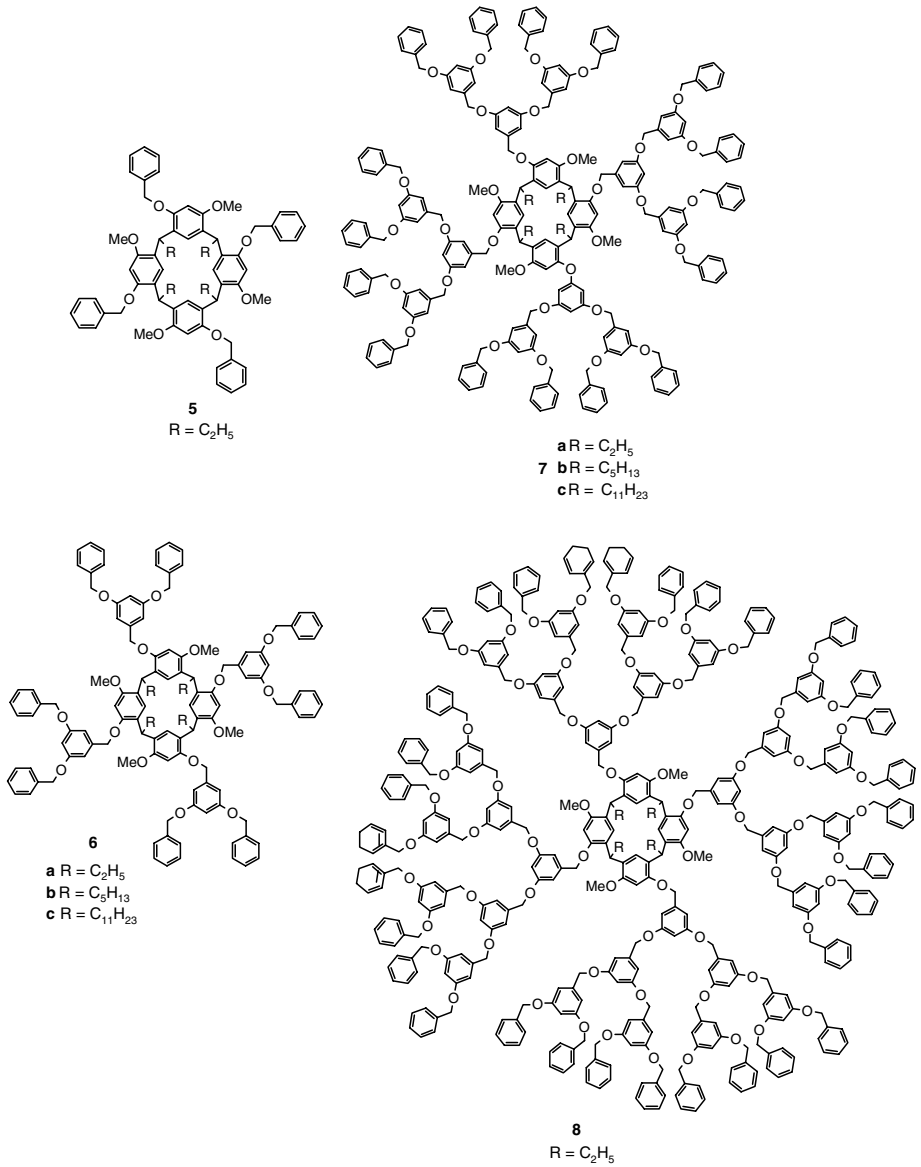


Figure 3. Tetramethylated resorcarene dendrimers **5**–**8**.

of **5**. The boat conformation is also observed in variable temperature NMR measurements. At ambient temperature the NMR spectrum shows one set of averaged signals for all protons due to fast boat-to-boat interconversion. When the temperature is lowered to 0 °C, the aromatic signals for the resorcarene core protons start to broaden, and finally at −50 °C the whole spectrum resolves into a spectrum corresponding to a pattern arising from the boat conformation and C_2 symmetry with two sets of resonances for both aromatic protons and the methine bridges (Figure 4).

Unlike the larger dendrimers **6**–**8**, the zero generation dendrimer **5** could be crystallised, and it crystallises, both the left- and right-handed enantiomers in the asymmetric unit. The boat conformation in the solid state is described by the dihedral angles between the opposite resorcinol rings, which are 14.0 or 12.3° and 184.2 or 186.0° for the two crystallographically independent molecules, and the distances between the opposite ring centroids are 4.71 or 4.79 and 8.04 or 8.01 Å, respectively. In the unsubstituted tetramethoxy resorcarene, for example in the structure of **3b**, the respective values are on average 45.3° and 72.0° and 6.16 Å and 7.54 Å as expected for a pinched crown conformation (see Figure 5).

As for the zero generation dendrimer **5**, the ^{1}H NMR spectra of the higher generation dendrimers **6**–**8** also show one set of signals for all protons due to the fast boat–boat interconversion (Figure 6). The 4–8 ppm region, in which the boat conformation is most clearly seen by the splitting of the aromatic and the bridging methine protons, however, is more complicated because of the overlapping aromatic, methine and O–CH_2–Ph resonances. Although this area was obscured from a closer examination, variable temperature ^{1}H NMR measurements for the higher generation dendrimers resulted in a similar pattern compared to that observed for the zero generation dendrimer **5** (Figure 4), and boat

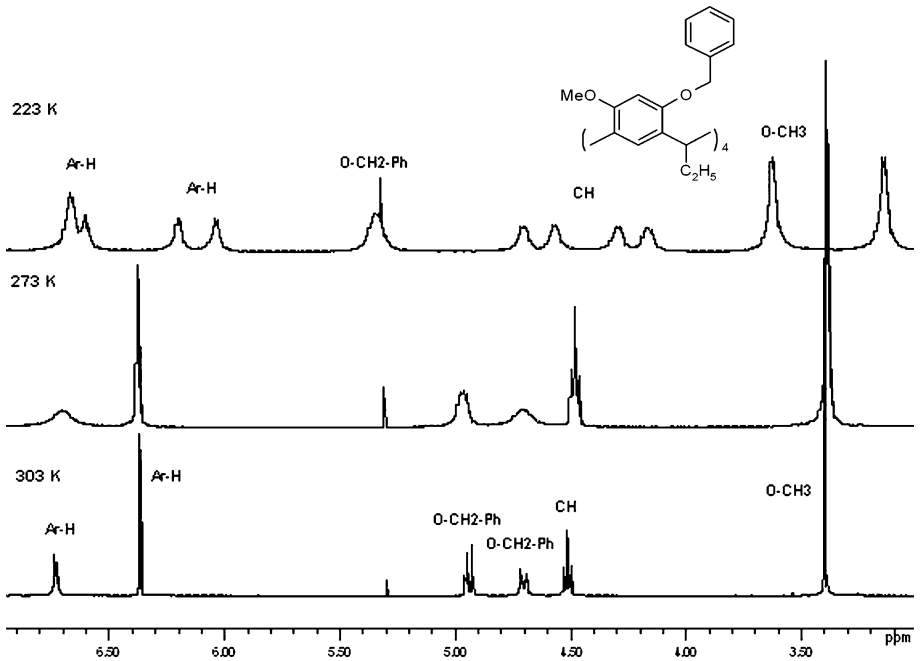


Figure 4. ^{1}H NMR spectra of **5** measured at three different temperatures. At lower temperatures the signals for aromatic and methine protons have split into two sets, which is to be expected in the boat conformation (only 3–7 ppm area of the spectra shown).

conformation could be reasoned from the splitting of the methoxy and methyl protons of the core resorcarene. NMR experiments of compounds **6**–**8** with the chiral shift reagent europium tris[3-(heptafluoro propylhydroxy methylene)-(+)-camphorate] did not result in doubling of the signals. Therefore, it could not be used to detect the racemic nature of the products. However, since the reactant was racemic, we infer that the product also contains both enantiomers in equal amounts.

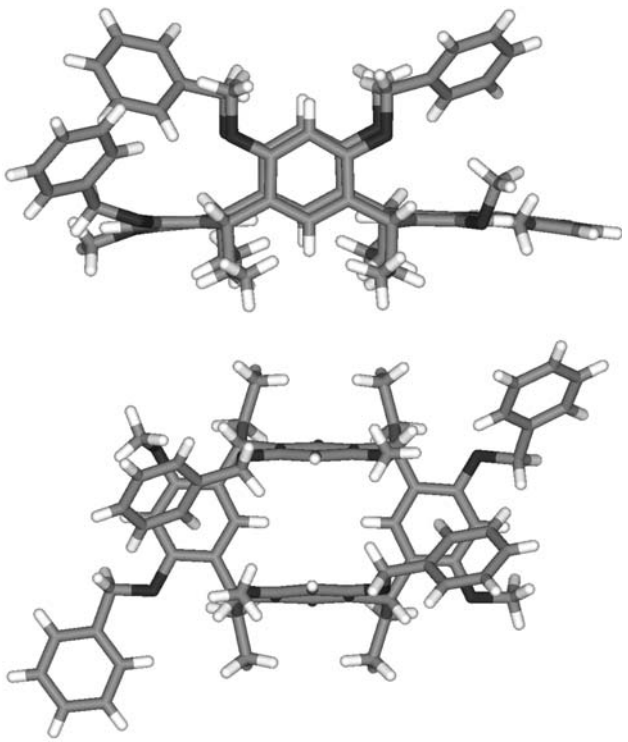


Figure 5. Side and top view of the crystal structure of **5** showing the clear boat conformation. The other molecule of the asymmetric unit is omitted for clarity.

Mass spectrometry offers a great potential for the characterisation of dendrimers, in particular, because it yields detailed molecular weight information, and thus makes the detection of defects easily possible, which are hardly detectable in NMR spectra [10]. The first and second-generation dendrimers under study were characterised by ESI mass spectrometry. Since all attempts to ionise these samples by either protonation or addition of a sodium salt, and also the strategy to utilise the host–guest properties of the resorcarene core for the binding of tetramethyl ammonium ions failed, CsCl was added to a 2:1 dichloromethane:acetonitrile solution of the dendrimers. Earlier reports provided evidence that the smaller and harder alkali metal ions preferentially bind to the oxygen atoms at the resorcarene periphery, while larger, softer ions such as Cs^+ can favourably interact with the π-systems of the resorcarene cavity [11]. In addition, they are smaller than the ammonium cations used before and thus should more easily find their way into the cavity. Indeed, this approach turned out to be successful. Figure 7 shows two representative examples. The first generation dendrimer **6c** gives a clean ESI mass spectrum (Figure 7, top trace) with the Cs^+ adduct corresponding to the base peak at m/z 2504. The isotope pattern is in agreement with the pattern calculated on the basis of natural abundances (inset). A low-intensity signal for a resorcarene substituted with three dendrons only is observed at m/z 2202. The bottom trace depicts the ESI mass spectrum of second-generation dendrimer **7c**. Again, the Cs^+ adduct at m/z 4202 is the most prominent signal, which, however, is accompanied

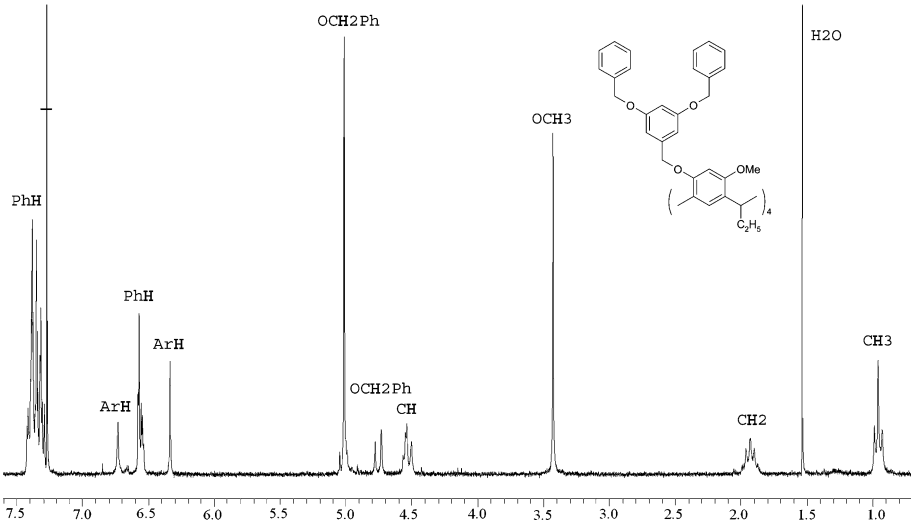


Figure 6. ^{1}H NMR spectrum of **6a** in $CDCl_3$.

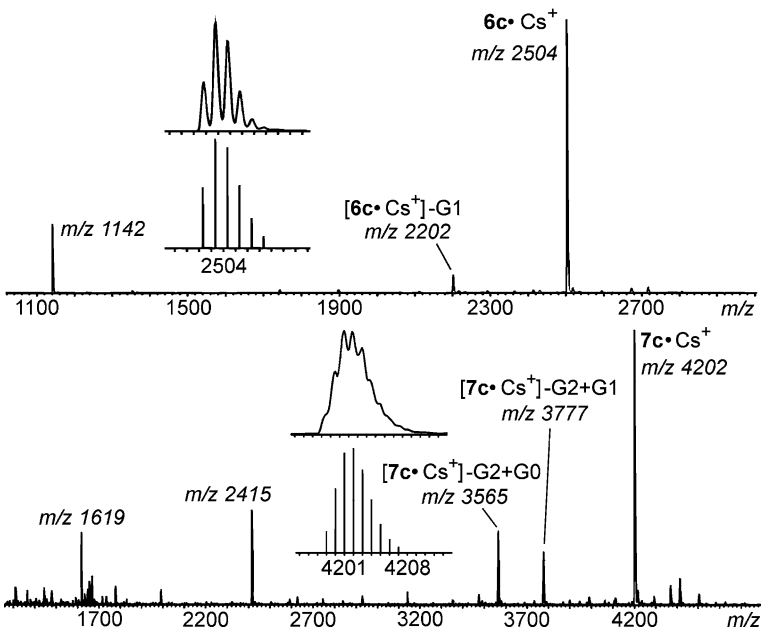


Figure 7. ESI-TOF mass spectra of 2:1 dichloromethane:acetonitrile solutions of [G-1] dendrimer **6c** (top trace) and its G2 analogue **7c** (bottom trace) with a small amount of CsCl added to the sample solution. The insets represent the isotope patterns obtained by experiment (top) and by calculation based on natural abundances (bottom).

by three defects, which can be explained by invoking small contributions of G0 (i.e. benzylbromide) and G1 bromides in the G2 Fréchet dendron used in the synthesis: $[MCs^+ - G2 + G0]^+$ appears at m/z 3565, $[MCs^+ - G2 + G1]^+$ at m/z 3777. It is, however, not straightforward to draw quantitative conclusions from the peak intensities, because resorcarene substituted by smaller dendrons may be ionised more easily. Finally, it should be noted that we were not able to successfully ionise G3 dendrimer **8**, which is beyond the mass range of our instrument. All attempts to find a suitable doubly charged cation, which would provide access to dications appearing within the available mass range have been unsuccessful so far.

Conclusion

Tetramethylated resorcarenes are good core molecules for the synthesis of dendrimers. In general, Fréchet-type dendrons can easily be attached to the tetramethylated resorcarene core to obtain quite pure products in high yields under phase-transfer conditions. The yields are much higher than those obtained in our earlier study [7], where dendritic amines were attached to the resorcarene core by a Mannich reaction. The present study shows that the dendrons to be attached can be rather large in size. The tetramethyl resorcarene scaffold with its unique chiral arrangement of substituents provides the basis for the synthesis of dendrimers with a chiral core if

the enantiomers of the resorcarene are separated for example by using chiral reagents [12].

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