Supporting information for:

Enzyme Triggered Disassembly of Dendrimer-based Amphiphilic Nanocontainers

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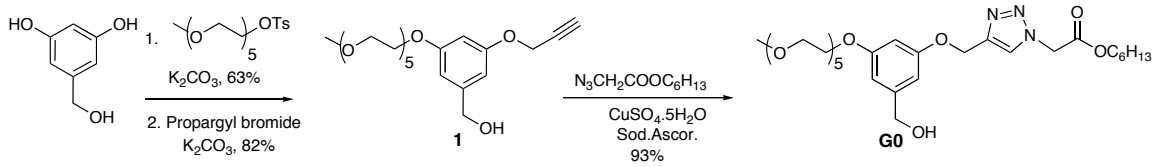
General:

Materials and Methods:

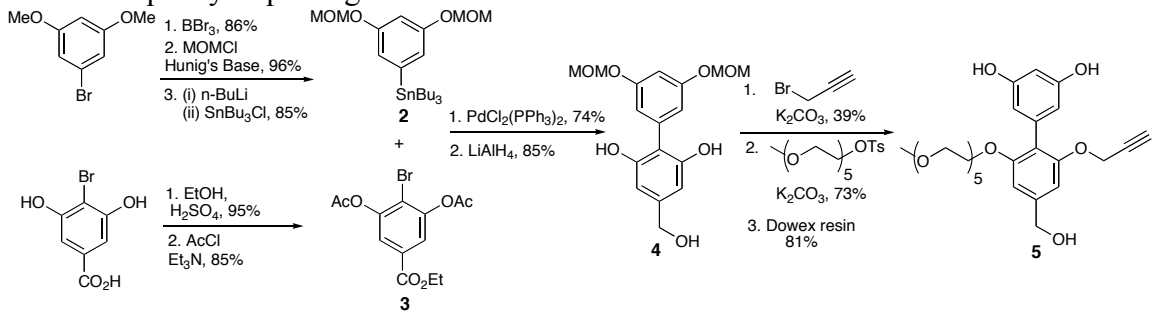
All chemicals and solvents were purchased from commercial sources and were used as such, unless otherwise mentioned. ^{1}H NMR spectra were recorded on a 400 MHz Bruker NMR spectrometer using the residual proton resonance of the solvent as the internal standard. Chemical shifts are reported in parts per million (ppm). When peak multiplicities are given, the following abbreviations are used: s, singlet; bs, broad singlet; d, doublet; t, triplet; m, multiplet. ^{13}C NMR spectra were proton decoupled and recorded on a 100 MHz Bruker spectrometer using carbon signal of the deuterated solvent as the internal standard.

Synthetic schemes for dendrons (G0-G3):

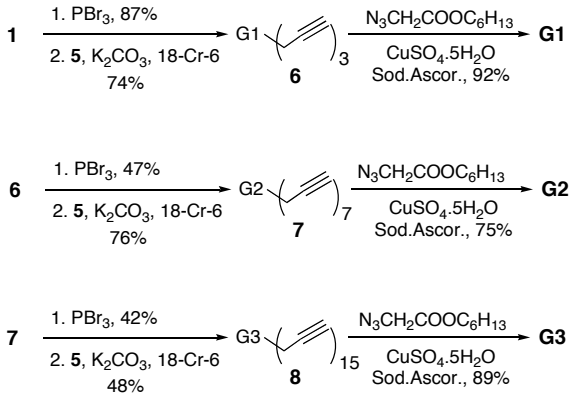
Synthesis of **G0**:



Synthesis of biphenyl repeating unit **5**:



Syntheses of **G1**, **G2** and **G3** dendrons:



General procedure for conversion of hydroxybenzyl to bromobenzyl compound:

To a stirring solution of appropriate hydroxybenzyl compound (1.0 equiv) in dichloromethane, was added PBr_3 (1.1 equiv) under argon at room temperature. The reaction was monitored using thin layer chromatography (TLC). After complete disappearance of the hydroxybenzyl compound, the remaining PBr_3 was quenched by slow addition of saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted twice with dichloromethane and the combined organic layer was concentrated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography.

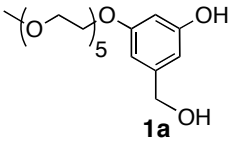
General procedure for the synthesis of dendritic hydroxymethyl compound:

To the solution of biphenyl monomer **5** (1.0 equiv) and appropriate bromobenzyl compound (2-3 equiv) in dry acetone, was added K_2CO_3 (3 equiv) and 18-crown-6 (0.1 equiv). The reaction mixture was refluxed under argon atmosphere for 12-48 h (more reaction times for the synthesis of higher generation dendrons). Progress of the reaction was monitored by TLC. After completion of the reaction, acetone was evaporated and the crude reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate and the combined organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography.

General procedure for the formation of triazole using "click" reaction:

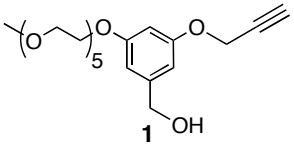
The dendritic acetylene compound (1.0 equiv) was dissolved in THF/H_2O (1:1) solvent mixture along with hexyl azidoacetate (2.0, 5.0, 10.0 and 20.0 equiv for **G0**, **G1**, **G2** and **G3** dendrons respectively), $CuSO_4$. $5H_2O$ (0.2 equiv.) and sodium ascorbate (0.2 equiv.). The reaction mixture was heated at 50 ^oC for 12-72 h (longer reaction times for the synthesis of higher generation dendrons). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was portioned between ethyl acetate and saturated aqueous NH_4Cl solution. The aqueous layer was extracted twice with ethyl acetate and the combined organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was isolated by silica gel column chromatography.

Synthesis of compound 1a:



3,5-Dihydroxy benzyl alcohol (3.0 g, 21.4 mmol), tosylate of pentaethylene glycol monomethyl ether (8.7 g, 21.4 mmol), K_2CO_3 (5.9 g, 42.8 mmol) and 18-crown-6 (0.55 g, 2.1 mmol) were mixed together in acetone (100 mL) and refluxed for 20 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in water and extracted twice with ethyl acetate. Upon evaporation of the solvent, the crude product was purified by silica gel column chromatography to afford 5 g (63%) of the product **1a** as viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48-6.35 (m, 3H), 4.55 (s, 2H), 4.07-4.05 (m, 2H), 3.83-3.55 (m, 18H), 3.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 157.7, 143.5, 106.8, 104.9, 101.6, 71.9, 70.8, 70.6, 70.5, 70.4, 70.4, 69.8, 67.5, 65.0, 59.0; FAB/MS m/z (r.i.) 374 (M+, 98), 281 (28), 237 (57), 154 (82), 59 (100).

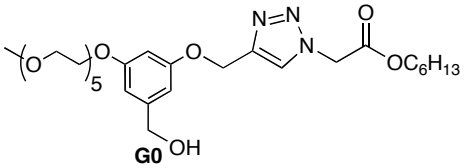
Synthesis of compound 1:



1

The mixture of compound **1a** (1.6 g, 4.41 mmol), propargyl bromide (0.75 mL, 4.41 mmol), K_2CO_3 (0.61 g, 4.41 mmol) and 18-crown-6 (0.06 g, 0.22 mmol) in acetone (50 mL) was refluxed for 12 h. Upon evaporation of the solvent, the mixture was dissolved in water and extracted twice with ethyl acetate and the combined extracts were dried over Na_2SO_4. The crude product obtained upon evaporation of solvent was purified by silica gel column chromatography to yield 1.5 g (82%) of compound **1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55-6.40 (m, 3H), 4.61 (d, *J* = 2.4 Hz, 2H), 4.56 (s, 2H), 4.06 (t, *J* = 4.4 Hz, 2H), 3.79 (t, *J* = 4.8 Hz, 2H), 3.68-3.50 (m, 14H), 3.48 (t, *J* = 4.4 Hz, 2H), 3.32 (s, 3H), 2.50 (t, *J* = 2.4 Hz, 1H), 2.47 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 158.7, 139.8, 108.5, 108.1, 102.0, 78.3, 75.9, 71.9, 70.8, 70.6, 70.6, 70.6, 70.5, 69.6, 67.6, 59.0, 55.9, 33.4; FAB/MS m/z (r.i.) 413 (M+1, 35), 412 (M+, 20), 307 (28), 154 (100).

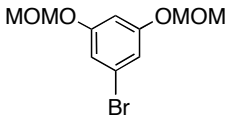
Synthesis of compound G0:



G0

According to the general procedure for click reaction, compound **1** (0.06 g, 0.15 mmol) was treated with hexyl azidoacetate (0.53 g, 0.30 mmol) to yield 0.08 g (93%) of **G0**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 6.58-6.45 (m, 3H), 5.19 (s, 2H), 5.15 (s, 2H), 4.59 (s, 2H), 4.18 (t, *J* = 6.8 Hz, 2H), 4.09 (t, *J* = 4.4 Hz, 2H), 3.82 (t, *J* = 3.6 Hz, 2H), 3.80-3.50 (m, 16H), 3.35 (s, 3H), 1.70-1.56 (m, 2H), 1.40-1.18 (m, 6H), 0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.9, 160.2, 159.7, 145.2, 143.7, 125.1, 105.2, 105.2, 99.9, 71.8, 70.5, 70.4, 70.4, 70.2, 69.5, 67.5, 65.5, 63.7, 61.5, 57.9, 50.5, 31.2, 25.2, 22.3, 13.4; FAB/MS m/z (r.i.) 598 (M+, 75), 580 (22), 196 (45), 112 (60), 59 (100).

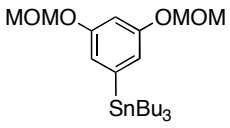
Synthesis of compound 2a:



2a

To a solution of bromoresorcinol (20 g, 105.8 mmol) in dry THF (500 mL) was added Hunig's base (55 mL, 317.4 mmol) and allowed to stir at room temperature under argon atmosphere for 15 min. After cooling the mixture to ice-bath temperature, methoxymethyl chloride (MOM-Cl) (26 mL, 317.4 mmol) was added drop wise and the reaction mixture was allowed to stir for 24 h at room temperature. The reaction mixture was poured into water and extracted thrice with dichloromethane. The combined organic layer was rotavapored and subjected to silica gel column chromatography to yield 28 g (96%) of compound **2a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (t, J = 2.6 Hz, 2H), 6.36 (t, J = 2.0 Hz, 1H), 5.11 (s, 4H), 3.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 122.7, 113.1, 103.9, 94.4, 56.1. EI/MS m/z (r.i.) 277 (M+, 97), 275 (100), 244.9 (32), 197 (10), 63 (10).

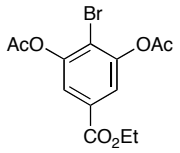
Synthesis of compound 2:



2

To a solution of compound **2a** (10 g, 36.1 mmol) in anhydrous THF (100 mL) was added *n*-BuLi (27.2 mL of 1.6 M hexane solution, 43.3 mmol) under argon atmosphere at -78 ^{o}C and stirred for 30 min at the same temperature. Then Bu_3SnCl (11.7 mL, 43.3 mmol) was added and stirred at -78 to 25 ^{o}C for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The solvent was removed under reduced pressure to afford the crude reaction mixture, which was purified by silica gel column chromatography to afford 15 g (85%) of product **2** as viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80-6.66 (m, 3H), 5.15 (s, 4H), 3.46 (s, 6H), 1.63-1.03 (m, 27H).

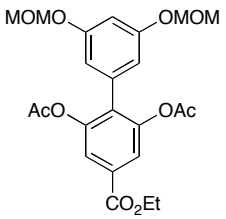
Synthesis of compound 3:



3

To a solution of ethyl ester of 3,5-dihydroxy-5-bromobenzoic acid (48 g, 184.0 mmol) in anhydrous dichloromethane (500 mL) was added triethylamine (132 mL 916.0 mmol) and cooled to 0 ^{o}C. Then, acetylchloride (52 mL, 732.8 mmol) was added dropwise and stirred at room temperature for 12 h. The reaction mixture was quenched with water and extracted thrice with dichloromethane. The solvent was removed under reduced pressure to afford the crude product, which was purified by silica gel column chromatography to afford 15 g (85%) of product **3** as viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 2H), 4.35 (q, J = 7.2 Hz, 2H), 2.36 (s, 6H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 164.4, 149.5, 122.0, 117.0, 61.7, 20.7, 14.2; FAB/MS *m/z* (r.i) 345 (M+, 100), 154 (50), 137 (85).

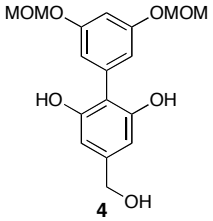
Synthesis of compound 4a:



4a

Compound **2** (10 g, 20.5 mmol) and bromo ester **3** (7 g, 20.5 mmol) were dissolved in deoxygenated DMF (20 mL) under argon atmosphere. To this 2.5 mol% of $Pd(PPh_3)_2Cl_2$ (0.36 g, 0.51 mmol) was added and the reaction mixture heated at 120-130 ^oC for 24 h. After cooling the reaction mixture to room temperature, the mixture was passed through a celite pad and washed with ethyl acetate. Finally the filtrate was washed with water and the organic layer was evaporated to dryness. The crude product was purified by silica gel chromatography to afford 7.0 g of compound **4a** (74% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 2H), 6.74 (s, 1H), 6.63 (d, J = 2.0 Hz, 2H), 5.16 (s, 4H), 4.40 (q, J = 7.2 Hz, 2H), 3.49 (s, 6H), 2.08 (s, 6H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 164.7, 157.8, 148.9, 133.4, 133.0, 131.2, 121.9, 110.9, 105.3, 94.5, 61.5, 56.1, 20.5, 14.3; FAB/MS *m/z* (r.i.) 462 (M+, 100), 431 (30), 401 (28), 378 (25).

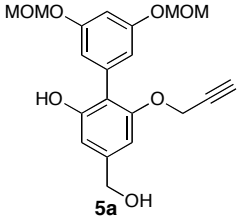
Synthesis of compound 4:



4

To $LiAlH_4$ (2.1 g, 56.2 mmol) in dry THF (50 mL), was added a solution of biaryl compound **4a** (13.0 g, 28.1 mmol) in THF (100 mL) at 0 ^oC under argon atmosphere and stirred at room temperature for 12 h. The reaction mixture was quenched with ethyl acetate and then acidified using dilute HCl (1 N) solution. The resultant mixture was extracted twice with ethyl acetate and the combined organic extracts were dried over Na_2SO_4. Upon evaporation of solvent, the crude was purified by silica gel chromatography to afford 8.0 g of compound **4** (85% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (t, J = 2.0 Hz, 1H), 6.69 (d, J = 2.4 Hz, 2H), 6.53 (s, 2H), 5.38 (s, 2H), 5.16 (s, 4H), 4.58 (s, 2H), 3.47 (s, 6H); ^{13}C NMR (100 MHz, acetone-d_6) δ 158.2, 155.1, 143.6, 136.3, 114.6, 112.6, 105.3, 103.3, 94.5, 63.6, 55.2; FAB/MS *m/z* (r.i) 336 (M+, 100), 319 (60), 154 (58), 136 (45).

Synthesis of compound 5a:

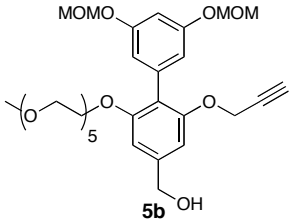


5a

The mixture of compound **4** (2.3 g, 6.8 mmol), K_2CO_3 (1.0 g, 7.5 mmol), 18-crown-6 (0.18 g, 0.68 mmol) and propargyl bromide (1.2 mL, 6.8 mmol) in acetone (70 mL) was refluxed

for 12 h under argon atmosphere. After the completion of the reaction, acetone was evaporated and the resultant mixture was poured into water and extracted twice with ethyl acetate. Upon evaporation of solvent of the combined organic extracts, the crude product was purified by silica gel chromatography to afford 1.0 g of compound **5a** (39% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80-6.68 (m, 5H), 5.55 (s, 1H), 5.20 (s, 4H), 4.69-4.60 (m, 4H), 3.50 (s, 6H), 2.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 155.4, 153.9, 142.5, 134.0, 116.7, 112.0, 107.6, 104.6, 103.4, 94.6, 78.7, 75.5, 65.1, 56.3, 56.2; FAB/MS *m/z* (r.i) 374 (M+, 100), 329 (53), 297 (72), 267 (50), 69 (85).

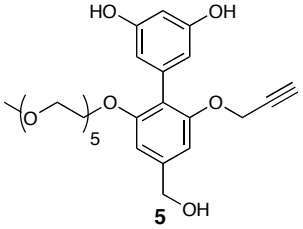
Synthesis of compound 5b:



5b

Compound **5a** (1.0 g, 2.67 mmol), K_2CO_3 (0.56 g, 4.0 mmol), 18-crown-6 (0.35 g, 1.3 mmol) and the tosylate of pentaethylene glycol monomethyl ether (1.3 g, 3.2 mmol) were mixed together in acetone (70 mL) and refluxed for 12 h under argon atmosphere. After the completion of the reaction, acetone was evaporated and the crude mixture was poured into water and extracted twice with ethylacetate. Upon evaporation of solvent of the combined organic extracts, the crude product was purified by silica gel chromatography to afford 1.8 g of compound **5b** (73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75-6.65 (m, 5H), 5.14 (s, 4H), 4.66 (s, 2H), 4.59 (d, J = 2.4 Hz, 2H), 4.05 (m, 2H), 3.75-3.45 (m, 24H), 3.34 (s, 3H), 2.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 157.0, 155.5, 142.3, 135.4, 119.4, 112.8, 105.2, 104.8, 103.6, 94.6, 78.8, 75.4, 71.9, 70.8,70.6, 70.6, 70.5, 70.5, 69.5, 68.5, 65.2, 59.0, 56.4, 56.0; FAB/MS *m/z* (r.i) 608 (M+, 30), 607 (12), 577 (75), 154 (50), 59 (100).

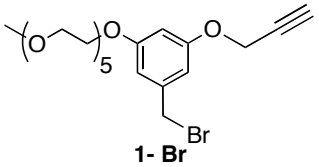
Synthesis of biaryl monomer 5:



5

To the solution of compound **5b** (1.0 g, 1.6 mmol) in methanol (25 mL), dioxane (2 mL) and water (1 mL), was added Dowex resin (2.0 g) and refluxed for 4 h under argon atmosphere. After the completion of the reaction, the crude mixture was filtered and washed with ethyl acetate. Upon evaporation of solvent of the filtrate, the crude product was purified by silica gel chromatography to afford 0.7 g of compound **5** (81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 1H), 6.21 (s, 1H), 6.47 (d, J = 2.4 Hz, 2H), 6.31 (d, J = 2.4 Hz, 1H), 4.67 (s, 2H), 4.57 (d, J = 2.4 Hz, 2H), 4.02 (t, J = 3.6 Hz, 2H), 3.70-3.45 (m, 18H), 3.33 (s, 3H), 2.43(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 157.1, 155.6, 143.3, 136.0, 119.6, 109.8, 104.7, 104.5, 101.0, 79.3, 75.8, 71.7, 70.6, 70.3, 70.1, 69.2, 68.9, 63.9, 57.8, 55.9; FAB/MS *m/z* (r.i) 521 (M+1, 20), 307 (22), 289 (18), 154 (100).

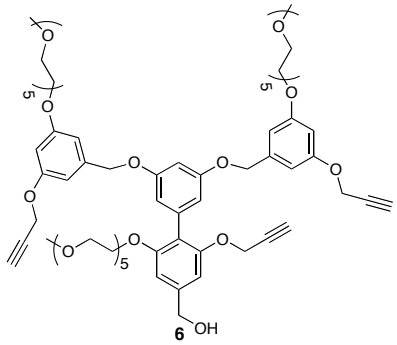
Synthesis of compound 1- Br:



1- Br

According to the general procedure for the conversion of hydroxybenzyl to bromobenzyl, compound **1** (1.0 g, 2.4 mmol) was converted to its corresponding bromide **1- Br** (0.9 g, yield: 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59-6.46 (m, 3H), 4.65 (d, J = 2.4 Hz, 2H), 4.39 (s, 2H), 4.10 (t, J = 4.8 Hz, 2H), 3.83 (t, J = 4.8 Hz, 2H), 3.72-3.61 (m, 14H), 3.54-3.51 (m, 2H), 3.36 (s, 3H), 2.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 158.7, 139.8, 108.5, 108.1, 102.0, 78.3, 75.9, 71.9, 70.8, 70.6, 70.6, 70.5, 69.6, 67.6, 59.0, 55.9, 33.4. FAB/MS *m/z* (r.i) 475 (M+, 30), 307 (20), 154 (100).

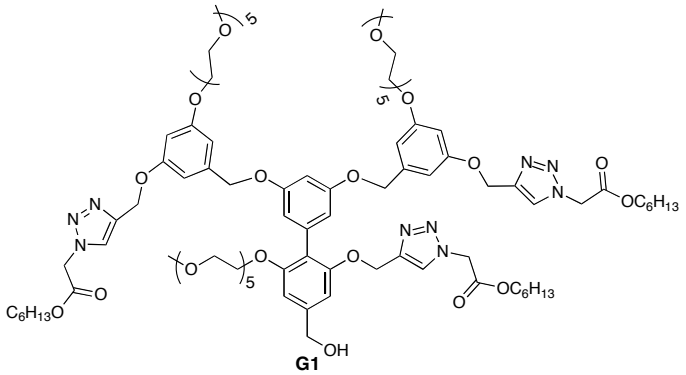
Synthesis of compound 6:



6

According to the general procedure for synthesis of dendritic hydroxymethyl compound, the monomer **5** (1.0 g, 1.92 mmol) was reacted with the bromomethyl compound **1-Br** (2.7 g, 5.77 mmol) to give 1.8 g (yield: 74%) of compound **6**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78-6.48 (m, 11H), 4.96 (s, 4H), 4.70-4.60 (m, 6H), 4.56 (d, J = 2.0 Hz, 2H), 4.10-4.04 (m, 6H), 3.80-3.45 (m, 54H), 3.40-3.30 (m, 9H), 2.53 (s, 2H), 2.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 159.0, 158.8, 157.2, 155.6, 142.2, 139.7, 135.6, 119.9, 110.4, 106.7, 106.3, 105.5, 105.0, 101.4, 101.2, 78.9, 78.4, 75.8, 75.6, 71.9, 70.8, 70.6, 70.6, 70.6, 70.5, 70.5, 69.8, 69.7, 69.6, 68.9, 67.6, 65.2, 59.0, 56.4, 55.9; MALDI-ToF *m/z* 1332.0 ($C_{69}H_{96}O_{24}$+Na^+ requires 1332.5).

Synthesis of compound G1:

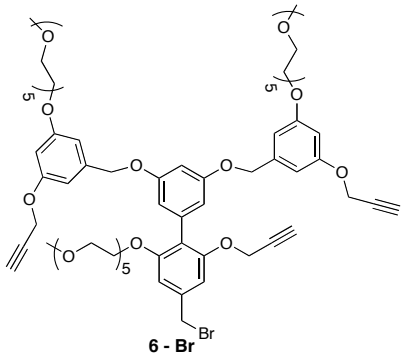


G1

According to general procedure for click reaction, compound **6** (0.05 g, 0.04 mmol) was treated with hexyl azidoacetate (0.04 g, 0.2 mmol) to give 0.07 g (yield: 92%) of **G1** dendron.

^{1}H NMR (400 MHz, acetone-d_6) δ 8.11 (s, 2H), 7.87 (s, 1H), 7.00-6.50 (m, 11H), 5.38-5.00 (m, 16H), 4.67 (s, 2H), 4.20-4.02 (m, 12H), 3.82-3.51 (m, 54H), 3.30-3.25 (m, 9H), 1.70-1.55 (m, 6H), 1.40-1.22 (m, 18H), 0.92-0.85 (m, 9H); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.0, 166.9, 160.3, 159.8, 159.0, 156.9, 156.3, 143.9, 143.8, 143.5, 140.3, 136.2, 125.3, 125.0, 118.7, 110.5, 106.3, 106.2, 104.6, 104.4, 100.8, 100.6, 71.8, 71.7, 70.5, 70.4, 70.4, 70.3, 70.3, 70.2, 70.1, 69.5, 69.4, 69.2, 68.6, 67.6, 65.6, 65.6, 63.9, 62.3, 61.6, 57.9, 50.5, 31.2, 28.3, 25.2, 22.3, 13.4; MALDI-ToF *m/z* 1887.3, 1865.3 ($C_{93}H_{141}N_9O_{30}$+Na^+ requires 1888.1 and $C_{93}H_{141}N_9O_{30}^+$ requires 1865.1).

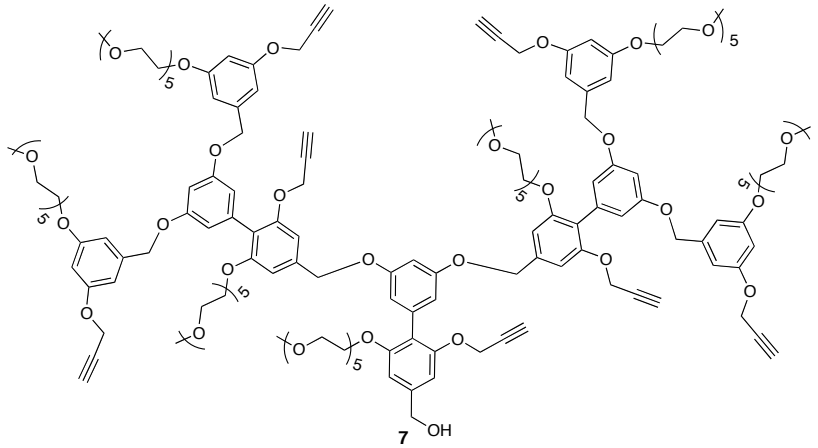
Synthesis of compound 6-Br:



6 - Br

According to the general procedure for bromination of hydroxymethyl compound, compound **6** (0.75 g, 0.57 mmol) was converted to its corresponding bromide **6-Br** (0.5 g, yield: 47%). ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85-6.48 (m, 11H), 4.96 (s, 4H), 4.68 (s, 4H), 4.60 (s, 2H), 4.52 (s, 2H), 4.16-4.00 (m, 6H), 3.90-3.50 (m, 54H), 3.40-3.30 (m, 9H), 2.50-2.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.1, 159.1, 158.8, 157.1, 155.6, 139.6, 138.3, 135.2, 121.0, 110.3, 107.7, 107.5, 106.7, 106.3, 101.4, 78.7, 78.4, 75.8, 75.8, 71.9, 70.9, 70.8, 70.6, 70.6, 70.5, 70.5, 69.8, 69.7, 69.4, 68.9, 67.6, 60.4, 59.0, 56.5, 55.9; MALDI-ToF *m/z* 1395.8 ($C_{69}H_{95}BrO_{23}$+Na^+ requires 1395.4).

Synthesis of compound 7:

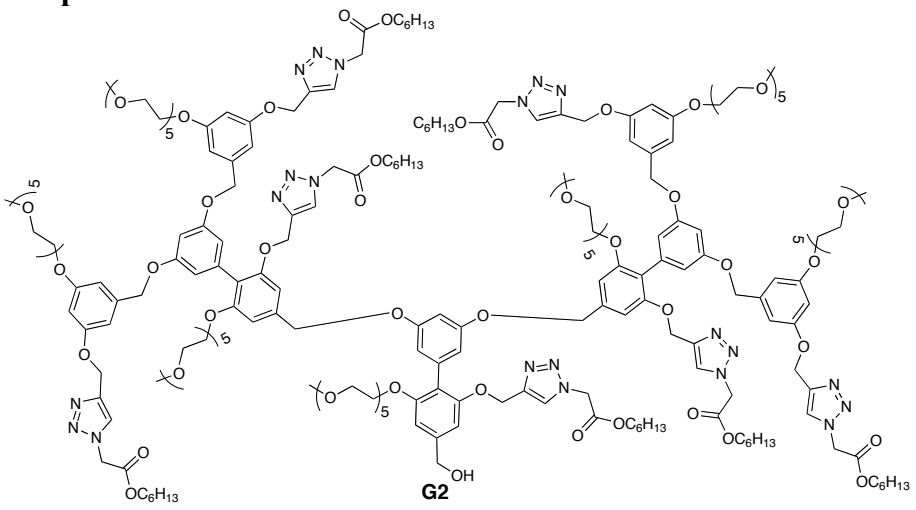


7

According to the general procedure for synthesis of dendritic hydroxymethyl compound, the monomer **5** (0.04 g, 0.07 mmol) was reacted with the bromomethyl compound **6-Br** (0.23 g,

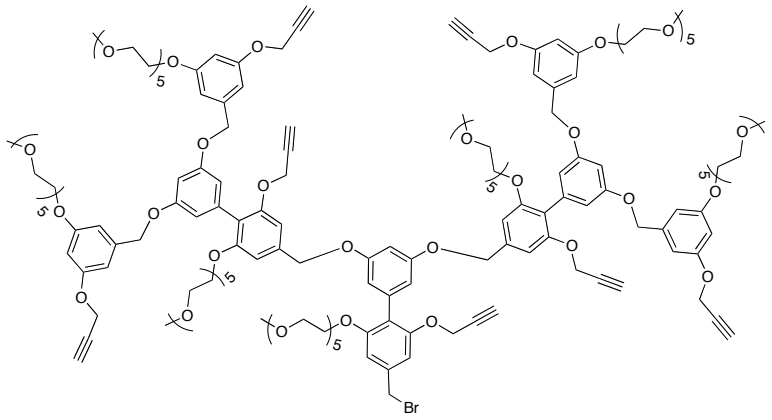
0.17 mmol) to yield 0.12 g of compound **7** (76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87-6.48 (m, 27H), 5.05 (s, 4H), 4.96 (s, 8H), 4.66-4.56 (m, 16H), 4.12-4.04 (m, 14H), 3.85-3.58 (m, 126H), 3.40-3.30 (m, 21H), 2.60-2.45 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 159.1, 159.1, 158.8, 157.1, 157.1, 155.6, 142.4, 139.6, 138.1, 136.9, 135.7, 135.5, 133.9, 120.2, 119.9, 113.8, 112.6, 110.3, 109.4, 108.3, 106.8, 106.3, 105.9, 105.8, 105.6, 105.0, 103.9, 101.4, 101.2, 79.0, 78.8, 78.5, 77.2, 75.9, 75.8, 75.7, 71.9, 71.9, 71.9, 70.8, 70.6, 70.6, 70.6, 70.5, 70.5, 70.5, 70.5, 70.1, 69.8, 69.7, 69.4, 68.9, 67.6, 65.1, 59.0, 59.0, 57.8, 56.5, 56.4, 55.9, 54.4, 53.8; MALDI-ToF *m/z* 3127.2 ($C_{165}H_{224}O_{56}$+Na^+ requires 3126.5).

Synthesis of compound G2:



According to general procedure for click reaction, the treatment of compound **7** (0.075 g, 0.03 mmol) with hexyl azidoacetate (0.04 g, 0.3 mmol) yields 0.08 g (yield: 75%) of **G2** dendron. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.12 (s, 4H), 7.92 (s, 1H), 7.85 (s, 2H), 7.13-6.60 (m, 27H), 5.38-5.04 (m, 38H), 4.68 (s, 2H), 4.19-4.09 (m, 28H), 3.86-3.80 (m, 8H), 3.70-3.40 (m, 120H), 3.30-3.20 (m, 21H), 1.70-1.52 (m, 14H), 1.40-1.20 (m, 42H), 0.90-0.80 (m, 21H); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.0, 166.9, 160.3, 159.8, 159.1, 157.1, 156.9, 156.4, 156.3, 143.9, 143.7, 143.6, 143.5, 140.3, 138.9, 136.0, 125.3, 125.1, 119.6, 118.7, 110.7, 110.4, 106.3, 106.2, 105.7, 105.5, 100.8, 101.0, 100.6, 71.8, 71.7, 70.5, 70.4, 70.4, 70.3, 70.3, 70.2, 70.1, 69.8, 69.5, 69.4, 69.3, 69.2, 68.6, 67.6, 65.6, 65.6, 63.9, 62.3, 61.6, 57.9, 50.5, 31.2, 28.3, 25.2, 22.3, 13.4, 13.4; MALDI-ToF *m/z* 4422.9 ($C_{221}H_{329}N_{21}O_{70}$+$Na^+$ requires 4423.0).

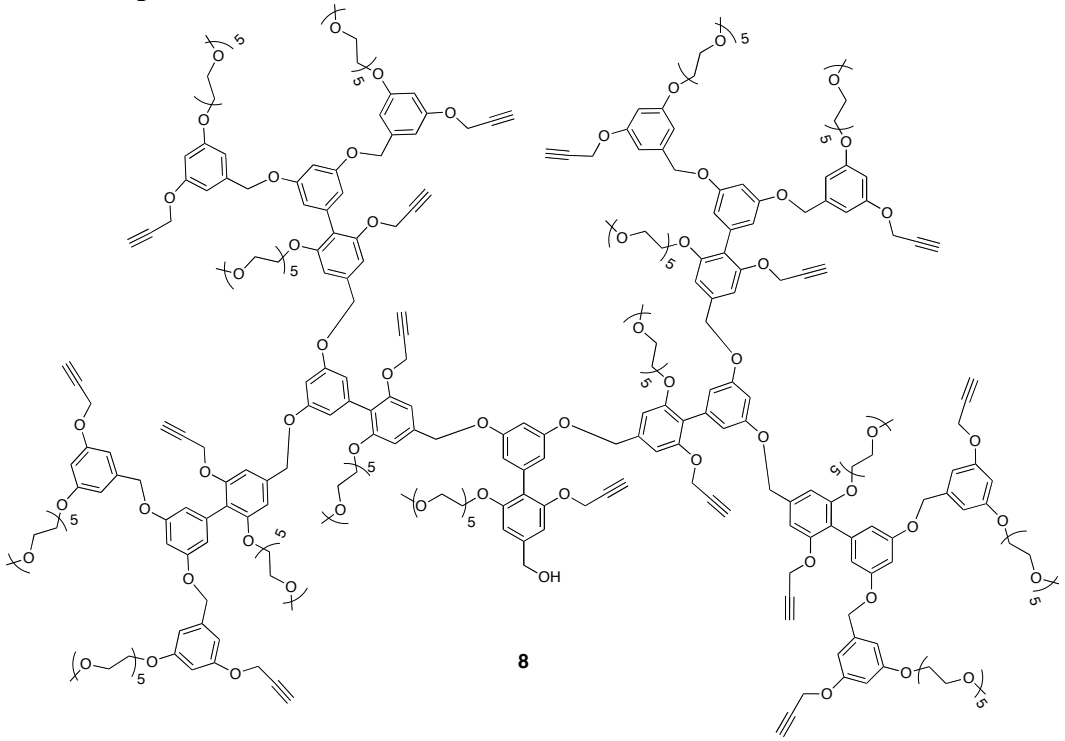
Synthesis of compound 7-Br:



7- Br

According to general procedure for conversion of hydroxymethyl to bromomethyl, compound **7** (0.3 g, 0.09 mmol) was converted to the bromo compound **7-Br** (0.1 g, yield: 42%). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.05-6.80 (m, 6H), 6.78-6.52 (m, 21H), 5.20-5.00 (m, 12H), 4.82-4.65 (m, 16H), 4.20-4.05 (m, 14H), 3.85-3.40 (m, 126H), 3.30-3.20 (m, 21H), 3.13-3.00 (m, 7H); ^{13}C NMR (100 MHz, acetone-d_6) δ 160.3, 159.3, 159.2, 159.1, 157.1, 155.7, 155.7, 140.2, 138.9, 138.7, 135.9, 135.6, 120.6, 119.8, 110.5, 107.6, 107.4, 106.5, 106.4, 105.7, 105.7, 101.1, 100.8, 79.2, 79.0, 78.9, 76.5, 76.4, 76.3, 71.8, 70.6, 70.5, 70.5, 70.4, 70.3, 70.3, 70.2, 70.1, 69.8, 69.5, 69.4, 69.2, 68.8, 68.8, 67.6, 58.0, 58.0, 56.2, 55.6.

Synthesis of compound 8:

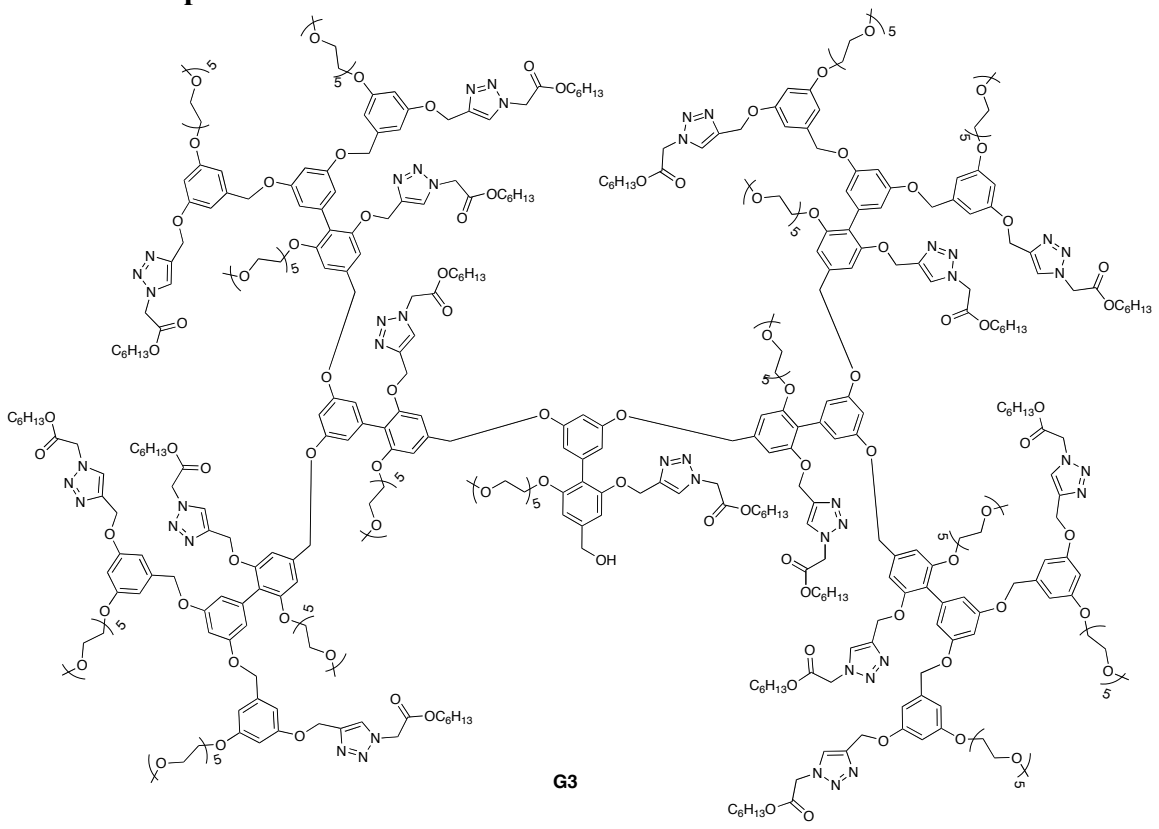


8

According to the general procedure for synthesis of dendritic hydroxymethyl compound, the monomer **5** (0.02 g, 0.04 mmol) was reacted with the bromomethyl compound **7-Br** (0.27 g, 0.08 mmol) to yield 0.12 g of compound **8** (48% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.06-6.56 (m, 59H), 5.20-5.02 (m, 28H), 4.80-4.65 (m, 32H), 4.18-4.06 (m, 30H), 3.88-3.40 (m,

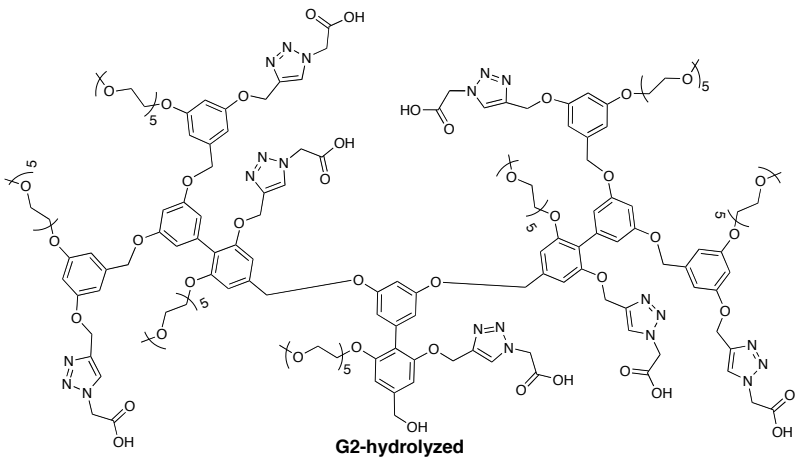
270H), 3.32-3.20 (m, 45H), 3.10-3.01 (m, 15H); ^{13}C NMR (100 MHz, acetone-d_6) δ 160.3, 159.2, 159.2, 159.0, 157.1, 157.0, 155.7, 155.6, 140.2, 138.8, 138.7, 136.0, 136.0, 119.8, 110.6, 110.5, 106.5, 106.4, 105.8, 105.7, 100.9, 79.4, 79.2, 79.2, 79.0, 76.5, 76.4, 76.3, 76.2, 71.8, 70.6, 70.4, 70.4, 70.3, 70.3, 70.2, 70.2, 69.8, 69.5, 69.4, 69.2, 68.8, 68.6, 67.6, 58.0, 56.2, 56.1, 55.6; MALDI-ToF *m/z* 6711.3 ($C_{357}H_{480}O_{120}$+Na^+ requires 6714.5).

Synthesis of compound G3:



According to general procedure for click reaction, the treatment of compound **8** (0.04 g, 0.006 mmol) with hexyl azidoacetate (0.02 g, 0.120 mmol) yields 0.05 g (89%) of **G3** dendron. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.12 (s, 8H), 7.95-7.80 (m, 7H), 7.15-6.60 (m, 59H), 5.40-5.00 (m, 80H), 4.70 (s, 2H), 4.20-4.05 (m, 58H), 3.90-3.40 (m, 280H), 3.30-3.20 (m, 45H), 1.70-1.55 (m, 30H), 1.50-1.20 (m, 90H), 0.95-0.82 (m, 45H); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.0, 166.9, 160.3, 159.9, 159.2, 159.1, 157.1, 156.4, 143.6, 143.5, 140.3, 139.9, 138.9, 137.3, 136.3, 136.1, 136.0, 127.4, 125.5, 125.3, 125.2, 125.1, 121.8, 119.6, 119.5, 114.0, 110.6, 110.4, 106.4, 106.2, 105.8, 105.5, 101.0, 100.6, 71.8, 71.7, 70.5, 70.4, 70.3, 70.3, 70.3, 70.2, 70.1, 69.5, 69.4, 69.2, 68.7, 67.6, 65.7, 65.6, 65.6, 62.7, 62.4, 62.3, 61.6, 58.0, 55.6, 50.5, 31.2, 28.2, 25.2, 22.3, 13.5, 13.4. MALDI-ToF *m/z* 9474.9 ($C_{477}H_{705}N_{45}O_{150}^+$ requires 9469.9).

Synthesis of compound G2:



G2-hydrolyzed

To a solution of **G2** dendron containing hexyl esters (1.0 eq.) in tetrahydrofuran and methanol (volume 2:1) was added aqueous potassium hydroxide (2.0 eq for each ester group) solution. The mixture was refluxed for 12-24 hrs. The solvents were evaporated and the crude product was redissolved in water and the resulting solution was refluxed for another 24 hrs. The solution was brought to room temperature and neutralized using 2N HCl to precipitate the product. The product was isolated by centrifugation. The dendrimers were purified by several water wash followed by centrifugation. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.15 (s, 4H), 7.90 (s, 1H), 7.80 (s, 2H), 7.15-6.55 (m, 27H), 5.38-5.04 (m, 38H), 4.68 (s, 2H), 4.19-4.09 (m, 14H), 3.86-3.80 (m, 8H), 3.70-3.40 (m, 120H), 3.30-3.20 (m, 21H).

Preparation of micellar solution of dendrons:

To an appropriate amount of dendron in a vial was added Milli Q water and the resultant mixture was stirred at 5 ^{o}C for 5 h to make the dendron soluble in water. The solution of dendrons was prepared well above the expected CACs of the dendrons.

Spectroscopic Measurements:

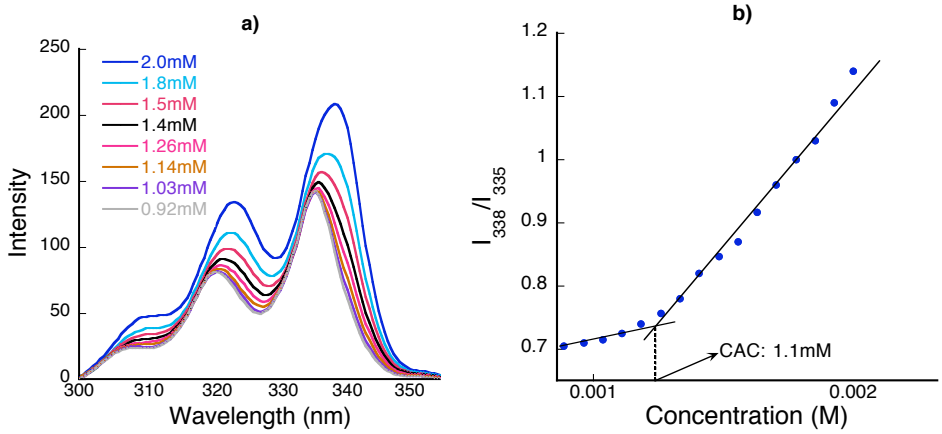
Emission and excitation spectra were recorded on a JASCO (FP-6500) fluorimeter using a 700 μL quartz cuvette. Excitation and emission bandwidth were kept at 3 and 1 nm respectively.

Determination of CACs of the dendrons (G0-G3):

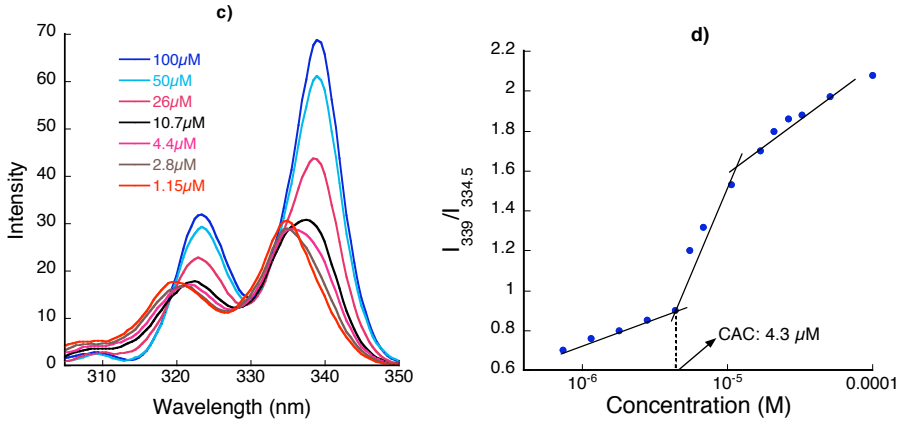
The CACs of the dendrons in aqueous solutions has been determined using the ratio of peak intensities at 339 and 335nm (I_{339}/I_{335}) from excitation spectra of pyrene.[1] For this purpose, 20 μL of pyrene solution (10^{-4} M) in acetone was taken in a vial and the acetone was evaporated by a mild blow of argon gas. To this vial, 2 mL solution of the dendron (concentration well above its anticipated CAC; the exact concentration of each dendron varies and can be found in the corresponding plot) was added and the solution was stirred for 5 h at 5 ^{o}C to encapsulate the pyrene. The solution was filtered through a syringe filter (0.22 μm) and transferred to a cuvette. The concentration of dendron in the cuvette was varied by replacing a measured volume of this solution with the same volume of 10^{-6} M pyrene solution in water. An excitation spectrum (λ_{em} = 374 nm) was recorded for each concentration of the dendron and an I_{339}/I_{335} value was obtained from each excitation spectrum. When the concentration of the dendron was low, the I_{339}/I_{335} value was the same as that of pyrene in water. When the concentration of the dendron increased,

the red shift from 335 to 339 nm in the pyrene excitation spectra indicated the movement of pyrene into a more hydrophobic environment. The I_{339}/I_{335} values were plotted against the concentration of dendron to get a sigmoidal curve. The inflection point of this curve was taken as the CAC. The CACs of **G0**, **G1**, **G2** and **G3** are given in Table S1.

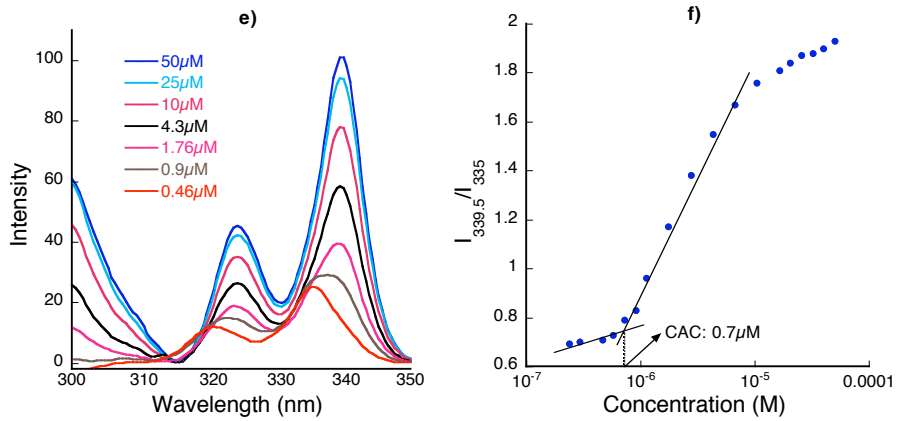
G0 dendron:



G1 dendron:



G2 dendron:



G3 dendron:

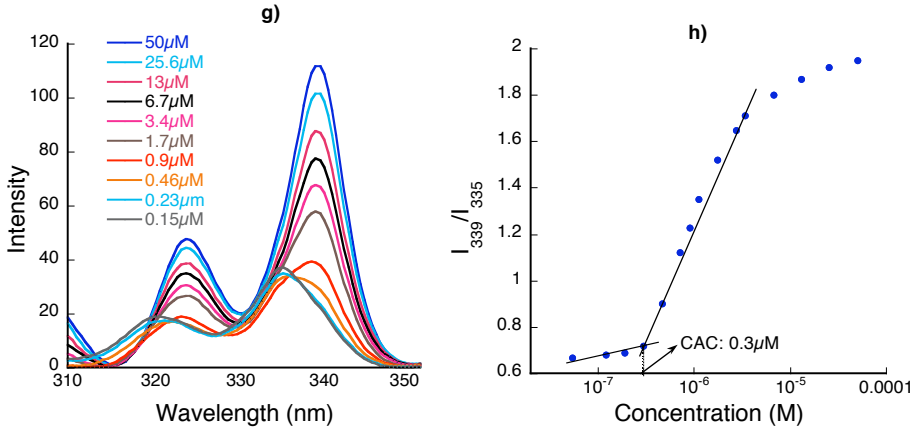


Figure S1: (Left) *Excitation spectra of pyrene in various concentration of dendrons: (a)* ***G0****, (c)* ***G1****, (e)* ***G2*** *and (g)* ***G3****.* ***(Right)*** *The corresponding CMC plots for (b)* ***G0****, (d)* ***G1****, (f)* ***G2*** *and (h)* ***G3****.*

Table S1: *CAC values of amphiphilic dendrons (****G0-G3****) in water.*

Generation	G0	G1	G2	G3
CAC (M)	1.1×10^{-3}	4.3×10^{-6}	0.7×10^{-6}	0.3×10^{-6}

DLS measurements to monitor the disassembly:

Dynamic light scattering (DLS) experiments were performed using a Malvern Zeta-sizer. The solution of dendron was diluted to the required concentration using HEPES buffer so that the concentration of HEPES was 50 mM in the resultant solution. For example, if 1 mL of 50 μM solution of dendron was needed for studies, 0.5 mL of 100 μM solution of dendron would be diluted with 0.5 mL of 100 mM HEPES buffer (pH 7.5). To a 1 mL solution of dendron in HEPES buffer was added 1 μL of PLE solution (Aldrich, 16.5 mg/mL in 3.2 M $(NH_4)_2SO_4$, pH 8.0, 177units/mg protein)[2] and mixed well. The DLS experiment was performed during each time intervals. The dendritic micellar disassembly was monitored by the change in size of aggregates over time. Prior to the DLS experiment, the dust in the dendrimer solution was removed by passing the dendrimer solution through a syringe filter (0.22 μm). The temperature

was maintained at 25 ^{o}C through out the experiment.

The number of ester functionalities in the solution was kept same for all the generations. Since **G1**, **G2** and **G3** dendrons contain 3, 7 and 15 ester functionalities respectively, for 25 µM concentration of **G1** dendron, the concentrations of **G2** and **G3** dendron were taken as 10 µM and 5 µM respectively. Note that the concentrations of all these dendrons were well above their CACs to make sure that their assemblies remained intact. Thus, in case of **G0**, the DLS studies were carried out at 2.0 mM, since the CAC of **G0** was 1.1 mM.

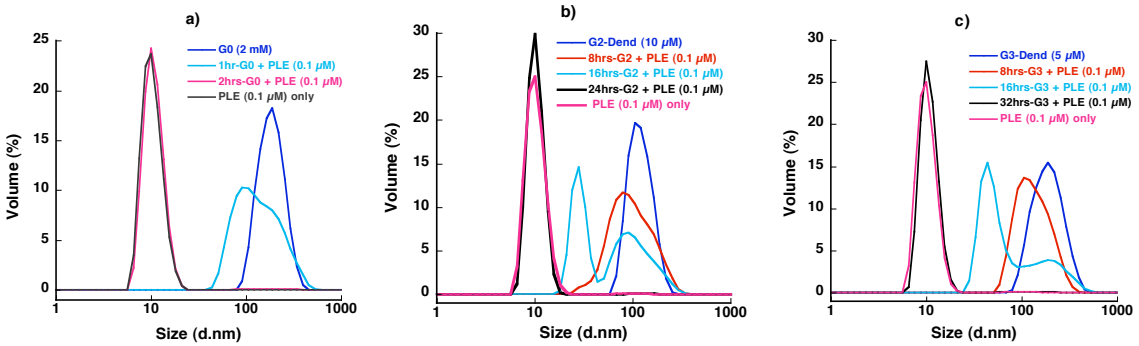


Figure S2: *DLS studies on disassembly of dendrimer aggregates: (a)* ***G0*** *(2 mM), (b)* ***G2*** *(10 µM) and (c)* ***G3*** *(5 µM).*

Encapsulation of a pyrene for dye release studies:

Excess amount of pyrene was first added to the micellar solution of dendron and the resulting mixture was stirred at 5 ^{o}C for 12 h to encapsulate the pyrene. The mixture was filtered through a syringe filter (0.22 µm) and diluted to the required concentration using HEPES buffer so that in the resultant solution the concentration of HEPES was 50 mM (For example if 1mL of 50 µM solution of dendron was required for studies, 0.5 mL of 100 µM solution of dendron would be diluted with 0.5 mL of 100 mM HEPES buffer at pH 7.5).

Dye release studies:

To the pyrene encapsulated 1 mL solution of dendron in HEPES buffer (50 mM, pH = 7.5) was added 1 µL of PLE solution (16.5 mg/mL in 3.2 M $(NH_4)_2SO_4$, pH 8.0, 177units/mg)[2] and mixed well. The emission spectrum of pyrene was recorded at every time interval. (λ_{ex} = 339 nm, the excitation and emission band width were 3 and 1 nm respectively and the scanning speed was 50 nm/min).[1c] The dye release was monitored by the decrease in the emission intensity of pyrene, while the temperature was maintained at 25^{o} C through out the experiment.

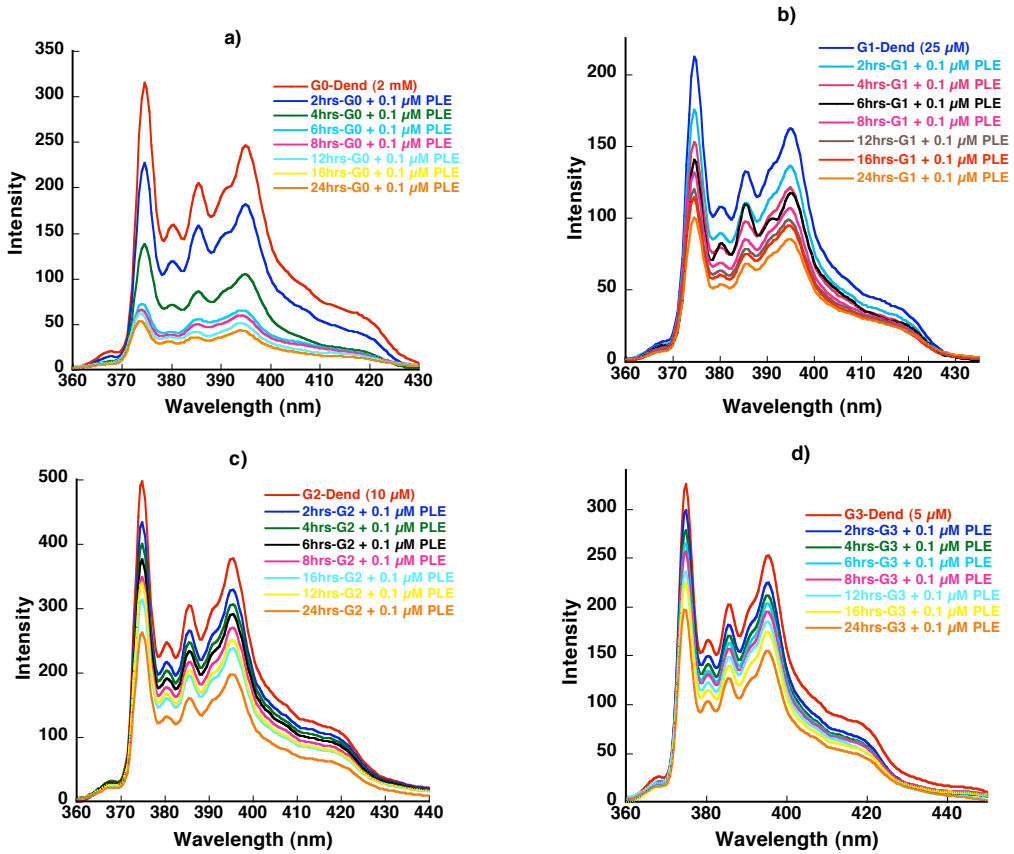


Figure S3: *Emission spectra of pyrene with time upon addition of 0.1 μM solution of PLE into the solution of (a)* ***G0*** *(2 mM), (b)* ***G1*** *(25 μM), (c)* ***G2*** *(10 μM) and (d)* ***G3*** *(5 μM)) dendrons.*

Control Experiment with G1-control:

To prove that the disassembly indeed happens due to the hydrolysis of ester functionalities, we performed control experiment where we utilized **G1-control** dendron that does not contain ester functionalities. The CAC of **G1-control** was found to be 4 μM in our previous report.[1d]

The DLS and fluorescence studies upon exposing to PLE are shown below.

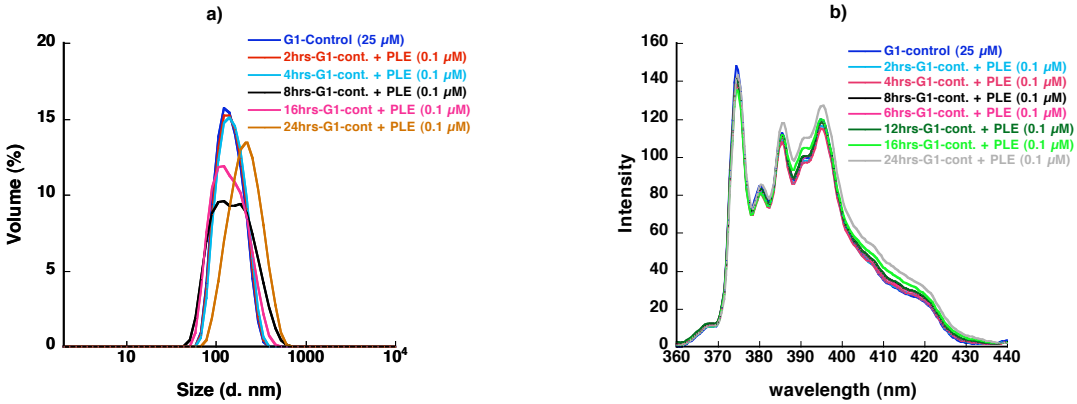


Figure S4: *Upon addition of 0.1μM solution of PLE into the solution of* ***G1-Control*** *(25 μM): (a) Size evolution analysis with respect to time using DLS. (b) Emission spectra of pyrene as a*

function of time.

Pyrene encapsulation into our dendrimer backbone:

To test whether our dendrimer backbone itself is capable of encapsulating pyrene, we have fully hydrolyzed the ester functionalities of **G2** dendron (Please see the procedure for hydrolysis in the synthetic section) and then allowed to encapsulate pyrene. The encapsulation data is shown below. This data shows that the residual amount of pyrene left in solution after enzymatic hydrolysis of the ester dendrons can be attributed to the ability of the carboxylic acid dendron itself to solvate a smaller amount of pyrene molecules.

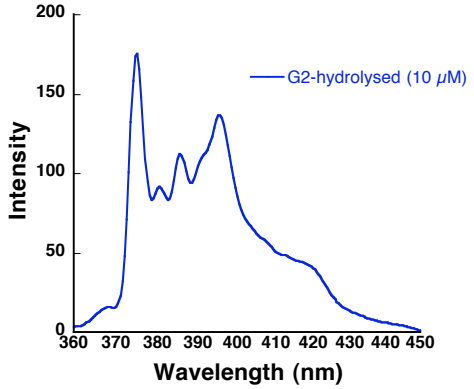
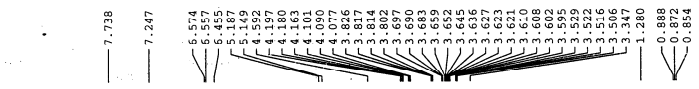


Figure S5: *Emission spectra of pyrene for solution G2-hydrolyzed dendron (10 μM).*

References:

1) (a) Lavasanifar, A.; Samuel, J.; Kwon, G. S. *Colloids Surf., B* **2001**, *22*, 115-126. (b) Wilhelm, M.; Zhao, C. L.; Wang, Y.; Xu, R.; Winnik, M. A.; Mura, J. L.; Riess, G.; Croucher, M. D. *Macromolecules* **1991**, *24*, 1033-1040. (c) Savariar, E, N.; Ghosh, S.; González, D, C.; S. Thayumanavan, S. *J. Am. Chem. Soc.* **2008**, *130*, 5416-5417. (d) Aathimanikandan, S. V.; Savariar, E. N.; Thayumanavan, S. *J. Am. Chem. Soc.* **2005**, *127*, 14922-14929.

2) Patel, K.; Angelos, S.; Dichtel, W, R.; Coskun, A.; Yang, Y,-W.; Zink, J, I.; Stoddart, J, F. *J. Am. Chem. Soc.*, **2008**, *130*, 2382-2383.



No title

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F2 - Processing parameters
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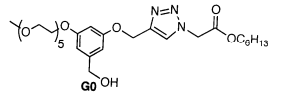
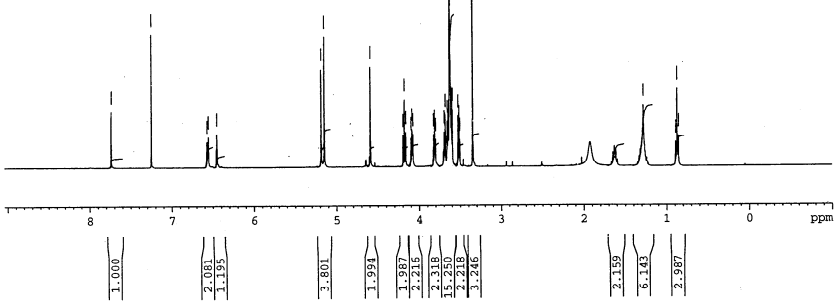
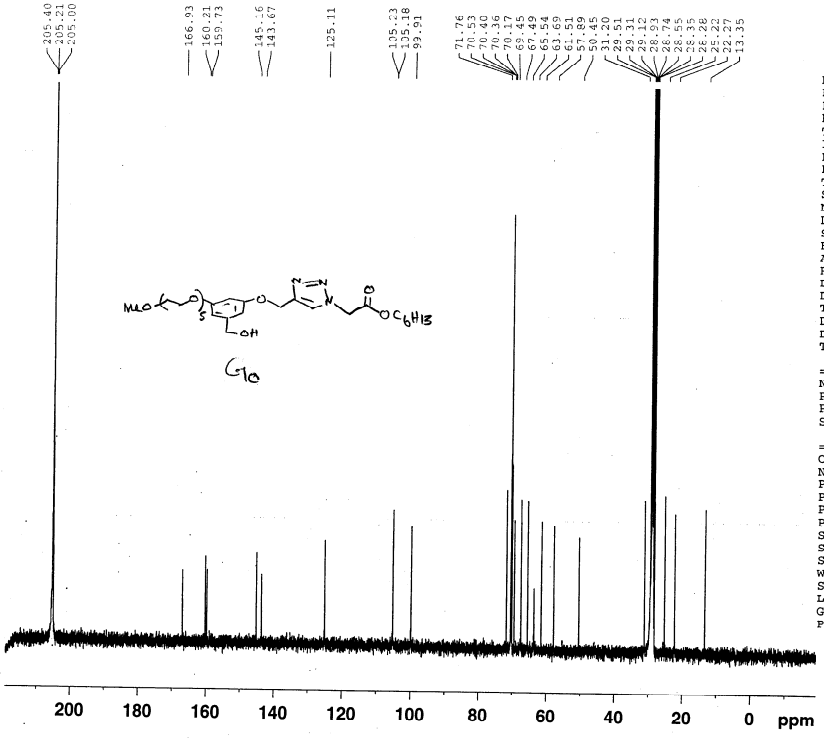
GB 0
PC 1.00





std 13c

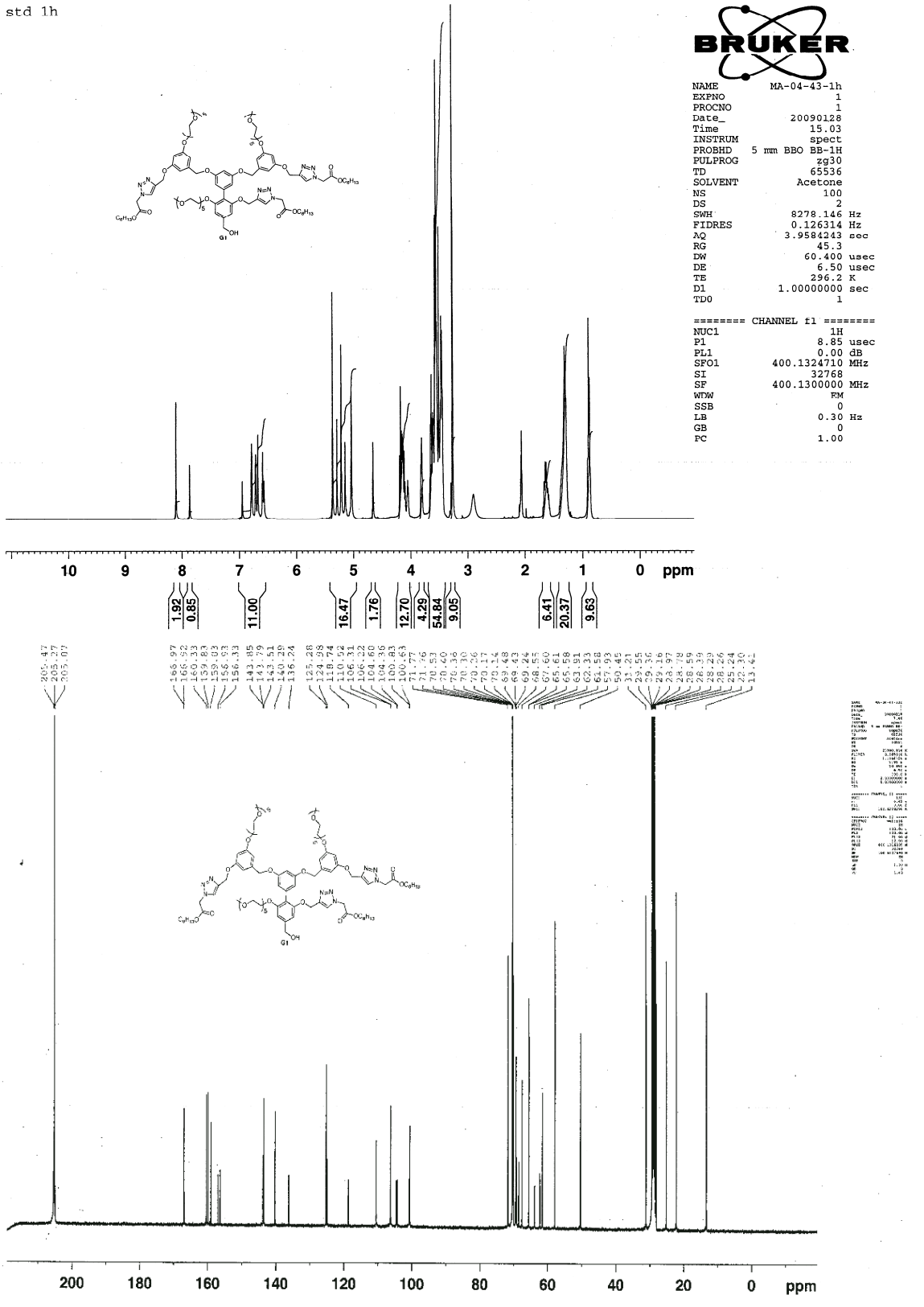


BRUKER

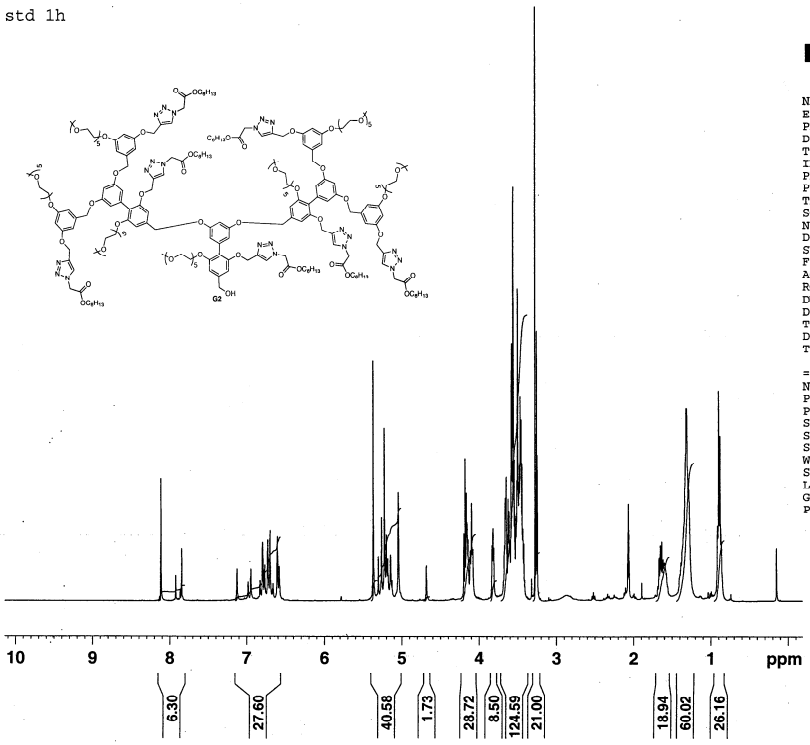
NAME MA-04-G0-CLICK-13c
EXPNO 1
PROCNO 1
Date_ 20090217
Time 21.27
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT Acetone
NS 2144
DS 4
SWH 23980.014 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 5792.6
DW 20.850 usec
DE 6.50 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 6.85 usec
PL1 0.00 dB
SFO1 100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 21.00 dB
PL13 12.00 dB
SFO2 400.1316005 MHz
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

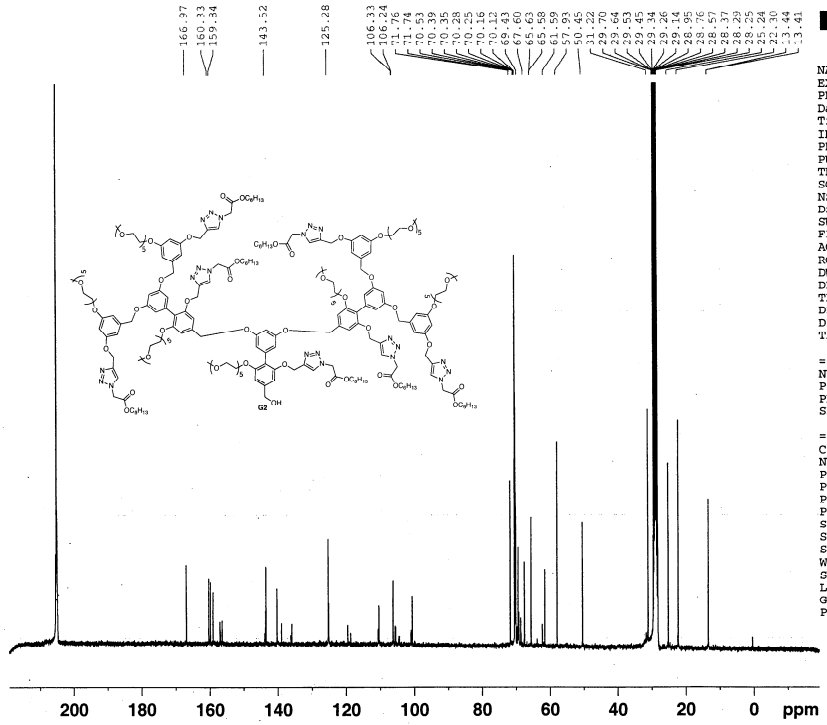

std 1h
BRUKER
NAME MA-04-43-1h
EXPNO 1
PROCNO 1
Date_ 20090128
Time 15.03
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT Acetone
NS 100
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 45.3
DW 60.400 usec
DE 6.50 usec
TE 296.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.85 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10 9 8 7 6 5 4 3 2 1 0 ppm
1.92 0.85 11.00 16.47 1.76 12.70 4.29 54.84 9.05 6.41 20.37 9.63
205.47 205.27 205.07
200 180 160 140 120 100 80 60 40 20 0 ppm

std 1h

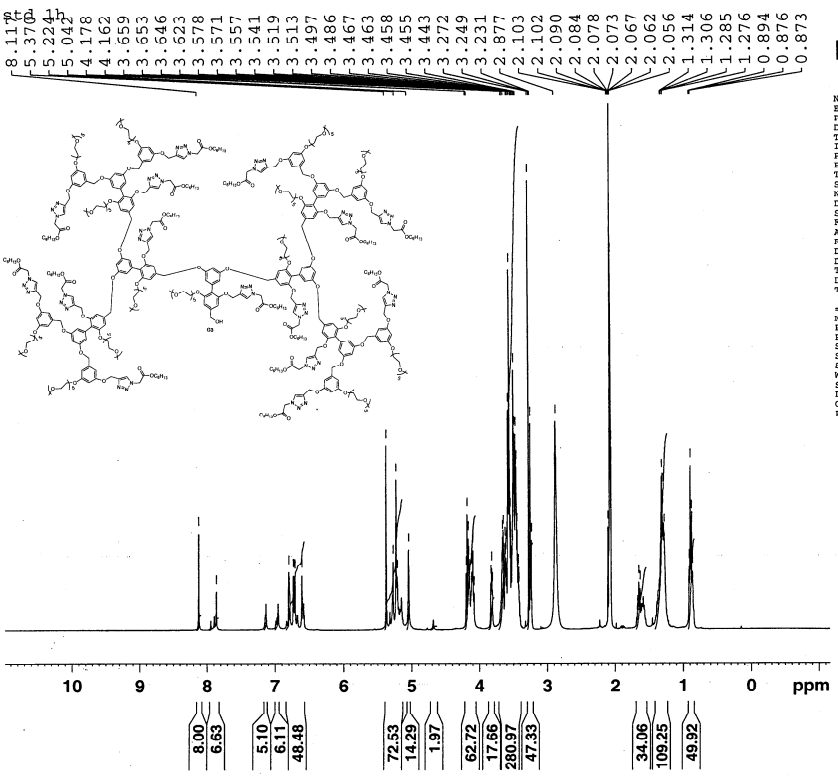


```
NAME            MA-04-46-1h
EXPNO                     1
PROCNO                    1
Date_              20090211
Time                 20.03
INSTRUM              spect
PROBHD    5 mm BBO BB-1H
PULPROG               zg30
TD                   65536
SOLVENT            Acetone
NS                       342
DS                         2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                        64
DW                   60.400 usec
DE                    6.50 usec
TE                   297.0 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     8.85 usec
PL1                    0.00 dB
SFO1          400.1324710 MHz
SI                     32768
SF            400.1300000 MHz
WDW                       EM
SSB                        0
LB                     0.30 Hz
GB                         0
PC                     1.00
```


std 13c

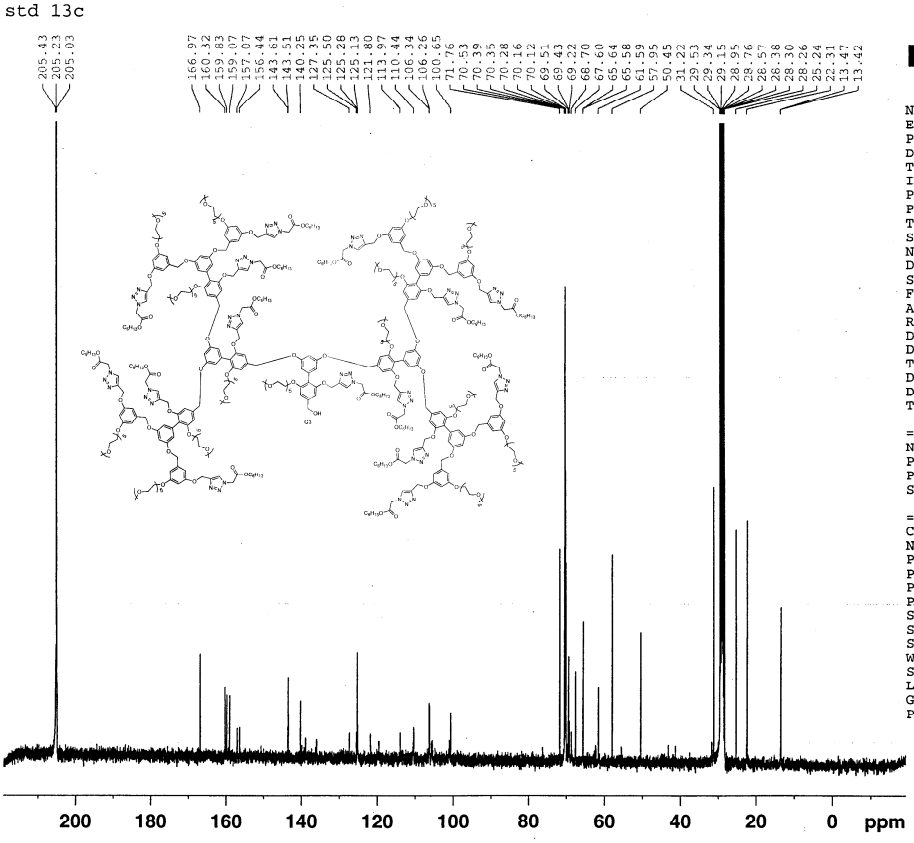



```
NAME            MA-04-46-13c
EXPNO                     1
PROCNO                    1
Date_              20090217
Time                 8.01
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT            Acetone
NS                     11719
DS                         4
SWH              23980.814 Hz
FIDRES            0.365918 Hz
AQ                1.3664756 sec
RG                   5792.6
DW                   20.850 usec
DE                    6.50 usec
TE                   299.0 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                     6.85 usec
PL1                    0.00 dB
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                100.00 usec
PL2                  120.00 dB
PL12                  21.00 dB
PL13                  12.00 dB
SFO2          400.1316005 MHz
SI                     32768
SF            100.6127690 MHz
WDW                       EM
SSB                        0
LB                     1.00 Hz
GB                         0
PC                     1.40
```



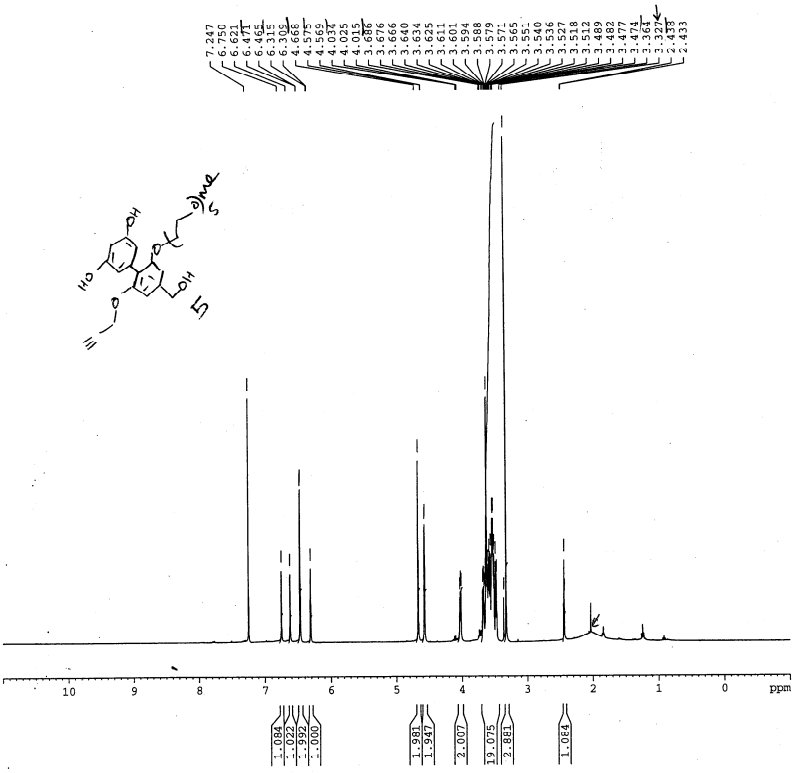
BRUKER

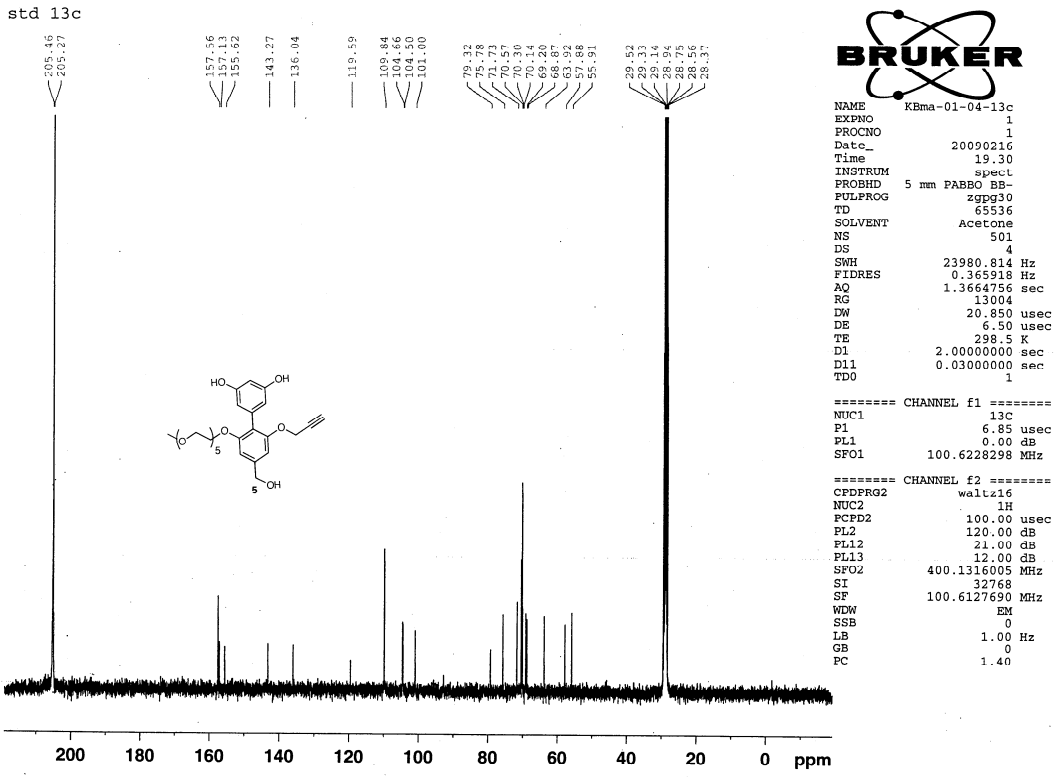
NAME	MA-04-G3 cleav-after click-1h
EXPNO	1
PROCNO	1
Date_	20090418
Time	14.34
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	762
DS	2
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	181
DW	60.400 usec
DE	6.50 usec
TE	296.0 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	8.85 usec
PL1	0.00 dB
SFO1	400.1324710 MHz
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



BRUKER

NAME	MA-04-53-13c
EXPNO	1
PROCNO	1
Date_	20090228
Time	21.41
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	Acetone
NS	1400
DS	4
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	6502
DW	20.850 usec
DE	6.50 usec
TE	298.8 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	6.85 usec
PL1	0.00 dB
SFO1	100.6228298 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	120.00 dB
PL12	21.00 dB
PL13	12.00 dB
SFO2	400.1316005 MHz
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40


No title
Current Data Parameters
NAME MA-03-152-1h
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080808
Time 16.15
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 256
DW 60.400 usec
DE 6.00 usec
TE 296.1 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300144 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


std 13c
NAME KBma-01-04-13c
EXPNO 1
PROCNO 1
Date_ 20090216
Time 19.30
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT Acetone
NS 501
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 13004
DW 20.850 usec
DE 6.50 usec
TE 298.5 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 6.85 usec
PL1 0.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 21.00 dB
PL13 12.00 dB
SFO2 400.1316005 MHz
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40