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Synthesis of large generation poly(propyl ether imine) (PETIM) dendrimers

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Abstract—Large generation poly(propyl ether imine) (PETIM) dendrimers are synthesized in iterative synthetic cycles of two reductions and two Michael addition reactions. Dendrimers up to sixth generation, containing up to 128 peripheral functionalities, are synthesized. Growth of the PETIM dendrimers, possessing a tertiary amine as the branch juncture and an ether as the linker component, is assessed systematically by routine spectroscopic methods. The peripheries of these dendrimers possess either alcohols, amines, carboxylic acids, esters, or nitriles, thereby opening up possibilities for varied studies involving PETIM dendrimers.

1. Introduction

The number of studies involving dendrimers has increased remarkably, ever since the dendrimers came to prominence in the chemical literature. The unique architectures, nanometric dimensions, ability to exercise *endo*- and *exo*-receptor properties, and monomolecular features have, in part, contributed to the general acceptance of dendrimers in many varied types of studies.[1] More often, monomers of the type AB_2, AB_3, and occasionally AB_4 and higher order are subjected to grow uniformly, leading, thereby, to a dendritic architecture.[2] Prominent among the dendrimers are the poly(amido amine),[3] poly(propylene imine),[4] poly(benzyl aryl ether),[5] polysilane,[6] polyphosphane,[7] polylysine,[8] and triallyl phenol based dendrimers.[9] Few of these dendrimers, namely, poly(amido amine), poly(propylene imine), polyphosphane, and triallyl phenol also represent the highest generation systems known in the literature. Synthesis of high generation dendrimers, useful for exploring the nature of the dendritic architecture, depends critically on the nature of the constituent monomers, their reactivities, and the method of their preparation. Larger generation dendrimers tend to provide a 'dendritic state', in which the peripheries become more dense than the corresponding lower generation dendrimers. A few common features of currently known large generation dendrimer synthesis are: (i) a divergent synthetic route for their preparation, (ii) the use of linear linkers, and (iii) avoiding protection/deprotection synthetic sequences. In a program aimed to develop dendrimers initiated with 3-amino-propan-1-ol as the monomer, a series of lower generation poly(propyl ether imine) (PETIM) dendrimers were reported previously.[10] A tertiary amine and an ether functionality form the branch juncture and the linker of the PETIM dendrimers, respectively. Iterative synthetic sequences of two alternate Michael additions and two reduction reactions were established to synthesize the PETIM dendrimers. Continuing efforts to produce larger generation dendrimers led to the isolation of PETIM dendrimers up to sixth generation, with 128 peripheral functionalities. Details of the synthesis of the larger generation PETIM dendrimers are presented herein.

2. Results and discussion

2.1. Synthesis

A tertiary amine branch juncture and an ether linker represent an AB_2 type monomer and, in PETIM dendrimers, 3-amino-propan-1-ol constitutes the required monomer. Synthesis of the PETIM dendrimers was initiated from a Michael addition reaction between acrylonitrile and water, to afford 2-cyanoethyl ether. Subsequent reduction of the nitrile groups, Michael addition with *tert*-butyl acrylate, reduction of the ester to an alcohol, and Michael addition of the resulting alcohol with acrylonitrile form an iterative cycle for the divergent synthesis of PETIM dendrimers. Three generations of PETIM dendrimers with up to 16 peripheral functionalities were synthesized previously,[10] thereby evolving the synthetic route to this new class of dendrimers. An advantage of the synthetic protocol is that it allows installation of varied functional groups, namely an acid, an alcohol, an amine, an ester, and a nitrile at the peripheries of the dendrimers. Synthesis of larger generation

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dendrimers was initiated from the third generation ester dendrimer (Fig. 1). Thus, reduction of dendrimer containing 16 *tert*-butyl esters with $LiAlH_4$, provided the third generation dendrimer **1** containing 16 alcohol group (Scheme 1). Complete removal of the inorganic salts was possible through solubilization of the crude product in MeOH, filtration, and evaporation of MeOH. Repetition of the process with MeOH, followed by $CHCl_3$, a few times led to the isolation of alcohol containing dendrimers with excellent purities and yields. Michael addition of the resulting alcohol **1** with excess acrylonitrile, in the presence of aq NaOH (cat.), provided the 16-nitrile containing dendrimer **2**, quantitatively. Excess acrylonitrile was transformed to an intractable polymer and 2-cyanoethyl ether, both of which could be separated through column chromatography (Al_2O_3 (neutral)). Reduction of nitrile **2** to amine **3** was conducted in the presence of Raney Co catalyst, under a moderately high pressure of H_2 (46 atm). The reduction reaction required control of temperature, pressure, and the solution concentrations. Thus, dilute solutions of the nitrile in MeOH (0.26 mM) at a temperature of 70 °C and at a pressure of 46 atm were found to be optimal for the reduction reaction. The progress of the reaction was followed upon analyzing the IR spectrum of an aliquot of the reaction mixture. The complete disappearance of nitrile stretching frequency at 2251 cm^{-1} was used to confirm the reduction reaction. Michael addition of 16 amine-terminated dendrimer **3** with *tert*-butyl acrylate in MeOH led to the isolation of fourth generation 32 ester-functionalized dendrimer **4**, in excellent yields. Solubility differences between the amine and the ester in hexane allowed facile separation of the ester from the amine component. The ester dendrimer, devoid of polar impurities was purified further by column chromatography (Al_2O_3 (neutral)). Iteration of the synthetic sequence of (i) reduction of ester **4** to alcohol **5**, (ii) reaction of alcohol **5** with acrylonitrile to afford nitrile **6**, (iii) reduction of nitrile **6** to amine **7**, and (iv) reaction of amine **7** with *tert*-butyl acrylate led to the preparation of fifth generation 64 ester-functionalized PETIM dendrimer **8**. Continuation of the iterative cycle, starting from ester **8** afforded alcohol **9**, nitrile **10**, amine **11**, and 128 ester-functionalized sixth generation dendrimer **12**. Molecular structures of the four, five, and six generation dendrimers are shown in Figures 1 and 2.

2.2. Characterization

Characterization of the newly formed dendrimers was possible through routine physical methods of analysis. As the synthetic sequence involved functional group changes at the peripheries of the dendrimers, following the IR spectral changes was useful to assess the presence or disappearance of the functional groups. Thus, spectral frequencies at 2251 cm^{-1} (–CN), 3460 cm^{-1} ($–NH_2$), 1729 cm^{-1} ($–CO_2{}^tBu$), and 3390 cm^{-1} (–OH) were diagnostic to estimate the presence or absence of the respective functional groups. The IR spectral changes for the conversion of the fifth generation ester **8** to the sixth generation ester **12** are compiled in Figure 3. Such a pattern of IR spectral changes could be observed for all other dendrimers, thereby IR spectroscopy became a diagnostic tool to assess the growth of dendrimers. Characterization of the newly formed dendrimers by ^1H and ^{13}C NMR spectroscopies further confirmed the constitution and the growth of dendrimers. The relative change in the chemical shifts of the $–CH_2–$ group adjacent to the peripheral functionality was observed to be a characteristic feature of each dendrimer growth reaction.

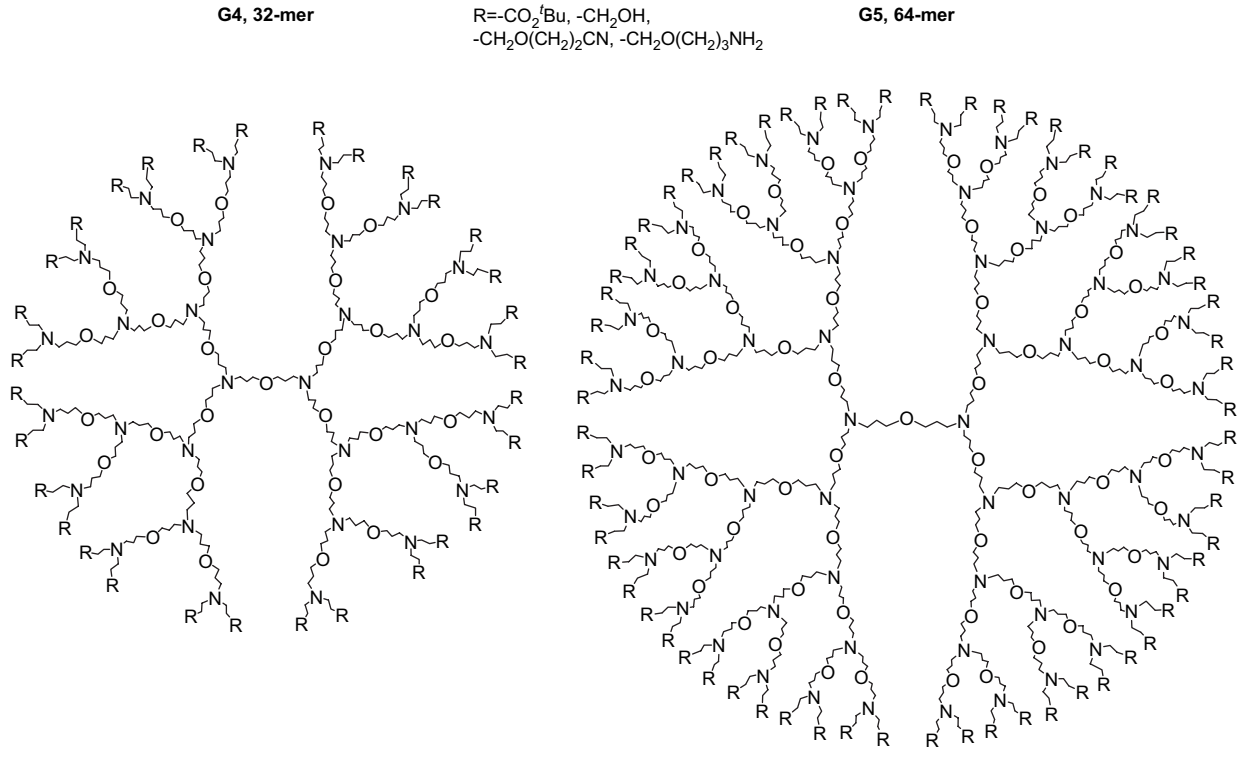
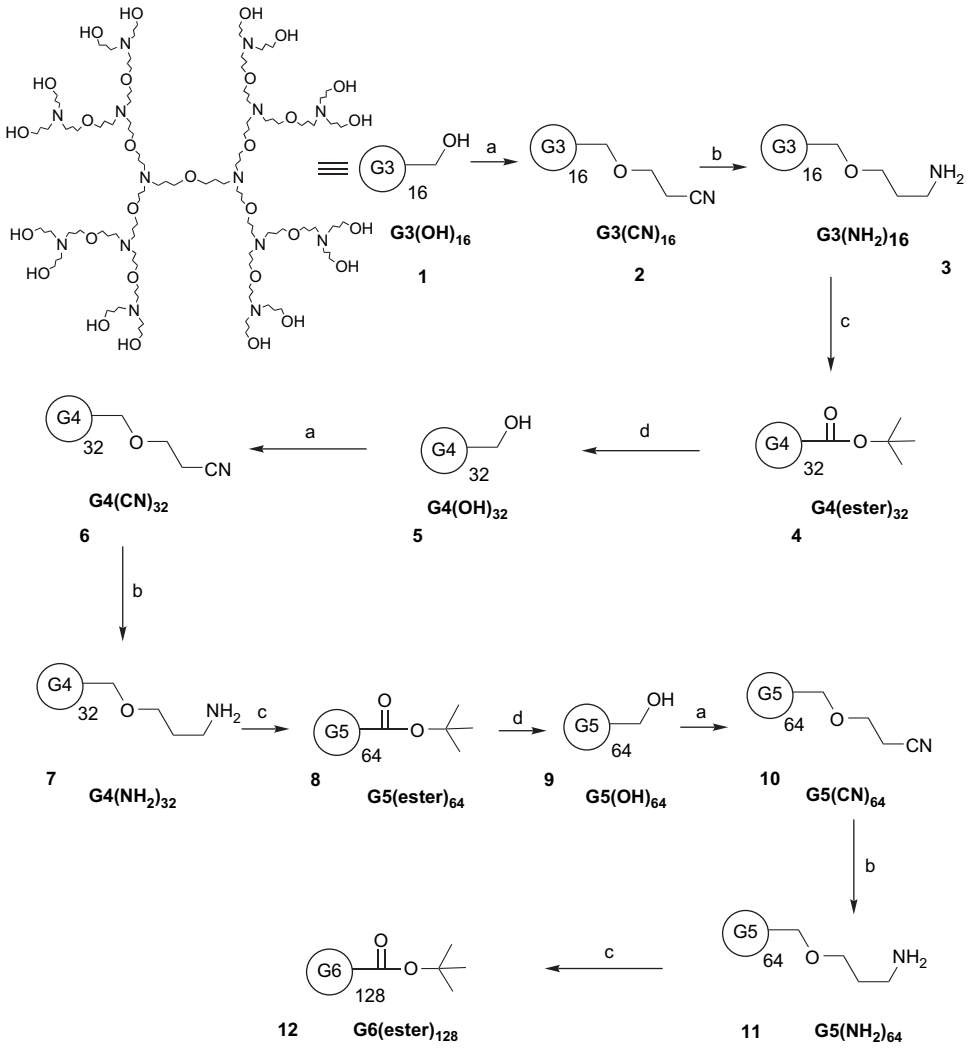


Figure 1. Molecular structures of the fourth and the fifth generation PETIM dendrimers.



Scheme 1. Reagents and conditions: (a) 40% aq NaOH (cat.), acrylonitrile, rt, 15 h; (b) Raney Co, H_2O, H_2 (46 bar), 3 h, 70 °C; (c) *tert*-butyl acrylate, MeOH, rt, 72 h; (d) $LiAlH_4$, THF, 0 °C to rt, 4 h.

Thus, disappearance of resonances at ~2.60 ppm and appearance of resonances at ~1.70 and ~2.50 ppm signified the reduction of peripheral nitrile functionality and formation of aminopropyl functionality, respectively. Ester-terminated dendrimers showed the $–CH_2–CH_2–CO_2{}^tBu$ protons at 3.40 and 2.34 ppm and, upon reduction of the esters with $LiAlH_4$, disappearance of the peak at 2.34 ppm and appearance of a resonance at ~3.70 ppm, corresponding to the formation of $–CH_2–CH_2OH$ peripheral functionalities, were observed. Finally, Michael addition of the alcohol-functionalized dendrimers with acrylonitrile provided a spectrum showing disappearance of the peak at ~3.70 ppm and appearance of a set of triplet peaks at ~3.55 and 3.65 ppm. The relative intensity changes of the respective resonances confirmed the constitution of the dendrimers. The series of ^1H NMR spectra, corresponding to the growth of G5-(ester)$_{64}$ (**8**) to the G6-(ester)$_{128}$ (**12**), are presented in Figure 4.

Changes at the peripheries of the dendrimers as a result of advancing the generations could be confirmed by ^{13}C NMR spectroscopy. Complete disappearance of –CN resonance in the ^{13}C NMR spectrum at ~117.9 ppm and the appearance of carbonyl group resonance of the ester functionality at ~172 ppm provided the completion of nitrile reduction to amine followed by Michael addition with *tert*-butyl acrylate. Similarly reduction of the ester to the alcohol (CH_2OH ~62 ppm) and the Michael addition of alcohol to the nitrile could be ascertained by appropriate changes in the ^{13}C NMR resonances.

Characterization of the dendrimers by gel permeation chromatography (GPC), MALDI-TOF mass spectrometry, and elemental analysis was also performed. GPC was performed on a Phenogel (1000 Å) semipreparative column (300× 7.80 mm), and eluted with THF (flow rate: 1 mL/min), using a refractive index detector. The GPC chromatograms of each *tert*-butyl ester terminated poly(propyl ether imine) dendrimers exhibited decreasing retention time from first generation dendrimer to the sixth generation poly(propyl ether imine) dendrimers (Fig. 5).

MALDI-TOF mass spectra up to four generations could be secured (Table 1). The observed mass spectrometric peaks corresponded to the $[M]^+$ or $[M+1]^+$ molecular ion largely. The mass spectrum of fifth and sixth generation dendrimers could not be secured, however. Elemental composition

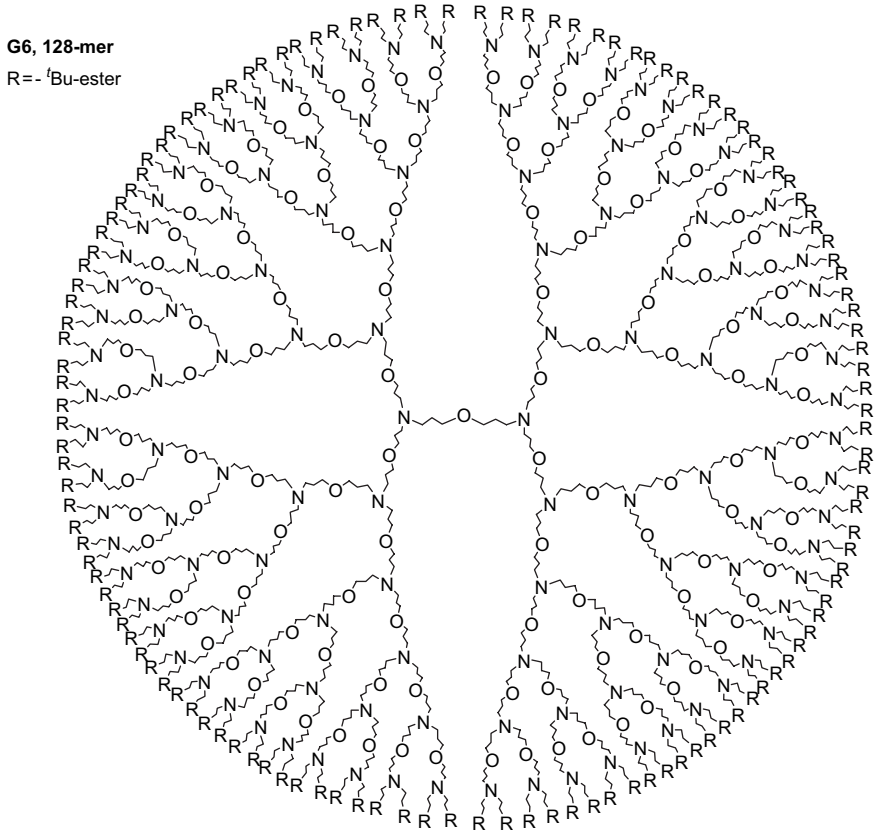


Figure 2. Molecular structure of the sixth generation of ester-functionalized PETIM dendrimer.

analyses were performed mostly with the ester-functionalized dendrimers. The alcohol and the amine-terminated dendrimers were hygroscopic and their elemental analysis could not be routinely secured.

3. Conclusion

Following the earlier synthesis of PETIM dendrimers up to three generations, the present report establishes the synthesis of PETIM dendrimers up to the sixth generation, presenting 128 peripheral functionalities at their peripheries. Facile synthesis, with high yields in each synthetic step, and easy characterization made these PETIM dendrimers attractive for further studies. Accordingly, studies of the *endo*- and *exo*-receptor properties of the PETIM dendrimers are currently being undertaken.

4. Experimental

4.1. General methods

Chemicals were purchased from commercial sources and were used without further purification. Solvents were dried and distilled according to literature procedures. Analytical TLC was performed on commercial Merck plates coated with alumina GF_{254} (0.25 mm). Neutral alumina was used for column chromatography. Microanalyses were performed on an automated C, H, and N analyzer. ^{1}H and ^{13}C NMR spectral analyses were performed on a 300 and 75.5 MHz spectrometer, respectively, with residual solvent signal acting as the internal standard. The following abbreviations are used to explain the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet.

4.2. General procedure for Michael addition of acrylonitrile

Acrylonitrile and aq NaOH (40%) were added to the alcohol-functionalized dendrimer at room temperature and the mixture was allowed to stir for 15 h. Excess acrylonitrile was added further and the reaction mixture left to stir for another 6 h, then diluted with $CHCl_3$, filtered through Celite, and the filtrate concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (neutral Al_2O_3), to afford the desired compound.

4.3. General procedure for the reduction of nitrile-functionalized PETIM dendrimer using Raney Co and subsequent Michael addition of the resulting amines

The nitrile-functionalized PETIM dendrimer was transferred to a hydrogenation reactor vessel and was mixed with Raney Co in H_2O. The mixture was hydrogenated (H_2, 46 atm) at 70 °C for 3 h. The reaction mixture was cooled and filtered through a Celite pad. The filtrate was concentrated to afford the corresponding amine-functionalized dendrimer. A solution of the crude amine in MeOH was treated with excess *tert*-butyl acrylate and stirred for 72 h at room temperature. Excess *tert*-butyl acrylate and MeOH were removed under reduced pressure and the crude

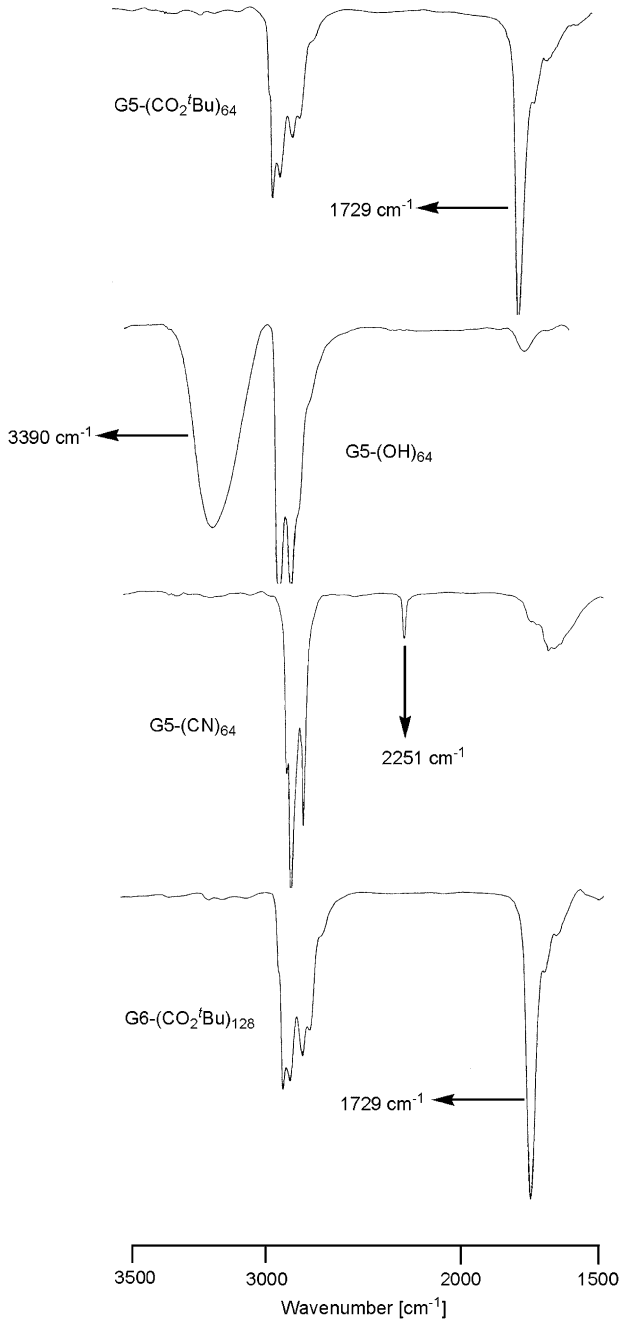


Figure 3. IR spectral comparison of the conversion of fifth generation ester **8** to sixth generation ester **12**.

product was purified by column chromatography (neutral Al_2O_3).

4.4. General procedure for reduction of *tert*-butyl esters

A solution of the ester-functionalized dendrimer in THF was added drop-wise to a suspension of $LiAlH_4$ (2.0 equiv per one ester group) in THF over a period of 15 min, at 0 °C, and the stirring was continued for 4 h at room temperature. The reaction mixture was cooled to 0 °C, quenched with excess ice, passed through Celite, and the filtrate concentrated under reduced pressure. The inorganic material was precipitated using MeOH, filtered, and the filtrate concentrated. The alcohol-functionalized PETIM dendrimer was obtained upon extraction of the crude material with $CHCl_3$ and removal of the solvents.

4.4.1. G3-$(CN)_{16}$ (2). A mixture of **1** (0.73 g), acrylonitrile (0.63 mL), and aq NaOH (40%, 53 μL) was stirred for 15 h. Acrylonitrile (1 mL) was added, the reaction mixture stirred for 6 h and worked up as described in Section 4.2 to obtain **2**, as a colorless liquid (0.93 g, 94%). TLC (Al_2O_3): R_f 0.45 ($CHCl_3$/MeOH=94:6). FTIR (neat) ν: 2250, 1466, 1367, 1116. MALDI-TOF *m/z*: 3292.36 $[M]^+$ (100%), 3066.23 (30%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.68 (m, 84H), 2.46 (m, 84H), 2.59 (t, 32H, J=6.3 Hz), 3.40 (t, 52H, J=6.0 Hz), 3.51 (t, 32H, J=6.0 Hz), 3.63 (t, 32H, J=6.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 18.8, 27.3, 27.4, 50.5, 50.8, 65.3, 69.1, 69.2, 69.3, 69.4, 117.9. Anal. Calcd for $C_{174}H_{316}N_{30}O_{29}$: C, 63.47; H, 9.68; N, 12.76. Found: C, 63.33; H, 9.69; N, 12.59.

4.4.2. G4-$(CO_2{}^tBu)_{32}$ (4). The nitrile derivative **2** (0.20 g) was added with Raney Co (0.80 g) in water (150 mL) and the reaction was continued further as given in Section 4.3 to afford amine **3** derivative. A solution of amine in MeOH (5 mL) was treated with *tert*-butyl acrylate (3 mL) and the reaction was followed as given in Section 4.2 to afford ester **4**, as a colorless liquid (0.42 g, 93% combined yield for nitrile reduction and Michael addition reaction). TLC (Al_2O_3): R_f 0.52 ($CHCl_3$/MeOH=97:3). FTIR (neat) ν: 1730, 1462, 1367, 1157. MALDI-TOF *m/z*: 7465.46 $[M+Li]^+$ (99%), 7408.09 (100%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.44 (s, 288H), 1.68 (q, 116H, J=6.9 Hz), 2.34 (t, 64H, J=7.2 Hz), 2.47 (t, 116H, J=6.9 Hz), 2.72 (t, 64H, J=7.5 Hz), 3.39 (t, 116H, J=6.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 27.4, 27.7, 28.1, 33.8, 47.4, 50.5, 50.8, 68.9, 69.2, 69.3, 80.1, 172.0. Anal. Calcd for $C_{398}H_{764}N_{30}O_{93}$: C, 64.02; H, 10.25; N, 5.63. Found: C, 64.12; H, 9.92; N, 5.69.

4.4.3. G4-$(OH)_{32}$ (5). To a suspension of $LiAlH_4$ (0.20 g) in THF (5 mL), **4** (0.60 g) in THF (20 mL) was added drop-wise, at 0 °C, the reaction continued further as described in Section 4.4 to obtain **5**, as a colorless liquid (0.41 g, 98%). FTIR (neat) ν: 3388, 1658, 1469, 1370, 1114, 1059. MALDI-TOF *m/z*: 5217.12 $[M+H]^+$ (100%), 5158.88 (78%), 5100.23 (30%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.71 (m, 180H), 2.50 (m, 116H), 2.60 (t, 64H, J=6.6 Hz), 3.41 (m, 116H), 3.70 (t, 64H, J=5.7 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 26.9, 27.2, 28.7, 28.77, 50.7, 50.8, 50.9, 52.7, 62.3, 68.8, 69.1, 69.2.

4.4.4. G4-$(CN)_{32}$ (6). A mixture of **5** (0.40 g), acrylonitrile (0.32 mL), and aq NaOH (40%, 27 μL) was stirred for 15 h. Acrylonitrile (0.80 mL) was added further, left to stir for 6 h, and worked up as described in Section 4.2 to obtain **6**, as a colorless liquid (0.49 g, 93%). TLC (Al_2O_3): R_f 0.60 ($CHCl_3$/MeOH=92:8). FTIR (neat) ν: 2251, 1467, 1367, 1117. MALDI-TOF *m/z*: 6913.23 $[M]^+$ (18%), 6460.28 (100%), 6686.85 (45%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.69 (m, 180H), 2.48 (m, 180H), 2.60 (t, 64H, J=6.0 Hz), 3.41 (t, 116H, J=6 Hz), 3.52 (t, 64H, J=6.3 Hz), 3.63 (t, 64H, J=6.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 18.9, 27.3, 27.4, 50.5, 50.8, 65.3, 69.1, 69.20, 69.24, 69.4, 118.0.

4.4.5. G5-$(CO_2{}^tBu)_{64}$ (8). The nitrile derivative **6** (0.21 g) was added with Raney Co (0.6 g) in water (150 mL) and

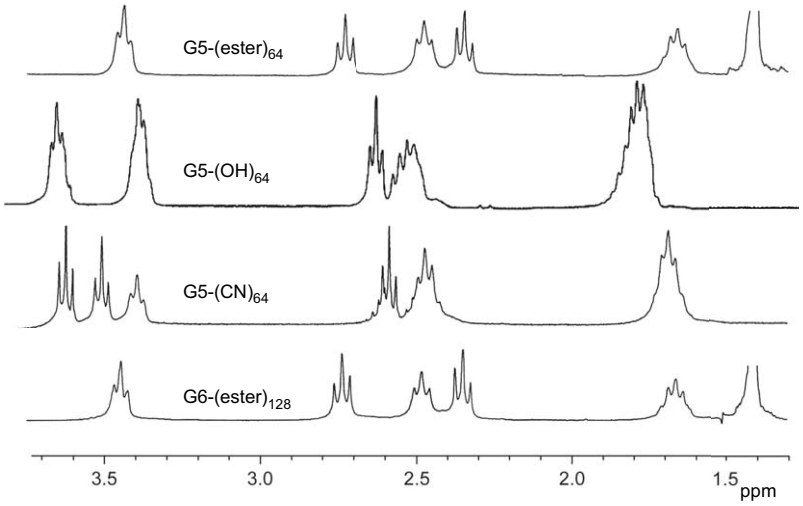


Figure 4. ^{1}H NMR spectral changes during the conversion of the fifth generation ester **8** to the sixth generation ester **12**.

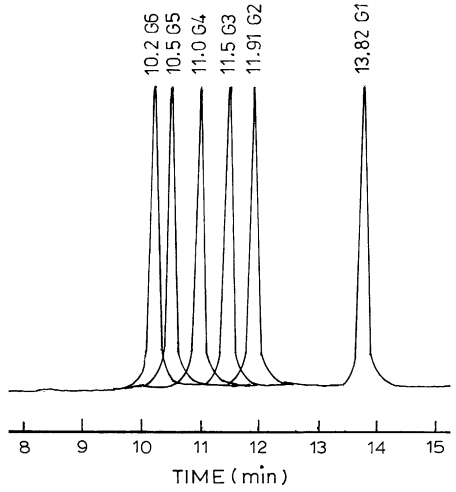


Figure 5. Gel permeation chromatography traces of *tert*-butyl ester group functionalized PETIM dendrimers.

Table 1. Physical characteristics of PETIM dendrimers

Compound[a]	Molecular formula	Molecular mass[b]	R_g (Å)[11]
G1-($CO_2{}^tBu$)$_4$	$C_{34}H_{64}O_9N_2$	644.88 (645.47)	5.65
G1-(OH)$_4$	$C_{18}H_{40}O_5N_2$	364.52 (365.30)	
G1-(CN)$_4$	$C_{30}H_{52}O_5N_6$	576.77 (577.41)	
G1-(NH_2)$_4$	$C_{30}H_{68}O_5N_6$	592.90 (594.40)	
G2-($CO_2{}^tBu$)$_8$	$C_{86}H_{164}O_{21}N_6$	1618.25 (1618.40)	8.90
G2-(OH)$_8$	$C_{54}H_{116}O_{13}N_6$	1057.53 (1087)	
G2-(CN)$_8$	$C_{78}H_{140}O_{13}N_{14}$	1482.032 (1482)	
G2-(NH_2)$_8$	$C_{78}H_{172}O_{13}N_{14}$	1514.29	
G3-($CO_2{}^tBu$)$_{16}$	$C_{190}H_{364}O_{45}N_{14}$	3564.99 (3563.80)	14.14
G3-(OH)$_{16}$	$C_{126}H_{268}O_{29}N_{14}$	2443.55 (2442.73)	
G3-(CN)$_{16}$	$C_{174}H_{316}O_{29}N_{30}$	3292.55 (3292.37)	
G3-(NH_2)$_{16}$	$C_{174}H_{380}O_{29}N_{30}$	3357.06	
G4-($CO_2{}^tBu$)$_{32}$	$C_{398}H_{764}O_{93}N_{30}$	7458.47 (7465.46)	17.73
G4-(OH)$_{32}$	$C_{270}H_{572}O_{61}N_{30}$	5215.60 (5217.14)	
G4-(CN)$_{32}$	$C_{366}H_{668}O_{61}N_{62}$	6913.60 (6913.23)	
G4-(NH_2)$_{32}$	$C_{366}H_{796}O_{61}N_{62}$	7042.62	
G5-($CO_2{}^tBu$)$_{64}$	$C_{814}H_{1564}O_{189}N_{62}$	15245.43	21.13
G5-(OH)$_{64}$	$C_{558}H_{1180}O_{125}N_{62}$	10759.68	
G5-(CN)$_{64}$	$C_{750}H_{1372}O_{125}N_{126}$	14155.70	
G5-(NH_2)$_{64}$	$C_{750}H_{1628}O_{125}N_{126}$	14413.72	
G6-($CO_2{}^tBu$)$_{128}$	$C_{1646}H_{3164}O_{381}N_{126}$	30819.35	26.63

[a] Codes for various dendrimers.
[b] Molecular mass obtained from mass spectrometric analysis is given in parenthesis.

the reaction was continued further as given in Section 4.2 to afford amine **7** derivative. A solution of amine **7** in MeOH (3 mL) was treated with *tert*-butyl acrylate (2.84 mL) and the reaction was followed as given in Section 4.3 to afford **8**, as a colorless liquid (0.36 g, 78% combined yield for nitrile reduction and Michael addition reaction). TLC (Al_2O_3): R_f 0.66 ($CHCl_3$/MeOH=95:5). FTIR (neat) ν: 1729, 1462, 1367, 1157. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.44 (s, 576H), 1.69 (q, 244H, J=6.3 Hz), 2.34 (t, 128H, J=6.9 Hz), 2.47 (t, 244H, J=6.9 Hz), 2.71 (t, 128H, J=6.9 Hz), 3.39 (t, 244H, J=6.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 27.5, 27.7, 28.1, 33.8, 49.4, 50.6, 50.9, 69.0, 69.3, 80.2, 172.1. Anal. Calcd for $C_{398}H_{764}N_{30}O_{93}$: C, 64.09; H, 10.33; N, 5.71. Found: C, 63.89; H, 9.92; N, 5.45.

4.4.6. G5-(OH)$_{64}$ (9). To a suspension of $LiAlH_4$ (0.13 g) in THF (5 mL), **8** (0.4 g) in THF (15 mL) was added drop-wise, at 0 °C, the reaction continued further as described in the Section 4.4 to obtain **9** quantitatively, as a colorless liquid. FTIR (neat) ν: 3384, 1656, 1464, 1371, 1113, 1058. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.72 (m, 372H), 2.51 (m, 244H), 2.60 (t, 128H, J=6.6 Hz), 3.41 (m, 244H), 3.70 (t, 128H, J=5.7 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 26.9, 27.2, 28.7, 29.8, 50.7, 50.8, 50.9, 52.8, 62.3, 62.6, 68.8, 69.1, 69.2.

4.4.7. G5-(CN)$_{64}$ (10). A mixture of **9** (0.55 g), acrylonitrile (0.43 mL), and aq NaOH (40%, 72 μL) was stirred for 15 h. Acrylonitrile (0.43 mL) was added further, left to stir for 6 h, and worked up as described in Section 4.2 to obtain **10**, as a colorless liquid (0.66 g, 91%). TLC (Al_2O_3): R_f 0.46 ($CHCl_3$/MeOH=92:8). FTIR (neat) ν: 2251, 1464, 1377, 1115. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.71 (m, 372H), 2.48 (m, 372H), 2.60 (t, 128H, J=6.0 Hz), 3.41 (t, 244H, J=6 Hz), 3.52 (t, 128H, J=6.3 Hz), 3.64 (t, 128H, J=6.3 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 18.9, 27.3, 27.4, 50.5, 50.8, 65.3, 69.1, 69.2, 69.3, 69.4, 118.0.

4.4.8. G6-($CO_2{}^tBu$)$_{128}$ (12). The nitrile derivative **10** (0.10 g) was added with Raney Co (0.5 g) in water (120 mL) and the reaction was continued further as given in Section 4.3 to afford amine **11** derivative. A solution of amine **11** in MeOH (2 mL) was treated with excess *tert*-butyl

acrylate (1.32 mL) and the reaction was followed as given in Section 4.3 to afford **12**, as a colorless liquid (0.16 g, 73% combined yield for nitrile reduction and Michael addition reaction). TLC (Al_2O_3): R_f 0.6 ($CHCl_3$/MeOH=93:7). FTIR (neat) ν: 1729, 1458, 1367, 1157. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.44 (s, 1152H), 1.69 (q, 500H, J=6.9 Hz), 2.34 (t, 256H, J=7.2 Hz), 2.47 (t, 500H, J=7.2 Hz), 2.71 (t, 256H, J=7.2 Hz), 3.39 (t, 500H, J=6.9 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 27.3, 27.6, 28.1, 33.7, 49.4, 50.5, 50.8, 68.9, 69.2, 69.3, 80.1, 172.1.

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References and notes

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