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Accelerated Growth of Dendrimers via Thiol−Ene and Esterification Reactions

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ABSTRACT: By taking advantage of the orthogonal nature of thiol−ene coupling and anhydride based esterification reactions, a facile and chemoselective strategy to dendritic macromolecules has been developed. The ability to interchange growth steps based on thiol−ene and anhydride chemistry allows the synthesis of fifth-generation dendrimers in only five steps and under benign reaction conditions. In addition, the presented coupling chemistries eliminate the traditional need for protection/deprotection steps and afford dendrimers in high yield and purity. The modularity of this strategy coupled with the latent reactivity of the alkene/hydroxyl chain ends was demonstrated by using different cores (alkene and hydroxyl functional), various AB_2 and CD_2 monomers and a range of chain end groups. As a result, three dendritic libraries were prepared which exhibited tunability of both the chemical functionality and physical properties including the fabrication of PEG hydrogels.

Introduction

The development of robust and efficient strategies for the synthesis of macromolecules with well-defined architecture and chemical functionality is a continuing theme in polymer chemistry.[1−3] Recent success in the identification of orthogonal reaction pairs has facilitated the large scale synthesis and subsequent introduction of dendrimers to numerous applications.[4,5] No longer an academic curiosity, the increased availability of dendrimers has allowed their unique physical properties; globular structure, tunable periphery,[6,7] and interior[8] to be exploited in drug delivery and microelectronic applications.[4,9] In turn, this has spurred a need for greater structural versatility and overall synthetic ease in the construction of dendritic libraries.[10−16]

Traditional strategies for dendrimer construction has relied on amidation, etherification, esterification and Michael reactions resulting in dendritic macromolecules based upon aryl ethers,[3] poly(amido amine) (PAMAM),[17] propyleneimines,[18] triazoles,[19] and 2,2-bis(hydroxylmethyl)propionic acid (bis-MPA) repeat units.[20] These systems display interesting physical properties that are derived from both their unique macromolecular architecture as well as their chemical composition, for example thermal stability (aryl ethers) and biodegradability (bis-MPA polyesters). Dendrimers based on bis-MPA have been widely studied since their introduction by Hult et al in 1996,[20] due to their biocompatibility and pH-induced degradation. Initially, the bis-MPA dendrimers were synthesized by a convergent growth approach leading to high purity materials. However, the procedure requires 10 steps for a fourth generation material and involves a series of tedious purification steps. To address this challenge, Fréchet and co-workers presented an effective divergent approach to prepare bis-MPA dendrimers through the esterification of an alcohol and an anhydride under mild conditions, for which facile purification techniques were applied.[21] While a modified version[22] of this procedure allowed the synthesis of the bis-MPA dendrimers through mild acidic conditions, it still involves multiple reaction steps and purification protocols.

On the basis of the philosophy of click chemistry[23−26] and the demonstrated ability to prepare dendrimers through the copper-catalyzed azide−alkyne cycloaddition (CuAAC) reaction,[19,27,28] thiol−ene coupling has been successfully employed to synthesize dendrimers divergently.[7] In demonstrating the applicability of click chemistry to accelerate dendrimer strategies, aryl ether-based and bis-MPA-based dendrimers have been prepared by alternate coupling of AB_2 and CD_2 monomers via CuAAC and etherification/esterification reactions, increasing the dendrimer generation at each iterative step.[10] While a valuable demonstration, for biomaterial applications the use of copper is a major drawback for biological systems. Given that the metal-free thiol−ene coupling reaction has been shown to be a powerful synthetic tool, especially for the preparation of functional biomaterials,[29−31] herein we describe an accelerated growth strategy for the synthesis of a series of bis-MPA based dendrimers using a library of interchangeable modular AB_2/CD_2 monomers (Scheme 1). This allows the divergent synthesis of fifth generation dendrimers in only 5 steps with minor purification protocols, greatly decreasing the synthetic efforts toward multifunctional dendritic macromolecules (Scheme 2).

Experimental Section

Materials. All materials were obtained from Sigma-Aldrich, unless otherwise noted. Bis-MPA was kindly donated by Perstorp AB. F-moc protected cysteine was purchased from Iris Biotech GmbH. Flash chromatography was performed using Acros silica gel pore size 60 Å, 40−60 μm.

Instrumental. NMR experiments were performed on a Bruker Avance 400 MHz NMR instrument. The MALDI−TOF MS analyses were conducted on a Bruker UltraFlex MALDI−TOF

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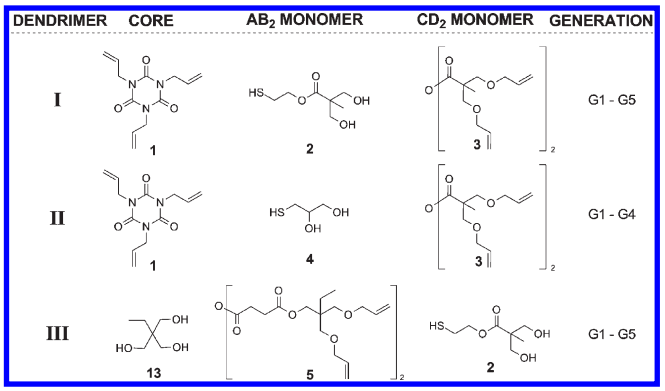
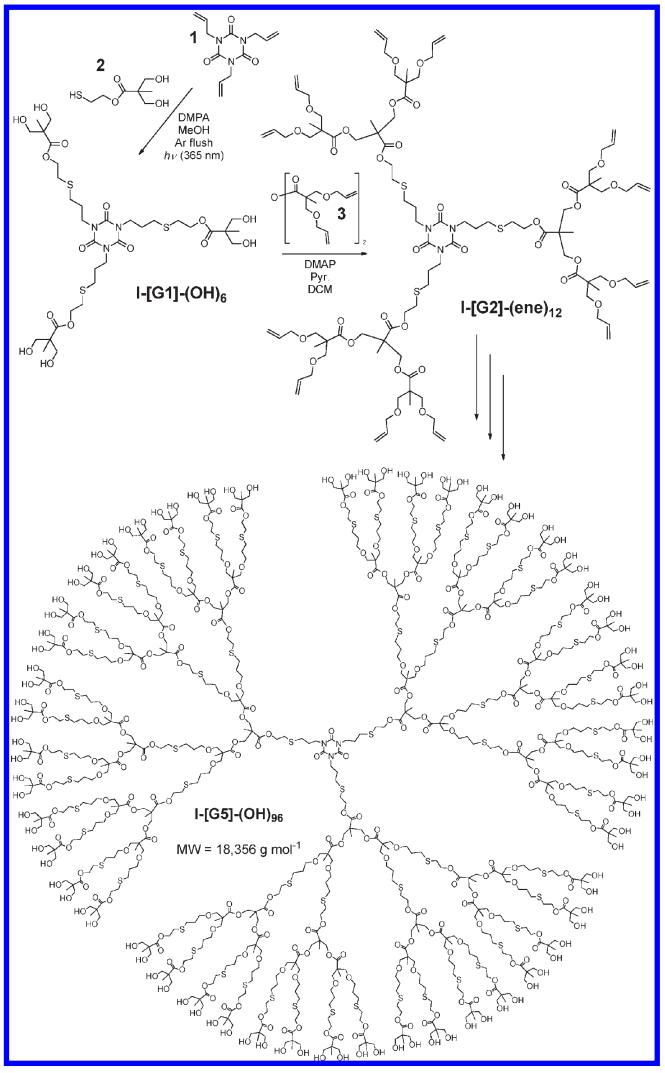
Scheme 1. Range of Momoners and Cores Employed for the Synthesis of Dendritic Libraries Using Thiol−Ene and Esterification Reactions



Scheme 2. Accelerated Synthesis of I-[G5]-$(OH)_{96}$, a Fifth Generation Dendrimer Using Thiol−Ene/Esterification Chemistry



MS with SCOUT-MTP Ion Source (Bruker Daltonics, Bremen) equipped with a nitrogen laser (337 nm), a gridless ion source, and reflector design. Size exclusion chromatography (SEC) analysis was performed on a TDA 301 Viscotek instrument equipped with two GMH_{HR}-M columns with TSK-gel. Measurements were carried out at 35 °C using THF (1.0 mL min^{-1}) as mobile phase. A calibration method was created using narrow linear polystyrene standards. Corrections for the flow rate fluctuations were made using toluene as an internal standard. R_g values for the dendrimers were calculated by the OmniSec 4.5 software using the Flory−Fox equation. Ultraviolet (UV) light irradiation of the samples was carried out with a Hamamatsu L5662 equipped with a L 6722 Hg−Xe lamp. The intensity was 20−60 mW cm^{-2}, measured with a Hamamatsu C6080−03 light power meter, calibrated for 365 nm. Differencial scanning calorimetry (DSC) was performed on a Mettler Toledo DSC 820, equipped with a sample robot and a cryocooler. The heating and the cooling rates were 10 °C min^{-1} in the temperature range of −80 to +150 °C. The DSC runs were carried out with two heating and one cooling cycles under nitrogen (flow rate 10 mL/min). The glass transition temperature (T_g) was determined from the second heating scan cycle and taken at the midpoint of the transition. Hydrogel UV curing was induced using a Fusion UV Curing System Model F300, equipped with Fusion electrodeless bulbs standard type BF9 (Lamp power 300W/inch, 1800 W total). A Perkin−Elmer Spectrum 2000 NIR FT-Raman instrument was employed on dehydrated hydrogel subtrates using 32 scans at 1500 mW laser power.

MALDI−TOF Characterization. MALDI MS analysis was conducted using either 9-nitroantracene, 2,5-dihydroxybenzoic acid (DHB) or 2-(4-hydroxyphenylazo)benzoic acid (HABA) as matrix materials. Matrix solutions were prepared as 0.1 M solutions in THF and either sodium trifluoroacetate or silver trifluoroacetate (5 mg) was added to each solution. Sample preparation for MALDI: First, 5 mg of sample was dissolved in 1 mL of THF. Then, 5 μL of the sample solution was added to 20 μL of the matrix solution. Finally, 0.05 μL of the sample-matrix solution were added to the MALDI target plate, and the solution was left to crystallize at room temperature. Spectra were acquired using a reflector-positive method with an acceleration voltage of 25 kV and a reflector voltage of 26.3 kV. The detector mass range was set to 500−10000 Da in order to exclude high intensity peaks from the lower mass range. For the highest molecular weight dendrimers, a linear positive method was employed with the laser intensity set to the lowest value possible to acquire high resolution spectra. The spectra were analyzed with FlexAnalysis Bruker Daltonics, Bremen, version 2.2.

Synthesis of Bis[2-(acetonide-2,2-bis(methoxy)propanoate)-1-ethyl] Disulfide (9). The esterification reaction was carried out by the previously published procedures[32] using the following compounds (amounts): compound **8** (128 g, 0.39 mol), bis(2-hydroxyethyl)disulfide **7** (20 g, 0.13 mol), DMAP (3 g, 0.03 mol), in CH_2Cl_2 (180 mL) and pyridine (63 mL). Compound **9** was obtained a viscous, yellowish product (55 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 4.39 (t, J = 6.4 Hz, 4H, $-SCH_2CH_2O-$), 4.17 (d, J = 12.0 Hz, 4H, $-CH_2O-$), 3.63 (d, J = 12.0 Hz, 4H, $-CH_2O-$), 2.93 (t, J = 6.4 Hz, 4H, $-SCH_2CH_2O-$), 1.41 (s, 6H, CH_3), 1.37 (s, 6H, CH_3), 1.18 (s, 6H, $-CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$), δ, ppm: 174.2, 98.3, 66.1, 62.6, 42.1, 37.2, 24.9, 22.7, 18.8. Calculated: $[M]^+$ m/z = 466.6. Found: MALDI−TOF MS, $[M + Na]^+$ m/z = 489.2.

Synthesis of Bis[2-(2,2-bis(hydroxymethyl)propanoate)-1-ethyl] Disulfide (10). The deprotection reaction was carried out by the previously published procedures[32] using the following compouds (amounts): compound **9** (37 g, 0.08 mol), Dowex (30 g), and MeOH (0.5 L). The pure product was obtained as a colorless viscous oil (28 g, 91%). ^{1}H NMR (400 MHz, CD_3OD), δ, ppm: 4.31 (t, 4H, J = 6.8 Hz, $-CH_2O-$), 3.64 (d, 4H, J = 10.8 Hz, $-CH_2O-$), 3.57 (d, 4H, J = 10.8 Hz, $-CH_2O-$), 2.93 (t, 4H, J = 6.8 Hz, $-SCH_2-$), 1.11 (s, 6H, $-CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD), δ, ppm: 176.2, 65.6, 63.3, 51.5, 37.8, 17.1. Calculated: $[M]^+$ m/z = 386.5. Found, MALDI−TOF MS: $[M + Na]^+$ m/z = 409.1.

Synthesis of 2,2-Bis(hydroxymethyl)-2-mercaptoethylpropanoate (2). The reduction reaction was carried out by the previously published procedures[33] using the following compounds (amounts): **10** (33 g, 0.09 mol), DTT (26 g, 0.17 mol), triethylamine (47 mL, 0.69 mol), and MeOH (0.5 L). The mixture was purified by flash chromatography eluting the product with EtOAc/heptane (20:80)

to yield 28.2 g (85%) of yellowish oil. ^{1}H NMR (400 MHz, CD_3OD), δ, ppm: 4.21 (t, 2H, J = 6.8 Hz, $HSCH_2CH_2O-$), 3.70 (d, 2H, J = 11.2 Hz, $-CH_2OH$), 3.62 (d, 2H, J = 11.2 Hz, $-CH_2OH$), 2.73 (2H, t, J = 6.8 Hz, $-CH_2SH$), 1.18 (3H, s, $-CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD), δ, ppm: 176.4, 67.3, 65.9, 51.8, 23.8, 17.5.

Synthesis of Bis(allyl propionic acid), BAPA (11). One equivalent of bis-MPA (20 g, 0.15 mol) and 7 equiv of NaOH (58 g, 1.44 mol) were added to a round-bottomed flask containing 300 mL of toluene. The reaction vessel was heated to 110 °C, and 10 equiv of allyl bromide (125 g, 1.04 mol) was added. The reaction mixture was refluxed overnight under vigorous stirring. After the reaction slurry was acidified using concentrated HCl (pH ca. 1−2), the mixture was washed using 200 mL of water. The organic phase was dried using $MgSO_4$ followed by removal of the solvents under vacuum. The product was isolated as slightly viscous and colorless liquid (32 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 10.23 (s, 1H, OH), 5.85 (m, 2H, $-CH{=}CH_2$), 5.24 (d, J = 17.2 Hz, 2H, $=CHH$), 5.15 (d, J = 10.3 Hz, 2H, $=CHH$), 3.99 (d, J = 5.5 Hz, 4H, $-OCH_2CH-$), 3.56 (d, J = 4.2 Hz, 4H, $-CCH_2O-$), 1.23 (s, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$), δ, ppm: 180.3, 134.5, 116.8, 72.3, 71.7, 48.1, 17.9.

Synthesis of Bis(allyl propionic acid anhydride), BAPA Anhydride (3). Compound **3** was synthesized by the previously published procedures[21] using the following amounts: BAPA **11** (8 g, 37.0 mmol), DCC (3.8 g, 18.5 mmol) and CH_2Cl_2 (20 mL). The pure anhydride was obtained as colorless viscous liquid (8 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 5.87 (m, 4H, $-CH{=}CH_2$), 5.26 (d, J = 17.2 Hz, 2H, $=CHH$), 5.17 (d, J = 12.1 Hz, 2H, $=CHH$), 4.00 (d, J = 5.6 Hz, 4H, $-OCH_2CH-$), 3.56 (d, J = 2.8 Hz, 4H, $-CCH_2O-$), 1.26 (s, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$), δ, ppm: 169.7, 134.7, 116.9, 72.5, 71.6, 50.0, 17.4.

General Procedure for the Synthesis of [*Gn*]-$(OH)_x$ *Dendrimers.* To a vial were added the alkene functional dendrimer, 1.3−5.0 equiv of thiol monomer (per alkene unit) and 0.02 equiv of DMPA (per alkene unit). The mixture was dissolved in the corresponding solvent and purged with argon and then irradiated with a 365 nm UV lamp for 20−30 min at room temperature. The products were subsequently purified.

General Procedure for the Synthesis of [*Gn*]-$(ene)_x$ *Dendrimers.* A solution of hydroxyl functional dendrimer, 0.2 equiv of DMAP (per hydroxyl group), and 5−10 equiv of pyridine (per hydroxyl group) in CH_2Cl_2 was prepared in a round-bottom flask and placed in a cold bath. Then, 1.2−3.0 equiv of alkene functional anhydride monomer (per hydroxyl group) dissolved in CH_2Cl_2 was added dropwise to the solution and the reaction stirred overnight at room temperature. The reaction mixture was then quenched with water, diluted with CH_2Cl_2 and extracted with 10% aqueous $NaHSO_4$ solution (×5), 10% aqueous $NaHCO_3$ solution (×5), and brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness. In the case of **III-[Gn]-(ene)$_x$** dendrimers, the extraction with $NaHCO_3$ was not needed and the products were purified by flash chromatography, eluting the acid with heptane/diethyl ether (90:10) containing 1% of AcOH, increasing the polarity to EtOAc to elute the product.

Synthesis of Dendrimer I-[G1]-(OH)$_6$. To a vial were added triallyl-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione **1** (920 mg, 3.69 mmol), **2** (2.8 g, 14.40 mmol), DMPA (57 mg, 0.22 mmol) and MeOH (2 mL). See general procedure for [Gn]-$(OH)_x$ reaction. The mixture was purified by flash chromatography eluting the product with EtOAc/heptane to yield 2.2 g (71%) of a clear viscous liquid. ^{1}H NMR (400 MHz, CD_3OD), δ, ppm: 4.24 (t, J = 6.8 Hz, 6H, $-CH_2O-$), 3.98 (t, J = 7.1 Hz, 6H, $-CH_2N-$), 3.69 (d, J = 10.8 Hz, 6H, $-HCHOH$), 3.62 (d, J = 10.8 Hz, 6H, $-HCHOH$), 2.79 (t, J = 6.8 Hz, 6H, $-SCH_2CH_2O-$), 2.64 (t, J = 7.1 Hz, 6H, $-CH_2CH_2CH_2S-$), 1.95 (p, J = 7.1 Hz, 6H, $-CH_2CH_2CH_2-$), 1.16 (s, 9H, $-CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD), δ, ppm: 176.6, 151.0, 66.0, 64.9, 51.7, 43.3, 31.2, 30.4, 28.8, 17.5. Calcd: $[M]^+$ ($C_{99}H_{153}N_3O_{33}S_3$) m/z = 831.30. Found, MALDI−TOF MS: $[M + Na]^+$ m/z = 854.66, $[M + K]^+$ m/z = 870.65. T_g: −19 °C.

Synthesis of Dendrimer I-[G2]-(ene)$_{12}$. Dendrimer **I-[G1]-(OH)$_6$** (1.25 g, 1.5 mmol), anhydride **3** (4.8 g, 110 mmol), and DMAP (220 mg, 1.80 mmol) were reacted in pyridine (3.6 mL, 45 mmol) and CH_2Cl_2 (5 mL) as described in the general procedure for [Gn]-$(ene)_x$, to yield 1.8 g (62%) of a clear viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 5.84 (m, 12H, $-CH{=}CH_2$), 5.24 (dd, J = 17.3 Hz, J = 1.6 Hz, 12H, $=CHH$), 5.14 (dd, J = 10.7 Hz, J = 1.6 Hz, 12H, $=CHH$), 4.26 (d, J = 3.7 Hz, 12H, $-CCH_2OCO-$), 4.23 (t, J = 7.2 Hz, 6H, $-SCH_2CH_2O-$), 3.97 (t, J = 6.9 Hz, 6H, $-NCH_2-$), 3.95 (d, J = 5.3 Hz, 24H, $-CH_2CH{=}CH_2$), 3.52 (s, 24H, $-CCH_2O-$), 2.74 (t, J = 7.2 Hz, 6H, $-SCH_2CH_2O-$), 2.60 (t, J = 7.2 Hz, 6H, $-CH_2CH_2CH_2S-$), 1.93 (p, J = 7.2 Hz, 6H, $-CH_2CH_2CH_2-$), 1.24 (s, 9H, $-CH_3$), 1.19 (s, 18H, $-CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$), δ, ppm: 173.8, 172.5, 148.8, 134.7, 116.6, 72.2, 71.9, 65.1, 63.6, 48.5, 46.6, 42.1, 30.11, 29.4, 27.5, 17.9, 17.5. Calcd: $[M]^+$ ($C_{99}H_{153}N_3O_{33}S_3$) m/z = 2007.95. Found, MALDI−TOF MS: $[M + Na]^+$ m/z = 2031.60, $[M + Ag]^+$ m/z = 2115.12. T_g: −46 °C.

Synthesis of Dendrimer I-[G3]-(OH)$_{24}$. To a vial were added dendrimer **I-[G2]-(ene)$_{12}$** (1.0 g, 0.50 mmol), **2** (1.5 g, 7.77 mmol), DMPA (30 mg, 119 mmol) and MeOH (1.3 mL). See the general procedure for [Gn]-$(OH)_x$ reaction. The mixture was dissolved in a small amount of MeOH and precipitated twice into diethyl ether, to yield 1.7 g (79%) of a clear viscous liquid. ^{1}H NMR (400 MHz, CD_3OD), δ, ppm: 4.31 (m, 6H, $-CH_2O-$), 4.25 (t, J = 6.9 Hz, 36H, $-CH_2O-$), 4.02 (t, J = 7.1 Hz, 6H, $-CH_2N-$), 3.70 (d, J = 11.1 Hz, 24H, $-HCHOH$), 3.64 (d, J = 11.1 Hz, 24H, $-HCHOH$), 3.53 (m, 48H, $-CCH_2OCH_2-$), 2.83 (t, J = 6.0 Hz, 6H, $-SCH_2CH_2O-$), 2.79 (t, J = 6.9 Hz, 24H, $-SCH_2CH_2O-$), 2.65 (m, 30H, $-CH_2CH_2CH_2S-$), 1.97 (m, 6H, $-NCH_2CH_2CH_2-$), 1.84 (p, J = 6.6 Hz, 24H, $-OCHH_2-CH_2CH_2-$), 1.19 (s, 18H, $-CH_3$), 1.17 (s, 45H, $-CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD), δ, ppm: 177.7, 176.2, 174.9, 151.6, 74.7, 71.6, 67.3, 66.7, 66.1, 65.6, 52.4, 48.9, 44.1, 32.0, 32.1, 31.3, 31.7, 30.5, 29.6, 19.4, 19.2, 18.3. Calcd: $[M]^+$ ($C_{183}H_{321}N_3O_{81}S_{15}$) m/z = 4336.69 Found, MALDI−TOF MS: $[M + Na]^+$ m/z = 4362.97. T_g: −20 °C.

Synthesis of Dendrimer I-[G4]-(ene)$_{48}$. Dendrimer **I-[G3]-(OH)$_{24}$** (1.4 g, 0.32 mmol), anhydride **3** (3.5 g, 10 mmol) and DMAP (188 mg, 1.50 mmol) were reacted in pyridine (6.2 mL, 360 mmol) and CH_2Cl_2 (10 mL) as described in general procedure for [Gn]-$(ene)_x$ reaction, to yield 1.3 g (45%) of a clear viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 5.82 (m, 48H, $-CH{=}CH_2$), 5.22 (dd, J = 15.7 Hz, J = 1.6 Hz, 48H, $=CHH$), 5.12 (dd, J = 8.8 Hz, J = 1.6 Hz, 48H, $=CHH$), 4.23−4.18 (m, 90H, $-CH_2OCO-$), 3.92 (d, J = 5.3 Hz, 102H, $-CH_2CH{=}CH_2$ + $-NCH_2-$), 3.54−3.40 (m, 144H, $-CH_2O-$), 2.69 (m, 30H, $-SCH_2CH_2O-$), 2.56, (t, 30H, $-CH_2CH_2CH_2S-$), 1.91 (m, 6H, $-CH_2CH_2CH_2-$), 1.78 (q, J = 6.6 Hz, 24H, $-OCHH_2-CH_2CH_2-$), 1.23 (s, 9H, $-CH_3$), 1.22 (s, 36H, $-CH_3$), 1.17 (s, 72H, $-CH_3$), 1.13 (s, 18H, $-CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$), δ, ppm: 173.8, 173.6, 172.4, 148.8, 134.7, 116.5, 72.2, 71.9, 69.6, 65.1, 63.7, 48.5, 48.4, 46.7, 46.6, 42.1, 30.3, 30.3, 30.1, 29.6, 28.9, 28.8, 17.9, 17.8, 17.7, 17.5. Calcd: $[M]^+$ ($C_{447}H_{705}N_3O_{153}S_{15}$) m/z = 9043.33. Found, MALDI−TOF MS: $[M + Na]^+$ m/z = 9065.00. T_g: −52 °C

Synthesis of Dendrimer I-[G5]-(OH)$_{96}$. To a vial were added dendrimer **I-[G4]-(ene)$_{48}$** (40 mg, 4.4 × 10^{-3} mmol), **2** (53 mg, 0.28 mmol), DMPA (11 mg, 4 × 10^{-3} mmol), and MeOH (0.5 mL). See the general procedure for the [Gn]-$(OH)_x$ reaction. The mixture was dissolved in a small amount of MeOH and precipitated twice into diethyl ether, to yield 60 mg (74%) of a clear viscous liquid. ^{1}H NMR (400 MHz, CD_3OD), δ, ppm: 4.23 (m, 186H, $-CH_2OCO-$), 4.02 (m, 6H, $-CH_2N-$), 3.66 (d, J = 10.8 Hz, 96H, $-HCHOH$), 3.60 (d, J = 10.8 Hz, 96H,

−HC*H*OH), 3.49 (m, 240H, −CCH_2OCH_2−), 2.75 (bt, 136H, −SCH_2CH$_2$O−), 2.71 (bt, 136H, −CH$_2$CH$_2$CH_2S−), 1.99 (m, 6H, −NCH$_2$CH_2CH$_2$−), 1.80 (m, 120H, −OCHH$_2$CH_2CH$_2$−), 1.16 and 1.13 (bs, 279H, −CH_3). ^{13}C{^{1}H} NMR (100 MHz, CD$_3$OD), δ, ppm: 177.3, 177.0, 176.2, 173.3, 151.0, 74.8, 71.8, 69.7, 67.4, 66.8, 66.2, 65.7, 52.9, 52.8, 52.5, 49.0, 46.5, 32.3, 32.2, 31.8, 30.8, 30.7, 27.5, 19.8, 19.6, 19.4, 18.5, 18.4. T_g: −10 °C.

Synthesis of Dendrimer II-[G1]-(OH)$_6$. The first generation dendrimer was synthesized by the previously published procedure.[7]

Synthesis of Dendrimer II-[G2]-(ene)$_{12}$. II-[G1]-OH$_6$ (800 mg, 1.4 mmol), **3** (4.8 g, 11.8 mmol), DMAP (205 mg, 1.68 mmol), and pyridine (3.3 g, 42 mmol) were reacted. See the general procedure for the reaction conditions. Yield: 68%. ^{1}H NMR (500 MHz, CDCl$_3$), δ, ppm: 5.87 (m, 12H), 5.24 (dd, 24H), 5.11 (m, 3), 4.31 (ddd, 6H), 3.99 (d, 24 + 6H), 3.55 (m, 24H), 2.71 (d, 6H), 2.60 (m, 6H), 1.91 (m, 6H), 1.21 (s, 18H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$), δ, ppm: 174.03, 173.76, 148.89, 134.80, 134.77, 116.62, 116.53, 72.28, 72.27, 72.25, 71.98, 71.93, 70.69, 63.36, 48.50, 42.12, 31.78, 29.77, 27.54, 17.97. SEC PDI: 1.02

Synthesis of Dendrimer II-[G3]-(OH)$_{24}$. II-[G2]-ene$_{12}$ (700 mg, 0.30 mmol), **4** (580 mg, 5.36 mmol) and DMPA (21 mg, 0.07 mmol) were used. See the general procedure for the reaction conditions. Yield: 93%.^{1}H NMR (500 MHz, DMSO), δ, ppm: 1.12 (s, 18H), 1.73 (m, 25H), 1.82 (m, 6H), 2.60−2.42 (m, 54H), 2.62 (d, 6H), 3.35 (m, 48H), 3.54 (m, 12H), 3.83 (b, 6H), 4.17−4.27 (m, 6H), 4.53 (t, 12H), 4.70 (dd, 12H), 5.03 (m, 3H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$), δ, ppm: 173.77, 173.47, 149.48, 72.61, 71.82, 70.87, 69.80, 67.49, 65.01, 63.75, 48.53, 35.72, 29.75, 29.50, 29.16, 27.74, 25.59, 18.03. SEC PDI: 1.05.

Synthesis of Dendrimer II-[G4]-(ene)$_{48}$. II-[G3]-OH$_{24}$ (400 mg, 1.31 mmol), **3** (1.7 g, 4.05 mmol), DMAP (77 mg, 0.63 mmol) and pyridine (1.2 g, 15.7 mmol) were used. See the general procedure for the reaction conditions. Yield: 44%. ^{1}H NMR (500 MHz, CDCl$_3$), δ, ppm: 1.23, 1.26 (s, s, 90H), 1.83 (b, 24H), 1.93 (b, 6H), 2.58−3.0 (b, m, 36H), 3.49 (b, 24H), 3.52−3.65 (m, 122H), 3.99 (b, 96H), 4.10−4.55 (b, m, 10H), 5.1−5.35 (m, 101H), 5.89 (m, 48H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$), δ, ppm: 178.49, 155.96, 149.03, 144.05, 136.61, 134.52, 123.92, 116.59, 106.22, 76.71, 76.44, 74.79, 72.26, 71.97, 49.85, 48.44, 39.42, 32.38, 30.78, 29.49, 26.17, 25.53, 24.73, 18.21, 17.96. SEC PDI: 1.05.

Synthesis of dendrimer III-[G1]-(ene)$_6$. Trimethylolpropane **13** (244 mg, 1.82 mmol), anhydride **5** (4.0 g, 6.55 mmol), and DMAP (133 mg, 1.09 mmol) were reacted in pyridine (2 mL, 27 mmol) and CH$_2$Cl$_2$ (4 mL) as described in general procedure for [Gn]-(ene)$_x$ reaction. The mixture was purified by flash chromatography eluting the product with heptane/EtOAc (80:20), to yield 1.5 g (80%) of a clear viscous liquid. ^{1}H NMR (400 MHz, CDCl$_3$), δ, ppm: 5.87 (m, 6H, −C*H*=CH$_2$), 5.23 (dd, *J* = 1.7 Hz, *J* = 17.4 Hz, 6H, =CH*H*), 5.14 (dd, *J* = 1.7 Hz, *J* = 10.3 Hz, 6H, =CH*H*), 4.06 (s, 6H, −COOCH_2C−), 4.04 (s, 6H, −COOCH_2C−), 3.93 (d, *J* = 5.6 Hz, 12H, CH_2CH=CH$_2$), 3.31 (s, 12H, −CCH_2O−), 2.62 (s, 12H, −COCH$_2$CH$_2$CO−), 1.45 (m, 8H,−CH_2CH$_3$), 0.85 (m, 12H, −CH$_2$CH_3). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$), δ, ppm: 172.0, 171.9, 135.0, 116.4, 72.2, 70.2, 65.3, 63.9, 42.3, 40.7, 29.0, 22.9, 22.8, 7.6, 7.3. Calcd [M]$^+$ (C$_{54}$H$_{86}$O$_{18}$) *m*/*z* = 1022.58. Found, MALDI−TOF MS: [M + Na]$^+$ *m*/*z* = 1046.03. PDI: 1.02. T_g: −26 °C.

Synthesis of Dendrimer III-[G2]-(OH)$_{12}$. To a vial were added dendrimer **III-[G1]-(ene)$_6$** (700 mg, 0.68 mmol), **2** (1.2 g, 6.15 mmol), DMPA (0.2 g, 0.82 mmol), and DMF (2.5 mL). See the general procedure for the [Gn]-(OH)$_x$ reaction. The mixture was dissolved in a small amount of DMF and precipitated twice into diethyl ether, to yield 1 g (67%) of a clear viscous liquid. ^{1}H NMR (400 MHz, CD$_3$OD), δ, ppm: 4.24 (t, *J* = 7.1 Hz, 12H, −CH_2COO−), 4.06 (s, 6H, −COOCH_2C−), 4.02 (s, 6H, −COOCH_2C−), 3.69 (s, d, *J* = 10.8 Hz, 12H, −C*H*HOH), 3.62 (s, d, *J* = 10.8 Hz, 12H, −C*H*HOH), 3.48 (t, *J* = 6.8 Hz, −CH$_2$OCH_2−), 2.77 (t, *J* = 7.1 Hz, 12H, −SCH_2−), 2.67−2.64 (m, 24H, −COCH$_2$CH$_2$CO− + −SCH_2−), 1.82 (m, 12H, −CH$_2$CH_2CH$_2$−), 1.45−1.40 (m, 8H,−CH_2CH$_3$), 1.16 (s, 18H, −CCH_3), 0.94−0.84 (m, 12H, −CH$_2$CH_3). ^{13}C{^{1}H} NMR (100 MHz, CD$_3$OD), δ, ppm: 176.5, 174.0, 173.7, 71.9, 70.8, 66.4, 66.0, 65.3, 64.9, 51.7, 43.7, 42.3, 31.3, 31.0, 30.2, 30.1, 29.9, 24.2, 17.6, 8.2, 8.0. Calcd: [M]$^+$ (C$_{96}$H$_{170}$O$_{42}$S$_6$) *m*/*z* = 2186.95. Found, MALDI−TOF MS: [M + Na]$^+$ *m*/*z* = 2210.91, [M + K]$^+$ *m*/*z* = 2226.91. PDI: 1.03. T_g: −20 °C

Synthesis of III-[G3]-(ene)$_{24}$. Dendrimer **III-[G2]−OH$_{12}$** (0,9 g, 0.41 mmol), anhydride **5** (3.6 g, 5.92 mmol) and DMAP (120 mg, 0.98 mmol) were reacted in pyridine (2 mL, 25 mmol) and CH$_2$Cl$_2$ (8 mL) as described in general procedure for [Gn]-(ene)$_x$ reaction. The mixture was purified by flash chromatography eluting the product with EtOAc, to yield 1.9 g (80%) of a clear viscous liquid. ^{1}H NMR (400 MHz, CDCl$_3$), δ, ppm: 5.91−5.80 (m, 24H, −C*H*=CH$_2$), 5.24 (dd, *J* = 1.8 Hz, *J* = 17.3 Hz, 24H, =CH*H*), 5.14 (dd, *J* = 1.8 Hz, *J* = 10.4 Hz, 24H, =CH*H*), 4.25 (m, 36H, −CH_2OCO−), 4.05 (bs, 30H, −COOCH_2C−), 4.00 (s, 6H, −COOCH_2C−), 3.92 (d, *J* = 5.4 Hz, 48H, CH_2CH=CH$_2$), 3.43 (t, *J* = 6.0 Hz, 12H, −OCHH_2-), 3.30 (s, 48H, −CCH_2O−), 3.26 (s, 12H, −CCH_2O−), 2.72 (t, *J* = 7.1 Hz, 12H, −SC*H*−-), 2.63−2.56 (bs, 72H, −COCH$_2$CH$_2$CO− + −SCH_2−), 1.81 (m, 12H, −CH$_2$CH_2CH$_2$−), 1.47−1.38 (m, 32H,−CH_2CH$_3$), 1.24 (s, 18H, −CCH_3), 0.84 (m, 48H, −CH$_2$CH_3). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$), δ, ppm: 172.4, 172.0, 171.9, 171.7, 135.0, 116.4, 72.2, 70.5, 70.2, 69.5, 65.4, 65.3, 63.8, 46.3, 42.2, 30.14, 29.7, 29.0, 28.9, 22.9, 17.8, 7.6. Calcd: [M]$^+$ (C$_{288}$H$_{458}$O$_{102}$S$_6$) *m*/*z* = 5740.90. Found, MALDI−TOF MS: [M + Na]$^+$ *m*/*z* = 5768.39. PDI: 1.03. T_g: −46 °C

Synthesis of III-[G4]-(OH)$_{48}$. To a vial were added dendrimer **III-[G3]-(ene)$_{24}$** (1.0 g, 0.18 mmol), **2** (1.6 g, 8.52 mmol), DMPA (0.2 g, 0.82 mmol), and DMF (3 mL). See the general procedure for the [Gn]-(OH)$_x$ reaction. The mixture was dissolved in a small amount of DMF and precipitated twice into diethyl ether, to yield 1.1 g (60%) of a clear viscous liquid. ^{1}H NMR (400 MHz, CD$_3$OD), δ, ppm: 4.30−4.21 (m, 84H, −CH_2COO−), 4.08 (s, 12H, −COOCH_2−), 4.02 (s, 12H, −COOCH_2-), 3.69 (s, d, *J* = 10.8 Hz, 48H, −C*H*HOH), 3.63 (s, d, *J* = 10.8 Hz, 48H, −C*H*HOH), 3.50 (t, *J* = 5.9 Hz, 60H, −CH$_2$OCH_2−), 3.30 (bs, 60H, −CCH_2O−), 2.77 (t, *J* = 6.9 Hz, 60H, −SCH_2−), 2.67−2.63 (m, 120H, −COCH_2CH_2CO− + −SCH_2−), 1.87−1.80 (m, 60H, −CH$_2$CH_2CH$_2$−), 1.46−1.40 (m, 32H, −CH_2CH$_3$), 1.16 (s, 90H, −CCH_3), 0.88 (bt, 48H, −CH$_2$CH_3). ^{13}C{^{1}H} NMR (100 MHz, CD$_3$OD), δ, ppm: 176.5, 173.8, 173.5, 173.2, 72.0, 71.4, 70.8, 67.0, 66.4, 66.0, 64.9, 51.7, 47.8, 43.7, 31.3, 31.0, 30.1, 29.9, 24.3, 18.6, 17.6, 8.5, 8.4. Calcd: [M]$^+$ (C$_{456}$H$_{794}$O$_{198}$S$_{30}$) *m*/*z* = 10398.37. Found, MALDI−TOF MS: [M + Na]$^+$ *m*/*z* = 10448, [M + K]$^+$ *m*/*z* = 10509. PDI: 1.04. T_g: −18 °C

Synthesis of III-[G5]-(ene)$_{96}$. Dendrimer **III-[G4]-(OH)$_{48}$** (0,9 g, 0.08 mmol), anhydride **5** (3.0 g, 4.98 mmol), and DMAP (101 mg, 0.83 mmol) were reacted in pyridine (5 mL) and CH$_2$Cl$_2$ (20 mL) as described in the general procedure for the [Gn]-(ene)$_x$ reaction. The mixture was purified by flash chromatography eluting the product with EtOAc/MeOH (70:30), to yield 1.6 g (73%) of a yellowish viscous liquid. ^{1}H NMR (400 MHz, CDCl$_3$), δ, ppm: 5.91−5.78 (m, 96H, −C*H*=CH$_2$), 5.24 (dd, *J* = 1.7 Hz, *J* = 17.3 Hz, 96H, =CH*H*), 5.14 (dd, *J* = 1.7 Hz, *J* = 10.5 Hz, 96H, =CH*H*), 4.34−4.21 (m, 180H, −CH_2OCO−), 4.05 (s, 96H, −COOCH_2C−), 3.99 (s, 36H, −COOCH_2C−), 3.92 (d, *J* = 5.4 Hz, 192H, CH_2CH=CH$_2$), 3.44 (t, *J* = 6.1 Hz, 60H, −OCHH_2−), 3.31 (bs, 144H, −CCH_2O−), 3.26 (s, 12H, −CCH_2O−), 2.84−2.69 (m, 60H, −SCH_2−), 2.61(bs, 312H, −COCH$_2$CH$_2$CO− + −SCH_2−), 1.81 (m, 60H, −CH$_2$CH_2CH$_2$−), 1.47−1.38 (m, 128H,−CH_2-CH$_3$), 1.10 (s, 90H, −CCH_3), 0.84 (m, 192H, −CH$_2$CH_3). ^{13}-C{^{1}H} NMR (100 MHz, CDCl$_3$), δ, ppm: 173.0, 172.4, 172.2, 171.9, 171.7, 135.0, 116.4, 72.2, 70.2, 65.3, 65.2, 65.1, 63.8, 62.6, 46.3, 42.3, 29.7, 28.9, 28.5, 28.1, 23.5, 22.9, 22.5, 21.7, 7.7, 7.6, 7.5. Calcd: [M]$^+$ (C$_{1224}$H$_{1946}$O$_{438}$S$_{30}$) *m*/*z* = 24614.16. Found, MALDI−TOF MS: [M + Na]$^+$ *m*/*z* = 25032. PDI: 1.04. T_g: −43 °C

Synthesis of I-[G2]-11-mercapto-1-undecanol Adduct. To a vial were added dendrimer **I-[G2]-(ene)$_{12}$** (60 mg, 0.03 mmol),

14 (150 mg, 0.72 mmol), and DMPA (18 mg, 0.07 mmol). The reactants were dissolved in THF and purged with argon for 10 min. Irradiation with a 365 nm UV lamp was carried out for 20 min. The solvent was evaporated and the resulting reaction mixture was dissolved in the minimal amount of CH_2Cl_2 and precipitated three times in cold heptanes and one in cold diethyl ether to give 60 mg (45%) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD), δ, ppm: 4.29 (m, 18H, $-CH_2OCO-$), 3.97 (m, 6H, $-CH_2N-$), 3.56 (m, 72H, $-CCH_2OCH_2-$ + CH_2-OH), 2.81 (m, 6H, $-CH_2S-$), 2.67 (m, 6H, $-CH_2S-$), 2.56 (t, J = 7.3 Hz, 24H, $-CH_2S-$), 2.51 (t, J = 7.3 Hz, 24H, $-CH_2S-$), 1.97 (m, 6H, $-NCH_2CH_2CH_2-$), 1.81 (q, J=7.3 Hz, 24H, $-OCHH_2CH_2CH_2-$), 1.53 (m, 48H, $-CH_2CH_2OH$ + $-CH_2CH_2S$), 1.31 (m, 168H, $-CH_2CH_2CH_2-$), 1,23 (s, 9H, $-CH_3$), 1.19 (s, 18H, $-CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$ + CD_3OD), δ, ppm: 173.2, 171.8, 148.5, 71.7, 68.9, 64.4, 63.1, 61.0, 50.9, 45.9, 41.2, 37.8, 31.6, 31.0, 28.8, 28.7, 28.6, 28.5, 28.4, 28.1, 28.0, 27.9, 27.6, 27.4, 24.9, 16.7, 16.5. Calcd: $[M]^+$ ($C_{231}H_{441}N_3O_{45}S_{15}$) m/z=4457.81 Found, MALDI−TOF MS: $[M + Na]^+$ m/z = 4498.94, $[M + Na + K]^+$ m/z = 4519.08. T_g: 5 °C.

Synthesis of I-[G2]-(monoethyl ether triethylenglycol)-3-mercaptopropionate) Adduct. To a vial were added dendrimer **I-[G2]-(ene)$_{12}$** (60 mg, 0.03 mmol), **15** (858 mg, 3.23 mmol), and DMPA (18 mg, 0.07 mmol). The reactants were purged with argon for 10 min. Irradiation with a 365 nm UV lamp was carried out for 20 min. The product was purified by flash chromatography eluting with EtOAc/MeOH (80:20) to yield 102 mg (65%) of a yellowish viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 4.27−4.16 (m, 42H, $-CH_2OCO-$), 3.94 (bt, 6H, $-CH_2N$-), 3.67 (t, J = 6.9 Hz, 24H, $-CH_2O-$), 3.64−3.58 (m, 72H, $-CH_2O-$), 3.58−3.53 (m, 24H, $-CH_2O-$), 3.49 (q, J= 6.9 Hz, $-OCH_2CH_3$), 3.45−3.42 (m, 24H, $-CCH_2OCH_2-$), 2.88 (bt, 6H, $-SCH_2-$), 2.80−2.70 (m, 30H, $-SCH_2-$), 2,59 (t, J = 7.2 Hz, 24H, $-SCH_2CH_2CO-$), 2.53 (t, J = 7.2 Hz, 24H, $-SCH_2CH_2CO-$), 1.89 (q, J= 7.2 Hz, 6H, $-NCH_2CH_2CH_2-$), 1.76 (q, J = 6.8 Hz, 24H,$-OCHH_2CH_2CH_2-$), 1.21 (s, 18H), 1.20 (s, 9H, $-CH_3$), 1.17 (t, J = 6.9 Hz, $-CH_2CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$), δ, ppm: 173.6, 172.3, 171.7, 148.7, 72.2, 70.6, 70.5, 70.4, 69.7, 69.6, 68.9, 66.5, 65.0, 63.8, 63.7, 53.4, 48.4, 43.9, 34.6, 29.3, 28.6, 26.9, 26.7, 23.8, 17.8, 17.4, 15.06. Calcd: $[M]^+$ ($C_{231}H_{417}N_3O_{93}S_{15}$) m/z = 5201.38. Found, MALDI−TOF MS: $[M + Na + K]^+$ m/z = 5261.19. T_g: −55 °C.

Synthesis of I-[G4]-(3-mercaptopropionic acid) Adduct. To a vial were added dendrimer **I-[G4]-(ene)$_{48}$** (80 mg, 8.8×10^{-3} mmol), 3-mercaptopropionic acid **16** (71 μL, 0.849 mmol), and DMPA (22 mg, 0.08 mmol). The reactants were dissolved in the minimal amount of DMF and purged with argon for 10 min. Irradiation with a 365 nm UV lamp was carried out for 20 min. The resulting reaction mixture was precipitated once into diethyl ether to give 75 mg (60%) of clear viscous liquid. ^{1}H NMR (400 MHz, CD_3OD), δ, ppm: 4.28 (m, 90H, $-CH_2OCO-$), 4.02 (m, 6H, $-CH_2N-$), 3.53 (m, 240H, $-CCH_2OCH_2-$), 2.90−2.75 (m, 126H, $-SCH_2CH_2O-$ + $-SCH_2CH_2COOH$), 2.70−2.59 (m, 222H, $-CH_2CH_2CH_2S-$), 2.02 (m, 6H, $-NCH_2CH_2-$), 1.83 (m, 120H, $-OCHH_2CH_2CH_2-$), 1.30 (bs, 45H, $-CH_3$), 1.20 (bs, 90H, $-CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD), δ, ppm: 175.8, 175.5, 175.4, 174.3, 174.2, 151.0, 74.1, 71.1, 66.7, 65.5, 52.6, 48.3, 39.7, 35.9, 31.5, 31.2, 30.9, 30.4, 30.02, 29.7, 28.1, 27.1, 19.0, 18.8, 18.7, 18.6. T_g: −30 °C

Synthesis of I-[G4]-benzyl mercaptan Adduct. To a vial were added **I-[G4]-(ene)$_{48}$** (80 mg, 8.8×10^{-3} mmol), **17** (105 mg, 0.85 mmol), and DMPA (22 mg, 0.08 mmol). The reactants were dissolved in THF and purged with argon for 10 min. Irradiation with a 365 nm UV lamp was carried out for 20 min. The solvent was evaporated and the resulting reaction mixture was dissolved in the minimal amount of chloroform and precipitated once into methanol to give 80 mg (60%) of clear viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.30 (m, 192H, Ar), 7.24 (m, 48H, Ar), 4.23 (m, 90H, $-CH_2OCO-$), 3.97 (m, 6H, $-CH_2N-$), 3.69 (s, 96H, $-CH_2$-Ar), 3.43 (m, 240H, $-CCH_2OCH_2-$), 2.71 (m, 30H, $-SCH_2CH_2O-$), 2.58 (m, 30H, $-CH_2CH_2CH_2S-$), 2.45 (t, 96H, $-CH_2SCH_2Ar$), 1.93 (m, 6H, $-NCH_2CH_2-$), 1.76 (m, 120H, $-OCHH_2CH_2CH_2-$), 1.25 (s, 9H, $-CH_3$), 1.22 (s, 36H, $-CH_3$), 1.13 (s, 72H, $-CH_3$), 1.10 (s, 18H, $-CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$), δ, ppm: 173.8, 173.7, 172.4, 172.3, 148.7, 138.5, 128.8, 128.4, 126.8, 72.5, 72.3, 69.8, 69.7, 65.01, 63.69, 48.4, 46.7, 36.2, 30.33, 30.14, 29.6, 29.2, 28.8, 28.0, 27.6, 18.2, 17.9, 17.7, 17.5. T_g: −27 °C

Synthesis of I-[G4]-*N*- α -(9-Fluorenylmethyloxycarbonyl)-L-cysteine Adduct. To a vial were added dendrimer **I-[G4]-(ene)$_{48}$** (57 mg, 6.3×10^{-3} mmol), **18** (436 mg, 1.21 mmol), and DMPA (15 mg, 0.06 mmol). The reactants were dissolved in the minimal amount of DMF and purged with argon for 10 min. Irradiation with a 365 nm UV lamp was carried out for 1 h. The mixture was precipitated into cold EtOAc to give 102 mg (63%) of a yellowish solid. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.94 (s, 48H, NH), 7.87 (bd, 96H, Ar), 7.81 (bd, 96H, Ar), 7.35 (bd, 96H, Ar), 7.26 (bd, 96H, Ar), 4.42−3.91 (m, 282H, $-CH_2OCO-$ + $-CHNH-$ + $-CCHC-$), 3.32 (m, $-CCH_2S-$, 96H), 2.89 (m, 30H, $-SCH_2CH_2O-$), 2.78−2.58 (m, 126H, $-CH_2CH_2CH_2S-$), 1.81 (m, 6H, $-NCH_2CH_2-$), 1.64 (m, 120H, $-OCHH_2CH_2CH_2-$), 1.17−0.94 (m, 135H, $-CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, DMSO-d_6), δ, ppm: 173.1, 172.4, 172.3, 170.5, 162.5, 156.1, 143.9, 140.8, 127.7, 125.3, 124.1, 120.1, 72.9, 72.3, 69.3, 65.9, 59.9, 46.8, 35.9, 30.8, 30.0, 29.1, 28.3, 20.8, 19.7, 19.0, 17.5. T_g: 30 °C.

Fabrication of III-[G3]-(ene)$_{24}$ Cross-Linked PEG Hydrogel. The **III-[G3]-(ene)$_{24}$** dendrimer (40 mg, 0.07 mmol), dithiol functionalized 3k-PEG (234 mg, 0.08 mmol), and the photoinitiator 2,2-dimethoxy-1,2-diphenylacetophenone (DMPA) (5 mg, 2 wt %) were dissolved in THF (500 mg). The solution was drop cast in a Teflon mold, covered with a glass plate, and exposed to UV irradiation at a dose of 1.66 J/cm^2 for a duration of 10 s using a Hg-lamp. All fabricated hydrogels were soaked at room temperature in distilled water. A total of five cycles were efficient for solvent exchange and resulted in a clear hydrogel.

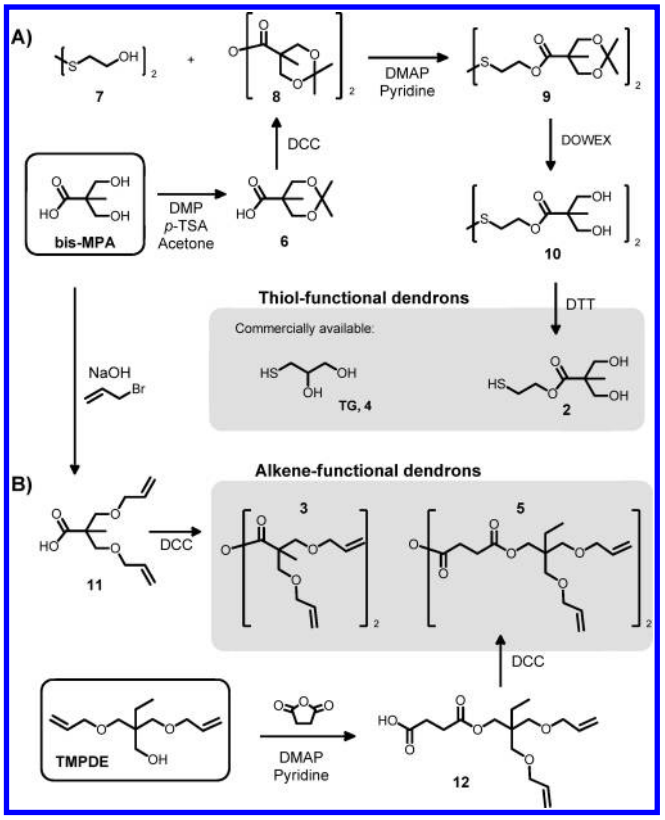
Results and Discussion

The AB_2 and CD_2 monomers shown in Scheme 1 were selected based on commercial availability and their facile synthesis from readily available starting materials. Three basic building blocks were examined to illustrate the modular nature of this accelerated approach to dendrimers; thioglycerol (TG, **4**),[7] bis-MPA, and trimethylolpropane diallyl ether (TMPDE). The chemical versatility of these building blocks allowed for a range of synthetic approaches and dendritic structures to be developed.

For the AB_2 monomers based on a single thiol group and 2 hydroxyl groups, two starting materials were chosen; thioglycerol (TG), **4**, which is commercially available and the bis-MPA derivative, **2**. As shown in Scheme 3A, the parent bis-MPA building block could be converted into the acetonide protected anhydride **8** through previously published procedures.[21,22] Esterification of 2-hydroxyethyl disulfide (HED, **7**) with **8** using catalytic amounts of 2-(dimethylamino)pyridine (DMAP) and excess pyridine afforded the diester, **9** in good yield. When the carboxylic acid **6** was directly coupled to **7** using *N,N′*-dicyclohexylcarbodiimide[34,35] (DCC), the resulting product **9** was obtained in lower yields and column chromatography was required to isolate the product. Deprotection of the acetonide using acidic DOWEX gave the alkoxy-functional disulfide **10**[32] and reduction with DL-dithioerythritol (DTT)[33] afforded the desired monomer, 2′-mercaptoethyl 2,2-bis(hydroxymethyl)propionate (bis-MEP, **2**). It should be noted that four out of the five steps in the synthesis of **2** did not involve any chromatography and each of the five steps resulted in yields greater than 85%.

For the corresponding AB_2 and CD_2 monomers based on 2 alkene units and an anhydride group, **3** and **5**, high yielding and

Scheme 3. Synthetic Path To Obtain the AB_2 and CD_2 Monomers



efficient chemistry was again employed. The synthesis of the ene-functional monomer **3** was accomplished in two steps with an overall yield of 85%, starting from bis-MPA, and again no chromatography was required which allowed multigram quantities of all monomers to be easily prepared (Scheme 3B).

The key to accelerated synthesis inherent in this AB_2 and CD_2 approach is a high degree of orthogonality for the coupling reactions. To initially demonstrate the combination of thiol−ene chemistry and esterification reactions, the synthesis of a fifth generation dendrimer, **I-[G5]-(OH)$_{96}$**, starting from the core triallyl isocyanurate **1** is shown in Scheme 2. To a mixture of **1** and the monomer **2** in a 1.3 to 1, thiol to alkene ratio, was added the radical initiator 2,2-dimethoxy-2-diphenylacetophenone (DMPA), in a 0.02 of initiator to 1 of alkene ratio. Unlike the thiol−ene-based dendrimer previously reported, in which the core was miscible with the monomer,[7] the immiscibility of **1** and **2** required the use of solvent. For this purpose, the reaction mixture was deoxygenated by purging with nitrogen,[36] followed by irradiation with a 365 nm UV lamp (intensity of 20−60 mW cm^{-2}) for 20 min which resulted in quantitative conversion. The first generation dendrimer was subsequently esterified with anhydride **3** to yield **I-[G2]-(ene)$_{12}$**. An advantage of thiol−ene chemistry for these reactions is that only 1.3−5.0 equiv of thiol to alkene is required for essentially quantitative conversion even at high generations. This is in direct contrast to other divergently grown dendrimers, such as PAMAM, which require the use of increasingly larger excesses of monomer as the generation number of the dendrimer increases.[17] At higher generations of the **I-[G*x*]** dendrimers, minimum amounts (< 5%) of dendrimer coupling were observed when using 1.3 equiv of monomer. In order to prevent dendrimer couplings, the use of 5 equiv of thiol per alkene were used, with the SEC traces displaying only minimal higher molecular weight, coupled species. Similarly, the esterification reaction requires only 3 equiv of anhydride per −OH functionality at higher generations, again leading to divergent growth strategies that were efficient in terms of materials used and purifications required, the final result being a chemoselective approach for the accelerated synthesis of **I-[G5]-(OH)$_{96}$** in gram quantities.

The facile growth of the **I-[G*x*]** dendrimers and the efficient conversion of the chain end functional groups is illustrated in Figure 1. ^{1}H NMR analysis reveals the complete substitution of the end-functional groups at each step with essentially quantitative conversion being observed at generation 4, which contains 48 chain end groups. In the case of the thiol−ene growth step, the alkene decorated moieties (G0, G2, and G4) are completely substituted with monomer **2**, disappearance of the peaks at 5.25 and 5.80 ppm, while the resonances for the hydroxymethyl groups are similarly shifted during esterification, 3.65 ppm to 3.95 ppm. This high level of efficiency and associated purity is also illustrated by comparison of the size exclusion chromatography traces for the first four dendrimer generations (Figure 2A). In all cases, the polydispersity indices (PDIs) varied from 1.02 to 1.04 and symmetrical peaks were observed. The purity of the third generation dendrimer is evident from the mass spectrum in Figure 2B. The higher generation dendrimers were analyzed using linear mode and due to their high molecular weight and chemical structure, the laser intensity was set to a relatively high level, resulting in spectra with low isotopic resolution.[37]

Similar to the synthesis of the dendrimer in Scheme 2, other dendrimers were fabricated using the AB_2 and CD_2 monomer combinations shown in Scheme 1. In order to add architectural variability and to use an alternate, commercially available monomer, thioglycerol **4** was examined as an alternate AB_2 thiol functional monomer. While **4** is commercially available as a racemic mixture, it is asymmetric and it contains a primary, and a secondary alcohol which can be exploited for subsequent modification reactions. For the dendrimer family **II-[G*x*]** prepared from **1**, **3**, and **4**, the first thiol−ene coupling was performed under solvent-free conditions, and the product was obtained after precipitation into diethyl ether.[7] The sequential dendrimer growth process involved similar conditions as the **I-[G*x*]** family of dendrimers which allows the fourth generation, alkene-functional dendrimer (M.W. = 7759 g/mol) to be prepared in only 4 steps, Figure 3. In addition, **4** is a low molecular weight, sterically compact monomer, which allows dendrimers with different density profiles to be prepared. Such difference can also lead to a difference in the overall globular size of the dendrimers. In fact, a direct comparison between **I-[G*x*]** and **II-[G*x*]** dendrimers in THF revealed the impact of the chosen monomer on the density profile, Table 1. The fourth generation **I-[G4]-(ene)$_{48}$** based on the more extended bis-MEP **2** displayed a radius of gyration of 31 Å which was 7 Å larger than the **II-[G4]-(ene)$_{48}$** counterpart (R_g 24 Å) with the more dense thioglycerol monomer **4**.

To demonstrate the versatility inherent with this chemoselective strategy, the modular building blocks could be modified to prepare dendrimers with complementary functionality at the periphery. For example, the dendrimers **I-[G*x*]** and **II-[G*x*]** in Scheme 1, have hydroxyl functionality at generations 1, 3, and 5, and alkenes at generations 2 and 4. To switch the functionality sequence, dendrimers **III-[G*x*]** bearing a trimethylolpropane core were synthesized by the initial esterification of **13** with anhydride **5**. Through this route, alkene-functional dendrimers can be obtained at generations 1, 3, and 5, while hydroxyl groups are present at the periphery of the even-number generations. In this reverse sequence of generation growth steps, the reaction between **5** and **13** proceeded in a similar fashion to previous esterifications with **3**, the main difference being observed during the work-up process. In this case, the resulting carboxylic acid byproduct was not easily removed by a basic wash due to the formation of persistent emulsions. Therefore, a lower excess of anhydride was employed for the esterification and the acid byproduct was primarily

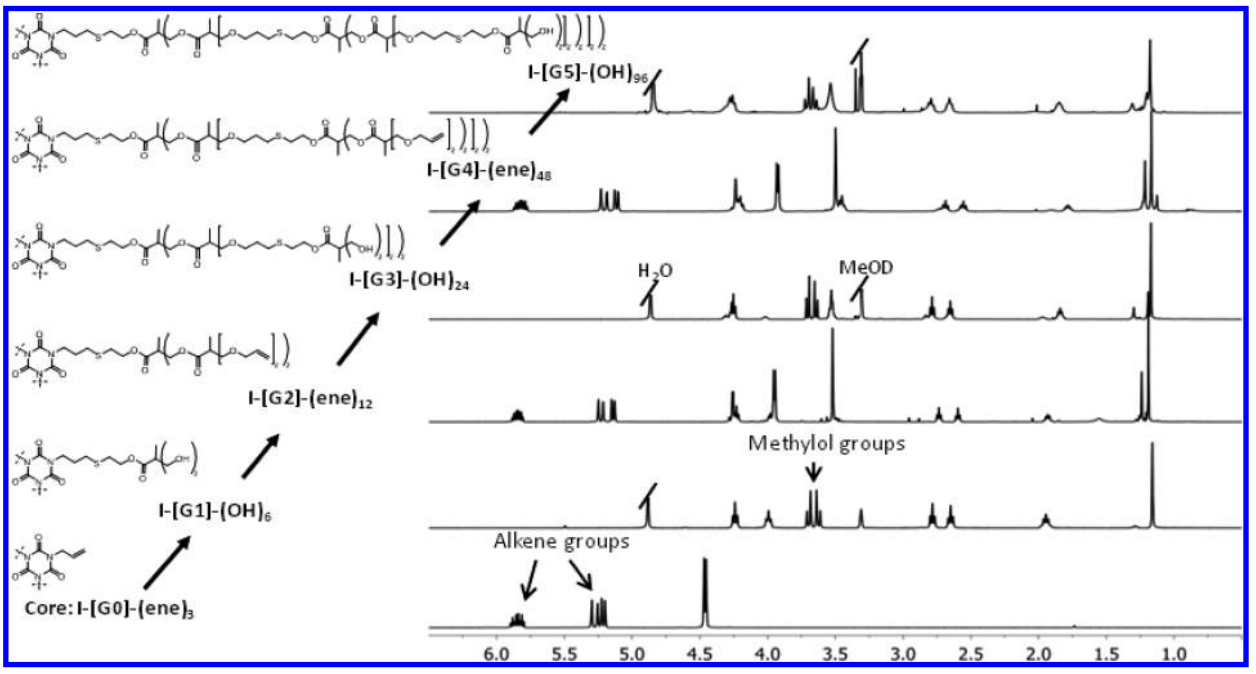


Figure 1. ^{1}H NMR spectra of **I-[G*x*]** in methanol-d_4 (OH-functionalized) and $CDCl_3$ (ene-functionalized). Generation growth is shown by the disappearance of resonances for the chain end functional groups, i.e., alkene or methylol groups.

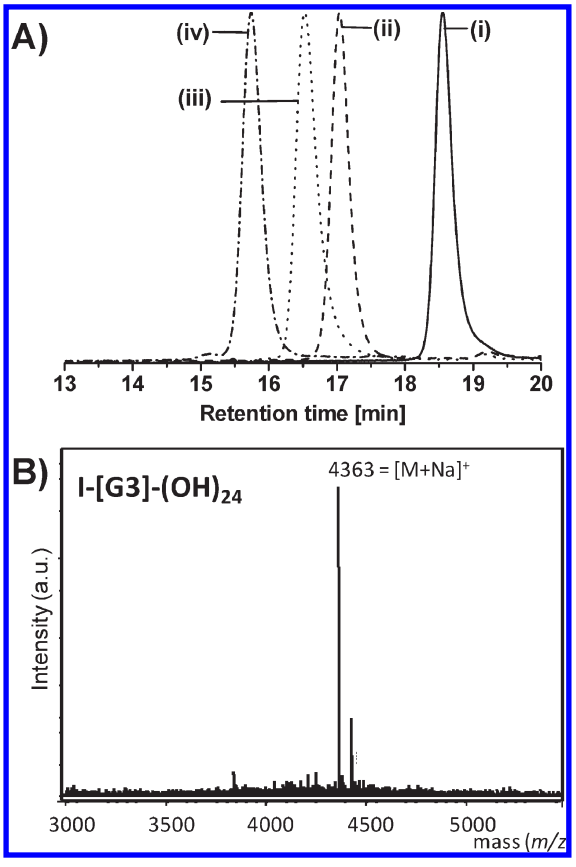


Figure 2. (A) Size exclusion chromatography (SEC) traces of (i) **I-[G1]-(OH)$_6$**, (ii) **I-[G2]-(ene)$_{12}$**, (iii) **I-[G3]-(OH)$_{24}$**, and (iv) **I-[G4]-(ene)$_{48}$**. (B) MALDI−TOF spectrum of **I-[G3]-(OH)$_{24}$**.

removed by column chromatography. SEC and MALDI−TOF traces for this family of dendrimers, **III-[G*x*]**, are shown in Figure 4. The different building blocks led to a higher molecular weight and R_g (24 632 g/mol; 73 Å) for the fifth generation derivative when compared to the corresponding fifth generation dendrimer,

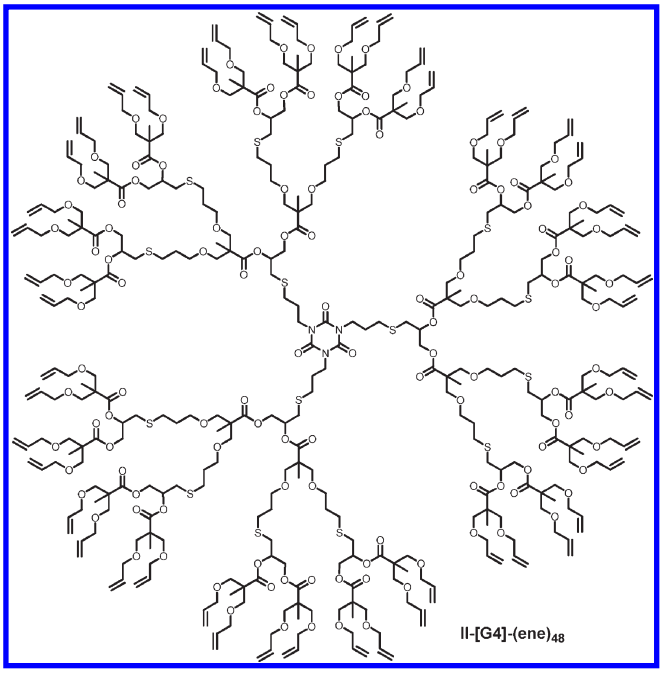


Figure 3. Fourth generation dendrimer, **II-[G4]-(ene)$_{48}$**, based on bis-MEP **2** and TG **4** monomers.

Table 1. Theoretical Molecular Weights and Radius of Gyration for I-[G*x*], II-[G*x*], and III-[G*x*] Dendrimers

	I-[G*x*]		II-[G*x*]		III-[G*x*]	
generation	M_{calc} (Da)	R_g (Å)	M_{calc} (Da)	R_g (Å)	M_{calc} (Da)	R_g (Å)
G1	831	13	574	7,0	1023	6.0
G2	2008	24	1751	8,0	2187	7.0
G3	4337	28	3049	17	5741	13
G4	9043	31	7759	24	10 398	44
G5	18 372	47			24 616	74

I-[G5]-(OH)$_{96}$ (18 372 g/mol; 47 Å). Additionally, the alkene functionality at the periphery of dendrimer **III-[G5]-(ene)$_{96}$** rendered it soluble in THF, which is in direct contrast to the

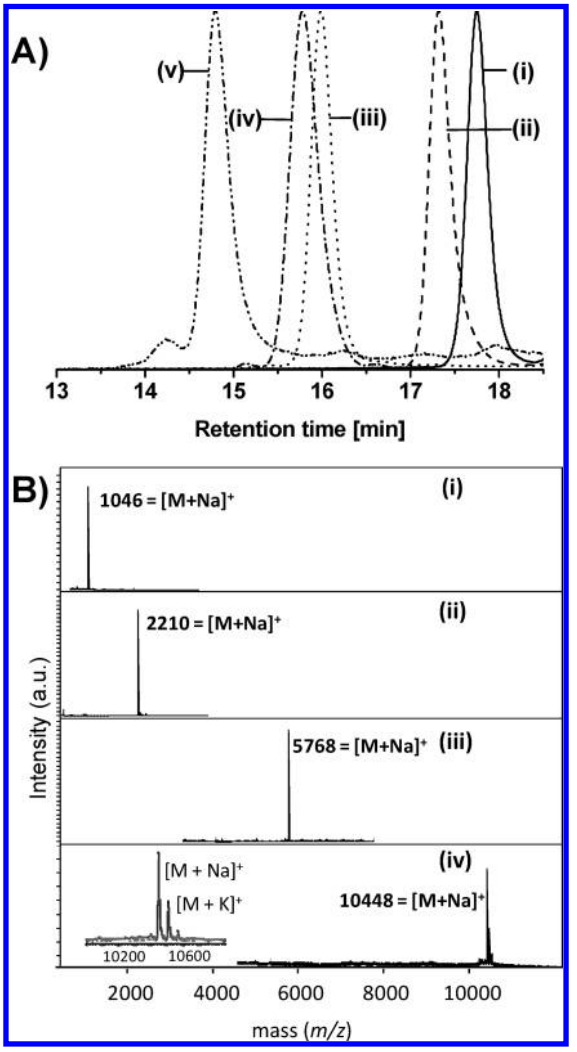
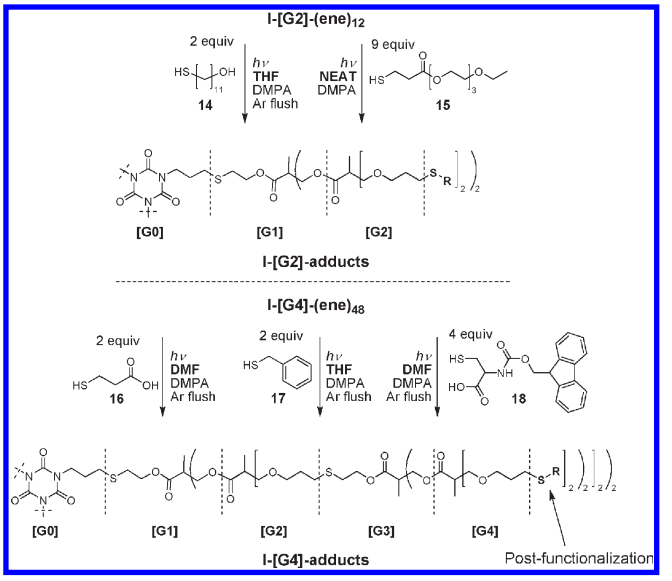


Figure 4. (A) Size exclusion chromatography traces and (B) MALDI−TOF Spectra of (i) **III-[G1]-(ene)$_6$**, **III-[G2]-(OH)$_{12}$**, (ii) **III-[G3]-(ene)$_{24}$**, (iii) **III-[G4]-(OH)$_{48}$**, and (iv) **III-[G5]-(ene)$_{96}$**.

solubility observed with **I-[G5]-(OH)$_{96}$**, thus allowing for characterization by SEC. As can be seen in Figure 4, a high molecular weight shoulder (< 5%) is observed which corresponds to double the molecular weight of the fifth generation dendrimer. Given the high density of alkenes at higher generations, and the fact that the thiol−ene coupling occurs via a radical mechanism,[29] the high molecular weight shoulder may arise from dendrimer-dendrimer coupling during the previous thiol−ene generation growth step. The simple order exchange in the reaction sequence delivered fifth generation dendrimers, **I-[G5]-(OH)$_{96}$** and **III-[G5]-(ene)$_{96}$**, with distinctively dissimilar solubility profiles. Consequently, by carefully designing the AB_2 and CD_2 monomers and their order of use during growth, the switching approach becomes a valuable tool for dendrimer chemists to predetermine the physical properties of a desired dendrimer i.e. being soluble in polar or nonpolar solvents.

In order to compare the effect of the alternating sequence of chemical functionality and thermal properties between dendrimers **I** and **III**, the glass transition temperatures were analyzed by differential scanning calorimetry (DSC). The hydroxyl functional dendrimers exhibit the highest glass transition temperatures (T_g), as compared to the alkene-functional dendrimers, due to the ability to form hydrogen bonds, with the T_g of the dendrimers **I-[G1]-(OH)$_6$**, **I-[G3]-(OH)$_{24}$**, **III-[G2]-(OH)$_{12}$**, and **III-[G4]-(OH)$_{48}$**, and **I-[G5]-(OH)$_{96}$**, being −19, −20, −20, −18, and

Scheme 4. Chemical Modifications of I-[G2]-(ene)$_{12}$ and I-[G4]-(ene)$_{48}$ via Thiol−Ene Couplings



−10 °C respectively. It is interesting to note that these values are much lower than for the corresponding hydroxyl-terminated TMP-core, Bis-MPA dendrimers, which have T_g values in the range of 15 to 25 °C.[38] This difference can be attributed to the nature of the molecular architecture with the thiol−ene dendrimers containing more flexible repeat units. As expected, the change of the end group functionality from hydroxyl to alkene resulted in a lowering of T_g values for all the dendrimers due to the lack of secondary interactions (**I-[G2]-(ene)$_{12}$**, **I-[G4]-(ene)$_{48}$**, **III-[G1]-(ene)$_6$**, **III-[G3]-(ene)$_{24}$**, and **III-[G5]-(ene)$_{96}$** exhibited T_g values of −46, −52, −26, −46, and −43, °C respectively).

To vary the properties and functionality of the alkene-functional dendrimers, coupling with a variety of mercaptans under thiol−ene conditions was carried out with **I-[G2]-(ene)$_{12}$** and **I-[G4]-(ene)$_{48}$**. The commercially available thiols **14-18** were selected and the thiol−ene couplings were carried out under similar conditions as described for the dendrimer growth (Scheme 4).[7] In most examples, only 2 equiv of thiol per alkene unit were used with the coupling of **15** to the dendrimer proceeding without any solvent due to the miscibility of all starting materials. The dendrimers were purified by simple trituration, with the exception of the adduct resulting from **I-[G2]-(ene)$_{12}$** and **15**, which needed flash chromatography.

Additionally, to illustrate the ability to tailor physical properties, the thiols, **16**−**18,** were reacted with **I-[G4]-(ene)$_{48}$**. The 3-mercaptopropionic acid **16** was chosen for its ability to introduce carboxylic groups at the periphery and, therefore, change the solubility and pH responsive properties of the resulting dendrimer. As expected, the carboxylic acid-terminated dendrimer was soluble in methanol, water, dimethyl sulfoxide (DMSO), and *N*,*N*-dimethylformamide (DMF), and insoluble in chloroform and THF. In contrast, the use of benzylmercaptan **17** allowed aromatic moieties to be introduced at the periphery, resulting in solubility in aprotic solvents such as chloroform, benzene and THF and insolubility in protic solvents, such as methanol and water. The protected amino acid **18** was selected as a model for the coupling of cysteine-functionalized peptide fragments and in contrast to the reactions above, reaction with **18** required a longer period of time to reach complete conversion (1 h), as well as increased amounts of thiol and radical initiator.

As expected, the thermal properties of the functionalized dendrimers displayed significant differences. The T_g values of

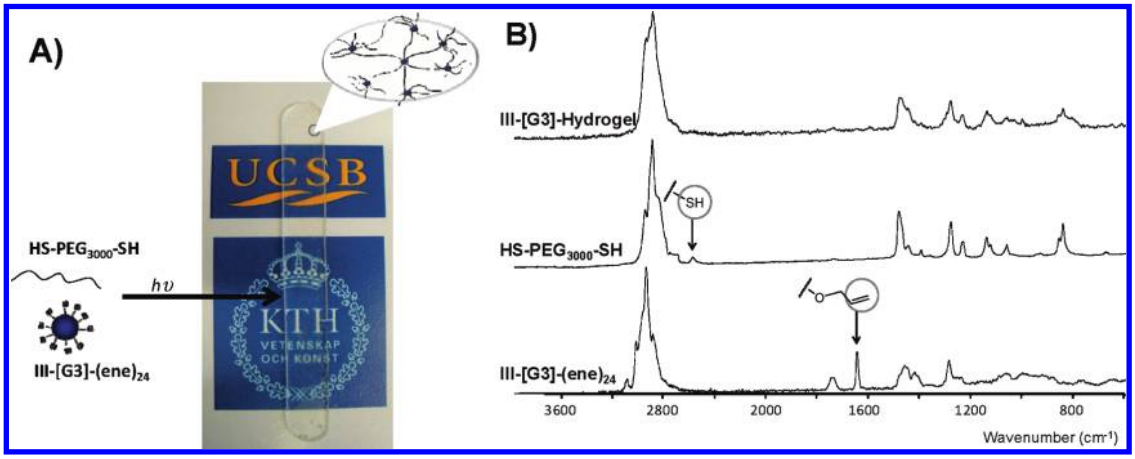


Figure 5. (A) Thiol−ene initiated PEG hydrogel based on dendritic cross-linker. (B) Raman spectrum displayed the efficient consumption of enes and thiols.

the adducts between **I-[G2]-(ene)$_{12}$** and dodecanol, **14**/methoxy-(triethylene glycol), **15**, were +5 and −55, °C respectively, yielding both higher and lower values when compared to the starting material (T_g of −46 °C). The adducts obtained from **I-[G4]-(ene)$_{48}$** and thiols **16**, **17**, and **18**, showed higher T_g values compared to the starting material (T_g of −30, −27, and +30, °C respectively).

Finally, to illustrate the potential of these chain-end functionalized dendrimers for the fabrication of functional materials, the preparation of hydrogels based on linear poly(ethylene glycol) PEG chains and dendritic cross-linkers was examined.[39] In order to fully exploit the multiple nature of alkene groups, **III-[G3]-(ene)$_{24}$** was employed as cross-linker for the fabrication of polyethylenglycol (PEG) based hydrogel. **III-[G3]-(ene)$_{24}$** was reacted with dithiol PEG (3K), in equimolar amounts, with a relative mass % of 35:65 (solids:THF). The UV initiated reaction was performed in the presence of small amounts of DMPA and the cross-linking efficacy was observed immediately leading to a white hydrogel. After solvent to water exchange, a transparent gel was obtained, Figure 5. The fully swollen hydrogel contained 86% of water and was found to fully degrade within 3 days at pH 11, while no degradation was observed when held for 12 days at pH 1. Raman spectroscopy of the **III-[G3]-(ene)$_{24}$**, PEG and the dehydrated hydrogel revealed the effectiveness of the thiol−ene reaction for the formation of novel cross-linked hydrogels.

Conclusions

The accelerated synthesis of functional dendrimers from readily available starting materials is a continuing challenge in polymer chemistry. By employing tandem thiol−ene coupling and anhydride based esterification reactions and AB_2/CD_2 monomers, a highly efficient and chemoselective approach to dendritic macromolecules has been developed. This strategy allows fifth-generation dendrimers to be synthesized in only five steps under benign reaction conditions with the use of orthogonal coupling chemistries eliminating the need for protection/deprotection steps. The modularity of this strategy and the latent reactivity of the alkene/hydroxyl chain ends were demonstrated by using different cores (alkene and hydroxyl functional), various AB_2 and CD_2 monomers and chain end groups. This afforded three dendritic libraries which exhibited tunability of both the chemical functionality and physical properties including hydrogel formation.

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