# Dendrimers Clicked Together Divergently

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ABSTRACT: Dendrimers containing 1,4-triazole linkages between each generation were grown divergently via the Click chemistry inspired Huisgen 1,3-dipolar cycloaddition reaction in the presence of a Cu(I) catalyst. The monomeric unit (1-propargylbenzene-3,5-dimethanol) contained the alkyne functionality, while the core (1,2-bis(2-azidoethoxy)ethane) and growing dendrimers presented the azide groups necessary for this type of Click reaction. The first generation dendrimer was also functionalized with alkyne termini to demonstrate an alternative pathway allowed by this chemistry. Synthesis and characterization, with infrared (IR), $^1$H and $^{13}$C NMR spectroscopies, high-resolution mass spectrometry, gel permeation chromatography (GPC), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA), are reported for these divergently grown dendrimers.

## Introduction

The ability to tune the properties of dendrimers[1−5] has allowed their development for use in diverse applications, including drug delivery,[6−15] biomimicry,[8,9,16−19] catalysis,[15,20−26] organic light emitting diodes,[15,21,27−29] molecular wires,[30,31] sensors,[32−35] imaging agents,[7,9] and various other utilities.[15,36−42] Coincident with these developments is the increasing need for facile, cost-effective methods that provide covalent connections between dendrimer generations, either convergently[43] or divergently,[44,45] and for variability in the composition and properties of the dendritic scaffold. Although many families of dendrimers have been produced, there remain opportunities for further developments, especially given the iterative growth scheme, which require efficient and versatile chemistries for the preparation of well-defined dendrimers. One type of chemistry that lends itself to such requirements is Click chemistry.

The Click chemistry concept encompasses a set of reliable regiospecific chemical transformations that give products that are easily isolated in high yields, benign byproducts (or none), and utilize readily available starting materials.[46] The Huisgen 1,3-dipolar cycloaddition between azides and alkynes[47] to yield triazoles meets the requirements for definition as a Click reaction[48] and has recently been utilized to functionalize surfaces,[49−52] polymers,[53,54] and sugars,[55−57] probe biological systems,[58−62] participate in multicomponent cascade reactions,[63,64] build libraries,[65,66] and synthesize analogues of vitamin D.[67] Because of toleration of a wide range of functionalities and high yielding reactions, the Huisgen 1,3-dipolar cycloaddition Click reaction between azides and alkynes is an obvious tool for building macromolecules,[68−71] and dendritic macromolecules, as demonstrated by the recent employment of this Click reaction to construct dendrimers convergently.[72]

Both the convergent and divergent synthetic methodologies provide routes for the production of dendritic macromolecules; however, each has specific advantages.[73] The convergent growth approach has been shown to provide for more exact macromolecular architectures having less defects, greater monodispersity, and greater control over the placement of desired functionalities, facilitated by fewer coupling reactions at each generation growth step and convenient purifications. The advantages of the divergent strategy are related to the ability to achieve higher generation growth by avoiding steric effects and to the employment of large molar equivalents of readily accessible small molecules to add mass to the structure at each generation growth. Because of the high yields and lack of byproducts provided by the Click strategy for stitching together each generation, the ease of dendrimer purification is enhanced and the disadvantages from the increasing number of reactions for each generation are curbed, thus improving the divergent methodology. The fundamental study reported herein details the growth of dendrimers divergently with triazole linkages between the core and each generation, established via repetitive Click reactions between alkyne and azide moieties. Ultimately, the resulting alkynyl- and azido-terminated dendrimers may be interesting as multifunctional, highly branched globular macromolecules, and this study represents an initial investigation into their preparation and properties.

## Experimental Section

**Instrumentation.** Infrared spectra were obtained on a Perkin-Elmer Spectrum BX FT-IR system using diffuse reflectance sampling accessories or salt plates. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were recorded as solutions on a Varian Mercury 300 spectrometer with the solvent signal as reference. Glass-transition temperatures ($T_g$), crystalline temperatures ($T_c$), and melting temperatures ($T_m$) were measured on a Mettler Toledo (Columbus, OH) DSC822 differential scanning calorimeter and analyzed with Thermal Analysis PC software (version 7.01; Mettler Toledo). Heating rates were 10 °C/min. The $T_g$ was taken as the midpoint of the inflection tangent, upon the third heating scan, the $T_c$ was

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taken as the maximum upon the third heating scan, and the $T_m$ was taken as the minimum upon the third heating scan. Thermogravometric analysis was performed on a Mettler Toledo SDTA851 TGA module with Thermal Analysis PC software (version 7.01; Mettler Toledo). Heating rates were 10 °C/min, and the onset temperature for weight loss was the point at which two tangential lines in the TGA curves intersected.

Gel permeation chromatography injections were made on a Waters Chromatography, Inc. (Milford, MA), 1515 isocratic HPLC pump, equipped with a Waters Chromatography, Inc., inline degasser AF, Breeze (version 3.30, Waters Chromatography, Inc.) software, a model 2414 differential refractometer (Waters Inc.), a Precision Detectors, Inc. (Bellingham, MA), model PD2020 dual-angle (15° and 90°) light scattering detector, and four PLgel polystyrene-*co*-divinylbenzene gel columns supplied by Polymer Laboratories, Inc. (Amherst, MA), connected in the following series: 5 $\mu$m Guard (50 × 7.5 mm), 5 $\mu$m Mixed-C (300 × 7.5 mm), 5 $\mu$m $10^4$ Å (300 × 7.5 mm), and 5 $\mu$m 500 Å (300 × 7.5 mm). Data collection was performed with Precision Detectors, Inc., Precision Acquire 32 Acquisition Program. Data analysis was performed with Precision Detectors, Inc., Discovery 32 (version 1.027.000) software. Interdetector delay volume and the light scattering detector calibration constant were determined from a nearly monodisperse polystyrene calibrant (Pressure Chemical Co., $M_n$ = 90 000 g/mol, $M_w/M_n$ < 1.04). The d*n*/d*c* values of the analyzed polymers were then determined from the differential refractometer response. Data from the differential refractometer response was exported to Origin (Origin Lab Corporation, Northampton, MA, version 7.0300) and fit with either Gaussian or Lorentzian curves to determine the relative percent area of each peak.

**Materials.** The procedures were performed on a double manifold, vacuum (0.1 mmHg), 99.99% $N_2$. Thionyl chloride (99%) was received from Sigma-Aldrich Co. (St. Louis, MO) and distilled from triphenyl phosphite (10 wt %) under $N_2$ prior to use. All other materials were used as received from Sigma-Aldrich Co. Flash column chromatography was performed using 32−63 D 60 Å silica gel from ICN SiliTech (ICN Biomedicals GmbH, Eschwege, Germany).

**Synthesis of 1,2-Bis(2-azidoethoxy)ethane (1).** A 250 mL round-bottom flask fitted with a condenser was charged with $NaN_3$ (13.81 g, 212.4 mmol), water (100 mL), and 1,2-bis(2-chloroethoxy)ethane (6.0 mL, 38 mmol). The reaction was allowed to stir at reflux for 4 days, while being monitored by $^1$H NMR spectroscopy. Upon cooling to RT, the reaction was extracted with $CH_2Cl_2$ (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, and filtered, and the filtrate was concentrated by rotary evaporation. The resulting colorless liquid was then dried under vacuum: Isolated yield 7.45 g (97%). DSC: ($T_g$) = −112 °C, ($T_c$) = −76 °C, ($T_m$) = −20 °C, TGA: 84−220 °C = 100% mass loss. IR: 3000−2800, 2103, 1442, 1345, 1286, 1123, 932 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.38 (t, $J$ = 5 Hz, 4H, $N_3CH_2CH_2OCH_2)_2$), 3.67 (s, 4H, $(N_3CH_2CH_2OCH_2)_2$), 3.68 (t, $J$ = 5 Hz, 4H, $(N_3CH_2CH_2OCH_2)_2$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ 50.8, 70.3, 70.9 ppm. HRMS (FAB): calcd for $(C_6H_{12}N_6O_2 + H)^+$: 201.1100; found: 201.1105 ± 2.4 ppm $(MH)^+$.

**Synthesis of the Propargyl Ether of Dimethyl 5-Hydroxyisophthalate (2).** A two-neck 1 L round-bottom flask was charged with dimethyl 5-hydroxyisophthalate (10.0 g, 47.6 mmol), acetone (200 mL), $K_2CO_3$ (7.9 g, 57 mmol), 18-crown-6 (0.13 g, 0.49 mmol), and propargyl bromide (80 wt %) in xylene (6.3 mL, 57 mmol). The reaction was allowed to stir under $N_2$ at reflux overnight. Upon cooling to RT, the reaction mixture was filtered, the filter cake was washed (3×) with acetone, and the filtrate was concentrated by rotary evaporation. The residue was recrystallized in ethanol and dried under vacuum overnight: Isolated yield 10.45 g (89%). TGA: 132−276 °C = 97% mass loss, % mass remaining at 600 °C = 1. IR: 3274, 3081, 3011, 2960, 1722, 1597, 1433, 1248, 1052, 996, 753 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.56 (t, $J$ = 2 Hz, 1H, $CH_2C{\equiv}CH$), 3.95 (s, 6H, $COOCH_3$), 4.79 (d, $J$ = 2 Hz, 2H, $CH_2C{\equiv}CH$), 7.84 (d, $J$ = 2 Hz, 2H, Ar**H**), 8.34 ppm (t, $J$ = 2 Hz, 1H, Ar**H**). $^{13}$C ($CDCl_3$): $\delta$ 52.7, 56.4, 76.5, 77.8, 120.5, 124.0, 132.1, 157.7, 166.1 ppm. HRMS (FAB): calcd for $(C_{13}H_{12}O_5 + H)^+$: 249.0763; found: 249.0766 ± 2.4 ppm $(MH)^+$.

**Synthesis of 1-Propargylbenzene-3,5-dimethanol (3).** Prior to use, all glassware and the magnetic stir bar were dried in an oven (110 °C) for 1 h. To a slurry of $LiAlH_4$ (5.80 g, 153 mmol) in THF (400 mL) within a flame-dried, two-neck 1 L round-bottom flask and cooled in an ice bath was added **2** (10.10 g, 40.69 mmol) as a solution in THF (100 mL) dropwise via an addition funnel. The reaction mixture was then allowed to stir under $N_2$, at reflux, for 18 h, while being monitored by TLC (10% MeOH/$CH_2Cl_2$). A saturated aqueous solution of $NH_4OH$ was added until no more $H_2$ gas evolved, and then dilute aqueous HCl was added until the pH reached 7. The reaction mixture was filtered, the filter cake was washed with THF, and the filtrate was concentrated by rotary evaporation. The resulting solid was recrystallized in 1:1, EtOAc:hexane. Isolated yield 5.82 g (75%). DSC: ($T_g$) = −34 °C, ($T_c$) = 22 C, ($T_m$) = 81 °C, TGA: 157−295 °C = 39% mass loss, 351−414 °C = 6% mass loss, 423−467 °C = 6% mass loss, % mass remaining at 600 °C = 39. IR: 3650−3050, 2924, 2874, 1599, 1464, 1171, 849, 693 cm$^{-1}$. $^1$H NMR (300 MHz, $CD_3OD$): $\delta$ 2.92 (t, $J$ = 2 Hz, 1H, $CH_2C{\equiv}CH$), 4.58 (s, 4H, $CH_2OH$), 4.73 (d, $J$ = 2 Hz, 2H, $CH_2C{\equiv}CH$), 6.89 (d, $J$ = 2 Hz, 2H, Ar**H**), 6.96 ppm (t, $J$ = 2 Hz, 1H, Ar**H**). $^{13}$C ($CD_3OD$): $\delta$ 56.7, 65.1, 76.8, 80.0, 113.3, 119.4, 144.6, 159.6 ppm. HRMS (FAB): calcd for $(C_{11}H_{12}O_3 + H)^+$: 193.0865; found: 193.0857 ± 3.9 ppm $(MH)^+$.

**Synthesis of (HO)$_4$-[G-1] (4).** A 250 mL round-bottom flask fitted with an $N_2$ inlet was charged with **3** (10.59 g, 55.09 mmol), *t*-BuOH:$H_2O$ (1:1, 65 mL total volume), and $CuSO_4 \cdot 5H_2O$ (1.56 g, 6.25 mmol). The mixture was allowed to stir at RT for 15 min. A freshly prepared 5 wt % aqueous solution of sodium ascorbic acid (49.5 mL, 12.5 mmol) was added to the reaction flask, followed by **1** (5.0 g, 25 mmol). The reaction was allowed to stir at RT for 46 h and was monitored by TLC (30% $H_2O$/isopropyl alcohol). The reaction mixture was concentrated by rotary evaporation. The residue was dissolved in MeOH and eluted on a silica gel column with 20% diethyl ether/ethyl acetate. Upon elution of the excess monomer, the eluent was changed to 30% $H_2O$/isopropyl alcohol. The product-containing fractions were combined, concentrated via rotary evaporation, and placed under vacuum overnight. Isolated yield 13.73 g (94%). DSC: ($T_g$) = 20 °C. TGA: 33−118 °C = 13% mass loss, 290−407 °C = 43% mass loss, % mass remaining at 600 °C = 32. IR: 3600−3300, 3150−3000, 3000−2800, 1597, 1452, 1290, 1060, 825 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 3.48 (s, 4H, $CH_2OCH_2CH_2$), 3.77 (t, $J$ = 5 Hz, 4H, $CH_2OCH_2CH_2$), 4.45 (s, 8H, $CH_2OH$), 4.50 (t, $J$ = 5 Hz, 4H, $CH_2OCH_2CH_2$), 5.10 (s, 4H, triazole-$CH_2O$), 5.17 (br s, 4H, O**H**), 6.84 (s, 4H, Ar**H**), 6.88 (s, 2H, Ar**H**), 8.16 (s, 2H, triazole) ppm. $^{13}$C (DMSO-$d_6$): $\delta$ 49.4, 61.0, 62.9, 68.7, 69.4, 110.9, 117.0, 124.8, 142.8, 144.0, 158.0 ppm. HRMS (FAB): calcd for $(C_{28}H_{36}N_6O_8 + H)^+$: 585.2673; found: 585.2684 ± 1.9 ppm $(MH)^+$.

**Synthesis of (N$_3$)$_4$-[G-1] (5).** A 250 mL two-neck round-bottom flask was charged with **4** (7.44 g, 12.7 mmol). One neck was fitted with a septum, and the other neck was fitted with a condenser that was attached to a dual inlet stopper. One inlet was attached to the manifold and the other to a drying tube, filled with NaOH and $CaCl_2$, that was also attached to an inverted funnel partially submerged in an aqueous NaOH bath. The reaction vessel was charged with $SOCl_2$ (80 mL, 1.1 mol) under $N_2$ via cannula. The reaction was allowed to stir in a 65 °C oil bath, under $N_2$ overnight, and was monitored by TLC (10% MeOH in $CH_2Cl_2$, $R_{f(\text{product})}$ = 0.67). The dual inlet stopper was replaced with a single inlet stopper that was connected to the manifold, and the reaction flask was placed under vacuum to remove thionyl chloride. The reaction vessel was charged with DMSO (100 mL) and $NaN_3$ (15.0 g, 231 mmol) and allowed to stir in a 90 °C oil bath, under $N_2$, for 8 h, while being monitored by TLC (10% MeOH in $CH_2Cl_2$, $R_{f(\text{product})}$ = 0.56). The reaction mixture was allowed to cool to RT and partitioned between $H_2O$ (100 mL) and $CH_2Cl_2$ (100 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3×). The

combined organic layers were dried with $MgSO_4$ and filtered, and the filtrate was concentrated via rotary evaporation. The residue was dried under vacuum overnight. Isolated yield 7.60 g (87%). $M_n$ = 600 Da, $M_w/M_n$ = 1.04 from GPC. DSC: ($T_g$) = −30 °C. TGA: 45−177 °C = 4% mass loss, 180−267 °C = 18% mass loss, 296−427 = 21% mass loss, % mass remaining at 600 °C = 47. IR: 3200−3000, 3000−2600, 2124, 1602, 1459, 1303, 1056, 846 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 3.53 (s, 4H, C**H**$_2$OCH$_2$CH$_2$), 3.82 (t, $J$ = 5 Hz, 4H, CH$_2$OC**H**$_2$CH$_2$), 4.31 (s, 8H, C**H**$_2$N$_3$), 4.50 (t, $J$ = 5 Hz, 4H, CH$_2$OCH$_2$C**H**$_2$), 5.21 (s, 4H, triazole-C**H**$_2$O), 6.89 (s, 2H, Ar**H**), 6.90 (s, 4H, Ar**H**), 7.75 (s, 2H, triazole) ppm. $^{13}C$ ($CDCl_3$): $\delta$ 159.1, 143.6, 137.9, 124.1, 120.6, 114.4, 70.5, 69.5, 62.3, 54.5, 50.4 ppm. HRMS (FAB): calcd for $(C_{28}H_{32}N_{18}O_4 + Li)^+$: 691.3014; found: 691.2983 ± 4.5 ppm $(MLi)^+$.

**Synthesis of (Alkyne)$_4$-[G-1] (6).** A 250 mL two-neck round-bottom flask was charged with **4** (0.5456 g, 0.9332 mmol). One neck was fitted with a septum, and the other neck was fitted with a condenser that was attached to a dual inlet stopper. One inlet was attached to the manifold and the other to a drying tube, filled with NaOH and $CaCl_2$, that was also attached to an inverted funnel partially submerged in an aqueous NaOH bath. The reaction vessel was charged with $SOCl_2$ (8.0 mL, 0.1 mol) under $N_2$ via cannula. The reaction was allowed to stir in a 65 °C oil bath, under $N_2$ overnight, and was monitored by TLC (10% MeOH in $CH_2Cl_2$, $R_{f(product)}$ = 0.67). The reaction flask was placed under vacuum to remove the thionyl chloride. The dual inlet stopper was replaced with a single inlet stopper that was connected to the manifold. The reaction vessel was charged with propargyl alcohol (3.0 mL, 51 mmol) followed by a solution of potassium *tert*-butoxide (0.8458 g, 7.548 mmol) dissolved in propargyl alcohol (10.0 mL, 169 mmol) under $N_2$ via syringes. The reaction was allowed to stir under $N_2$ in an 80 °C oil bath overnight and was monitored by $^1H$ NMR spectroscopy ($CD_2Cl_2$). The reaction mixture was concentrated via rotary evaporation, and the resultant residue was dissolved in $CH_2Cl_2$ and then eluted on a silica gel column with EtOAc:hexane 1:1, followed by 10% MeOH in $CH_2Cl_2$ ($R_{f(product)}$ = 0.80). Isolated yield 0.459 g (68%). DSC: ($T_g$) = −19 °C. TGA: 242−317 °C = 8% mass loss, 318−398 °C = 22% mass loss, 403−589 °C = 19% mass loss, % mass remaining at 600 °C = 51. IR: 3283, 3143, 2900−2600, 2113, 1599, 1458, 1296, 1108, 848, 682 $cm^{-1}$. $^1H$ NMR (300 MHz, $CD_2Cl_2$): $\delta$ 2.54 (t, $J$ = 2 Hz, 4H, CH$_2$C≡C**H**), 3.52 (s, 4H, C**H**$_2$-OCH$_2$CH$_2$-triazole), 3.80 (t, $J$ = 5 Hz, 4H, CH$_2$OC**H**$_2$CH$_2$-triazole), 4.15 (d, $J$ = 2 Hz, 8H, C**H**$_2$C≡CH), 4.49 (t, $J$ = 5 Hz, 4H, CH$_2$OCH$_2$C**H**$_2$-triazole), 4.54 (s, 8H, C**H**$_2$OCH$_2$C≡CH), 5.17 (s, 4H, triazole-C**H**$_2$), 6.92 (s, 4H, Ar**H**), 6.93 (s, 2H, Ar**H**), 7.76 (s, 2H, triazole) ppm. $^{13}C$ ($CD_2Cl_2$): $\delta$ 159.1, 144.0, 139.9, 124.5, 120.5, 114.0, 80.2, 75.0, 71.7, 70.9, 69.8, 62.4, 57.7, 50.8 ppm. HRMS (ESI): calcd for $(C_{40}H_{44}N_6O_8 + Na)^+$: 759.3118; found: 759.3107 ± 1.5 ppm $(MNa)^+$.

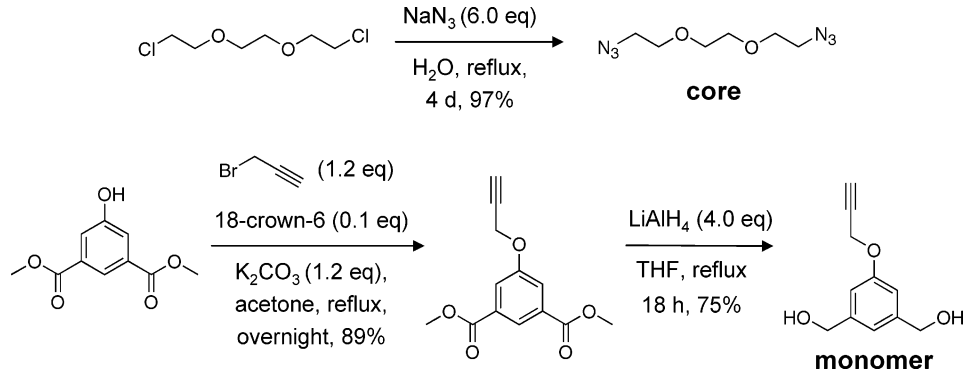
**Synthesis of (HO)$_8$-[G-2] (7).** A 500 mL round-bottom flask fitted with an $N_2$ inlet stopper was charged with a magnetic stir bar, **3** (5.70 g, 29.6 mmol), EtOH (70 mL), $CuSO_4 \cdot 5H_2O$ (0.44 g, 1.76 mmol), and a freshly prepared 5 wt % aqueous solution of sodium ascorbic acid (14.0 mL, 3.53 mmol). The mixture was allowed to stir at RT for 15 min and was then added to a 1 L round-bottom flask that was charged with **5** (4.84 g, 7.07 mmol) and a magnetic stir bar. DMSO (2 mL) was added, and the reaction was allowed to stir at RT for 24 h. The precipitated product was collected via filtration, washed (3×) with MeOH, and then placed under vacuum for 9 h. Isolated yield 9.40 g (91%). DSC: ($T_g$) = 33 °C. TGA: 33−110 °C = 3% mass loss, 124−254 °C = 5% mass loss, 270−446 °C = 35% mass loss, % mass remaining at 600 °C = 50. IR: 3620−3000, 3254, 3133, 3000−2800, 1597, 1458, 1290, 1022, 838 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 3.47 (s, 4H, C**H**$_2$OCH$_2$-CH$_2$), 3.75 (t, $J$ = 5 Hz, 4H, CH$_2$OC**H**$_2$CH$_2$), 4.45 (d, $J$ = 5 Hz, 16H, C**H**$_2$OH), 4.48 (t, $J$ = 5 Hz, 4H, CH$_2$OCH$_2$C**H**$_2$), 5.10 (s, 12H, G1-triazole-C**H**$_2$O, G1-C$_6$H$_3$C**H**$_2$), 5.16 (t, $J$ = 5 Hz, 8H, O**H**), 5.58 (s, 8H, G2-triazole-C**H**$_2$O), 6.80 (s, 8H, G2-Ar**H**), 6.85 (s, 4H, G2-Ar**H**), 6.90 (s, 2H, G1-Ar**H**), 6.95 (s, 4H, G1-Ar**H**), 8.15 (s, 2H, G1-triazole), 8.25 ppm (s, 4H, G2-triazole). $^{13}C$ (DMSO-$d_6$): $\delta$ 158.5, 158.0, 144.0, 143.3, 138.0, 125.1, 124.7, 120.1, 117.0, 114.2, 110.9, 69.4, 68.6, 62.9, 61.2, 61.0, 52.6, 49.5 ppm. HRMS (ESI): calcd for $(C_{72}H_{80}N_{18}O_{16}+2H)^{2+}$: 727.3078; found: 727.3055± 3.2 ppm $(M2H)^{2+}$.

**Synthesis of (N$_3$)$_8$-[G-2] (8).** A 250 mL three-neck round-bottom flask was charged with **7** (3.04 g, 2.09 mmol). One neck was fitted with a septum, one with a glass stopper, and the third neck with a condenser that was attached to a dual inlet stopper. One inlet was attached to the manifold and the other to a drying tube, filled with NaOH and $CaCl_2$, that was also attached to an inverted funnel partially submerged in an aqueous NaOH bath. The reaction vessel was charged with $SOCl_2$ (40 mL, 0.5 mol) under $N_2$ via a cannula. The reaction was allowed to stir in a 40 °C oil bath, under $N_2$ overnight, and was monitored by $^1H$ NMR spectroscopy (DMSO-$d_6$). The dual inlet stopper was replaced with a single inlet stopper that was connected to the manifold, and the reaction flask was placed under vacuum to remove the thionyl chloride. The reaction vessel was charged with DMSO (50 mL) and $NaN_3$ (4.91 g, 75.5 mmol). The reaction was allowed to stir in a 95 °C oil bath, open to the air, for 24 h and was monitored by $^1H$ NMR spectroscopy (DMSO-$d_6$). The reaction was allowed to cool to RT, and then $CH_2Cl_2$ (100 mL) was added followed by $H_2O$ (100 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3×). The combined organic layers were dried over $MgSO_4$ and filtered, and the filtrate was concentrated via rotary evaporation. The residue was dried under vacuum overnight. Isolated yield 2.80 g (81%). $M_n$ = 1610, $M_w/M_n$ = 1.1 from GPC. DSC: ($T_g$) = −10 °C, TGA: 40−145 °C = 5% mass loss, 145−266 °C = 20% mass loss, 290−451 °C = 19% mass loss, % mass remaining at 600 °C = 49. IR: 3422, 3139, 3000−2800, 2113, 1600, 1458, 1299, 1057, 845 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 3.46 (s, 4H, C**H**$_2$OCH$_2$CH$_2$), 3.75 (t, $J$ = 5 Hz, 4H, CH$_2$-OC**H**$_2$CH$_2$), 4.42 (s, 8H, C**H**$_2$N$_3$), 4.49 (t, $J$ = 5 Hz, 4H, CH$_2$OCH$_2$C**H**$_2$), 5.10 (s, 4H, G1-triazole-C**H**$_2$O), 5.15 (s, 8H, G1-C$_6$H$_3$C**H**$_2$), 5.55 (s, 8H, G2-triazole-C**H**$_2$O), 6.91 (s, 2H, G1-Ar**H**), 6.96 (s, 4H, G1-Ar**H**), 6.98 (d, $J$ = 0.9 Hz, 4H, G2-Ar**H**), 7.02 (d, $J$ = 0.9 Hz, 8H, G2-Ar**H**), 8.15 (s, 2H, G1-triazole), 8.30 ppm (s, 4H, G2-triazole). $^{13}C$ (DMSO-$d_6$): $\delta$ 158.5, 158.4, 142.8, 142.1, 138.0, 137.7, 125.0, 124.8, 120.7, 114.3, 114.2, 69.4, 68.6, 61.2, 53.3, 52.6, 49.4 ppm. HRMS (ESI): calcd for $(C_{72}H_{72}N_{42}O_8+2H)^{2+}$: 827.3337; found: 827.3309 ± 3.4 ppm $(M2H)^{2+}$.

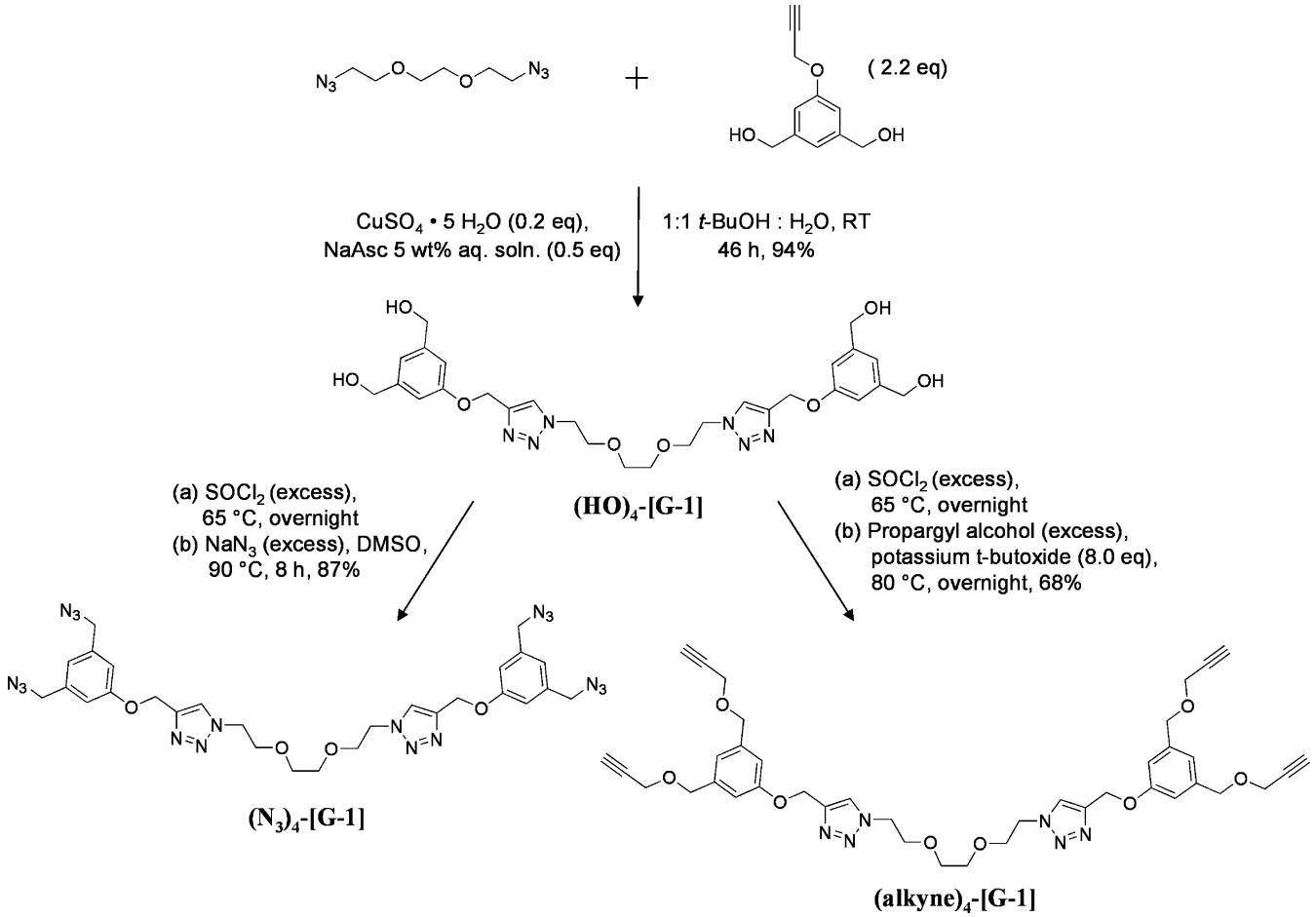
**Synthesis of (HO)$_{16}$-[G-3] (9).** A 100 mL round-bottom flask fitted with an $N_2$ inlet stopper was charged with a magnetic stir bar, **8** (0.8 g, 0.5 mmol), DMSO (9 mL), and **3** (0.76 g, 3.95 mmol). A freshly prepared solution of sodium ascorbic acid (0.48 g, 2.42 mmol) in 10% $H_2O$ in DMSO (10 mL DMSO, 1 mL $H_2O$) was added followed by $CuSO_4 \cdot 5H_2O$ (0.030 g, 0.120 mmol). The reaction was allowed to stir at RT for 42 h and was monitored by $^1H$ NMR (DMSO-$d_6$). The reaction was precipitated into cold $H_2O$, and the solid was isolated by vacuum filtration and redissolved in DMSO. The solution was placed under vacuum overnight, the resulting concentrated solution was precipitated in cold $H_2O$, and the product was isolated by centrifugation. Isolated yield 1.34 g (87%). DSC: ($T_g$) = 91 °C, TGA: 31−96 °C = 8% mass loss, 101−146 °C = 6% mass loss, 272−467 °C = 25% mass loss, % mass remaining at 600 °C = 55. IR: 3600−3000, 3000−2800, 1600, 1458, 1297, 1059, 825 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 3.46 (s, 4H, C**H**$_2$OCH$_2$CH$_2$), 3.75 (br s, 4H, CH$_2$OC**H**$_2$-CH$_2$), 4.48 (d, $J$ = 5 Hz, 36H, C**H**$_2$OH, CH$_2$OCH$_2$C**H**$_2$), 5.12 (s, 28H, G1-triazole-C**H**$_2$O, G1-C$_6$H$_3$C**H**$_2$, G2-C$_6$H$_3$C**H**$_2$), 5.21 (br t, $J$ = 5 Hz, 16H, O**H**), 5.57 (s, 24H, G2-triazole-C**H**$_2$O, G3-triazole-C**H**$_2$O), 6.85 (s, 24H, G2-Ar**H**, G3-Ar**H**), 6.90 (s, 12H, G2-Ar**H**, G3-Ar**H**), 6.93 (s, 2H, G1-Ar**H**), 7.00 (s, 4H, G1-Ar**H**), 8.16 (s, 2H, G1-triazole), 8.29 (s, 12H, G2-triazole, G3-triazole) ppm. $^{13}C$ (DMSO-$d_6$): $\delta$ 158.5, 158.0, 144.0, 143.3, 138.1, 125.0, 124.7, 120.2, 117.1, 114.3, 110.9, 69.4, 68.6, 62.9, 61.2, 52.6, 49.5 ppm. HRMS (ESI): calcd for $(C_{160}H_{168}N_{42}O_{32}+3H)^{3+}$: 1064.4358; found: 1064.4342 ± 1.5 ppm $(M3H)^{3+}$.

**Synthesis of (N$_3$)$_{16}$-[G-3] (10).** A scintillation vial charged with **9** (0.4050 g, 0.1269 mmol) and a magnetic stir bar was fitted with a septum that had a needle connected to the manifold and another needle connected to a drying tube, filled with NaOH and $CaCl_2$, that was also attached to an inverted

**Scheme 1. Synthesis of the Bis(azide) Dendrimer Core and Alkyne-Functionalized Monomer**




**Scheme 2. Synthesis of First Generation Dendrimers and Functionalization with Azido and Alkyne Termini**




funnel partially submerged in an aqueous NaOH bath. The reaction vessel was charged with $SOCl_2$ (5.0 mL, 68 mmol) under $N_2$ via a cannula. The reaction was allowed to stir and a 40 °C oil bath, under $N_2$ overnight, and was monitored by $^1$H NMR spectroscopy (DMSO-$d_6$). The needle connected to the drying tube was removed and the reaction flask was placed under vacuum to remove the thionyl chloride. The reaction vessel was charged with DMSO (5 mL) and $NaN_3$ (0.6 g, 9.2 mmol) and then allowed to stir in a 90 °C oil bath, open to the air, overnight and was monitored by $^1$H NMR spectroscopy (DMSO-$d_6$). The reaction was allowed to cool to RT, $CH_2Cl_2$ (10 mL) was added followed by $H_2O$ (10 mL), and the aqueous layer was extracted (3×) with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$ and filtered, and the filtrate was concentrated via rotary evaporation. The residue was dried under vacuum overnight. Isolated yield 0.23 g (50%). $M_n$ = 3850, $M_w/M_n$ = 1.01 from GPC. DSC: ($T_g$) = −9 °C. TGA: 32−87 °C = 1% mass loss, 89−179 °C = 11% mass loss, 183−270 °C = 14% mass loss, 276−434 °C = 16% mass loss, % mass remaining at 600 °C = 49. IR: 3200−3000, 3000−2800, 2960, 2108, 1600, 1458, 1298, 1052, 844 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 3.44 (s, 4H, C**H**$_2$OCH$_2$CH$_2$), 3.73 (s, 4H, CH$_2$-OC**H**$_2$CH$_2$), 4.42 (s, 36H, C**H**$_2$N$_3$, CH$_2$OCH$_2$C**H**$_2$), 5.09 (s, 12H, G1-triazole-C**H**$_2$O, G1-C$_6$H$_3$C**H**$_2$), 5.14 (s, 16H, G2-C$_6$H$_3$C**H**$_2$), 5.53 (s, 24H, G2-triazole-C**H**$_2$O, G3-triazole-C**H**$_2$O), 6.84−7.10 (br m, 42H, G1-Ar**H**, G2-Ar**H**, G3 Ar**H**), 8.14 (s, 2H, G1-triazole), 8.30 ppm (s, 12H, G2-triazole, G3-triazole). $^{13}$C (DMSO-$d_6$): $\delta$ 158.6, 143.1, 142.9, 138.3, 137.9, 125.4, 125.2, 120.9, 120.4, 114.5, 114.2, 61.4, 61.2, 53.6, 52.9, 49.0 ppm. HRMS (ESI): calcd for ($C_{160}H_{152}N_{90}O_{16}$+3H)$^{3+}$: 1197.4694; found: 1197.4670 ± 2.0 ppm (M3H)$^{3+}$.

## Results and Discussion

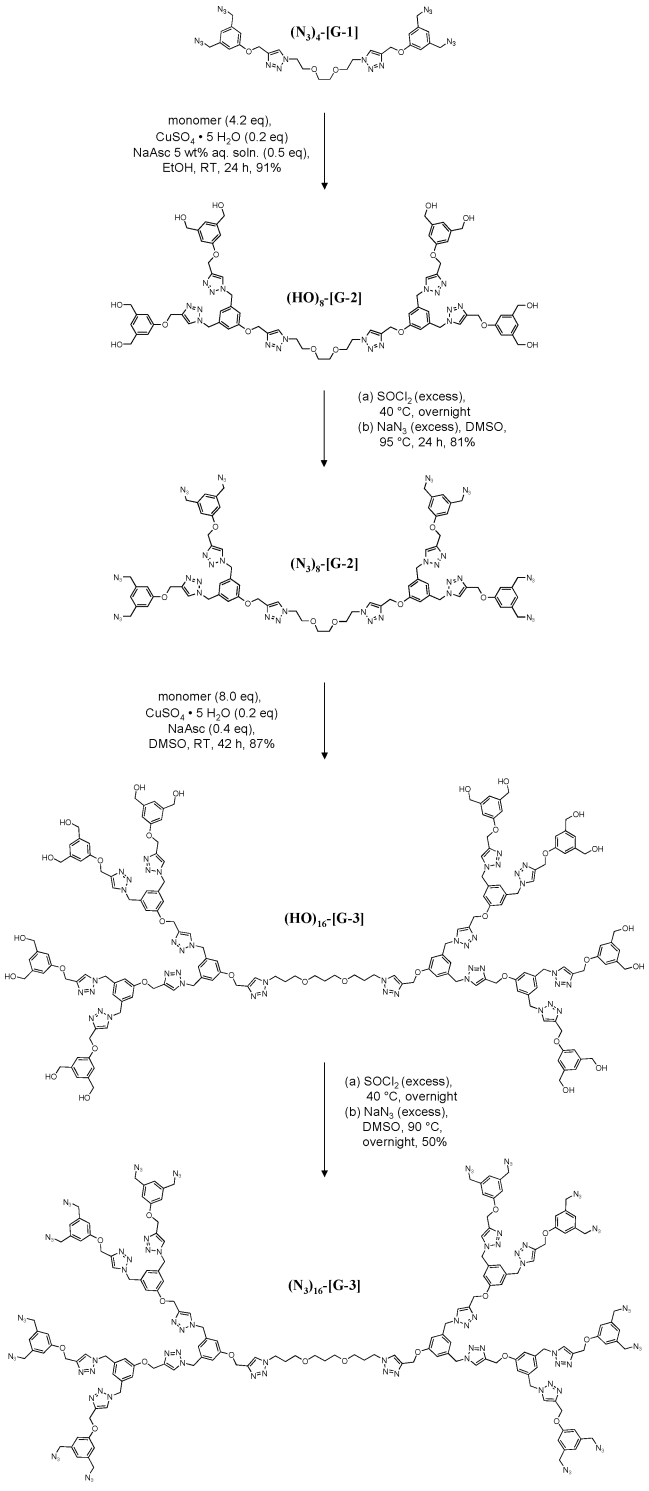
**Core and Monomer Syntheses.** The bis(azide) core, designed to present two azide functionalities available for dendrimer growth via Click reactions with the monomer, was synthesized readily, as shown in Scheme

1, from 1,2-bis(2-chloroethoxy)ethane and sodium azide. Similarly, the monomer was crafted to present an alkyne functionality available to participate in Click reactions with the core or growing dendrimer during the generation growth steps and began with the transformation of the alcohol group of dimethyl 5-hydroxyisophthalate into a propargyl ether functionality. Reduction of the methyl esters to alcohols afforded a monomer with alcohol functionalities available for conversion to either azide or alkyne groups during an activation step via a chloro intermediate, thus providing a handle for generation growth.

**Dendrimer Syntheses.** Dendrimers were assembled through an iterative process involving a Click reaction followed by activation via in situ halogenation and azido nucleophilic substitution, as illustrated in Schemes 2 and 3. The Click reactions were conducted in the presence of Cu(I) generated in situ from $CuSO_4 \cdot 5H_2O$ and sodium ascorbic acid. Catalysis by Cu(I) ensured regioselective formation of the 1,4-disubstituted 1,2,3-triazole isomer, rather than a mixture with the corresponding 1,5-disubstituted 1,2,3-triazole isomer.[74] The alcohol termini of the first generation dendrimer ($(HO)_4$-[G-1]) could be transformed into either alkyne groups ($(alkyne)_4$-[G-1]) or azide groups ($(N_3)_4$-[G-1]), demonstrating the versatility of the synthetic approach. The alkyne-terminated dendrimer was synthesized from a one-pot, two-step reaction sequence by initial reaction of $(HO)_4$-[G-1] with an excess of thionyl chloride to yield as an intermediate, chloro terminal groups. Following removal of the thionyl chloride in vacuo, a solution of potassium *tert*-butoxide dissolved in propargyl alcohol was added to transform the chloro termini into alkyne termini. The azide-terminated dendrimer was prepared by a similar process with the chloro-terminated intermediate being dissolved in DMSO and then allowed to undergo reaction with an excess of sodium azide. The desired first generation azide-terminated dendrimer ($(N_3)_4$-[G-1]) was obtained in >97% purity by a simple extraction into dichloromethane.

Dendrimer growth then proceeded via an iterative sequence that involved Click reactions between azido chain ends of the growing dendrimers with the alkynyl group of the monomer, followed by reactivation via transformation of the hydroxyl groups to azides, until the third generation azide-terminated dendrimer was afforded. The second generation hydroxyl-terminated dendrimer ($(HO)_8$-[G-2]) was obtained via a Click reaction between the first generation azide-terminated dendrimer ($(N_3)_4$-[G-1]) and the monomer. The desired product formed as a precipitate during the reaction and was isolated in >95% purity (as determined by GPC) without further purification and represents ca. 99+ % yield for each Click coupling reaction. The alcohol termini of $(HO)_8$-[G-2] were transformed into azide groups, by the same procedure as was employed for the first generation material, to yield $(N_3)_8$-[G-2]. Again, the desired product was isolated by simple extraction into dichloromethane to achieve >94% purity and was not purified further. The third generation dendrimer ($(HO)_{16}$-[G-3]) was synthesized using the same Click reaction and obtained in >95% purity via precipitation into water, without further purification. The alcohol termini of the third generation dendrimer were transformed into azide groups by the in situ two-step reaction described previously for the earlier generations. The desired third generation azide-terminated dendrimer

**Scheme 3. Synthesis of Generation 2 and 3 Dendrimers by a Divergent Click Strategy**




($(N_3)_{16}$-[G-3]) was isolated from the reaction mixture by extraction into dichloromethane in >87% purity and was not purified further.

**Characterization.** $^1$H NMR spectroscopy was an especially useful tool for illustrating the growth of each new dendrimer generation, as shown from the stacked plots in Figure 1. As successive generations were added, new resonances corresponding to the additional generations of monomer appeared as well as unique triazole proton signals. Upon growth of the second generation, the first generation triazole proton (d) remained visible at 8.16 ppm in the $(HO)_8$-[G-2] spectrum, while a second

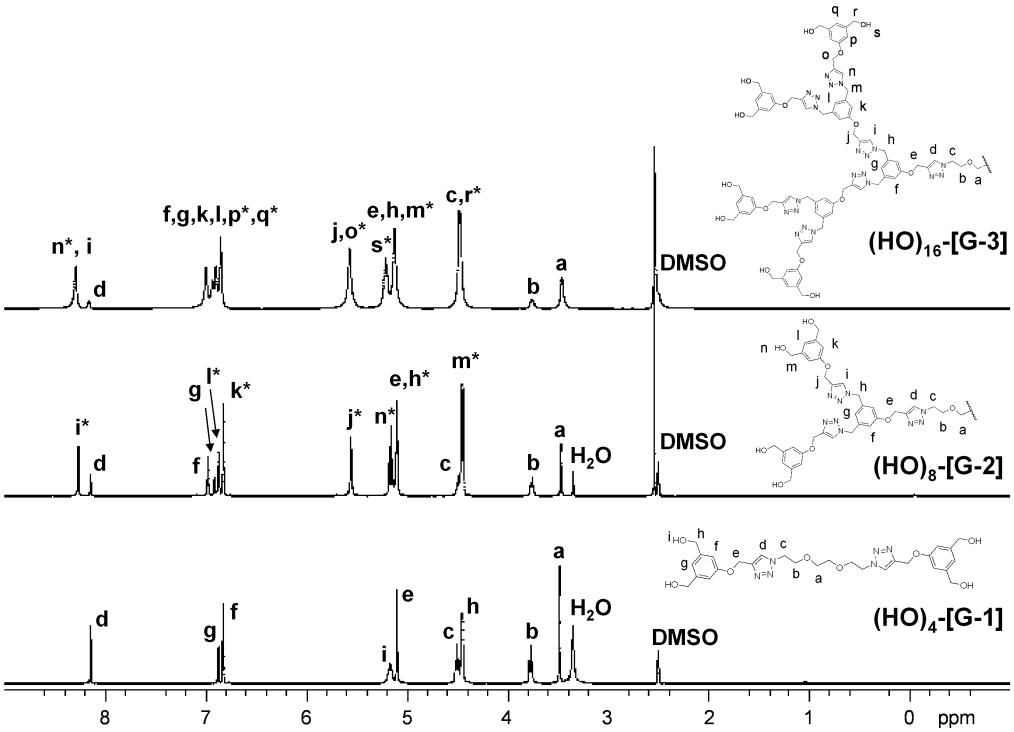



**Figure 1.** $^1$H NMR spectra of alcohol-terminated first, second, and third generation dendrimers. On going from generation 1 to 2 to 3, the resonances due to protons from the new generations are designated with asterisks.

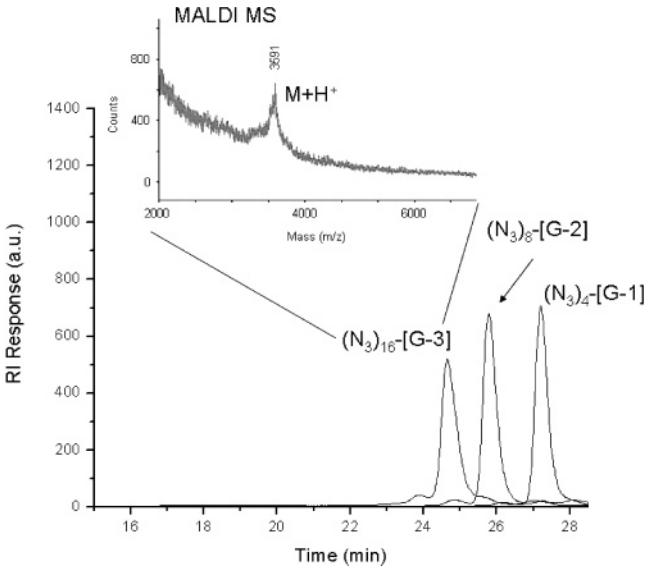



**Figure 2.** GPC traces for azide terminated dendrimers and MALDI MS spectrum for $(N_3)_{16}$-[G-3].

triazole resonance (integration ratio of i:d was 2:1) corresponding to the new generation (i) was observed at 8.25 ppm. The triazole proton (d) for the first generation layer was also apparent at 8.16 ppm in the $(HO)_{16}$-[G-3] spectrum; however, the signals due to the second and third generation triazole protons (i and n, respectively) were observed at overlapping chemical shifts. The ratio of integrations for peaks i + n:d was 6:1 and corresponds with the expected structure based on divergent growth of the third generation.

Because of a lack of solubility in THF for the alcohol-terminated derivatives, analysis of the dendritic growth strategy by gel permeation chromatography (GPC) was performed for the azido-terminated species (Figure 2). Small amounts of impurities were detected in each generation. The contaminant in $(N_3)_4$-[G-1] was of higher molecular weight, corresponding to that of a dimeric, [G-2]-like species, which constituted ca. 3% of the total sample. Both higher molecular weight, [G-3]-like species and lower molecular weight, [G-1]-like species were observed in the GPC traces for $(N_3)_8$-[G-2]; however, these impurities were present as only ca. 4% and 2%, respectively, of the total sample. Similarly, the $(N_3)_{16}$-[G-3] dendrimer contained multiple low molecular weight impurities that totaled ca. 13% of the entire sample and a high molecular weight contaminant that was ca. 0.5% of the total product. The impurities detected by GPC were also observed in the mass spectra, for example, as shown for the MALDI-TOF spectrum of $(N_3)_{16}$-[G-3] (Figure 2, inset). Although the structures of the impurities could not be assigned definitively, the observed levels of purity are expected given the absence of any purification by chromatography, with the crude reaction mixtures only having undergone precipitation or extraction.

Each product was also characterized by IR spectroscopy, which clearly illustrated the terminal group transformations, as shown in Figure 3. The alcohol termini gave rise to a characteristic broad and strong stretch from 3620 to 3000 cm$^{-1}$, while the azide termini produced a characteristic strong stretch at 2110 cm$^{-1}$. With each activation step, upon conversion of the OH termini into azide groups, the OH stretch was eliminated and the azide stretch became visible.

As expected, the behavior of the dendrimers was controlled by the terminal functional groups and the generation number. For example, the alkyne- and azide-terminated dendrimers were soluble in a broad range of organic solvents, such as THF, $CH_2Cl_2$, DMSO, etc. In contrast, the alcohol-terminated dendrimers, beyond the first generation, were only sparingly soluble in DMSO and DMF. The first generation dendrimer, $(HO)_4$-[G-1], was soluble in methanol and aqueous solvents, while higher generations, with increasing

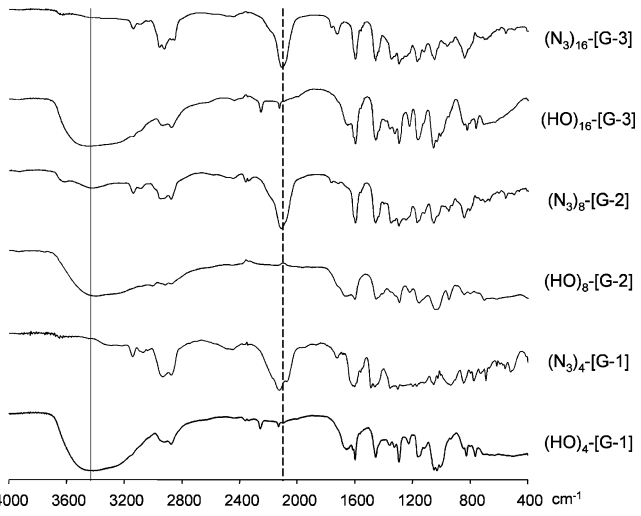



**Figure 3.** IR spectra (diffuse reflectance) of alcohol and azide-terminated first, second, and third generation dendrimers. Alcohol stretch region (solid line), azide stretch region (dashed line), *y*-axis % transmittance (arbitrary units).

amounts of aromatic hydrophobic monomer units, were insoluble.

The effects of the generation number and terminal group composition were further demonstrated in the thermal transition temperatures, as observed by DSC.[75,76] The glass transition temperature ($T_g$) increased with increasing generation number, and this trend was observed in both the alcohol-terminated and the azido-terminated series. For the alcohol-terminated dendrimers, the $T_g$ increased from the first generation, 20 °C, to the second generation, 33 °C, and then further increased to the third generation, 91 °C. The $T_g$ increased from −30 to −10 °C, and then to −9 °C, for the first, second, and third generation azido-terminated dendrimers. Relative to the alcohol-terminated dendrimers, the less polar azido-terminated dendrimers showed lower glass transition temperatures, which was expected on the basis of the behavior of the core and monomer small molecules, as well as earlier reports in the literature.[75]

## Conclusions

Divergent construction utilizing a Click reaction as the generation growth step has been shown to provide facile synthetic routes for obtaining dendritic macromolecules with little or no purification. Availability of azide and alkyne functionalized cores and monomers allows for the possibility of numerous synthetic pathways and, thus, many other dendrimers than those demonstrated. The azide- and alkyne-functionalized dendrimers have capability for undergoing further Click reactions and also possess branching architectures. This combination of functionality and architecture lend the dendrimers toward use as cross-linkers by a process that is similar to that demonstrated for other dendrimers[77,78] and hyperbranched polymers.[79,80] Investigations of the applications of these Click-constructed dendrimers as reactive and multifunctional globular macromolecules are underway.

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