Linear−Dendritic Poly(ester)-*block*-poly(ether)-*block*-poly(ester) ABA Copolymers Constructed by a Divergent Growth Method[1]

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ABSTRACT: The divergent synthesis of amphiphilic linear−dendritic block copolymers, LDBCs, that contain linear poly(ethylene glycol), PEG, and dendritic poly(benzyl ester)s is explored in this report. First [G1]- and second [G2]-generation LDBCs are constructed from PEG with a molecular weight of 5000 Da and 3,5-dioxy benzoate as the fundamental dendritic repeat unit. The synthetic strategy is based on the initial coupling of the protected monomer 3,5-bis(*tert*-butyldimethylsiloxy)benzoyl chloride to PEG (yield 98%) followed by removal of the silyl protective groups under mild conditions to give $(HO)_2$[G1]-PEG5K-[G1]$(OH)_2$, yield 97%. Subsequent coupling of the acid chloride monomer proceeds with 96% yield, and the final deprotection yields 94% of pure $(HO)_4$[G2]-PEG5K-[G2]$(OH)_4$. Two different chemical reactions (acid−alcohol and alcohol−halide interaction) are evaluated as possible routes to facile surface modification of the aromatic polyester monodendrons.

Introduction

The poly(ethylene glycol), PEG, based copolymers and their biomedical application continue to attract considerable academic and industrial interest.[2] The main emphasis is currently placed on the design of materials with novel architectures and improved exploitation characteristics. In the past few years a series of studies were devoted to the synthesis and properties of a novel class of amphiphilic materials containing PEG as the hydrophilic block—the linear−dendritic block copolymers.[3] Some of these hybrid copolymers rapidly formed well-defined micelles in aqueous media[3c,f] and were shown capable of physically binding polyaromatic compounds, PACs, with great variety in size, from phenanthrene to C_{60}.[4] The complexes were remarkably stable—the micelles successfully maintained their integrity and PAC load for extended periods of time, C_{60} remained bound in the micellar core for more than 1 year,[4a] and pyrene remained encapsulated for more than 3 years.[5] The inherent solution properties and biological behavior of the PEG component make the linear−dendritic block copolymers (LDBC) rather suitable also for selective surface coating,[6] drug and DNA delivery systems,[7] and other advanced biomedical applications.[8] If amphiphilic linear−dendritic copolymers are to be used as carriers in medicinal applications, it is important that they contain hydrolyzable dendritic linkages to facilitate the degradation and eventual elimination (excretion) of the dendritic capsule in vivo. In an attempt to model this process, we are exploring the formation and surface modification of PEG based hybrid ABA block copolymers with terminal dendritic fragments constructed of aromatic polyester linkages.

Poly(benzyl ester) monodendrons[9] were previously created by convergent techniques,[10] but their coupling to PEG by Williamson ether reaction[3a] or metal-catalyzed transesterification[3b] is obviously not suitable due to the chemical nature of the monodendrons. For the same reasons, the growth of the linear PEG chain through an anionic ring-opening polymerization on preformed poly(benzyl ester) monodendrons would be prohibited.[11] Therefore, in this study we are utilizing a divergent growth strategy with specific coupling and deprotection sequence at both ends of the PEG chain that would not affect the resulting ester linkages. An additional advantage of this approach would be the possibility to modify the surface of the dendritic fragments, thus adjusting the final properties of the copolymers formed to their desired application.[12] The accessibility of the monodendritic surface groups in the hybrid copolymer is tested by two model reactions: an acid−alcohol and alcohol−halide interaction.

Experimental Section

Materials. All reagents utilized are of the highest purity available and are used as provided from the manufacturer unless otherwise noted. PEG with molecular weight 5000 Da (PEG5K) was acquired from Polyscience, Inc. 3,5-Dihydroxybenzoic acid, benzoic acid, benzyl bromide, oxalyl chloride, sodium hydroxide, and zinc tetrafloroborate hydrate were all purchased from Aldrich Chemical; *tert*-butyldimethylsilyl chloride was obtained from Acros Organics. Triethylamine (Fischer) was dried over 4 Å molecular sieves (Fischer), and toluene (Fisher) was dried over calcium hydride. Benzyltrimethylammonium chloride (Fischer) was recrystallized from methanol and dried at 150 °C. Dichloromethane (J.T. Baker) was dried over phosphorus pentoxide (Fischer). Tetrahydrofuran, THF (Mallinckrodt), was dried with benzophenone sodium.

Instrumentation. Size-exclusion chromatography (SEC) in THF was used to monitor the progress of dendrimer synthesis and aid in the confirmation of product purity. The SEC system consisted of a M 510 pump, U6K universal injector, column heater, M 450 UV detector (all from Waters), 250 dual refractometer/viscometer detector, and 400 data manager (both from Viscotek Corp.). Separations were carried out across three 5 μm American Polymer Standards AmGel columns (10^3 Å, 10^2 Å, and linear) at an eluent flow rate of 1 mL/min and temperature settings at 40 °C. The molecular weights were calculated using a standard calibration curve generated by narrow poly(styrene) standards (American Polymer Standards) with molecular weights from 194 to 1 030 000 Da and Viscotek TriSEC software, Version 3.0, Revision B.01.04.

Nuclear magnetic resonance (NMR) measurements were performed at room temperature with a Bruker Avance 300 MHz spectrometer using deuterated chloroform or methanol as the sample solvent and internal standard. Infrared spectra

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were recorded on a Nicolet IR 400 spectrophotometer with sample films deposited on ZnSe plates (Infracal).

LDBC Synthesis. *tert*-Butyldimethylsilyl 3,5-Bis(*tert*-butyldimethylsiloxy)benzoate (1). 3,5-Dihydroxybenzoic acid (10 g, 64 mmol) and *tert*-butyldimethylsilyl chloride (31.35 g, 208 mmol) were combined with 100 mL of dry toluene in a 250 mL two-neck round-bottom flask. The reagents were stirred vigorously, triethylamine (29.83 mL, 214 mmol) was added dropwise, and the mixture was refluxed under nitrogen for 24 h. The mixture was then placed into a 1000 mL separatory funnel and was washed with 350 mL of water and 25 mL of brine. The toluene layer was collected and washed twice more with 100 mL of water. The organic fraction was then dried with magnesium sulfate and filtered, and the solvent was removed by rotary evaporator under reduced pressure and heating. The product was then allowed to dry under reduced pressure in a vacuum oven overnight at 90 °C. The triprotected ester appeared as a light-brown solid and was stored in a desiccator prior to use; yield 91%.

^{1}H NMR ($CDCl_3$): δ 0.21 (s, 12 H, PhOSi(C*H*$_3$)$_2$), 0.37 (s, 6 H, CO_2Si(C*H*$_3$)$_2$), 0.98 (s, 18 H, PhOSiC(C*H*$_3$)$_3$, 1.02 (s, 9 H, CO_2SiC(C*H*$_3$)$_3$), 6.47−6.55 (t, 1 H Ar*H*), 7.13−7.14 (d, 2 H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ −4.86 (2 C, COOSi(*C*H$_3$)$_2$), −4.47 (4 C, PhOSi(*C*H$_3$)$_2$), 17.73 (1 C, COOSi*C*), 18.20 (2 C, PhOSi*C*), 25.55 (3 C, COOSiC(*C*H$_3$)$_3$) d, 26.62 (6 C, PhOSiC(*C*H$_3$)$_3$), 114.87 (2 C, Ar*C*H), 117.02 (1 C, Ar*C*H), 133.15 (1 C, Ar*C*-COOSi), 156.47 (2 C, Ar*C*O), 166.18 (1 C, Ph*C*OOSi).

3,5-Bis(*tert*-butyldimethylsiloxy)benzoyl Chloride (2). To a 250 mL two-neck pear-shaped flask were added 10 mL of dry dichloromethane, the triprotected ester **1** (10 g, 20.1 mmol), and benzyltrimethylammonium chloride (0.0689 g, 0.371 mmol). The mixture was set to a medium stir and flushed with dry nitrogen while fresh oxalyl chloride (3.5 mL, 40.4 mmol) was slowly added dropwise. The reaction mixture was then heated at reflux for 18 h. The solvent and excess oxalyl chloride were removed via rotary evaporator under reduced pressure and heating to 70 °C, and the residue was subsequently placed in a vacuum oven for 8 h at 70 °C. The crude product was then purified by short-column flash chromatography, eluting with hexane/methylene chloride (4:1, v/v). The solvent was removed by rotary evaporator under reduced pressure. The solid residue was dried in a vacuum oven for 8 h under reduced pressure at 60 °C. When cooled to room temperature, the product appeared as a white crystalline solid; yield 90%.

^{1}H NMR ($CDCl_3$): δ 0.23 (s, 12 H, PhOSi(C*H*$_3$)$_2$), 0.99 (s, 18 H, PhOSiC(C*H*$_3$)$_3$), 6.62−6.64 (t, 1 H, Ar*H*), 7.19−7.20 (d, 2 H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ −4.48 (4 C, PhOSi*C*H$_3$), 18.18 (2 C, PhOSi*C*), 25.56 (6 C, PhOSiC(*C*H$_3$)$_3$), 116.13 (2 C, Ar*C*H), 119.01 (1 C, Ar*C*H), 134.73 (1 C, Ar*C*COCl), 156.86 (2 C, Ar*C*O), 167.94 (1 C, Ph*C*OCl).

P$_2$[G1]-PEG5K-[G1]P$_2$ (3). To a 50 mL two-neck pear-shaped flask with a dry nitrogen feed were added PEG (0.500 g, 0.100 mmol), 3,5-bis(*tert*-butyldimethylsiloxy)benzoyl chloride (**2**) (0.143 g, 0.357 mmol), and 10 mL of THF, freshly distilled from sodium benzophenone. Dry toluene (0.010 mL) was also added as a SEC marker. The reaction mixture was gently heated to promote dissolution and then allowed to mix well for 15 min. Sodium hydroxide (0.100 g, 2.5 mmol) was added, and the reaction mixture was stirred at room temperature for 1.5 h. SEC was used to monitor the reaction progress. Upon the reaction's completion, the mixture was filtered through a 30 mL, 10−20 μm, Buchner glass-frit filter. The collected clear solution was added dropwise to 200 mL of hexane under stirring. The desired product formed a white precipitate. The mixture was allowed to stir for no less than 15 min to remove the unreacted monomer; then the precipitate was collected on a 30 mL, 6−10 μm, Buchner glass-frit filter. After drying the product appeared as a white powder; yield 98%.

^{1}H NMR ($CDCl_3$): δ 0.19 (s, 12 H, PhOSi(C*H*$_3$)$_2$), 0.97 (s, 18 H, PhOSiC(C*H*$_3$)$_3$), 3.35−3.90 (m, 452 H, PEG C*H*$_2$O), 4.40−4.45 (t, 4 H, PEG(C*H*$_2$OCOPh)$_2$), 6.49−6.52 (t, 2 H, G1Ar*H*), 7.10−7.13 (d, 4 H, G1 Ar*H*). ^{13}C NMR ($CDCl_3$): δ −4.44 (4 C, PhOSi(*C*H$_3$)$_2$), 18.15 (2 C, PhOSi*C*), 25.66 (6 C, PhOSiC(*C*H$_3$)$_3$), 64.10, 69.13, 70.53, 70.91 (228 C, *C*H$_2$O), 110.34 (4 C, Ar *C*-2), 112.60 (2 C, Ar *C*-4), 131.55 (2 C, Ar *C*-1), 156.64 (4 C, Ar *C*-3), 166.44 (2 C, *C*O). FT-IR: ν (cm^{-1}) (PEG *CH*$_2$) 2885, (G1 *C*═*O*) 1716.

(HO)$_2$[G1]-PEG5K-[G1](OH)$_2$ (4). To a 25 mL pear-shaped flask was added zinc tetrafluoroborate hydrate (0.120 g, 0.564 mmol) with 5 mL of deionized (DI) water. P$_2$[G1]-PEG5K-[G1]-P$_2$ (**3**) (0.520 g, 0.091 mmol) was then added together with an additional 5 mL of water. The mixture was stirred at 70 °C for 24 h, the clear solution was extracted three times with 15 mL of chloroform, and all collected organic fractions were combined and dried with magnesium sulfate. The drying agent was filtered off, and the solvent was removed by rotary evaporator under reduced pressure at 60 °C. The viscous product was then placed in a vacuum oven for 8 h at 60 °C. When cooled to room temperature, the product appeared as a clear glassy solid; yield 97.0%.

^{1}H NMR ($CDCl_3$): δ 3.34−3.91 (m, 452 H, PEG C*H*$_2$O), 4.39−4.46 (t, 4 H, PEG(C*H*$_2$OCOPh)$_2$) 6.61−6.67 (t, 2 H, G1Ar*H*), 7.01−7.09 (d, 4 H, G1Ar*H*). ^{1}H NMR (CD_3OD): δ 3.36−3.91 (m, 452 H, PEG C*H*$_2$O), 4.37−4.44 (t, 4 H, PEG-(C*H*$_2$OCOPh)$_2$), 6.45−6.49 (t, 2 H, G1Ar*H*), 6.91−6.97 (d, 4 H, G1Ar*H*). ^{13}C NMR ($CDCl_3$): δ 64.07, 69.14, 70.52, 70.68, 70.91 (228 C, *C*H$_2$O), 107.96 (4 C, Ar *C*-2), 108.53 (2 C, Ar*C*-4), 131.85 (2 C, Ar *C*-1), 157.87 (4 C, Ar *C*-3), 166.48 (2 C, *C*O). FT-IR: ν (cm^{-1}) (Ar*OH*) 3313, (PEG *CH*$_2$) 2883, (G1 *C*═*O*) 1721.

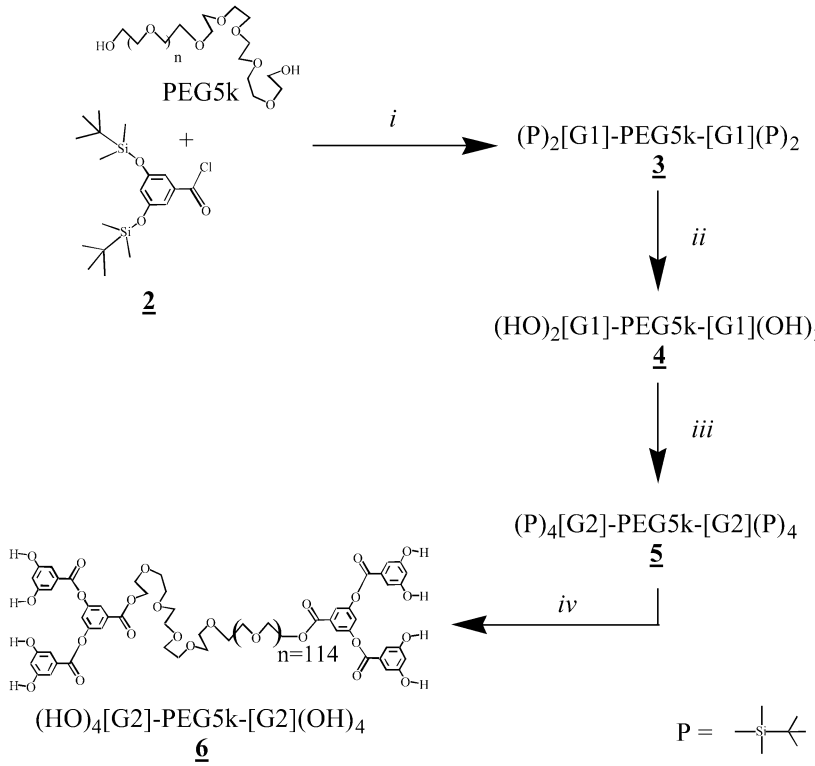
P$_4$[G2]-PEG5K-[G2]P$_4$ (5). (HO)$_2$[G1]-PEG5K-[G1](OH)$_2$ (**4**) (0.500 g 0.095 mmol), 3,5-bis(*tert*-butyldimethylsiloxy)-benzoyl chloride (**2**) (0.275 g, 0.686 mmol), and 18-crown-6 (0.012 g, 0.046 mmol) were combined in a 50 mL two-neck pear-shaped flask with dry nitrogen feed. 10 mL of dry THF was added together with 0.10 mL of dry toluene as a SEC marker. The reactants were gently heated and allowed to mix well. Potassium carbonate (0.252 g, 1.82 mmol) was added, and the reaction proceeded for 2.5 h at room temperature. The potassium carbonate was then filtered off, and the solution of crude product was added dropwise to 200 mL of hexane under stirring. The product formed a white precipitate. The mixture was allowed to stir for 15 min, and the precipitate was collected in a 30 mL, 6−10 μm, Buchner glass frit-filter; yield 96%.

^{1}H NMR (CD_3OD): δ 0.24 (s, 24 H, PhOSi(C*H*$_3$)$_2$), 1.01 (s, 36 H, PhOSiC(C*H*$_3$)$_3$), 3.34−3.91 (m, 452 H, PEG C*H*$_2$O), 4.46−4.53 (t, 4 H, PEG(C*H*$_2$OCOPh)$_2$), 6.60−6.67 (t, 4 H, G2Ar*H*), 7.23−7.31 (d, 8 H, G2Ar*H*), 7.49−7.54 (t, 2 H, G1Ar*H*), 7.82−7.88 (d, 4 H, G1Ar*H*). ^{13}C NMR ($CDCl_3$): δ −4.41 (16 C, PhOSi-(*C*H$_3$)$_2$), 18.20 (8 C, PhOSi*C*), 25.64 (24 C, PhOSiC(*C*H$_3$)$_3$), 64.55, 69.04, 70.54, 72.32 (228 C, *C*H$_2$O), 113.37 (8 C, G2 Ar *C*-2), 115.60 (4 C, G2 Ar*C*-4), 117.82 (4 C, G1 Ar *C*-2), 120.63 (2 C, G1 Ar*C*-4),130.45 (4 C, G2 Ar *C*-1), 132.27 (2 C, G1 Ar *C*-1), 151.26 (4 C, G1 Ar *C*-3),156.78 (8 C, G2 Ar *C*-3), 164.29 (4 C, G2 *C*O). 164.29 (2 C, G1 *C*O). FT-IR: ν (cm^{-1}) (PEG *CH*$_2$) 2883, (G2 *C*═*O*) 1740, (G1 *C*═*O*) 1727.

(HO)$_4$[G2]-PEG5K-[G2](OH)$_4$ (6). To a 25 mL pear-shaped flask were added zinc tetrafluoroborate hydrate (0.360 g, 1.510 mmol) and 5 mL of DI water, and the solution was allowed to stir. P$_4$[G2]-PEG5K-[G2]P$_4$ (**5**) (0.550 g, 0.0818 mmol) was added with an additional 3 mL of water and 2 mL of methanol. After stirring at 70 °C for 24 h, the reaction mixture was extracted three times with 15 mL of chloroform, and all collected organic fractions were combined and dried with magnesium sulfate. The mixture was then filtered into a 100 mL round-bottom flask, and the solvent removed by rotary evaporator under reduced pressure and heating at 60 °C. The viscous product was placed in a vacuum oven for 8 h at 60 °C. After cooling to room temperature the product appeared as a clear glassy solid; yield 94%.

^{1}H NMR (CD_3OD): δ 3.34−3.90 (m, 452 H, PEG C*H*$_2$O), 4.46−4.53 (t, 4 H, PEG(C*H*$_2$OCOPh)$_2$), 6.54−6.57 (t, 4 H, G2Ar*H*), 7.08−7.11 (d, 8 H, G2Ar*H*), 7.42−7.47 (t, 2 H, G1Ar*H*), 7.79−7.82 (d, 4 H, G1Ar*H*). ^{13}C NMR ($CDCl_3$): δ 64.60, 69.01, 70.51, 70.73, 72.51 (228 C, *C*H$_2$O), 108.97 (8 C, G2 Ar *C*-2), 109.04 (4 C, G2 Ar*C*-4), 120.48 (4 C, G1 Ar *C*-2), 120.61 (2 C, G1 Ar*C*-4), 130.40 (4 C, G2 Ar *C*-1), 132.27 (2 C, G1 Ar *C*-1), 151.26 (4 C, G1 Ar *C*-3), 158.13 (8 C, G2 Ar *C*-3),

Scheme 1. Synthesis of Poly(benzyl ester)-*block*-poly(ethylene glycol)-*block*-poly(benzyl ester)



i: THF, NaOH, N_2, 1.5 h, 25°C

ii: Zinc tetrafluoroborate hydrate, H_2O, 24 h, 70°C

iii: **2**, THF, K_2CO_3, 18-C-6, 2.5 h

iv: Zinc tetrafluoroborate hydrate , H_2O/MeOH, 24 h, 70°C

164.57 (4 C, G2 *C*O), 164.87 (2 C, G1 *C*O). FT-IR: ν (cm^{-1}) (Ar*OH*) 3308, (PEG CH_2) 2883, (G2 *C*=*O*) 1741, (G1 *C*=*O*) 1727.

$(BzAc)_4$[G2]-PEG5K-[G2]$(AcBz)_4$ (7). In a 50 mL two-neck pear-shaped flask with dry nitrogen feed were combined $(HO)_4$-[G2]-PEG5K-[G2]$(OH)_4$ (**6**) (0.500 g, 0.086 mmol), benzoic acid (0.140 g, 1.14 mmol) with 4-(dimethylamino)pyridinium *p*-toluenesulfonate (0.007 g, 0.024 mmol), and 10 mL of dry dichloromethane. The reactants were gently heated and allowed to mix well. *N*,*N*′-Dicyclohexylcarbodiamide (0.252 g, 1.22 mmol) was then added, and the reaction was allowed to proceed for 12 h at room temperature. A white precipitate of dicyclohexylurea byproduct developed as the reaction proceeded. The mixture was cooled to −5 °C to aid in complete precipitation of the urea and then cold-filtered using a 30 mL, 10−20 μm, Buchner glass-frit filter. The methylene chloride was distilled off. The solid residue was dissolved in THF/methanol (1/1, v/v) and upon chilling to −5 °C formed a white precipitate. This mixture was again rapidly cold-filtered, washed with cold THF, and collected as a white granular powder. It was placed in a vacuum oven at 80 °C overnight to dry. When cooled to room temperature, the product appeared as a clear glassy solid; yield 89%.

^{1}H NMR ($CDCl_3$): δ d 3.34−3.91 (m, 452 H, PEG CH_2O), 4.46−4.53 (t, 4 H, PEG(CH_2OCOPh)$_2$), 7.39−8.28 (m, 58 H, Ar*H*).

$(Bz)_4$[G2]-PEG5K-[G2]$(Bz)_4$ (8). To a 50 mL two-neck pear-shaped flask with dry nitrogen feed were added $(HO)_4$-[G2]-PEG5K-[G2]$(OH)_4$ (**6**) (0.500 g 0.086 mmol), benzyl bromide (0.153 mL, 1.29 mmol), and 18-crown-6 (0.022 g, 0.086 mmol). 10 mL of dry THF was added with 0.010 mL of dry toluene as a SEC marker. The reactants were gently heated until they were completely dissolved. Potassium carbonate (0.380 g, 2.75 mmol) was then added, and the reaction proceeded for 12.5 h at room temperature. The potassium carbonate was filtered off on a 30 mL, 10−20 μm, Buchner glass-frit filter, and the crude product was collected and then added dropwise to 200 mL of hexane under stirring. The mixture was allowed to stir for 15 min, and the off-white precipitate was collected in a 30 mL, 6−10 μm, Buchner glass-frit filter. The purified product appeared as a white solid; yield 93%.

^{1}H NMR (CD_3OD): δ 3.34−3.90 (m, 452 H, PEG CH_2O), 4.44−4.51 (t, 4 H, PEG(CH_2OCOPh)$_2$), 5.11 (s, 16 H, Ph*H*), 7.28−7.48 (m, Ar *H*), 7.82−7.84 (d, 4 H, G1Ar*H*).

Results and Discussion

The synthesis of the dendritic monomer begins with the full protection of 3,5-dihydroxybenzoic acid with *tert*-butyldimethylsilyl chloride to give product **1** in 91% yield. After isolation, the triprotected ester is treated with oxalyl chloride to yield the protected acid chloride monomer, **2**, with 90% yield. This two-stage synthesis is based on modified previously published procedures[13] and proceeds with little difficulty. Originally,[1] we utilized thionyl chloride[13] in combination with benzyltrimethylammonium chloride for the production of **2** but found oxalyl chloride to give significantly better yields (90% vs 48%, respectively).

First- and second-generation linear−dendritic block copolymers, LDBCs, are constructed from PEG with a molecular weight of 5000 Da and a fundamental den-

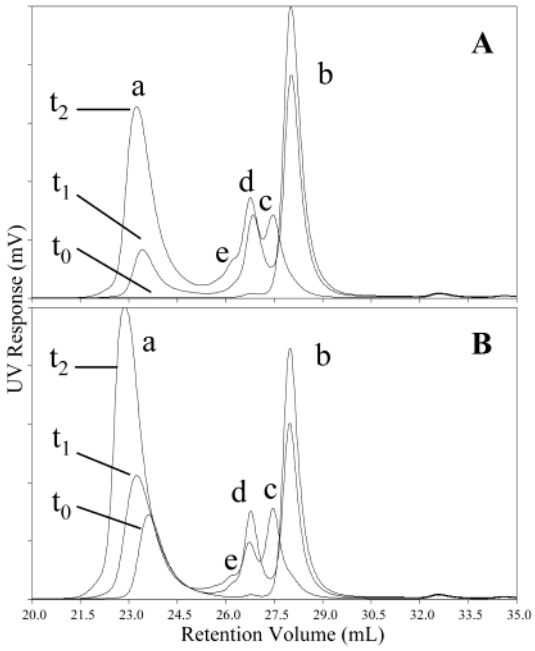


Figure 1. Coupling of the protected monomer 3,5-bis(*tert*-butyldimethylsiloxy)benzoyl chloride (**2**) to PEG monitored by double-detection SEC in THF. (A) UV (254 nm) chromatogram: a, $(P)_2$[G1]-PEG5K-[G1]$(P)_2$ **3**; b, protected monomer **2**; c−e, reaction byproducts. $t_0 = 0$ min, $t_1 = 40$ min, $t_2 = 90$ min. (B) RI chromatogram: a, $(P)_2$[G1]-PEG5K-[G1]$(P)_2$ **3**; b, protected monomer **2**; c−e, reaction byproducts. $t_0 = 0$ min, $t_1 = 40$ min, $t_2 = 90$ min.

dritic repeat unit derived from 3,5-dihydroxybenzoic acid (Scheme 1).

The coupling of the protected monomer **2** to PEG is a typical nucleophilic displacement reaction. Initially, we employed NaH as the base catalyst. This reaction often suffered from incomplete addition of monomer, and extended reaction periods were required for the full substitution. When sodium hydroxide is used for the PEG alkoxide ion formation instead, the coupling of the protected monomer to the PEG proceeds smoothly in 1.5 h. Notably, the coupling should be followed immediately by the deprotection step. The latter procedure is required because of the unexpected degradation of product **3** upon storage over a period of a few days. Most probably, this decomposition is caused by a residual NaOH that remains complexed within the PEG and leads to the hydrolysis of the ester linkages in the presence of moisture. The selective deprotection of the silyl residues without a simultaneous cleavage of the ester links to PEG and 3,5-dihydroxybenzoyl branching moieties is the key step in the synthetic pathway. It is achieved by a manipulation with zinc tetrafluoroborate under conditions that do not affect the acid-sensitive ester groups[14] (Scheme 1). After the deprotection step the undesired NaOH traces are conveniently washed away from the PEG derivative and completely removed upon extraction with chloroform. The formation of the more reactive phenolic OH groups allows the usage of milder Williamson reaction conditions for the growth to the second-generation copolymer **5**. The reaction proceeds nicely in 2.5 h with K_2CO_3 and 18-crown-6 in THF (Scheme 1). Unlike the first-generation products, the resulting protected linear−dendritic copolymer can be stored for extended periods without observed polymer degradation.

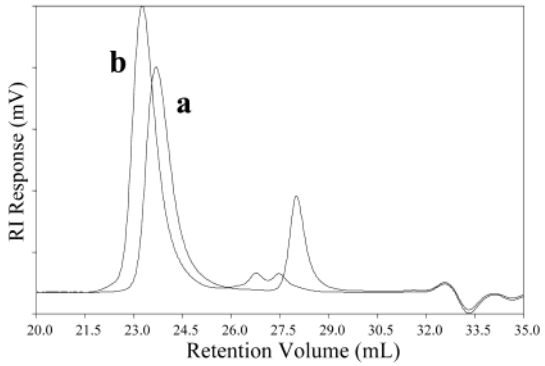


Figure 2. Coupling of protected monomer 3,5-bis(*tert*-butyldimethylsiloxy)benzoyl chloride **2** to $(HO)_2$[G1]-PEG5K-[G1]-$(OH)_2$ **4** monitored by SEC in THF. RI traces of the reaction mixture at (a) $t = 0$ and (b) $t = 90$ min.

A convenient aspect of the divergent dendrimer growth method with PEG as the linear "core" is the ease of product purification through exploitation of PEG's solution properties. It should also be noted that in all coupling reactions an excess amount of growth agent (i.e., protected monomer) ensures complete monomer addition at the branching point (Scheme 1). The requirement of excess monomer is a common feature in divergent growth methods[15] and is an acceptable cost due to the easy purification procedures.

SEC with double detection is used to monitor the progress of each coupling reaction. The eluograms of aliquot samples taken at time intervals of $t = 0$, 40, and 90 min during the synthesis of **3** are presented in Figure 1. There is no peak for the initial PEG fragment in the UV trace of the reaction mixture at $t = 0$ min, and the peak development at 23.2 mL for $t = 40$ and 90 min indicates coupling of the monomer to PEG (Figure 1A). In the RI chromatograms for the same reaction (Figure 1B) a left shift from the original elution volumes of the PEG to the higher molecular weight **3** can be seen from $t = 0$ to 90 min. SEC traces during the synthesis of the second-generation hybrid copolymer show the same tendency. The initial peak of **4** at 23.6 mL changes to a higher molecular weight peak at 22.5 mL for **5** (Figure 2). Note the higher elution volume for **4** after the deprotection of **3** (Figures 1 and 2). When both growth reactions are complete, the peak of the monomer (**2**) at 28.0 mL disappears.

Complete generation growth is also confirmed by NMR and FT-IR spectra for both protected and deprotected products (Figures 3 and 4) (copolymers **3**−**6**). The analyses show that there is no chemical shift for any residual PEG hydroxyl groups (^{1}H NMR: $\delta(CD_3OD) \sim$ 2.87 ppm), and the ratio of observed integral values matches those predicted for the ester-PEG and benzoate protons.

The completeness of the second monomer addition is evidenced by the downfield shift of the [G1] C_4 and $C_{2,6}$ protons to 7.4 and 7.8 ppm, respectively, with an observed doubling of the intensities at 6.5 and 7.1 ppm for the peripheral aromatic protons (Figure 3C,D). Fréchet and co-workers noted similar changes in the NMR spectra during the synthesis of polyester dendrimers of different generations.[10] The full silyl group removal is confirmed by the disappearance of the methyl and *tert*-butyl groups at 0.24 and 1.01 ppm in ^{1}H NMR spectra for **4** and **6** (Figure 3C,D). FT-IR spectroscopy is particularly useful at this step and confirms the formation of the peripheral aromatic hydroxyl groups

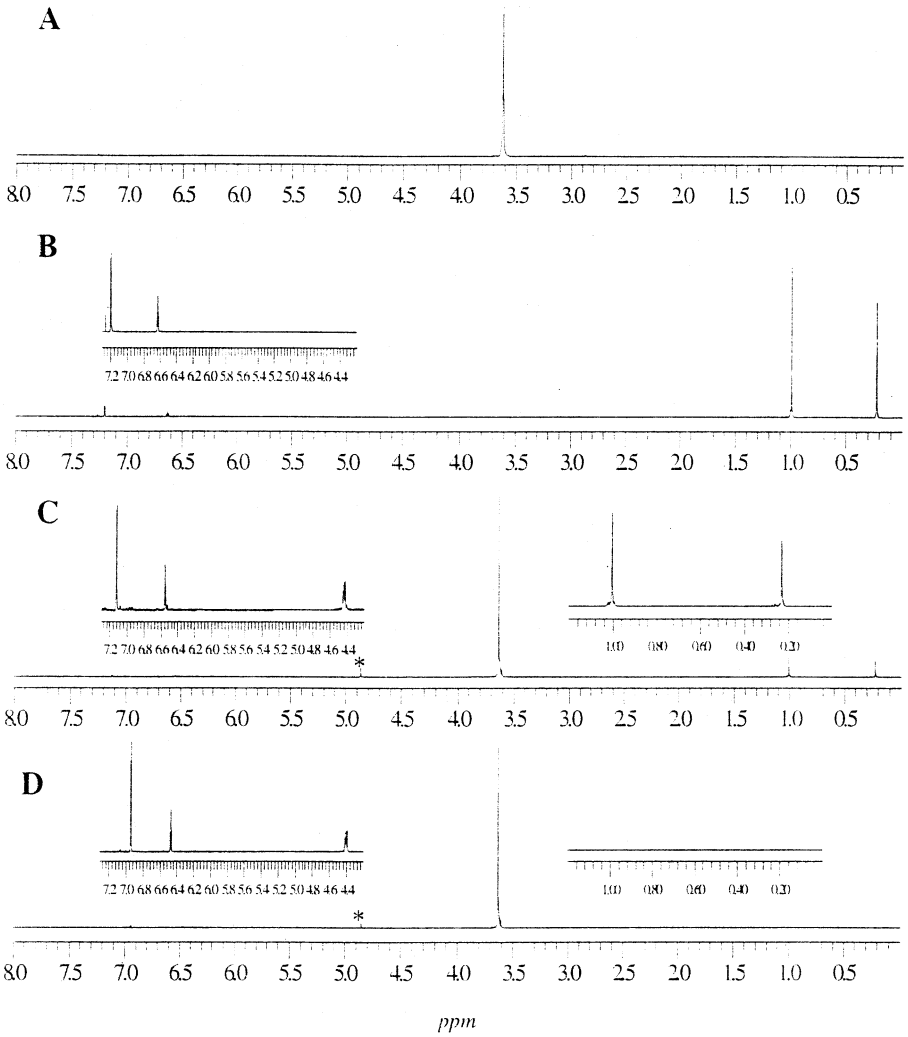


Figure 3. ^{1}H NMR spectra of (A) PEG5K ($CDCl_3$), (B) 3,5-bis(*tert*-butyldimethylsiloxy)benzoyl chloride ($CDCl_3$), (C) $(P)_2$[G1]-PEG5K-[G1]$(P)_2$ (CD_3OD), and (D) $(HO)_2$[G1]-PEG5K-[G1]$(OH)_2$ (CD_3OD). (*) The solvent peak ($CDCl_3$, CD_3OD) has been removed from inlaid spectra.

by the appearance of absorption bands at around 3313 cm^{-1} (Figure 4). Their intensity is doubled for the second-generation derivative. The carbonyl absorption bands show also a notable split from 1716/1721 cm^{-1} (first generation) to 1727−1741 cm^{-1} doublet (second generation) (Figure 4). The apparent molecular weights and polydispersity indices for PEG, and copolymers **3**−**6**, obtained by SEC in THF, are presented in Table 1. Interestingly, the observed molecular weights at the peak apex (Table 1, M_p) are remarkably close to the theoretical values for the protected copolymers (**3** and **5**), while the system slightly overestimates the molecular weights of their deprotected derivatives (**4** and **6**). The traditional underestimation of the PEG molecular weight parameters by a conventional poly(styrene) based calibration curve[16] is also encountered (Table 1).

In view of the future applications for these linear−dendritic copolymers, the evaluation of the surface accessibility in the polyester monodendrons is one the most important aspects of the work presented here. The potential for peripheral attachment of various compounds is explored by two different model reactions. When describing surface modifications, the terminology used here follows the convention where each branching point is designated as [Gx] and the accompanying surface modification is presented in parentheses, i.e., (Bz) for benzyl- and (BzAc) for benzoyl-terminated dendrons.

One of the possible methods for surface modification is based on the DCC/DPTS chemistry pioneered for linear aromatic polyesters by Moore and Stupp.[17] Later, the same catalytic system was used for the growth of dendritic polyesters.[10,18] The DCC-mediated modification of poly(amidoamine) dendrons by Hammond and co-workers[12d] is also of notable interest. In this study we are attempting to couple benzoic acid to the peripheral aromatic hydroxyl groups of the deprotected second-generation copolymer **6** (Scheme 2). The progress of this reaction can be qualitatively followed by the appearance of dicyclohexylurea over time. The increased steric crowding at the periphery of the monodendrons necessitates extended reaction times (12 h) to ensure that all of the available phenolic groups have reacted. The quantitative surface modification is confirmed by ^{1}H NMR. The chemical shifts for all aromatic protons in each dendritic layer are difficult to resolve, but the integration ratio for ester-PEG protons (δ = 4.46−4.53 ppm) to the aromatic ones (δ = 7.39−8.28 ppm) is 4:60, relatively close to the predicted ratio of 4:58.

The second model reaction is based on the same Williamson ether synthesis conditions used for second-generation growth. Here we are coupling benzyl bromide

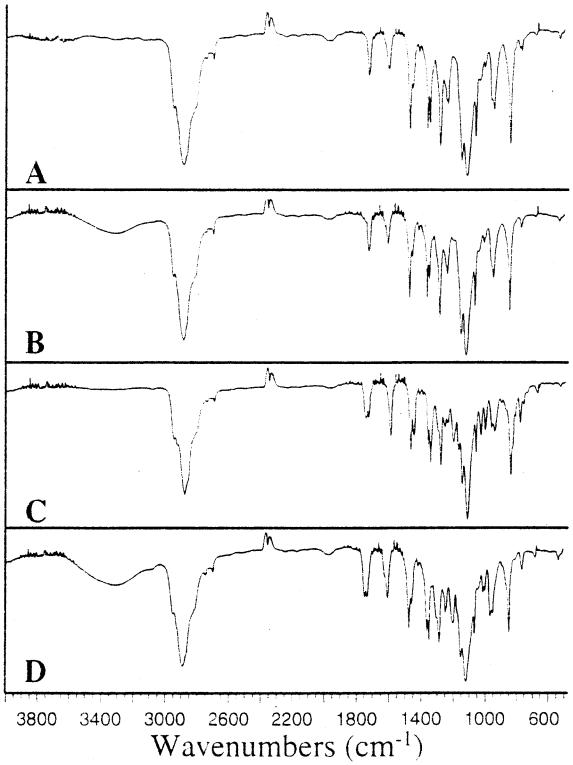


Figure 4. FT-IR spectra of (A) $(P)_2$[G1]-PEG5K-[G1]$(P)_2$, (B) $(HO)_2$[G1]-PEG5K-[G1]$(OH)_2$, (C) $(P)_4$[G2]-PEG5K-[G2]$(P)_4$, and (D) $(HO)_4$[G2]-PEG5K-[G2]$(OH)_4$.

Table 1. Copolymer Molecular Weights Determined by SEC in THF

copolymer	M_{theo}[a]	$M_{p,obs}$[b]	M_n	M_w	PDI[c]
PEG5K	5000	4600	4100	4300	1.04
$(P)_2$[G1]-PEG5K-[G1]$(P)_2$	5728	5700	5100	5400	1.06
$(HO)_2$[G1]-PEG5K-[G1]$(OH)_2$	5272	5400	4600	5200	1.07
$(P)_4$[G2]-PEG5K-[G2]$(P)_4$	6728	6700	6100	6300	1.03
$(HO)_4$[G2]-PEG5K-[G2]$(OH)_4$	5816	6100	5600	5800	1.02

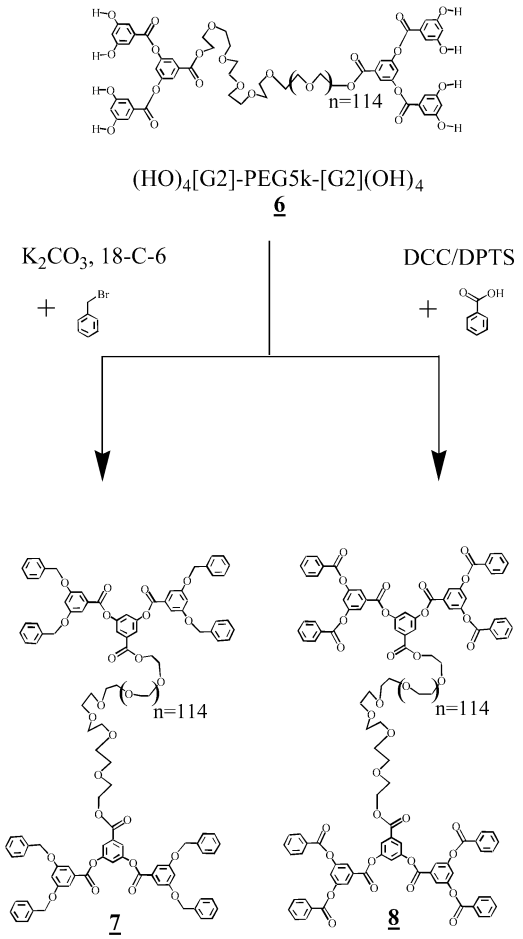
[a] Theoretical (calculated) molecular weight. [b] Molecular weight at the peak apex in the SEC eluogram. [c] Polydispersity index: M_w/M_n.

to the phenolic moieties at the periphery. Again, SEC is used to monitor growth and purity, and ^{1}H NMR analysis confirms the attachment. The observed integration ratio of ester-PEG protons ($\delta = 4.46-4.53$ ppm) to benzyl protons ($\delta = 5.08-5.14$ ppm) is 4:15.5. This value is satisfactory close to the predicted ratio of 4:16. The same reaction is performed successfully with Fréchet-type monodendrons of first generation having a benzyl bromide moiety at the focal point as well. It should be noted, however, that at this time we have not found the reaction conditions that would enable the defect-free attachment of higher generations.

Conclusions

The results obtained demonstrate the successful divergent growth of aromatic polyester dendritic fragments from linear poly(ethylene glycol) chains with high yields and chemical purity. NMR, FT-IR, and SEC data confirm the complete attachment and deprotection at each branching sequence. The surface of the dendritic fragments in the copolymers is quantitatively modified via two distinct chemical pathways. Therefore, these amphiphilic copolymers hold great promise as model platforms for potential applications in drug delivery, nanocatalysis, and surface coating. Preliminary experiments show that the second-generation copolymers containing protective benzyl or benzoyl groups at the periphery easily self-assemble in water at very low concentrations ($\sim 10^{-6}$ mol/L), while the deprotected copolymer $(HO)_4$[G2]-PEG5K-[G2]$(OH)_4$ is completely (at the monomolecular level) dissolved under the same conditions. Detailed studies into the solution and binding properties of these interesting "multipurpose" copolymers are presently underway in our research group.

Scheme 2. Surface Modification of the Poly(ester) Monodendron in LDBC



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Supporting Information Available: SEC traces of P_2[G1]-PEG5K-[G1]P_2 (**3**) and $(HO)_2$[G1]-PEG5K-[G1]$(OH)_2$ (**4**); ^{1}H NMR spectra of P_4[G2]-PEG5K-[G2]P_4 (**5**), $(HO)_4$[G2]-PEG5K-[G2]$(OH)_4$ (**6**), benzoic acid, $(BzAc)_4$[G2]-PEG5K-[G2]$(BzAc)_4$ (**7**), and $(Bz)_4$[G2]-PEG5K-[G2]$(Bz)_4$ (**8**). This material is available free of charge via the Internet at http://pubs.acs.org.

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