Synthesis and Characterization of Polyether−Ester Dendrimers from Glycerol and Lactic Acid

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Dendrimers are globular monodisperse polymers composed of branched repeating units emitting from a central core.[1−8] These macromolecules are synthesized using either a divergent (from core to surface)[9−12] or a convergent (from surface to core)[13] approach. Since the reports by Tomalia and Newkome, this research area has undergone tremendous growth in the past decade.[1−8,13−16] Compared to linear polymers, dendrimers possess high surface area-to-volume ratios, exhibit numerous end groups for functionalization, and have small polydispersity indices (PDI) with well-defined interior and exterior regions. These characteristics translate to unique properties such as low viscosity, high solubility and miscibility, and adhesiveness;[1−8] consequently, dendrimers are of interest for a wide range of industrial and medical applications. Dendrimers currently available and investigated for medical applications (e.g., MRI and drug delivery) are limited to derivatives of aromatic polyethers, aliphatic polyethers, or aliphatic amines.[16−32] New synthetic procedures and materials are needed to address this present limitation. "Biodendrimers" are a new class of dendritic polymers. These dendrimers are comprised of building blocks known to be biocompatible or degradable to natural metabolites in vivo. Herein, we report the divergent synthesis and characterization of novel dendrimers composed of glycerol and lactic acid.

Linear polymers of lactic acid and other such polymers (e.g., poly(glycolic acid), poly(ϵ-caprolactone), poly(ethylene glycol), and poly(trimethylene carbonate)) constitute a class of materials well suited for research and clinical applications ranging from drug delivery to tissue engineering.[33−38] Specifically, poly(lactic acid) (PLA) and its closely related analogue poly(glycolic acid) (PGA) are polyesters of naturally occurring hydroxy acids, and are used for biomedical applications since these polymers possess favorable biocompatibility and mechanical strength.[39,40] First used as bioresorbable surgical sutures,[41] these polymers are also widely investigated for applications in orthopedics (e.g., screws, pins, scaffolds), wound closure (e.g., staples, dressings, meshes), and drug delivery (e.g., microspheres, hollow fibers). Incorporation of similar biocompatible monomers in dendrimers represents a new means to create well-defined polymeric structures for biomedical and tissue engineering applications.

Scheme 1 shows a divergent strategy to synthesize a third generation [G3] *p*oly(*gl*ycerol-*l*actic *a*cid) dendrimer, **[G3]-PGLLA**. First, a tetrafunctional core is produced in three steps. *cis*-1,3-*O*-Benzylideneglycerol, **1**, is treated with NaH followed by the addition of 2-bromopropionic acid to afford 2-[(*cis*-1,3-*O*-benzylideneglycerol)-2-propionic acid], **2**, which is easily purified by recrystallization in cold (−20 °C) ethyl ether (77% yield). Compounds **1** and **2** are next coupled in the presence of 1.5 equiv of *N*,*N*-dicyclohexylcarbodiimide (DCC) and 0.5 equiv of 4-(dimethylamino)pyridinium 4-toluenesulfonate (DPTS)[42] to afford the key protected tetrahydroxy-core in 94% yield. The protected **[G0]-PGLLA** core is easily separated from the remaining carboxylic acid starting material by column chromatography. The core is subsequently deprotected by hydrogenolysis (10% (w/w) of 10% Pd/C; 50 psi of H_2) in ethyl acetate/MeOH (3:1) to yield the G0 dendrimer, **3** (**[G0]-PGLLA**-OH; 94% yield). Next, 4 equiv of **2** are coupled to **[G0]-PGLLA**-OH in the presence of 6 equiv of DCC and 2 equiv of DPTS to produce **[G1]-PGLLA**-bzld, **4**, in 88% yield. Again, column chromatography is used to isolate **4** and residual DCC is removed by precipitation of **4** in cold ethyl ether. Subsequent hydrogenolysis in THF affords **[G1]-PGLLA**-OH, **5** (94% yield). The **[G2]-PGLLA**-bzld, **6**, dendrimer is prepared by reacting 8 equiv of **2** with **[G1]-PGLLA**-OH in the presence of 10 equiv of DCC and 4 equiv of DPTS (77% yield). Hydrogenolysis of **6** affords the G2 dendrimer, **[G2]-PGLLA**-OH, **7** (88% yield). Reiteration of

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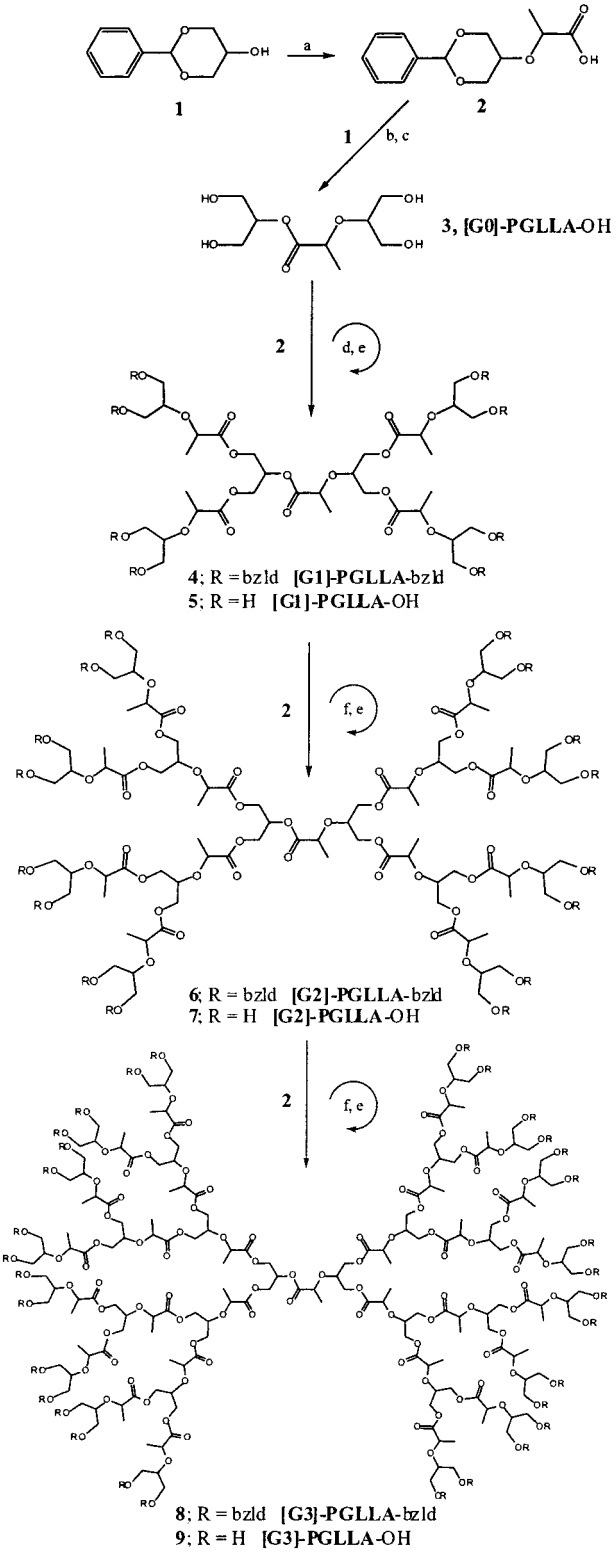
Scheme 1[a]



[a] Reagents and conditions: (a) 2-bromopropionic acid, NaH, 1,4-dioxane, 50 °C, 13 h; (b) **1**, DCC, DPTS, CH_2Cl_2, 25 °C, 14 h; (c) 50 atm of H_2, Pd/C, ethyl acetate MeOH (3:1), 25 °C, 20 min; (d) **2**, DCC, DPTS, DMF, 25 °C, 14 h; (e) 50 atm of H_2, Pd/C, THF, 25 °C, 15 min; (f) **2**, DCC, DPTS, THF, 25 °C, 14 h.

the esterification reaction with **7** (89% yield) followed by hydrogenolysis affords the G3 dendrimer, **[G3]-PGLLA**-OH, **9** (95% yield).

Table 1. FAB/MALDI MS and SEC Data for the Dendrimers

no.	dendrimer	calcd MW	FAB/MALDI MW	SEC[a] Mn
4	**[G1]-PGLLA**-bzld	1175.2	1174.6	1260
5	**[G1]-PGLLA**-OH	822.8	822.3	1090
6	**[G2]-PGLLA**-bzld	2696.8	2696.0	2310
7	**[G2]-PGLLA**-OH	1991.9	1990.8	2130
8	**[G3]-PGLLA**-bzld	5739.9	5742.3	4310
9	**[G3]-PGLLA**-OH	4330.2	4331.5	4060

[a] Relative molecular weights by size exclusion chromatography and polystyrene standards. All PDIs are less than 1.02.

The benzylidene acetal group (bzld) is used to protect the hydroxyls of 1,3-glycerol since it can be readily and selectively cleaved by hydrogenolysis (Pd/C, H_2).[43] In addition, the benzylidene acetal group serves as a diagnostic NMR tag to monitor each successive generation of the dendrimer and ensures sufficient solubility in common organic solvents for purification. The methyl protons of the lactic acid also provide additional structural information. As the generation number increases, the surface methyl protons shift downfield (1.45 ppm) relative to the internal methyl protons (1.32 ppm), and the integrated areas change in accordance with the generation number. The FTIR spectra of the deprotected **PGLLA** dendrimers contain the expected broad O−H stretch at ∼3400 cm^{-1}. Molecular weight data determined by FAB/MALDI MS and size exclusion chromatography (SEC) for the benzylidene protected and deprotected **[G1]-PGLLA**, **[G2]-PGLLA**, and **[G3]-PGLLA** dendrimers are summarized in Table 1. The protected **PGLLA** dendrimers are soluble in halogenated solvents, aromatic solvents, THF, and ethyl acetate. The deprotected **PGLLA** dendrimers are soluble in DMF, EtOH, MeOH, and H_2O. The glass transition temperatures (T_g) of the protected **[G2]-PGLLA** and **[G3]-PGLLA** dendrimers and deprotected **[G2]-PGLLA** and **[G3]-PGLLA** dendrimers are 31, 19, −34, and −28 °C, respectively, as determined by modulated differential scanning calorimetry (MDSC).

In summary, an efficient divergent procedure for synthesizing novel aliphatic biodendrimers composed of glycerol and lactic acid is described. The key constituents of the polymer are combined in reiterative reaction steps from simple and abundant starting materials. These polyether−ester dendrimers expand the repertoire of polymers available for study. Current investigations are primarily limited to linear polymers, such as PLA, which possess ill-defined solution structures and fewer hydroxyl groups for further modification. The introduction of biocompatible building blocks (e.g., glycerol and lactic acid) augments the favorable and already known physical properties of dendrimers. These properties are likely to facilitate the design and development of new materials for specific medical and tissue engineering applications.

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Supporting Information Available: Detailed experimental information and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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