Communications to the Editor

Chemoenzymatic Synthesis of a Multiarm Poly(lactide-*co*-ϵ-caprolactone)

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Copolymers of L-lactide and ϵ-caprolactone [poly(LA-*co*-CL)] are of interest for use as biodegradable and biocompatible materials. By variation in copolymer structure, products may be designed that offer "tailored" physicomechanical properties and controlled degradation rates. In contrast to the extensive efforts made to prepare linear block copolymers from L-LA and other monomers such as caprolactone, glycolide, and ethylene oxide,[1−3] there are few reports on the preparation of their counterparts with alternative architectural structures.[4,5]

The design and synthesis of macromolecules with well-defined spatial architecture such as stars and dendrimers have been of intense interest in recent years.[6] Heteroarm or miktoarm star block copolymers have been successfully prepared by living anionic[7] and cationic polymerization.[8,9] Structure−property studies have shown that variations in the macromolecular architecture from linear to multiarm can have substantial effects on the morphological and physical−mechanical properties of the corresponding materials.[7] The above findings provide incentive to further expand the synthetic arsenal that may be used to facilitate the preparation of related structures.

The exceptional regio- and stereoselectivity of enzymes under mild reaction conditions, and the fact that enzymes are natural catalysts, are both compelling reasons to explore their use for polymerizations in anhydrous organic media. In vitro lipase-catalyzed ring-opening polymerization of lactones has been used to synthesize biodegradable polyesters. Recent publications from our laboratories and others have demonstrated that, by properly controlling the reaction parameters and by selecting suitable monomer−enzyme pairs, high molecular weight polyesters can be prepared.[10] The advantage of enzyme catalysis becomes apparent when multifunctional structures are encountered. Tedious and costly protection/deprotection steps can be minimized by using enzyme catalysis. For example, we recently reported that when α,β-ethyl glucopyranoside (EGP) was used as a multifunctional initiator for ϵ-caprolactone (ϵ-CL) and trimethylene carbonate (TMC) lipase-catalyzed ring-opening bulk polymerizations, polyester and polycarbonate chain segments with an EGP headgroup were formed in one-pot reactions.[11] The reactions proceeded in a highly regioselective fashion with the exclusive acylation of the primary hydroxyl group of EGP.

In this report, we describe a chemoenzymatic route to synthesize a novel multiarm heteroblock copolymer of PLA and PCL with a well-defined spatial architecture. For this purpose, the macromer 1-ethyl 6-oligo(ϵ-CL) glucopyranoside was prepared by a highly regioselective lipase-catalyzed ring-opening polymerization of ϵ-CL with multifunctional 1-ethyl glucopyranoside as an initiator.[11] The ω-hydroxyl group of the macromer 1-ethyl 6-oligo(ϵ-CL) glucopyranoside was then regioselectively protected by lipase-catalyzed acetylation. Subsequently, the polymerization of L-LA was initiated from the remaining free hydroxyl groups at the carbohydrate core to form the heteroblock copolymer.

Regioselective End-Capping. 1-Ethyl 6-oligo(ϵ-CL) glucopyranoside was prepared and purified as described previously.[11] In summary, the ϵ-CL ring-opening bulk polymerization catalyzed by porcine pancreatic lipase (PPL) was conducted at 70 °C in the presence of EGP. The resulting 1-ethyl 6-oligo(ϵ-CL) glucopyranoside (M_n = 1120 g/mol, M_w/M_n = 2.1) was separated from unreacted EGP and fractionated by column chromatography following a previously published method.[11] To exclusively perform the initiation of L-LA polymerization at the three sugar-ring secondary hydroxyl groups, it was first necessary to protect the terminal ω-hydroxyl group of the oligo(ϵ-CL) chain. The lipases PS-30 (from *Pseudomonas cepacia*) was evaluated for this transformation using vinyl acetate as an irreversible acetylating agent (Scheme 1).[12] The progress of the reaction was monitored by ^{1}H NMR. When the molar ratio of vinyl acetate to 6-oligo(ϵ-CL) EGP was 5 to 1, the lipase PS-30 catalyzed selective acetylation of the ω-hydroxyl oligo(ϵ-CL) terminal groups was complete within 8 h. Furthermore, under these reaction conditions, acetylation at the sugar secondary hydroxyl positions was not observed. (See the DEPT-135 NMR spectra of 1-ethyl 6-oligo(ϵ-CL) glucopyranoside prior to and after end-capping in Supporting Information.) The ^{1}H NMR spectra of 6-oligo(ϵ-CL) EGP before and after the reaction are displayed in Figure 1. The triplet at 3.66 ppm characteristic of the ω-hydroxylmethylene protons (−CH_2-OH) of the PCL chains disappeared, and a new singlet at 2.05 ppm due to the corresponding acetyl (−$COCH_3$) chain end group protons was observed. Since unreacted vinyl acetate and the byproduct acetaldehyde are volatile compounds, they were easily removed in vacuo during product isolation. A comparison of the ^{13}C NMR

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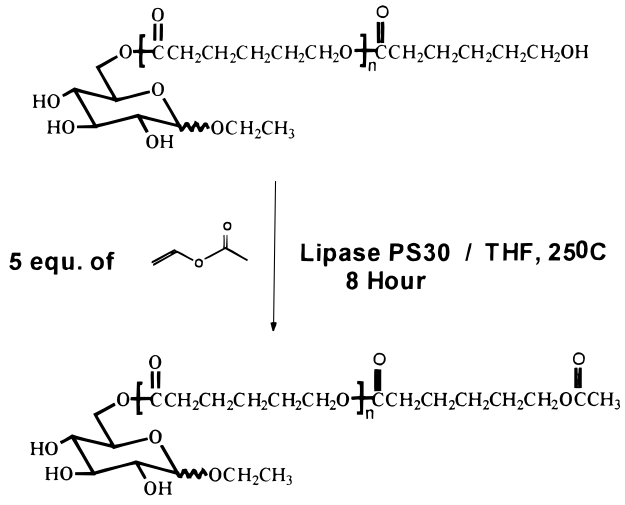
Scheme 1



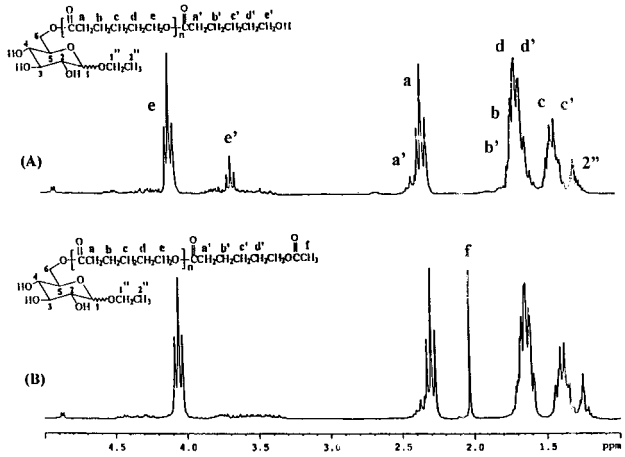


Figure 1. ^{1}H NMR spectra (250 MHz, solvent: $CDCl_3$) of EGP-oligo(ϵ-CL) (M_n = 1120 g/mol): (A) prior to (B) after end-capping.

spectra of EGP oligo(ϵ-CL) conjugate before and after the reaction showed a downfield shift of 1.70 ppm for the signal due to the ω-hydroxylmethylene carbon of the PCL segment (see Supporting Information).[11] Additional resonance due to the acetyl group appeared at 21.06 ppm. All other carbon resonances assigned to the EGP oligo(ϵ-CL) conjugate showed no substantial change which excluded any possible transesterification between EGP secondary hydroxyl groups and main chain esters. Molecular weight analysis of the reaction product (M_n = 1085 g/mol, M_w/M_n = 2.10) showed that no chain degradation occurred during chain-end acetylation.

Synthesis of [(PLA)$_3$(PCL)$_1$ EGP]. Due to its low toxicity and high efficiency, stannous octanoate has been the most frequently used catalyst for synthesizing PLAs. Previous work by Spinu[13] showed that the bulk polymerization of L-LA, conducted in the presence of a multifunctional hydroxyl initiator such as inositol, gave star-shaped products. Han et al. prepared a lactide-based poly(ethylene glycol) polymer network for tissue engineering scaffolds by using glycerol as an initiator.[14] In these stannous octanoate-catalyzed polymerizations, both primary and secondary hydroxyl groups were effective for the initiation of L-LA polymerization. These polymerizations were believed to proceed via an insertion coordination mechanism.[15]

In this report, we used the spatially organized 6-oligo-(ϵ-CL) EGP as the multifunctional hydroxyl initiator to

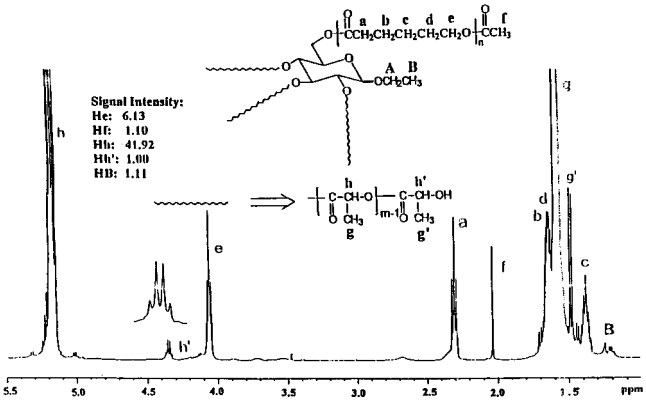
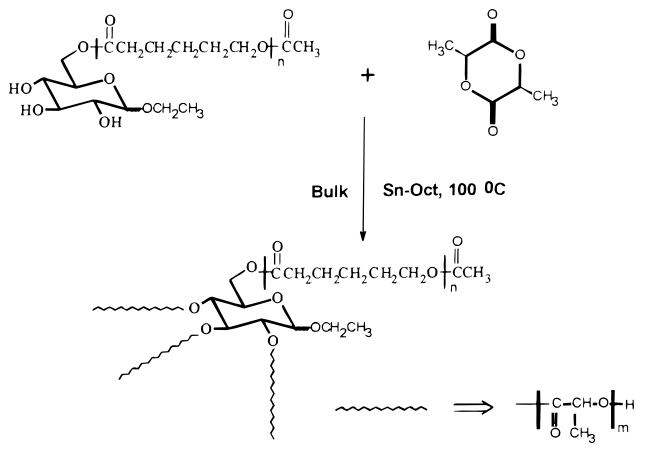


Figure 2. ^{1}H NMR spectrum (250 MHz, solvent: $CDCl_3$) of four-armed block copolymer of [(PLA)$_3$(PCL)$_1$ EGP]. (M_n = 11 500 g/mol, M_w/M_n = 1.10).

Scheme 2



prepare a novel heteroarm multiblock PLA-*co*-PCL copolymer (Scheme 2). The L-LA polymerization was performed solventless in the melt at 100 °C for 6 h. The residual monomer was removed by precipitation of the product in cold methanol, which showed the monomer conversion was 80%. The ^{1}H NMR spectrum of purified copolymer is shown in Figure 2. The assignments of the main signals were made by comparison to literature data[4] and our own previous work.[11] ^{1}H−^{1}H COSY45 2D NMR experiment further confirmed the above assignments (Supporting Information). By comparison of the signal intensities of the PCL methylene protons H_e (4.07 ppm) to protons H_f of the acetyl group (2.05 ppm), the M_n of the PCL chain segment was determined ($I_e/2 \div I_f/3$) to be 1270 g/mol. Also, the signal intensities of protons H_h (5.17 ppm) and $H_{h'}$ (4.35 ppm) of oligo-PLA chain segments were used to determine the M_n value of the PLA arms (3107 g/mol for each arm). The values of M_n for oligo-PCL determined by ^{1}H NMR and GPC were in close agreement (1270 and 1300 g/mol, respectively). Furthermore, the similar signal intensities of protons $H_{h'}$ (1H) and H_f (3H) suggest that the product has a ratio of oligo-PLA to oligo-PCL chain segments of 3:1. This conclusion was further strengthened by the similar signal intensities of protons $H_{h'}$ and H_B. On the basis of the above ^{1}H NMR experiments, the product M_n based on a 3:1 ratio of PLA (M_n = 3107 g/mol) to PCL (M_n = 1270 g/mol) was calculated to be 10 591 g/mol. Comparison of the GPC chromatograms of the block copolymer to the starting material [ω-acetyl 6-oligo(ϵ-CL) EGP] showed an increase in M_n from 1300 to 11 500 g/mol, a narrowed polydispersity (2.10 to 1.10)

and a unimodal distribution with no evidence of unreacted ω-acetyl 6-oligo(ϵ-CL) EGP. The absence of homo-PLA in the product was confirmed by its derivatization with the diazomethane method. In this respect, low molecular weight oligo(lactide) prepared separately was subjected to derivatization with diazomethane. After the derivatization, the carboxylic acid end group was converted to methyl ester. Correspondingly, the ^{13}C NMR carbonyl signal, due to the carboxyl chain end at 178.5 ppm disappeared. A new signal at 175.9 ppm ascribed to methyl ester was observed (Supporting Information). On the other hand, no signals were observed between 176 and 178 ppm in the ^{13}C NMR spectrum of the product [$(PLA)_3(PCL)_1$ EGP]. Furthermore, the ^{13}C NMR spectra of the copolymer product prior to and after diazomethane derivatization showed no observable change. Therefore, it is concluded that no homo-PLA is present in the product that is due to the possible chain initiation by water.

Since the branching parameters to modify the universal calibration curve were not available for this product, further conclusions based on the GPC determined M_n are not appropriate. Also, we cannot exclude the possibility that low levels of intermolecular transesterification reactions between PCL and PLA chain segments occur. However, the relatively low polymerization temperature used would minimize such events.

In summary, to the best of our knowledge, this is the first report that describes the synthesis of a heteroarm multiblock star copolymer consisting of PLA and PCL chain segments. The novel [$(PLA)_3(PCL)_1$ EGP] was prepared by exploiting the selectivity in two enzymatic steps that gave an ω-acetyl-terminated PCL chain segment linked to the 6-position of EGP. The nonselective L-lactide ring-opening polymerization initiated by all three of the EGP free secondary hydroxyl groups was then carried out using the chemical catalyst stannous octanoate. This resulted in a spatially well-defined multiarm heteroblock copolymer organized around a carbohydrate core.

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Supporting Information Available: Experimental details of the product synthesis and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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