Ethyl Glucoside as a Multifunctional Initiator for Enzyme-Catalyzed Regioselective Lactone Ring-Opening Polymerization

Kirpal S. Bisht,[†] Fang Deng,[†] Richard A. Gross,*[,†] David L. Kaplan,[‡] and Graham Swift[§]

Contribution from the Department of Chemistry, University of Massachusetts—Lowell, One University Avenue, Lowell, Massachusetts 01854, the Department of Chemical Engineering, Tufts University, 4 Colby Street, Medford, Massachusetts 02155, and Rohm & Hass Company, Spring House, Pennsylvania 19477

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Abstract: The one-pot biocatalytic synthesis of novel amphiphilic products consisting of an ethyl glucopyranoside (EGP) headgroup and a hydrophobic chain is described. The porcine pancreatic lipase (PPL) catalyzed ring-opening polymerization of ϵ-caprolactone (ϵ-CL) by the multifunctional initiator EGP was carried out at 70 °C in bulk. Products of variable oligo(ϵ-CL) chain length (M_n = 450, 2200) were formed by variation of the ϵ-CL/EGP ratio. Extension of this approach using *Candida antarctica* lipase (Novozym-435) and EGP as the initiator for trimethylene carbonate (TMC) ring-opening polymerization also resulted in the formation of an EGP−oligo(TMC) conjugate (M_n = 7200). Structural analysis by ^{1}H, ^{13}C, and COSY (^{13}C-^{13}C) NMR experiments showed that the reaction was highly regiospecific; i.e., the oligo(ϵ-CL)/oligo(TMC) chains formed were attached by an ester/carbonate link exclusively to the primary hydroxyl moiety of EGP.

Introduction

Water soluble and dispersible polymers are in great demand for applications as detergents and surfactants.[1] Low molecular weight amphiphilic compounds such as fatty acid esters of carbohydrates also function as useful surfactants.[2] Therefore, incorporation of sugars as components of aliphatic polyesters appears to be a promising strategy for the design of new amphiphilic structures. Although chemical methods for the regioselective esterification of carbohydrates and their derivatives have been extensively studied,[3] many challenges remain due to the similar reactivities of multiple hydroxyl groups. Tedious protection/deprotection steps involved in the preparation of selectively modified sugars greatly reduce yields and increase the cost of the process.[4] However, enzyme-mediated reactions offer the potential for discovery of important routes to surface active molecules with exceptional control over product structural variables that ultimately determine their functional properties.

Recently, enzyme-catalyzed reactions have been demonstrated to provide high selectivity for the acylation of various carbohydrates. Specifically, lipases and proteases have been successfully used for the acylation of the primary hydroxyl group(s) of sugars (glucose, lactose, maltose, etc.) in polar aprotic solvents.[5] However, the need for solvents such as dimethylformamide and pyridine limits the utility of these reactions due to low yields and solvent toxicity. Work showing that ethylglucoside can be regioselectively monoacylated with fatty acids by *Candida antarctica* lipase without solvent and in high yield is a promising development.[6]

The use of enzymes to carry out polymer-forming reactions is gaining increased attention. A recent summary of this activity was published elsewhere.[7] Of particular interest in our laboratories has been the investigation of enzyme-catalyzed ring-opening polymerizations. Inherent advantages of this approach are as follows: (i) monomer ring-opening does not produce a leaving group that must be removed from reactions to achieve high product molecular weights, (ii) the ring-strain of the system can be altered to modulate polymerization kinetics, and (iii) chiral lactones can be polymerized by enantioselective mechanisms. Enzyme-catalyzed polymerizations of macrolactones

* To whom correspondence should be addressed.
[†] University of Massachusetts—Lowell.
[‡] Tufts University.
[§] Rohm & Hass Company.

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have resulted in improved propagation kinetics and/or molecular weights when compared to chemical preparative routes.[8] Recently, we reported the ring-opening polymerization of ω-pentadecalactone (PDL) and trimethylene carbonate (TMC) catalyzed by the lipase PS-30 and Novozym 435, respectively.[7b,8d] High number average molecular weight (M_n = 62 000) and moderate dispersity (M_w/M_n = 1.9) poly(PDL) was obtained in bulk polymerizations at 70 °C.[8d] Also, a 48 h polymerization of TMC catalyzed by Novozym-435 at 55 °C gave poly(TMC) with an M_n = 25 000 without detectable decarboxylation.[7b] The reaction water content and temperature were important factors that controlled not only the rate of monomer conversion but also the polymer molecular weight.[8d] Specifically, we showed that, by decreasing the water content in reactions, slower polymerization rates but higher molecular weights resulted.

The goal of this work was to demonstrate a route to versatile amphiphilic oligomers and polymers that consist of biodegradable aliphatic polyesters or polycarbonates that are regioselectively linked to carbohydrate terminal groups. These products would provide numerous opportunities for further modification. For example, they could be used as macromers to prepare various heteromultiarm block copolymer structures of well-defined spatial architecture. Furthermore, it is envisioned that, by combining traditional chemical and enzyme-catalyzed transformations, it also may be possible to control the repeat unit composition of each arm. Alternatively, modification of the carbohydrate free hydroxyl groups with charged moieties can be used to "tailor" product hydrophilic−hydrophobic balance to develop biodegradable "tunable" surfactants.

Materials and Methods

General Chemicals and Procedures. All chemicals and solvents were of analytical grade and were used as received unless otherwise noted. ϵ-CL was distilled at 97−98 °C over CaH_2 at 10 mmHg. Trimethylene carbonate (TMC) was synthesized following a procedure described elsewhere.[9] The product was recrystallized twice from diethyl ether. White crystals were obtained in 55% yield: mp 45 °C (lit.[9] mp 45 °C). The ^{1}H NMR spectrum (4H, 4.50 ppm; 2H, 2.21 ppm) was consistent with that reported previously.[9] Prior to its use TMC was dried over P_2O_5 in a desiccator (0.1 mmHg, 38 h, room temperature). Ethyl glucopyranoside (EGP) and [$^{13}C_6$]EGP (from [$^{13}C_6$]glucose), prepared according to the procedure described in ref 6b, were mixtures of α- and β-anomers. EGP was dried over P_2O_5 in a vacuum oven (0.1 mmHg, 38 h, 50 °C).

Porcine pancreatic lipase (PPL) type II crude (activity 61 units/mg of protein) and *Candida rugosa* lipase (CCL) type VII (activity 4570 units/mg of protein) were obtained from Sigma Chemical Co. The lipases PS-30, AK, and MAP-10 from *Pseudomonas cepacia*, *Pseudomonas fluorescens*, and *Mucor javanicus*, respectively, were obtained from Amano Enzymes (USA) Co., Ltd. (specified activities at pH 7.0 were 30 000 u/g, 20 000 u/g and 10 000 u/g, respectively. Immobilized lipases from *C. antarctica* (Novozym-435) and *Mucor miehei* (lipozyme IM) were gifts from Novo Nordisk Bioindustrials, Inc. All enzymes, prior to their use, were dried over P_2O_5 (0.1 mmHg, 25 °C, 16 h).

^{1}H NMR spectra were recorded on a Bruker ARX-250 spectrometer at 250 MHz. ^{1}H NMR chemical shifts in parts per million are reported downfield from 0.00 ppm using trimethylsilane (TMS) as the internal reference. The concentration used was 4% (w/v) in $CDCl_3$. The instrumental parameters were as follows: temperature 300 K, pulse width 7.8 μs (30°), 32K data points, 3.178 s acquisition time, 1 s relaxation delay, and 16 transients. ^{13}C NMR spectra were recorded at 62.9 MHz on a Bruker ARX-250 spectrometer with chemical shifts in parts per million referenced relative to DMSO-d_6 or TMS at 39.7 or 0.00 ppm, respectively. Spectral acquisitions were conducted with 10% (w/v) DMSO-d_6 or $CDCl_3$ solutions using the following parameters: 300 K, pulse width 6.3 μs (30°), 64K data points, 1.638 s acquisition time, 1 s relaxation delay, and 15000−18000 transients. DEPT-135 spectra were recorded at 62.9 MHz using a Bruker ARX-250 spectrometer with 10% (w/v) DMSO-d_6 solutions at 300 K, 64 K data points, 1.638 s acquisition time, 1 s relaxation delay, and 10000−15000 transients. For the (^{1}H−^{1}H) COSY experiment (4% (w/v) product in DMSO-d_6) the data were collected in a 1024 × 128 data matrix and zero filled to 512 × 512 using eight scans per increment, a 1915 Hz sweep width, and 1.93 s delay between transients.

All molecular weight measurements were performed by gel permeation chromatography (GPC). Analyses were carried out using a Waters model 510 pump equipped with a model 410 refractive index detector, model 486 UV detector and model 717 autosampler with 500, 10^3, 10^4, and 10^5 Å Ultrastyragel columns in series. Chloroform (HPLC grade) was used as the eluent at a flow rate of 1.0 mL/min. The sample concentration and injection volumes were 0.3% (w/v) and 100 μL, respectively. The molecular weight was calculated on the basis of comparison to polystyrene standards without further correction.

The surface tension measurements were conducted at 25 °C, using a Fisher Scientific Surface Tensiomat 21 equipped with a 6 cm platinum−iridium ring.

PPL-Catalyzed EGP-Initiated Ring-Opening Polymerization of ϵ-Caprolactone. The enzyme-catalyzed ring-opening of ϵ-CL by EGP was carried out as follows. Using a glovebag and dry argon to maintain an inert atmosphere, 200 mg of EGP and 500 mg of PPL (type II, Sigma) which had previously been dried in a vacuum desiccator (0.1 mmHg, 25 °C, 16 h) were transferred to an oven-dried 20 mL reaction vial. The vial was immediately stoppered with a rubber septum and purged with argon, and 0.8 mL of ϵ-CL (distilled at 97−98 °C over CaH_2 at 10 mm of Hg) was added via syringe under argon. The reaction vial was then placed in a constant temperature oil bath maintained at 70 °C for 96 h. A control reaction was set up as described above except PPL was not added. More than 95% EGP (determined by TLC) was consumed in 96 h. The reaction was quenched by removing the enzyme by vacuum filtration (glass fritted filter, medium-pore porosity), the enzyme was washed 3−4 times with 5 mL portions of chloroform, the filtrates were combined, and solvent was removed in vacuo to give 950 mg of product. To remove unreacted EGP, the biotransformation product (500 mg) was purified by column chromatography over silica gel (10 g, 130−270 mesh, 60 Å, Aldrich) using a gradient solvent system of hexanes−ethyl acetate (2 mL/min) with increasing order of polarity to give 450 mg of purified product, M_n = 2200 and M_w/M_n = 1.2. ^{1}H NMR ($CDCl_3$): 4.88 (d, J = 3.8 Hz), 4.45−4.25 (m), 4.08 (t, J = 6.6 Hz), 3.94−3.30 (m), 3.65 (t, J = 6.6 Hz), 2.38 (m), 1.65 (m), 1.39 (m), and 1.25 (t, J = 7.5 Hz) ppm. Also, a reaction conducted exactly as is described above but with 200 mg of EGP and 3.2 g of ϵ-CL (ϵ-CL/EGP, 30:1 mol/mol, bulk, 70 °C) and catalyzed by Novozym-435 gave 3.0 g of product (M_n = 12 500).

PPL/Novozym-435-Catalyzed EGP-Initiated ϵ-Caprolactone Dimer Synthesis. The reaction was conducted by adapting the procedure described above (ϵ-CL:EGP = 2:1 mol/mol, bulk, 70 °C). Fractionation of the product by column chromatography (silica gel, 15% EtOH/$CHCl_3$) resulted in the isolation of a diadduct (EGP linked to the ring-opened ϵ-CL dimer). ^{1}H NMR (250 MHz, $CDCl_3$): 4.88 (1H, d, J = 3.8 Hz, H1(α)), 4.45−4.25 (3H, m, H6 (α and β) and H1(β)), 4.08 (2H, t, J = 6.6 Hz, 6′H), 3.94 (1H, m, 1″H (α)), 3.78 (3H, m, H3 (α and β) and H5(α)), 3.65 (2H, t, J = 6.6 Hz, 12′H), 3.50−3.48 (3H, m, 1″H(β), H5(β), and H2(α)), 3.46−3.37 (3H, m, H4 (α and β) and H2-(β)), 2.38 (4H, m, 2′ and 8′H), 1.65 (8H, m, 3′, 5′, 9′, and 11′H), 1.39 (4H, m, 4′ and 10′H), 1.25 (3H, t, J = 7.5 Hz, 2″H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): 174.0 (C═O), 173.8 (C═O), 102.74 (C1 β), 98.40 (C1 α), 76.56 (C3 β), 74.73 (C3 α), 74.14 (C5 β), 73.85 (C2 β), 72.39 (C2 α), 70.48 (C4 α and β), 70.04 (C5 α), 65.74 (C1″ β), 64.29 (C6′), 64.10 (C1″ β), 63.55 (C6 α and β), 62.69 (C12′), 34.46 (C2′), 34.19 (C8′), 32.41 (C5′), 28.51 (C11′), 25.69 (C4′), 25.49 (C10′), 24.89 (C3′), 24.69 (C9′), 15.33 (C2″ β), 15.21 (C2″ α) ppm.

Novozym-435-Catalyzed EGP-Initiated Ring-Opening Polymerization of Trimethylene Carbonate (TMC). The enzyme-catalyzed

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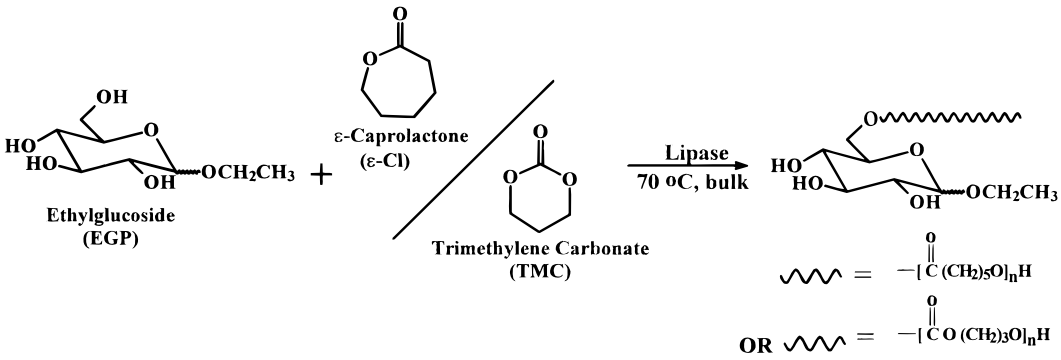
Scheme 1



ring-opening polymerization of TMC by EGP was carried out by a method similar to that described above for PPL-catalyzed ϵ-CL ring-opening. Using a glovebag and dry argon to maintain an inert atmosphere, 200 mg of EGP, 714 mg of TMC, and 500 mg of Novozym-435 which had previously been dried in a vacuum desiccator (0.1 mmHg, 25 °C, 16 h) were transferred to an oven-dried 20 mL reaction vial. The vial was immediately stoppered with a screw cap and sealed with Teflon tape. The reaction vial was then placed in a constant temperature oil bath maintained at 70 °C for 96 h. A control reaction was set up as described above except Novozym-435 was not added. The reaction was quenched by removing the enzyme by vacuum filtration (glass-fritted filter, medium-pore porosity), the enzyme was washed 3−4 times with 5 mL portions of chloroform, the filtrates were combined, and the solvent was removed in vacuo to give 850 mg of product, $M_n = 7200$ and $M_w/M_n = 2.5$. ^{1}H NMR ($CDCl_3$): 4.88 (d, $J = 3.8$ Hz), 4.44−4.37 (m), 4.31 (t, $J = 4.8$ Hz), 4.24 (t, $J = 12.4$ Hz), 4.10−3.82 (m), 3.80−3.70 (m), 3.70−3.30 (m), 2.06 (t, $J = 12.5$ Hz), 1.94 (t, $J = 12.0$ Hz), 1.25 (t, $J = 7.0$ Hz) ppm.

Results and Discussion

α,β-Ethyl glucopyranoside (EGP) was used as the multifunctional initiator for ϵ-caprolactone (ϵ-CL) and trimethylene carbonate (TMC) ring-opening polymerizations (Scheme 1). This provided a novel route for the one-pot synthesis of oligomers with ethyl glucose headgroups.

EGP was evaluated as the multifunctional initiator in this study because of its simple synthesis and more rapid reaction kinetics than either methyl glucopyranoside (MGP) or glucose.[6] Unlike α,β-methyl glucopyranoside (MGP) or its pure α- and β-anomers which are solids, EGP as a mixture of α- and β-anomers is a viscous oil. Since our goal was to conduct solvent-free reactions, the selection of EGP instead of MGP allowed us to work with fluid reaction media.

Commercially available lipases were evaluated for EGP-initiated ϵ-CL ring-opening polymerization (ϵ-CL:EGP = 7:1 mol/mol, 70 °C, 96 h). The lipases from *C. rugosa* (formerly known as *Candida cylindracea*, CCL), *P. cepacia* (PS-30), *M. miehii* (lipozyme IM), *M. javanicus* (MAP-10), and *P. fluorescens* (AK) gave low conversions of ϵ-CL to ring-opened product (2, 9, 15, 29, and 54%, respectively). In contrast, the lipase from *C. antarctica* (Novozym-435) and porcine pancreatic lipase (PPL) gave relatively higher ϵ-CL conversion (>80%) under identical reaction conditions. The same lipases and protocol as above were used to establish conditions for EGP-initiated TMC ring-opening polymerization (TMC:EGP = 7:1 mol/mol, 70 °C, 96 h). There were significant differences in the activity of the lipases for the EGP-initiated TMC ring-opening polymerization reaction. Low conversions were observed with lipases PS-30, CCL, lipozyme IM, and MAP-10 (20, 5, <2, and 15%, respectively). However, the lipases PPL, Novozym-435, and AK gave much higher conversions for the same reaction (>78%). Of all the lipases screened, Novozym-435 gave the highest TMC conversion (97%). Work was then performed to establish the chain end structure of the products.

For the enzyme-catalyzed ring-opening of ϵ-CL by EGP (ϵ-CL:EGP ratio of 7:1) at 70 °C for 96 h in bulk, we obtained a product which was purified by column chromatography to remove unreacted EGP. Product purification was by silica gel chromatography, and the resulting end-group "tailored" oligopolyester had a number average molecular weight (M_n) and polydispersity (M_w/M_n) of 2200 and 1.26, respectively. The reaction was highly regioselective and resulted in oligo(ϵ-CL) chains which were attached by an ester group exclusively to the primary hydroxyl moiety of EGP as discussed below. The structure of the product was confirmed by nuclear magnetic resonance (NMR) experiments as is elaborated below.

During the lipase-catalyzed bulk polymerization of lactones and cyclic carbonates, water is known to act as an initiator.[10] Therefore, there is the possibility of competitive initiation by EGP and water. However, if a fraction of the oligo(ϵ-CL) chains were initiated by water, this would result in carboxyl terminal chain ends having a carbonyl signal in the region between 178 and 176 ppm.[11] Comparison to spectra of PCL showed that the signal at 173.8 ppm is due to the intrachain carbonyl groups of oligo(CL). The absence of any resonances in the 176−178 ppm region suggested that the initiation of the oligo(ϵ-CL) chains occurred exclusively by EGP (Figure 1A). This conclusion was further strengthened by comparing the ^{13}C NMR spectra of these products prior to and after diazomethane derivatization. Conversion of carboxyl terminal groups to their methyl ester derivative would be expected to shift corresponding carbonyl signals upfield by about 4 ppm.[12] Since there was no notable change in the spectra displayed in Figures 1A and 1B, this supports that if both water and EGP functioned as competitive initiators, the initiation of chains by water occurred infrequently. Furthermore, the ^{13}C NMR spectrum of the diadduct (EGP linked to two ϵ-CL repeat units) showed two partially resolved signals centered at 174.0 ppm. This suggests that the ϵ-CL repeat unit linked to EGP and the repeat unit at the hydroxyl terminus of oligo(ϵ-CL) have ester carbonyl groups with signals at ~174.0 ppm (see Figure 1).

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(12) Oligo(CL) was prepared by the PPL-catalyzed ring-opening polymerization of ϵ-CL in *tert*-butyl alcohol. Terminal carboxyl functionalities of oligo(CL) were esterified with diazomethane, and its ^{13}C-NMR spectrum was compared with that of the product where EGP was used as the initiator. The signals observed for oligo(ϵ-CL) at 177.8 and 178.1 ppm assigned to carboxylic acid C═O groups were shifted upfield by 4 ppm after esterification.

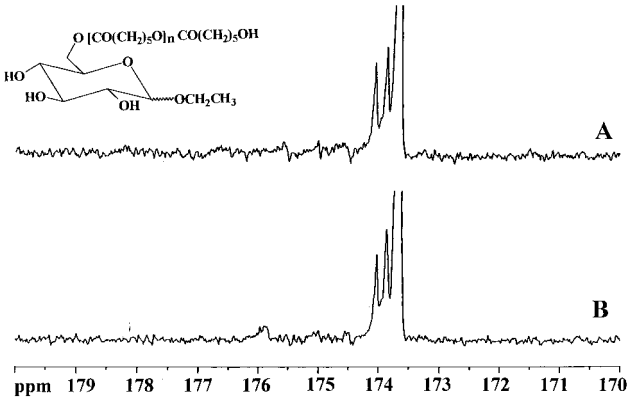


Figure 1. Spectral regions (170−180 ppm) of the ^{13}C NMR spectra (62.5 MHz, solvent $CDCl_3$) of (A) the product, EGP−oligo(CL), M_n = 2200, and (B) the product in (A) after its derivatization with diazomethane.

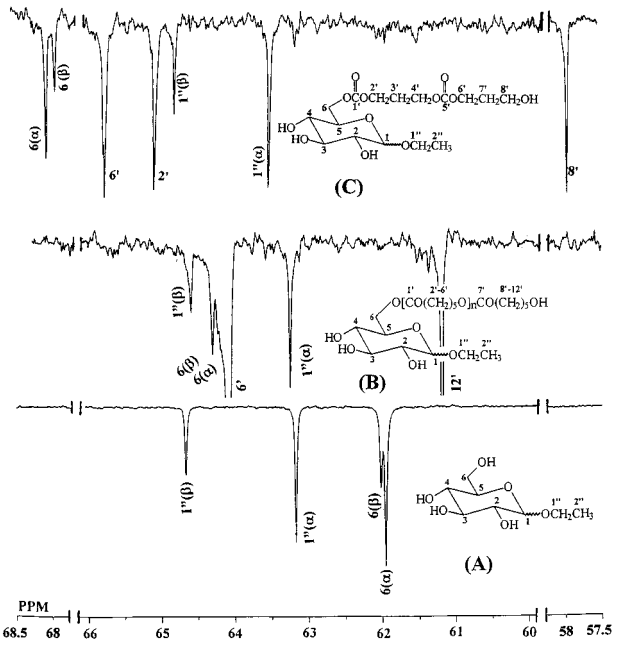


Figure 2. Spectral regions (57.5−68.5 ppm) of the DEPT-135 NMR spectra (62.5 MHz, solvent DMSO-d_6) of (A) ethyl glucopyranoside, EGP; (B) EGP−oligo(CL), M_n = 2200, and (C) EGP−TMC diadduct.

The ^1H NMR spectrum of the EGP−oligo(ϵ-CL) conjugate in $CDCl_3$ contained peaks due to oligo(ϵ-CL) {4.08 (t, J = 6.6 Hz), 3.65 (t, J = 6.6 Hz), 2.38 (m), 1.65 (m), and 1.39 (m) ppm} and the reacted ethyl glucoside {4.88 (d, J = 3.8 Hz), 4.45−4.25 (m), 3.94−3.30 (m), and 1.25 (t, J = 7.5 Hz) ppm}. This spectrum, due to poorly resolved signals, was not useful in determining the position at which oligo(ϵ-CL) was linked to the sugar headgroup. Also, an inspection of the literature describing the NMR characterization of EGP did not provide a suitable basis for assignments of ^{13}C NMR signals.[6] Therefore, assignment of signals in the ^{13}C NMR spectrum of EGP was confirmed from a $^{13}C-^{13}C$ COSY experiment on [$^{13}C_6$]EGP (see the Supporting Information). Also a DEPT-135 spectrum of EGP gave additional support for the assignment of the C-6 signals at 61.9 (α) and 62.0 (β) ppm (Figure 2A). A comparison of the DEPT-135 spectrum of EGP and the ring-opened products from PPL-catalyzed reactions between EGP and ϵ-CL showed that, for the latter, signals corresponding to the EGP C-6 α- and β-anomers were shifted downfield by 2.4 ppm (Figure 2B). Furthermore, signals in Figure 2A observed at 61.9 and 62.0 ppm were no longer detected in the product (Figure 2B). These

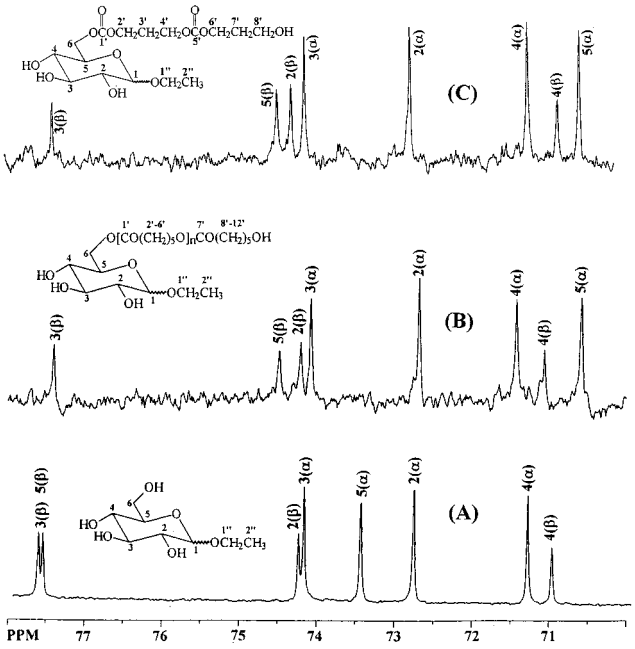


Figure 3. Spectral regions (70−78 ppm) of the DEPT-135 NMR spectra (62.5 MHz, solvent DMSO-d_6) of (A) ethyl glucopyranoside, EGP; (B) EGP−oligo(CL), M_n = 2200, and (C) EGP−TMC diadduct.

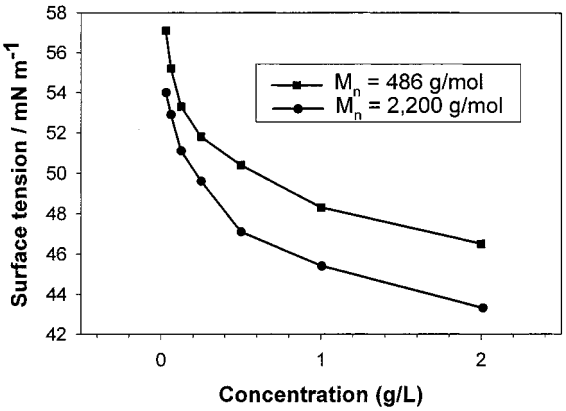


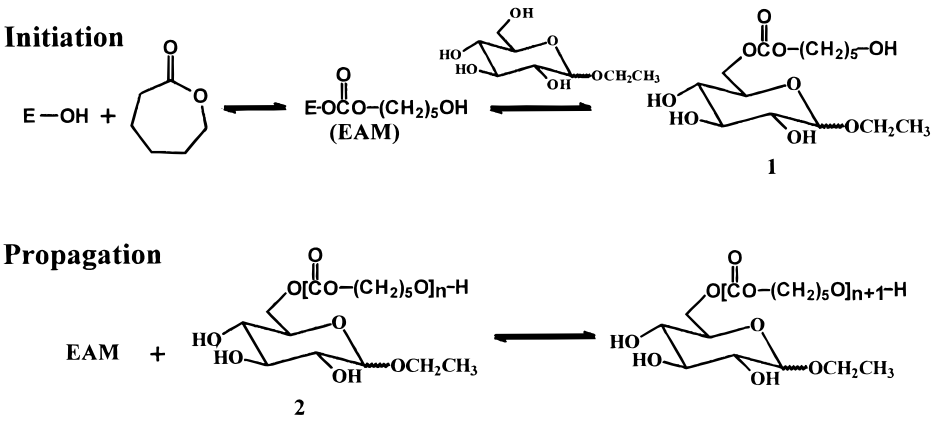
Figure 4. Surface tension versus concentration for oligo(ϵ-CL)−EGP conjugates at 25 °C.

results indicated that the C-6 primary hydroxyl position of EGP served as sites for initiation of ϵ-CL polymerzation. This conclusion was supported by an upfield shift for EGP C-5 of 3.0 ppm after ϵ-CL polymerization (Figure 3B). The upfield shift is consistent with substitution at the γ-position relative to C-5.[13] Moreover, all other carbon resonances assigned to EGP showed no substantial change in chemical shift after ϵ-CL polymerization (Figures 2 and 3). Additionally, ^1H, $^1H-^1H$ COSY, and $^1H-^{13}C$ HETCOR NMR experiments on EGP linked to two ϵ-CL unit(s) confirmed the high regioselectivity of the PPL-catalyzed transformation (see the Supporting Information). Therefore, it was concluded that PPL catalysis resulted in regioselective initiation by EGP at C-6 to form well-defined macromers containing oligo(ϵ-CL) with an EGP headgroup. It is noteworthy to mention that there was no observed preference between the α- and β-anomers of EGP for PPL-catalyzed reaction with ϵ-CL.

The Novozym-435-catalyzed formation of an EGP−oligo-(TMC) conjugate was highly regiospecific, and only the primary

(13) Breitmaier, E.; Bauer, G. *^{13}C NMR Spectroscopy- a working manual with exercises*; Harwood Academic Publishers: New York, 1984; pp 54−57.

Scheme 2



hydroxyl moiety of EGP was attached to the oligo(TMC) chains. After column chromatographic purification to remove unreacted EGP (see earlier), a EGP−oligo(TMC) having an M_n and M_w/M_n of 7200 and 2.5, respectively, was obtained. An analysis by NMR was then undertaken to establish the site of reaction in the EGP−oligo(TMC) conjugate. A similar reaction with a 1:2 molar ratio of EGP to TMC followed by column chromatographic purification gave the EGP−TMC diadduct. The DEPT-135 carbon spectral region showing the carbon resonances due to the EGP in the EGP−TMC diadduct is shown in Figures 2C and 3C. On comparison with the DEPT-135 carbon spectra of EGP, the EGP−oligo(TMC) conjugate showed a downfield shift (∼6 ppm) in the resonance positions of carbon-6 from ∼62.1 to ∼68.0 ppm (Figure 2C). Also, the carbon-5 signals were shifted upfield (∼3 ppm) due to the γ-shift (Figure 3C: C-5b from 77.5 to 74.4 ppm, C-5a from 73.8 to 70.5 ppm). Furthermore, all other signals assigned to EGP showed no substantial shift after TMC polymerization (Figures 2C and 3C). Therefore, it was concluded that the Novozym-435-catalyzed ring-opening polymerization initiated by EGP led to the exclusive participation of EGP C-6 hydroxyl groups. Again, there was no observed preference between the α- and β-anomers of EGP for the Novozym-435-catalyzed reaction between EGP and TMC. Additional spectral evidence for regioselective initiation by the primary EGP hydroxyl position is given in the Supporting Information.

It was possible to control the length of the polyester chain by variation in the molar ratio of EGP to lactone monomer. Similar reactions catalyzed by Novozym-435 using 1:2 and 1:30 ratios of the EGP to ϵ-CL resulted in the synthesis of EGP−oligo/poly(ϵ-CL) conjugates, M_n = 486 and 12 500, respectively. Detailed characterization of high molecular weight products from Novozym-435-catalyzed EGP-initiated ϵ-CL ring-opening polymerization is currently in progress. As expected, these amphiphilic oligomeric conjugates are surface active on the basis of tensiometric measurements at the air−water interface (Figure 4). The efficiency and effectiveness of these conjugates for surface tension reduction was a function of the oligoester chain length (Figure 4). Therefore, the potential exists to enhance the surface activity of these conjugates by careful modulation of their hydrophilic/hydrophobic balance.

It is noteworthy to point out that when MGP was used instead of EGP as the initiator under similar reaction conditions, reactions between MGP and either ϵ-CL or TMC did not occur. Also, numerous reports in the literature attest to the biodegradability and biocompatibility of poly(ϵ-CL) and poly(TMC).[14] Therefore, amphiphilic structures generated in this work are likely to be biodegradable.

Proposed Mechanism. On the basis of the defined structure of the products synthesized herein and related work which is further elaborated below, a general mechanism for the lipase-catalyzed EGP-initiated ring-opening polymerization reaction was proposed (see Scheme 2). The monomer ϵ-CL was selected for the purpose of illustration. Initiation is believed to involve (i) reaction between the lipase and ϵ-CL to form an enzyme-activated monomer (EAM) complex and (ii) reaction of EGP with the EAM complex to form ethyl 6-(6-hydroxyhexanoyl)-glucopyranoside (structure **1**).[15] The regioselectivity of chain initiation must be controlled by the lipase. Propagation then occurs by reaction of either **1** or **2** with the EAM complex. This reaction scheme is consistent with the general mechanism of lipase-catalyzed ring-opening polymerization of lactones proposed by MacDonald et al.,[10a] Henderson et al.,[10c] and Uyama et al.[8a]

Conclusions

In summary, a convenient one-pot biocatalytic synthesis of novel biodegradable amphiphilic oligomers is described. The selectivity of different lipases and general applicability of the method was also demonstrated by screening a number of commercial lipases and two very different monomer/enzyme systems, i.e., ϵ-CL/PPL and TMC/Novozym-435. Thus, by this strategy, chains were formed having sugar headgroups without using protection−deprotection strategies. Further reactions of these macromonomers at positions 2, 3, and 4 of the EGP ring will be used in future work to (1) develop a new family of well-defined multiarm block copolymer architectures and (2) regulate the ionic character of the headgroup to develop biodegradable tailored surfactants. Furthermore, this versatile synthetic strategy is currently being extended to other carbohydrate initiators and cyclic monomers. Reactions conducted using denatured lipases which were inactive for ϵ-CL and TMC polymerizations showed that the EGP-initiated oligomerizations were indeed enzyme-catalyzed.

Acknowledgment. We are grateful for the financial support received from Rohm & Hass Co., Pennsylvania.

Supporting Information Available: Spectral data of products (8 pages). See any current masthead page for ordering information and Web access instructions.

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(14) Benedict, C. V.; Cameron, J. A.; Huang, S. J. *J. Appl. Polym. Sci.* **1983**, *28*, 335. Bucholtz, B. *J. Mater. Sci., Mater. Med.* **1993**, *4*, 381.

(15) It is assumed that the serine residue present at the active site of PPL activates the lactone for subsequent polymerization by forming the EAM complex (Scheme 2). This model of enzyme−substrate reaction and substrate activation is based on studies with triglycerides (Brockerhoff, H.; Jensen, R. G. *Lipolytic Enzymes*; Academic Press: New York, 1974).