Macromolecules **2003,** *36,* 8219−8221

Versatile Route to Polyol Polyesters by Lipase Catalysis

Ajay Kumar, Ankur S. Kulshrestha,[†] Wei Gao, and Richard A. Gross*

NSF Center for Biocatalysis and Bioprocessing of Macromolecules, Department of Chemistry and Chemical Engineering, Polytechnic University, Six Metrotech Center, Brooklyn, New York 11201

Received August 11, 2003

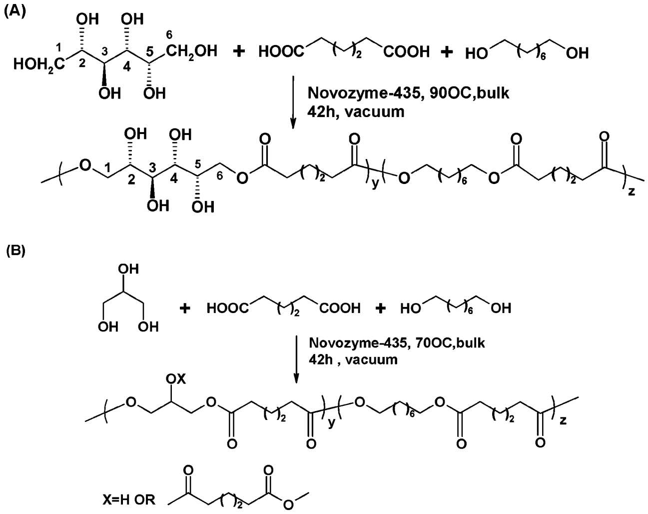
The incorporation of carbohydrates into nonpolysaccharide structures is an important strategy to attain (i) highly functional polymers, (ii) specific biological functions, and (iii) complex systems that act as “smart” materials.[1] Polyesters with carbohydrate or polyol repeat units in the chain can be produced by chemical methods.[2a] However, elaborate protection−deprotection steps[2a−e] are needed to avoid cross-linking between polyol units. Multistep routes to non-cross-linked polyol polyesters limit the potential of their practical use.

Lipases and proteases are well-known to provide regioselectivity during esterification reactions at mild temperatures.[3a,b] These characteristics motivated their study as catalysts for selective polyol polymerizations. The activation of carboxylic acids with electron-withdrawing groups was thought to be necessary for enzyme-catalyzed copolymerizations with polyols.[4a−j] For example, the copolymerization of sucrose with bis(2,2,2-trifluoroethyl) diester[4i] (45 °C, 30 days) gave in 20% yield an oligomer with an average degree of polymerization (dp_{avg}) of 11. Russell and co-workers[4a] used the lipase catalyst Novozyme-435 to form polyester with M_w 10 025 from the monomers divinyl adipate and glycerol.

An obstacle to lipase- or protease-catalyzed polymerizations of polyols is their insolubility in nonpolar organic media. Polyols are soluble in polar solvents[4f−j] such as pyridine, dimethyl sulfoxide, 2-pyrrolidone, and acetone. However, these solvents cause large reductions in enzyme activity. For example, Patil et al.[4j] copolymerized sucrose with bis(2,2,2-trifluoroethyl) adipate in pyridine that, after nearly a month, gave the corresponding sucrose polyester with an M_w of 2100. Also, Dordick et al.[4f] copolymerized divinyl adipate with sorbitol in acetonitrile for 94 h at 45 °C to give poly(sorbityl adipate) in 34% yield with M_w 13 660. In addition to the use of activated esters and polar solvents, large quantities of lipases were thought to be necessary. Uyama et al. used 75 wt % (relative to total monomers) of the lipase from *Candida antarctica* to copolymerize sorbitol with divinyl sebacate at 60 °C in acetonitrile.[4h]

This paper describes a simple and versatile strategy to perform selective lipase-catalyzed condensation polymerizations between diacids and reduced sugar polyols (Scheme 1). Instead of using organic solvents, the monomers adipic acid, glycerol, and sorbitol were solubilized within binary or ternary mixtures. The polymerization reactions were performed without activation of adipic acid. The absolute molecular weight of the polymeric products was analyzed by light scattering, and the regioselectivity of monomer esterification reactions was analyzed by inverse-gated ^{13}C NMR experiments.

Scheme 1. Novozyme-435-Catalyzed Polymerization of (A) Sorbitol and (B) Glycerol To Form Terpolyesters



The direct condensation of adipic acid and sorbitol was performed in bulk for 48 h at 90 °C using Novozyme-435 (10 wt % relative to monomers) (entry 1, Table 1). The product, poly(sorbityl adipate), was water-soluble. Molecular weight averages (M_n and M_w) of the nonfractionated poly(sorbityl adipate), determined by SEC-MALLS in DMF, were 10 880 and 17 030 g/mol, respectively. The polymer structure was analyzed by ^1H NMR and inverse-gated ^{13}C NMR spectroscopy in *d*-methanol (see Supporting Information, Figures S-1 and S-2, respectively). The major signals at 66.6, 67.3, 70.4, 70.5, 72.5, and 73.0 ppm in the spectrum were assigned to the sorbitol C-1, C-6, C-3, C-4, C-2, and C-5 carbons, respectively (see Figure S-2 and numbering in Scheme 1).[4h] Analysis of this spectrum revealed that sorbitol was esterified with high regioselectivity (85 ± 5%) at the primary 1- and 6-positions.

Uyama et al.[4h] formed a similar polymer by a polymerization in acetonitrile between divinyl sebacate and sorbitol using 75 wt % (relative to monomers) Novozyme-435. They reported that the polymerization proceeded by exclusive acylation at the sorbitol 1- and 6-positions. This difference in regioselectivity may be due to (i) Uyama et al.[4h] analyzed only a water-insoluble product fraction (64% of total) and/or (ii) differences in the reaction conditions used (e.g., solvent vs bulk).

To obtain water-insoluble sorbitol copolyesters, 1,8-octanediol was used in place of a fraction of sorbitol in the monomer feed. Adipic acid, 1,8-octanediol, and sorbitol were copolymerized in the molar ratio 50:35:15 (Table 1, entry 2). The methanol-insoluble product had an M_w of 1.17×10^5. The solubility in water and THF of entry 1 and 2 products, respectively, is direct proof that they have few interchain cross-links.

The repeat unit composition and regioselectivity of P(OA-11 mol % SA) was analyzed by inverse-gated ^{13}C NMR (75.5 MHz). The spectrum in *d*-chloroform (Supporting Information Figure S-3) showed that for adipate units linked to 1,8-octanediol (A*O) the methylene

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[†] This paper is a part of the thesis dissertation of Ankur S Kulshrestha, Polytechnic University.

10.1021/ma0351827 CCC: $25.00

Table 1. Synthesis of Aliphatic Polyesters with Sorbitol and Glycerol Repeat Units[a]

entry	X	A:O:X feed ratio	obsd A:O:X[b] (mol %)	MeOH insol[c] (%)	M_w[d] × 10^{-3}	M_w/M_n
1	S	50:0:50	50:0:50	np[e]	17	1.6
2	S	50:35:15	50:39:11	80	117	3.4
3	G	50:0:50	50:0:50	50	3.7	1.4
4	G	50:40:10	50:41:9	90	75.6	3.1

[a] Reaction conditions: bulk, 90 °C (entries 1−3), 70 °C (entry 4), Novozyme-435 (10% w/w of monomers), reaction times were 48 h for entry 1 and 42 h for entries 2−4, in vacuo (40 mmHg). [b] A is adipic acid, O is octanediol, X = S (sorbitol) or G (glycerol); the mol % was calculated from ^{13}C NMR signals of A*O vs A*S for X = S and from ^1H NMR signals of A*O vs A*G for X = G. [c] Percent of product that precipitated in methanol (for entries 2 and 4). [d] Determined by size exclusion chromatography (SEC) multiangle laser light scattering (MALLS) measurements in THF (entries 2−4) and DMF (entry 1, 10 mM LiBr). [e] np is not precipitated.

carbons $O(C{=}O){-}CH_2$ and $O(C{=}O){-}CH_2CH_2$ have signals at 34.35 and 24.15 ppm, respectively. Similarly, for adipate linked to sorbitol (A*S), the methylene carbons $O(C{=}O){-}CH_2$ and $O(C{=}O){-}CH_2CH_2$ have signals at 34.30 and 23.88 ppm, respectively. From the relative intensities of the A*O and A*S signals, the content of 1,8-octanediol and sorbitol in the terpolymer was found to be 39 and 11 mol %, respectively. The regioselectivity of esterification at the sorbitol repeat units was also determined from the inverse-gated ^{13}C NMR spectrum. The spectrum of P(OA-11 mol % SA) in d_6-DMSO at 75.5 MHz (Supporting Information Figure S-4) shows signals at 71.30, 70.40, 69.27, 68.99, 66.30, and 65.52 ppm which were assigned to the sorbitol carbons C-5, C-2, C-4, C-3, C-6, and C-1, respectively.[4f] Furthermore, the signals at 63.40 and 62.35 ppm were assigned to 1,8-octanediol $(O{=}C)OCH_2$ and CH_2OH carbons, respectively. Weak signals that have a cumulative intensity below ∼5 ± 2% of the above-mentioned signals were observed in the 65.5−73 ppm region. These signals are due to sorbitol esters other than those at the primary 1- and 6-hydroxyl positions. Thus, the regioselectivity of esterification at the 1- and 6-carbons of sorbitol was ∼95 ± 2%.

Similar experiments as above were performed where, in place of sorbitol, glycerol was used as the natural polyol. The M_n and M_w values of the resulting poly(glyceryl adipate), P(GA), determined by SEC-MALLS in THF, were 2500 and 3700 g/mol, respectively. Thus, substitution of sorbitol by glycerol without 1,8-octanediol resulted in a product of much lower molar mass. The terpolymerization of the monomers adipic acid, 1,8-octanediol, and glycerol, in the ratio 50 to 40 to 10 mol %, was performed in-bulk at 70 °C using Novozyme-435 as the catalyst (Scheme 1B). Analysis by SEC-MALLS of the resulting glycerol terpolyester P(OA-9 mol % GA) (see Table 1, entry 4) in THF gave values for M_w and M_w/M_n of 75 600 and 3.1, respectively. The solubility of P(OA-9 mol % GA) shows that, without using protection−deprotection chemistry, the product formed has few intermolecular cross-links. The ^1H NMR spectrum of P(OA-9 mol % GA) (Supporting Information Figure S-5) has signals due to the glycerol protons $-CH_2-O(C{=}O)$ and $-CH-O-(C{=}O)$ at 4.17 and 4.30 ppm, respectively. The ^1H NMR signals due to 1,8-octanediol $-CH_2-O(C{=}O)$ and adipate $-CH_2-(C{=}O)$ protons are at 4.07 and 2.39 ppm, respectively. The mol % incorporation of glycerol in the copolyester was determined from the additive intensity of the signals at 4.17 and 4.3 relative to that at 4.07 ppm. The inverse-gated ^{13}C NMR spectrum (Supporting Information Figure S-6) has resolved signals at 71.9, 69.8, 68.8, and 67.5 ppm. These signals were assigned to the glycerol repeat unit methine carbons, A to D, that are 1-substituted, 1,2-disubstituted, 1,2,3-trisubstituted, and 1,3-disubstituted, respectively.[4c] The relative intensity of these signals is 17:17:27:39. Thus, the product has a complex substitution pattern at the glycerol units. Unlike the high selectivity at sorbitol primary hydroxyl groups, the selectivity at glycerol primary sites is only 66%.[5] Furthermore, the product has a high level of trisubstituted glycerol repeat units and a high molecular weight and is organosoluble. Thus, the product is highly branched but has few cross-links. In fact, 27 mol % of glycerol units are branch sites, of which almost 17 mol % terminate in monosubstituted glycerol units. Work is in progress to determine the average length and substitution of branches.

The role of the enzyme was verified by control reactions. No-enzyme control experiments showed that little (<2%) acylation of the hydroxyl monomers took place in the absence of Novozyme-435. Furthermore, elsewhere we reported the irreversible inactivation of Novozyme-435 by modification of its active site with diethyl *p*-nitrophenyl phosphate (paraoxon).[6] Novozyme-435 modified in this way was inactive for the catalysis of ϵ-caprolactone polymerization at 60 °C. In contrast, the active enzyme catalyzes ϵ-caprolactone polymerization to form a high molar mass chain (>10 000 g/mol) in high yield (>80%). When the polymerizations described in entries 2 and 4 were performed using tetrabutyl titanate (1% w/w relative to monomers, 60 mg) as the catalyst at 180 °C for 2 h in a vacuum (10 mmHg),[7] the products formed were gels. Hence, by using Novozyme-435 instead of a chemical catalyst, cross-linking was largely avoided, and the reaction temperature was dramatically reduced.

The thermal stability, melting transitions, and crystallinity (χ) of selected glycerol and sorbitol terpolyesters were studied.[8] Thermogravimetric analysis of P(OA-11 mol % SA) and P(OA-9 mol % GA) showed they had onset of decomposition values of 394 and 401 °C, respectively. Hence, these copolymers have high thermal stability. Thermograms recorded by differential scanning calorimetry during the first heating scan gave values of the melting enthalpies and peak melting temperatures. These values for P(OA-11 mol % SA) are 59 J/g and 58 °C, respectively. The identical studies performed for P(OA-9 mol % GA) gave values of 97 J/g and 62 °C. The percentages of crystallinity, measured by wide-angle X-ray diffraction, were 32% and 52%, for P(OA-11 mol % SA) and P(OA-9 mol % glycerol), respectively. Hence, these copolyesters are semicrystalline, low melting, soft materials. The copolyester from adipic acid and 1,8-octanediol, without natural polyol units, has an enthalpy of melting, peak melting temperature, and percent crystallinity of 136 J/g, 74 °C, and 65%, respectively. Thus, incorporation of sorbitol and glycerol into poly(octanyl adipate) results in a decrease in the polymer melting point and degree of crystallinity.

The percent activity retained by the enzyme after the above 42 h reactions to form the 11 mol % sorbitol and 9 mol % glycerol copolymers was 82% and 90%, respectively. The assay to evaluate the enzyme activity of the recovered catalyst is based on catalysis of propyl laurate formation and is described elsewhere.[9]

Conclusion. A simple, environmentally friendly, and practical route is described for the preparation of polyesters from polyols. For the first time, soluble polymers from reduced sugars were synthesized with molecular weights up to 117 000 (M_w) and without the need to activate monomer acid groups or add an organic solvent. The key to the success of the method is the use of a highly active and selective lipase as the catalyst as well as adjusting the reaction mixture so that it is monophasic. Polyesters rich in hydroxyl functionality such as poly(sorbityl adipate) were prepared without the need to use protection−deprotection chemistry. Furthermore, the inability of the lipase to exert high selectivity for glycerol polymerizations led to polymers that are rich in monosubstituted glycerol pendant groups. Thermal analysis of the products showed they have high thermal stability and are low melting. We believe the simplicity of the polyol condensation polymerizations will lead to practical processes and products.

Acknowledgment. We acknowledge members of the NSF Center for Biocatalysis and Bioprocessing of Macromolecules at the Polytechnic University for their financial support.

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

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MA0351827