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Protic acid-catalyzed polymerization of β-lactones for the synthesis of chiral polyesters

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Abstract—Chiral poly(β-hydroxybutyrate) was prepared with retention of configuration from (*R*)-β-butyrolactone by ring-opening polymerization catalyzed by triflic acid in an aprotic solvent. At higher temperatures, triflic acid could also be used to depolymerize chiral poly(hydroxybutyrate) to form enantiopure β-hydroxybutyric acid building blocks.

1. Introduction

Poly(β-hydroxybutyrate) (PHB), a member of a larger family of polymers named poly(hydroxyalkanoates) (PHA), is produced by a large number of bacteria as an energy storage medium, playing a role analogous to mammalian fat.[1] Stereoregular PHB is a semicrystalline thermoplastic and has properties similar to such commonly used plastics as polypropylene but with the added feature of having chiral repeat units when derived from biological sources.[2] The optically active naturally-derived polymers harbour a stereogenic site in each molecular repeat unit, all of which are of the *D*- (or *R*) configuration, which substantially change the polymer properties compared to the racemic polymers. In addition, poly(hydroxyalkanoates) are biodegradable polymers that can serve as speciality biomedical materials and bulk-application thermoplastics[3] as well as a source of chiral building blocks for synthesis.[4]

The recent large-scale commercial production of poly (L-lactide) in particular has fuelled rising interest in the practical potential of polymers from renewable resources, especially as a source of chirality in polymer design.[5] Fermentation processes can provide a chiral monomer stock, such as L-lactic acid, or produce the polymers themselves when natural biosynthetic processes exist, such as those producing poly(hydroxyalkanoates). Within the context of a broader program of harnessing biosynthetic processes in vivo and in vitro for the design of complex chiral compounds for natural product-like materials, bioactive compounds, and new sources of chiral building blocks for synthesis, we are studying the enzymes involved in the biosynthesis of various natural polymers. Herein we report the successful polymerization of β-butyrolactone using a protic organic acid along with details of the stereochemical course of this reaction and a new method for the depolymerization of this class of polymers to produce chiral β-hydroxyacids. These results indicate that metal catalysts may be unnecessary in metal-triflate-catalyzed polymerization reactions. In addition, the same conditions promote lactide polymerizations.

2. Results and discussion

Initial studies centered on an organocatalytic method using dimethylaminopyridine (DMAP) catalysis that has been used to produce poly(lactide).[6] Unfortunately, polymerization attempts of β-butyrolactone using DMAP resulted in only oligomers with a degree of polymerization (DP) of less than eight at the temperatures required for the reaction, and a longer oligomer was necessary for studies with the poly(hydroxyalkanoate) depolymerase enzymes. ^{1}H NMR analysis and MALDI-mass spectrometry data indicate that crotonate end groups are formed in to chain terminating step (Scheme 1). In fact, heating the polymerization reaction above 80°C promoted elimination of water and chain termination by a pathway that is not of concern in the synthesis of poly(lactide). We, therefore, sought an alternate organocatalytic method that could be carried out at lower temperatures.

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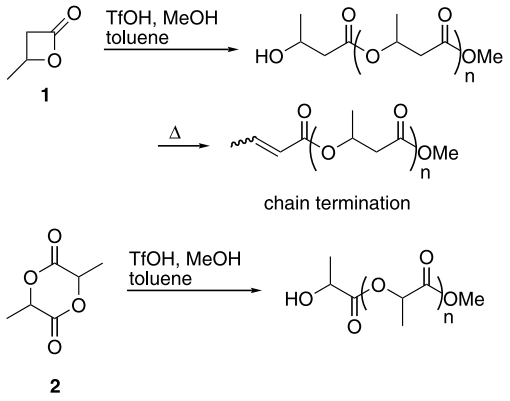


Scheme 1. Polymerization of β-butyrolactone compared to lactide polymerization.

Protic acids have not been employed for the polymerization of β-lactones since an early report using sulfuric acid produced only oligomers (DP below 12).[7] We hypothesized that dehydrative chain termination was probably responsible for the low molecular weight (MW) polymers and that use of a stronger acid in a relatively non-polar environment would allow a greater degree of reaction control than has been previously obtained. Similar work in the polymerization of dilactide has shown that triflic acid can be used as a potential initiator for the cationic polymerization of L,L-dilactide.[8] At temperatures below 100°C the resulting poly(L-lactide) was found to be 100% enantiomerically pure, but at temperatures above 100°C racemization was observed. We wanted to test whether acidic conditions could be found to carry out the cationic polymerization of β-butyrolactone without crotonate-forming termination steps and whether these conditions led to racemization of the monomer units.

In toluene at room temperature or 35°C, β-butyrolactone could be polymerized with triflic acid as a catalyst and methanol as an initiator (Scheme 1). The advantage of these conditions over many of the organometallic reagents that have been used for the polymerization of β-butyrolactone[9] is the simplicity of work-up to get a polymer sample free of metals, which could interfere in a bioassay. These results also call into question what the active species is in metal triflate-catalyzed polymerization reactions of this lactone previously described.[9c]

The monomer conversion was followed using ^{1}H NMR spectroscopy. The degree of polymerization was calculated by end-group analysis as well as by gel permeation chromatography (GPC). Polymerization of β-butyrolactone was studied using different monomer to initiator ratios (Table 1). With careful exclusion of water, the polydispersities observed in all polymerization reactions were close to 1.1. The degree of polymerization correlated with the expected value based on the monomer to initiator ratios; the polymerization reactions may be living polymerizations based on integration of the ^{1}H NMR spectrum. The integration of the methyl-initiator group has a 3 to 1 ratio to the proton on the hydroxylated carbon of the terminal monomer.

Table 1. Selective polymerization data for triflic acid-catalyzed polymerizations of β-butyrolactone in toluene with methanol as an initiator at 35°C

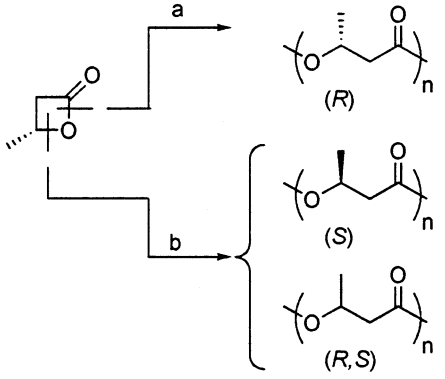
Entry	t (h)	M/I[a]	DP[a]	PDI[a]	Conversion
1	4	30	38	1.08	97
2	10	60	54	1.12	85

[a] M/I: monomer to initiator ratio, DP: degree of polymerization, PDI: polydispersity index.

The same conditions were also effective in polymerizing lactide monomer (Scheme 1).

Nafion NR50 and Nafion SAC-13 were also investigated as solid acid catalysts for the polymerization of β-butyrolactone. An advantage of Nafion is that, unlike mineral acids, this perfluorinated ion-exchange polymer is a solid resin that can be handled without the safety hazards associated with strong acids and is reusable.[10] Heterogeneity of these reactions resulted in much longer reaction time (>50 h) as compared to the solution based triflic acid, and water was difficult to remove from both solid catalysts. Therefore the polymers obtained were lower DP (9- to 11-mers) than expected from the solution phase triflic acid results.

Because chiral polymers are desirable, especially for biological studies, questions about the mechanism of this polymerization and possible racemization were posed. Depending on the reaction conditions, the ring opening of β-butyrolactone with oxygen nucleophiles may proceed by bond breaking either between the carbonyl carbon and oxygen atom of the β-lactone ring (acyl cleavage) with retention of configuration as shown in path a (Scheme 2) or by bond breaking between the β-carbon and oxygen atom (alkyl cleavage), which could lead to either inversion of configuration or racemization, indicated by path b.[9a]



Scheme 2. Possible mechanisms for the ring-opening polymerization of (*R*)-β-butyrolactone.

The mechanism of the ring-opening polymerization of β-butyrolactone was studied using (*R*)-β-butyrolactone as a stereochemical probe. The (*R*)-β-butyrolactone was obtained with 94% enantiomeric excess by lipase resolution of commercially available racemic β-butyrolactone

using porcine pancreatic lipase (PPL) as previously reported.[11] This chiral butyrolactone was polymerized using the above mentioned procedure to produce poly(β-hydroxybutyrate). The stereochemical configuration of the repeating units in the polymer was determined by degradation of the polymer to its corresponding ethyl β-hydroxybutyrate units with ethanolic sulfuric acid.[4a] Interestingly, triflic acid could also be used for this degradation reaction starting from the commercially available polymer to synthesize the acid instead of the ester.

The reaction mixture was analyzed on a chiral gas chromatography column to separate the two enantiomers as previously described[12] and ethyl-(*R*)-3-hydroxybutyrate was found to be the predominant enantiomer possessing enantiomeric excess in the same ratio as the starting lactone. This evidence indicated that the reaction proceeds with the retention of configuration of the repeating units in the polymer. This polymerization method, therefore, complements the polymerization of (*S*)-β-butyrolactone initiated with sodium salt of (*R*)-3-hydroxybutyric acid in the presence of crown ether, which proceeds by inversion of configuration and yields polymers of comparable molecular weights.[13] In contrast, the triflic acid catalyzed polymerization of β-butyrolactone proceeds through the cleavage of the bond between the carbonyl carbon and oxygen (acyl cleavage) as shown by path a.

3. Conclusion

In summary, a novel method for the synthesis of biomimetic polymers analogous to natural PHB polyester produced by enzymes in living organisms is presented. The polymerization proceeds with the retention of configuration and can be accomplished using triflic acid as a catalyst without a metal species present and with methanol as an initiator in an aprotic solvent. Triflic acid in acetonitrile with water could also serve to depolymerize this polymer to produce chiral β-hydroxyalkanoic acid building blocks. In addition to serving as a soluble substrate to study the enzymes involved in degrading this class of polymers, this synthetic PHB could be used for medical applications, for example drug delivery systems, or solid-surface coatings.[14]

4. Experimental

All reagents were bought from Aldrich (Milwaukee, WI) and used as received except as noted below. β-Butyrolactone was purified as previously described.[15a] Methanol was distilled over calcium hydride. Other solvents were purified by standard procedures.[15b] Purification by flash chromatography was performed on Selecto Scientific silica gel (32–63). The commercial natural poly(β-hydroxybutyrate) for hydrolysis was purchased from Aldrich. ^{1}H and ^{13}C NMR on a Varian VXR-300 using TMS as an internal standard. Optical rotations were measured using sodium D line on a Jasco DIP-370 digital polarimeter. Molecular weights, relative to polystyrene, were measured using a Waters gel permeation chromatography (GPC) system consisting of a Waters 510 pump, a Waters 717plus autosampler, and a Water 410 refractive index detector. The measurements were taken at 40°C with THF as mobile phase on four columns (Polymer labs Plgel 100, 500, 1×10^4, 1×10^5 angstrom).

4.1. Polymerization of β-butyrolactone

An oven dried round bottom flask equipped with a stir bar and sealed with a septum was purged with nitrogen. β-Butyrolactone (500 mg, 5.81 mmol), triflic acid (8.67 μl, 0.098 mmol, for DP = 30), and methanol (7.88 μl, 0.195 mmol) were added to the round bottom flask containing toluene (5 mL) and the mixture was stirred at 35°C. The mixture was poured into water and extracted with chloroform (3×20 mL). The organic layer was washed with sodium bicarbonate, water and brine and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the polymer was isolated as a colorless gel. Characterization data matched previously reported data.[13]

4.2. Depolymerization of poly(hydroxybutyrate)

A mixture of poly(β-hydroxybutyrate) (1.48 g) and dichloroethane (15 mL) was heated at reflux until the poly(hydroxybutyrate) completely dissolved. The solution was cooled to 40°C and acetonitrile (15 mL) was added followed by triflic acid (0.47 mL) and water (2 mL). The solution was refluxed for 70 h. The reaction was quenched with brine/water (1:1, 15 mL) and the organic layer was removed. The aqueous layer was extracted with chloroform (3×50 mL) and the combined organic layers were washed with brine (10 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the resulting crude mixture was purified by flash column chromatography (silica gel, 30% ethyl acetate/hexane) to yield (*R*)-3-hydroxybutyric acid (1.3 g, 88% conversion) as yellow oil. Characterization data matched previously reported data.[4a,d] $[\alpha]_D^{20} = -22.5$ (*c* 6.0, water). [lit.[4d] $[\alpha]_D^{RT} = -24.7$ (*c* 5.0, water).] ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.28 (d, $J = 6.9$ Hz, 3H), 2.42–2.52 (m, 2H), 4.18–4.25 (m, 1H), 7.79 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 22.6, 42.8, 64.6, 177.9.

4.3. Polymerization of L-lactide

To an oven dried round bottom flask equipped with a stir bar was added L-lactide (444 mg, 3.08 mmol); the flask was sealed with a septum and was purged with nitrogen. Triflic acid (4.60 μL, 0.052 mmol, for DP = 30), methanol (4.00 μL, 0.103 mmol), and toluene (5 ml) were added to the lactide and the mixture was stirred at 50°C for 14 h. The solvent was removed under reduced pressure and the resulting solid was suspended in methanol (10 ml) for 30 min to dissolve triflic acid and any oligomers present. The white solid was then filtered and washed with methanol (2×5 mL). Poly(L-lactide) was obtained as a white powder. When a 30:1 monomer to initiator ratio was used, DP = 30

and the PDI was around 1.28. For a 60:1 ratio, the resulting polymer had a DP = 58 and the PDI was around 1.45. Characterization data matched previously reported data.[6]

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