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A New Synthetic Route to Poly[3-hydroxypropionic acid] (P[3-HP]): Ring-Opening Polymerization of 3-HP Macrocyclic Esters

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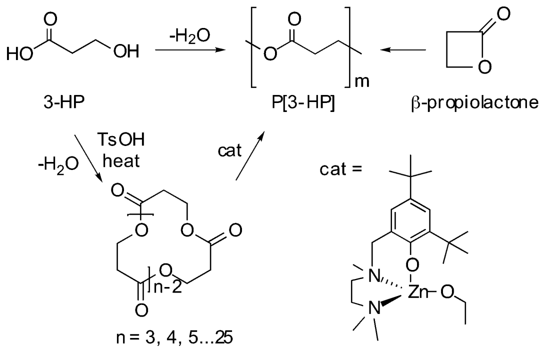
Introduction. The necessity of environmentally friendly replacements for commodity plastics has stimulated the development of polymers from biorenewable sources.[1] A notable example is polylactide, a commercially important material derived from lactic acid.[2] Recent efforts in the chemical industry have been focused on new bioderived starting materials that can be used for the preparation of new plastics, as well as other useful products and precursors.[3] 3-Hydroxypropionic acid (3-HP), a structural isomer of lactic acid, is such a material,[4] which comprises the repeat unit of a useful polymer, P[3-HP] (Scheme 1). High molecular weight P[3-HP] has attractive mechanical properties, such as rigidity, ductility, and exceptional tensile strength in drawn films (>400 MPa).[5] In addition, P[3-HP] has been shown to be enzymatically and hydrolytically degradable, thus enhancing its environmental appeal.[6] P[3-HP] has been prepared by the condensation of 3-HP esters[7] and the ring-opening polymerization (ROP) of β-propiolactone (Scheme 1),[8] but both methods suffer from disadvantages. Relative to condensations, ROP generally provides a greater degree of control over molecular weight, comonomer incorporation, and end group definition. Yet while highly strained β-propiolactone can readily be ring opened to yield high molecular weight P[3-HP], it is carcinogenic[9] and its large-scale synthesis is difficult, especially when starting with the preferred precursor 3-HP.[10] Thus, it would be desirable to develop an alternative ROP route to P[3-HP] that avoids the use of β-propiolactone.

We reasoned that less strained macrocyclic esters could be constructed from 3-HP directly and would be susceptible to ROP. Such macrocyclic esters of 3-HP have been generated from β-propiolactone.[11] While their lower degree of strain implies resistance to ROP, various low-strain macrocylic monomers have nonetheless been polymerized.[12] In a recent example from our group,[13] an entropic driving force was identified, and by using a highly active catalyst,[14] high conversions were attained. Inspired by these precedents, we have developed a new methodology for the preparation of high molecular weight P[3-HP] employing macrocyclic monomers[11] derived directly from 3-HP.

Results and Discussion. Commercially available aqueous solutions of 3-HP (20 wt %) were converted via acid-catalyzed (1−10 mol %) self-condensation with concomitant removal of water to a mixture of macrocycles and linear oligomers. After limited optimization, the macrocycles were isolated in good yield (as high as 60%) using a straightforward protocol (Supporting Information). In principle, the oligomeric fraction could be recycled and a continuous process for the isolation of the macrocycles could be devised. The identity of the macrocycles was confirmed by NMR spectroscopy by comparison with literature data (Figure S1).[11b] Additional mass spectrometric characterization (Figure S3) indicated that the macrocyclic mixture contained predominantly trimer ($n = 3$), tetramer, and pentamer, but cyclics with up to 25 3-HP subunits were observed. By $^{13}C\{^1H\}$ NMR spectroscopy, we determined the following weight percentages in the mixture: trimer 31%, tetramer 17%, pentamer 17%, hexamer 12%, and heptamer 8%. For initial polymerization studies, we isolated and purified the trimer[11] by column chromatography and recrystallization.

Scheme 1



Use of the ubiquitous[15] catalyst Sn(octanoate)$_2$ in the presence of benzyl alcohol for the polymerization of the trimer was not successful; no polymerization occurred either in solution state at room temperature (RT) or in the melt (70 °C) after 48 h at high catalyst loadings (Supporting Information). With a more active Zn−alkoxide reagent,[14] however, ROP of the trimer proceeded rapidly at RT in CH_2Cl_2 (Scheme 1). In less than 30 min, 90% of the trimer was converted into P[3-HP] ($[\text{trimer}]_0 = 1.2$ M, $[\text{trimer}]_0:[\text{Zn}]_0 = 50:1$), which was isolated by precipitation from THF/hexane (1:1). The product was characterized by SEC (Table 1) and NMR (^1H and $^{13}C\{^1H\}$) spectroscopy (Figure S2). Further analysis of a similarly prepared low molecular weight P[3-HP] sample ($M_n = 2.4$ kg·mol^{-1}, PDI = 1.7) by matrix assisted laser desorption/ionization (MALDI) MS revealed three envelopes of peaks (Figure S4). Of these, two were assigned to P[3-HP], with the third indicative of cyclic oligomers (see below). The P[3-HP] fractions contain ethoxy ester and hydroxyl end groups or ethoxy ester and acrylate end groups. These assignments were confirmed by ^1H NMR spectroscopy, which indicated a ratio of 1:3 for the two types of polymers (Figure S2). The formation of ethoxy ester end groups confirms that the ROP occurs through the cleavage of the acyl-C−O bond and insertion of an ethoxy group from the catalyst. By monitoring the reaction in situ, we established that the acrylate end group was formed during the course of the reaction, but mechanistic details are still under investigation.

To assess the control of polymer molecular weight, reaction aliquots were analyzed by $^1H\{^1H\}$ NMR spectroscopy and SEC (Figure S5). At early reaction times, the M_n increased linearly with conversion, followed by

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Table 1. Data for ROP Reactions of Trimer in Solution Stateand in Melt[a]

$[M]_0/[Zn]_0$	convn (%)	M_n(theor)	M_n(SEC)	PDI(SEC)
10^b	94	2.0	2.4	1.7
50^b	94	10.2	11.6	1.5
100^b	95	20.5	19.5	1.6
200^b	95	41.0	32.0	1.6
400^b	88	76.4	53.0	1.6
800^b	91	157	66.5	1.5
50^c	∼100	10.8	12.3	1.5
100^c	93	20.1	15.3	1.6
200^c	88	38.1	27.6	1.9
400^c	78	67.6	43.6	1.8
800^c	40	69.9	52.7	1.7

[a] M_n values are in units of kg·mol^{-1}; $[M]_0$ = initial concentration of the trimer of 3-HP; $[Zn]_0$ = initial concentration of the catalyst (Scheme 1); M_n(theor) is based on the conversion from$^1H\{^1H\}$ NMR spectra. [b] Reactions quenched at different times between 2 and 60 min. Conditions: room temperature, CH_2Cl_2, $[M]_0$ = 1.54 M. [c] Reactions were quenched after 80 min. Conditions: 80 °C, no solvent.

a modest decrease in molecular weight at high conversions. This behavior is consistent with intramolecular transesterification and concomitant extrusion of cyclic oligomers. The proposed formation of cyclic oligomers was supported by the ^1H and $^{13}C\{^1H\}$ NMR spectra and MALDI-MS data (third set of peaks, Figure S4). Importantly, by controlling the reaction time and catalyst loading, we were able to obtain P[3-HP] with molecular weights (M_n) between 2.4 and 67 kg·mol^{-1} (Table 1). The M_n values we determined by SEC using polystyrene standards were in reasonable agreement with the M_n values calculated considering the initial monomer-to-catalyst ratios and trimer conversion for the first five entries in Table 1.

All P[3-HP] samples generated by polymerization of the trimer were semicrystalline by differential scanning calorimetry (DSC, 18−47% depending on M_n). Both glass transition temperatures (T_g) and melting temperatures (T_m) generally increased with increasing M_n between 2.4 and 30.7 kg·mol^{-1} and remained constant at higher molecular weight (Figure S7). The T_g (≈ −22 °C) and T_m (≈76 °C) of the high molecular weight P[3-HP] generated from the polymerization of the trimer agreed with those reported in the literature (T_g = −21 °C, T_m = 79 °C;[16a] T_g = −23 °C, T_m = 73 °C[16b]).

With the successful controlled ROP of the trimer in CH_2Cl_2 solution at RT demonstrating that 3-HP may be converted to P[3-HP] via the macrocyclic approach, we assessed variations with the aim of further enhancing practical utility. For example, melt polymerizations are desirable since they avoid the use of solvent. Given the low melting point of the trimer (56 °C)[11a] and the high-temperature stability of the Zn catalyst,[17] we explored the polymerization of the neat trimer at 80 °C (Table 1). While the molecular weight control was not quite at the level demonstrated for the solution polymerizations, we were able to generate high molecular weight P[3-HP] using as little as 0.13 mol % catalyst in 80 min.

It would also be desirable to be able to polymerize the larger ring macrocycles present in the macrocyclic fraction obtained from the self-condensation of aqueous 3-HP. Indeed, we isolated a fraction containing only tetramer and pentamer (85:15) and found that it was rapidly converted (83%) into high molecular weight P[3-HP] (M_n = 74.3 kg·mol^{-1}, PDI = 1.6) in CH_2Cl_2 at RT in 60 min ([tetramer + pentamer]$_0$ = 1.1 M, [tetramer + pentamer]$_0$:[Zn]$_0$ = 572:1). These results imply that the ability to polymerize the macrocycles derived from 3-HP is not limited by ring strain, and that it may ultimately be practical to use the macrocyclic ester mixtures in large scale polymerizations.

In conclusion, we have implemented a new synthetic route for preparing P[3-HP] through ROPs of macrocyclic esters prepared directly from commercial aqueous solutions of 3-HP, an inexpensive and renewable starting material. Good control over the molecular weights of the P[3-HP] polymers was observed and high molecular weight samples were accessed, both from pure trimer (n = 3) as well as from a mixture of larger cyclics (n = 4 and 5). Moreover, we successfully performed the ROP of the trimer without solvent at 80 °C. End group analysis indicated the partial formation of acrylate groups during the ROP in solution, which may enable further elaboration of P[3-HP] into more complex macromolecular architectures (e.g., graft polymers).

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Supporting Information Available: Text giving experimental details, figures plotting NMR spectroscopic, MALDI MS, and DSC data and showing plots of the dependence of M_n on reaction time and conversion, and tables showing the depenence of yield on reaction conditions and DSC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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