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Syndiospecific Ring-Opening Polymerization of β-Butyrolactone To Form Predominantly Syndiotactic Poly(β-hydroxybutyrate) Using Tin(IV) Catalysts

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ABSTRACT: In a previous report, we have documented the ability of tri-*n*-butyltin methoxide (Sn(*n*-Bu)$_3$OCH$_3$) to catalyze the ring-opening polymerization of racemic β-butyrolactone ((±)-BL) to form poly(β-hydroxybutyrate) (PHB) with a preference for syndiotactic (syn) placement. In this report, bis(tri-*n*-butyltin) oxide ((*n*-Bu$_3$Sn)$_2$O), bis(triphenyltin) oxide (Ph$_3$Sn)$_2$O), and di-*n*-butyltin dimethoxide (Sn(*n*-Bu)$_2$(OCH$_3$)$_2$) were all shown to catalyze the syndiospecific polymerization of (±)-BL. Of these catalysts, the Sn(*n*-Bu)$_2$(OCH$_3$)$_2$ system showed dramatically decreased polymerization times for correspondingly high monomer conversion. This catalyst system was used to form syn-PHB with an M_n and syn diad fraction of 8.4×10^4 and 0.62, respectively. Analysis of the stereochemical sequence distributions at various polymerization temperatures for all of the Sn(IV) catalysts investigated showed an ($E_s - E_i$) of ca. −2 kcal/mol for syndiotactic versus isotactic diad formation. Therefore, the syndiospecificity exhibited little dependence on the catalyst structure over a limited, but significantly broad range of Sn(IV) organometallic systems. The triad stereosequence distributions of syn-PHB samples agrees very well with the Bernoulli model of chain end stereocontrol. Furthermore, the degree of Sn(IV)-catalyst syndiospecificity increased at correspondingly lower polymerization temperatures. Polymerizations carried out at −15 and +90 °C with the Sn(*n*-Bu)$_2$-(OCH$_3$)$_2$ catalyst system gave syn-PHB with syn diad fractions of 0.72 and 0.54, respectively. The polymers formed from (*R*)-BL (>98% ee) all showed significant (~13%) degrees of configurational inversion at the stereogenic center, with little dependence on the catalyst used or the polymerization temperature. This result indicates that while the preferred mode of ring opening is primarily acyl cleavage (bond breaking between the carbonyl carbon and oxygen of the lactone), a mechanism for stereocenter inversion is operative.

Introduction

Classical synthetic methods can be used to obtain structures which mimic those found in nature. An excellent example of such work is that which has been carried out for the preparation of the poly(β-hydroxybutyrate) (PHB) from butyrolactone (BL) using various organometallic species to catalyze the ring-opening polymerization.[1-9] The corresponding natural polymer (*R*)-PHB is a member of a family of poly(β-hydroxyalkanoates) (PHAs) that are formed by a wide variety of bacteria.[10] An important consideration for the purposes of this paper is that the natural polymer has to date been found exclusively in the enantiomerically pure form where the stereocenters are in the (*R*) configuration. Clearly, an important advantage associated with the ring-opening route to PHB and other PHAs is the possibility of preparing these polymers in a variety of stereochemical forms having tailored physical and biological characteristics.

There has been increased interest in the use of PHB synthetic analogues as biodegradable polymers. In addition, PHB synthetic analogs have been viewed as interesting model systems to investigate effects of stereochemical and morphological parameters on the biodegradation kinetics. In our laboratory, we have investigated the relative enzymatic degradability of random PHB stereocopolymers containing various (*R*)-hydroxybutyrate ((*R*)-HB) contents (4–100%).[11] This study was performed using a depolymerase isolated from *Penicillium funiculosum*, and the initial surface degradation rate was measured by monitoring pH change. It was found that the preference for (*R*)-HB repeat units appears to dominate over crystalline morphology effects for the compositional range 81–100% (*R*)-HB. However, dramatically larger initial surface degradation rate values observed for 67 and 77% (*R*)-HB contents suggested that a critical degree of

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disruption of the crystalline order occurred at these stereochemical compositions accelerating the observed degradation kinetics. Furthermore, it was shown that 50% (*R*)-atactic PHB (M_n = 50000) was a poor substrate for the enzyme after rapid initial surface degradation of (*R*)-HB-rich polymer chain segments at the film surface. In contrast, 50% (*R*)-syndiotactic PHB (M_n = 9200, syn diad fraction of 0.66) was found to be degradable by the depolymerase of *P. funicolusum* both in short- and long-term studies. Kumagai and Doi have reported on the enzymatic degradability of (*R*)-PHB (natural origin) blended with (*R,S*)-atactic PHB.[12] The degradation measurements were made by exposure of these blends to the extracellular PHB depolymerase isolated from *Alcaligenes faecalis* T1.[12] It was shown that the rate of enzyme-mediated blend biodegradation (as measured by weight loss) increased with increasing content of the (*R,S*)-atactic PHB such that the highest rate was observed at a 50 wt % blend. Furthermore, it was reported that the blend component (*R,S*)-atactic PHB was degraded by the *A. faecalis* depolymerase to form 3-hydroxybutyric acid and oligomers, although the rate of biodegradation was relatively slower than that measured for (*R*)-PHB.[13] Pearce et al. have studied blends of bacterial PHB and predominantly isotactic and atactic 50% (*R*)-PHB.[14] Blends of predominantly isotactic 50% (*R*)-PHB and bacterial PHB showed a single melting point which decreased with increasing 50% (*R*)-isotactic PHB blend content. In addition, the melting point of these blends was between that of its component materials. Therefore, it was concluded by these workers that the two components are cocrystallizing and that the inclusion is essentially complete. In contrast, synthetic atactic PHB was found to be incompatible with the bacterial PHB.[14]

The first preparation of predominantly syn-PHB was reported as part of a study directed at the measurement of initial surface degradation kinetics of PHB stereocopolymers.[11] That study, carried out in our laboratory, was summarized above. Further work by our research group documented the preparation of predominantly syn-PHB from (±)-BL using tri-*n*-butyltin methoxide as catalyst.[15] Interestingly, to our knowledge, these experimental results provided the first example of a syndiospecific ring-opening polymerization. More recently, Hocking and Marchessault[16] observed that polymerization of (±)-BL catalyzed by methylaluminoxane gave a product fraction that was syn-PHB. Unfortunately, using this approach, the maximum conversion of monomer to syn-PHB was only 2%. In addition, typical M_w and M_n values of the syn-PHB fraction were ca. 3000 and 600, respectively, and racemic diad fractions up to 0.68 were measured. The major products of (±)-BL polymerization catalyzed by methylaluminoxane, as well as other aluminum-based catalyst systems derived from trialkylaluminum/water, are relatively higher molecular weight predominantly isotactic PHB.[16-22] It is interesting to note that the observation by Hocking and Marchessault[16] of drastically different active site catalyst mechanisms present in methylaluminoxane polymerizations resulting in polymer fractions of variable tacticity is consistent with a previous study by Zhang et al.[4] which indicated that both acyl cleavage (bond breaking between the carbonyl carbon and oxygen of the lactone) and alkyl cleavage (cleavage of the bond between the β-carbon and oxygen of the lactone) ring-opening modes were operative in BL polymerization catalyzed by ethylaluminoxane.

The ring-opening polymerization of lactones using group IV organometallic reagents, specifically Sn(IV) compounds, has recently been described by Kricheldorf and co-workers.[5,23,24] They have demonstrated that tributyltin methoxide is very active in the polymerization of ε-caprolactone, (L,L)-lactide, β-propiolactone, and BL.[5,23,24] Mechanistic studies carried out by these workers indicate that the lactone polymerizations proceed by a coordination–insertion mechanism where chain growth involves cleavage of the acyl-oxygen lactone bond and yields polyester chains with a methyl ester end group.[23,24] Recently, our laboratory has reported that (±)-BL polymerization by the Sn(IV) catalyst $Sn(n\text{-}Bu)_3OCH_3$ resulted in the preparation of syn-PHB with racemic (r) diad fractions as high as 0.70.[15] It was also found by ^1H NMR end group analysis that the polymers formed did not have predominantly methyl ester end groups. In fact, the ratio of carboxylic acid to methyl ester end groups ranged from 2.5 to 3.1.[15] The syn-PHB samples that were prepared were found to be crystalline and had a crystalline structure which was different from that of bacterial PHB.[15]

In this paper, the syndiospecificity of the Sn(IV) catalysts bis(tri-*n*-butyltin) oxide ($(n\text{-}Bu_3Sn)_2O$), bis(triphenyltin) oxide ($(Ph_3Sn)_2O$), and di-*n*-butyltin dimethoxide ($Sn(n\text{-}Bu)_2(OCH_3)_2$) for the formation of syn-PHB from (±)-BL was investigated. The temperature effect on syndiospecificity was used to determine the activation energy ($\Delta E = E_s - E_i$) for syndiotactic versus isotactic diad placement. Polymerization of enantiomerically pure BL and determination of the corresponding polymer stereochemistry were used to determine the preferred mode of ring opening (acyl vs alkyl cleavage) as well as whether mechanisms for stereochemical inversion are operative.

Experimental Section

Instrumental Methods. Nuclear Magnetic Resonance (NMR). Proton (^1H) NMR spectra were recorded on a Bruker WP-270 SY spectrometer at 270 MHz. ^1H NMR chemical shifts in parts per million (ppm) are reported downfield from 0.00 ppm using tetramethylsilane (TMS) as an internal reference. The parameters for the polymer spectra are as follows: 3.5% w/w polymer in $CDCl_3$, temperature 308 K, pulse width 90°, 32K data points, relaxation delay 0.50 s, and 100–200 transients. The determination of the enantiomeric excess (ee) values for (*R*)- and (*S*)-methyl 3-hydroxybutyrate and (*R*)- and (*S*)-BL, respectively, were carried out as 0.5% w/w solutions in CCl_4/benzene-d_6 (9/1, w/w) containing 30 mol % of europium(III) tris[3-((heptafluoropropyl)hydroxymethylene)-(+)-camphorato] Eu[(+)-(hfc)$_3$] (Aldrich Chemical Co.) at 25 °C. Peak areas were determined by spectrometer integration and are reported as relative intensities representing a given number of hydrogens. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad.

Carbon-13 (^{13}C) NMR spectra were recorded at 67.9 MHz on a Bruker WP-270 SY spectrometer in 10-mm tubes as $CDCl_3$ solutions, with chemical shifts in parts per million referenced relative to chloroform ($CHCl_3$) as an internal reference at 77.00 ppm. Polymer spectral acquisitions were conducted as 4.0% w/w $CDCl_3$ solutions using the following parameters: temperature 308 °K, 90° pulse width, 16K data points, acquisition time 0.5 s, delay time 1.0 s, 2500 transients.

^{13}C NMR measurements for the quantitation of racemic (r) and meso (m) diads by analysis of the carbonyl carbon signals were recorded using the same parameters as above, with the exception that the spectral acquisition window was narrowed to include only the carbonyl resonances, giving a spectral resolution of 0.220 Hz/point (compared with 1.890 Hz/point over the 0–200 ppm range above). The data workup used a Gaussian multiplication function with line broadening = −0.220 Hz/point and Gaussian broadening = 0.05. Consequently, the aquisition time used for this experiment was 4.5 s and the time between pulses was 5.5 s.

Table I. Data on the Bulk Polymerization of (±)-BL Using Different Sn(IV) Catalyst Systems and Polymerization Temperatures

initiator	[M]/[I]	polym temp (°C)	polym time (days)	% yield MeOH insol (MeOH sol)	MeOH-insol fract		MeOH-sol fract	
					racemic diad frac[d]	$M_n \times 10^{-3}$ (M_w/M_n)[e]	racemic diad frac[d]	$M_n \times 10^{-3}$ (M_w/M_n)[e]
$(n\text{-}Bu_3Sn)_2O$	60	40	34	53 (47)	0.67	6.5 (1.36)	0.61	4.5 (1.36)
$(n\text{-}Bu_3Sn)_2O$	60	60	8	39 (61)	0.64	8.9 (1.55)	0.60	3.6 (1.89)
$(n\text{-}Bu_3Sn)_2O$	60	75	8	61 (39)	0.63	9.7 (1.80)	0.61	1.6 (2.30)
$(n\text{-}Bu_3Sn)_2O$	60	90	8	51 (49)	0.58	11.4 (1.73)	0.57	1.5 (2.64)
$(Ph_3Sn)_2O$	60	40	34	40 (60)	0.70	3.7 (1.29)	0.66	2.7 (1.37)
$(Ph_3Sn)_2O$	60	60	13	70 (30)	0.67	8.2 (1.76)	0.62	1.4 (2.23)
$(Ph_3Sn)_2O$	60	75	13	67 (23)	0.64	9.0 (1.94)	0.59	1.3 (2.28)
$(Ph_3Sn)_2O$	60	90	11	42 (58)	0.57	12.5 (1.62)	0.54	1.9 (2.26)
$Sn(n\text{-}Bu)_2(OMe)_2$	60	0	13	43 (57)	0.73	3.4 (1.25)	0.64	1.1 (1.35)
$Sn(n\text{-}Bu)_2(OMe)_2$	60	25	4	42 (58)	0.68	3.7 (1.55)	0.60	2.0 (1.57)
$Sn(n\text{-}Bu)_2(OMe)_2$	60	40	2	62 (38)	0.67	4.3 (1.67)	0.62	1.8 (1.86)
$Sn(n\text{-}Bu)_2(OMe)_2$	60	60	2	31 (69)	0.63	6.2 (1.84)	0.59	1.8 (2.48)
$Sn(n\text{-}Bu)_2(OMe)_2$	60	75	2	24 (76)	0.55	7.3 (1.66)	0.52	2.0 (2.31)
$Sn(n\text{-}Bu)_2(OMe)_2$	60	90	2	11 (89)	0.54	6.4 (1.67)	0.49	1.8 (2.33)
$Sn(n\text{-}Bu)_2(OMe)_2$[a]	140	−15	75	30	0.72	4.1 (1.16)	ND[c]	ND[c]
$Sn(n\text{-}Bu)_2(OMe)_2$[b]	5585	60	18	80	0.62	83.7 (1.74)	ND[c]	ND[c]

[a] 16-g (±)-BL (0.19 mol) polymerization in a 50-mL sealed ampule. [b] 19-g (±)-BL (0.22 mol) polymerization in a 50-mL sealed ampule. [c] Not determined. [d] Determined by GPC (see Experimental Section). [e] Determined by ^{13}C NMR of the carbonyl carbon (see Experimental Section).

^{13}C NMR measurements for triad quantitation using the methylene carbon were recorded using the following parameters: temperature 308 °K, 90° pulse width, 32K data points, acquisition time 7.9 s, delay time 3.25 s, 500 transients. The spectral acquisition window was narrowed to include only the methylene carbon resonances, giving a spectral resolution of 0.127 Hz/point. The data workup included using a Gaussian multiplication function with line broadening = −0.127 Hz/point, Gaussian broadening = 0.05, and baseline correction.

The diad and triad stereosequences are referred to herein using the terms racemic (r) and meso (m). These terms are commonly accepted and are equivalent to the descriptors syndiotactic and isotactic, respectively.[15]

Polarimetry. Optical rotation measurements were recorded using a Perkin-Elmer 241 polarimeter attached to a refrigerated constant-temperature circulator and are reported as follows: $[\alpha]_{\lambda(nm)}^{T(°C)}$ = specific rotation (concentration in grams per 100 mL of solvent). A 1.0-dm path length quartz microcell was used for these measurements.

Gel Permeation Chromatography (GPC). All molecular weights reported were determined by GPC using a Waters Model 510 pump, Model 410 refractive index detector, and Model 730 data module with 10^3-, 10^4-, 10^5-, and 10^6-Å Ultrastyragel columns in series. Chloroform was used as the eluent at a flow rate of 1.0 mL/min. Sample concentrations of 0.3% w/v and injection volumes of 125 μL were used. Polystyrene standards with a low polydispersity (Polysciences) were used to generate a calibration curve.

Water Analyses. Water content was measured using a Mettler DL18 Karl Fischer titrator, with Hydranal-Titrant 5 (methanol/I_2) and Hydranal-Solvent (methanol/imidazole/sulfur dioxide).

Synthetic Procedures. (±)-β-Butyrolactone ((±)-BL, Aldrich, >98%) was stirred over CaH_2 for 48 h under an Ar atmosphere and then fractionally distilled (63 °C, 14 mmHg) using an Ar bleed. (*R*)-β-Butyrolactone ((*R*)-BL) was prepared as previously described,[11] stirred over CaH_2 for 48 h under an Ar atmosphere, and fractionally distilled (62–63 °C, 14 mmHg) using an Ar bleed (ee > 98% by Eu[(+)-(hfc)$_3$] ^1H NMR). Tri-*n*-butyltin methoxide (Aldrich, 97%), di-*n*-butyltin dimethoxide (Aldrich), bis(tri-*n*-butyltin) oxide (Aldrich, 96%), and bis(triphenyltin) oxide (Aldrich, 97%) were all used as received.

All glassware was silanized with trimethylchlorosilane, washed with methanol, oven-dried, and subsequently flame-dried under vacuum and purged with argon. All transfers were carried out by syringe through rubber septum caps under an argon atmosphere.

To each polymerization ampule was added either 3.0 g of (±)-BL (0.035 mol) or 1.0 g of (*R*)-BL (0.012 mol) followed by two freeze/pump/thaw cycles. A specified amount/type of initiator (see Tables I and II) was then charged to the ampule containing the appropriate monomer. Tri-*n*-butyltin methoxide, di-*n*-butyltin dimethoxide, and bis(tri-*n*-butyltin) oxide are all liquids at room temperature and therefore were transferred neat. Bis(triphenyltin) oxide is a solid (mp 119–123 °C) and was transferred as a 0.50 M toluene (dried and distilled over Na^0/benzophenone under argon) solution.

The ampules were sealed under vacuum (<1.0 mmHg) with slight cooling. The ampules were then placed into constant-temperature baths at 20 ± 3, 40 ± 2, 60 ± 2, 75 ± 3, and 90 ± 4 °C for various time periods (see Tables I and II).

The polymer isolation procedure involved dissolution of the ampule contents in chloroform (4 mL), precipitation into cold methanol (−10 °C, 75 mL), and storage of the mixture for 48 h in a freezer (−15 °C). The precipitated polymer was isolated by vacuum filtration on Whatman 1 paper, washed two times with methanol (15 mL each), and dried in vacuo (30 °C, 50 μmHg, 24 h). Isolation of the methanol-soluble fractions consisted of concentrating the methanol filtrate by rotary evaporation (50 °C, 125 mmHg) and further drying in vacuo (30 °C, 50 μmHg, 24 h).

The incomplete polymerization of (*R*)-BL was used to determine whether racemization of the monomer was taking place prior to its polymerization. To a 5-mL polymerization flask fitted with a rubber septum was added 0.92 g of (*R*)-BL (0.011 mol) followed by 0.14 g of $Sn(n\text{-}Bu)_2(OCH_3)_2$ (4.75×10^{-4} mol). The polymerization flask was then placed in a 75 °C oil bath for 15 min, at the end of which time a short-path distillation head was attached and a bulb-to-bulb distillation of unpolymerized monomer was carried out. This gave 0.12 g of distilled monomer, which suggests that under these polymerization conditions 87% of the monomer was converted to polymer. The enantiomeric excess of the remaining monomer was determined by optical rotation and ^1H NMR measurements as was described in the Instrumental Methods section. An earlier attempt to recover monomer after a 45-min polymerization time period under the identical polymerization conditions described above was unsuccessful due to complete conversion of the (*R*)-BL to polymer.

Results and Discussion

We have reported that the bulk polymerization of (±)-BL using $Sn(n\text{-}Bu)_3OCH_3$ as catalyst resulting in a predominantly syn-PHB. One logical question which followed was whether additional Sn(IV) and possibly Sn(II) catalyst systems would also show syndiospecificity in the ring-opening polymerization of (±)-BL. In this paper, we describe results of research directed at extending our initial discovery of $Sn(n\text{-}Bu)_3OCH_3$-catalyzed (±)-BL syndiospecific polymerization to other Sn(IV) catalyst systems.

Table II. Repeat Unit Stereochemical Analyses on the Bulk Polymerization of (*R*)-BL by the Various Sn(IV) Systems[a]

initiator	polym temp (°C)	polym time (days)	% yield MeOH insol (MeOH sol)	MeOH-insol fract [R]/[S][b]	MeOH-insol fract racemic diad fract[c]	MeOH-insol fract $M_n \times 10^{-3}$ (M_w/M_n)	MeOH-sol fract [R]/[S][b]	MeOH-sol fract racemic diad fract[c]	MeOH-sol fract $M_n \times 10^{-3}$ (M_w/M_n)
$Sn(n\text{-}Bu)_3OCH_3$	75	4	60 (40)	87/13	0.19 (0.23)	2.9 (1.53)	87/13	0.32 (0.23)	1.2 (1.44)
$(Ph_3Sn)_2O$	75	4	53 (47)	87/13	0.22 (0.23)	2.5 (1.65)	84/16	0.27 (0.27)	1.0 (1.48)
$(n\text{-}Bu_3Sn)_2O$	75	4	51 (57)	85/15	0.17 (0.26)	2.1 (1.32)	82/18	0.30 (0.30)	1.1 (1.28)
$Sn(n\text{-}Bu)_2(OMe)_2$	20	3	32 (49)	87/13	0.22 (0.23)	2.4 (1.13)	81/19	0.30 (0.31)	ND[d]
$Sn(n\text{-}Bu)_2(OMe)_2$	75	4	71 (29)	88/12	0.14 (0.21)	2.8 (1.95)	79/21	0.30 (0.33)	0.7 (1.36)
$Sn(n\text{-}Bu)_2(OMe)_2$	75	9	47 (53)	88/12	0.17 (0.21)	5.0 (1.39)	79/21	0.26 (0.33)	ND[d]

[a] [M]/[I] = 35. [b] % ee determined by ^1H NMR (see Experimental Section). [c] Determined by ^{13}C NMR analysis (see Experimental Section); values in parentheses were calculated assuming that a random stereocopolymer was formed using the equations(r) = 2[R][S] and (m) = [R][R] + [S][S], where (r) and (m) represent racemic (syndiotactic) and meso (isotactic) diads, respectively, and [R] and [S] are the stereochemical contents of the final polymer as determined by ^1H NMR of the methanolysis products (see Experimental Section). [d] Not determined.

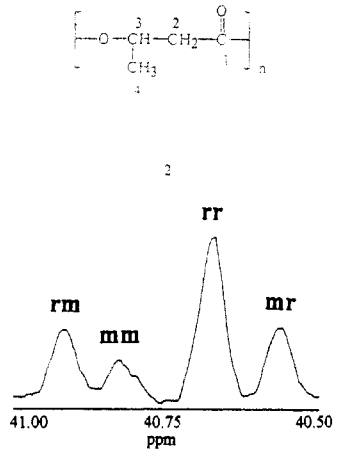

Figure 1. 67.9-MHz ^{13}C NMR spectrum recorded at 35 °C in $CDCl_3$ of the methylene carbon region of syn-PHB using a narrowed spectral acquisition window (see Experimental Section). The syn-PHB sample was the insoluble fraction obtained by polymerization of (±)-BL using the $Sn(n\text{-}Bu_3)_2(OCH_3)_2$ catalyst at [M]/[I] = 60 and a polymerization temperature of 60 °C (see Table I).

Results on the bulk polymerization of (±)-BL and (*R*)-BL catalyzed by $Sn(n\text{-}Bu)_2(OCH_3)_2$, $(n\text{-}Bu_3Sn)_2O$, and $(Ph_3Sn)_2O$ are presented in Tables I and II, respectively. In all cases, complete conversion of monomer to polymer was achieved as determined by NMR spectroscopic analysis (see Experimental Section). Table II also includes results on (*R*)-BL polymerization using the $Sn(n\text{-}Bu)_3OCH_3$ catalyst system. The molecular weight measurements were determined by GPC, and the diad stereosequence analyses were determined by ^{13}C NMR by observation of the carbonyl carbon resonances (see Experimental Section).[25] The products were fractionated during purification (see Experimental Section) into methanol-soluble and methanol-insoluble components which were analyzed separately with respect to molecular weight and diad stereosequence distribution. It should first be pointed out that by increasing the monomer [M] to initiator [I] ratio to 5585 for the $Sn(n\text{-}Bu)_2(OCH_3)_2$ catalyst system, syn-PHB was formed with an M_n value of 83 700 (see Table I). The development of a method to prepare syn-PHB at this high molecular weight value is of great importance since it facilitates studies directed at elucidating the physical–mechanical properties of this product.

As is clearly shown in Tables I and II, in all cases, the degree of syndiotacticity decreases with an increase in the polymerization temperature. Furthermore, the temperature-dependent syndiospecificity observed by analysis of the diad stereosequence distributions of the methanol-insoluble fractions shows a strikingly similar degree of polymer stereoregulation for all of the catalyst–(±)-BL systems studied herein. In other words, changes in the ligand structure of the Sn(IV) catalyst systems did little to change the syndiospecificity exhibited by the respective catalyst systems. The triad stereosequence distribution for selected products was analyzed by ^{13}C NMR spectral integration of the resonances observed for the methylene carbon (see Figure 1). The time between pulses used when acquiring data for this analysis was 11.2 s (see Experimental Section), which is greater than 5 times the T_1 value (T_1 = 0.37 s) measured for the methylene carbon of natural-origin PHB under comparable experimental conditions.[26] Therefore, quantitation of the triad stereosequences as described herein is justifiable. The rationale for assignment in Figure 1 of the (rm), (mm), (rr), and (mr) triad stereosequences to their respective ^{13}C NMR signals was discussed in an earlier publication.[15] The triad stereosequence distributions for the methanol-insoluble fractions of syn-PHB samples prepared at 60 °C polymerization temperatures using $(n\text{-}Bu_3Sn)_2O$, $(Ph_3Sn)_2O$, $Sn(n\text{-}Bu)_2(OCH_3)_2$, and $Sn(n\text{-}Bu)_3OCH_3$ as catalysts are shown in Table III. In addition, Table III provides the triad analysis for a 50% (*R*)-PHB sample, which approximates an atactic stereosequence distribution. The atactic PHB sample was prepared by carrying out a ring-opening polymerization of (±)-BL using a $ZnEt_2/H_2O$ (1.0/0.6) catalyst system at 75 °C.[11]

Table III. Diad and Triad Stereosequence Distributions and Statistical Analyses for Atactic and Syndiotactic PHB Samples

polym conditions	catalyst	diad fract[c] (m)	diad fract[c] (r)	triad fract[d] (mm)	triad fract[d] (rr)	triad fract[d] (rm)	triad fract[d] (mr)	B[e]
a	$ZnEt_2/H_2O$ (1.0/0.6)	0.54	0.46	0.29 (0.29)[f]	0.23 (0.21)	0.23 (0.25)	0.25 (0.25)	1.16
b	$(Ph_3Sn)_2O$	0.33	0.67	0.10 (0.11)	0.45 (0.45)	0.24 (0.22)	0.22 (0.22)	0.85
b	$Sn(n\text{-}Bu)_2(OCH_3)_2$	0.37	0.63	0.12 (0.14)	0.46 (0.40)	0.19 (0.23)	0.23 (0.23)	1.25
b	$Sn(n\text{-}Bu)_3OCH_3$	0.34	0.66	0.11 (0.12)	0.42 (0.44)	0.23 (0.22)	0.24 (0.22)	0.84
b	$(n\text{-}Bu_3Sn)_2O$	0.36	0.64	0.12 (0.13)	0.41 (0.41)	0.23 (0.23)	0.24 (0.23)	0.89

[a] Polymerization conducted at 60 °C for 6 days using 18.0 mL of (±)-BL and 0.75 mL of a $ZnEt_2/H_2O$ (1.0/0.6) solution in dioxane. The polymerization conditions and method for the catalyst preparation were previously described.[11] $M_n = 1.94 \times 10^5$, $M_w/M_n = 1.61$, 98% yield. [b] syn-PHB prepared at 60 °C, [M]/[I] = 60 (data from Table I). [c] Given as the fraction of (r) (racemic) and (m) (meso) diads as determined by ^{13}C NMR analysis (see Experimental Section). [d] Given as the fraction of (mm), (rr), (rm), and (mr) triads as determined by ^{13}C NMR analysis (see Experimental Section). [e] The Bernoulli model triad test, where B = (mm)(rr)/(mr)^2, such that B = 1 for perfect chain end control. [f] The numbers in parentheses are the calculated triad stereosequence values using the experimentally determined diad stereosequence values and the following relationships: (mm) = (m)^2, (rr) = (r)^2, (rm) = (mr) = (m)(r).

Of interest is the fact that, for all of the catalysts and polymerization temperatures investigated, a significant fraction of the product was soluble in methanol and had a relatively lower degree of syndiotacticity and molecular weight (see Tables I and II). Furthermore, examination of Table II shows that when the polymerization catalyzed by the $Sn(n\text{-}Bu)_2(OCH_3)_2$ was carried out for 4 and 9 days, the percent methanol solubles increased from 29 to 53%, respectively. Moreover, on further inspection of the results in Table I, a general trend of increased polydispersity (M_w/M_n) values at higher polymerization temperatures is observed. These characteristics of the Sn(IV)–BL polymerization systems studied may be attributed to rearrangements by inter- and intramolecular transesterification reactions. Kricheldorf and co-workers have studied the role of transesterification reactions catalyzed by tin alkoxides on polymers from ϵ-caprolactone, δ-valerolactone, β-propiolactone, glycolide, and (L,L)-lactide and determined that there was extensive back-biting with the formation of cyclic products.[5,24,27,28] This was especially apparent in their work at polymerization temperatures or polymer–initiator incubation temperatures that were above 100 °C. In the work described in this paper, no attempts were made to identify whether the methanol-soluble products contained primarily cyclic or linear oligomers. The possibility must also be considered that the Sn(IV) catalyst systems studied herein are each nonuniform in structure so that (±)-BL polymerizations proceed at distinctly different catalyst sites. This could result in catalyst sites operative (in a given polymerization reaction) with different syndiospecificity as well as relative rates of propagation and chain transfer/termination. Polymeric product fractions with distinctly different molecular weight and stereoregularity would then be formed as was indeed observed herein (see Tables I and II). Studies are in progress to determine the mechanism by which the low molecular weight methanol-soluble fractions are formed in these polymerization reactions.

At higher polymerization temperatures, a slight increase in molecular weight of the methanol-insoluble fractions was observed (see Table I). This increase in molecular weight at higher polymerization temperatures may be due to several factors, but one probable explanation is the observation that at lower polymerization temperatures the precipitation of polymer from the reaction solution was observed. Precipitation of the polymer product from the polymerization solution may result in a "deactivation" of the propagating chain end. Additionally, as the polymerization proceeds, there is an increase in the viscosity of the system whereby access of the propagating chain end to monomer becomes diffusion-controlled. At temperatures of 60 °C and above, the polymerization is typically a clear, colorless, and homogeneous system and will generally exhibit flow dependent upon the temperature, polymer molecular weight, and the degree of conversion achieved. Thus, at higher polymerization temperatures, the diffusivity of the monomer and the rate of monomer-propagating chain end collisions should increase so that competitive reactions such as chain end back-biting will become less favorable relative to propagation, leading to higher molecular weight products.

The triad stereosequence distributions of the syn-PHB methanol-insoluble polymer samples (see Table III) agrees very well with the Bernoulli model of chain end control, where ideally $B = 4(mm)(rr)/(mr)^2 = 1$ for perfect chain end control.[29] The experimental values, which range between 0.84 and 1.25, are well within an acceptable range that is consistent with this model.[30,31] Deviations from

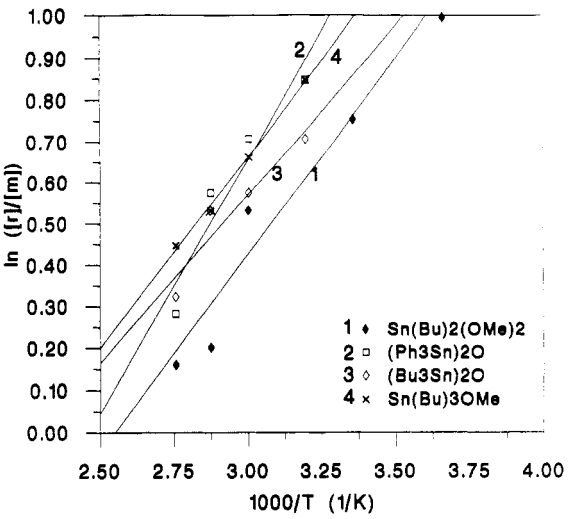

Figure 2. Arrhenius plot of ln[(r)/(m)] versus the inverse polymerization temperature (1000/T (K)) constructed using the r and m diad fractions reported in Table I and ref 15 for the corresponding methanol-insoluble syn-PHB samples.

the value of 1 may be due to errors in determining the relative areas under the four respective triad peaks in the ^{13}C NMR spectrum of these polymer samples (see Figure 1), but as seen in Table III there is excellent agreement between the calculated and empirically obtained triad data. This suggests that the stereochemical distribution of repeat units is controlled by the chain end stereochemistry and not by the catalyst structure. It is generally accepted that this model describing chain end control (when $B \approx 1$) is a consequence of either (1) interactions between the last two units in the chain (penultimate control) or (2) interactions between the last unit in the chain and the incoming monomer (ultimate control).

It is generally agreed that formation of stereoregularity along a polymer chain is kinetically controlled and that the degree of stereosequence control achieved is dependent on the difference in free energy of activation (ΔE) between the two nonreversible steps during propagation leading to either syndiotactic or isotactic sequences.[30-32] Since the ratio of the relative amounts of syndiotactic and isotactic diads, (r)/(m), corresponds to the ratio between the rate constants of the reaction steps leading to the respective sequences (k_s/k_i, where s and i correspond to syndiotactic and isotactic, respectively), we can then determine the ΔE value from information on the temperature dependence of (r)/(m) and the following relationships:[30,33]

$$k_s = A_s \exp(-E_s/RT)$$

$$k_i = A_i \exp(-E_i/RT)$$

$$k_s/k_i = (r)/(m)$$

$$\ln[(r)/(m)] = \ln(A_s/A_i) + (E_s - E_i)/RT$$

where $E_s - E_i = \Delta E$, E is the empirical activation energy for the system, and the quantity $E_s - E_i$ determines the stereospecificity attained. The above analysis assumes that propagation is chain-end-controlled (as was discussed above) and, consequently, the configurational statistics are Bernoullian.[34] Arrhenius plots of ln [(r)/(m)] versus the reciprocal polymerization temperature were constructed (see Figure 2) using the results obtained for the Sn(IV)–BL polymerization systems conducted at different temperatures (see Table I and ref 15). The results obtained for $E_s - E_i$ from the Arrhenius plots are shown in Table IV. It is interesting to note that the ΔE values for syndiospecific Sn(IV)-catalyzed (±)-BL polymerizations

Table IV. Activation Energies $\Delta E(E_a - E_i)$ for Syndiotactic versus Isotactic BL Additions as a Function of the Sn(IV) Catalyst Used for the syn-PHB Methanol Insolubles[a]

catalyst	ΔE (kcal/mol)
$(Ph_3Sn)_2O$	-2.43 ± 0.47[b]
$Sn(n\text{-}Bu)_2(OCH_3)_2$	-1.88 ± 0.35[c]
$Sn(n\text{-}Bu)_3OCH_3$	-1.83 ± 0.06[d]
$(n\text{-}Bu_3Sn)_2O$	-1.61 ± 0.38[e]

[a] ΔE was calculated from the slope ($\Delta E/R$) of the line generated by plotting ln [(r)/(m)] vs $1000/T$ (K) (see Figure 2). [b] Correlation coefficient $r^2 = 0.911$ of the appropriate line shown in Figure 2 generated by linear regression. [c] Correlation coefficient $r^2 = 0.933$ of the appropriate line shown in Figure 2 generated by linear regression. [d] Correlation coefficient $r^2 = 0.996$ of the appropriate line shown in Figure 2 generated by linear regression. [e] Correlation coefficient $r^2 = 0.910$ of the appropriate line shown in Figure 2 generated by linear regression.

compare well with those obtained for many other chain-end-controlled syndiospecific polymerizations.[33h]

To our initial surprise, the ΔE values shown in Table IV are rather similar for the different catalysts studied. If the asymmetric spatial arrangement of the ligands coordinated to the Sn does indeed play an important role in the syndiospecificity, it should then follow that changes in the catalyst structure would result in significant differences in the measured ΔE values for the respective catalyst systems.[35] Since changes in the catalyst structure did not change ΔE appreciably, this indicates that steric control leading to the observed syndiospecificity is due predominantly to diastereomeric interactions between the Sn(IV)-coordinated PHB chain end having a specific chain end stereochemistry and the incoming BL enantiomeric monomers. The model we are proposing here is consistent with that of the Bernoulli model of chain end control which was supported by the calculated B values reported in Table III.

A speculative model of a $Sn(n\text{-}Bu)_3AB$ organometallic complex, where A is the PHB propagating chain end and B is the activated lactone monomer, can be obtained by consideration of other related organometallic systems. For example, triorganotin derivatives of strongly chelating oxygen ligands, including acetylacetonates, are well known to exhibit *cis* trigonal-bipyramidal geometry.[36,37] Furthermore, the X-ray crystallographic structure of trimethyltin methoxide was found to have a structure similar to that of triorganotin acetylacetonates where the trimethyltin groups are approximately planar and are linked by methoxides to form infinite zigzag –O–Sn–O–Sn– chains.[38] Moreover, diorganotin derivatives of acetylacetonate are known to exhibit *trans* octahedral geometry.[39] On the basis of structural similarities, the geometry of the acetylacetonate chelating group in Sn(IV) organometallic complexes will be used herein as a model which approximates the manner in which the propagating PHB chain end is coordinated to Sn(IV) organometallic complexes. Furthermore, on the basis of other related studies,[27] it seems reasonable to consider complexation of BL to Sn(IV) through the carbonyl functionality. Association of monoalkoxides would not be expected since di- and trialkoxides with less sterically demanding substituents that have a higher tendency to associate form mononuclear species in donor solvents.[36] Clearly, BL would be classified as a donor solvent. From this information on related organometallic Sn(IV) complexes and ligand chelation, Figure 3 is presented as a plausible mechanism which depicts the $Sn(n\text{-}Bu)_3OMe$ catalyst structure with chelated monomer, and initiation and subsequent propagation steps. However, it must be stressed that determination

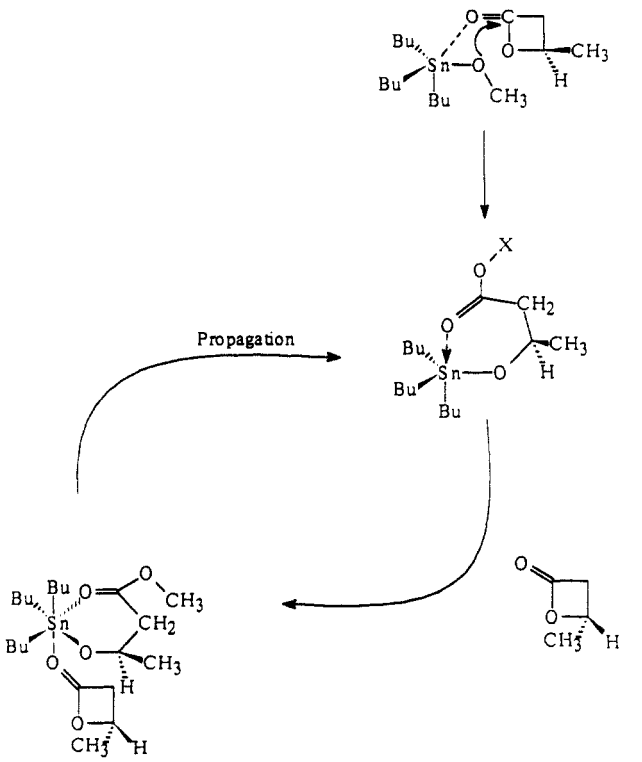

Figure 3. A mechanism for the initiation and propagation steps of syn-PHB synthesis from (±)-BL using the $Sn(n\text{-}Bu_3)_3OCH_3$ catalyst system.

initiation and propagation reactions have not as yet been attempted by using various computational modeling methods. Also, experiments have not as yet been carried out to gain similar structural information. Therefore, the mechanism presented in Figure 3 only represents our current working hypothesis.

Mechanistic investigations of BL[5,15,24] and β-propiolactone[40–42] ring-opening polymerization catalyzed by $Sn(n\text{-}Bu)_3OCH_3$ and other Sn(IV) catalysts, respectively, have been reported. End group analysis provides information on the mode of ring opening occurring during initiation and has been used by some investigators to infer that a similar mode of ring opening occurs during subsequent propagation steps.[5,24] Another approch is the use of enantiomerically pure monomer as a stereochemical probe to investigate the mode of ring opening as well as the presence of mechanisms which are operative that result in stereocenter inversion.[43] This latter approach, which gives information on the stereochemical course of a polymerization throughout the polymerization process, has been adopted for studies carried out herein. Thus, (*R*)-BL (ee > 98%) was polymerized using the $Sn(n\text{-}Bu)_2(OCH_3)_2$, $Sn(n\text{-}Bu)_3OCH_3$, $(n\text{-}Bu_3Sn)_2O$, and $(Ph_3Sn)_2O$ catalyst systems (see Experimental Section). The polymers formed were depolymerized without racemization[44] to the corresponding methyl β-hydroxybutyrate,[45] and the [*R*]/[*S*] distribution of methyl β-hydroxybutyrate was determined by ^1H NMR spectral integration using the chiral Eu[(+)-(hfc)$_3$] shift reagent (see Experimental Section). Results of this work are shown in Table II.

The polymerization of (*R*)-BL using the $Sn(n\text{-}Bu)_2(OCH_3)_2$, $Sn(n\text{-}Bu)_3OCH_3$, $(n\text{-}Bu_3Sn)_2O$, and $(Ph_3Sn)_2O$ catalyst systems resulted in a degree of stereocenter inversion of ~13% for the methanol-insoluble fractions that was clearly independent of the catalyst structure. Furthermore, a decrease in the polymerization temperature from 75 to 20 °C (for similar polymerization times) as well as an increase in the polymerization time from 4 to 9 days

(n-Bu)$_2$(OCH$_3$)$_2$-catalyzed polymerizations had little effect on the resulting polymer stereochemistry. Moreover, the methanol-soluble fractions when compared to the methanol-insoluble fractions showed slightly higher degrees of stereocenter inversion with values as high as 21% (see Table II). The fact that an increase in polymerization time from 4 to 9 days did little to change the stereochemistry of the product suggests that the mechanism of stereocenter inversion is not due to reactions between the catalyst and the preformed polymer chains in the reaction vessel. Also, the observation that decreasing the polymerization temperature from 75 to 20 °C did not change the stereochemical outcome indicates that the reaction rate constants for stereocenter inversion have a similar temperature dependence as that for propagation events which lead to stereocenter retention. For comparative purposes, it is interesting to note that in the case of (L,L)-lactide polymerization catalyzed by stannous octanoate, stereocenter inversion in the transformation of monomer to polymer does not take place at temperatures up to 120 °C but is observed for polymerizations conducted above 150 °C.[46] When tin(II) oxide was used as the catalyst for (L,L)-lactide polymerization, stereocenter inversion was not observed at polymerization temperatures up to 180 °C.[46]

A mechanism that could lead to the observed stereocenter inversion discussed above is racemization of the monomer by the respective Sn(IV) catalyst systems prior to polymerization. To determine if this is indeed the case, (R)-BL (ee > 98%) was polymerized using Sn(n-Bu)$_2$(OCH$_3$)$_2$ as catalyst to ~90% conversion (see Experimental Section). The monomer was then recovered by distillation from the product mixture. Analysis of the recovered monomer showed that it had the same optical rotation as the starting monomer and had an ee of >98% based upon ^{1}H NMR meaurements using Eu[(+)-(hfc)$_3$].[47] Thus, racemization of the monomer is not an operative mechanism here.

Another possible explanation of the results in Table II that must be evaluated is that events of alkyl cleavage (CH_3CH–O) may compete with the predominant mechanism of acyl (CO–O) cleavage. The former mode of ring opening is likely to occur with stereocenter configurational inversion, while the latter mode of ring opening is expected to occur with configurational retention during chain growth. It is important to note that previous work on BL polymerization using certain aluminum-based organometallic catalyst systems indicates that the alkyl cleavage mechanism is operative, resulting in stereocenter inversion.[4] Alkyl cleavage of BL could take place by a nucleophilic attack on the methine carbon of an incoming BL monomer by an alkoxy chain terminus coordinated to Sn(IV). This would lead to the formation of an ether linkage with stereocenter inversion. In one model for this mechanism, the propagating chain ends coordinated to the Sn(IV) atom would alternate between alkoxy and carboxylate terminal groups. However, ^{1}H and ^{13}C NMR spectra analyses do not show any evidence for the existence of ether linkages in the product polymers. An additional model which can be considered to describe concurrent mechanisms of alkyl and acyl ring-opening events during polymerization reactions is the existence of structurally different catalyst sites with preferences for one of the two respective modes of lactone ring opening. Such a mechanism would lead to the formation of individual polymer chains of different stereochemistry. This model is not consistent with the unimodal molecular weight distribution observed by GPC-analysis of the methanol-insoluble and -soluble fractions (see Experimental Section) for all the syn-PHB polymers synthesized herein. Furthermore, a mechanism by which a fraction of catalyst sites exist in the polymerization reaction that prefer the alkyl cleavage mechanism would then produce chains that are optical antipodes of those produced at other operative catalyst sites favoring acyl ring opening. This model would require dramatic deviation of the stereocopolymer stereosequence distribution from that of a random distribution. However, Table II shows that the stereopolymers formed by stereocenter inversion during polymer formation are indeed random stereocopolymers.

From the results and discussion presented above, it appears that stereocenter inversion is occurring at the Sn(IV)-coordinated chain terminal repeat unit by a currently unknown random process either prior to or during monomer insertion. Further mechanistic study of this intriguing result is in progress.

Further illustrations that serve to highlight the degree of uncertainty which exists in the mechanism for Sn(IV)-catalyzed lactone polymerization are readily seen by review of the existing literature. For example, studies by Kricheldorf and co-workers on Sn(IV) alkoxide catalyzed polymerization of ε-caprolactone, (L,L)-lactide, β-propiolactone, and (±)-BL claim that insertion is via acyl cleavage, yielding exclusively the corresponding ester end group.[5,24] This conclusion was based on the observation of the ester end group formed that would be expected based upon the initiator. In a previous publication, we have shown by ^{1}H NMR end group analysis that the polymerization of (±)-BL with Sn(n-Bu)$_3$OCH$_3$ resulted in PHB chains with methyl ester as well as carboxylic acid end groups in a ratio of ca. 1:3.[15]

Therefore, a number of challenging mechanistic questions regarding Sn(IV)-catalyzed lactone ring-opening polymerization reactions remain unanswered. Studies are currently in progress in our laboratory which are directed at addressing these questions. Furthermore, work is also in progress in our laboratory which seeks to gain an understanding of both catalyst and monomer structural considerations which leads to syndiospecificity in lactone polymerization reactions.

Summary

In this paper, we have shown that Sn(n-Bu)$_2$(OCH$_3$)$_2$, (n-Bu$_3$Sn)$_2$O, and (Ph$_3$Sn)$_2$O catalyze the syndiospecific polymerization of BL. In addition, in all cases investigated herein the Sn(IV)-catalyzed polymerization of BL resulted in a significant fraction of the product being soluble in methanol. This methanol-soluble fraction had a relatively lower degree of syndiotacticity and molecular weight.

The triad stereosequence distributions of the syn-PHB methanol-insoluble polymer samples agree favorably with the Bernoulli model of chain end control, where ideally $B = 4(mm)(rr)/(mr)^2 = 1$ for perfect chain end control. This then implies that the chain end control is a consequence of either (1) interactions between the last two units in the chain (penultimate control) or (2) interactions between the last unit in the chain and the incoming monomer (ultimate control). Arrhenius plots of ln[(r)/(m)] versus the reciprocal polymerization temperature were constructed for polymerization reactions catalyzed by (n-Bu$_3$Sn)$_2$O, (Ph$_3$Sn)$_2$O, Sn(n-Bu)$_2$(OCH$_3$)$_2$, and Sn(n-Bu)$_3$OCH$_3$. The similarity of the ΔE values for the different catalysts studied indicates that the asymmetric spatial arrangement of the ligands coordinated to the Sn does not play an important role in the syndiospecificity. This then argues that the driving force of steric control leading to the observed syndiospecificity is due to the asymmetry of the chain end coordinated to the respective Sn catalysts.

The polymerization of (*R*)-BL using the $Sn(n\text{-}Bu)_2(OCH_3)_2$, $Sn(n\text{-}Bu)_3OCH_3$, $(n\text{-}Bu_3Sn)_2O$, and $(Ph_3Sn)_2O$ catalyst systems resulted in a degree of stereocenter inversion of ~13% for the methanol-insoluble fractions that was clearly independent of the catalyst structure. Evaluation of a number of mechanisms which, in theory, could lead to the observed stereocenter inversion was carried out. It was concluded that stereocenter inversion is taking place by a presently unknown mechanism at the Sn(IV)-coordinated PHB chain terminus either prior to or during monomer insertion.

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