Ring-Opening Polymerization of Optically Active β-Butyrolactone Using Distannoxane Catalysts: Synthesis of High Molecular Weight Poly(3-hydroxybutyrate)

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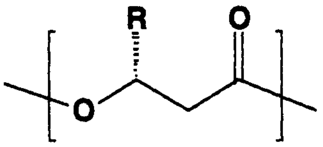
Introduction. Poly[(*R*)-3-hydroxyalkanoates] (P(HA)s, 1) are produced by a wide variety of microorganisms as intracellular carbon and energy supply.[1,2] In most cases, the P(HA)s (1) consist mainly of (*R*)-3-hydroxybutyrate ((*R*)-HB) which plays an important role in their biodegradability, biocompatibility, and other physical properties.[1,2] Recently, the pilot scale production of poly[(*R*)-3-hydroxybutyrate] (P[(*R*)-HB]) by fermentation was begun.[3,4]

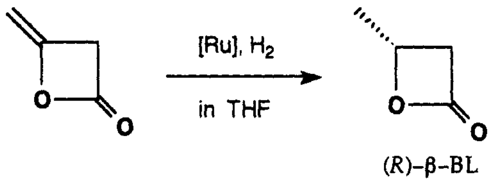


1

R = $(CH_2)_nCH_3$ (n = 0-12)

The synthesis of P[(*R*)-HB] by ring-opening polymerization of (*R*)- or (*S*)-β-butyrolactone ((*R*)- or (*S*)-β-BL) has also been reported.[5] In these reports, all the ring-opening polymerizations were carried out using aluminum- or zinc-based catalysts. However, the chemical synthesis of optically active polyesters of high molecular weight by this method is inefficient since the synthesis of (*R*)- or (*S*)-β-BL is difficult[5a,b] and Al- or Zn-based catalysts do not produce a high molecular weight P[(*R*)-HB] (M_n > 100 000) in a good yield.

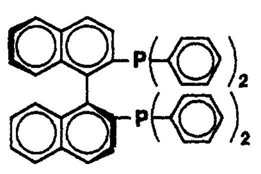
Recently, Takaya et al. reported that the optically active β-butyrolactone was easily prepared by the asymmetric hydrogenation of diketene catalyzed by Ru-(*S*)-binap ((*S*)-binap = (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) complexes (eq 1).[6]



(1)

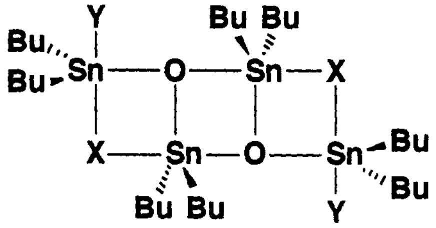
[Ru] : $Ru_2Cl_4[(S)\text{-binap}]_2 \cdot Et_3N$

(*S*)-binap :



This prompted us to explore the chemical synthetic methods in order to prepare a high molecular weight P[(*R*)-HB].

We disclose here that the distannoxane catalysts (2) exhibit a high reactivity in the ring-opening polymerization of β-butyrolactone to afford poly[(*R*)-3-hydroxybutyrate] of high molecular weight (M_n > 100 000).



2

2a: X= OEt, Y= Cl **2c**: X= OH, Y= Cl
2b: X= OH, Y= NCS **2d**: X= Cl, Y= Cl

Experimental Section. Distannoxanes **2a**,[7] **2b**,[8] **2c**,[7], and **2d**[7] were prepared using the literature methods. All catalysts were dried in vacuo at 100 °C for 20 h. (*R*)-β-Butyrolactone[9] ((*R*)-β-BL) and racemic β-butyrolactone (β-BL) were dried by CaH_2 and distilled under reduced pressure. Toluene was dried by sodium and distilled under an argon atmosphere. Bacterially produced P[(*R*)-HB] was purchased from Aldrich Chemical Co. Molecular weights of the polymers were determined by GPC using a polystyrene calibration. Proton and carbon-13 nuclear magnetic resonance spectra were recorded on a Bruker AM-400 spectrometer. Calorimetric measurements (DSC) of polymers were carried out on a Shimadzu thermal analysis system in a temperature range of -50 to +200 °C at a heating rate and a cooling rate of 10 °C/min. The melting temperature (T_m) was taken as the peak temperature of the melting endotherm (first run). The glass transition temperature (T_g) was taken as the inflection point of the specific heat increment at the glass transition (second run).

Ring-Opening Polymerization of (*R*)-β-BL without a Solvent. (*R*)-β-BL (3.44 g, 40 mmol) and 1-ethoxy-3-chlorotetrabutyldistannoxane (**2a**; 5.6 mg, 5×10^{-3} mmol) were heated in a 20-mL Schlenk tube at 100 °C for 4 h. The resulting mixture was dissolved in trichloromethane and then was added to a mixture of diethyl ether and hexane (1:3; 300 mL) to afford the white solid of the P[(*R*)-HB] (3.42 g) in 99.4% yield.

Ring-Opening Polymerization of β-BL with a Solvent. β-BL (6.88 g, 80 mmol), 1-ethoxy-3-chlorotetrabutyldistannoxane (**2a**; 5.6 mg, 5×10^{-3} mmol), and dry-degassed toluene (6 mL) were heated in a 80-mL Schlenk tube at 100 °C for 16 h. The resulting mixture was dissolved in trichloromethane and then was added to a mixture of diethyl ether and hexane (1:3; 500 mL) to afford the white solid of the P(HB) (6.81 g) in 99.0% yield.

Results and Discussion. (*R*)-β-Butyrolactone (with enantioselectivity of 92%)[9] and racemic β-BL were easily polymerized in the presence of a catalytic amount of distannoxanes **2a–d** with or without a solvent to afford high molecular weight polyesters as shown in Table I. The GPC traces of all polymers were unimodal. It was found that *n*-dibutyltin oxide (Bu_2SnO) also had the catalytic activity for these types of ring-opening polymerization (entry 5 and 9). However, the catalytic activity of Bu_2SnO is lower than that of distannoxanes.

Isotactic diad fractions of P[(*R*)-HB] and P(HB) were 0.94 and 0.30, respectively (entries 1 and 6).[10] The melting temperature (T_m), glass transition temperature (T_g), and enthalpy of fusion (ΔH_m) of the P[(*R*)-HB] which was

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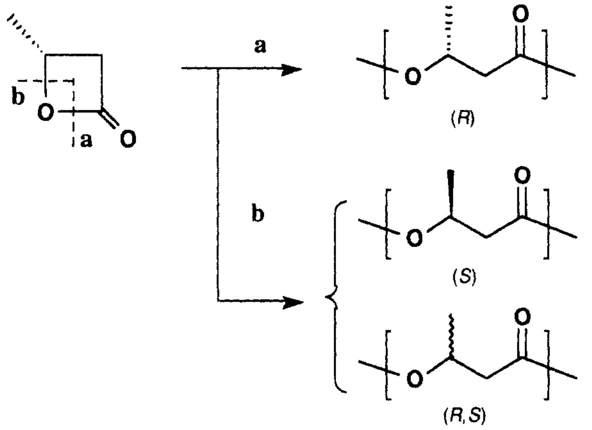
Table I. **Polymerization Results of (*R*)-β-BL and β-BL with the Distannoxane Catalysts 2**[a]

entry	2 (concn)[b]	monomer	mol wt[c] M_w	mol wt[c] M_n	yield (%)
1	**2a** (1/8000)	(*R*)-β-BL	424 000	178 000	99[e]
2	**2a** (1/4000)	(*R*)-β-BL	255 000	147 000	95
3	**2b** (1/4000)	(*R*)-β-BL	230 000	132 000	99
4	**2c** (1/4000)	(*R*)-β-BL	172 000	99 000	94
5	Bu_2SnO (1/1000)	(*R*)-β-BL	193 000	119 000	87
6[d]	**2a** (1/16000)	β-BL	841 000	311 000	99[f]
7[d]	**2a** (1/8000)	β-BL	334 000	159 000	99
8[d]	**2d** (1/8000)	β-BL	703 000	310 000	93
9[d]	Bu_2SnO (1/2000)	β-BL	398 000	187 000	94

[a] Polymerization conditions: (*R*)-β-BL = 40 mmol, 100 °C, 4 h. [b] Molar ratio of catalyst to β-BL. [c] Determined by GPC analysis, calibrated with a polystyrene standard. [d] Polymerization conditions: β-BL = 80 mmol, toluene = 6.0 mL, 100 °C, 16 h. [e] Isotactic diad fraction was observed to be 0.94. [f] Isotactic diad fraction was observed to be 0.30.

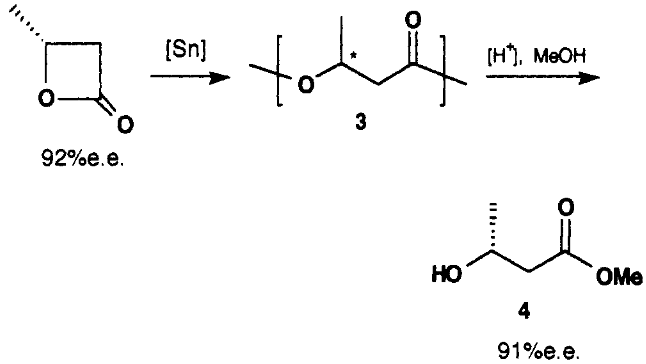
Scheme I



synthesized by the ring-opening polymerization (entry 1) were found to be 163 °C, 5.3 °C, and 92.7 J/g, respectively. These values for the bacterially produced P[(*R*)-HB] (M_w = 477 000, M_n = 210 000) are 175 °C, 5.3 °C, and 99.2 J/g, respectively. Both the T_m value and ΔH_m value of the chemically synthesized P(*R*)-HB] are less than those of the bacterially produced P[(*R*)-HB]. This is due to the decrease in the isotactic diad fraction (from 1.00 to 0.94) of P[(*R*)-HB].[5c,10] The difference between the T_g values of the chemically synthesized P[(*R*)-HB] and the bacterially produced one is unknown.[5c]

This type of ring-opening polymerization of β-BL may proceed either by bond breaking between the carbonyl carbon and oxygen atom of the lactone ring (acyl cleavage) with retention of the configuration as shown in path a (Scheme I) or by bond breaking between the β-carbon and oxygen atom (alkyl cleavage), which could lead to either inversion of the configuration, path b, or racemization. Lenz et al. reported that using the $ZnEt_2/H_2O$ (1:0.6) or EAO (ethylaluminoxane) as a catalyst the polymerization of (*S*)-β-BL proceeded primarily via path a with retention of the configuration and little or no racemization, whereas by using the $AlEt_3/H_2O$ (1:1) in situ catalyst the reaction proceeded primarily via path b with inversion of the configuration and little or no racemization.[5b]

Scheme II



To elucidate the stereochemistry of the ring-opening polymerization of (*R*)-β-BL catalyzed by distannoxane complexes, the optical purities of (*R*)-β-BL and of methyl 3-hydroxybutyrate which was synthesized by the methanolysis[11] of P[(*R*)-3HB] were compared (Scheme II). The enantiomeric excess of (*R*)-β-BL was determined to be 92% by HPLC analysis.[9] The enantiomeric excess of the methyl 3-hydroxybutyrate was found to be 91% by HPLC analysis after converting an aliquot of this compound to the (*R*)-MTPA [(*R*)-2-methoxy-2-(trifluoromethyl)phenylacetic acid] ester.[12] HPLC analysis of this ester (column, COSMOSIL; eluent, 9:1 hexane/ether mixture; flow rate, 1.0 mL/min, detection, 254-nm light) showed two signals with t_R = 21.7 and 24.7 min in a 95.6:4.4 ratio assignable to the *R,R*- and *R,S*-diastereomers, respectively. Thus, indicating that the polymerization of (*R*)-β-BL catalyzed by the distannoxane complexes proceeded by path a with retention of the configuration and with little or no racemization (Scheme I).

In conclusion, when the distannoxane catalysts are used for the ring-opening polymerization of (*R*)-β-butyrolactone, we can easily obtain the synthetic P[(*R*)-3-hydroxybutyrate] which is quite similar to that produced by the fermentation method. This chemical method is a novel and practical route for the production of P[(*R*)-3-HB].

References and Notes

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(9) The enantiomeric excess of (*R*)-β-BL was determined to be 92% by HPLC analysis. HPLC analysis of this lactone (column, chiralcel OA; eluent, 9:1 hexane/2-propanol mixture; flow rate, 0.5 mL/min; detection, 220-nm light; 40 °C) showed two signals with t_R = 27.0 and 29.6 min in a 4.2:95.8 ratio assignable to the *S*- and *R*-enantiomers, respectively.
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