Ring-Opening Copolymerization of Optically Active β-Butyrolactone with Several Lactones Catalyzed by Distannoxane Complexes: Synthesis of New Biodegradable Polyesters

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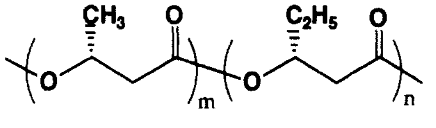
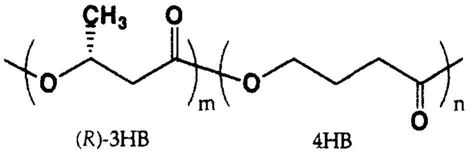
Introduction. A wide variety of microorganisms produce poly[(*R*)-3-hydroxyalkanoates] (P(3HA)s) as a carbon and energy supply.[1-3] Recently, Imperial Chemical Industries (ICI) has developed a controlled fermentation process for the production of optically active copolyesters of (*R*)-3-hydroxybutyrate and (*R*)-3-hydroxyvalerate (P(3HB-*co*-3HV), 1).[2] Doi et al. reported the synthesis of polyesters of (*R*)-3-hydroxybutyrate and 4-hydroxybutyrate (P(3HB-*co*-4HB), 2).[4] In these types of polyesters, the optically active (*R*)-3-hydroxyalkanoic acids play an important role in their biodegradability, biocompatibility, and other physical properties.[1-4] The production of these bacterial polyesters is limited to only a few copolyesters such as P(3HB-*co*-3HA) and P(3HB-*co*-4HB).



1

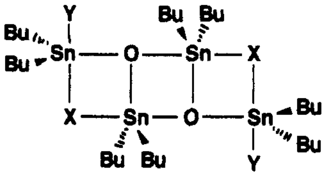
1a: (*R*)-3HB 89%, (*R*)-3HV 11%.



2

The synthesis of poly[(*R*)-3-hydroxybutyrate] (P(3HB)) by ring-opening polymerization of (*R*)- or (*S*)-β-butyrolactone ((*R*)- or (*S*)-β-BL) has been previously shown.[5] The copolymerization of racemic β-BL with other β-lactones,[6] ϵ-caprolactone (ϵ-CL),[7] or δ-valerolactone (δ-VL)[7] has also been reported. However, it is difficult to synthesize new biodegradable polyesters comprised of (*R*)-3-hydroxybutyrate by a chemical method since the synthesis of (*R*)- or (*S*)-β-BL is difficult,[5a,b] and Al- or Zn-based catalysts used to polymerize (*R*)-, (*S*)-β-BL,[5] or racemic β-BL with other lactones[6,7] do not produce high molecular weight polyesters ($M_n > 100\,000$) in a good yield.

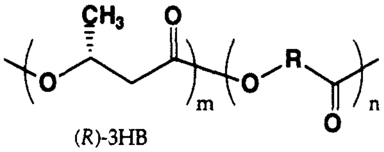
Recently, Takaya et al. reported that the optically active β-BL was easily prepared by the asymmetric hydrogenation of diketene catalyzed by Ru-(*S*)-binap ((*S*)-binap = (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) complexes.[8] Further, we found that the distannoxane catalysts (3) exhibit a high reactivity in the ring-opening polymerization of (*R*)-β-BL to afford P(3HB) of high molecular weight ($M_n > 100\,000$).[9] These facts prompted us to explore chemical synthetic methods in order to prepare new biodegradable polyesters containing the (*R*)-3HB unit with high molecular weights.



3

3a: X= OEt, Y= Cl 3c: X= OH, Y= Cl
3b: X= OH, Y= NCS

Here we report on the synthesis and biodegradation of a new series of copolyesters (4–7) containing the (*R*)-3HB unit with high molecular weights catalyzed by distannoxanes (3).



4-7

R

4: $(CH_2)_5$
5: $(CH_2)_4$
6: $CH_2CH_2CH(CH_3)CH_2$
7: $CH(CH_3)COOCH(CH_3)$

Experimental Section. Distannoxanes, **3a**,[11] **3b**,[12] and **3c**,[11] were prepared using the literature methods and dried in vacuo at 80 °C for 20 h. (*R*)-β-Butyrolactone[13] ((*R*)-β-BL, 92% ee), ϵ-CL, δ-VL, β-methyl-δ-valerolactone (β-Me-δ-VL), and L-lactide (L-LA) were dried by CaH_2 and distilled under reduced pressure. P(3HB-*co*-11% 3HV) was purchased from Aldrich Chemical Co. Molecular weights of the polyesters were determined by GPC using a polystyrene calibration. Chloroform was used as the eluent at a flow rate of 1.0 mL/min. Proton nuclear magnetic resonance spectra were recorded on a Bruker AM-400 spectrometer at 400 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: ca. 1% w/w polymer in $CDCl_3$, temperature 300 K, pulse width 45°, 32K data points, relaxation delay 2.5 s, and 8–16 transients. Calorimetric measurements (DSC) of polyesters were carried out on a Shimadzu thermal analysis system in a temperature range of −80 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 Copolymerization. The reaction of (*R*)-β-BL with ϵ-CL is a representative example.

(*R*)-β-BL (3.10 g, 36 mmol), ϵ-CL (0.46 g, 4 mmol), and 1-ethoxy-3-chlorotetrabutyldistannoxane (**3a**; 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 to afford the white solid of the polyester **4a** (3.35 g) in 94% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 1.20–1.32 (m, 3H, CH_3 for the 3HB unit), 1.32–1.45 (m, 2H, CH_2 for the 6-hydroxyhexanoate (6HH) unit),

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Table I. Polymerization Results of (*R*)-*β*-BL with Various Lactones at 100 °C for 4 h[a]

entry	cat.	monomer (feed ratio)	polymer (obsd ratio)[b]	T_m, °C	T_g, °C	mol wt[c] M_w	mol wt[c] M_n	yield, %	$[\alpha]^{25}_D$ (c = 1, $CHCl_3$)
1	**3a**	(*R*)-*β*-BL	P[(*R*)-3HB]	163	5.3	424 000	178 000	99	−1.6[d]
2	**3a**	(*R*)-*β*-BL/*ε*-CL (90/10)	**4a** (90/10)	126	−7.4	320 000	200 000	94	−1.9
3	**3b**	(90/10)	(88/12)	119	−9.3	316 000	180 000	87	−1.4
4	**3c**	(90/10)	(89/11)	119	−7.9	379 000	209 000	99	−1.5
5	**3a**	(80/20)	**4b** (80/20)	97	−16.5	282 000	154 000	97	−1.9
6	**3a**[e]	(10/90)	**4c** (9/91)	47	−61.1	482 000	255 000	99	−0.2
7	**3a**	(*R*)-*β*-BL/*δ*-VL (90/10)	**5** (90/10)	113	−4.3	313 000	191 000	96	−1.1
8	**3a**	(*R*)-*β*-BL/*β*-Me-*δ*-VL (90/10)	**6** (91/9)	115	−2.8	280 000	176 000	93	−1.3
9	**3a**	(*R*)-*β*-BL/L-LA (90/10)	**7** (83/17)[f]	120	12.3	208 000	124 000	83	−32.6

[a] Polymerization conditions: catalyst = 5 × 10^{-3} mmol, lactones = 40 mmol, no solvent was used. [b] Determined by ^1H NMR analysis. [c] Determined by GPC analysis, calibrated to a polystyrene standard. [d] c = 0.25, $CHCl_3$. [e] 2 h. [f] The observed ratio was calculated as (*R*)-*β*-BL/L-LA.

1.60–1.70 (m, 4H, CH_2 for the 6HH unit), 2.23–2.32 (m, 2H, CH_2 for the 6HH unit), 2.41–2.53 (m, 1H, CH_2 for the 3HB unit), 2.55–2.67 (m, 1H, CH_2 for the 3HB unit), 4.04–4.10 (m, 2H, CH_2 for the 6HH unit), 5.20–5.32 (m, 1H, CH for the 3HB unit). Other reactions were carried out in a similar manner.[14]

Biodegradation Test. Biodegradation tests of polyester films were carried out at 25 °C in a 500 ppm activated sludge.[15] The standard activated sludge was purchased from Chemicals Inspection and Testing Institute, Japan. Polyester films (initial weights, 37.5–61.8 mg; initial film dimensions, 10 × 10 mm wide and 0.30–0.45 mm thick) were placed in 100-mL bottles. The reaction was started by the addition of 50 mL of an aqueous solution of the activated sludge and then was incubated at 25 ± 0.1 °C with shaking for 4 weeks. Samples were removed once a week, washed with water, and dried to constant weight in vacuo.

Results and Discussion. A new series of biodegradable copolyesters of (*R*)-*β*-BL (**4**–**7**) with *ε*-CL, *δ*-VL, *β*-Me-*δ*-VL, or L-LA were easily obtained in the presence of a catalytic amount of distannoxane complexes in excellent yields (Table I). All polyesters have high molecular weight (M_n > 100 000). (*R*)-*β*-Butyrolactone reacted with *ε*-CL at various ratios to afford the corresponding polyesters (entries 2–6). Single T_g values and single melting endotherms were observed for all polyesters. The GPC traces of all polyesters were unimodal. A comparison ^1H NMR spectrum of poly(3HB-*co*-*L*-LA) (**7**) with a (*R*)-poly(3HB)–poly(L-LA) diblock copolyester[16] showed that these two polymers have different structures. Therefore, all polyesters **4**–**7** turned out to be random. T_m and T_g values decreased with increasing the *ε*-CL ratio in the polyesters (entries 1–6). The observed ratios of 3HB, 6HH, 5-hydroxyvalerate (5HV), and 3-methyl-5-hydroxyvalerate (3Me-5HV) units in the polyesters **4**–**6** were almost the same as the feed ratios of the monomers (entries 2–8). In the copolymerization of (*R*)-*β*-BL with L-LA, the ratio of the (*S*)-2-hydroxypropionate (2HP) unit increased from the feed ratio of the monomers (entry 9).

In another study, we have shown that the distannoxane-catalyzed ring-opening polymerization of (*R*)-*β*-BL (entry 1) proceeded by breaking the bond between the carbonyl carbon and oxygen atom of the (*R*)-*β*-BL ring (acyl cleavage) with retention of the configuration.[9,10] It is also considered that the copolymerization of (*R*)-*β*-BL with various lactones proceeds by acyl cleavage with retention of the configuration since the decrease of T_m is not dramatic (entries 2–5 and 7–9) and the optical rotations of polyesters show negative values ranging from −1.9° to −0.2° (entries 1–8). If the ring-opening copolymerization proceeded by bond breaking between the *β*-carbon and oxygen atom (alkyl cleavage) which could lead to either inversion of configuration or racemization,[5b] the dramatic decrease of T_m and disappearance or inversion of optical rotations of the copolyesters would occur. With the exception of **4c** and **7**, the correlation between the observed monomer ratios in polyesters and their optical rotations is within experimental errors. The value of the optical rotation for **4c** was −0.2° which decreased with decreasing the feed ratio of (*R*)-*β*-BL (entry 6). The optical rotation of the copolyester **7** has a larger negative value than that of P(3HB) due to the optical rotation of the poly(L-LA) (M_n 110 000, M_w/M_n = 1.8) which also has a large negative value ($[\alpha]^{25}_D$ −150.8°).

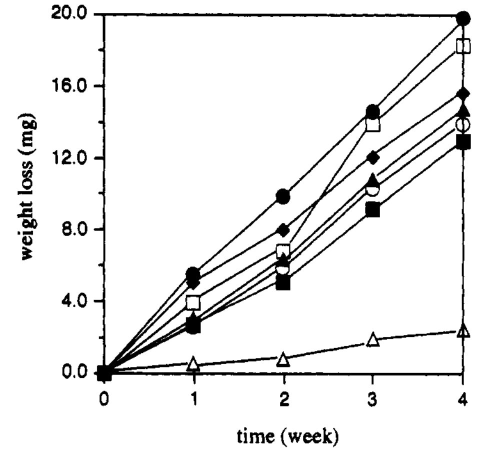

Figure 1. Biodegradation profiles on solution-cast films of polyesters 4–7 and P(3HB-*co*-11% 3HV) (**1a**) samples in an aqueous solution of standard activated sludge at 25 °C: (■) **4a**; (**fdt**) **4b**; (△) **4c**; (◆) **5**; (□) **6**; (○) **7**; (▲) **1a**.

The biodegradability of polyesters **4**–**7** was assessed using solution-cast films at 25 °C in aqueous solutions of a standard activated sludge. It has been confirmed that no erosion occurs at 25 °C in the absence of the activated sludge.

Figure 1 shows the weight loss profiles of **4**–**7** and P(3HB-*co*-11% 3HV) (**1a**; M_n 246 000, M_w/M_n = 2.1) films as a function of degradation time. The average weight losses of **4a**,**b**, **5**–**7**, and **1a** were 12.9 (25.0%), 19.8 (32.0%), 15.6 (33.5%), 18.2 (35.9%), 13.8 (32.8%), and 14.7 mg (39.2%), respectively. Polyesters **4a**,**b** and **5**–**7** which have over 80 mol % of the (*R*)-3HB unit showed almost the same degree of biodegradability in comparison with **1a**. Polyester **4c** which has 10 mol % of the (*R*)-3HB unit showed a lower weight loss than that of other polyesters. These facts remarkably showed that microorganisms discriminate the (*R*)-3HB unit to degrade the polyesters.

Summary. It has been disclosed that the reactions of the (*R*)-*β*-butyrolactone (92% ee) with *ε*-caprolactone, *δ*-valerolactone, *β*-methyl-*δ*-valerolactone, and L-lactide in the presence of distannoxane complexes as catalysts at

100 °C gave the new series of copolyesters of high molecular weights, comprised of (*R*)-3-hydroxybutyrate. The copolyesters containing more than 80% of the 3HB unit were almost as biodegradable as P(3HB-*co*-11% 3HV) by the standard activated sludge.

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(10) The enantiomeric excess of the methyl 3-hydroxybutyrate which was synthesized by the methanolysis (see ref 17) of a synthetic P[(*R*)-3HB] (entry 1) was found to be 91% of the *R* configuration by HPLC analysis after converting an aliquot of this compound to the (*R*)-MTPA ((*R*)-2-methoxy-2-(trifluoromethyl)phenylacetic acid) ester (see ref 18), thus indicating that the polymerization of (*R*)-β-BL (92% ee) catalyzed by the distannoxane complexes proceeds by acyl cleavage with retention of the configuration.

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(13) 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.

(14) ^{1}H NMR data of **5**–**7** are as follows. **5**: δ 1.21–1.37 (m, 3H, CH_3 for the 3HB unit), 1.61–1.73 (m, 4H, CH_2 for the 5HV unit), 2.26–2.35 (m, 2H, CH_2 for the 5HV unit), 2.41–2.53 (m, 1H, CH_2 for the 3HB unit), 2.55–2.67 (m, 1H, CH_2 for the 3HB unit), 4.03–4.13 (m, 2H, CH_2 for the 5HV unit), 5.20–5.32 (m, 1H, CH for the 3HB unit). **6**: δ 0.97 (d, *J* = 6.4 Hz, 3H, CH_3 for the 3Me-5HV unit), 1.18–1.37 (m, 3H, CH_3 for the 3HB unit), 1.45–1.58 (m, 1H, 3Me-5HV unit), 1.63–1.78 (m, 1H, CH_2 for the 3Me-5HV unit), 2.01–2.20 (m, 2H, CH_2 for the 3Me-5HV unit), 2.26–2.38 (m, 1H, CH_2 for the 3Me-5HV unit), 2.41–2.53 (m, 1H, CH_2 for the 3HB unit), 2.55–2.67 (m, 1H, CH_2 for the 3HB unit), 4.06–4.18 (m, 2H, CH_2 for the 3Me-5HV unit), 5.20–5.32 (m, 1H, CH for the 3HB unit). **7**: δ 1.21–1.36 (m, 3H, CH_3 for the 3HB unit), 1.41–1.61 (m, 3H, CH_2 for the 2HP unit), 2.42–2.80 (m, 2H, CH_2 for the 3HB unit), 5.02–5.20 (m, 1H, CH for the 2HP unit), 5.20–5.35 (m, 1H, CH for the 3HB unit).

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