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Ring-Opening Copolymerization of (*R*)-*β*-Butyrolactone with (*R*)-3-Methyl-4-oxa-6-hexanolide: A New Biodegradable Poly(ester−ether)

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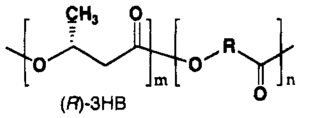
Introduction. Poly((*R*)-3-hydroxyalkanoate)s (PHAs) are a class of (*R*)-3-monoalkyl-substituted polyesters which are naturally occurring in a wide variety of microorganisms.[1] The bacterial copolyester of (*R*)-3-hydroxybutyrate (3HB) and (*R*)-3-hydroxyvalerate (3HV) (P(3HB-*co*-3HV)) has recently attracted industrial attention as a possible candidate for large-scale biotechnological production since the copolyester is an environmentally degradable thermoplastic.[2]

In the course of our study to establish a new field of the chemical synthesis of biodegradable polymers[3−5] which have structures similar to that of P(3HB), P(3HB-*co*-3HV), or P(3HB-*co*-4HB),[1d] we have reported the ring-opening polymerization of (*R*)-*β*-butyrolactone ((*R*)-*β*-BL) with several lactones using distannoxane complexes as a new catalytic system to obtain a new series of biodegradable random polyesters (**1**) of high molecular weights containing 3HB units.[4,5]

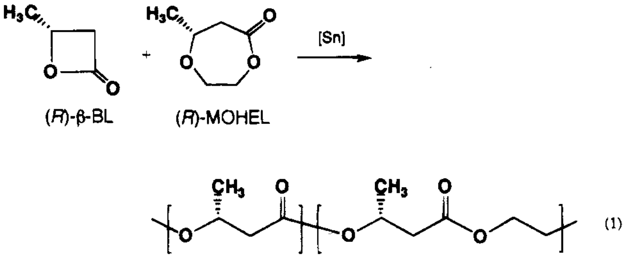


1

1a: R= $(CH_2)_5$ 1c: R= $CH_2CH_2CH(CH_3)CH_2$
1b: R= $(CH_2)_4$ 1d: R= $CH(CH_3)COOCH(CH_3)$

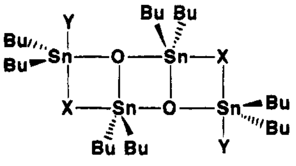
In order to synthesize a biodegradable poly(ester−ether) which has 3HB units, we prepared (*R*)-3-methyl-4-oxa-6-hexanolide ((*R*)-MOHEL, 100% ee) as a monomer for the ring-opening polymerization. Recently, Yasuda et al. reported that when (*R*)-MOHEL reacted with *ϵ*-caprolactone or *δ*-valerolactone, the corresponding copolymers were afforded.[6]

Here we report on the synthesis of a new biodegradable polymer, poly[(*R*)-*β*-butyrolactone-*co*-(*R*)-3-methyl-4-oxa-6-hexanolide] (P[(*R*)-*β*-BL-*co*-(*R*)-MOHEL], **2**), with a high molecular weight from the reaction of (*R*)-*β*-BL and (*R*)-MOHEL in the presence of distannoxane catalysts (**3**) (eq 1).



P[(*R*)-β-BL-*co*-(*R*)-MOHEL], 2

Experimental Section. (*R*)-*β*-Butyrolactone[7] ((*R*)-*β*-BL, 92% ee) and (*R*)-MOHEL (100% ee)[8] were prepared using the literature methods, dried by CaH_2, and distilled under reduced pressure. Distannoxanes **3a**[9] and **3b**[10] were prepared using the literature methods



3

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

and dried in vacuo at 80 °C for 20 h. Molecular weights of the polymers 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. Differential scanning calorimetry (DSC) studies of P[(*R*)-*β*-BL-*co*-(*R*)-MOHEL]s were carried out on a Shimadzu thermal analysis system in a temperature range of −80 to +200 °C at heating and cooling rates of 100 °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. (*R*)-*β*-BL (3.18 g, 36.9 mmol), (*R*)-MOHEL (0.60 g, 4.6 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 chloroform and then was added to a mixture of diethyl ether and hexane (the ratio is 1:3) to afford the white solid of the P[(*R*)-*β*-BL-*co*-(*R*)-MOHEL]: yield 3.56 g (94%); ^1H NMR (400 MHz, $CDCl_3$) δ 1.16−1.34 (m, 3H, CH_3 for the 3HB unit), 2.30−2.71 (m, 2H, CH_2 for the 3HB unit), 3.56−3.71 (m, 2H CH_2 for the ethylene glycol (EG) unit), 4.11−4.25 (m, 2H, CH_2 for the EG unit), 3.18−3.93 and 5.20−5.32 (m, 1H, CH for the 3HB unit).

Biodegradation Test. Biodegradation tests of P(3HB)[11] and poly(ester−ether) films were carried out at 25 °C in a 500 ppm activated sludge.[12] The standard activated sludge was purchased from Chemicals Inspection and Testing Institute, Japan. P(3HB) and poly(ester−ether) films (initial weights, 23.4−45.1 mg; initial film dimensions, 10 × 10 mm wide and 0.18−0.43 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 poly(ester−ether) (P[(*R*)-*β*-BL-*co*-(*R*)-MOHEL], **2**) of (*R*)-*β*-BL with (*R*)-MOHEL at various ratios was easily obtained in the presence of a catalytic amount of distannoxane complexes (**3**) in excellent yields (Table 1). All polymers which are shown in Table 1 have high molecular weights (M_n > 100 000). Single T_g values and single melting

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Table 1. Polymerization Results of (*R*)-β-BL with (*R*)-MOHEL[a]

polymer	(*R*)-β-BL/(*R*)-MOHEL (feed ratio) (3HB/EG (calcd ratio)[b])	3HB/EG (obsd ratio)[c]	T_m, °C	T_g, °C	mol wt[d] M_w	M_n	yield, %	$[\alpha]^{25}_D$ (c = 1, $CHCl_3$)
P(3HB)[e]	100/0	100/0	163	5.3	424 000	178 000	99	−1.6[f]
2a	89/11 (90/10)	89/11	129	−4.2	235 000	146 000	94	−6.3
2b[g]	89/11 (90/10)	88/12	122	−3.8	172 000	114 000	84	−6.5
2c	75/25 (80/20)	79/21	90	−11.3	243 000	152 000	89	−10.7
2d	57/43 (70/30)	68/32	63	−22.1	281 000	172 000	92	−16.9
2e	33/67 (60/40)	59/41	35	−27.9	254 000	148 000	94	−20.8
P(MOHEL)	0/100 (50/50)	50/50	11	−37.1	350 000	199 000	94	−27.5

[a] Polymerization conditions: catalyst **3a**, 5 × 10^{-3} mmol; lactones, 40 mmol; 100 °C, 4 h. [b] 3HB ratio was calculated as follows: 3HB ratio (%) = 100 × {(*R*)-β-BL + (*R*)-MOHEL}/{(*R*)-β-BL + 2(*R*)-MOHEL}. [c] Determined by ^{1}H NMR analysis. [d] Determined by GPC analysis, calibrated to a polystyrene standard. [e] Obtained by the ring-opening polymerization of (*R*)-β-BL. [f] c = 0.25, $CHCl_3$. [g] Catalyst **3b** (1 × 10^{-2} mmol) was used.

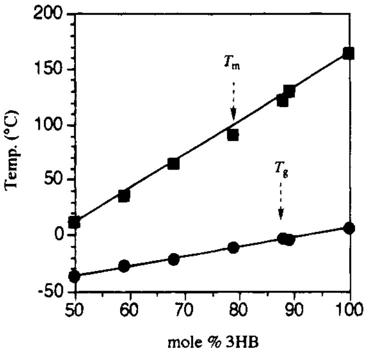

Figure 1. Relation of T_m (■) and T_g (●) values with the mole percentage content of 3HB.

Table 2. Biodegradation of the Polymers: Weight Loss of the Polymers after 4 Weeks of Incubation

entry	polymer	wt loss, mg (%)
1	P(3HB)[a]	12.0 (26.7)
2	**2a**	6.7 (17.7)
3	**2b**	8.2 (19.3)
4	**2c**	7.5 (23.5)
5	**2d**	22.8 (60.2)

[a] Obtained by the ring-opening polymerization of (*R*)-β-BL.

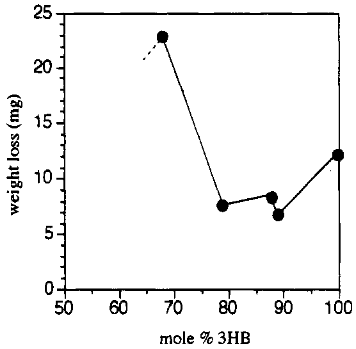

Figure 2. Relation between the mole percentage of 3HB units and the weight loss after a 4-week period.

endotherms were observed for all poly(ester−ether)s. The GPC traces of all poly(ester−ether)s were unimodal. Therefore, all poly(ester−ether)s turned out to be random. The observed ratio of 3HB and EG units in the polymers was almost the same as the feed ratio of the monomers. The elasticity of the polymers increases as the mole percentage of the 3HB units decreases. In the case of **2e** and P[(*R*)-MOHEL], solvent-casted films could not be obtained.

Figure 1 illustrates the relation of T_m and T_g values with the mole percentage content of 3HB of polymers P(3HB), **2**, and P[(*R*)-MOHEL]. All T_m and T_g values are directly related to the content of the 3HB unit. Thus, by increasing the 3HB content polymers with both higher T_m and T_g values can be obtained. In addition, by increasing the 3HB content polymers with lower specific rotation values can be obtained (Table 1).

The biodegradability of the polymers 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 activated sludge. After 4 weeks the weight loss of the polymers was measured. These data are listed in Table 2.

The weight loss profiles of synthetic P(3HB) and **2a−d** films are presented as a function of weight percentage of 3HB units (Figure 2). Figure 2 shows that the poly(ester−ether) **2d** containing 68% 3HB units has the highest degradation rate as compared to the other polymers. This result is similar to the enzymatic degradability of P(3HB) stereoisomers described by Kemnitzer et al.[13] Thus, accordingly, the dramatic increase in the biodegradation rate for the polymer **2d** (containing 68% 3HB) may be due to the decrease in crystallinity.[14]

Conclusion. In this study, we have prepared the new poly(ester−ether) by the ring-opening copolymerization of (*R*)-β-BL with (*R*)-MOHEL using distannoxane catalysts. All P[(*R*)-β-BL-*co*-(*R*)-MOHEL] films showed good degradabilities by a standard activated sludge.

References and Notes

(1) For reviews. see: (a) *Novel Biodegradable Microbial Polymers*; Dawes, E. A., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1990. (b) Brandl, H.; Gross, R. A.; Lenz, R. W.; Fuller, R. C. *Advances in Biochemical Engineering/Biotechnology*; Ghose, T. K., Fiechter, A., Eds.; Springer: Berlin, 1990; Vol. 41, p 77. (c) Steinbüchel, A.; Schlegl, H. G. *Mol. Microbiol.* **1991**, *5* (3), 535. (d) Doi, Y. *Microbial Polyesters*; VCH Publishers: New York, 1990. (e) Holmes, P. A. *Developments in Crystalline Polymers-2*; Bassett, D. C., Ed.; Elsevier Applied Science: London, 1988; pp 1−65.

(2) Holmes, P. A. *Phys. Technol.* **1985**, *16*, 32.

(3) Hori, Y.; Suzuki, M.; Okeda, Y.; Imai, T.; Sakaguchi, M.; Takahashi, Y.; Yamaguchi, A.; Akutagawa, S. *Macromolecules* **1992**, *25*, 5117.

(4) Hori, Y.; Suzuki, M.; Yamaguchi, A.; Nishishita, T. *Macromolecules* **1993**, *26*, 5533.

(5) Hori, Y.; Takahashi, Y.; Yamaguchi, A.; Nishishita, T. *Macromolecules* **1993**, *26*, 4388.

(6) Shirahama, H.; Mizuma, K.; Kawaguchi, Y.; Shiomi, M.; Yasuda, H. *Kobunshi Ronbunshu* **1993**, *50*, 821.

(7) Ohta, T.; Miyake, T.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1992**, 1725. 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.

(8) Yamagushi, A.; Hori, Y.; Akutagawa, S. U.S. Patent 5 221 755, 1993. Data of (*R*)-MOHEL are as follows: colorless solid; mp 46 °C; $[\alpha]^{20}_D$ −14.2° ($c = 1.0$, $CHCl_3$); IR (KBr) 2980, 2925, 2865, 1745, 1355, 1180, 1135, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, dd, $J = 8.3, 2.4$ Hz), 2.72 (1H, dd, $J = 4.8, 0.8,$ Hz), 2.92 (1H, dd, $J = 14.9, 9.4$ Hz), 3.83 (2H, qdd, $J = 14.3, 8.8, 0.6$ Hz), 4.06 (1H, ddd, $J = 14.3, 3.9, 0.6$ Hz), 4.22 (1H, ddd, $J = 13.6, 4.1, 0.5$ Hz), 4.43 (1H, dd, $J = 13.7, 8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 45.2, 69.3, 70.1, 70.8, 173.1; MS *m/z* 130 [M^+]. The enantiomeric excess of MOHEL was determined to be 100% 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 $t_R = 25.0$ and 27.7 min in a 0:100 ratio assignable to the *S*- and *R*-enantiomers, respectively.

(9) Okawara, R.; Wada, M. *J. Organomet. Chem.* **1963**, *1*, 81.

(10) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307.

(11) P(3HB) was obtained by the ring-opening polymerization of (*R*)-β-butyrolactone (92% ee).

(12) The test was conducted in accordance with OECD Test Guideline No. 302 and modified in accordance with the method described in the literature: Doi, Y.; Segawa, A.; Kunioka, M. *Int. J. Biol. Macromol.* **1990**, *12*, 106.

(13) Kemnitzer, J. E.; McCarthy, S. P.; Gross, R. A. *Macromolecules* **1992**, *25*, 5927.

(14) Similar results were obtained: Abe, H.; Matsubara, I.; Doi, Y.; Hori, Y.; Yamaguchi, A. *Macromolecules* **1994**, *27*, 6018.

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