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Synthesis of poly(3-hydroxyalkanoate)s by ring-opening copolymerization of (*R*)-β-butyrolactone with other four-membered lactones using a distannoxane complex as a catalyst

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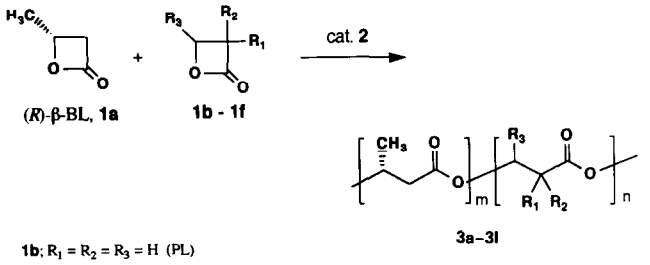
The reaction of optically active β-butyrolactone with other four-membered lactones in the presence of 1-ethoxy-3-chlorotetrabutyldistannoxane as a catalyst at 100°C gave a series of poly(3-hydroxyalkanoate)s with high molecular weight in good yields.

(Keywords: distannoxane; ring-opening copolymerization; poly(3-hydroxyalkanoate)s)

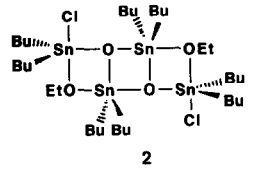
Introduction

A wide variety of microorganisms produce poly[(*R*)-3-hydroxybutyrate] [P(3HB)] as an intracellular storage material[1]. P(3HB) is a thermoplastic which is degradable in the environment by either hydrolytic or enzymatic degradation processes[2–5]. However, there are several drawbacks to the use of P(3HB), mainly based on its tendency to be rather brittle. This problem could be solved by the synthesis of copolymers of 3-hydroxybutyrate and other hydroxyalkanoates. Several authors have described the synthesis of 3HB copolymers by biochemical methods[6–11], whereas the bacterial synthesis of P(3HB) analogues is limited to only a few copolyesters.

Recently, much attention has been paid to the synthesis of P(3HB) by the ring-opening polymerization of β-butyrolactone (β-BL)[12–14], and this reaction can also be used to prepare 3HB copolymers that are not available from the biosynthetic route. We have already reported new biodegradable copolyesters synthesized by the ring-opening copolymerization of (*R*)-β-BL with six- or seven-membered lactones using distannoxane complexes as a catalyst[15,16]. Here, we report on the ring-opening copolymerization of (*R*)-β-BL (*Scheme 1*, **1a**) with other four-membered lactones (*Scheme 1*, **1b–1f**) using distannoxane complex (*Scheme 1*, **2**) and the biodegradation of the resulting polyesters (*Scheme 1*, **3**) in activated sludge.



1b; $R_1 = R_2 = R_3 = H$ (PL)
c; $R_1 = CH_3$, $R_2 = R_3 = H$ (α-MePL)
d; $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$ (α,β-diMePL, erythro/threo = 9/1)
e; $R_1 = R_2 = CH_3$, $R_3 = H$ (α,α-diMePL)
f; $R_1 = R_2 = H$, $R_3 = CH_2CH_3$ ((*R*)-β-VL)



Scheme 1

Experimental

Materials. (*R*)-β-BL (*Scheme 1*, **1a**, 92% ee) was prepared by the Ru-(*S*)-BINAP-catalysed asymmetric hydrogenation of diketene[17] (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl). α-Methyl-β-propiolactone[18] (*Scheme 1*, **1c**, α-MePL) was prepared from 3-bromoisobutyric acid trimethylsilyl ester according to the procedure described in the literature[19]. α,β-Dimethyl-β-propiolactone[20] (**1d**, α,β-diMePL, erythro/threo = 9/1) and α,α-dimethyl-β-propiolactone[21] (*Scheme 1*, **1e**, α,α-diMePL) were synthesized by the lactonization of 3-bromo-2-methylbutyric acid and 3-chloropivalic acid, respectively, using sodium carbonate[22]. (*R*)-β-Valerolactone (*Scheme 1*, **1f**, (*R*)-β-VL) was synthesized from methyl (*S*)-3-hydroxyvalerate[23], which was prepared by the Ru-(*S*)-BINAP-catalysed asymmetric hydrogenation of methyl propionylacetate. (The enantiomeric excess of methyl (*S*)-3-hydroxyvalerate was 99.1%, obtained by the h.p.l.c. analysis of its (*R*)-MTPA esters.) This was done in four steps, as shown in *Scheme 2*, by the same procedure employed by Lenz *et al.*[12] for the synthesis of optically active β-BL. The enantiomeric excess of **1f** was 98.7%, as determined by the h.p.l.c. analysis of (*R*)-MTPA ester of methyl (*R*)-3-hydroxyvalerate derived from **1f** (MTPA = α-methoxy-α-trifluoromethylphenylacetyl). **1f** was converted into methyl (*R*)-3-hydroxyvalerate by methanol and potassium hydroxide. Propiolactone (*Scheme 1*, **1b**) was purchased from Tokyo Kasei Co. All the lactones were dried by

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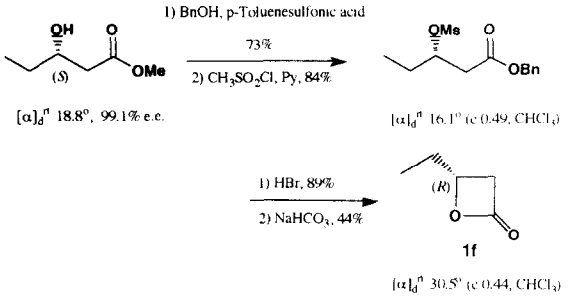

Scheme 2

CaH_2 and distilled under reduced pressure. Biologically synthesized poly(3-hydroxybutyrate-*co*-11% 3-hydroxyvalerate) [P(3HB-*co*-11%3HV)] was purchased from Aldrich Chemical Co. Distannoxane **2** was prepared by the procedure described in the literature[24] and dried *in vacuo* at 80°C for 20 h.

Measurement. I.r. spectra were recorded on a JASCO IR-810 spectrophotometer. ^{1}H n.m.r. spectra were measured on a Bruker AMX 400 spectrometer using tetramethylsilane as the internal standard. Optical rotation measurements were performed on a JASCO DIP-360 spectrometer. Differential scanning calorimetry (d.s.c.) was performed with Shimadzu thermal analysers DSC-50, and measurements were made at heating and cooling rates of 10°C min^{-1} under nitrogen. 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). Weight-average molecular weight (M_w) and number-average molecular weight (M_n) were obtained by gel permeation chromatography (g.p.c) with polystyrene calibration, using chloroform as an eluent.

Ring-opening copolymerization. The reaction of (*R*)-β-BL (**1a**) and (*R*)-β-VL (**1f**) is a representative example. **1a** (2.75 g, 32.0 mmol), **1f** (0.80 g, 8.0 mmol), and 1-ethoxy-3-chlorotetrabutyldistannoxane (**2**, 11.2 mg, 10 μmol) were heated in a 20 ml Schlenk tube at 100°C for 5 h. The resulting mixture was dissolved in chloroform, and the solution was then added to a mixture of diethyl ether and hexane to afford the white solid of the polyester **3k** (3.05 g) in 87% yield. I.r. ν (film, cm^{-1}): 2980, 2940, 2880, 1740 (C=O), 1455, 1380, 1280, 1185, 1130, 1100, 1060 and 980. ^{1}H n.m.r. (in $CDCl_3$): δ = 0.90 (t, J = 7.4 Hz, CH_3 for 3HV unit), 1.28 (d, J = 6.8 Hz, CH_3 for 3HB unit), 1.65 (m, CH_2 for 3HV unit), 2.40–2.69 (m, CH_2 for 3HB and 3HV units), 5.15 (m, CH for 3HV unit) and 5.25 (m, CH for 3HB unit).

Representative ^{1}H n.m.r. data (**3a**, **3c**, **3d** and **3g**) measured in $CDCl_3$ are as follows. **3a**: δ = 1.22–1.33 (m, CH_3 for 3HB unit), 2.42–2.56 (m, CH_2 for 3HB unit), 2.56–2.70 (m, CH_2 for 3HB and 3HP units), 4.28–4.38 (m, CH_2 for 3HP unit) and 5.20–5.35 (m, CH for 3HB unit). **3c**: δ = 1.18 (d, J = 6.3 Hz, CH_3 for 2-Me-3HP unit), 1.21–1.34 (m, CH_3 for 3HB unit), 2.42–2.52 (m, CH_2 for 3HB unit), 2.55–2.67 (m, CH_2 for 3HB unit), 2.69–2.80 (m, CH for 2-Me-3HP unit), 4.10–4.27 (m, CH_2 for 2-Me-3HP unit) and 5.19–5.31 (m, CH for 3HB unit). **3d**: δ = 1.10–1.16 (m, CH_3 for 2,3-diMe-3HP unit), 1.16–1.23 (m, CH_3 for 2,3-diMe-3HP unit), 1.23–1.33 (m, CH_3 for 3HB unit), 2.40–2.52 (m, CH_2 for 3HB unit), 2.55–2.67 (m, CH_2 for 3HB and 2,3-diMe-3HP units), 5.06–5.17 (m, CH for 2,3-diMe-3HP unit) and 5.18–5.31 (m, CH for 3HB unit). **3g**: δ = 1.19 (s, CH_3 for 2,2-diMe-3HP unit), 1.21–1.32 (m, CH_3 for 3HB unit), 2.41–2.52 (m, CH_2 for 3HB unit), 2.56–2.68 (m, CH_2 for 3HB unit), 4.03–4.17 (m, CH_2 for 2,2-diMe-3HP unit) and 5.20–5.31 (m, CH for 3HB unit).

Biodegradation test. Biodegradation tests of polyester films were carried out at 25°C in 500 ppm of activated sludge. The test was conducted in accordance with OECD Test Guideline No. 302 and modified in accordance with the method described in the literature[25]. The standard activated sludge was purchased from the

Table 1 Polymerization results of (*R*)-β-BL with **1b**–**1f** at 100°C[a]

Entry	Monomer (feed ratio)	Polymer (obsd ratio)[b]	T_m[c] (°C)	T_g[c] (°C)	Mol. wt[d] M_w	Mol. wt[d] M_n	Yield (%)	$[\alpha]_d^{rt}$[e] (degree)
1[f]	**1a**	P(3HB)[28]	163	5.3	424000	178000	99	−1.6
2	**1a**/**1b** (90/10)	**3a** (90/10)	135	−3.1	96000	54000	99	−1.1
3	**1a**/**1b** (60/40)	**3b** (59/41)	93	−11.7	60000	36000	89	−0.3
4	**1a**/**1c** (95/5)	**3c** (95/5)	143	3.3	118000	80000	85	−1.5
5	**1a**/**1d** (95/5)	**3d** (95/5)	139	4.0	112000	67000	90	−1.7
6	**1a**/**1d** (90/10)	**3e** (92/8)	121	5.6	111000	67000	81	−2.2
7	**1a**/**1d** (80/20)	**3f** (83/17)	82	6.2	103000	63000	78	−3.0
8	**1a**/**1e** (95/5)	**3g** (96/4)	142	[g]	122000	83000	94	−1.6
9	**1a**/**1e** (90/10)	**3h** (91/9)	124	5.1	103000	63000	90	−2.1
10	**1a**/**1e** (80/20)	**3i** (82/18)	83	−1.1	105000	63000	93	−2.8
11[h]	**1a**/**1f** (90/10)	**3j** (91/9)	124	1.4	198000	130000	95	−0.7
12[h]	**1a**/**1f** (80/20)	**3k** (83/17)	100	0.1	160000	107000	87	1.3
13	**1a**/**1f** (60/40)	**3l** (58/42)	62	−6.6	66000	39000	84	4.6

[a] Polymerization conditions: lactone = 40 mmol, lactone/catalyst = 2000, no solvent was used
[b] Determined by ^{1}H n.m.r. analysis
[c] Measured by d.s.c in nitrogen at a heating rate of 10°C min^{-1}
[d] Determined by g.p.c. analysis, calibrated to a polystyrene standard
[e] Measured in chloroform
[f] Lactone/catalyst = 8000
[g] Not observed
[h] Lactone/catalyst = 4000

Chemicals Inspection and Testing Institute, Japan. Polyester films (initial weights, 16.0–42.7 mg; initial film dimensions, 10 × 10 mm^2 and 0.13–0.41 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

Table 1 summarizes the results of ring-opening copolymerization using catalytic distannoxane complex **2**. All the polyesters were obtained with good to excellent yield and with high molecular weight by g.p.c. analyses. ^1H n.m.r. studies revealed that the ratios of 3HB units in the polyesters were almost the same as those of the (*R*)-β-BL feed ratios. The T_g values of the polyesters **3a**–**3c** and **3h**–**3l** obtained by d.s.c. measurement decreased as the 3HB contents decreased. It seems that the content of the 2,3-dimethyl-3-hydroxypropionate unit does not affect the T_g values of the polymers (**3d**–**3f**). The peak melting temperature (T_m) of all the polyesters also observed by d.s.c. decreased with decreasing 3HB fraction from 163°C. This fact indicates that the other 3-hydroxyalkanoate units in the 3HB repeating sequence in the main chain decrease the crystallinity of the P(3HB) crystalline structure. Poly(3-hydroxybutyrate-*co*-3-hydroxypropionate) [P(3HB)-*co*-3HP)][26] and P(3HB-*co*-3HV)[27] have already been synthesized biologically. The melting points of **3a**–**3c** and **3j**–**3l** are lower than those of the corresponding bacterial PHAs, probably because the enantiomeric excess of (*R*)-β-BL (**1a**) used in this study was 92%. We have already reported that the bond between the carbonyl carbon and oxgen atom of (*R*)-β-BL was cleaved by the distannoxane complex with retention of the configuration to yield P(3HB)[28]. It is also considered that the copolymerization of (*R*)-β-BL with other four-membered lactones proceeds by acyl cleavage with retention of the configuration.

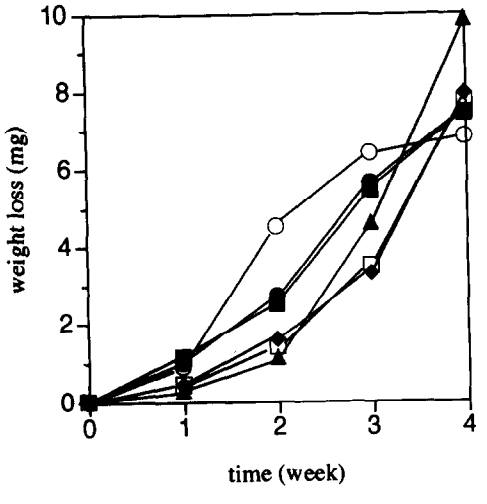

Figure 1 Biodegradation profiles of solution-cast films of polyesters **3a**, **3c**, **3e**, **3f**, **3h** and bacterial P(3HB-*co*-11%3HV) samples in aqueous solutions of standard activated sludge at 25°C: (■) **3a**; (●) **3c**; (▲) **3e**; (◆) **3f**; (□) **3h**; (○) bacterial P(3HB-*co*-11%3HV)

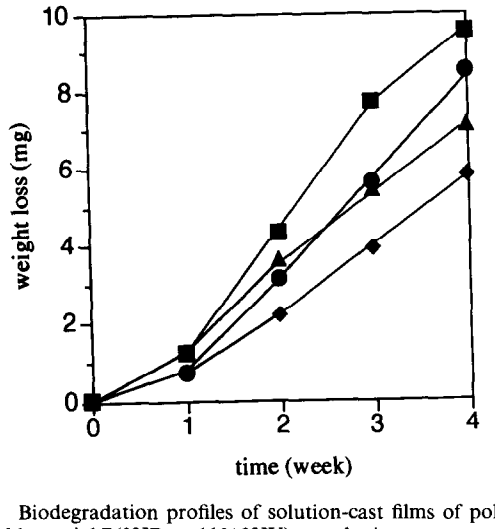

Figure 2 Biodegradation profiles of solution-cast films of polyesters **3j**–**3l**, and bacterial P(3HB-*co*-11%3HV) samples in aqueous solutions of standard activated sludge at 25°C: (●) **3j**; (▲) **3k**; (◆) **3l**; (■) bacterial P(3HB-*co*-11%3HV)

The biodegradability of the polyester films was studied at 25°C in aqueous solutions of a standard activated sludge. *Figures 1* and *2* show the weight loss profiles of the polyesters **3a**, **3c**, **3e**, **3f**, **3h** and polyesters **3j**–**3l**, respectively, as a function of degradation time. The polyesters **3a**, **3c**, **3e**, **3f**, **3h** and **3k** are almost as biodegradable as bacterial P(3HB-*co*-11%3HV) in 4 weeks (*Figure 1*), whereas the erosion rates of the polyesters **3k** and **3l** with 17% and 42% 3HV units, respectively, were slower than bacterial P(3HB-*co*-11%3HV) in the activated sludge (*Figure 2*).

In conclusion, new and known poly(3-hydroxyalkanoate)s were successfully synthesized by the ring-opening polymerization of (*R*)-β-BL with other four-membered lactones in the presence of 1-ethoxy-3-chlorotetrabutyldistannoxane as a catalyst at 100°C. These polyesters showed biodegradability in a standard activated sludge at 25°C.

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