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Ring-Opening Copolymerization of (*R*)-*β*-Butyrolactone with Macrolide: A New Series of Poly(Hydroxyalkanoate)s

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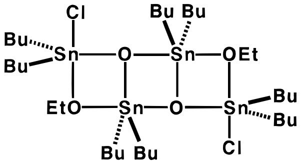
Introduction. A wide variety of microorganisms are known to produce poly[(*R*)-3-hydroxyalkanoate]s, (PHAs) as intracellular energy and carbon storage materials.[1] The PHAs produced by a fermentation process are limited to only a few copolyesters such as P[(*R*)-3-hydroxybutanoate-*co*-(*R*)-3-hydroxyalkanoate]s and P[(*R*)-3-hydroxybutanoate-*co*-4-hydroxybutanoate], since no microorganism can synthesize PHAs which contain 16- or 17-hydroxy-substituted or higher hydroxy-substituted alkanoate units.

We reported on the ring-opening copolymerization of (*R*)-*β*-butyrolactone ((*R*)-BL) with several lactones using distannoxane complexes as new catalysts to produce a new series of biodegradable PHAs,[2−6] which are difficult to obtain by a fermentation method. Furthermore, we reported on the preparation of biodegradable poly(ester−ether)s by the copolymerization of (*R*)-BL with (*R*)-3-methyl-4-oxa-6-hexanolide[7] and on the preparation of poly(ester−carbonate)s by the copolymerization of (*R*)-BL with cyclic carbonates.[8]

We tried the ring-opening copolymerization of (*R*)-BL with macrolides (all of them are used as musk odorants) to prepare a new series of polymers containing (*R*)-3-hydroxybutanoate units. In this paper we report on the synthesis of poly[(*R*)-3-hydroxybutanoate-*co*-macrolide]s and their physical properties (eq 1).



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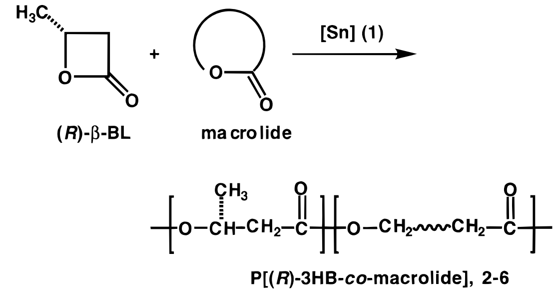
Experimental Section. (*R*)-*β*-Butyrolactone[9] ((*R*)-BL, 94% ee) was prepared by the literature method, dried with CaH_2 for 2 days by stirring, and distilled under reduced pressure. Ethylene dodecanedioate and ethylene tridecanedioate are produced by Takasago International Corp. 15-Pentadecanolide, 16-hexadecanolide, 11-oxa-16-hexadecanolide, and ϵ-caprolactone are commercially available. These macrolides were dried with CaH_2 overnight, and distilled under reduced pressure. Molecular weights of the polymers were determined by GPC using a polystyrene calibration. Chloroform was used as an eluent at a flow rate of 1.0 mL/min. ^1H NMR 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 were as follows: 1 % w/w of polymer in $CDCl_3$, temperature 27 °C, pulse width 45°, 32K data points, relaxation delay 2.5 s, and 8−16 transients. Differential scanning calorimetric (DSC) studies of polymers were carried out on a Shimadzu thermal analysis system in a temperature range of −80 to +200 °C at heating and cooling rates of 10 °C/min. The melting temperature (T_m) was taken as a peak temperature of the melting endotherm (first run). The glass transition temperature (T_g) was taken as the inflection point of a specific heat increment at the glass transition (second run).

1-Ethoxy-3-chlorotetrabutyldistannoxane ([$Bu_2SnClOSnBu_2(EtO)]_2$, 1). A mixture of Bu_2SnO (76.1 g, 306 mmol), Bu_2SnCl_2 (31.0 g, 102 mmol), in 99.5% ethanol (1.0 L) was refluxed. After 6 h, the clear solution that resulted was concentrated to give a white powder. Recrystallization (hexane, 0 °C) of the crude product afforded 1-ethoxy-3-chlorotetrabutyldistannoxane (**1**) (72.0 g, 64.0 mmol, 63%): mp 106−107 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, $J = 7.3$ Hz, 12H), 0.95 (t, $J = 7.3$ Hz, 12H), 1.13 (t, $J = 7.0$ Hz, 6H), 1.28−1.60 (m, 32H), 1.60−1.90 (m, 16H), 3.62 (q, $J = 7.0$ Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 13.6, 19.9, 25.0, 26.4, 26.8, 27.1, 27.3, 27.5, 58.8. The compound was dried in vacuo at 80 °C for 10 h before use.



(1)

Ring-Opening Copolymerization. A mixture of (*R*)-BL (15.50 g, 180 mmol), 15-pentadecanolide (15-PD) (4.81 g, 20 mmol), and 1-ethoxy-3-chlorotetrabutyldistannoxane (**1**) (56.2 mg, 0.05 mmol) was heated in a 80-mL Schlenk tube at 95 °C for 40 h. The resulting mixture was dissolved in dichloromethane and then added to a mixture of diethyl ether and hexane (the volume ratio being 1:3) to afford a white solid of P[(*R*)-BL-*co*-15-PD] (**4a**); yield 18.08 g (89%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.20−1.40 (m), 1.55−1.65 (m, 2H), 2.20−2.30 (m, $-CH_2-CO-$ for the 15-PD unit), 2.40−2.70 (m, 2H, CH_2 for the 3HB unit), 4.00−4.10 (m, 2H, $-O-CH_2-$ for the 15-PD unit), 5.20−5.30 (m, 1H, $-CH-$ for the 3HB unit). Other reactions were carried out in a similar manner.

Tensile Strength and Elongation to Break. Polymer dumbbells were obtained on a Custom Scientific Instruments Inc. MINI MAX MOLDER (CS-183MMX). The dumbbells were then aged at least for 2 weeks at room temperature to reach equilibrium crystallinity prior to analysis. Data of tensile strength and elongation to break tests of polymer dumbbells were obtained on a Shimadzu tensile machine (Model AGS-500B).

Results and Discussion. A new series of poly(hydroxyalkanoate)s (P[(*R*)-3HB-*co*-macrolide]s, **2-6**) were easily obtained by the ring-opening polymerization of (*R*)-BL with ethylene dodecanedioate (EDD), ethylene tridecanedioate (ETD), 15-pentadecanolide (15-PD), 16-

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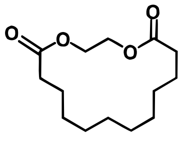
Table 1

entry	monomer (molar ratio of feed)	polymer (obsd molar ratio)[a]	mol wt[c]		T_m, °C	T_g, °C	yield, %	reaction time, h	s/c[b]
			10^{-3} M_n	10^{-3} M_w					
1	(*R*)-BL	P[(*R*)-3HB]	234	438	160	ND[d]	91.4	16	8000
2	(*R*)-BL/EDD (90/10)	**2a** (89/11)	163	273	130	−22	93.0	48	4000
3	(*R*)-BL/EDD (80/20)	**2b** (80/20)	156	252	44	−32	97.3	48	4000
4	(*R*)-BL/EDD (50/50)	**2c** (49/51)	123	195	58	ND[d]	94.4	48	4000
5	(*R*)-BL/EDD (20/80)	**2d** (20/80)	128	191	73	ND[d]	98.2	48	2000
6	EDD	P(EDD)	148	235	82	ND[d]	97.8	96	2000
7	(*R*)-BL/ETD (90/10)	**3** (89/11)	108	195	130	−23	91.6	27	4000
8	(*R*)-BL/15-PD (90/10)	**4a** (90/10)	178	302	144	−13	89.0	40	4000
9	(*R*)-BL/15-PD (80/20)	**4b** (80/20)	166	300	138	−12	91.2	48	4000
10	(*R*)-BL/16-HD (90/10)	**5** (90/10)	132	225	146	−12	87.8	24	4000
11	(*R*)-BL/11-O-16-HD (90/10)	**6** (90/10)	126	219	147	−15	87.8	24	4000
12	(*R*)-BL/CL (90/10)	**7a** (89/11)	132	221	128	−10	91.5	24	4000
13	(*R*)-BL/CL (80/20)	**7b** (79/21)	126	213	80	−20	94.4	24	4000

[a] Determined by ^{1}H NMR analysis. [b] s/c = substrate/catalyst. [c] Determined by GPC analysis, calibrated with a polystyrene standard. [d] Not detected.

hexadecanolide (16-HD), or 11-oxa-16-hexadecanolide (11-O-16-HD) in the presence of the distannoxane catalyst (**1**) in excellent yields (Table 1). All polyesters have high molecular weights (M_n > 100 000). The observed molar ratios of 3HB and macrolide units in the polymers were almost the same as that in the feed.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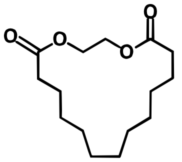
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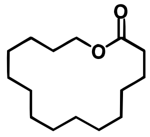
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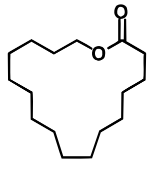
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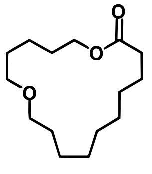
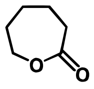

11-O-16-HD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The copolymerization of (*R*)-BL with ethylene dodecanedioate (EDD) catalyzed by 1-ethoxy-3-chlorotetrabutyldistannoxane (**1**) afforded the corresponding copolyester (P[(*R*)-3HB-*co*-EDD]s, **2**) at any ratios (entries 2−5) in excellent yields, respectively. Other copolymers were investigated only at 90/10 and 80/20 ratios, but were also obtained in excellent yields. Single T_g values were observed for all copolyesters except **4** and **5**. The GPC traces of all polymers were unimodal. Although the copolymers were expected to be block copolymers, ^{1}H and ^{13}C NMR spectra suggest that all the P[(*R*)-3HB-*co*-macrolide]s are random copolymers. Major melting endotherms (T_m) are shown in Table 1. Minor melting endotherms of about 40 °C were observed for **2a**, **4a**, **4b**, **5**, and **6**. This could indicate that these copolymers might be mixtures of random copolymers with large and small contents of the 3-HB unit.

The T_m values of the polymers P[(*R*)-3HB], **2a**−**2d**, and P(EDD) are directly related to the content of 3HB unit (entries 1−6). The copolymers (**2a**, **3**, **4a**, **5**, and **6**) contain the same percentage of respective macrolides. It is not clear why the T_m values of **4a**, **5**, and **6** are about 15 °C higher than those of **2a** and **3**, which are similar to that of P[(*R*)-3HB-*co*-CL] (**7a**). One possibility is that the two ester groups of EDD or ETD may decrease the T_ms of **2a** and **3**; the monomers for **4a**, **5**, and **6** each have only one ester group.

Table 2

entry	polymer (obsd molar ratio)[a]	tensile strength (kg/cm^2)	elongation to break (%)
1	P[(*R*)-3HB]	228	3
2	**2a** ((*R*)-BL/EDD = 89/11)	110	44
3	**2b** ((*R*)-BL/EDD = 80/20)	*b*	*b*
4	**2c** ((*R*)-BL/EDD = 49/51)	128	942
5	**2d** ((*R*)-BL/EDD = 20/80)	205	418
6	P(EDD)	440	678
7	**3** ((*R*)-BL/ETD = 89/11)	116	21
8	**4a** ((*R*)-BL/15-PD = 90/10)	182	749
9	**4b** ((*R*)-BL/15-PD = 80/20)	150	744
10	**5** ((*R*)-BL/16-HD = 90/10)	189	466
11	**6** ((*R*)-BL/11-O-16-HD = 90/10)	93	9
12	**7a** ((*R*)-BL/CL = 89/11)	100	7
13	**7b** ((*R*)-BL/CL = 79/21)	42	14

[a] Determined by ^{1}H NMR analysis. [b] Dumbbells were not obtained.

Table 2 lists the data of tensile strength and elongation-to-break of the copolymers P[(*R*)-3HB], P(EDD), and **2**−**7**. No dumbbell of **2b** was obtained because the crystallization rate of **2b** was too slow for it to solidify. A tensile strength of P[(*R*)-3HB] was 228 kg/cm^2 and the elongation-to-break was 3%. The tensile strength of **2a** which contained 11% of the EDD unit was 110 kg/cm^2 and the elongation-to-break was 44% (entry 15). The elongation-to-break of **2a** (44%) increases from that of 3% of P[(*R*)-3HB]. When the contents of EDD increase, tensile strengths of the copolymers **2c** and **2d** also increase. The data of elongation-to-break of **2c** and **2d** increased remarkably to 942 and 418%, respectively. Those are similar to that of P(EDD) homopolymer.

The tensile strength and elongation-to-break of **3** (11% of ETD unit) and **6** (10% of 11-O-16-HD unit) showed similar properties of **2a** and P[(*R*)-3HB-*co*-10% ϵ-caprolactone] (**7a**) (entries 20, 24, and 25).

To our surprise, the elongation-to-breaks of the copolymers **4a** and **5** were 749 and 466%, respectively (entries 21 and 23). Only 10% of the contents of 15-PD and 16-HD increased these elongation-at-breaks drastically. The such data have not been expected, so far. In general, P[(*R*)-3HB] random copolymers such as **7a** which contains 10% ϵ-caprolactone unit have given far smaller elongation-to-break than those of **4a** and **5**.

We cannot explain why the 10% amounts of 15-PD and 16-HD units increase the elongation of the copolymers **4a** and **5** remarkably; and why EDD, ETD, and 11-O-16-HD units do not increase the elongation of the copolymers **2a**, **3**, and **6** so much. However there are the differences in the structures between a group of 15-PD and 16-HD and a group of EDD, ETD, and 11-O-16-HD, explicitly. 15-PD and 16-HD do not contain any heteroatom other than the ester group in their molecules. EDD, ETD, and 11-O-16-HD contain one ester group or one heteroatom in addition to one ester group in their molecules. The difference may be related to the elongation effect of the copolymers. Further investigation is required on this problem.

Conclusion. The reaction of the (*R*)-β-butyrolactone with macrolides catalyzed by the distannoxane complex gave a new series of poly(hydroxyalkanoate)s, comprised of (*R*)-3-hydroxybutanoate. The elongation-to-breaks of P[(*R*)-3HB-*co*-10% 15-PD] and P[(*R*)-3HB-*co*-10% 16-HD] were unexpectedly and extremely large, 749 and 466%, respectively.

References and Notes

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