Macromolecules

Synthesis and Properties of Alternating Copolymers of 3-Hydroxybutyrate and Lactate Units with Different Stereocompositions

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Supporting Information

ABSTRACT: Alternating copolymers of (R)-3-hydroxybutyrate ((R)-3HB) and lactate (2-hydroxypropionate: 2HP) units were synthesized by polycondensation reaction of preprepared dimeric monomers, (R)-3HB-(R)-2HP and (R)-3HB-(S)-2HP, in the presence of condensation agent. On the basis of the NMR analyses, it was confirmed that the obtained copolymers had an alternating sequence of (R)-3HB and 2HP units. In contrast to random copolymers of (R)-3HB and 2HP units, the repeating sequence of alternately connected (R)-3HB and 2HP units formed crystalline region. The copolymer with alternating sequence of (R)-3HB and (S)-2HP units had a melting temperature at 83 °C. On the other hands,



the melting temperature of copolymer of (R)-3HB and (R)-2HP units was quite higher than those of the corresponding homopolymers (around 180 °C) and reached to 233 °C. When the alternating copolymers were prepared from a mixture of stereoisomeric dimers, both the melting temperature and crystallinity varied in the wide ranges depending on the composition of stereoisomeric dimers.

■ INTRODUCTION

Nowadays, aliphatic polyesters have attracted an industrial attention as environmentally degradable thermoplastics to be used for a wide range of applications.¹⁻²¹ Among a family of aliphatic polyesters, poly[(R)-3-hydroxybutyrate] (P[(R)-3HB]),¹⁻⁴ poly(L-lactate) (PLLA, poly[(S)-2-hydroxypropionate]; P[(S)-2HP]),⁵⁻⁸ and their copolymers⁹⁻¹⁸ have been most extensively investigated. Bacterially synthesized P[(R)-3HB] has a melting temperature around 180 °C, and the value is very close to that of polypropylene which is a commodity plastic. The introduction of second monomer units into P[(R)-3HB] molecules by copolymerization varies their melting temperatures in the range from 50 to 180 °C, depending on both the chemical structure of second monomer and the composition, and P[(R)-3HB]-based copolymers offer a wide variety of polymeric materials in properties, from hard crystalline plastic to elastic rubber.9-14 Optically pure PLLA also show a melting temperature at around 180 °C. Since the PLLA has a glass-transition temperature of 60 °C, the transparent materials can be provided. It has been found that the PLLA molecules form a stereocomplex crystalline structure in the presence of stereoisomeric poly(D-lactate) segments.^{19,20} The melting temperature of the stereocomplex crystal reaches

to 230 $^{\circ}$ C, and the value is the highest ones, along with poly(glycolate), in the aliphatic polyesters.²¹

For copolymerization, the regulation of sequential structure is powerful tool to design the polymeric materials with appropriate properties.^{22–25} Various types of copolymers with statistically random,^{26,27} blocking tendency,^{28,29} or alternative distributions^{30,31} have been produced, and the structure and physical properties were characterized. We previously investigated the effects of sequential structure on the thermal properties by preparing the copolymers of (R)-3HB and 2HP units with various sequential distributions from random to blocking tendency.³² The obtained results indicate that the melting temperature of copolymers be tuned to the averaged sequential length of crystallizable monomer units. However, in each case, the second monomer units introduced with statistical regularity act as defects of crystalline state consisting of repeating crystallizable monomer units and induce the inhibition of crystallization and the depression of melting temperature.

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With the progresses in polymer synthesis techniques, approaches to the precise regulation of monomer sequence in copolymer molecules have been attempted, instead of usual statistical regulation of sequential structure.^{33–39} For olefinic monomers, Wagener et al. synthesized the copolymers possessing an ethyl branch on every ninth, 15th and 21st carbon along the backbone of polyethylene via acyclic diene metathesis.³³ Satoh et al. succeeded in 1:2-sequence-regulated radical copolymerization of maleimide and terpenes in the presence of fluorinated alcohol.^{34–36} In the case of polyesters, Meyer et al. synthesized the various types of copolymers with precise repeating sequence of lactate and glycolate units by condensation reactions of oligomeric precursors of two monomers.^{37–39} They investigated the effects of sequence structure in the copolymers containing both α -hydroxyl acid monomeric units on the physical properties and biodegradability. Kramer et al. succeeded in syntheses of sequenceregulated copolymers consisted of β -hydroxyl acid monomeric units by polymerization of a mixture of enantiopure two β lactone monomers as pairing the opposite configuration using syndiospecific catalysts.⁴⁰ They reported that the melting temperatures of the synthesized copolymers with alternating sequence structure were strongly influenced by characteristics of side-chain groups.

The simplest type of sequence-regulated copolymer is an alternating copolymer. In this study, we focused the structure and physical properties of alternating copolymers consisting of α -hydroxyl acid monomeric unit of lactate (2HP) and β -hydroxyl acid monomer unit of (R)-3HB. Taking into account the chiral structure of monomeric units, two types of stereoisomeric dimers ((R)-3HB-(R)-2HP and (R)-3HB-(S)-2HP) were respectively prepared, and the alternating copolymers with different stereocompositions were synthesized from the dimeric monomers by condensation reaction. The structure and physical properties of obtained copolymers were characterized by NMR, DSC, and WAXD. On the basis of the obtained results, the relationships among the molecular structure, thermal properties, and crystalline structure in the alternating copolymers were discussed.

EXPERIMENTAL SECTION

Materials. Methyl (R)-3-hydroxybutyrate, methyl (R)-lactate, tertbutyldiphenylchlorosilane (TBDPSCl), benzyl bromide (BnBr), and N,N'-diisopropylcarbodiimide (DIC) were purchased from Tokyo Chemical Industry Co. (S)-Lactic acid, benzyl alcohol (BnOH), 1,8diazobicycloundec-7-ene (DBU), and N,N-dimethyl-4-aminopyridine (DMAP) were purchased from Wako Chemical Industry Co. p-Toluenesulfonate (TsOH), dimethylformamide (DMF), triethylamine (TEA), lithium hydroxide monohydrate (LiOH·H₂O), and N,N'dicyclohexylcarbodiimide (DCC) were purchased from Kanto Chemical Co. The 5% Pd on silica sample was purchased from Strem Chemicals, Inc. All of these chemical reagents were used as supplied without further purification. 4-(Dimethylamino)pyridinium ptoluenesulfonate (DPTS) was prepared from TsOH and DMAP according to the reported procedure.⁴¹ Dichloromethane (DCM) and THF (Kanto Chemical Co, super dehydrated grade) were passed through activated alumina using the SPS 800 (Innovative Technology).

Analytical Procedures. All molecular weight data were obtained by gel-permeation chromatography at 40 °C, using a Shimadzu 10A GPC system and 10A refractive index detector with Shodex K-806 M and K-802 columns. Chloroform was used as an eluent at a flow rate of 0.8 mL/min, and sample concentration of 1.0 mg/mL was applied. Polystyrene standards with a low polydispersity were used to make a calibration curve. ¹H and ¹³C NMR analyses of copolymer samples were carried out on a Varian NMR System 500 spectrometer. The samples (2 mg/mL) were dissolved in CDCl₃ or 7.5% HFIP in CDCl₃ and the 500 MHz ¹H NMR spectra were recorded at 25 °C with a 5.45 μ s pulse width (45° pulse angle), 3.2 s pulse repetition, 8000 Hz spectral width, and 16 K data points. The 125 MHz ¹³C NMR spectra were recorded at 25 °C in a CDCl₃ solution of polymer (30 mg/mL) with a 4.15 μ s pulse width (45° pulse angle), 1.3 s pulse repetition, 30 000 Hz spectral width, and 32 K data points. Data were calibrated by tetramethylsilane (TMS, δ 0.00) Data were analyzed by JEOL ALICE 2 software.

High-resolution solid-state ¹³C NMR measurements were carried out by using a Chemagnetics CMX Infinity 400 spectrometer in under a static magnetic field of 9.4 T. Both the ¹H and ¹³C radio field strength γ B1/2 π were 52.0 kHz. The magic angle spinning (MAS) rate was set to 9.0 kHz to avoid the overlapping of spinning side bands on other resonance lines. The contact time for the cross- polarization (CP) process was 3.0 ms throughout this work. ¹³C chemical shifts were expressed as values relative to tetramethylsilane (TMS) by using the CH₃ line at 17.36 ppm of hexamethylbenzene as an external reference.

Differential scanning calorimetry (DSC) data of copolymer samples were recorded in the temperature range of $-120-250\ ^\circ\text{C}$ on a Perkin-Elmer DSC 8500 equipped with a liquid nitrogen cooling accessory under a helium flow of 20 mL/min. Samples of 3–5 mg were encapsulated in aluminum pans and heated from -100 to $+250\ ^\circ\text{C}$ at a rate of 20 $^\circ\text{C}/\text{min}$ (first heating scan). The melting temperature $(T_{\rm m})$ and enthalpy of fusion $(\Delta H_{\rm m})$ were determined from the DSC endotherms of first heating scan. The $T_{\rm m}$ value was taken as the peak temperature of the main endothermal peak. For measurement of the glass-transition temperature $(T_{\rm g})$, the samples were maintained at 250 $^\circ\text{C}$ for 1 min, and then rapidly quenched at $-120\ ^\circ\text{C}$. They were then reheated from -100 to $+250\ ^\circ\text{C}$ at a heating rate of 20 $^\circ\text{C}/\text{min}$ (second heating scan). The $T_{\rm g}$ was taken as the midpoint of the heat capacity change.

Thermogravimetric (TG) analysis was performed on a Seiko instruments TG/DTA 220U using nitrogen as a purge gas. About 3.0 mg of each sample was heated from room temperature to 500 °C at 20 °C/min. $T_{\rm dmax}$ is the temperature corresponding to the inflection point of the thermodegradation curves that corresponds to the maximum reaction rate.

Wide angle X-ray diffraction (WAXD) patterns of copolymer samples were recorded at 23 °C on a Rigaku RINT 2500 system using a nickel-filtered Cu K α radiation (λ = 0.154 nm; 40 kV; 100 mA) in the 2 θ range of 6 to 60° at a scanning speed of 2.0°/min. The crystallinity of copolymer samples was calculated from diffracted intensity data according to Vonk's method.⁴²

Synthesis of Dimeric Monomers. *Benzyl* (*R*)-*Lactate* (1: (*R*)-2*HP*-*Bn*). Methyl (*R*)-lactate (22.6 mL, 20.8 g, 200.0 mmol) was added to a solution of benzyl alcohol (104.0 mL, 108.0 g, 1.0 mol) and *p*-toluenesultanate (0.2 g, 1.0 mmol). The reaction mixture was stirred at 80 °C for 2 h, and the pressure was reduced subsequently at 9 kPa for 10 h. Diethyl ether (400 mL) was added, and an organic extracts were successively washed with saturated sodium hydrogen carbonate (2 × 200 mL), 5% sodium carbonate (4 × 50 mL), saturated sodium chloride (6 × 50 mL), dried over anhydrous magnesium sulfate, and evaporated. The crude product was distilled, to give a colorless oil (bp 1 kPa, 125–130 °C, 25.2 g, yield = 70%). ¹H NMR (CDCl₃, 500 MHz): δ 7.4–7.2 (m, SH, ArH), δ 5.21 (s, 2H, PhCH₂O), δ 4.31 (m, 1H, CH), δ 2.90 (d, *J* = 4.9 Hz, 1H, OH), δ 1.43 (d, *J* = 5.5 Hz, 3H, CH₃). Anal. CHN Calcd: C₁₀H₁₂O₃: C, 66.7; H, 6.7; N, 0.0. Found: C, 65.7; H, 6.7; N, 0.0.

Benzyl (S)-Lactate (2: (S)-2HP-Bn). Benzyl (S)-lactate was prepared following Wolfe et al.⁴³ 1,8-Diazobicyclo[5.4.0]undeca-7-ene (DBU) (90.0 mL, 94.5 g, 600.0 mmol) was added slowly with stirring to a solution of 90% (S)-lactic acid (59.4 mL, 54.0 g, 600.0 mmol) in methanol (250 mL). The solvent was removed under reduced pressure at 70–80 °C, and the resulting oil, in DMF (250 mL), was cooled to 15 °C. Benzyl bromide (59.5 mL, 85.5 g, 500.0 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 30 h. After removal of approximately 200 mL of solvent by vacuum

Scheme 1. Synthetic Procedures of Dimeric Monomers and Polymers with Alternating Sequences of (R)-3HB and 2HP Units



distillation, ethyl acetate (500 mL) was added, followed by water (150 mL). The aqueous layer was washed with ethyl acetate (3 × 150 mL), and the combined organic extracts were washed successively with water (150 mL), 5% citric acid (150 mL), water (150 mL), saturated sodium chloride (2 × 150 mL), dried over anhydrous magnesium sulfate, and evaporated. The crude product was distilled, to give a colorless oil (bp 1 kPa, 125–130 °C, 91.8 g, yield = 85%). ¹H NMR (CDCl₃, 500 MHz): δ 7.4–7.2 (m, 5H, ArH), δ 5.21 (s, 2H, PhCH₂O), δ 4.32 (m, 1H, CH), δ 2.89 (d, *J* = 5.9 Hz, 1H, OH), δ 1.43 (d, *J* = 7.1 Hz, 3H, CH₃). Anal. CHN Calcd: C₁₀H₁₂O₃: C, 66.7; H, 6.7; N, 0.0. Found: C, 65.5; H, 6.7; N, 0.0.

(R)-3-(tert-Butyldiphenylsilanyloxy)butanoic Acid (3: TBDPS-(R)-3HB). Methyl (R)-3-hydroxybutyrate (11.8 g, 100.0 mmol), triethylamine (20.2 g, 200.0 mmol), DMAP (6.1 g, 50.0 mmol), and dichloromethane (400 mL) were added under nitrogen to an 1 L oven-dried two-neck eggplant-shaped flask. After cooling the reaction mixture to 0 °C, TBDPSCl (30.2 g, 110.0 mmol) was added by syringe. The ice bath was removed and the reaction was stirred at room temperature overnight (24 h). The reaction mixture was filtered, and the filtrate was washed with 2 \times 300 mL 10% HCl, 2 \times 200 mL H₂O, and dried with MgSO₄. Removal of the solvent under vacuum gave a colorless oil (37.4 g). The resultant oil (37.4 g) was dissolved in THF (1500 mL) and cooled in an ice bath. LiOH·H₂O (9.4 g, 200.0 mmol) in 600 mL of H₂O was added dropwise for over 15 min. The ice bath was removed, and the reaction was stirred for 10 min. Water (100 mL) was added and the THF was removed under vacuum. The aqueous phase was extracted with 2×150 mL of ether to remove starting material, acidified using 1.0 M HCl, and then extracted with 2 \times 150 mL of ether. The second ethereal phase was dried with MgSO₄ and the solvent was removed to give a colorless oil, and recrystallized from hexane solution under isothermal condition at 4 °C (20.6 g, yield = 60%). ¹H NMR (CDCl₃, 500 MHz): δ 7.7–7.6 (m, 4H, ArH), δ 7.5–7.2 (m, 6H, ArH), δ 4.27 (m, 1H, CH), δ 2.49 (m, 2H, CH₂), δ 1.13 (d, J = 6.4 Hz, 3H, CH_3), δ 1.03 (s, 9H, CH_3). Anal. CHN Calcd: C20H26O3Si: C, 70.1; H, 7.7; N, 0.0. Found: C, 70.1; H, 7.7; N, 0.0.

(R)-2-[(R)-3-(tert-Butyldiphenylsilanyloxy)butoxy]propionic Acid Benzyl Ester (4: TBDPS-(R)-3HB-(R)-2HP-Bn). TBDPS-(R)-3HB (3) (34.3 g, 100.0 mmol), (R)-2HP-Bn (1) (18.0 g, 100 mmol), and DMAP (6.1 g, 50 mmol) were combined under nitrogen with 600 mL of methylene chloride. DCC (20.6 g, 100 mmol) was added, and the reaction was stirred for 18 h. The reaction mixture was filtered to remove DCU, and the filtrate was concentrated under vacuum. The crude oil was chromatographed over silica gel (5% ethyl acetate in hexanes) to give a colorless oil (37.8 g, yield = 75%). ¹H NMR (CDCl₃, 500 MHz): δ 7.7–7.6 (m, 4H, ArH), δ 7.5–7.2 (m, 11H, ArH), δ 5.14 (m, 2H, PhCH₂O), δ 5.03 (m, 1H, CH), δ 4.31 (m, 1H, CH), δ 2.55 (m, 2H, CH₂), δ 1.36 (d, J = 7.1 Hz, 3H, CH₃), δ 1.13 (d, J = 6.2 Hz, 3H, CH₃), δ 1.03 (s, 9H, CH₃). Anal. CHN Calcd: C₃₀H₃₆O₅Si: C, 71.4; H, 7.2; N, 0.0. Found: C, 71.3; H, 7.2; N, 0.0.

(S)-2-[(R)-3-(tert-Butyldiphenylsilanyloxy)butoxy]propionic Acid Benzyl Ester (5: TBDPS-(R)-3HB-(S)-2HP-Bn). In the same way as TBDPS-(R)-3HB-(R)-2HP-Bn (4), TBDPS-(R)-3HB-(S)-2HP-Bn (5) was prepared from TBDPS-(R)-3HB and (S)-2HP-Bn (2). The product was obtained as colorless oil (15.2 g, yield = 83%). ¹H NMR (CDCl₃, 500 MHz): δ 7.7–7.6 (m, 4H, ArH), δ 7.5–7.2 (m, 11H, ArH), δ 5.14 (m, 2H, PhCH₂O), δ 5.06 (m, 1H, CH), δ 4.31 (m, 1H, CH), δ 2.55 (m, 2H, CH₂), δ 1.46 (d, J = 7.1 Hz, 3H, CH₃), δ 1.12 (d, J = 6.1 Hz, 3H, CH₃), δ 1.02 (s, 9H, CH₃). Anal. CHN Calcd: C₃₀H₃₆O₅Si: C, 71.4; H, 7.2; N, 0.0. Found: C, 71.3; H, 7.3; N, 0.0.

(*R*)-2-[(*R*)-3-Hydroxybutoxy]propionic Acid Benzyl Ester (**6**: (*R*)-3HB-(*R*)-2HP-Bn). The diprotected dimeric monomer (4) (4.0 g, 8.0 mmol) and acetic acid (1.5 g, 25.0 mmol) were combined under nitrogen with 60 mL of THF. TBAF (1 M in THF) (12.0 mL) was added, and the reaction mixture was allowed to stir for 3 day at 50–60 °C. Brine (30 mL) was added and extracted with 2 × 40 mL with ether. The ethereal phase was washed with 3 × 30 mL saturated NaHCO₃, 2 × 30 mL H₂O, and dried with MgSO₄. The crude oil was chromatographed over silica gel (10% ethyl acetate in hexanes) to give a colorless liquid (5.8 g, yield = 72%). ¹H NMR (CDCl₃, 500 MHz): δ 7.4–7.2 (m, 5H, ArH), δ 5.19 (m, 2H, PhCH₂O), δ 5.19 (m, 1H, CH), δ 4.19 (m, 1H, CH), δ 3.22 (s, 1H, OH), δ 2.52 (m, 2H, CH₂), δ 1.50 (d, *J* = 7.1 Hz, 3H, CH₃), δ 1.24 (d, *J* = 6.4 Hz, 3H, CH₃). Anal. CHN Calcd: C₁₄H₁₈O₅: C, 63.2; H, 6.8; N, 0.0. Found: C, 62.1; H, 6.8; N, 0.0.

(*S*)-2-[(*R*)-3-(Hydroxybutoxy)]propanoic Acid Benzyl Ester (7: (*R*)-3HB-(*S*)-2HP-Bn). In the same way as (*R*)-3HB-(*R*)-2HP-Bn (6), (*R*)-3HB-(*S*)-2HP-Bn (7) was prepared from TBDPS-(*R*)-3HB-(*S*)-2HP-Bn (5). The product was a clear liquid (4.6 g, yield = 89%). ¹H NMR (CDCl₃, 500 MHz): δ 7.5–7.2 (m, 5H, ArH), δ 5.20 (m, 2H, PhCH₂O), δ 5.17 (m, 1H, CH), δ 4.26 (m, 1H, CH), δ 3.03 (s, 1H, OH), δ 2.54 (m, 2H, CH₂), δ 1.52 (d, *J* = 13.5 Hz, 3H, CH₃), δ 1.24 (d, *J* = 12.0 Hz, 3H, CH₃). Anal. CHN Calcd: C₁₄H₁₈O₅: C, 63.2; H, 6.8; N, 0.0. Found: C, 62.4; H, 6.8; N, 0.0.

(R)-2-[(R)-3-(Hydroxybutoxy)]propanoic Acid (8: (R)-3HB-(R)-2HP). The benzyl dimeric monomer (6) (266.0 g, 10.0 mmol) was hydrogenated by a flow reactor, using an EYELA CCR-1000G system with 10% Pd on silica and an Air-tech NM-H-100. Hydrogen gas was used at a flow rate of 10.0 mL/min, ethanol was used as an eluent at a flow rate of 0.5 mL/min, and a concentration of 0.1 M was applied. After reaction, the solvent was removed to give a colorless oil (1.75 g,

Table 1. Molecular	Weights of A	Iternating Cope	olymers of (R)	-3HB and 2	2HP Units

	dimeric monomer feed ratio (mol %)		dimeric monomer composition $(mol \ \%)^a$			molecular weight b	
sample	(R)-3HB-(R)-2HP	(R)-3HB-(S)-2HP	(R)-3HB-(R)-2HP	(R)-3HB-(S)-2HP	yield (%)	$\frac{M_{\rm n}}{(\times 10^3 {\rm g/mol})}$	$M_{\rm w}/M_{\rm n}$
P[(R)-3HB-alt-(S)-2HP] $(R/S = 0/100)$	0	100	0	100	41	72	1.5
P[(R)-3HB-alt-(R,S)-2HP] (R/S = 33/67)	33	67	37	63	42	54	1.3
P[(R)-3HB-alt-(R,S)-2HP] (R/S = 50/50)	50	50	54	46	37	46	1.5
P[(R)-3HB-alt-(R,S)-2HP] (R/S = 67/33)	67	33	64	36	78	32	1.8
P[(R)-3HB-alt-(R,S)-2HP] (R/S = 75/25)	75	25	72	28	57	20	1.7
P[(R)-3HB-alt-(R)-2HP] (R/S = 100/0)	100	0	100	0	77	7	2.0

^aDetermined from ¹H NMR spectra. ^bDetermined by GPC measurements.

yield = 99%). ¹H NMR (CDCl₃, 500 MHz): δ 5.19 (m, 1H, CH), δ 4.27 (m, 1H, CH), δ 2.56 (m, 2H, CH₂), δ 1.56 (d, J = 7.0 Hz, 3H, CH₃), δ 1.28 (d, J = 6.5 Hz, 3H, CH₃). Anal. CHN Calcd: C₇H₁₂O₅: C, 47.7; H, 6.9; N, 0.0. Found: C, 45.5; H, 6.9; N, 0.0.

(S)-2-[(R)-3-(Hydroxybutoxy)]propanoic Acid (9: (R)-3HB-(S)-2HP). In the same way as (R)-3HB-(R)-2HP (8), (R)-3HB-(S)-2HP (9) was prepared from (R)-3HB-(S)-2HP-Bn (7). The product was a colorless oil (2.29 g, yield = 100%). ¹H NMR (CDCl₃, 500 MHz): δ 5.19 (m, 1H, CH), δ 4.28 (m, 1H, CH), δ 2.54 (m, 2H, CH₂), δ 1.52 (d, *J* = 7.5 Hz, 3H, CH₃), δ 1.24 (d, *J* = 4.0 Hz, 3H, CH₃). Anal. CHN Calcd: C₇H₁₂O₅: C, 47.7; H, 6.9; N, 0.0. Found: C, 46.8; H, 6.9; N, 0.0.

Condensation of Dimeric Monomers. 3HB-2HP dimeric monomer (176.0 mg, 1.0 mmol) was added to 1 mL of methylene chloride. DPTS (64.7 mg, 0.2 mmol) was added, and the reaction mixture cooled to 0 °C. Then, DIC (189.3 mg, 232 μ L, 1.5 mmol) was added slowly for over 1 min. The reaction mixture was allowed to stir for 5 h at room temperature (25 °C). The urea was removed by filter, then taken up in methylene chloride and precipitated in cool 2-propanol (IPA).

RESULTS AND DISCUSSION

Synthesis of Alternating Copolymers of P[(*R*)-3HB-*alt*-2HP]. The dimeric monomers of (*R*)-3HB and 2HP were synthesized by coupling reaction of benzyl lactate with silyl protected 3-hydroxybutanoic acid in the presence of DCC and DMAP, according to the method reported by Meyer et al.,³⁷ with modification of the conditions as necessary (see Scheme 1). Two types of stereoisomeric dimers ((*R*)-3HB-(*R*)-2HP and (*R*)-3HB-(*S*)-2HP) were obtained by selecting the enantiomer of the lactate monomer. By mixing the stereoisomers, dimeric monomers with different stereocompositions were prepared.

Polymerization of dimeric monomers was carried out by using condensation reaction in the presence of DIC/DPTS as a condensation agent.⁴¹ As the condensation reaction progressed, solidified urea was generated in the reaction mixture. The polymer products were still soluble in methylene chloride after the removal of urea by filtration. The polymer solution was poured into cold 2-propanol to precipitate as a solid product. Table 1 lists the polymerization results of stereoisomeric (*R*)-3HB-2HP dimeric monomers. Polymer yields were varied from 37 to 78%. Except for the product from (*R*)-3HB-(*R*)-2HP dimeric monomer yields were soluble in methylene chloride or chloroform. However, the polymer from (*R*)-3HB-(*R*)-2HP dimeric monomer became to be insoluble in methylene chloride or chloroform once it was solidified. The

solidified polymer of (R)-3HB-(R)-2HP was dissolved in a mixture solution of chloroform with 7.5% HFIP. The numberaverage molecular weights $(M_{\rm n})$ and polydispersities $(M_{\rm w}/M_{\rm n})$ of the samples were determined from GPC analysis and ranged from 7000 to 72 400 g/mol and from 1.3 to 2.0 by using a polystyrene calibration, respectively. For the polymer obtained from (R)-3HB-(S)-2HP dimeric monomer, the sample was subjected to GPC analysis without precipitation treatment in cool 2-propanol. Both the $M_{\rm p}$ and $M_{\rm w}/M_{\rm p}$ values of crude sample were almost identical with those of purified sample by precipitation. This result indicates that the polymerization of (R)-3HB-(S)-2HP dimeric monomer facilely gives product with higher molecular weight than that of (R)-3HB-(R)-2HP dimeric monomer. The M_n values of samples tended to decrease with an increase of feed ratio of (R)-3HB-(R)-2HP dimeric monomer.

Sequence structure of the obtained copolymers was examined by ¹H and ¹³C NMR analyses. Figures 1 and 2 show ¹H and ¹³C NMR spectra of the polymers obtained from 3HB-2HP dimeric monomers, respectively. As previously reported,³² the majority of both proton and carbon resonances



Figure 1. 500 MHz ¹H NMR spectra of P[(R)-3HB-alt-2HP] alternating copolymer in $CDCl_3$ containing 7.5% HFIP at 25 °C. Key: (a) P[(R)-3HB-alt-(R)-2HP], (b) P[(R)-3HB-alt-(S)-2HP], and (c) P[(R)-3HB-alt-(R,S)-2HP] (R/S = 50/50).



Figure 2. 125 MHz ¹³C NMR spectra of P[(R)-3HB-*alt*-2HP] alternating copolymer in CDCl₃ containing 7.5% HFIP at 25 °C. Key: (a) P[(R)-3HB-*alt*-(R)-2HP], (b) P[(R)-3HB-*alt*-(S)-2HP], and (c) P[(R)-3HB-*alt*-(R,S)-2HP] (R/S = 50/50).

for the random copolymers of 3HB and 2HP units were split into multiple peaks due to diad or triad sequences of 3HB and 2HP units (see Figures S1 and S2 in the Supporting Information). On the other hand, the polymers obtained from 3HB-2HP dimeric monomers in this paper exhibited the simple signals in each resonance. This result indicates that the polymers have an alternating sequence of (R)-3HB and 2HP units. Here, it is of important to note that the chemical shifts of signals arising from the identical functional group were different between the polymers obtained from (R)-3HB-(R)-2HP and (R)-3HB-(S)-2HP dimeric monomers. Especially, significant differences in the chemical shifts were detected at the signals from methyl group of 2HP units in proton resonance and signals from methylene group of (R)-3HB units in carbon resonance, and the gaps between chemical shifts of two stereoisomeric polymers were 0.04 ppm in proton resonance of methyl group of 2HP units and 0.25 ppm in carbon resonance of methylene group of (R)-3HB units, respectively. In the NMR spectra for the polymers obtained from a mixture of (R)-3HB-(R)-2HP and (R)-3HB-(S)-2HP dimeric monomers, the characteristic signals from both stereoisomers were detected. From the peak intensities of the signals, it was confirmed that the stereoisomeric compositions of the obtained polymers were in good agreement with the dimeric monomer feed ratios. The signals from methylene group of (R)-3HB units in carbon resonance were split into totally four peaks, and it was attributed to the difference in stereosequence of 2HP units adjoining both sides of (R)-3HB unit.

Physical Properties of Alternating Copolymers of P[(*R*)-3HB-*alt*-2HP]. Thermal properties of alternating copolymers of (*R*)-3HB and 2HP units were determined by DSC. Figure 3 shows typical DSC thermograms of P[(*R*)-3HB-*alt*-2HP] samples. All of the copolymers with alternating sequence structure showed melting behavior during the first heating scan. The values of melting temperatures (T_m) and heat of fusion (ΔH_m) are summarized in Table 2. The T_m value of P[(*R*)-3HB-*alt*-(*S*)-2HP] was detected at 83 °C. On the other hand, the P[(*R*)-3HB-*alt*-(*R*)-2HP] had the T_m at 233 °C, and the value was much higher than those of homopolymers of (*R*)-



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Figure 3. DSC thermograms of alternating copolymer samples at a heating rate of 20 °C: (A) first heating scans and (B) second heating scans after rapid quenching from the melt at 250 °C. Key: (a) P[(R)-3HB-*alt*-(R)-2HP], (b) P[(R)-3HB-*alt*-(S)-2HP], and (c) P[(R)-3HB-*alt*-(R,S)-2HP] (R/S = 50/50).

3HB and 2HP and was comparable to those of poly-(glycolate)²¹ and stereocomplex poly(lactate).¹⁹ It was found that the random copolymers of (R)-3HB and 2HP units with almost equimolar composition were completely amorphous. Therefore, the precise regulation of sequential structure as alternating manner brought about the crystallization of copolymer chains. For the samples prepared from a mixture of (R)-3HB-(R)-2HP and (R)-3HB-(S)-2HP dimeric monomers, the $T_{\rm m}$ values increased linearly from 53 to 174 °C as the (R)-3HB-(R)-2HP dimeric monomer feed ratio was increased from 33 to 75 mol % (see Figure 4A). The $\Delta H_{\rm m}$ values also increased with an increase in the (R)-3HB-(R)-2HP dimeric monomer feed ratio (Figure 4B). These results indicate that the incorporation of stereoisomeric dimer inhibits the formation of crystalline state composed of the repeating sequences of the other stereoisomeric dimers. Thus, by selecting the combinations of the enantiomeric 3HB and 2HP monomers, the melting temperatures of the copolymers with alternating sequence structure varied in the wide range.

For the samples with (R)-3HB-(R)-2HP dimeric monomer contents less than 67 mol %, the change in heat capacity corresponding to the glass transition phenomenon could be

Table 2. Thermal Properties and X-ray Crystallinities of Alternating Copolymer Samples

	thermal properties					
sample	T_{g}^{a} (°C)	$T_{\rm m}^{\ b}$ (°C)	$\Delta H_{\rm m}^{\ c}$ (J/g)	T_{dmax}^{d} (°C)	crystallinity, X_c^{e} (%)	
P[(R)-3HB-alt-(S)-2HP] (R/S = 0/100)	18	84	41	300	57 ± 5	
P[(R)-3HB-alt-(R,S)-2HP] (R/S = 33/67)	14	53	2	296	7 ± 5	
P[(R)-3HB-alt-(R,S)-2HP] (R/S = 50/50)	19	126	14	298	24 ± 5	
P[(R)-3HB-alt-(R,S)-2HP] (R/S = 67/33)	21	151	42	299	37 ± 5	
P[(R)-3HB-alt-(R,S)-2HP] (R/S = 75/25)	n.d. ^f	174	78	301	48 ± 5	
P[(R)-3HB-alt-(R)-2HP] (R/S = 100/0)	n.d.	233	116	304	78 ± 5	
P[(R)-3HB-co-47 mol %(R)-2HP]	15	n.d.	0	300	n.m. ^g	
P[(R)-3HB]	4	176	96	299	74 ± 5	
P[(S)-2HP]	60	176	43	378	47 ± 5	

^{*a*}Glass-transition temperature; measured by DSC (second scan) from -100 to 250 °C at a rate of 20 °C/min. ^{*b*}Melting temperature; measured by DSC (first scan) from -120 to 250 °C at a rate of 20 °C/min. ^{*c*}Enthalpy of fusion; measured by DSC (first scan). ^{*d*}Thermal degradation; measured by TG analysis from 25 to 500 °C at a rate of 20 °C/min. ^{*c*}Degree of crystallinity; determined from X-ray diffraction patterns. ^{*J*}Not detected. ^{*g*}Not measured.



Figure 4. Effect of stereocomposition of dimeric monomer on the melting temperature (A) and the heat of fusion (B) of alternating copolymer samples.

detected in the DSC endotherms of second heating scan. The $T_{\rm g}$ values of copolymers were in the range from 14 to 21 °C. However, the $T_{\rm g}$ could not be detected in the DSC thermograms for the samples with (*R*)-3HB-(*R*)-2HP dimeric monomer contents over than 75 mol %, since the crystallization took place during the cooling process from the melt state at 250 °C.

As well as the random copolymers of (R)-3HB and 2HP units mentioned above, the most of copolymers with a random sequence of almost equimolar two monomeric units become to be amorphous. However, the polymer obtained from the equimolar mixture of (R)-3HB-(R)-2HP and (R)-3HB-(S)-2HP dimeric monomers formed crystalline state and showed relative high melting temperature. As shown in Figure 2, in the ¹³C NMR spectrum for the polymer obtained from the equimolar mixture of (R)-3HB-(R)-2HP and (R)-3HB-(S)-2HP dimeric monomers, the methylene carbon signals of (R)-3HB units were split into four peaks corresponding to the different stereosequence of 2HP units adjoining both sides of (R)-3HB unit. Since the peak intensities of each sequence were not equivalent, the obtained polymer rather had blocking tendency repeating the identical stereoisomeric dimers than random sequence. Taking account of the difference in solubility of precipitated polymers in methylene chloride, it was expected that the dispersibility of resultant oligomers in the reaction mixture changed during the polymerization dependent on both the degree of condensation and the sequence of stereoisomeric dimers. As a result, the sequential distribution of the polymers

from a mixture of (R)-3HB-(R)-2HP and (R)-3HB-(S)-2HP dimeric monomers was inclined to have blocking tendency.

The thermal degradation profiles of alternating copolymers of P[(R)-3HB-alt-2HP] were examined by TG analysis. The temperatures of maximum degradation rate (T_{dmax}) were in the range from 296 to 304 °C for the alternating copolymers of P[(R)-3HB-alt-2HP]. It is well-known that the degradation of P[(R)-3HB] occurs exclusively via random chain scission reaction (*cis*-elimination), which has a six-membered ring ester intermediate.44 On the other hand, the dominant thermal decomposition of PLLA (P[(S)-2HP]) progresses via cyclic rupture of polymer molecules by unzipping reaction from the hydroxyl chain-end or/and random intramolecular transesterification at the main-chain.⁴⁵ The T_{dmax} values of the alternating copolymers of P[(R)-3HB-alt-2HP] were very close to that of P[(R)-3HB] (299 °C), rather than P[(S)-2HP] (374 °C). Therefore, it was expected that the chain scission by ciselimination occurred at the (R)-3HB units in the alternating copolymers molecules during thermal degradation.

Figure 5 shows the X-ray diffraction patterns of alternating copolymer samples, together with those of P[(R)-3HB] and P[(S)-2HP]. The diffraction patterns of P[(R)-3HB] and



Figure 5. Wide-angle X-ray diffraction patterns of alternating copolymers.

P[(S)-2HP] showed typical reflections arising from the α -forms of the P[(R)-3HB] and P[(S)-2HP] crystalline lattice, respectively. The alternating copolymer samples revealed different patterns from neither P[(R)-3HB] nor P[(S)-2HP]. In addition, the diffraction patterns were quite different between the two types of copolymers composed of (R)-3HB-(R)-2HP and (R)-3HB-(S)-2HP dimeric monomers (see the calculated *d*-spacing values listed in Table S2 of Supported Information). Since the crystalline structure of these alternating copolymers have not been characterized, further investigation on the relationship between the thermal properties and crystalline structure of these samples is necessary. However, it is concluded that both the (R)-3HB and 2HP units participate into the formation of crystalline region by repeating the alternating sequence. The degrees of X-ray crystallinity (X_c) of alternating copolymers samples are also listed in Table 2. The X_c values of P[(R)-3HB-alt-2HP] samples decreased from 78% to 7% as the fraction of (R)-3HB-(S)-2HP dimeric monomers was increased from 0 to 67 mol %. The X_c value of P[(R)-3HBalt-(S)-2HP] sample was 73%.

Figure 6 shows high-resolution solid-state CP/MAS 13 C NMR spectra of P[(R)-3HB-alt-(R)-2HP] and P[(R)-3HB-alt-



Figure 6. Cross-polarization magic-angle spinning ¹³C NMR spectra of alternating copolymers of P[(R)-3HB-*alt*-(R)-2HP] (a) and P[(R)-3HB-*alt*-(S)-2HP] (b).

(S)-2HP]. In both of the P[(R)-3HB-*alt*-(R)-2HP] and P[(R)-3HB-alt-(S)-2HP], the carbonyl signals from (R)-3HB and 2HP units were overlapped, and the single peak was detected. The chemical shifts of carbonyl resonances were differed P[(R)-3HB-alt-(R)-2HP] and P[(R)-3HB-alt-(S)-2HP] samples. The carbonyl signal of P[(R)-3HB-alt-(R)-2HP] was shifted around 2 ppm toward lower magnetic field, compared with that of P[(R)-3HB-alt-(S)-2HP]. The peak of methylene group of (R)-3HB units also appeared at different chemical shifts between the P[(R)-3HB-alt-(R)-2HP] and P[(R)-3HB-alt-(R)-2HP]alt-(S)-2HP]. In contrast to the carbonyl groups, the chemical shifts of methylene group were shifted 3 ppm toward higher magnetic field as changing from connecting with (R)-2HP to with (S)-2HP units. The differences in chemical shifts of resonance from the identical functional groups were also detected in the ¹³C NMR spectra of solution dependent on configuration of 2HP units (see Figure 2), however, the gaps in

the chemical shifts in the solution state were quite smaller than those in the solid-state. This result suggests that the differences in the chemical shifts in the solid-state CP/MAS ¹³C NMR spectra are predominantly attributed to the conformational structure of monomeric units in the crystalline states.

CONCLUSION

Novel alternating copolymers of (R)-3HB and 2HP units were synthesized by condensation reaction of stereoisomeric dimers of (R)-3HB-(R)-2HP and (R)-3HB-(S)-2HP. The effects of enantiomeric structure of 2HP units and stereocomposition of dimeric monomers on the thermal properties and crystalline structure of alternating copolymers were investigated. Precisely regulated alternating sequence of (R)-3HB and 2HP units were crystallizable, and the formed crystals had different structure from both P[(R)-3HB] and P[(S)-2HP] crystals. The melting of the crystalline region for alternating copolymers varied in the wide range of temperatures depending on both the enantiomeric structure of 2HP units and stereocomposition of dimeric monomers. In particular, the melting temperature of P[(R)-3HB-alt-(R)-2HP] was reached to 233 °C, and the copolymers was one of the aliphatic polyesters with highest melting temperature. Further work to obtain details in crystalline structure of alternating copolymers is currently underway.

ASSOCIATED CONTENT

Supporting Information

¹H and ¹³C NMR spectra and tables of chemical shifts of alternating copolymers and interplanar *d*-spacing values measured from X-ray diffraction patterns of copolymer samples. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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