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Stereocomplex Formation between Enantiomeric Substituted Poly(lactide)s: Blends of Poly[(*S*)-2-hydroxybutyrate] and Poly[(*R*)-2-hydroxybutyrate]

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Introduction. When the interaction between polymers having different tacticities or configurations prevails over that between those having the same tacticity or configuration, a stereoselective association of the former polymer pair takes place. Such association is described as stereocomplexation or a stereocomplex formation and some pairs of optically inactive isotactic and syndiotactic polymers and of optically active *S*- and *R*- polymers (or L- and D- polymers) are reported to form a stereocomplex.[1−4] With respect to enantiomeric, optically active polyester blends, Grenier and Prud'homme first reported stereocomplexation between *S*- and *R*-poly(α-methyl-α-ethyl-β-propiolactone)s (PMEPLs).[5] The monomer of PMEPL, 2-hydroxymethyl-2-methyl-butanoic acid, is a β-hydroxycarboxylic acid with a chiral α-carbon. Later, Ikada et al. found stereocomplexation between poly[(*S*)-lactide] (PSLA) and poly[(*R*)-lactide] (PRLA).[6] The monomer of poly(lactide) (PLA), lactic acid (2-hydroxypronanoic acid), is an α-hydroxycarboxylic acid with a chiral α-carbon. Although these polyesters, PMEPL and PLA, have chiral α-carbons, Voyer and Prud'homme reported stereocomplexation between *S*- and *R*-polyesters with chiral β-carbons, poly(β-proriolactone)s with different side groups containing chlorides.[7] The monomers of these polymers are β-hydroxycarboxylic acids with chiral β-carbons.

The stereocomplex of enantiomeric, optically active polyesters has a melting temperature (T_m) much higher than that of either pure *R*- or *S*-polyesters and a crystalline lattice which is completely different from that of constituent polyesters.[1−4,8] In regard to biodegradable polyester stereocomplexes, intensive studies have been carried out for the PLA stereocomplex,[1−4] which can be formed by various methods, including the crystallization of stereoblock copolymers.[9−14] On the other hand, poly(2-hydroxybutyrate) [P(2HB)], i.e., poly(2-hydroxybutyric acid) or poly(2-hydroxybutanoic acid) can be synthesized from α-hydroxycarboxylic acid with a chiral α-carbon (2-hydroxybutanoic acid). P(2HB) has the structure of PLA, the methyl group of which is substituted with an ethyl group (Figure 1). P(2HB) is susceptible to hydrolytic degradation and, therefore, can be utilized as a biodegradable material for biomedical, pharmaceutical, and environmental applications.[15] Baker et al. intensively synthesized a wide variety of substituted PLAs, including P(2HB), and investigated their physical properties and thermal degradation.[16−18] In their study, most of the synthesized polymers were racemic, optically inactive, and noncrystallizable.

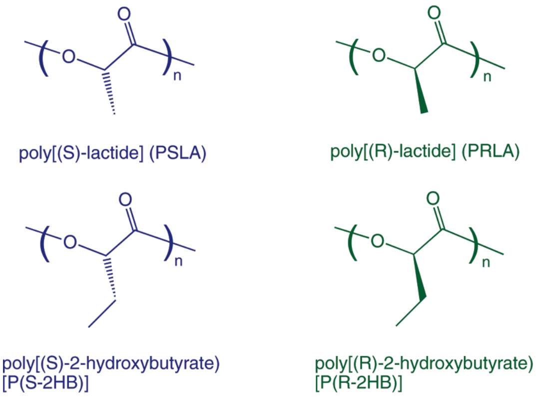

Figure 1. Molecular structures of PSLA [i.e., poly(L-lactide) (PLLA)], PRLA [i.e., poly(D-lactide) (PDLA)], P(*S*-2HB), and P(*R*-2HB).

In the present study, we synthesized enantiomeric, optically active, and crystallizable poly[(*S*)-2-hydroxybutyrate] [P(*S*-2HB)] and poly[(*R*)-2-hydroxybutyrate] [P(*R*-2HB)] by a conventional polycondensation method and herewith first report stereocomplexation between P(*S*-2HB) and P(*R*-2HB).

Experimental Section. *Materials.* The P(*S*-2HB) [number-average molecular weight (M_n) $= 3.3 \times 10^3$ g mol^{-1}, weight-average molecular weight (M_w)/M_n = 3.9] and P(*R*-2HB) ($M_n = 3.6 \times 10^3$ g mol^{-1}, $M_w/M_n = 3.7$) were synthesized by polycondensation of (*S*)- and (*R*)-2-hydroxybutanoic acids (hydroxybutyric acids) (≥97.0%, enantiomeric ratio ≥ 99:1, Sigma-Aldrich Co.), respectively,[19] and purified[20,21] according to the previous literature.

Pure polymers and blend specimens were prepared by solution casting with dichloromethane and dried according to the previously reported method.[20,21] We call the thus prepared specimens "solution-crystallized specimens". Melt-crystallization of the solution-crystallized specimens sealed under reduced pressure was carried out at crystallization temperatures (T_c) of 70 (pure polymers) and 130 °C (blends) for 10 h after melting at 130 (pure polymers) and 240 °C (blends) for 5 min. These T_c were set below the T_m of the respective specimens. However, the T_c of 130 °C was selected to be the polymerization temperature to avoid thermal degradation during crystallization. We call the thus prepared specimens "melt-crystallized specimens".

Physical Measurements and Observation. The M_w and M_n of the polymers were evaluated in chloroform at 40 °C using a Tosoh (Tokyo, Japan) GPC system. The specific optical rotation ($[\alpha]^{25}{}_{589}$) values of P(*S*-2HB) and P(*R*-2HB) were −117 and 114 deg dm^{-1} g^{-1} cm^3, respectively, confirming the high optical activity of the synthesized polymers. In addition to the increased molecular weights of P(*S*-2HB) and P(*R*-2HB) compared to those of the monomers, further evidence for polymerization of 2-hydroxybutanoic acid was the methine peak shift of the ^{1}H NMR spectra from 4.3 ppm of the monomer to 5.1 ppm of the polymer. Similar methine peak shifts were observed for the polymerization of lactic acid[22] and phenyllactic acid.[19] The thermal properties of the specimens were determined with a Shimadzu (Kyoto, Japan) DSC-50 differential scanning calorimeter under a nitrogen gas flow. The specimens were heated from 0 to 240 °C at a rate of 10 °C min^{-1}. Wide-angle X-ray scattering (WAXS) was carried out at 25 °C using a Rigaku (Tokyo, Japan)

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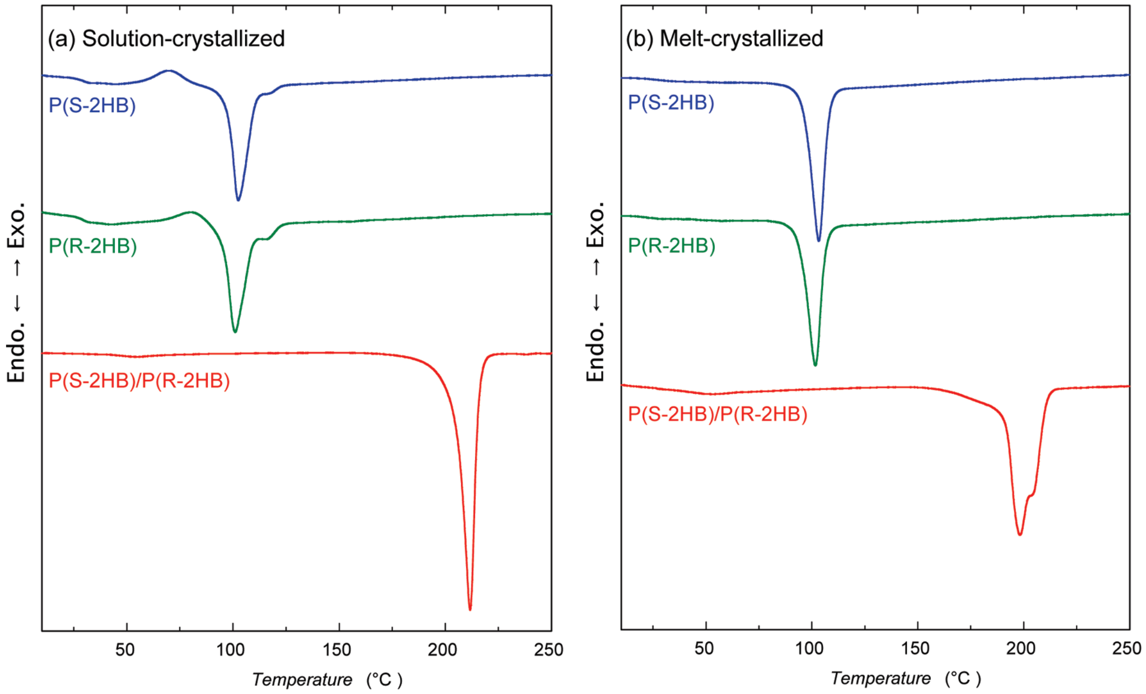

Figure 2. DSC thermograms of solution-crystallized (a) and melt-crystallized (b) pure P(*S*-2HB), P(*R*-2HB), and P(*S*-2HB)/P(*R*-2HB) blends.

RINT-2500 equipped with a Cu Kα source ($\lambda = 0.1542$ nm). Spherulite growth in the specimens was observed using an Olympus (Tokyo, Japan) polarized optical microscope (BX50) equipped with a Linkam (Surrey, U.K.) heating−cooling stage (LK-600PM) under a constant nitrogen gas flow. The crystallization of the specimens was observed as follows. The specimens were first heated at 100 °C min^{-1} to 130 (pure polymers) and 240 °C (blends), held at these temperatures for 5 min, and cooled at 100 °C min^{-1} to the T_c of 70 (pure polymers) and 130 °C (blends), at which temperatures crystallization was observed. Further information for the synthetic procedure and characterization is available as Supporting Information.

Results and Discussion. *Differential Scanning Calorimetry*. Figure 2 shows the DSC thermograms of the P(2HB) specimens. The glass transition, cold crystallization, and melting were respectively observed at 20−30, 70−80, and 100−120 °C for the solution-crystallized pure P(*S*-2HB) and P(*R*-2HB), whereas the melt-crystallized pure P(*S*-2HB) and P(*R*-2HB) had broad glass transition and sharp melting peaks, but no cold crystallization peak. The thermal properties of the P(2HB) specimens obtained from Figure 2 are summarized in Table S1, together with those of pure PLLA ($M_n = 2.7 \times 10^3$ g mol^{-1}), PDLA ($M_n = 3.0 \times 10^3$ g mol^{-1}), and PLLA/PDLA blends having M_n values similar to those of the P(2HB) specimens. The T_m of pure P(*S*-2HB) and P(*R*-2HB) (ca. 100 °C) are comparable to those of pure PLLA and PDLA (ca. 110 °C) when compared at similar molecular weights. On the other hand, solution- and melt-crystallized P(*S*-2HB)/P(*R*-2HB) blends had glass transition peaks at around 40 °C and melting peaks at around 200 °C. It is interesting to note that no melting peak at around the T_m of pure P(*S*-2HB) and P(*R*-2HB) (ca. 100 °C) was observed for the P(*S*-2HB)/P(*R*-2HB) blends and the observed T_m of 212 and 198 °C for the solution- and melt-crystallized P(*S*-2HB)/P(*R*-2HB) blends were about 100 °C higher than the T_m of pure P(*S*-2HB) and P(*R*-2HB). This is consistent with the fact that the T_m of the PLLA/PDLA stereocomplex (ca. 190 °C) was much higher than those of pure PLLA and PDLA (ca. 110 °C) (Table S1). These results strongly suggest that a stereocomplex was formed by blending P(*S*-2HB) with P(*R*-2HB).

Wide-Angle X-ray Scattering. Figure 3 shows the WAXS profiles of the P(2HB) specimens. The two most intensive crystalline diffractions were observed at 14.7° (the highest) and 17.2° (the second highest) for pure P(*S*-2HB) and P(*R*-2HB), which diffraction profiles (and, therefore, lattice types) are similar to those of pure PLLA and PDLA, although the crystalline diffractions of the α- and α′-forms of pure PLLA and PDLA were observed at higher angles of 16.7° (the highest) and 19.0° (the second highest).[8] Meanwhile, new crystalline diffraction peaks at 10.7° (the highest), 18.5° [19.3° (subpeak)] (the second highest), and 21.5° (the third highest), which are completely different from those of pure P(*S*-2HB) and P(*R*-2HB), were observed for the P(*S*-2HB)/P(*R*-2HB) blends. In addition to the elevated T_m of P(*S*-2HB)/P(*R*-2HB) blends compared to those of pure P(*S*-2HB) and P(*R*-2HB), the appearance of completely different crystalline diffraction peaks indicated the formation of a new cocrystal (stereocomplex) structure between P(*S*-2HB) and P(*R*-2HB). The diffraction profile of the P(*S*-2HB)/P(*R*-2HB) stereocomplex is very similar to that of the PLLA/PDLA stereocomplex, suggesting similar lattice types, although the crystalline diffractions of the PLLA/PDLA stereocomplex were observed at higher angles of 11.9° (the highest), 20.7° (the second highest), and 24.0° (the third highest). Probably due to the fact that the ethyl side group of P(2HB) is bulkier than that of the methyl side group of PLA, the interplane distance (*d*) values are higher for P(2HB) specimens than for PLA specimens (Table S2). It is noteworthy that the enantiomeric, optically active poly[(*S*)-3-hydroxybutyrate] and poly[(*R*)-3-hydroxybutyrate][23,24] [isomers of P(*S*-2HB) and P(*R*-2HB)] and poly[(*S*)-3-hydroxyvalerate] and poly[(*R*)-3-hydroxyvalerate],[24] the monomers of which are *β*-hydroxycarboxylic acids with chiral *β*-carbons, are not reported to form stereocomplexes even when they coexist.

Polarized Optical Microscopy. Figure 4 shows polarized optical photomicrographs of P(2HB) specimens crystallized from the melt. Here, the photos for pure P(*R*-2HB) are not shown, because its morphology was very similar to that of pure P(*S*-2HB). The spherulites of pure P(*S*-2HB) appeared

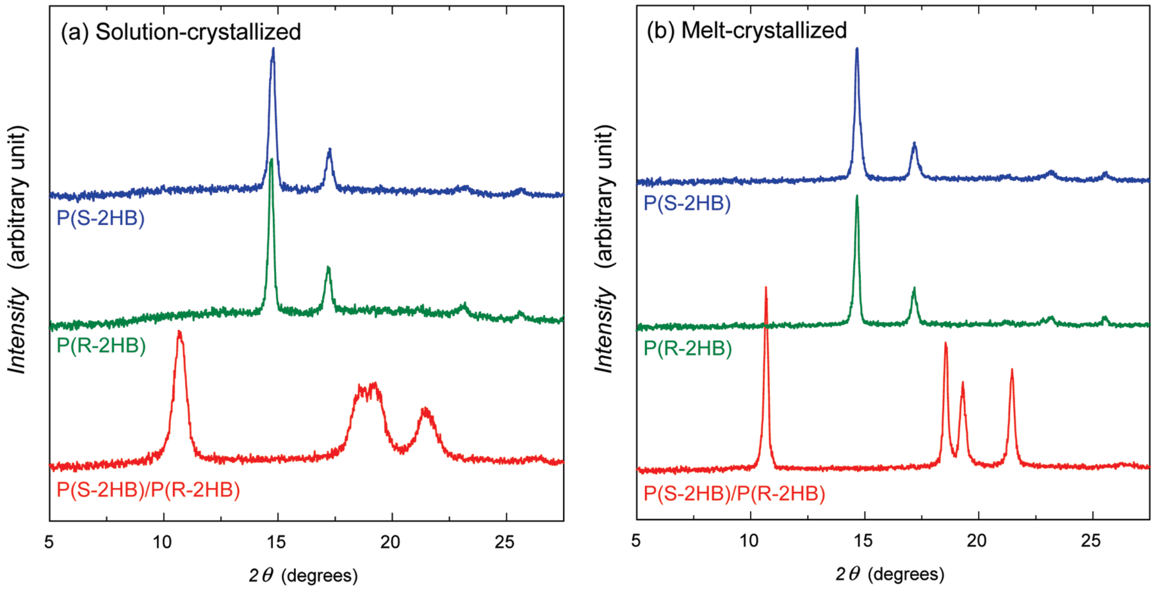

Figure 3. WAXS profiles of solution-crystallized (a) and melt-crystallized (b) pure P(*S*-2HB), P(*R*-2HB), and P(*S*-2HB)/P(*R*-2HB) blends.

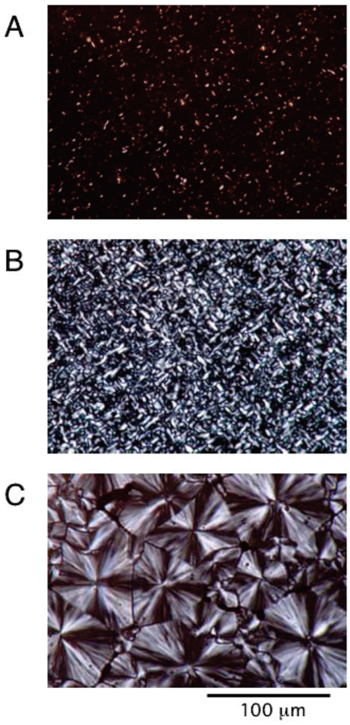

Figure 4. Polarized optical photomicrographs of pure P(*S*-2HB) crystallized at 70 °C for 2.5 (A) and 5 min (B) and a P(*S*-2HB)/P(*R*-2HB) blend crystallized at 130 °C for 0.5 min (C).

at 0.5 min of crystallization (photo not shown here) and the specimen became completely occupied by spherulites with the highest maximum radius of as low as 10 μm in 5 min. Meanwhile, the growth of stereocomplex spherulites started without any induction periods and the specimen was completely occupied by spherulites with the highest maximum radius of about 50 μm in 0.5 min. Such rapid completion of overall crystallization was observed for the PLA stereocomplex when it was crystallized from the melt.[20,25] The spherulites of the P(*S*-2HB)/P(*R*-2HB) stereocomplex had normal Maltese crosses, as reported for the stereocomplexes of PMEPL[5] and PLA.[20,25]

In conclusion, the present study revealed that stereocomplexation in solution and in bulk takes place between enantiomeric P(*S*-2HB) and P(*R*-2HB) and that the T_m of the P(*S*-2HB)/P(*R*-2HB) stereocomplex was ca. 100 °C higher than that of pure P(*S*-2HB) and P(*R*-2HB). Moreover, spherulites with normal Maltese crosses were observed for the P(*S*-2HB)/P(*R*-2HB) stereocomplex.

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Supporting Information Available: Appendices for the synthetic procedure and characterization of P(*S*-2HB) and P(*R*-2HB), the thermal properties of the P(*S*-2HB), P(*R*-2HB), P(*S*-2HB)/P(*R*-2HB) stereocomplexes, PLLA, PDLA, and the PLLA/PDLA stereocomplex during heating from 0 °C (Table S1), and the interplane distance (*d*) values of the P(*S*-2HB), P(*R*-2HB), P(*S*-2HB)/P(*R*-2HB) stereocomplex crystals, assuming that the P(2HB) specimens have the same crystalline lattice types as those of the PLA specimens, together with those of the PLA specimens (Table S2). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Slager, J.; Domb, A. J. *Adv. Drug Delivery Rev.* **2003**, *55*, 549–583.
(2) Tsuji, H. *Macromol. Biosci.* **2005**, *5*, 569–597.
(3) Fukushima, K.; Kimura, Y. *Polym. Int.* **2006**, *55*, 626–642.
(4) Tsuji, H., Ikada, Y., In *Biodegradable Polymer Blends from Renewable Resources*, Yu, L., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2009; p 165.
(5) Grenier, D.; Prud’homme, R. E. *J. Polym. Sci. Polym. Phys. Ed.* **1984**, *22*, 577–587.
(6) Ikada, Y.; Jamshidi, K.; Tsuji, H.; Hyon, S.-H. *Macromolecules* **1987**, *20*, 904–906.
(7) Voyer, R.; Prud’homme, R. E. *Eur. Polym. J.* **1989**, *25*, 365–369.
(8) Okihara, T.; Tsuji, M.; Kawaguchi, A.; Katayama, K.; Tsuji, H.; Hyon, S.-H.; Ikada, Y. *J. Macromol. Sci., Phys.* **1991**, *B30*, 119–140.

(9) Yui, N.; Dijkstra, P. J.; Feijen, J. *Makromol. Chem.* **1990**, *191*, 481–488.

(10) Spassky, N.; Wisniewski, M.; Pluta, C.; Le Borgne, A. *Macromol. Chem. Phys.* **1996**, *197*, 2627–2637.

(11) Fukushima, K.; Furuhashi, Y.; Sogo, K.; Miura, S.; Kimura, Y. *Macromol. Biosci.* **2005**, *5*, 21–29.

(12) Li, S.; Vert, M. *Macromolecules* **1994**, *27*, 3107–3110.

(13) Li, S.; Vert, M. *Polym. Int.* **1994**, *33*, 37–41.

(14) Spinu, M.; Jackson, C.; Keating, M. Y.; Gardner, K. H. *J. Macromol. Sci.—Pure Appl. Chem.* **1996**, *A33*, 1497–1530.

(15) Pitt, C. G.; Marks, T. A.; Schindler, A. In *Biodegradable Drug Delivery Systems Based on Aliphatic Polyesters: Application to Contraceptive and Narcotic Antagonists, Research Monograph Series*; Willette, R. R., Barnett, G., Eds., National Institute on Drug Abuse: Bethesda, MD, 1981, *Vol. 28*, pp 232−253.

(16) Yin, M.; Baker, G. L. *Macromolecules* **1999**, *32*, 7711–7718.

(17) Jing, F.; Smith, M. R.III; Baker, G. L. *Macromolecules* **2007**, *40*, 9304–9312.

(18) Liu, T.; Simmons, T. L.; Bohnsack, D. A.; Mackay, M. E.; Smith, M. R.III; Baker, G. L. *Macromolecules* **2007**, *40*, 6040–6047.

(19) Tsuji, H.; Matsuoka, H.; Itsuno, S. *J. Appl. Polym. Sci.* **2008**, *110*, 3954–3962.

(20) Tsuji, H.; Tezuka, Y. *Biomacromolecules* **2004**, *5*, 1181–1186.

(21) Tsuji, H.; Hyon, S.-H.; Ikada, Y. *Macromolecules* **1991**, *24*, 5651–5656.

(22) Espartero, J. L.; Rashkov, I.; Li, S. M.; Manolova, N.; Vert, M. *Macromolecules* **1996**, *29*, 3535.

(23) Yokouchi, M.; Chatani, Y.; Tadokoro, H.; Teranishi, K.; Tani, H. *Polymer* **1973**, *14*, 267–272.

(24) Bloembergen, S.; Holden, D. A.; Bluhm, T. L.; Hamer, G. K.; Marchessault, R. H. *Macromolecules* **1989**, *22*, 1656–1663.

(25) Tsuji, H.; Ikada, Y. *Macromolecules* **1993**, *25*, 6918–6926.