Summary: Poly(lactide)s [i.e. poly(lactic acid) (PLA)] and lactide copolymers are biodegradable, compostable, producible from renewable resources, and nontoxic to the human body and the environment. They have been used as biomedical materials for tissue regeneration, matrices for drug delivery systems, and alternatives for commercial polymeric materials to reduce the impact on the environment. Since stereocomplexation or stereocomplex formation between enantiomeric PLA, poly(1-lactide) [i.e. poly(1-lactic acid) (PLLA)] and poly(1-lactide) [i.e. poly(1-lactic acid) (PDLA)] was reported in 1987, numerous studies have been carried out with respect to the formation, structure, properties, degradation, and applications of the PLA stereocomplexes. Stereocomplexation enhances the mechanical properties, the thermal-resistance, and the hydrolysis-resistance of PLA-based materials. These improvements arise from a peculiarly strong interaction between 1-lactyl unit sequences and 3-lactyl unit sequences, and stereocomplexation opens a new way for the preparation of biomaterials such as hydrogels and particles for drug delivery systems. It was revealed that the crucial parameters affecting stereocomplexation are the mixing ratio and the molecular weight of 1-lactyl and 3-lactyl unit sequences. On the other hand, PDLA was found to form a stereocomplex with 1-configured polypeptides in 2001. This kind of stereocomplexation is called “hetero-stereocomplexation” and differentiated from “homo-stereocomplexation” between 1-lactyl and 3-lactyl unit sequences. This paper reviews the methods for tracing PLA stereocomplexation, the methods for inducing PLA stereocomplexation, the parameters affecting PLA stereocomplexation, and the structure, properties, degradation, and applications of a variety of stereocomplexed PLA materials.

Poly(lactide) Stereocomplexes: Formation, Structure, Properties, Degradation, and Applications

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1. Introduction

When the interaction between polymers having different tacticities or configurations prevails over that one between polymers with the same tacticity or configuration, a stereoselective association of the former polymer pair takes place. Such association is described as stereocomplexation or stereocomplex formation. A well known and typical example of stereocomplexation is the one between isotactic and syndiotactic poly(methyl methacrylate) (PMMA), which was first reported by Fox et al. in 1958. The first example of stereocomplexation (stereoselective association) for enantiomeric polymers, i.e. between R- and S-configured (or 1- and 3-configured) polymer chains, was reported by Pauling and Corey for a polypeptide in 1953. However, it seems that the detailed structures of the polypeptide and its assemblies are unclear. With respect to optically active polysteres, Grenier and Prud’homme...
found stereocomplexation between enantiomeric poly(ε-
methyl-β-ethyl-β-propiolactone) (PMEPL), R- and
S-PMEPL, in 1984. Later, Ikada et al. reported stereo-
complexation between enantiomeric polylactide [i.e. poly-
(lactic acid) (PLA)], poly(ε-lactide) [i.e. poly(ε-lactic acid)
(PLLAs)] and poly(δ-lactide) [i.e. poly(δ-lactic acid)
(PDLA)] in 1987.[5] Although these polyesters, PMEPL
and PLA, are z-substituted, Voyer and Prud’homme
reported stereocomplexation between β-substituted poly-
esters, poly(β-propiolactone)s, having different side groups
(1,1-dichloroethyl or 1,1-dichloropropyl).[5] The typical
polymers having stereocomplexationability are summa-
ized in Table 1.[6] Stereocomplexation can occur between
isotactic and syndiotactic polymers or R- and S-configured
polymers having different chemical structures. The
reported examples are stereocomplexation between iso-
tactic PMMA and syndiotactic poly(methacrylic acid),[7]
between isotactic PMMA and syndiotactic poly(isobutyl
methacrylate),[8] and between PDLA and L-configured pep-
tides.[9] Slager and Domb described such kinds of stereo-
complexation between polymers with different chemical
structures as “hetero-stereocomplexation” and discrimi-
nated it from stereocomplexation between polymers
having identical chemical structures (“homo-stereocom-
plexation”).[9]

Stereocomplexation between PLLA and PDLA can
occur in solution, in a solid (bulk) state from the melt,
during polymerization, or during hydrolytic degradation,
as long as L-lactide (or L-lactyl) unit sequences and D-lactide
(or D-lactyl) unit sequences coexist in a system.[6] In other
words, PLA stereocomplexation can take place both in
enantiomeric PLA-based polymer blends and in non-
bonded stereoblock PLA. Here, lactyl unit means a half
lactide unit. The synthetic procedures and structures of
PLLA, PDLA, and stereoblock PLA are given in Figure 1.
Stannous octoate (stannous 2-ethylhexanoate) and lauryl
alcohol (1-dodecanol) have been used frequently as initiator
and coinitiator, respectively, for the synthesis of PLA
homopolymers. These synthetic routes in the presence of
homopolymers can be utilized to prepare copolymers having
L- or D-lactyl units.

When L-chains and/or D-chains are present in a system,
various types of crystallites can be formed (Figure 2).[19]
Figure 2 parts (a) and (b) show crystallites composed solely
of L-chains and D-chains, respectively. We call such
crystallites “homo-crystallites” and the formation of
homo-crystallites “homo-crystallization”. In this case,
either L- or D-chains, not both, are present in the system.
However, when both L-chains and D-chains are present in a
system, three types of crystallites, Figure 2 parts (c)–(e),
can be formed. Figure 2(c) represents stereocomplex cry-
stallites (or racemic crystallites), where L-chains and
D-chains have a peculiarly strong interaction compared
with that between identical configurations and, therefore,
L- and D-chains are packed side by side. It should be noted
that the actual shape of the unit lattice of the PLA
stereocomplex showing in Figure 5 is different from that
showing in Figure 2(c). When an interaction between chains
having identical configurations prevails against that one
between polymers with different configurations, L-chains
and D-chains assemble separately to form homo-crystal-
lites, as illustrated in Figure 2(e). The formation of
crystallites where L- and D-chains are packed randomly, as
given in Figure 2(d), has not been reported so far. Such non-
selective packing is expected to occur when interactions
between chains with the same and different configurations
are identical. In the case of PLA, when L- and D-chains are
mixed non-equimolarly or when L- and D-chains have
relatively high molecular weights, homo-crystallites as well
as stereocomplex crystallites are formed.[6,20–24]

Stereocomplexation of PLA is composed solely of a
stereocomplex crystallization (racemic crystallization) process,
in marked contrast to stereocomplexation between
isotactic and syndiotactic PMMA, where an association
Table 1. Stereocomplexationable polymers.\[^{[6]}\]

<table>
<thead>
<tr>
<th>Isomeric type</th>
<th>Polymer type</th>
<th>Polymer</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syndiotactic and isotactic</td>
<td>Vinyl polymer</td>
<td>Poly(methyl methacrylate) (PMMA)</td>
<td>Fox et al.[^{[1]}]</td>
</tr>
<tr>
<td>Isotactic R- and S- (or L- and D-)</td>
<td>Polyether</td>
<td>Poly(tert-butylethylene oxide)</td>
<td>Sakakihara et al.[^{[10]}]</td>
</tr>
<tr>
<td>(chiral center in the main chain)</td>
<td>Polythioether</td>
<td>Poly(tert-butylethylene sulfide)</td>
<td>Signfield and Brown[^{[11]}]</td>
</tr>
<tr>
<td></td>
<td>Polyketone</td>
<td>Poly(propylene-carbon monoxide)</td>
<td>Jiang et al.[^{[13]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poly(1-butene-carbon monoxide)</td>
<td>Jiang et al.[^{[13]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poly(allylbenzene-carbon monoxide)</td>
<td>Jiang et al.[^{[13]}]</td>
</tr>
<tr>
<td></td>
<td>Polyamide (Polypeptidic)</td>
<td>Poly((\gamma)-methyl glutamate)</td>
<td>Yoshida et al.[^{[14]}]</td>
</tr>
<tr>
<td></td>
<td>Polyamide (Non-polypeptidic)</td>
<td>Poly((\gamma)-benzyl glutamate)</td>
<td>Tsuboi et al.[^{[15]}]</td>
</tr>
<tr>
<td></td>
<td>Polyester</td>
<td>Poly(hexamethylene-2,3-di-O-methyl-L-tartaramide)</td>
<td>Iribarren et al.[^{[16]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poly((\alpha)-methyl-(\alpha)-ethyl-b-propiolactone) (PMEPL)</td>
<td>Grenier and Prud’homme[^{[3]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poly((\beta)-(1,1-dichloroethyl)-(\beta)-propiolactone)</td>
<td>Voyer and Prud’homme[^{[5]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poly((\beta)-(1,1-dichloropropyl)-(\beta)-propiolactone)</td>
<td>Voyer and Prud’homme[^{[5]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poly(lactide, poly(lactic acid) (PLA)</td>
<td>Ikada et al.[^{[4]}]</td>
</tr>
<tr>
<td>Isotactic R- and S- (or L- and D-)</td>
<td>Vinyl polymer</td>
<td>Poly((\gamma)-methylbenzyl methacrylate)</td>
<td>Hatada et al.[^{[17]}]</td>
</tr>
<tr>
<td>(chiral center in the side chain)</td>
<td>Poly((N)-methylacryloyl-L-leucine methyl ester)</td>
<td>Sanda et al.[^{[16]}]</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Synthesis and molecular structures of PLLA [(a) and (b)], PDLA [(c) and (d)], and stereo-block isotactic PLA [(e) and (f)].
process of isotactic and syndiotactic PMMA is followed by crystallization of the associated PMMA chain pairs.\[^{25}\] Most of the reported stereocomplexation between enantiomeric polyesters are expected to proceed via the same process as that for PLA stereocomplexation, i.e., a stereocomplex crystallization process. With respect to PLA-based stereocomplexation, the ratio of stereocomplex crystallites to homo-crystallites is affected by numerous parameters, such as the molecular weights and optical purities of the polymers and the mixing ratio of the isomeric chains, as elucidated by intensive studies.\[^{6,20–24,26–29}\] Those parameters expected to affect PLA-based stereocomplexation are listed in Table 2 and detailed information is given below.

Since PLA and lactide copolymers are biodegradable, compostable, producible from renewable resources, and nontoxic to the human body and the environment, they have been used as biomedical materials for tissue regeneration, matrices for drug delivery systems, and alternatives for commercial polymeric materials to reduce the impact on the environment.\[^{30–37}\] PLA stereocomplexation due to the peculiarly strong interaction between \(\ell\)-lactyl unit sequences and \(d\)-lactyl unit sequences is expected to improve a variety of properties of PLA-based materials and open novel methods to prepare such materials. Although numerous reviews or feature articles with respect to PLA have been published, the PLA-based stereocomplex is described only in parts of these articles,\[^{9,30–37}\] excluding a short feature article published in 2000.\[^{6}\] This paper reviews the methods for tracing PLA stereocomplexation, the methods for inducing PLA stereocomplexation, the parameters affecting PLA stereocomplexation, and the structure, properties, degradation, and applications of a variety of stereocomplexed PLA materials.

### 2. Methods for Tracing PLA Stereocomplexation

Numerous methods have been reported for tracing PLA stereocomplexation. The representative methods are described in this section and such information is required to understand the subsequent sections.

#### 2.1. Differential Scanning Calorimetry (DSC)

DSC is one of the most effective and simple methods for monitoring PLA stereocomplexation. Figure 3 gives typical DSC curves for the blends of PLLA and PDLA with different mixing ratio ($X_D$) values.\[^{21}\] $X_D$ is defined as follows:

\[
X_D = \frac{\text{Weight of PDLA}}{\text{Weight of PLLA and PDLA}}\times (1)
\]

The specimens were prepared by precipitation of a methylene chloride mixed solution of PLLA and PDLA into stirred methanol. The peak at around 180 °C for PLLA or PDLA ($X_D = 0$ or 1) is ascribed to the melting of PLLA or PDLA homo-crystallites, while a new melting peak at around 230 °C appears in the blend specimens. The new peak is attributed to the melting of stereocomplex crystallites. A similar increase in melting temperature ($T_m$) upon stereocomplexation was reported by Grenier and Prud’homme for blends between R- and S-PMEPL.\[^{3}\] The enthalpy of melting ($\Delta H_m$) of stereocomplex crystallites gives a maximum at mixing ratio $X_D$ of 0.5 and with a deviation of $X_D$ from 0.5 the $\Delta H_m$ of homo-crystallites increases. This reflects the fact that equimolar mixing is favored for stereocomplexation.

Tsuji and Ikada have estimated the equilibrium melting temperature ($T_m^0$) of PLA stereocomplex crystallites by extrapolation of $T_m$ values for different optical purities, which were obtained by the Hoffman-Weeks procedure using experimental $T_m$ values, to 100% optical purity.\[^{23}\] The estimated $T_m^0$ value of 279 °C is much higher than the 205 °C (Tsuji and Ikada\[^{38,39}\]), 212 °C (Tsuji and Ikada\[^{40}\]), and 215 °C (Kalbs and Pennings\[^{41}\]) reported for homocrystallites of PLLA. The reported $\Delta H_m$ values for the crystals having an infinite thickness [$\Delta H_m(100\%)$] for PLA
Table 2. The parameters affecting PLA stereocomplexation.

<table>
<thead>
<tr>
<th>Molecular Structures</th>
<th>Molecular Characteristics</th>
<th>Procedures</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PLLA/PDLA</td>
<td>1. Overall molecular weight</td>
<td>1. Bulk</td>
<td>1. Mixing ratio of polymers (for polymer blending)</td>
</tr>
<tr>
<td>2. L-lactide copolymer/ D-lactide copolymer</td>
<td>2. Averaged sequence lengths (molecular weights) of L- and D-lactide (lactic acid) units (for linear copolymers).</td>
<td>1.1. Crystallization at a fixed temperature from the melt or after melt-quenching</td>
<td>2. Melting temperature and time 3. Crystallization or polymerization temperature and time (1.1 and 1.3) 4. Cooling rate from the melt (1.2.) or heating after melt-quenching</td>
</tr>
<tr>
<td></td>
<td>4. Degree of substitution or number of graft chain per unit length of main chain (for graft copolymers)</td>
<td>1.3. During polymerization</td>
<td>1. Precipitation 2. Precipitation or gel formation at a constant polymer concentration 3. Precipitation into non-solvent 4. Share rate (Stirring rate) of solvent or precipitant during precipitation</td>
</tr>
<tr>
<td></td>
<td>3. Precipitation</td>
<td>3.1. Precipitation or gel formation at a constant polymer concentration</td>
<td>1. Mixing ratio of polymers (for polymer blending) 2. Kinds of solvent and precipitant 3. Precipitation temperature 4. Share rate (Stirring rate) of solvent or precipitant during precipitation</td>
</tr>
<tr>
<td></td>
<td>4. Stepwise assembly in solution</td>
<td>3.2. Precipitation into non-solvent</td>
<td>1. Solution concentration and temperature 2. Immersion time (for one immersion) and number of times</td>
</tr>
<tr>
<td></td>
<td>5. Drawing or orientation (after preparation by the procedures 1–3)</td>
<td>4. Stepwise assembly in solution</td>
<td>1. Drawing method (Uniaxial or Biaxial) 2. Step number of drawing (One, two, or more) 3. Drawing temperature and annealing time</td>
</tr>
<tr>
<td></td>
<td>6. Compression (after preparation of monolayer film)</td>
<td>5. Drawing or orientation (after preparation by the procedures 1–3)</td>
<td>1. Compression temperature and pressure</td>
</tr>
</tbody>
</table>

stereocomplex, 142 J g⁻¹ (Loomis et al.[42]) and 146 J g⁻¹ (Tsuji et al.[43]) are in the range of ΔHₘ(100%) values for homo-crystallites, 93 J g⁻¹ (Fischer et al.[44]), 135 J g⁻¹ (Miyata and Masuko[45]), 142 J g⁻¹ (Loomis et al.[42]), and 203 J g⁻¹ (Jamshidi et al.[46]). In our case, the ΔHₘ(100%) for the PLA stereocomplex was calculated from the experimental ΔHₘ value (102 J g⁻¹) and the crystallinity (X_c) value (70%) obtained with wide-angle X-ray scattering,[43] whereas the procedure for the calculation of ΔHₘ(100%) for the PLA stereocomplex was not given in the literature.[42] The physical properties, including the detailed thermal properties of stereocomplexed PLA and nonblended PLLA in comparison with other biodegradable polyesters, are summarized in Table 3.[36]

2.2. Wide-Angle X-Ray Scattering (WAXS) and Small-Angle X-Ray Scattering (SAXS)

In the first report on PLA stereocomplexation, the WAXS profiles of blends having different X_c values are shown (Figure 4) and in the same report DSC thermograms are presented. The main peaks of PDLA (X_c = 1) film appear at
2\(\theta\) values of 15, 17, and 19\(^\circ\),\[4\] which are comparable with the results for the \(z\) form of PLLA crystallized in a pseudo-orthorhombic unit cell of dimensions: \(a = 1.07\) nm, \(b = 0.595\) nm, and \(c = 2.78\) nm, which contains two 10\(_3\) helices.\[36,47\] The most intense peaks of equimolarly blended film (\(X_D = 0.5\)) are observed at 2\(\theta\) values of 12, 21, and 24\(^\circ\). These peaks are for the PLA stereocomplex\[4\] crystallized in a triclinic unit cell of dimensions: \(a = 0.916\) nm, \(b = 0.916\) nm, \(c = 0.870\) nm, \(\alpha = 109.2\(^\circ\), \(\beta = 109.2\(^\circ\), and \(\gamma = 109.8\(^\circ\), in which L-lactide and D-lactide segments are packed parallel taking 31 helical conformation.\[47\] The crystal structure of the PLA stereocomplex proposed by Okihara et al.\[47\] is demonstrated in Figure 5. The lattice containing a PLLA or PDLA chain with a 31 helical conformation has the shape of an equilateral triangle, which is expected to form equilateral-triangle-shaped single crystals of the PLA stereocomplex.\[48\] On the other hand, Okihara et al. found that in the X-ray and electron diffraction patterns of drawn fibers of the PLA stereocomplex, the equatorial reflections were sharp, but those on the layer lines were largely broadened in the direction parallel to the layer line, becoming more diffuse as the layer order increases. On the basis of the paracrystalline theory, they estimated the degree of shift disorder among polymer chains in the direction parallel to the molecular axis to be 0.1.\[49\] Furthermore, Brizzolara et al. \[50\] compared the WAXS profiles from actual stereocomplexed specimens and a Force-Field simulated stereocomplex. They also proposed the growth mechanism of the stereocomplex equilateral-triangle-shaped single crystal.

![DSC thermograms of PLLA/PDLA blends with different X_D values.][21] Viscosity-average molecular weights (\(M_\text{v}\)) of PLLA and PLLA are both 3.6 \times 10^5 g \cdot mol^{-1}.

---

**Table 3. Physical properties of stereocomplexed PLA and some biodegradable polyesters.**\[36\]

<table>
<thead>
<tr>
<th>Physical properties</th>
<th>Stereocomplexed PLA</th>
<th>PLLA</th>
<th>PDLA</th>
<th>Syndiotactic PLA</th>
<th>PCL</th>
<th>Poly[(R)-3-hydroxybutyrate] (R-PHB)</th>
<th>Poly(glycolide) (PGA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(T_m (\degree C))</td>
<td>220–230</td>
<td>170–190</td>
<td>–</td>
<td>151</td>
<td>60</td>
<td>180</td>
<td>225–230</td>
</tr>
<tr>
<td>(T_m (\degree C))</td>
<td>279</td>
<td>205, 212, 215</td>
<td>–</td>
<td>–</td>
<td>71, 79</td>
<td>188, 197</td>
<td>–</td>
</tr>
<tr>
<td>(T_g (\degree C))</td>
<td>65–72</td>
<td>50–65</td>
<td>50–60</td>
<td>34</td>
<td>–60</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>(\Delta H_m (100%)) (J g(^{-1}))</td>
<td>142, 146</td>
<td>93, 135, 142, 203</td>
<td>–</td>
<td>–</td>
<td>142</td>
<td>146</td>
<td>180–207</td>
</tr>
<tr>
<td>(\Delta E_{\text{ad}}) (kJ mol(^{-1}))</td>
<td>205–297</td>
<td>87–104</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Density (g cm(^{-3}))</td>
<td>–</td>
<td>1.25–1.29</td>
<td>1.27</td>
<td>–</td>
<td>1.06–1.13</td>
<td>1.177–1.260</td>
<td>1.50–1.69</td>
</tr>
<tr>
<td>Solubility parameter ((\delta_p) (25 \degree C))(J(^{0.5}) cm(^{-3}))</td>
<td>–</td>
<td>19–20.5</td>
<td>21.1</td>
<td>–</td>
<td>20.8</td>
<td>20.6</td>
<td>–</td>
</tr>
<tr>
<td>([x]_{\text{D} 25}^\text{P} \text{in chloroform}(\degree\text{.dm}^{-1}\cdot\text{g}^{-1}\cdot\text{cm}^{-1}))</td>
<td>–</td>
<td>–155 ± 1</td>
<td>0</td>
<td>–</td>
<td>0</td>
<td>+44(^a)</td>
<td>–</td>
</tr>
<tr>
<td>WVTR(^b) (g m(^{-2}\cdot d^{-1}))</td>
<td>–</td>
<td>82–172</td>
<td>–</td>
<td>–</td>
<td>177</td>
<td>13(^b)</td>
<td>–</td>
</tr>
<tr>
<td>Tensile strength (GPa)</td>
<td>0.88(^f)</td>
<td>0.12–2.3(^g)</td>
<td>0.04–0.05(^f)</td>
<td>–</td>
<td>0.1–0.8(^e)</td>
<td>0.18–0.20(^f)</td>
<td>0.08–1(^f)</td>
</tr>
<tr>
<td>Young’s modulus (GPa)</td>
<td>8.6(^f)</td>
<td>7–10(^f)</td>
<td>1.5–1.9(^g)</td>
<td>–</td>
<td>–</td>
<td>5–6(^f)</td>
<td>4–14(^f)</td>
</tr>
<tr>
<td>Elongation at break (%)</td>
<td>30(^g)</td>
<td>12–26(^g)</td>
<td>5–10(^f)</td>
<td>–</td>
<td>20–120(^f)</td>
<td>50–70(^f)</td>
<td>30–40(^f)</td>
</tr>
</tbody>
</table>

\(^a\) Enthalpy of melting of crystal having infinite size.

\(^b\) Activation energy for thermal degradation estimated by thermogravimetry at a constant temperature (250–270 \degree C).

\(^c\) 300 nm, 23 \degree C.

\(^d\) Water vapor transmission rate at 25 \degree C.

\(^e\) Poly[(R)-3-hydroxybutyrate-co-3-hydroxyvalerate] (94/6).

\(^f\) Oriented fiber.

\(^g\) Non-oriented films.
The result obtained from SAXS analysis was solely for the long period of the PLA stereocomplex precipitated from acetonitrile solutions at 80 °C and annealed at 216 °C.[43] The estimated long period was 12 nm, which is much smaller than the 22–35 nm reported for PLLA films crystallized at 120–160 °C from the melt.[51] Using the crystallinity ($X_d$) value obtained by a WAXS profile (70%), the estimated thickness values of stereocomplex crystalline and amorphous regions were 8.4 and 3.6 nm, respectively.[43] The estimated thickness of stereocomplex crystalline regions is also much smaller than the 13–22 nm reported for PLLA films crystallized at 120–160 °C.[51] The differences in long period and crystalline thickness between the stereocomplex and PLLA are partly ascribed to the differences in the specimen preparation method and conditions.

2.3. Infrared (IR) and Raman Spectroscopy

Kister et al.[52] observed IR and Raman spectral changes in peak shapes and wavelengths upon PLA stereocomplexation. Later, by the use of FT-IR, Zhang et al.[53,54] found that a very small low-frequency shift (about 1 cm$^{-1}$) of $v_{\text{as}}$(CH$_3$) and a larger low-frequency shift (about 5 cm$^{-1}$) of $v$(C=O) were observed during stereocomplex crystallization from the melt (Figure 6). The low-frequency shifts of the stretching vibration modes of the methyl and carbonyl groups confirmed for the first time that the interaction between the chains in the PLA stereocomplex is ascribed to the CH$_3$/C=O hydrogen bonding. Another interesting result is that the peak shift of the $v$(C=O) band already occurs in the induction period, which indicates that the CH$_3$…O=C interaction is the driving force for the racemic nucleation of the PLA stereocomplex.[53,54] Moreover, 2D correlation analysis indicates that the structural adjustment of the CH$_3$ group occurs prior to that of the C–O–C backbone during the stereocomplexation process. Although van der Waals interaction between the hydrogen of CH$_3$ and the oxygen of O=C has been suggested by Brizzolara et al.,[56] Zhang et al. indicated for the first time that the hydrogen bonding is the driving force for the nucleation of PLA stereocomplex crystallites.[53,54]

Figure 4. WAXS profiles of PLLA/PDLA blends having different $X_d$ values.[4] Solid line, dashed line, and dashed/single dotted line are for $X_d = 0.5, 0.75,$ and 1, respectively.

Figure 5. Crystal structure of PLA stereocomplex.[47] The lines between PLLA and PDLA chains were added to original figure.
2.4. $^1H$ and $^{13}C$ NMR Spectroscopy

Tsuji et al. estimated the degree of PLA stereocomplexation in a concentrated solution of equimolar PLLA and PDLA by the use of $^1H$ NMR spectroscopy, as shown in Figure 7.[26] Broad peaks in addition to sharp peaks appeared in the resonance lines of the methine and methyl groups and the areas of the broad peaks increased with time. These broad peaks are ascribed to the chains adjacent to stereocomplex micro-crystallites, i.e. folding chains and tie chains. The total peak area decreased because the PLA chains in the stereocomplex crystallites gave no peaks. The shoulder which appeared in the resonance line of CHCl$_3$ may be due to the CHCl$_3$ surrounding the folding and tie chains. The decrease in the peak areas of the methine and methyl groups continued for more than fifty days and the peak areas decreased below 50% of the initial values. Such phenomena reflect the formation of stereocomplex crystallites in concentrated solutions and the increase in number and/or thickness of the stereocomplex crystalline regions.

![Figure 6](image1.png)  
**Figure 6.** Temporal changes of the IR spectra in the C–H stretching region of methyl group (a) and C=O stretching region (b) during the melt-crystallization process of PLLA/PDLA stereocomplex at 220 °C, respectively.[54]

![Figure 7](image2.png)  
**Figure 7.** 400 MHz $^1H$ NMR spectra of equimolarly mixed chloroform solution of PLLA and PDLA at 17.5 g · dL$^{-1}$ and 25 °C.[26]
13C NMR spectroscopy is also an effective method for tracing PLA stereocomplexation. Figure 8 gives high-resolution solid-state CP/MAS 13C NMR spectra of PLA stereocomplex precipitates and nonblended PDLA precipitates, and an as-cast amorphous poly(D,L-lactide) (PDLLA) film, together with a 13C NMR spectrum of PDLA in chloroform-d.

We performed a component analysis solely for carbonyl carbon because of the appearance of the new peak due to stereocomplexation. Figure 9 illustrates the component analysis for the total 13C NMR spectrum of carbonyl carbon in the stereocomplex precipitates, and the 13C chemical shifts and spin-lattice relaxation times ($T_{1C}$) of components A–D in resonance lines I–III are described in the caption of Figure 9. The assignments of components A–D in the reported article are as follows. Component A in line III is ascribed to PLA chains in the amorphous regions because the chemical shift of line III is very close to those of the amorphous PDLLA film and the PDLA in solution, and also because of its very short $T_{1C}$ value (5.4 s). Components C and D in line I are assignable to the PLA chains in the stereocomplex crystalline regions because line I is not observed for the crystallized nonblended PDLA and PLLA precipitates or for the amorphous PDLLA film. Relatively high and low $T_{1C}$ values of components C and D, 128 and 17 s, suggest that the chains of these components are in a rigid and disordered state, respectively. Component B corresponds to line II which may be ascribed to the chains in the homo-crystalline regions, because the $T_{1C}$ value is rather high (40 s) and has a very similar chemical shift to that of the precipitates of the nonblended PDLA or PLLA.

2.5. Light Scattering (LS) Measurements

The aggregation behavior of isotactic and syndiotactic PMMA was monitored by Vorenkamp and Challa using the LS method. They demonstrated that the aggregation of isotactic and syndiotactic PMMA caused no change in the radius of gyration (ca. 30 nm) but an increase in molecular weight. For stereocomplexation of PLA homopolymers, PLLA and PDLA, the LS method has not been applied, but Portinha et al. observed aggregation behavior in nonblended and blended solutions of poly(L-lactide)-block-poly(e-caprolactone) (PLLA-b-PCL) and poly(D-lactide)-block-poly(e-caprolactone) (PDLA-b-PCL). They revealed that the hydrodynamic radii of assemblies in the enantiomeric blended solution, 200 nm, were higher than those of nonblended polymer solutions and that the radius distribution in the enantiomeric blended solution was sharper than that in nonblended polymer solutions.

2.6. Viscometry

In concentrated solutions, the formed PLA stereocomplex crystallites acted as physical crosslinks. The crosslinks raise the solution viscosity and finally cause gel formation. Figure 10 depicts the time change of the relative viscosity of a mixed chloroform solution of equimolar PLLA and PDLA with different concentrations. The increase in viscosity occurs at concentrations exceeding a critical level. In Figure 10, the critical concentration is in the...
range of 10–12.5 g \cdot dL^{-1} and this value depends on various parameters such as the molecular weight, mixing ratio of PLLA and PDLA, and solution temperature, as mentioned below.

2.7. Rheological Measurements

Similar to the viscosity, the storage modulus ($G'$) of the PLA solution is increased by stereocomplexation due to the reason given by Tsuji et al. The dried specimen obtained by solvent evaporation of a PLA stereocomplex gel has higher $G'$ values for a wide temperature range. Figure 11 gives the $G'$ of a nonblended PLLA film ($X_D = 0$), and blended films of PLLA/PDLA = 3/1 ($X_D = 0.25$) and 1/1 ($X_D = 0.5$), respectively. Because of its high brittleness arising from a low molecular weight, measurements for nonblended PLLA film could not be carried out for temperatures exceeding 100 °C. The loss tangent (tan $\delta$) peaks at around 60 °C for all films and at around 180 °C for the 3/1 blended film are attributed to the glass transition and melting of homo-crystallites. The $G'$ of all films decreased above the glass transition temperature ($T_g$) and that of the 3/1 blended film became lower above the $T_m$ of the homo-crystallites. Although the 1/1 blended film having solely stereocomplex crystallites gradually decreased with temperature above $T_m$, it retained the highest $G'$ among the films from room temperature to $T_m$ of stereocomplex (ca. 220 °C). Even 3/1 film having homo-crystalline regions as well as the stereocomplex crystalline regions maintained non-zero $G'$ values for temperatures up to 220 °C, meaning that the presence of stereocomplex crystallites enhanced the heat-resistance of PLA-based materials for temperatures above $T_g$.

2.8. Tensile Properties

Stereocomplexation improves the tensile properties of PLA-based materials. Figure 12 shows the tensile properties of nonblended PLLA or PDLA films and their equimolarly ($X_D = 0.5$) blended films. At the weight-average molecular weight ($\bar{M}_w$) of $1 \times 10^5$–$1 \times 10^6$ g・mol$^{-1}$, the blended film surpassed the nonblended films in all the tensile properties (tensile strength, Young’s modulus, and elongation at break). The main reason for the improved tensile properties of equimolarly blended films at relatively low $\bar{M}_w$ is the formation of stereocomplex macro-gel during solvent evaporation, as stated in Section 2.6, whereas the reason for those at relatively high $\bar{M}_w$ is the formation of smaller spherulites in the blended films.

2.9. Polarization Optical Microscopy (POM)

The growth rate, induction period, and morphology of the spherulites of stereocomplex crystallites as well as those of homo-crystallites can be monitored by POM. The PLAs spherulites containing solely stereocomplex crystallites can be formed in the equimolarly blended film of PLLA and PDLA (Figure 13). The spherulitic structure of PLA stereocomplex crystallites was different from that of homo-crystallites with polygonal shapes, which can be seen for nonblended PLLA or PDLA having low molecular weights at low temperatures. On the other hand, by the use of POM as well as the scanning electron microscopy, the porous structure of dried stereocomplex gels can be observed (Section 3.2.1).
2.10. Scanning Electron Microscopy (SEM), Electron Diffraction (ED), and Transmission Electron Microscopy (TEM)

SEM observation revealed that PLA stereocomplex particulate precipitates (Figure 14) are formed in acetonitrile solution and their size and shape depends on various parameters, as shown in Table 2.[27] The stereocomplex particles were disk-shaped under the conditions of 1 g · dL⁻¹, 80 °C, and X₀ = 0.5. Upon decreasing the temperature or increasing the polymer concentration, the stereocomplex particles became more spherical, whereas upon deviation of X₀ from 0.5, the stereocomplex particles became equilateral-triangle-plate-shaped. The equilateral triangular shape is very similar to that of the PLA stereocomplex single crystals observed by TEM [Figure 15(A)].[47] Cartier et al.[61] found that such triangular crystals as observed for the PLA stereocomplex can be utilized as a morphological marker for the frustrated character of the chain packing of a polymer in the unit cell. On the other hand, Okihara et al.[47] demonstrated that PLA stereocomplexation can be traced by the use of obtained ED patterns.

2.11. Atomic Force Microscopy (AFM)

Similar to the SEM and TEM observation, AFM can monitor the equilateral triangle-shaped single crystal and disks of the PLA stereocomplex (Figure 16).[9]

3. Methods for Inducing PLA Stereocomplexation

PLA stereocomplexation takes place in the absence of a solvent (in bulk: crystallization from the melt or during polymerization), or in the presence of solvent (in solution). As tabulated in Table 2, PLA stereocomplexation is affected by numerous parameters. Tsuji et al.[6,20–24,26–29,36] and Murdoch and Loomis[62–66] investigated the parameters’ effects on the stereocomplexation of PLA homopolymers utilizing different methods under a wide variety of conditions.

3.1. In Bulk or Solid State

3.1.1. Crystallization from the Melt

There are four representative procedures for crystallization from the melt; (1) crystallization at a fixed temperature (T_c) directly from the melt, (2) crystallization at a fixed T_c after quenching from the melt, (3) crystallization during cooling from the melt, (4) crystallization during heating of melt-quenched specimens.[67] Procedure (1) is utilized to trace the radius growth rate of spherulites (G) and the induction period for spherulite formation (t_i). Figure 17 illustrates the G and t_i values for spherulites of stereocomplex crystallites and homo-crystallites in PLLA, PDLA, and equimolar PLLA/PDLA blended films crystallized through Procedure (1). The polarization optical photomicrographs are given in Figure 13.[58] The spherulites composed of stereocomplex crystallites have an extremely high G and a short t_i compared with those of the homo-crystallites of either PLLA or PDLA, as shown in Figure 17. Such rapid formation and growth of PLA stereocomplex crystallites were observed even when an equimolar mixture of PLLA and PDLA both...
Figure 13. Spherulites of PLLA \( (\overline{M}_w = 1.0 \times 10^4 \text{ g} \cdot \text{mol}^{-1}) \) (A), PDLA \( (\overline{M}_w = 2.2 \times 10^3 \text{ g} \cdot \text{mol}^{-1}) \) (B), and their equimolarly blended films (C, D) crystallized at 140°C (A–C) and 190°C (D) from the melt at 250°C. [58]

Figure 14. SEM photographs of PLA stereocomplex particles precipitated from acetonitrile solutions with different concentrations. [27] (A) 0.1 g·dL⁻¹; (B) 1 g·dL⁻¹; (C) 3 g·dL⁻¹; (D) 10 g·dL⁻¹.
with low molecular weights was quenched from the melt.\textsuperscript{[22,62]} The hydrogen bonding between methyl hydrogen and carbonyl oxygen as revealed by Zhang et al.\textsuperscript{[53,54]} is expected to enhance such rapid spherulite formation and growth of PLA stereocomplex crystallites. The spherulites of stereocomplex crystallites had normal morphology very similar to that of homo-crystallites when only stereocomplex crystallites were contained in the spherulites.\textsuperscript{[22,23]} In contrast, the spherulite morphology became complicated when both stereocomplex crystallites and homo-crystallites were formed simultaneously in the spherulites.\textsuperscript{[22,23]}

Although there has been no report with respect to Procedure (2), the quenching process should enhance stereocomplex crystallization by increasing the spherulite nuclei, as reported for homo-crystallization of PLLA.\textsuperscript{[67]} In Procedures (1) and (2), the stereocomplex crystallites are predominantly formed by crystallization at $T_c$ between the $T_m$ values of homo-crystallites (170–180 °C) and stereocomplex crystallites (220–230 °C).\textsuperscript{[22,62]} For Procedure (3), Brochu et al.\textsuperscript{[68]} reported the epitaxial crystallization of homo-crystallites of PLLA on the stereocomplex crystallites of PLLA and poly(t-lactide-co-d-lactide) (20/80) when the two polymers were mixed at a ratio of 80/20 and crystallized during slow cooling at 1 or 2 °C min$^{-1}$ from the melt. With regard to epitaxial crystallization of aliphatic polyesters, Soldera and Prud’homme\textsuperscript{[69]} observed epitaxial crystallization of $R$-configured poly(z-methyl-z-propyl-$\beta$-propiolactone) (PMPPL) onto $S$-configured PMEPL crystallites. For Procedure (4), Urayama et al.\textsuperscript{[70]} found that an aluminum complex of a phosphoric ester combined with hydrotalcite (NA) executively enhance the nucleation of stereocomplex crystallites, whereas talc cannot suppress the homo-crystallization of PLLA or PDLA.

### 3.1.2. During Polymerization
Spinu et al.\textsuperscript{[71–73]} proposed a novel method for stereocomplexation between PLLA and PDLA; polymerization of LLA and DLA in the presence of PDLA and PLLA, respectively, after mixing LLA and PDLA (or DLA and PLLA). With this method, they successfully prepared well-stereocomplexed PLA materials. In the strict sense of the word, this method may not be “template polymerization”,\textsuperscript{[74]} but effectively utilizes the fact that the polymerized chains have strong interaction with the template chains.

### 3.1.3. Upon Compression
Bourque et al.\textsuperscript{[75]} and Pelletier and Pézolet\textsuperscript{[76]} reported that stereocomplexation occurs upon the compression of the...
monolayer of PLLA/PDLA mixture films. They prepared Langmuir films of PLLA and PDLA and then observed their structural changes by the use of surface-pressure measurements and polarization modulation infrared reflecting-absorption spectroscopy (PM-IRRAS). They indicated that a stereocomplex bilayer in equilibrium with the monolayer was formed at the air-water interface by compression.

3.1.4. Upon Orientation

Tsuji et al. revealed that stereocomplex crystallization of the equimolar PLLA/PDLA fibers were enhanced by hot-drawing to high ratios.[77] The hot-drawing process causes expanded chains or increases the surface area per unit molecule and, therefore, raises the probability of interaction between PLLA and PDLA segments. This causes increased $X_c$ and $T_m$ of stereocomplex crystallites and enhances tensile properties.[62,77]

3.1.5. Upon Hydrolytic Degradation

Li et al. found that stereocomplexation can occur in poly(l-lactide-co-d-lactide) with a thickness of mm order after a long-term hydrolytic degradation (25 or 30 weeks) as mentioned in detail in Section 4.2.2.[78–82] The hydrolytic degradation induces a decreased molecular weight, which elevates the mobility of PLA chains in addition to the presence of water as a plasticizer, and selective removal of relatively atactic sequences, leaving relatively isotactic chains. These three factors enhance PLA stereocomplexation between remaining l-lactyl unit sequences and d-lactyl unit sequences. However, when thin specimens (thickness < 200 m) were used, no stereocomplexation was observed for poly(l,l-lactide)[83] and an amorphous-made equimolar blend of PLLA and PDLA,[84] even when hydrolytic degradation was continued for 20–24 months. This supports the fact that core-accelerated hydrolysis of thick specimens should have induced PLA stereocomplexation.

3.2. In Solutions

Once PLA stereocomplex crystallites are formed in solution, they are insoluble in good solvents for either PLLA or PDLA (e.g., chloroform, dichloromethane). This means high stability of the stereocomplex crystallites compared with that of homo-crystallites of either PLLA or PDLA. The stereocomplex crystallites can be dissolved in extremely good solvents at room temperature (e.g., 1,1,1,3,3,3-hexafluoro-2-propanol) or in generally good solvents at high temperatures near the boiling points (e.g., chloroform, 1,1,2,2-tetrachloroethane). However, the stereocomplex crystallites become insoluble in extremely good solvents even at elevated temperatures when the crystalline thickness is high.

3.2.1. At a Fixed Polymer Concentration

The crystallites of a polymer are formed when the polymer concentration in a solution exceeds a critical level. The critical concentration for PLA stereocomplex crystallite formation (stereocomplex crystallization) is much lower than that for homo-crystallite formation of either PLLA or PDLA (homo-crystallization). In other words, some good solvents [e.g., chloroform and dichloromethane at room temperature, acetonitrile around boiling temperature (ca. 80°C)] for either PLLA or PDLA are poor solvents or non-solvents for stereocomplex crystallites. Therefore, when an initial polymer concentration is lower than the critical level for homo-crystallite formation but higher than that for stereocomplex crystallite formation, mixing two separately prepared solutions of PLLA and PDLA results in the formation of stereocomplex crystallites. Such stereocomplex crystallite formation induces particulate precipitates or single crystals in dilute solutions (acetonitrile)[87] or gels in

![Figure 17. Radius growth rate of spherulites ($G$) and induction period of spherulite formation ($\tau_0$) of PLLA, PDLA, and their equimolar blends as a function of crystallization temperature ($T_c$).[58](58)
concentrated solutions (chloroform, dichloromethane). The shape and size of stereocomplex precipitates in acetonitrile depend on representative parameters: $X_D$, polymer concentration (Figure 14), molecular weights of PLLA and PDLA, and temperature. The stereocomplex particles grow in a suspended state, which is monitored by the turbidity of the solution (Figure 18). After sedimentation of the stereocomplex particles, the supernatant becomes transparent again.

Probably, Murdoch and Loomis first observed gel formation upon PLA stereocomplexation. Figure 19 shows a phase diagram of a PLLA/PDLA/chloroform system. The lines between phases I and II and between phases II and III are the critical concentrations for stereocomplex crystallite formation (micro-gel formation) and macro-gel formation, respectively. In stereocomplex gel formation, the PLA stereocomplex crystalline regions act as physical cross-links between the PLA chains (Figure 20). In the case of the PLA-based block copolymers mentioned below, when the tie chains or sequences which do not take part in the formation of cross-links or stereocomplex crystalline regions are hydrophilic, the materials will be biodegradable hydrogels in aqueous media. It is of great interest that although t-lactyl unit sequences and d-lactyl unit sequences become insoluble in water at a higher degree of polymerization ($DP$), such hydrogels can be formed through stereocomplexation in aqueous media upon mixing the enantiomeric suspensions.

3.2.2. Casting (Increasing Polymer Concentration by Solvent Evaporation)

In the solution casting method, solvent evaporation elevates the polymer concentration of the solution from an initial concentration to an infinite one. Therefore, during the course of solvent evaporation, the polymer concentration exceeds first the critical level of stereocomplex crystallite formation, and then that of homo-crystallite formation. This means that the stereocomplex crystallites are predominantly formed in equimolarly mixed solutions of PLLA and PDLA when the solvent evaporation rate is sufficiently low.
However, rapid solvent evaporation will not give the stereo-complex crystallites a sufficiently long time for their formation, and the polymer concentration will reach the critical level of homo-crystallite formation, resulting in the formation of homo-crystallites. Homo-crystallization predominantly occurs when the molecular weights of both PLLA and PDLA are high, the deviation of $X_D$ from 0.5 is large, or the solvent evaporation rate is high. Figure 21 illustrates a typical example of the effects of PLA molecular weights on the kind and amount of the crystallites. With increasing the molecular weights of PLLA and PDLA, a large fluctuation of microscopic $X_D$ from 0.5 occurs even in an equimolarly mixed solution, due to the large radii of the PLLA and PDLA molecules. This must retard the nuclei formation and growth of stereocomplex crystallites, resulting in the formation of a large amount of homo-crystallites. de Jong et al. synthesized polydisperse L- and D-lactic acid oligomers using stannous octoate and 2-(2-methoxyethoxy)ethanol as initiator and coinitiator, respectively, and subsequent preparative HPLC of polydisperse oligomers yielded monodisperse oligomers ($DP = 1–16$). They prepared nonblended and equimolarly blended specimens by solution-casting with dichloromethane. DSC and WAXS revealed that L- or D-oligomers were crystallizable for $DP$ above 11, while an equimolar mixture formed stereocomplex crystallites for $DP$ above 7, meaning high stability of the stereocomplex crystallites compared with that of homo-crystallites. However, WAXS analysis revealed that the mixture of L- and d-lactic acid oligomers ($DP = 7$) contained homo-crystallites as well as stereocomplex crystallites. This may have arisen from epitaxial crystallization of the homo-crystallites on the stereocomplex crystallites. Serizawa et al. reported that stepwise assembly between PLLA and PDLA on a quartz crystal microbalance (QCM) substrate gave rise to stereocomplexation. This was attained by alternate immersion of the substrate into acetonitrile solutions of PLLA and PDLA. They also indicated that the assembly of PLLA can grow epitaxially on the surface of stereocomplex crystallites, as shown by Brochu et al. 4. Homo-Stereocomplexation The reported examples for the PLA-based stereocomplex from various types of polymer blends or from copolymers are summarized in Table 4.

4.1. Stereocomplexation in Polymer Blend 4.1.1. Homopolymers For homopolymer blends of PLLA and PDLA, intensive studies have been carried out by Tsuji et al. and Murdoch and Loomis et al. with numerous varying parameters. They found that the dominant parameters for stereocomplexation are $X_D$ and the molecular weights of PLLA and PDLA. As stated earlier, the ratio of stereocomplex crystallites to homo-crystallites decreases with the deviation of $X_D$ from 0.5 (Figure 3) and increasing molecular weights of PLLA and PDLA (Figure 21). However, no crystallite formation occurs when the $DP$ values of PLLA and PDLA are lower than 7.

4.1.2. Random Stereocopolymers Tsuji and Ikada synthesized l-lactide-rich PLA and d-lactide-rich PLA having optical purities from 0–100% and traced the crystallization behavior of their nonblended and blended films at different $T_c$ from the melt as well as during solvent evaporation. The $\Delta H_m$ and $T_m$ of stereocomplex crystallites in blended films decreased with decreasing optical purity (OP), in agreement with those of homo-crystallites in nonblended films. It was found that
Table 4. Stereocomplexation (racemic crystallization) of lactic acid-based polymers.

<table>
<thead>
<tr>
<th>Polymer pair or polymer</th>
<th>Initiator, catalyst for synthesis of lactic acid chains</th>
<th>Stereocomplexation (racemic crystallization) Procedure</th>
<th>Conditions</th>
<th>Parameters</th>
<th>Monitoring Methods</th>
<th>Stereocomplexed materials</th>
<th>Shape</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLLA/PDLA</td>
<td>Stannous octoate (Stannous 2-ethylhexanoate/ Lauryl alcohol (1-Dodecanol)</td>
<td>Solution</td>
<td>Solvent: CHCl₃</td>
<td>Molecular weights of PLLA and PDLA, L- and D-Polymer ratio and concentration, Temperature, Time</td>
<td>Viscosity, Test tube tilting, 'H NMR, DSC</td>
<td>Gels, Micropellets</td>
<td>Tsuji et al. [26]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stannous octoate (Stannous 2-ethylhexanoate/ Lauryl alcohol (1-Dodecanol)</td>
<td>Solvent: CH₂CN</td>
<td>Molecular weights of PLLA and PDLA, L- and D-Polymer ratio and concentration, Temperature, Time</td>
<td>DSC, Polaritymetry, SEM, ¹³C NMR</td>
<td></td>
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<td>Tsuji et al. [27, 43]</td>
<td></td>
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<td></td>
<td>Stannous octoate (Stannous 2-ethylhexanoate/ Lauryl alcohol (1-Dodecanol)</td>
<td>Solvent: p-Xylene</td>
<td>Molecular weights of PLLA and PDLA, L- and D-Polymer ratio and concentration, Temperature, Time</td>
<td>WAXS, ED, TEM</td>
<td></td>
<td></td>
<td>Okihara et al. [47, 48]</td>
<td></td>
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<td></td>
<td>Stannous octoate (Stannous 2-ethylhexanoate/ Lauryl alcohol (1-Dodecanol)</td>
<td>Casting</td>
<td>Solvent: CH₂Cl₂, CHCl₃, Benzene, Dioxane</td>
<td>Molecular weights of PLLA and PDLA, L- and D-Polymer ratio and concentration, Temperature, Rotation rate of non-solvent</td>
<td>WAXS, DSC, SEM, Tensile testing</td>
<td></td>
<td></td>
<td>Cartier et al. [61]</td>
</tr>
<tr>
<td></td>
<td>Stannous octoate (Stannous 2-ethylhexanoate/ Lauryl alcohol (1-Dodecanol)</td>
<td>Precipitation</td>
<td>Solvent: CH₂Cl₂, CHCl₃, Benzene, Dioxane, Nonsolvent: CH₃OH</td>
<td>Molecular weights of PLLA and PDLA, L- and D-Polymer ratio and concentration, Temperature, Rotation rate of non-solvent</td>
<td>WAXS, DSC, SEM, Tensile testing</td>
<td></td>
<td></td>
<td>Tsuji et al. [20, 24, 77]</td>
</tr>
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<td></td>
<td>Stannous octoate (Stannous 2-ethylhexanoate/ Lauryl alcohol (1-Dodecanol)</td>
<td>Bulk</td>
<td>Crystallization from the melt</td>
<td>Molecular weights of PLLA and PDLA, L- and D-Polymer ratio, Crystallization temperature and time</td>
<td>DSC, POM</td>
<td></td>
<td></td>
<td>Tsuji et al. [22, 28]</td>
</tr>
<tr>
<td></td>
<td>Stannous octoate (Stannous 2-ethylhexanoate/ Lauryl alcohol (1-Dodecanol)</td>
<td>Bulk</td>
<td>In the melt</td>
<td>Molecular weights of PLLA and PDLA, L- and D-Polymer ratio, Concentration of catalyst</td>
<td>DSC, POM</td>
<td></td>
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<td>Okihara et al. [47, 48]</td>
</tr>
<tr>
<td></td>
<td>Stannous octoate (Stannous 2-ethylhexanoate/ Lauryl alcohol (1-Dodecanol)</td>
<td>Bulk, Solution</td>
<td>Solvent: CH₂CN (Solution)</td>
<td>Fixed</td>
<td>PM-IRRAS</td>
<td></td>
<td></td>
<td>Bouque et al. [75]</td>
</tr>
<tr>
<td></td>
<td>Stannous octoate (Stannous 2-ethylhexanoate/ Lauryl alcohol (1-Dodecanol)</td>
<td>Steppwise assembly</td>
<td>Alternate immersion into polymer solutions, Solvent: CH₂CN</td>
<td>Polymer concentration and Temperature, Immersion time</td>
<td>DSC, AFM</td>
<td></td>
<td></td>
<td>Brizard et al. [80]</td>
</tr>
<tr>
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<td>Stannous octoate (Stannous 2-ethylhexanoate/ Lauryl alcohol (1-Dodecanol)</td>
<td>Stepwise assembly</td>
<td>Precipitation</td>
<td>Solvent: CH₂Cl₂, Nonsolvent: CH₃OH</td>
<td>DSC</td>
<td></td>
<td></td>
<td>Sentzawa et al. [117, 115]</td>
</tr>
<tr>
<td></td>
<td>Stannous octoate (Stannous 2-ethylhexanoate/ Lauryl alcohol (1-Dodecanol)</td>
<td>Stepwise assembly</td>
<td>Zinc powder</td>
<td>DSC</td>
<td></td>
<td></td>
<td></td>
<td>Spina et al. [112–115]</td>
</tr>
<tr>
<td></td>
<td>Stannous octoate/2,2-Methoxy-ethoxyethanol</td>
<td>Stepwise assembly</td>
<td>Bulk</td>
<td>Crystallization from the melt</td>
<td>Molecular weights of PLLA and PDLA, L- and D-Polymer ratio, Crystallization temperature and time</td>
<td>DSC, WAXS, POM</td>
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<td>Stannous octoate/2,2-Methoxy-ethoxyethanol</td>
<td>Stepwise assembly</td>
<td>Precipitation</td>
<td>Solvent: CH₂Cl₂, Nonsolvent: CH₃OH</td>
<td>DSC</td>
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<td>Stannous octoate/Lauryl alcohol</td>
<td>Stepwise assembly</td>
<td>Bulk</td>
<td>Crystallization from the melt</td>
<td>Molecular weights of PLLA and PDLA, L- and D-Polymer ratio, Temperature program</td>
<td>DSC, WAXS, POM</td>
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<td>Stannous octoate/Lauryl alcohol</td>
<td>Stepwise assembly</td>
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<td>Crystallization from the melt</td>
<td>Molecular weights of PLLA and PDLA, L- and D-Polymer ratio, Temperature program</td>
<td>DSC, WAXS, POM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymer pair or polymer</td>
<td>Initiator, catalyst for synthesis of lactic acid chains</td>
<td>Procedure</td>
<td>Conditions</td>
<td>Parameters</td>
<td>Monitoring Methods</td>
<td>Stereocomplexed materials</td>
<td>Stereocomplexation (triclinic crystallization)</td>
<td>Shape</td>
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<td>-------------------------</td>
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<tr>
<td>PLLA-b-PCL/PDLA-b-PCL</td>
<td>Yttrium isopropoxide/ Stannous octoate</td>
<td>Precipitation</td>
<td>Solvent: CHCl₃, Nonsolvent: C₂H₅OC₂H₅</td>
<td>Molecular weight of PLA block, Molecular weight of PLA and PCL blocks</td>
<td>DSC, DSC</td>
<td>Stevels et al. [88]</td>
<td>Stereocomplexation (racemic crystallization)</td>
<td>Stereocomplexed materials</td>
</tr>
<tr>
<td>PLLA-b-PCL/PLA/</td>
<td>Yttrium alkoxide/Stannous octoate</td>
<td>Solution</td>
<td>Solvent: THF</td>
<td>Polymer concentration, Temperature</td>
<td>LS, DSC, 'H NMR, IR</td>
<td>DSC</td>
<td>Solvent: CHCl₃, Nonsolvent: CH₂OH</td>
<td>Yui et al., [89]</td>
</tr>
<tr>
<td>PDLA-b-PEG</td>
<td>Yttrium alkoxide/Stannous octoate</td>
<td>Solution</td>
<td>Solvent: CH₃CN</td>
<td>Molecular weight of PLA and PCL blocks</td>
<td>DSC, DSC</td>
<td>Ovitt et al. [114,115]</td>
<td>Stereocomplexation (racemic crystallization)</td>
<td>Stereocomplexed materials</td>
</tr>
<tr>
<td>PDLA-b-PEG</td>
<td>Stannous octoate/PEG</td>
<td>Precipitation</td>
<td>Solvent: CH₃CN</td>
<td>Fixed</td>
<td>WAXD, AFM</td>
<td>DSC</td>
<td>Yui et al., [89]</td>
<td>Dijkstra et al. [87]</td>
</tr>
<tr>
<td>PLLA-b-PEG</td>
<td>Stannous octoate/PEG</td>
<td>Casting</td>
<td>Solvent: CH₃CN</td>
<td>Fixed</td>
<td>DSC</td>
<td>Yui et al., [89]</td>
<td>Dijkstra et al. [87]</td>
<td></td>
</tr>
<tr>
<td>PLLA-b-PEG</td>
<td>Stannous octoate/PEG</td>
<td>Solution</td>
<td>Solvent: CH₃CN</td>
<td>Fixed</td>
<td>DSC</td>
<td>Yui et al., [89]</td>
<td>Dijkstra et al. [87]</td>
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<tr>
<td>PLLA-b-PEG</td>
<td>Zinc powder/PEG</td>
<td>Solution</td>
<td>Solvent: H₂O</td>
<td>Molecular weights of PLA and PCL blocks, Temperature, Time</td>
<td>DSC, WAXS, Ramun spectroscopy, Viscelasticity</td>
<td>Gels</td>
<td>Li and Vee [90]</td>
<td></td>
</tr>
<tr>
<td>PLLA-b-PSA</td>
<td>Polycondensation/PSA</td>
<td>Casting (Solution and melt)</td>
<td>Solvent: CH₃Cl</td>
<td>Molecular weights of PLA and PSA blocks, Polymer mixing ratio</td>
<td>DSC, SEM</td>
<td>Li and Vee [90]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLLA-b-PSA</td>
<td>Stannous octoate/HEMA</td>
<td>Solution</td>
<td>Solvent: Acetate-buffered solution (pH 4)</td>
<td>Molecular weight of PLA and PDLA chains</td>
<td>Storage modulus, FT-IR, Swelling</td>
<td>Films</td>
<td>de Jong et al. [90-92]</td>
<td></td>
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<td>PolylHEMA-graft-oligo-c-tacticity</td>
<td>Poly(HEMA-graft-oligo-c-tacticity)</td>
<td>Casting</td>
<td>Solvent: CH₃OH</td>
<td>Molecular weight of PLA and PDLA chains</td>
<td>Rheological measurements, Swelling</td>
<td>Gels</td>
<td>Lim et al. [93]</td>
<td></td>
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<td>pHPMAm-graft- lactic acid oligomers</td>
<td>Stannous octoate</td>
<td>Solution</td>
<td>Solvent: Acetate buffer (pH 4)</td>
<td>Molecular weight of PLA and PDLA chains</td>
<td></td>
<td></td>
<td>van Nostrum [94]</td>
<td></td>
</tr>
<tr>
<td>PMMA/PMMA</td>
<td>Stannous octoate/Lauryl alcohol</td>
<td>Solution</td>
<td>Solvent: CH₃OH/CHCl₃ × (s/v) = 2/1, in the presence of NaCl</td>
<td>Molecular weights of l- or D-lactide side chains, Solvent</td>
<td>DSC, WAXS</td>
<td>Li and Vee [90]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBLA-grafted film/PDLA</td>
<td>Stannous octoate</td>
<td>Solution</td>
<td>Solvent: CH₃CN, CHCl₃</td>
<td>Molecular weights of l- or D-lactide side chains, Solvent</td>
<td>DSC, WAXS</td>
<td>Li and Vee [90]</td>
<td></td>
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</tr>
<tr>
<td>Stereo-block PLA</td>
<td>Aluminum tri(2-propionate)</td>
<td>Precipitation</td>
<td>Solvent: Toluene, Nonsolvent: CH₃OH</td>
<td>Molecular weight of l-1-lactide side chains, Solvent</td>
<td>FT-IR, WAXS</td>
<td>Li and Vee [90]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLLA/PSA</td>
<td>Stannous octoate</td>
<td>Solution</td>
<td>Solvent: CH₃CN</td>
<td>Fixed</td>
<td>DSC</td>
<td>Li and Vee [90]</td>
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<td></td>
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<tr>
<td>PLLA/LDH</td>
<td>Zinc powder/Stannous octoate, or Polymers were supplied</td>
<td>Bulk during hydrolytic degradation</td>
<td>Solvent: CH₃CN</td>
<td>Fixed</td>
<td>DSC</td>
<td>Li and Vee [90]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLLA/b-PCL</td>
<td>Stannous octoate</td>
<td>Solution</td>
<td>Solvent: CH₃CN</td>
<td>Fixed</td>
<td>DSC</td>
<td>Li and Vee [90]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLLA/Leuprolide/PDLA/</td>
<td>Stannous octoate/Br-enzyl alcohol</td>
<td>Solution</td>
<td>Solvent: CH₃CN</td>
<td>Fixed</td>
<td>DSC</td>
<td>Li and Vee [90]</td>
<td></td>
<td></td>
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<tr>
<td>PLLA/b-PCL</td>
<td>Stannous octoate/Octanol</td>
<td>Solution</td>
<td>Solvent: CH₃CN</td>
<td>Fixed</td>
<td>DSC</td>
<td>Li and Vee [90]</td>
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stereocomplex crystallites in blended films as well as homo-crystallites in nonblended films can be formed as long as both L-lactide-rich PLA and D-lactide-rich PLA have OP values above 76% ($X_D = X_{DL}/C_{LC}$) (Figure 22). Only in this section is $X_D$ used as D-lactide unit content in a copolymer according to the following definition:

$$X_D = \frac{\text{Weight of D-lactide}}{\text{Weight of L- and D-lactide}}$$  \hspace{1cm} (2)

The L-lactyl unit sequence length ($l_L$) and D-lactyl unit sequence length ($l_D$) can be calculated from $X_D$ values using Equation (3) and (4):\textsuperscript{[88]}

$$l_L = 2/X_D$$  \hspace{1cm} (3)

$$l_D = 2/(1 - X_D)$$  \hspace{1cm} (4)

These equations assume that L-lactide and D-lactide were polymerized by their random addition and that no ester exchange reaction occurred during polymerization and thermal treatment. Figure 22 and Equation (2)--(4) indicate that for the solution-casting method at least 16.4 L-lactyl unit sequences and D-lactyl unit sequences are required for PLA stereocomplexation (stereocomplex crystallization) and homo-crystallization\textsuperscript{[28]} in agreement with the results for the melt-crystallization method\textsuperscript{[23]}. The critical sequence unit value is slightly higher than the 7 lactyl units for pairs of the L-lactic acid oligomer and D-lactic acid oligomer,\textsuperscript{[85]} in the case of melt-crystallization, by crystallization from the melt at temperatures between the $T_m$ values of stereocomplex crystallites and homo-crystallites (between the solid line and dashed/single dotted line for blended specimens in Figure 23), well-stereocomplexed PLA materials can be prepared.\textsuperscript{[23]} On the other hand, Brochu et al.\textsuperscript{[68]} synthesized PLLA, PDLA, and poly(L-lactide-co-D-lactide) [P(LLA-DL)](20/80) and investigated stereocomplexation between PLLA and P(LLA-DL)(20/80) as well as that between PLLA and PDLA during cooling from the melt under various mixing ratios of the two polymers.

### 4.1.3. Hetero Random Copolymers

Murdock and Loomis reported the effects of incorporated ε-caprolactone units on PLA stereocomplexation by preparing equimolar blends of poly(L-lactide-co-ε-caprolactone) [P(LLA-CL)] and poly(D-lactide-co-ε-caprolactone) [P(DLA-CL)]\textsuperscript{[62]} having ε-caprolactone unit content of up to 32 wt%. The $T_m$ of the stereocomplex decreased with increasing the ε-caprolactone unit content. However, the critical lactyl unit sequence length for stereocomplexation was not identified. By a procedure similar to that in Section 4.1.2., Tsuji and Ikada\textsuperscript{[29]} studied the effects of incorporated glycolyl unit (a half glycolide unit) content on PLA stereocomplexation. The $\Delta H_m$ and $T_m$ of stereocomplex crystallites in equimolarly ($X_D = 0.5$) blended films decreased with increasing glycolyl unit content, in agreement with those of homo-crystallites in nonblended films. The stereocomplex crystallites in blended films of poly(L-lactide-co-glycolide) [P(LLA-GA)] and poly(D-lactide-co-glycolide) [P(LDA-GA)] are formed with L- and D-lactide unit content as low as 72.1 and 68.6 wt%, respectively.
whereas the homo-crystallites in nonblended films are formed with l- or d-lactyl unit content above 81.0 wt% (Figure 24). The calculated critical l- or d-lactyl unit sequence length for stereocomplex crystallization in the blended films (5.5 lactyl units) is lower than 8.8 lactyl units for homo-crystallites in the nonblended films, reflecting the fact that the peculiarly strong interaction between the L-lactyl unit sequences and D-lactyl unit sequences enhances the stability of stereocomplex crystallites and the crystallizability of the blended films. Here, the calculation procedure for the lactyl unit sequence length is similar to the Equation (3) and (4), and is given in our recent article.[88] This value of 5.5 lactyl units is slightly lower than the 7 lactyl units for pairs of the L-lactic acid oligomer and D-lactic acid oligomer.[85] It should be noted that the critical values shown here are average values and, therefore, the copolymers contain l- or d-lactyl unit sequences longer than the average values. The critical value for the lactide-glycolide copolymer is lower than that for random lactide stereocopolymers (Section 4.1.2.), suggesting that the glycolide units in the copolymers must have enhanced the stereocomplexation between l-lactyl unit sequences and d-lactyl unit sequences. It seems probable that the lower steric hindrance of the ethylidene group of glycolyl units (compared with the high steric hindrance of the ethylidene group of l-lactyl or d-lactyl units) raises the chain mobility of glycolide copolymers, resulting in high stereocomplexation during solvent evaporation.

4.1.4. Hetero Block Copolymers

4.1.4(a). With Poly(ε-caprolactone) (PCL) Blocks

Dijkstra et al.[89] prepared an A-B diblock copolymer [number-average molecular weight (\(M_n\)) = 3.87 \times 10^4 g·mol⁻¹] of PLLA (A) and PCL (B) as well as PDLA (\(\overline{M}_n = 9.7 \times 10^3\) g·mol⁻¹). They indicated that PLA stereocomplexation takes place even in the presence of polymeric impurity of a PCL block. In this blend, ε-caprolactone unit sequences were phase-separated to form their crystalline regions.

Stevels et al.[90] synthesized A-B diblock copolymers of PLLA or PDLA (DP = 1–80) (A) and PCL (DP = 70) (B). Upon blending PLLA-b-PCL and PDLA-b-PCL, both having weight fractions of PLA blocks above 44%, a \(T_m\) increase (ca. 55°C) of the PLA crystalline regions was observed due to stereocomplexation, while for the blends composed of PLLA-b-PCL and PDLA-b-PCL, both having weight fractions of PLA blocks below 22%, no melting of the PLA crystalline regions was observed, meaning that the PLA blocks were noncrystallizable. On the other hand, crystallization of PCL blocks took place in the blended specimens as well as in the nonblended specimens. Portinha et al.[56] prepared A-B diblock copolymers of PLLA or PDLA (A) and PCL (B) and monitored their aggregation behavior in nonblended and blended THF solutions. The hydrodynamic radii of assemblies in enantiomeric blended solutions were 200 nm, which were higher than those in nonblended polymer solutions. The radius distribution in enantiomeric blend solutions was sharper than that of nonblended polymer solutions. Furthermore, the same research group[57] continued studies on the self-assembly of PLLA-b-PCL and PDLA-b-PCL in THF by the use of DSC, dynamic LS measurements, \(^1\)H NMR spectroscopy, and FT-IR. They revealed that, at higher concentrations such as 10 g·dL⁻¹, stereocomplexation was in competition with a solvophobically driven aggregation, whereas at lower concentrations, only the stereocomplexation process was involved.

Figure 24. Schematic representation for the phases and \(T_m\) in Blend 1 [nonblend P(DLA-GA), Blend 3 and 32 [blended films from PDLA and P(DLA-GA)] (a), Blend 2 [blended films from P(LLA-GA) and P(DLA-GA)], Blend 4 [blended films from PDLA and P(LLA-GA)], and Blend 42 [blended films from PLLA and P(DLA-GA)] (b).[29] The areas with horizontal stripes, vertical stripes, both horizontal and vertical stripes, and without stripes mean homo-crystalline + amorphous, stereocomplex crystalline + amorphous, stereocomplex crystalline + homo-crystalline + amorphous, and amorphous, respectively. \(T_{m1}\) and \(T_{m2}\) are the \(T_m\) of homo-crystallites and stereocomplex crystallites, respectively.

4.1.4(b). With Poly(ethylene glycol) (PEG) Blocks

Brizzolara et al.\(^{[50]}\) prepared A-B diblock copolymers (\(\bar{M}_n = 5.6 \times 10^4\) and \(5.9 \times 10^4\) g \(\cdot\) mol\(^{-1}\)) of PLLA or PDLA (A) and PEG (B). The molecular weight ratio of the PLA block to the PEG block was 1.5/1. They traced stereocomplexation between enantiomeric copolymer blends by WAXS, and the difference in the morphology between precipitates of nonblended and blended polymers by AFM.

Stevels et al.\(^{[92]}\) synthesized A-B-A triblock copolymers (\(\bar{M}_n = 6.7 \times 10^3\)–\(2.3 \times 10^4\) g \(\cdot\) mol\(^{-1}\), PEG content 27–86 wt\%) of PLLA or PDLA (A) and PEG (\(\bar{M}_n = 6 \times 10^3\)) (B) and prepared equimolar mixtures of PLLA-b-PEG-b-PLLA and PDLA-b-PEG-PDLA by two different procedures, precipitation and solution-casting. Although they investigated the effects of the procedures on stereocomplexation as reported for the blends from pure PLLA and PDLA,\(^{[20,21]}\) stereocomplexation occurred readily in specimens prepared by these two different procedures. Probably, the molecular weights of the block copolymers were sufficiently low to form stereocomplex crystals, irrespective of the procedure. Another probable explanation is that the PEG segments acted as a plasticizer for the PLA segments and consequently enhanced stereocomplexation of the block copolymers. On the other hand, Lim and Park\(^{[93]}\) prepared A-B-A triblock copolymers of PLLA (\(\bar{M}_n = 200, 250\)) or PDLA (\(\bar{M}_n = 208, 262\)) (A) and PEG (\(\bar{M}_n = 23, 77\)) (B). Stereocomplexation between the enantiomeric block copolymers was traced by DSC and WAXS. The cumulative release of bovine serum albumin (BSA) was lower for stereocomplexed microspheres than for those of nonblended block copolymers, when compared with the same period. Furthermore, Fujiwara et al.\(^{[94]}\) prepared synthesized A-B-A triblock copolymers (\(\bar{M}_n = 7 \times 200\) and \(6 \times 800\) g \(\cdot\) mol\(^{-1}\)) of PLLA or PDLA (A) and PEG (\(\bar{M}_n = 4 \times 600\) g \(\cdot\) mol\(^{-1}\)) (B). The enantiomeric triblock copolymers were separately dissolved in tetrahydrofuran (THF)/water (v/v) = 1/2 and then THF was removed by evaporation, leaving 10 wt.-% aqueous dispersion. They traced stereocomplexation between the enantiomeric triblock copolymers upon heating the aqueous dispersion from room temperature to 37°C by rheological measurements, the test tube tilting method, and WAXS.

Li and Vert\(^{[95,96]}\) synthesized A-B diblock and A-B-A triblock copolymers of PLLA or PDLA (\(\bar{M}_n = 12–52\), molar mass = 860–3 700) (A) and PEG (\(\bar{M}_n = 104–454\), molar mass = 4 600–20 000) (B). The crystallization of PEG was dominant in these block copolymers. On blending the enantiomeric block copolymers in an aqueous medium, gels were formed, as seen for the homopolymer blends of PLLA and PDLA in organic solvents.\(^{[26,62]}\) Such stereocomplexation was confirmed by Raman spectroscopy, WAXS, and rheological measurements.\(^{[95,96]}\)

4.1.4(c). With Poly(sebacic acid) (PSA) Blocks

Slivniak and Domb\(^{[97]}\) synthesized A-B-A triblock copolymers of PLLA or PDLA (\(\bar{M}_n = 20–30\)) (A) and PSA (\(\bar{M}_n = 2–40\)) (B) and observed stereocomplexation between these enantiomeric block copolymers.

4.1.5. Graft Copolymers

Lim et al.\(^{[98]}\) prepared poly[2-hydroxyethyl methacrylate-graft-\(\alpha\)-(or \(\beta\)-lactide)] and poly[2-hydroxyethyl methacrylate-graft-\(\alpha\)-(or \(\beta\)-lactide)] by radical polymerization of macromonomers 2-hydroxyethyl methacrylate-graft-\(\alpha\)-(or \(\beta\)-lactide) and 2-hydroxyethyl methacrylate-graft-\(\alpha\)-(or \(\beta\)-lactide), respectively, in the presence of \(2,2\)′-azoisobutyronitrile (AIBN). The macromonomers were synthesized by ring-opening polymerization of \(\alpha\)- or \(\beta\)-lactide in the presence of stannous octoate and 2-hydroxyethyl methacrylate as initiator and coinitiator, respectively. Stereocomplexation occurred during solution-casting of mixed solutions of enantiomeric graft polymers. The stereocomplexed films became hydrogels in aqueous media.

de Jong et al.\(^{[86,99–102]}\) synthesized dextran [degree of substitution (DS, number of lactic acid side chains per 100 glucopyranose units) = 3–17]-graft-\(\alpha\)-(or \(\beta\)-lactic acid oligomers [average degree of polymerization (\(\bar{M}_n\)) = 6–12] by forming a carbonate bond using \(N,N\)′-carbonyldiimidazole (CDI) and monitored their stereocomplexation in an acetate-buffered solution (100 \(\times\) 10\(^{-3}\)M, pH 4) by rheological measurements. Here, lactic acid oligomers were synthesized by ring-opening polymerization of LLA or DLA using stannous octoate and 2-(2-methoxyethoxy) ethanol (MEE) as initiator and coinitiator, respectively. At 20°C the storage modulus (\(G^′\)) of dextran-graft-enantiomeric lactic acid oligomers increased with time due to the formation of crosslinks composed of stereocomplex crystals, but decreased upon heating to 80°C due to their melting. They confirmed stereocomplexation by FT-IR\(^{[99]}\) as well as WAXS.\(^{[57]}\) The properties of stereocomplexed hydrogel can be manipulated by altering \(\bar{M}_n\) and DS. It was found that at least 11 lactyl units are required to obtain a stereocomplexed hydrogel.\(^{[99]}\) These results are summarized in detail in their review article.\(^{[101]}\) Furthermore, the same research group, van Nostrum et al.\(^{[103]}\) prepared...
poly(2-hydroxypropylmethylacrylamide) (pHPMAm)–graft-l- (or d-)lactic acid oligomers by forming an ester linkage using AIBN. The gels were formed from pHPMAm–graft-enantiomeric l- and d-lactic acid oligomers in an acetate-buffered solution (pH 4) as evidenced by rheological measurements (G').

Watanabe and Ishihara et al. synthesized graft–type copolymers containing l-lactic unit sequences or d-lactic acid sequences as side-chains (PMBLLA and PMBDLA, respectively) by copolymerization of 2-methacryloxyethyl phosphorylcholine (MPC), butyl methacrylate, and PLLA or PDLLA macromonomers. They prepared porous stereocomplexed films using an extraction method with water-soluble particles of NaCl. On the other hand, Tretinnikov et al. synthesized graft layers of PLLA with thicknesses from 7 to 35 nm from hydroxy end-groups of a self-assembled monolayer on gold and monitored the stereocomplexation between free PDLA and grafted PLLA chains on the surface by the use of WAXS and FT-IR. In other words, PDLA molecules were effectively adsorbed on or entrapped by the PLLA-grafted surface.

4.2. Stereocomplexation in Nonblended Polymers

4.2.1. Stereo-Block Copolymers

Yui et al. and Dijkstra et al. synthesized A-B diblock copolymers of PLLA (A) and PDLA (B) having l-lactyl unit content of from 82 to 37% through a ring-opening sequential two-step polymerization of l- and d-lactide [Figure 1(e)] initiated by aluminum tris(2-propanolate) Al[OCH(CH3)2]3. Although they observed stereocomplexation between l-lactyl unit sequences and d-lactyl unit sequences in a block copolymer (Mn = 2.01 × 103 g · mol⁻¹) even with l-lactyl unit content of 55%, further investigation on the block copolymer has not been reported so far.

Spaskey et al., Wisniewski et al., Sarasua et al., Radano et al., and Ovitt and Coates synthesized highly isotactic stereo-block copolymers from lactides with relatively low optical purities in one step [Figure 1(f)] using Schiff’s base/aluminum alkoxide initiators, [{−}(Salbinap)AlOMe], achiral SalennAlOMe, or racemic [{Salbinap}Al(O-iPr)]. They traced stereocomplexation in the stereo-block copolymers by DSC, WAXS, and/or POM. Sarasua et al. showed that stereocomplexation of PLLA with [2]25D of −66, −73, and −95 deg · dm⁻¹ · g⁻¹ · cm⁻² in chloroform can occur when the crystallization temperature and time are carefully selected.

Fukushima et al. proposed a novel procedure to synthesize stereo-block PLA by solid-state polycondensation of a stereocomplexed mixture of PLLA and PDLA. In the first step, homopolymers PLLA and PDLA having 2.0–4.6 × 10³ g · mol⁻¹ were prepared; in the second step the enantiomeric homopolymers were melt-mixed to form stereocomplex crystallites; in the third step further polycondensation of the stereocomplexed mixture was carried out.

4.2.2. Random Stereo Copolymers

Normally, in marked contrast to stereo-block copolymers and blends between l-lactide-rich PLA and d-lactide-rich PLA, no stereocomplexation occurs in relatively random stereo copolymers during materials preparation. However, Li et al. found stereocomplexation between l-lactyl unit sequences and d-lactyl unit sequences in poly(l-lactide-co-d-lactide)(62.5/37.5) (i.e. PDLLA) prepared with zinc powder, PDLLA prepared with stannous octoate, and supplied PDLLA, when thick plates of these copolymers were hydrolyzed to a great extent in a phosphate-buffered solution at 37 °C for 30 and 17 weeks, in an aqueous solution with a caffeine base for 27 weeks, and in a phosphate-buffered solution at 60 °C for 4 weeks, respectively. Stereocomplexation took place in a shorter period for plate specimens than for film specimens, reflecting the fact that accelerated hydrolytic degradation at the core parts of the plates enhances stereocomplexation. They suggested that although the initial fractions of l-lactyl unit sequences and d-lactyl unit sequences having high sequence numbers are low in these copolymers, the fractions will be increased by selective hydrolysis and removal of chains with relatively random sequences, resulting in stereocomplexation. Stereocomplexation can be ascribed to the predominantly isotactic structure of the copolymers obtained by ring-opening polymerization of lactides with low optical purities. Schwach et al. investigated the effects of the kinds of catalysts on stereocomplexation as well as tacticity, water uptake, weight loss, and release of acids. It was demonstrated that stereocomplexation during hydrolytic degradation was not influenced by the kind of catalyst and that PDLLA synthesized with stannous octoate had a predominantly isotactic structure.

5. Hetero-Stereocomplexation

In the previous sections, stereocomplexation is restricted to that between l-lactyl unit sequences and d-lactyl unit sequences (homo-stereocomplexation). In this section, stereocomplexation between the PDLA and the l-enantiomeric form of an optically active polymer or between PLLA and the d-enantiomeric form of another kind of optically active polymer (hetero-stereocomplexation) is described.

Slager and Domb et al. reported hetero-stereocomplexation between PDLA and l-configured peptides such as the lutetizing hormone-releasing hormone (LHRH), leupiride (an LHRH nonapeptides analogue), and vapreotide (a cyclic octapeptide somatostatin)
analogue). Hetero-stereocomplexation was observed by the use of DSC, SEM, SAXS, cryogenic transmission electron microscopy (Cryo-TEM), and confocal microscopy. In addition to DSC results, the increase in scattering intensity in SAXS suggested the formation of hetero-stereocomplex particles, which was further evidenced by SEM and Cryo-TEM and confocal microscopic photographs. The stereocomplex particles had a mean unweighted particle size of 1.7 \( \mu \text{m} \).

L-Insulin and PDLA form stereocomplex porous particulate precipitates and become insoluble in acetonitrile which dissolves isotactic PLLA or PDLA at an elevated temperature. The results of DSC measurements and the fact that after the formation of particles no free insulin was detected by HPLC supported their hetero-stereocomplexation. They also prepared hetero-stereocomplexed particles for drug delivery systems (DDS) of insulin with PDLA, PDLA-b-PEG, PDLA-b-PEG-PDLA, PLLA/PDLA, or PLLA-b-PEG/PDLA-b-PEG. When insulin, \( \alpha \)-lactyl unit sequences, and \( \beta \)-lactyl unit sequences were involved in a system, two types of stereocomplex can be formed, i.e., a homo-stereocomplex and a hetero-stereocomplex.

On the other hand, Force-Field simulation predicted that PLLA [\( (-)\)-PLA] can form a hetero-stereocomplex with (+)-alternating isotactic propylene-CO-copolymers [P(P-alt-CO)] and vice versa. However, Brizzolara et al. have not yet shown experimental evidence for hetero-stereocomplexation.

6. Degradation
6.1. Thermal Degradation

Tsuji and Fukui performed a thermogravimetric study on an equimolar (\( \chi_\text{D} = 0.5 \)) blend of PLLA and PDLA as well as nonblended PLLA and PDLA. These polymers were synthesized with stannous octoate (0.03 wt%, Sn content < 88 ppm) and lauryl alcohol (0.5 wt% for PLLA, 0.4 wt% for PDLA) and purified by precipitation using methylene chloride and methanol, as solvent and non-solvent, respectively. The initial \( M_n \) values of PLLA and PDLA before thermal degradation were \( 8.7 \times 10^4 \) and \( 9.5 \times 10^4 \) g \( \cdot \) mol\(^{-1} \), respectively. In heat scanning at a constant rate in thermogravimetry (TG), a very small difference was observed between the TG curves of the specimens, whereas at fixed temperatures of 250 and 260 \( ^\circ \text{C} \) exceeding the \( T_m \) of the stereocomplex, i.e. in the melt, the equimolar blend has higher stability than the nonblended PLLA or PDLA (Figure 25). It is expected that the \( 3_1 \) helical conformation remains even in the melt of the blend at temperatures exceeding the \( T_m \) of the stereocomplex and, therefore, the peculiarly strong interaction between \( \beta \)-lactyl chains and \( \alpha \)-lactyl chains has a significant effect in reducing the molecular mobility and, therefore, in disturbing the thermal degradation. However, it seems that, at temperatures far higher than the \( T_m \) of the stereocomplex, such peculiar interaction arising from the helical conformation disappears, resulting in a small difference in thermal stability between nonblended and blended films. The activation energy for the thermal degradation (\( \Delta E_{\text{td}} \)) values was estimated by the method recommended by MacCallum et al. The obtained \( \Delta E_{\text{td}} \) value of the equimolar blend was in the range of 205–297 kJ \( \cdot \) mol\(^{-1} \), which was higher by 82–110 kJ \( \cdot \) mol\(^{-1} \) than the averaged \( \Delta E_{\text{td}} \) values of nonblended PLLA and PDLA (87–104 kJ \( \cdot \) mol\(^{-1} \)).

On the other hand, Fan et al. reported \( \Delta E_{\text{td}} \) values of 80–100, 100–120, and 125–180 kJ \( \cdot \) mol\(^{-1} \) respectively for as-polymerized (Sn content: 286 ppm), purified by precipitation with methanol (Sn content: 266 ppm), and purified metal-free (Sn content < 10 ppm) equimolar blend specimens from PLLA (\( M_n = 1.2–1.3 \times 10^5 \) g \( \cdot \) mol\(^{-1} \)) and PDLA (\( M_n = 1.2–1.3 \times 10^5 \) g \( \cdot \) mol\(^{-1} \)). The thermal degradation of the three specimens proceeds through mecha-
isms of unzipping caused by the Sn-alkoxide chain end, Sn-catalyzed selective lactide elimination, and random degradation, respectively. In our study, constant temperature analysis was made in the temperature range where PLLA and PDLA have a peculiarly strong interaction, while Fan et al. analyzed the specimens under constant heating, and the procedure for $\Delta E_{\text{id}}$ estimation is different from our case.\textsuperscript{120–131} The $\Delta E_{\text{id}}$ value difference between the two articles (ours and Fan et al.) is attributable to the differences in initial molecular weights and terminal groups of PLLA and PDLA, the kind and concentration of the remaining catalyst, and the method and procedure for $\Delta E_{\text{id}}$ estimation.

6.2. Hydrolytic Degradation

Tsuji found that stereocomplexed PLA specimens have a higher hydrolysis-resistance compared with that of nonblended PLLA and PDLA specimens when they were hydrolyzed in a phosphate-buffered solution at pH 7.4 and 37°C (Figure 26).\textsuperscript{132} It is surprising that although the decrease in tensile strength of the nonblended specimens started even at 4 months, the stereocomplex specimens retained their initial tensile strength for a long period of 16 months. Similarly, de Jong et al.\textsuperscript{100} reported hydrolytic degradation of solution-cast L-lactic acid oligomers ($DP = 7$) and the stereocomplex of L- and D-lactic acid oligomers ($DP = 7$) at pH 7 and 37°C. They showed that the fraction of the L-lactic acid oligomer approached nil within 4 h, whereas 50% of the stereocomplex remained even after 96 h of degradation. Here, although the L-(or D-)lactic acid oligomer and stereocomplex are amorphous and crystalline, respectively, the obtained results are in agreement with our results.\textsuperscript{132} Such stereocomplex crystallization should have disturbed the hydrolytic degradation of stereocomplexed specimens compared with that of the L-lactic acid oligomer. However, hydrolytic degradation proceeds predominantly in the amorphous regions between the stereocomplex crystalline regions. This means that the PLLA chains and PDLA chains should have a peculiarly strong interaction even when they are in an amorphous state, as suggested by the aforementioned thermal degradation results.\textsuperscript{123} To confirm this assumption, we prepared various types of equimolarly blended specimens from PLLA and PDLA, i.e., amorphous-made\textsuperscript{133} and homo-crystallized,\textsuperscript{19} and carried out their hydrolytic degradation in a phosphate-buffered solution at pH 7.4 and 37°C, together with nonblended PLLA and PDLA specimens. We observed retarded hydrolytic degradation of the blended specimens compared with the nonblended specimens, irrespective of their state, amorphous or homo-crystallized, reinforcing the abovementioned hypothesis. Tsuji and Suzuki\textsuperscript{134} carried out the hydrolytic degradation of stereocomplexed fibers and films and revealed that the morphology of the stereocomplexed materials have crucial effects on their hydrolytic degradation rates.

There have been some reports that stereocomplexation between enantiomeric L-lactide unit sequences and D-lactide unit sequences retarded hydrolytic degradation; e.g., poly[2-hydroxyethyl methacrylate-graft-oligo(lactide)] (Lim et al.\textsuperscript{98}) and A-B-A triblock copolymers of
PLA (A) with poly(sebacic acid) (PSA) (B) (Slivniak and Domb\cite{97}). On the other hand, de Jong et al.\cite{102} indicated that hydrolytic degradation of the stereocomplex hydrogels from dextran (DS = 3–12)-graft-L- and D-lactic acid oligomers (DP = 6–12) depends on the number of lactate grafts (DS), the length (DP) and polydispersity of the grafts, and the initial water content, and that the degradation time varied from one to seven days. Moreover, van Nostrum et al.\cite{103} showed that the hydrolytic degradation time of the stereocomplex hydrogels from poly(2-hydroxypropylmethacrylamide) (pHPMAm)-graft-L- and D-lactic acid oligomers can be readily tailored from 1 week to almost 3 weeks by changing the grafting density of the polymers and the structure of the terminal group of the side chains.

6.3. Alkaline Degradation

Serizawa et al.\cite{135} prepared the PLA stereocomplex assembly and the assemblies composed of both a stereocomplex crystalline layer and a PLLA homo-crystalline layer deposited on QCM substrates by the procedure stated earlier (Section 3.2.4), and their alkaline hydrolytic degradation rates were investigated. They claimed that the hydrolysis-resistance of the PLLA crystalline layer having a 10 helical conformation is higher than the stereocomplex layer having a 3 helical conformation, in marked contrast to the abovementioned results in neutral media (Section 6.2).

6.4. Enzymatic Degradation

Proteinase K is an endo-protease having broad specificity but with preference for the cleavage of the peptide bond C-terminal to aliphatic and aromatic amino acids, especially alanine.\cite{136} The similar chemical structures of lactic acid and alanine are expected to induce the proteinase K-catalyzed hydrolysis of the C-terminal of PLLA or \( \alpha \)-lactyl unit sequences. As already found, proteinase K can catalyze the hydrolytic degradation of \( \alpha \)-lactyl chains in amorphous regions.\cite{137,138} The tie chains and chains with a long free end in amorphous regions can be enzymatically cleaved, whereas the folding chains and the chains with a short free end are highly resistant to enzymatic cleavage.\cite{139} Since hydrolytic degradation proceeds predominantly in amorphous regions, we investigated the effects of the presence of PDLA on proteinase K-catalyzed enzymatic degradation of PLLA in an amorphous state.\cite{140} Assuming that PLLA and PDLA have no interaction with each other, PLLA in blends with PDLA will be enzymatically degraded in the presence of proteinase K as in nonblended PLLA. However, the enzymatic hydrolysis rate (\( R_{EH} \)) of PLLA was largely reduced by the presence of PDLA (Figure 27). In other words, the presence of PDLA disturbed the adsorption or cleavage process of proteinase K. The finding here reflects the fact that PLLA and PDLA chains are well-mixed in the amorphous state and that they have strong interaction with each other.

7. Applications

7.1. Biodegradable Films

Biodegradable PLA-based stereocomplex films can be prepared by the solution-casting method with organic solvents such as chloroform and methylene chloride.\cite{20,62} In this method, the molecular weights of \( \alpha \)-lactyl unit sequences and \( \delta \)-lactyl unit sequences and the solvent evaporation rate are crucial parameters. Molecular weights and solvent evaporation rate which are too high disturb the stereocomplex formation, resulting in the formation of films containing a relatively large amount of homo-crystallites or having low crystallinities.\cite{20} Although PLA stereocomplex films can also be prepared by the melt-molding method, it should be noted that the critical molecular weights for PLLA and PDLA, below which only stereocomplex crystallites are formed, decrease dramatically compared with those in the solution-casting method.\cite{22} This indicates the difficulty in preparing well-stereocomplexed PLA materials with high molecular weights.

7.2. Biodegradable Fibers

Murdoch and Loomis\cite{62} prepared melt-spun PLA stereocomplex fibers from equimolar mixture of PLLA and PDLA, while Tsuji et al. obtained wet- and dry-spun PLA stereocomplex fibers\cite{77} from mixed chloroform solutions of equimolar PLLA and PDLA. In the former study no estimation of the fractions of stereocomplex crystallites and...
homo-crystallites was carried out, whereas in the latter study fraction estimation by DSC revealed that hot-drawing of as-spun fibers can increase the amount of stereocomplex crystallites and reduce that of homo-crystallites, resulting in the formation of fibers whose main crystalline kind is stereocomplex. The PLA stereocomplex fibers used by Tsuji and Suzuki, for hydrolysis experiments, which were prepared by melt-spinning and subsequent two-stage hot-drawing, contain only stereocomplex crystallites and no homo-crystallites.

Later, Takasaki et al. revealed that stereocomplexation is favored in melt-spun fibers from equimolar mixtures of PLLA and PDLA under the spinning conditions of higher take-up velocity, lower throughput rate, and lower extrusion temperature. This result suggests that these conditions can enhance the orientation-induced crystallization of the stereocomplex, as described above. They also confirmed that drawing at a lower temperature and annealing of stereocomplex crystallites and homo-crystallites further enhanced stereocomplexation in agreement with the aforementioned findings. The maximum tensile strength and Young’s modulus of stereocomplexed fibers were 530 MPa and 7.4 GPa for melt-spun and drawn stereocomplex fibers, 920 MPa and 8.6 GPa for solution-spun and drawn stereocomplex fibers, and 400 MPa and 4.7 GPa for as-spun stereocomplex fibers. These values are so far lower than the maximum tensile strength and Young’s modulus, 1.8 GPa and 14 GPa, of melt-spun and drawn PLLA fibers.

7.3. Biodegradable Microspheres for DDS

Loomis and Murdoch prepared injectable stereocomplex microspheres containing a naltrexone base using the oil-in-water (O/W) solvent-evaporation method (O: methyl chloride, W: water with a surfactant) and the release rate was determined in various media. The release of naltrexone was delayed by a lag time of 200, 230, and 240 h, and 35% of the drug released in water, acid, and buffer solutions, respectively. After the lag the release occurred in zero order up to 450 h with 46, 48, and 35% of the drug remaining in solution, acid, and buffer solutions, respectively. On the other hand, de Jong et al. prepared stereocomplex hydrogels from dextrans (DS = 3–12)-graft-L- and D-lactic acid oligomers (DP = 6–12) and showed that the stereocomplex gels released the entrapped model proteins (IgG and lysozyme) during six days.

Slager and Domb formulated hetero-stereocomplex DDS particles from L-configured peptides such as insulin with PDLA, PDLA-b-PEG, PDLA-b-PEG-PDLA, PLLA/PDLA, or PLLA-b-PEG/PDLA-b-PEG. The strong physical entrapment of peptides by the D-lactide unit sequence resulted in retarded release of the peptides. They also prepared hetero-stereocomplex DDS particles from an L-configured leuprolide and PLLA. Various factors affecting the release of leuprolide from the hetero-

7.4. Biodegradable Hydrogels

Stereocomplexed PLA hydrogels can be prepared in aqueous media by blending block or graft copolymers with hydrophilic segments and l-lactyl unit sequences or d-lactyl unit sequences. Stereocomplex hydrogels were reported for enantiomeric A-B diblock and A-B-A triblock copolymers of PLA (A) with PEG (B), poly[2-hydroxyethyl methacrylate-graft-oligo(lactide)], dextran-graft-lactic acid oligomers, and pHPMAM-graft-lactic acid oligomers.

On the other hand, Watanabe and Ishihara prepared porous stereocomplexed PLA films from graft-type copolymers, PMBLLA and PMBDLA, using an extraction procedure with water-soluble particles of NaCl and investigated the cell adhesion and morphology on the porous scaffolds. They revealed that the number of adhering cells is correlated with the PLLA or PDLA content, and that cell morphology is correlated with the MPC unit content. Fibroblast cells adhered on the surface and intruded into the scaffolds through the connected pores after 24 h. The cell morphology became round from spreading with the decreasing PLLA or PDLA content in the scaffolds.

7.5. Nucleation Agents

Schmidt and Hillmyer and Yamane and Sasai reported that stereocomplex crystallites formed by the addition of small amounts of PDLA to PLLA and act as heterogeneous nucleation sites for PLLA crystallization, or that PLLA homo-crystallites are formed epitaxially on the stereocomplex crystallites. Such nucleation agents increase the number of PLLA spherulites per unit volume and the total crystallization rate but does not alter spherulite growth rate G. The nucleation effects must arise from epitaxial crystallization of PLLA homo-crystallites on the stereocomplex crystallites, as reported for PLLA and poly(l-lactide-co-d-lactide) (20/80) when they were mixed at a ratio of 80/20 and crystallized during slow cooling from the melt.

8. Conclusions and Perspectives

Stereocomplexation gives PLA-based materials higher mechanical performance, thermal resistance, hydrolysis-resistance, and opens a new way to produce various types of...
biodegradable materials such as hydrogels and DDS particles. The former improvements arise from the peculiarly strong interaction between \( \varepsilon \)-lactyl unit sequences and \( \delta \)-lactyl unit sequences. A variety of properties of stereocomplexed PLA materials can be manipulated by molecular characteristics, highly-ordered structures, and additives. Some Lactobacilli are reported to produce exclusively \( \delta \)-lactic acid (not the mixture of \( \varepsilon \)- and \( \delta \)-lactic acids) from numerous kinds of renewable resources, and PDLA can be produced from \( \delta \)-lactic acid by the same procedure for PLLA production from \( \varepsilon \)-lactic acid. Therefore, the most crucial issue for stereocomplexed PLA materials, the reduction of the production cost of PDLA, can be solved by large-scale facilities. Reduced cost of PDLA will give stereocomplexed PLA materials further applications, not only as biomedical materials but also as alternatives for commercial polymeric materials.