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Molecular, Structural, and Material Design of Bio-Based Polymers

By Yoshiharu KIMURA*

Bio-based polymers are made from bio-originated feedstocks. Among those developed thus far, polylactides (PLA) stand at the forefront of practical use and are now manufactured on a commercial scale. However, the application of PLAs has been rather limited because of their higher cost, inferior thermal and mechanical properties, and worse processability as compared to the conventional oil-based polymers. Much effort has therefore been made to address it. Our major approach is to develop a direct polycondensation method to synthesize PLA and to use stereoblock-type PLA (sb-PLA) consisting of enantiomeric poly(L-lactide) (PLLA) and poly(D-lactide) (PDLA) because it can easily form stereocomplex (sc) showing a high melting temperature. Other specialty bio-based polymers are also synthesized for application to high-value fields. Particularly, with amphiphilic copolymers consisting of PLA and poly(oxyethylene) (PEG), new morphology change and sol-gel process have been disclosed. New bio-based polymers consisting of bio-derived monomeric units have also been synthesized to demonstrate their special functions. In addition, molecular and material design has been done with other biobased polymers such as poly(butylene succinate) (PBS) and poly(3-hydroxyalkanoate)s (PHA).

KEY WORDS: Biobased Polymer / Biodegradable Polymer / Aliphatic Polyester / Polylactide / Polycondensation / Ring-Opening Polymerization / Stereocomplex /

Polymeric materials synthesized from renewable resources such as biomasses and other bio-originated feedstocks are now being accepted as “bio-based polymers.” They are superior to the conventional petroleum-based polymers in reducing the emission of carbon dioxide because the carbon atoms incorporated in the bio-based polymers are those derived from the atmospheric carbon dioxide, and their incineration does not bring additional carbon dioxide to the atmosphere. Thus, making materials from renewable resources is to be a new concept of material production in this century and effective for reducing our dependency of energy and resources on petroleum. In this category, totally bio-based polylactides (PLA) and poly(3-hydroxyalkanoate)s (PHA) as well as partly bio-based poly(butylene succinate) (PBS) and poly(trimethylene terephthalate) (PTT) are now attracting the immediate attention. In the latter two polymers, one of the repeating units (succinate and 1,3-propanediol) are biochemically synthesized.

Historically, these bio-based polymers have been developed as biodegradable polymers. Therefore, each polymer should possess at least one of the three characters: (1) bioabsorbable polymers for biomedical use, (2) biodegradable plastics being able to be assimilated in natural environment, and (3) bio-based polymers synthesized from renewable resources as shown in Table I. In the first category, polyglycolide (PGA) and its derivatives showing fast hydrolyzability and high tenacity are commonly used,^{1,2} while PHA and PBS that are susceptible to microbial degradation are adequate to the second category.³ PLLA also shows excellent compostability in spite of being less degradable in soil and water.⁴ In the third category, the polymers are preferably made up of biomass and their

Table I. Characters of biodegradable polymers thus developed

Category	History	Alias and properties	Examples
Bio-absorbable polymer	late 1970-	Bio-resorbable polymers Biomedical materials	PGA, PLLA Polyanhydride, etc.
Biodegradable polymer	late 1980-	“Green polymer” “Green-Pla®” bio-recycle	PHA, PBS, PLLA PCL, Starch-based materials
Bio-based polymer	1998-	“Biomass plastics” Materials from renewable resources carbon neutral	PLLA, PHA, PTT Bio-succinate PBS Starch-based materials

breakdown products.⁵ This idea has emerged with increased recognition that massive consumption of fossil resources may increase the atmospheric content of radiant carbon dioxide to cause global warming. One approach to suppress the emission of carbon dioxide is to replace our energy source from fossil resources to renewable resources such as wind power and biomass that are ultimately produced by using solar energy. Consequently, a rapid paradigm shift is expected not only in the energy resources but also in the way of production of materials. Namely, the conventional petrochemical processes are substituted by the more environmentally friendly bioprocesses, and the conventional oil-based materials are replaced by the new materials based on renewable natural resources, making our production/consumption/waste treatment in a sustainable way.

We have done a pioneering work for developing such new polymers that are biodegradable and bio-based in the past 30

Department of Biomolecular Engineering, Kyoto Institute of Technology, Matsugasaki, Kyoto 606-8585, Japan

*To whom correspondence should be addressed (Tel: +81-75-724-7804, Fax: +81-75-712-3956, E-mail: ykimura@kit.ac.jp).

years.⁶ Here, we summarize our achievements by dividing them into four different parts: 1) polycondensation approach to high-molecular-weight PLLA, 2) development of stereoblock-type polylactides, 3) structure and functional properties of polylactide copolymers, and 4) synthesis of new environmentally friendly polymeric materials.

POLYCONDENSATION APPROACH TO HIGH-MOLECULAR-WEIGHT PLLA

Among the bio-based polymers thus developed, PLA derivatives stand at the forefront of practical use and are manufactured on a commercial scale.⁷ Since the monomers of PLA, L- and D-lactic acids, are enantiomeric, their polymers are also enantiomeric, and they are called poly(L-lactide) (PLLA) and poly(D-lactide) (PDLA), respectively. The polymers consisting of racemic monomers are also synthesized. PLLA obtained from naturally occurring L-form is generally produced in industrial scale. Two synthetic routes to PLLA have been known: one is ring-opening polymerization (ROP) of L-lactide and the other is the direct polycondensation of L-lactic acid. In the former method, bulk polymerization of lactide monomer in the presence of tin-based catalysts such as tin (II) bis-2-ethylhexanoate (tin octoate) is favored to avoid racemization and transesterification. This ROP method is convenient for controlling the molecular weight of PLLA and attaining a high polymer ($M_w > 1 \times 10^6$). The current manufacturers of PLLA, NatureWorks LLC (USA) and Hisun (China) depend on this ROP of L-lactide for their production.

The alternative direct polycondensation of L-lactic acid was less studied until 1995. No one believed that the polycondensation method can give a high molecular weight of PLLA, until Mitsui Chemical Co. first succeeded in obtaining a high molecular weight of PLLA by using a special solution polycondensation technique.⁸ With this epoch-making success, many researchers including the present author has made effort to establish the direct polycondensation of L-lactic acid.⁹

As shown in Scheme 1, two equilibria exist in the dehydrative polycondensation of L-lactic acid: one is hydration/dehydration equilibrium of carboxyl and hydroxyl terminals, and the other is ring/chain equilibrium between L-lactide

Scheme 1. Equilibrium reactions of PLLA and its monomers, L-lactic acid and L-lactide.

and PLLA. We first estimated the equilibrium constant K of the former reaction (eq 1) by hydrolysis of PLLA.¹⁰ In fact, a polymer sample of PLLA having high molecular weight ($>10^5$ Da) was dissolved in a deuterated chloroform, and a trace amount of water was added to it together with a catalyst amount of p-toluenesulfonic acid (TSA). The reaction system was left at room temperature for more than 2 months to reach an equilibrium state, and for which ^1H NMR spectrum was measured to determine the amounts of hydroxyl and carboxyl groups formed by the hydrolysis of PLLA as well as the amount of remaining water. The K value was readily determined from the ordinary equilibrium equation (eq 2) for the ester formation reaction, assuming that the relation $[\text{COOH}] = [\text{OH}]$ is always maintained.

$$K = [\text{COOH}][\text{OH}]/[-\text{COO}-][\text{H}_2\text{O}] \quad (2)$$

$$P-1 = [-\text{COO}-]/[\text{COOH}] = (1/xK)^{1/2} \quad (3)$$

The K values were 1.5 at room temperature and 0.5 at 50°C , being comparable with those for the ordinary ester formation reactions. Substituting the K value of eq 3 by that value, change of the average degree of polymerization (P) can be correlated with x that is the molar ratio of water relative to ester, *i.e.*, $x = [\text{H}_2\text{O}]/[-\text{COO}-]$. Figure 1 shows the change in number-average molecular weight (M_n) of PLLA deduced as a function of x . Since this result was based on the equilibrium constant at room temperature, the M_n value would be slightly different at higher equilibrium temperatures. At any rate, the water content should be less than 1 ppm if the M_n value of PLLA should be higher than 50 kDa which corresponds 100 kDa in weight-average molecular weight (M_w) assuming $M_w/M_n = 2.0$ in the polycondensation.

The other ring-chain equilibrium is driven by the back-biting reaction of the hydroxyl terminal, and for which the amount of L-lactide present was known to be less than 1.0 wt % at 120°C and higher than 5 wt % at 180°C in the ROP of L-lactide. High evacuation needed for removing condensed water

Figure 1. Relation of the molecular weight (M_n) and water content of PLLA in the polycondensation.

results in removal of L-lactide from the system to reduce the polymer yield. Therefore, reaction conditions should precisely be controlled for obtaining high molecular weight of PLLA by direct polycondensation.

This thermodynamic analysis of the polycondensation indicates that PLLA having high molecular weights may be produced when the condensed water is efficiently removed to a level of 1 ppm from the polymerization system. The ordinary reaction conditions that may allow the effective removal of the water may involve (1) a temperature range of 180–200 °C, (2) a low pressure below 5 torr, and (3) a long reaction time in the presence of an appropriate catalyst and, in some case, azeotropic solvent for removing water.¹¹ A too high reaction temperature for efficient removal of the water results not only in the polymer decomposition into lactide but also in the reduction of optical purity of the PLLA even when optically pure L-lactic acid is used as the monomer.

In 1995, as mentioned above, Ajioka *et al.* of Mitsui Chemical Co. first succeeded in synthesizing PLLA having a M_w higher than 1×10^5 Da using diphenyl ether as an azeotropic solvent.⁸ In this system the high boiling solvent is refluxed at reduced pressure to azeotropically distil the condensed water and to make it adsorb on molecular sieves. Following this success, bulk polycondensation of L-lactic acid in which the use of solvent can be eliminated was studied. We once tried to develop melt-polycondensation of L-lactic acid with various ionic metal catalysts.^{12,13} In this process, however, unfavorable discoloration of the product likely occurred with its depolymerization to L-lactide. We found out that use of a bi-component catalyst system comprising Sn(II) and TSA is effective not only for increasing the molecular weight but also for preventing the discoloration of PLLA in the melt polycondensation of L-lactic acid. As a result, a high molecular weight of PLLA ($M_w \geq 100,000$ Da) was obtained within a short reaction time. We also discovered that the alternative bi-component catalyst systems comprising Sn(II)-Ge(IV) and Sn(II)-Si(IV) can produce high-molecular-weight PLLA.¹⁴ The best was Sn(II)-Ge(IV) among the tested catalyst systems, and the highest M_w of PLLA obtained was 70 kDa with 0.16 mol % molar ratio of Ge(IV) ethoxide relative to L-lactic acid (Sn(II) (0.2 wt %)). These binary catalyst systems were also superior to the conventional ones in terms of racemization of the resultant polymer.

In order to further improve the bulk polycondensation of L-lactic acid, we established the melt/solid polycondensation by using the bi-component catalyst comprising tin dichloride hydrate and TSA.^{15,16} First, thermal dehydration of L-lactic acid was conducted to prepare an oligomeric PLLA having a degree of polymerization of *ca.* 8. It was mixed with the bi-component catalyst and subjected to melt-polycondensation at 180 °C for 5 h to obtain a melt-polycondensate having an average molecular weight of 13,000 Da. This melt-polycondensate was then heat-treated at 105 °C for 2 h and subjected to solid-state polycondensation (SSP) to allow chain extension. In a typical case, the SSP was conducted by raising the temperature from 130 to 155 °C or at a constant temperature of 140 or

Figure 2. Changes in M_w of PLLA as a function of polymer crystallinity in the solid-state polycondensation at (a) 140 °C and (b) 150 °C.

150 °C. In the former case the molecular weight of PLLA increased linearly with the reaction temperature increasing, while in the latter case the molecular weight increased above 500 kDa in a relatively short reaction time. In the solid-state polycondensation the polymer crystallization was found to play a key role for increasing the molecular weight, because with the polymer crystallization the polymer tails and catalysts are allowed to concentrate in the amorphous domain and in which the chain extension is efficiently induced. Figure 2 shows the typical changes in M_w as a function of crystallinity of PLLA at both temperatures. It is clearly shown that the time-dependent increase in crystallinity is well correlated with the increase in molecular weight. Since the SSP can be conducted in large scale in continuous way, it will afford a facile industrial route to the synthesis of PLLA. Figure 3 compares the SSP route with the conventional ROP route, showing the easiness and cost advantage of the former.

The direct polycondensation technique was applied to the synthesis of various copolymers that should have different properties and degradability. Particularly, copolymers of L-lactic acid and phenyl-substituted α -hydroxy acids such as L- and D-mandelic acids (L-, D-MA) and phenyllactic acid (Phe-LA) were prepared.¹⁷ It was found that the glass transition temperature of the copolymers comprising L-mandelic acid became significantly higher (from 58 to 69 °C) with increasing content of L-mandelic acid (from 0 to 50 mol %) although the M_w decreased with it (from 87,000 to 4,000 Da). Polyglactin was also synthesized by direct co-polycondensation of glycolic acid and L-lactic acid.^{18,19}

DEVELOPMENT OF STEREOBLOCK-TYPE POLYLACTIDES

In 1987 Ikada *et al.* discovered the phenomenon of stereocomplexation in a mixture of enantiomeric PLLA and PDLA.²⁰ The resultant polymer complex was crystalline and called stereocomplex-type PLA (sc-PLA). It is now believed that van der Waals interaction of enantiomeric polymer chains is responsible for the complexation.²¹ This sc-PLA exhibits high melting temperature of 230–240 °C, which is 50 °C higher than that of the single PLLA polymer. Therefore, it may

Figure 3. Comparison of the SSP and ROP routes to PLLA. The cost of PLLA will be decreased from 2.5 \$/kg for the ROP route to 1.0 \$/kg for the SSP route.

potentially possess high-performance and wide application by replacing most of the conventional petroleum polymers. However, melt-blending of PLLA and PDLA having high molecular weight is likely accompanied by their homo-chiral (hc) crystallization together with the stereocomplex (sc) crystallization, resulting in a mixed crystalline state and in deteriorated performance of the processed materials. Therefore, various trials have been done for improving the miscibility of PLLA and PDLA.²² Among them, making block copolymers of PLLA and PDLA, *i.e.*, stereoblock-type poly(lactic acid)s (sb-PLA), has been found highly effective for generating the stereocomplex, because the neighboring D- and L-stereosequences can readily interact with each other to fall into molecular mixing state.²³

ROP Route to sb-PLA

In 1990, Yui *et al.* first prepared a diblock copolymer of PLLA-*b*-PDLA by step-wise ROP of L- and D-lactide (Scheme 2) to demonstrate its easy stereocomplex formation with little single-polymer crystallization.²⁴ However, the highest molecular weight (M_n) obtained was as low as 20.1 kDa, with which the sc crystallization is known to predominantly occur by the simple solution mixing of PLLA and PDLA homopolymers. Synthesis of sb-PLA having defined block length and sequence has not easily been done.

After a long interval from the above report, a major breakthrough for the stepwise ROP method was made in our cooperative research work with Musashino Chemical Laboratory, Ltd. We found an easy technique for synthesizing the diblock sb-PLA having regulated sequences and high molecular weight of 80–500 kDa and demonstrated that the resultant polymers can induce predominant sc crystallization even when repeatedly melt-quenched.²⁵ This synthetic technique consists of three steps: 1) polymerization of either L- or D-lactide to obtain PLLA or PDLA having molecular weight of 7–100 kDa (preferably less than 50 kDa), 2) purification of the obtained polymer to remove residual lactide, and 3) polymerization of

Scheme 2. Synthetic route to diblock sb-PLA by the conventional two-step ROP.

Table II. Diblock sb-PLA obtained by the controlled two-step ROP

Sample No.	Feed ratio	M_w (GPC) Da	ΔH_{ms} (J/g)	X_s (%)	T_m (°C)
PLA 22	L 20/D 80	141,000	44.2	100	210.0
PLA 23	D 20/L 80	143,000	36.2	100	208.5
PLA 24	L 35/D 65	166,000	40.4	100	212.4
PLA 25	D 35/L 65	159,000	38.5	100	208.5

ΔH_{ms} : Heat of fusion of stereocomplex crystal. X_s : Percentage of stereocomplex crystal against homo-chiral crystal in sb-PLA.

the enantiomeric lactide in the presence of the purified polymer. The purification step is highly important to obtain sb-PLA having higher crystallinity and melting temperature without racemization of the second sequence. At step 3, the first polymer prepared *via* steps 1 and 2 is added with the monomer lactide having opposite chirality in a predetermined ratio together with a catalyst and heated around 190 °C for 0.5–2 h for polymerization. Table II shows some results together with the characteristics of the produced polymers.²² The most preferable PLLA/PDLA ratio is in the range from 85/15 to 15/85 where the resultant diblock sb-PLAs show almost exclusive sc formation without the hc crystallization occurring. The shorter and longer blocks of these copolymers must be synthesized in steps 1 and 3, respectively, because the prepolymer first prepared in steps 1 and 2 can be well solvated by the larger amount of lactide monomer with opposite

Method 1

Scheme 3. Synthetic route to multiblock sb-PLA by SSP with equimolar melt-blends of PLLA and PDLA.

chirality and promote the chain elongation from its terminal in step 3. If the longer block would be first made, it will not evenly react with the second monomer to retard the block copolymerization. When the PLLA/PDLA ratio is higher than 90/10 and lower than 10/90, the sc crystallinity of the resultant sb-PLA becomes lower than 80% in spite of the preferential sc formation exhibited. The sb-PLAs prepared by this method are useful not only because of their preferential sc crystallinity even at nonequivalent PLLA/PDLA ratios but also because of the cost-effectiveness due to the smaller amount of more expensive D-lactide monomer required for the synthesis with little affecting the polymer properties.

SSP Route to sb-PLA

A more practical route to sb-PLA is to rely on the method of direct polycondensation of lactic acid instead of the above ROP route.²⁶ Since the mixture of PLLA and PDLA having medium molecular weight (20–40 kDa) can easily form stereocomplex crystals, it can be subjected to SSP as in the case of PLLA. Scheme 3 shows our synthetic method involving five steps: dehydration of L- and D-lactic acids to obtain their oligomers, melt-polycondensations of the oligomers to prepare PLLA and PDLA with medium molecular weight, melt-blending of the resulting PLLA and PDLA to allow stereocomplexation, and the following SSP for the chain extension to yield a high polymer.²⁷ The polymer yielded by this way attained the stereoblock sequences by the cross propagation of the PLLA and PDLA chains in the SSP.

Figure 4 shows the increase in the molecular weight of the sb-PLA as a function of the degree of crystallinity of reactants in the SSP of a melt-blend of PLLA and PDLA whose initial molecular weights were 40 kDa. The resultant sb-PLA had increased molecular weight reaching 100 kDa in this method, although the molecular weight increase was limited as opposed to that noted in the corresponding polycondensation to yield

Figure 4. Changes in M_w of sb-PLA as a function of the reaction time through the whole process where the solid-state polycondensation was conducted at 170 °C (ref 21, 26).

PLLA or PDLA homopolymer. Furthermore, polymer recovery became low with increasing reaction temperature (43% at 200 °C) because of the increased depolymerization to lactides. In this stereo-mixture of PLLA and PDLA, the diad sequences formed by their hetero-chain couplings are racemic, and the crystallization of the extended chains is retarded. Besides, the polymer tails excluded out of the sc domain are likely to lose their mobility due to its strong bond to crystal lattices, having a retarded reactivity in the amorphous domain. In consequence, a high reaction temperature is needed for the polycondensation of the chain ends to trigger transesterification and depolymerization by which the randomized sequences are formed together with sublimation of lactides. Accordingly, high-molecular-weight sb-PLA cannot be synthesized by the present SSP procedure with the melt-blend of PLLA and PDLA in equivalent ratio.

The above data shows that the presence of homopolymer domains should be required for enhancing the crystallization-

Figure 5. Effect of the PDLA composition (X_D) on the M_w of the final sb-PLAs. The PLLA-rich ($0 \leq X_D \leq 50$) and PDLA-rich ($50 \leq X_D \leq 100$) systems were separately examined with different melt-blends. The SSP was conducted at constant temperature (150 °C) for 30 h and with stepwise temperature increase (at 140 °C, 150 °C, and 160 °C each for 10 h).

induced polycondensation. Therefore, we tried to control the blending state of PLLA and PDLA prepolymers so as for the hc crystal domain to coexist with the sc domain during SSP.²⁸ Thus, the melt-polycondensates of PLLA and PDLA having medium molecular weight were melt-blended in different ratios.²⁹ The following SSP was first started at 140 °C, and the temperature was raised up to 160 °C stepwise with a 10 °C increase every 10 h so as for the extended hc chains to crystallize out with the sc domain almost unchanged. By this way the molecular weight increased above 100 kDa, and the polymer recovery became as high as 70–85%. Figure 5 shows the changes in the M_w of the final sb-PLA as a function of PDLA ratio in the sb-PLA. It is clearly shown that the M_w became higher with the PLLA/PDLA ratio deviating from 1:1 or L- or D-rich compositions.

The obtained sb-PLAs having PLLA-rich and PDLA-rich compositions showed good stereocomplexibility in spite of involving long homopolymer sequences.³⁰ In fact, DSC curves of the melt-quenched samples of these sb-PLAs (in the 2nd DSC heating scan) showed a sole melting peak of sc crystals when the PLLA or PDLA composition was less than 85%. Even at 90% in PLLA or PDLA rich composition, the melting peak of sc crystals surpassed that of hc crystals in heat capacity. It is therefore indicated that the properties of sb-PLA can be widely tuned by changing the PLLA/PDLA composition, the length of the homopolymer sequences, and the relevant hc to sc crystal composition. This structural variety of sb-PLA will guarantee a wide range of properties and application of PLA materials.

APPLICATION OF SC-PLA AND SB-PLA

The sc-PLA and sb-PLA described above have high potential as high-performance polymeric materials. We therefore named these PLAs consisting of both D- and L-sequences “Neo-PLA.” Neo-PLA provides a wider application than the conventional PLLA as melt-spun fibers having excellent heat stability as well as dyeability with disperse dyestuff, melt-extruded films

Figure 6. Injection molds of sb-PLA for mechanical test.

Table III. Properties of injection molds of diblock sb-PLA having different PLLA/PDLA ratios

sb-PLA PDLA/PLLA	T_m (°C)	HDT ^{a)} (°C)	Tenacity MPa	Modulus MPa
20/80	214	180		
30/70	214	197	64.4	2030
50/50	216	198		

^{a)}Heat deformation temperature (Vicat softening temperature).

having size fastness and transparency, injection molds with heat resistivity, and stable coatings formed by solution or suspension method. The total properties of Neo-PLA are almost comparable to those of poly(butylene terephthalate) (PBT) used as an engineering plastic material. Recently, the Neo-PLA fibers have been applied to car sheet or other textiles for industrial use.³¹

Another potential application of Neo-PLA is based on injection molded sb-PLA.^{21,25} Figure 6 shows a sample for strength test that is made from diblock sb-PLA (PDLA/PLLA = 30/70) synthesized by the lactide method. It is shown that they are transparent in spite of crystallization. Table III compares the properties of injection molds of diblock sb-PLA having different compositions. These data reveal that the sb-PLA will possibly be applied to electric appliances or car parts.

For real manufacturing of Neo-PLA, supply of D-lactic acid is important. We therefore screened bacterial fermentation to find out that several bacterial strains can efficiently produce D-lactic acid by using rice as a starch source of the fermentation. Large-scale fermentation using *Lactobacillus delbrueckii* IFO 3202 strain gave D-lactic acid with a high optical purity above 97.5% in a yield around 70% from rice-saccharificate.³² These results suggest that D-lactic acid can readily be manufactured by the ordinary microbial fermentation process with different strains.

STRUCTURE AND FUNCTIONAL PROPERTIES OF POLYLACTIDE COPOLYMERS

Nano Structures Made from PLA-PEG Copolymers

The ordinary ROP of L- or D-lactide initiated with poly(ethylene glycol) (PEG) and poly(ethylene glycol) monomethyl ether (MePEG) can give PLA-PEG block copolymers with different types³³ (Scheme 4). Table IV summarizes a set of

ABA triblock

PLLA-PEG-PLLA (4300-4600-4300)

BAB triblock

PLLA-PEG (5500-5000)

AB diblock

PLLA-PEG (5500-5000)

Scheme 4. Polymer structures and schematics of their micelles formed in aqueous media.**Table IV.** Typical PLA-PEG block copolymers

Type	Abbreviation	PLA block (M_n)	PEG block (M_n)	Total (M_n)	PLA/PEG
AB	PLLA-PEG	1100	2000	3100	0.55
	PDLA-PEG	900	2000	2900	0.45
ABA	PLLA-PEG-PLLA	1300	4600	7200	0.56
	PDLA-PEG-PDLA	1100	4600	6800	0.48
BAB	PEG-PLLA-PEG	2000	2000	6000	0.50
	PEG-PDLA-PEG	2000	2000	6000	0.50

enantiomeric copolymers of ABA, BAB, and AB types that have been prepared by the authors.³⁴ The BAB triblock copolymers can be obtained by the coupling of the AB diblock copolymers with hexamethylene diisocyanate.³⁵ These amphiphilic copolymers readily form core-shell type micelles in water, placing the hydrophobic PLA and hydrophilic PEG segments in the core and shell, respectively, as shown in Scheme 4.³⁵ The average hydrodynamic diameters of the micelles measured by DLS are in the range of 20–30 nm for 1 wt % solutions of all the copolymers.

Each of the micelles of PLLA-PEG and PLLA-PEG-PLLA was cast on a flat surface of mica or silicon substrate and subjected to AFM measurements.^{36–38} Both particles deposited out on the flat surfaces were found to readily collapse into band structures, when annealed at 60 °C for 2 h. The resultant PLLA-PEG bands had a dimension of *ca.* 15 nm in width, 2 nm in thickness (height), and over 1 μm in length. The PLLA-PEG-PLLA bands, on the other hand, had a dimension of *ca.* 10 nm in width and 1.5 nm in thickness (height), being thinner than those of PLLA-PEG. They aligned and stacked to form wider bands.

Figure 7a and 7b show typical TEM images of the PLLA-PEG and PLLA-PEG-PLLA bands transferred from the flat silicon surface onto carbon meshes, respectively.³⁹ The PLLA-PEG bands, having a width of 9 nm, are arranged in parallel

with an inter-band distance of *ca.* 20 nm, while the PLLA-PEG-PLLA bands, having a width of 6 nm, come more closely together to have an inter-band distance of *ca.* 4 nm and form a network with branched structures. Their nano-beam electron diffraction analysis (Figure 7c and 7d) revealed that the PLLA chains align perpendicularly to the base of the bands. Accordingly, the two orthogonal axes, *i.e.*, the *a* and *b* axes of the crystal cells, are perpendicular and parallel to the longitudinal direction of the band, respectively. Figure 8a shows an optimal chain conformation of PLLA taken in the bands deduced from the crystal data. Here, the PLLA segmental helices should align by standing on the substrate to form a crystal lamella. Each dot in this Figure shows the position of the PLLA segmental helix in the crystal lamella whose height is as short as 1.5 nm corresponding to the band height. Each helix should have two turns in its both tails, occurring above and below the lamella to accomplish the chain folding. Since the chain folding preferentially arises along the *a* axis (as shown by the solid curve in Figure 8a), the crystal growth is driven in the direction of the *b* axis infinitely with the PEG blocks left in the crystal edge (*bc* plane), being compatible with the aforementioned band growth with the constant width maintained.

Figure 8b shows one of the most probable chain conformations of the PLLA blocks in which one helical unit and one turn consist of six units in all. With this arrangement repeated, folding of the helical chain is accomplished. After structural optimization, the length of this PLLA fold can be estimated to be 5.5 nm, which corresponds to the observed width of the bands of PLLA-PEG-PLLA by TEM. Similarly, the length of PLLA fold in the PLLA-PEG bands can also be estimated to be 7.5 nm, which is also comparable with the observed band width. This folding structure of the PLLA blocks is regarded as “a doubly twisted chain conformation” (so-called a super coil in which a helical chain forms the second large helix), although the second twist is significantly unsymmetrical. The double

Figure 7. Electron micrographs (a, b) and their electron diffraction diagrams (c, d) of the copolymer samples exfoliated from a silicon wafer surface after annealing at 60 °C for 10 h: (a,c) PLLA-PEG and (b,d) PLLA-PEG-PLLA. The nano-beam diffraction diagrams from the encircled area are properly oriented with respect to the image (ref 39).

Figure 8. (a) A chain-packing model of the α crystal of PLLA and (b) an optimum model structure (in a doubly twisted-form) of a PLLA block chain in the nano-band of PLLA-PEG-PLLA (ref 39).

twist structure of this type should be naturally formed if a straight chain is highly twisted in one direction.

The above highly ordered microdomain structures are created by the crystallization-mediated segment segregation and organization of crystallizable block copolymers in which the initial nanoparticle form can provide a seed of molecular organization.

Sol-Gel Transition of PLA-PEG Copolymer Micelles

A novel temperature-dependent sol-to-gel transition was found out when the above micellar solutions of enantiomeric copolymers of PLLA-PEG and PDLA-PEG were mixed together. For example,⁴⁰ the solutions containing enantiomeric ABA triblock copolymers, PLLA-PEG-PLLA and PDLA-PEG-PDLA, were mixed at low temperature (typically at 4 °C) and slowly warmed up to 75 °C. Around 37 °C the mixture spontaneously turned from sol to gel (Figure 9). Since the single solution containing one of the enantiomeric copoly-

mers showed no change, the transition of the mixture was thought to be driven by the stereocomplexation of the PLLA and PDLA block segments. This stereocomplexation-driven gelation was supported by analyzing the rheological behavior and WAXS pattern of the gel. Since the sol-to-gel transition occurred in an irreversible manner, the gel once formed by warming never turned to sol again.

On the other hand, the system consisting of the enantiomeric BAB triblock copolymers, PEG-PLLA-PEG and PEG-PDLA-PEG, exhibited a reversible sol-gel transition depending on temperature and polymer concentration.³⁵ The mixed solution with high concentration turned to gel on mixing at low temperature. The gel turned to sol with warming, and oppositely the sol became gel by cooling again. In this BAB system a sort of stereo interaction of L- and D-copolymers is responsible for the gelation, being much different from that of the single BAB (PEG-PLLA-PEG) system that has previously been reported to occur gelation by the ordinary hydrophobic/

Scheme 5. Ring-opening polymerization of BMD and subsequent hydrogenolysis for deprotection.

Figure 9. Rheological changes in G' (closed circle) and G'' (open circle) as a function of the temperature for a mixed dispersion of PLLA-PEG-PLLA and PDLA-PEG-PDLA. And photograph of sol-to-gel transition shown by the mixed dispersion: at room temperature (25°C), after heating at 37°C for 1 h, and after heating at 75°C for 1 h (ref 40).

hydrophilic interaction and also from the above ABA system for which the gelation is induced by the direct stereocomplexation of PLLA and PDLA segments.

These block copolymers are now under investigation for their use to protein delivery where they are used as carriers not only in the form of hydrogel but also in the form of branched-copolymer or as microparticles.⁴¹ The biodegradable thermo-sensitive hydrogels formed from the enantiomeric PLA-PEG block copolymers will have great potential for use as injectable biomedical matrix for tissue engineering.⁴²

PREPARATION OF VARIOUS ENVIRONMENTALLY FRIENDLY POLYMERIC MATERIALS

We have extensively studied on new bio-based and biodegradable polymers other than PLA. For example, new cyclic diester monomers, 3-(S)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione (BMD)⁴³ consisting of both glycolate and benzyl- α -malate units and [R]-4-methyl-1,5-dioxepane-2,6-dione ([R]-MDP)⁴⁴ consisting of [R]-3-hydroxybutyrate (3HB) and glycolate (GA) units were synthesized by base-catalyzed cyclization of the coupling products with bromoac-

Scheme 6. Synthetic route to [R]-MDP and P(3HB-GA).

tyl chloride. These monomers were homo-polymerized and copolymerized with other cyclic monomers to obtain new polymers. The malic acid-containing polymers prepared from BMD can be utilized as functional biomedical materials (Scheme 5). Poly([R]-3-hydroxybutyrate-co-glycolate) (P(3HB-GA)) prepared from [R]-MDP is a novel PHB derivative containing hydroxyacetate units (Scheme 6). These methods can afford reliable routes to the synthesis of biodegradable polymers that cannot be synthesized by the bacterial fermentation or by the ordinary chemical synthesis.

We also demonstrated that poly(3-hydroxyalkanoate)s (PHA) can be biosynthesized by using recycled waste edible oils and tallow with relatively high yield by bacterial fermentation.⁴⁵ The waste plant oils usually gave poly(3-hydroxybutyrate) (PHB) while waste tallow gave poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV). This result encourages the biorecycling of waste oils as renewable resources for making materials.

An aliphatic/aromatic copolyester, poly(butylene succinate-co-terephthalate) (PBST), was prepared to investigate the effect of the aromatic units on the enzymatic degradation of PBS derivatives in the presence of a lipase originated from *Pseudomonas cepacia* (Lipase PS®).^{46,47} The degradation products were analyzed in detail by liquid chromatographic mass spectrometry (LC-MS). Based on the data, the overall

mechanism of the enzymatic hydrolysis of this aliphatic/aromatic copolyester is proposed, in which PBST undergoes endo hydrolysis.

We also developed biodegradable fibers and films from PHB and other biodegradable polymers for real application in different fields.^{48–53}

CONCLUSIONS

Polymers made from renewable resources have been developed in the beginning of this century, and there have been limited number of such polymers industrialized until now. Several aliphatic polyesters such as PLA, PHA and PBS are now in marketing. Neo-PLAs consisting of sc-PLA and sb-PLA provide a wide range of properties that have never been attained with single PLLA polymers. In the near future, wide industrial applications of Neo-PLA will be possible. For replacing the conventional oil-based general plastics and even engineering plastics, the bio-based polymers ought to have excellent functional properties and high performance. Appropriate molecular and material designs will be needed for imparting such specialties and increasing material value to exceed those of the conventional oil-based polymeric materials.

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Dr. Yoshiharu Kimura was born in Shiga in 1948. He received his MS and PhD degrees from Kyoto University in 1973 and 1976, respectively. After doing postdoctoral work at the University of Iowa, USA, he served as an Assistant Researcher at Shiga Prefectural Junior College, Hikone, Japan. In 1981, he was appointed assistant professor of Fiber Chemistry at Kyoto Institute of Technology (KIT). He became an associate professor of Polymer Science and Engineering in 1985 and was nominated as full professor in 1990 at KIT. He is now serving as the directors at the Center for Fiber and Textile Science and the R&D Center for Bio-based Materials of KIT. Also, he is working as a vice director at Advanced Software Technology & Mechatronics Research Institute of Kyoto. Dr. Kimura received several awards for his research activities: The Award of the Society of Fiber Science and Technology, Japan in 1998, Harushige Inoue Award from Japan Science and Technology Agency in 2007, and SPSJ Mitsubishi Chemical Award from SPSJ in 2008. He was also awarded by Kyoto City and KIT in 2008. He has published more than 230 papers and has been the author and co-author of several books. His current research interests include development of bio-based polymers, inorganic polymers, and control of polymer-cell interaction. He has been and is an active member of the editorial boards of five scientific journals.