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Comparison of Sm complexes with Sn compounds for syntheses of copolymers composed of lactide and ε-caprolactone and their biodegradabilities

Hajime Yasuda[a], Katsuhiro Yamamoto[a], Yuushou Nakayama[a], Chikara Tsutsumi[b], Philippe Lecomte[c], Robert Jérôme[c], Stephan McCarthy[d], David Kaplan[e]

[a] *Department of Applied Chemistry, Graduate School of Engineering, Hiroshima University, Higashi Hiroshima 739-8527, Japan*
[b] *Department of Applied Chemistry and Biotechnology, Niihama National College of Technology, Yagumo 7-1, Niihama 792-8580, Japan*
[c] *Center for Education and Research on Macromolecules, University of Liege, Allee de la Chimie 3, B6 4000, Liege, Belgium*
[d] *Plastic Engineering Department, University of Massachusetts at Lowell, One University Avenue, MS 01854, USA*
[e] *Bioengineering Center, Tufts University, 4 Colby St. Medford, MS 02155, USA*

Abstract

The comparison of organolanthanide complexes, $(C_5Me_5)_2SmMe(THF)$ (Sm1) and $[(C_5Me_5)_2Sm]2(PhC{=}C{=}CPh)$ (Sm2), with tin compounds, $Bu_2Sn(OMe)_2$ (Sn1) and $Bu_2Sn(OCH_2CH_2CH_2O)$ (Sn2), in the preparation of random and diblock copolymers composed of L-lactide (L-LA) or D,L-LA and ε-caprolactone (CL), and the preparation of triblock copolymers composed of L-LA/CL/L-LA was studied and the biodegradabilities of the resulting copolymers with proteinase K and a compost were examined. Poly(L-LA-*ran*-CL) shows much higher degradability than poly(L-LA) with proteinase K, and poly(L-LA), poly(L-LA-*ran*-CL) and poly(L-LA-*b*-CL) (*b* means block) prepared with Sml had better degradability than those synthesized with the Snl compound. The degradability of poly(L-LA-*ran*-CL*)* with proteinase K is higher than that of poly(L-LA-*b*-CL). Poly(LA-*ran*-CL) and poly(LA-*b*-CL) prepared with Sm1 revealed higher degradability than those obtained with Snl using a compost. Triblock copolymers, poly(L-LA-*b*-CL-*b*-L-LA), synthesized with Sm2 revealed nearly the same degradability with those obtained with Sn2 using a compost. Finally, biocompatibility was studied with macrophage activation assay using RAW 264.7, and metabolic viability assay using Cell Titer Aqueous non-radioactive Cell.

Keywords: Biodegradability; Proteinase K; Compost; Poly(LA-ran-CL); Poly(LA-b-CL); Poly(LA-b-CL-b-LA); Tin compound; Rare earth metal complex; Polyesters; Copolymerization; Biocompatibility

1. Introduction

Poly(L-lactide) [poly(L-LA)] is known to be the most desirable biocompatible and biodegradable semicrystalline polymer obtainable from starch in high yield [1-5]. Because of these characteristics, poly(L-LA) is widely studied in detail for biomedical applications, particularly those that demand good mechanical properties for surgical sutures and devices for internal bone fixation [6-10]. However, in recent years, homopoly(L-LA) has been reported to exhibit relatively poor biodegradability. Furthermore, homopoly(L-LA) is found to exhibit too hard and too brittle characters as widely usable biodegradable materials. Therefore, physical properties must be improved by copolymerizations of lactide with other monomers in order to generate more elastic materials. High molecular weight poly(LA)s were prepared using tin compounds such as Sn(2-ethylhexanoate)$_2$ and $Bu_2Sn(OR)_2$ [11-17], and random copolymers composed of L-LA and ε-caprolactone (CL) unit were synthesized with $Al(OiPr)_3$ or tin compounds [18-23]. On the other hand, poly(L-LA) and poly(LA-*co*-cyclic carbonate) were synthesized by ring-opening polymerizatrions of these monomers [24-26] using $(C_5Me_5)_2SmMe(THF)$ [27]. This anionic initiator is also effective for living polymerizations of alkyl methacrylates [28,29], alkyl acrylates [30] and lactones [31]. Some epimerization occurs in this case during the polymerization of L-LA to lead to the polymers having good biodegradability. This paper describes the comparison of the activities between Sm complexes and Sn compounds for random and block copolymerization of LA and CL together with the triblock copolymerization to lead to poly(LA-*b*-CL-*b*-LA) (*b* means block), and their biodegradabilities with proteinase K and a compost. Biocompatibilities of the resulting copolymers were examined by macrophage activation assay using RAW 264.7 cells and by metaboric viability assay using the Cell Titer Aqueous non-radioactive cell to indicate that almost all these copolymers are highly biocompatible.

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2. Experimental

2.1. General

^{1}H NMR spectra were recorded on a JEOL JNM-LA400 spectrometer (400MHz). Chemical shifts were calibrated using $CHCl_3$ in $CDCl_3$ at 7.26 ppm. Number average molecular weights and molecular weight distributions of copolymers were determined by gel permeation chromatography (GPC) on a Tosoh SC-8010 high speed liquid chromatograph equipped with a differential refractometer, using $CHC1_3$ as an eluent at 40 °C (flow rate, 1.0 ml). The columns used were TSK gel $G5000_H$, $G4000_H$, $G3000_H$, and $G2000_H$. Molecular weights were determined by using a universal curve plotted with narrow-polydispersity polystyrene standards, whose M_w values were determined by a light-scattering method. T_g and T_m values were measured on a Seiko SSC-5100 DSC-22C apparatus. The polymer samples were scanned from -100 to 120 °C at a heating rate of 10 °C min^{-1} under nitrogen stream. T_m and —ΔH_m (heat of fusion) values were determined in the first heating, while the T_g in the second heating. Topological changes of the polymer surface were measured on a scanning electron microscope (SEM) Model Hitachi S-2150R after Pt + Pd coating of the films using an ion coater (Denton Vacuum Desc II). Tensile tests were conducted on an Orientec universal testing instrument type RTC-1210 and measured at 25 °C with a crosshead speed of 50 mm min^{-1}.

2.2. Materials

Tetrahydrofuran and toluene were dried over CaH_2 for 5 days, then over Na metal for 10 days and distilled before use. Commercially available L-lactide and D,L-lactide (Aldrich) were dissolved in THF, dried over CaH_2 for 10 days and sublimed twice before use at 110 °C. ε-Caprolactone (CL) was gifted from Daicel Co. and dried over CaH_2 for 10 days. Then it was further dried over molecular sieve 4A for 10 days, and distilled before use. $(C_5Me_5)_2SmMe(THF)$ [27] (Sm1) and $[(C_5Me_5)_2]_2(PhC{=}C{=}C{=}CPh)$ [32] (Sm2) were prepared according to the known methods. The enzyme, proteinase K *(Tritirachium album,* activity 20 IU/mg, Wako Pure Chemical), in Tricine buffer, *N*-[tris(hydroxymethyl)methyl]glycine, at pH 8.0, was used without further purification. Ion exchanged water was used for biodegradation tests.

2.3. Random and block copolymerizations of lactide with CL

Random copolymerizations were carried out as follows. A mixture of L-lactide (L-LA) (1.44 g, 10 mmol) or D,L-LA (1.44 g, 10 mmol) and CL (1.1 ml, 10 mmol) dissolved in toluene (4.0 ml) was placed in a 20 ml Schlenk tube. Then, $(C_5Me_5)2SmMe(THF)$ (Sm1: 0.1 ml of toluene solution, 4.0 x 10^{-2} mmol) or $Bu_2Sn(OMe)_2$ (Snl: 0.2 ml of toluene solution, 4.0 x 10^{-2} mmol) were added to the mixture and the random copolymerizations were carried out at 80 °C for 12 h (Sml system) or 110 °C for 12 h (Snl system), respectively. Resulting products were dispersed in excess MeOH to induce the white precipitates. Poly(L-LA-*ran*-CL): ^{1}H NMR ($CDC1_3$) δ 1.35 (m, $CH_2CH_2CH_2$), 1.54 (d, CH_3), 1.62 (m, $CH_2CH_2CH_2$), 2.29 [t, CH_2(CO)], 4.03 (t, OCH_2), 5. 13 (q, CH) ppm. Poly(D_L-LA-*ran*-CL): ^{1}H NMR ($CDC1_3$) δ 1.34 (m, $CH_2CH_2CH_2$), 1.53 (d, CH_3), 1.62 (m, CH_2-CH_2CH_2), 2.28 [t, CH_2(CO)], 4.03 (t, OCH_2), 5. 13 (q, CH) ppm.

The diblock copolymerizatins of L-LA (1.44 g, 10 mmol) or D,L-LA (1.44 g, 10 mmol) with CL (1.1 ml, 10 mmol) were carried out as follows using Sml or Snl (4.0 x 10^{-2} mmol) as an initiator. CL was first treated with the initiator Sml in toluene at 60 °C for 6 h or with Snl in toluene at 110 °C for 12 h, respectively, and subsequently L-LA or D,L-LA was added to the mixture followed by heating to 100 °C for 20 h (Sm system) or 110 °C for 24 h (Snl system), respectively. Resulting reaction mixture was poured into 100 ml of methanol in order to precipitate the resulting copolymer. The precipitate was dissolved in chloroform and then added again to excess methanol to induce the precipitation of the copolymer. Poly(L-LA-*b*-CL): ^{1}H NMR (CDCl3) δ 1.35 (m, $CH_2CH_2CH_2$), 1.54 (d, CH_3), 1.62 (m, $CH_2CH_2CH_2$), 2.29 [t, CH_2(CO)], 4.03 (t, OCH_2), 5. 17 (m, CH) ppm.

2.4. Triblock copolymerization of lactide with CL

Triblock copolymerization of L-LA (1.44 g, 10 mmol) or D,L-LA(1.44 g, 10 mmol) with CL (1.1 ml, 10 mmol) was carried out using $(C_5Me_5)_2$-Sm(PhC=C=C=CPH)Sm$(C_5Me_5)_2$ (Sm2, 2.0 x 10^{-2} mmol) or $Bu_2Sn(OCH_2CH_2CH_2O)$ (Sn2, 2.0 x 10^{-2} mmol) as an initiator. First CL was added to the toluene solution of the initiator Sm2 or Sn2 and the mixture was stirred at ambient temperature for 12 h (Sm2 system) or at 90 °C for 12 h (Snl system), respectively, and subsequently L-LA or D,L-LA was added to the mixture followed by heating to 90 °C (Sm2) or 110 °C (Sn2) for 12 h, respectively. Resulting reaction mixture was poured into 100 ml of methanol to induce the precipitation of the resulting copolymer. The precipitate was dissolved in chloroform and then added again to excess methanol to precipitate the copolymer. Poly(L-LA-*b*-CL-*b*-L-LA): ^{1}H NMR (CDCl3)

δ 1.33 (m, $CH_2CH_2CH_2$), 1.52 (d, CH_3), 1.60 (m, $CH_2CH_2CH_2$), 2.25 [t, $CH_2(CO)$], 4.04 (t, OCH_2), 5. 18 (m, CH) ppm.

2.5. Enzymatic degradation

Enzymatic degradations of copolymers by proteinase K were carried out in Tricine buffer (pH 8.0) by exposing the polymer samples in the solution followed by determining the weight loss gravimetrically after recovering the samples at intervals. The used polymer films were prepared by the solvent casting method. The size and weight of the films used were 5 x 5 mm (thickness 50-70 μm) and 10-15 mg, respectively. Three samples were used to obtain one data and the averaged value was used (standard deviation, ± 4%). The enzyme and the buffer solution were replaced every 24 h so that the enzyme activities maintain at a desired level throughout the experiment. The bottle (50 ml volume) containing a sample, an enzyme and the buffer solution were warmed to 37 °C with stirring. After a fixed time, the samples were removed from the bottle, washed with 99.5% ethanol and then dried to constant weight (5 h) in vacuo before weighing.

2.6. Degradation by a compost

Commercially available effective microorganism (EM) fermented solution (30 ml) containing *R hodospirillum, Rhodopseudomonas, Pseudomonas, Micrococcus, Bacillus, Lactobacillus, Streptococus, Saccharomyces, Aspergillus, Penicillium*, etc. and theriaca syrup (40 ml) were added to 2000 ml of water, and this solution was sprayed on the mixture of rice hulls (5 kg) and rice bran (15 kg). Resulting material was wrapped with a polyethylene film and then dried in the shade for 1 day. The content of water was evaluated by the weight loss of the samples after heating them to 200 °C. The samples were sealed in polyethylene mesh and it was hold in the resulting compost for a fixed time. The evaluation of the biodegradation was carried out by measuring the weight loss with a compost.

2.7. Biocompatible studies

2.7.1. Macrophage activation assays

RAW 264.7 cells were plated at 2 x 10^5 cells/ well in 100 ml of DMEM media with 10% FCS at the center of LA copolymer films. After 10 min of incubation at 37 °C to allow cells to adhere to the films, 1 ml of culture media was added. Cells were incubated for 48 h, and supernatants were then collected for subsequent assay. LPS at 100 ng/ml served as a positive control for macrophage stimulation.

2.7.2. Metabolic viability assay

At the conclusion of the macrophage activation, relative cell number and viability were determined by the Cell Titer Aqueous non-radioactive cell proliferation assay (Promega) according to manufacturer's instructions. Briefly, the media was replaced with 1 ml fresh DMEM, and then 200 ml of the MTS/PMS solution was added. After two hours, 100 ml of culture media was removed and absorbance at 490 nm was determined. Relative cell numbers were normalized to the average of the no-LA copolymer, and no-chloroform controls.

2.7.3. Determination of TNF release

TNF release was quantified by a sandwich ELISA according to the manufacturer's instructions (R&D System), with slight modifications as noted below. Briefly, Nunc Maxisorp 96-well plates were coated overnight at 4 °C with 6 μg/ml of capture antibody (goat anti-murine TNF). Plates were washed with PBS/Tween 20 three times, and blocked with 1% BSA in PBS. After two hours incubation at 37 °C, the plates were washed again, and 50 ml of wash buffer was added. Standards and macrophage supernatants were added (50 μl) to the plates and incubated overnight at 4 °C. Plates were washed, and scoring antibody (hamster anti-murine TNF conjugated to horseradish peroxidase) was added at 3 μg/ml diluted in 1% BSA in PBS/Tween 20. Plates were incubated for two hours at 37 °C and then washed. TMB substrate (Sigma) was added to each well and color was allowed to develop for 10-30 min. Color development was stopped by the addition of 2 N H_2SO_4, and plates were read at 450 nm. TNF released was determined by a standard curve based on recombinant murine TNF at several concentration.

3. Results

3.1. Synthesis of random and diblock copolymers composed of L- or D,L-lactide and ε-caprolactone

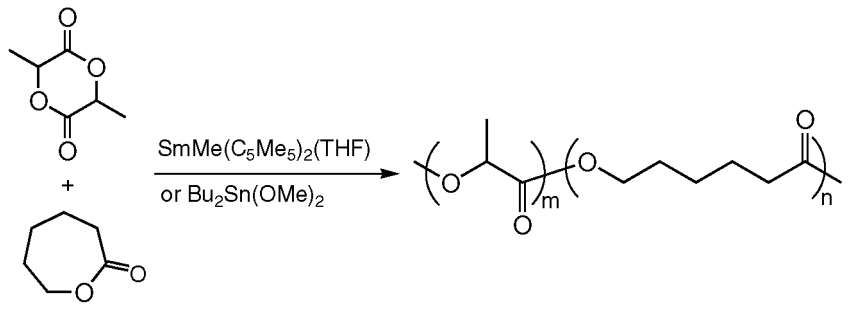
Random copolymerizations of L-LA or D,L-LA with CL were demonstrated in toluene using $(C_5Me_5)_2SmMe(THF)$ (Sm1) or $Bu_2Sn(OMe)_2$ (Sn1) as an initiator. An initiator, $(C_5Me_5)_2$ SmMe(THF), was prepared according to the procedure reported by Evans [27]. A mixture of L-LA or D,L-LA and CL was treated with Sml at 80 °C for 12 h, or with Snl at 110 °C for 12 h, respectively. The representative results are summarized in Table 1. We used excess L-LA for the purpose of obtaining good thermal property (T_m value of homopoly(L-LA) 174 °C, homopoly(CL) 60 °C). Thus feed ratio of LA and CL was controlled to be 95/5, 90/10 and 75/25 molar ratio. Sml initiated polymerizations proceeded in relatively low yield compared with the Snl initiated polymerizations, but the M_ns are high and M_w/M_ns are extremely low. Calculated M_n for 92/8 molar ratio of poly(L-LA-*ran*-CL) is 7.1 x 10^4, and that for 84/16 molar ratio is 6.9 x 10^4 by GPC. The absolute M_ns were also measured with DAWN DSP laser photometer equipped with GPC, that is, the molecular weights for above polymers were slightly lower, 5.6 x 10^4 and 5.3 x 10^4, respectively. Because these values were nearly identical, M_n was as a rule measured using a universal curve because of its convenience. Resulting T_m values using Sml are higher than those obtained by Snl system for poly(L-LA-*ran*-CL), suggesting somewhat block nature of the copolymers obtained with Sml. Lower —ΔH_m values of the copolymers obtained with Sml indicate their lower crystallinity in comparison with those obtained with Sn1. Random copolymerizations of D,L-LA with CL did not produce polymers possessing clear T_m values, indicating the formation of completely amorphous polymer. The T_g values of poly(L-LA-*ran*-CL) are higher than those of poly(D,L-LA-*ran*-CL). The Sn1 initiated copolymerization of D,L-LA with CL gave lower molecular weights than the calculated values.

Table 1: *Random copolymerization of L-LA or D,L-LA with CL using Sm1 and Sn1 compounds*

Catalyst	Polymer	LA fraction (mol %)		Yield (%)	$M_n(10^4)$	M_w/M_n	T_m (°C)	T_g (°C)	$-\Delta H_m$ (J/g)
		Feed	Found						
Sm1	Poly(L-LA-*ran*-CL)	95	98	75	7.75	1.48	163.5	56.2	44.4
Sm1		90	92	72	8.50	1.52	162.4	47.3	35.2
Sm1		75	84	75	9.51	1.55	163.7	38.1	27.8
Sn1		95	96	88	6.52	1.78	157.6	56.9	67.8
Sn1		90	91	90	6.55	1.82	155.3	50.8	56.4
Sn1		75	77	92	6.72	1.88	143.2	40.3	39.9
Sm1	Poly(D,L-LA-*ran*-CL)	95	98	71	6.21	1.45	-	42.3	-
Sm1		90	92	73	7.83	1.50	-	40.5	-
Sm1		75	81	74	7.89	1.67	-	30.2	-
Sn1		95	96	94	4.21	1.58	-	45.3	-
Sn1		90	92	92	4.35	1.64	-	38.5	-
Sn1		75	78	93	5.02	1.56	-	20.3	-

Reaction conditions: Sml system, 80 °C for 12 h in 4.0 ml toluene; Snl system, 110 °C for 12 h in 4.0 ml of toluene. Sml, $SmMe(C_5Me_5)_2(THF)$ 0.2 mol% of monomer; Snl, $SnBu_2(OMe)_2$ 0.2 ml% of monomer.

Scheme 1.



Block copolymerizations were performed by reacting first CL at 80 or 110 °C for 12 h using Sml or Snl, respectively, and then L-LA or D,L-LA was added to the resulting polymer complex at 110 °C for 24 h (Scheme 1). Reversed addition does not produce the desired copolymer and affords mainly poly (LA). Typical results are

given in Table 2. The block copolymerization of L-LA with CL proceeded in high yields (73-96%) to produce high molecular weight polymers (M_n= 11.39-3.45 x 10^4) with low polydispersities, (M_w/M_n = 1.72-1.75) using the Sml system, while Snl initiated copolymerization gave relatively low molecular weights, broad molecular weight distributions, and slightly low T_g values. The resulting molecular weights gradually increased with increasing the L-LA component. However, M_w/M_n values are constant regardless the L-LA/CL ratios. In contrast to poly(L-LA-*b*-CL), poly(D,L-LA-*b*-CL) showed the very low T_m and —ΔH_m values derived from poly(CL) (poly(D,L-LA) does not show clear T_m and —ΔH_m values because of its amorphousness. A series of poly(L-LA-*b*-CL) prepared with Sn1 catalyst reveals the presence of two T_g (glass transition temperature), one is originated from poly(CL) backbone and the other comes from poly(L-LA) sequence, suggesting poor miscibility of the poly(L-LA) sequence to poly(CL) part. In contrast to poly(L-LA-*b*-CL) prepared with Snl catalyst, the corresponding samples prepared with Sml catalyst revealed only one T_m. This is the result of epimerization of poly(L-LA) with Sml catalyst. Epimerization of L-LA into D,L-LA or *meso*-LA proceeds in 5% as judged from the change of $[\alpha]^D$, and resulting poly{(D,L-LA *meso*-LA)-*b*-CL)} serves as compatibilizer for poly(L-LA) and poly(CL) sequences.

Table 2 : *Block copolymerization of L-LA or D,L-LA with CL using Sm1 and Sn1 compounds*

Catalyst	**Polymer**	**LA fraction (mol %)**		**Yield (%)**	M_n (10_4)	M_w/M_n	T_m (°C)	T_g (°C)	$-\Delta H_m$ (J/g)
		Feed	**Found**						
Sm1	Poly(L-LA-*b*-CL)	95	96	84	13.45	1.75	174.2	53.7	31.3
Sm1		90	92	78	12.51	1.72	170.5	54.1	25.2
Sm1		75	78	74	11.39	1.74	168.5	53.5	15.3
Sn1		95	96	88	7.52	1.78	174.2, 52.5	56.3	40.3
Sn1		90	91	91	7.35	1.81	166.5, 50.8	55.8	26.8
Sn1		75	77	90	7.12	1.80	165.4, 49.8	45.3	17.9
Sn1		100	100	91	7.85	1.67	168.9	56.2	38.7
Sm1	Poly(D,L-LA-*b*-CL)	95	95	85	6.21	1.45	49.5	41.5	5.8
Sm1		90	93	73	5.83	1.50	41.8	31.6	3.0
Sm1		75	81	77	4.89	1.67	28.9	15..1	1.8
Sn1		95	96	94	4.21	1.52	52.5	42.3	6.9
Sn1		90	92	93	4.35	1.64	46.8	29.8	2.9
Sn1		75	77	95	5.02	1.56	29.8	16.7	1.9
Sn1		100	100	89	5.86	1.66	59.3	35.5	35.4

Reaction conditions: Sm system, CL was reacted at 60 °C for 6 h in 4.0 ml toluene, followed by the addition of LA at 100 °C for 20 h; Sn system, CL was reacted at 110 °C for 12 h in 4.0 ml toluene, followed by the addition of LA at 100 °C for 20 h. Sml, $SmMe(C_5Me_5)_2(THF)$ 0.2 mol% of monomer; Snl, $SnBu_2(OMe)_2$ 0.2 ml% of monomer.

3.2. Synthesis of triblock copolymers composed of lactidel ε-caprolactone/lactide

Triblock copolymerizations of LA/CL/LA take place using an unique bifunctional initiator, $(C_5Me5)_2Sm(PhC=C=C=CPh)Sm(C_5Me_5)_2$ (Sm2), to afford a new functionalized polymer material. Novak et al. reported the synthesis of bifunctional polymers from ε-caprolactone using this initiator [22]. The reaction starts by the reaction of CL with $(C_5Me_5)_2Sm(PhC=C=C=$ CPh)$Sm(C_5Me_5)_2$ to afford $(C_5Me_5)_2Sm(CL)_m$ (PhC=C=C=CPh)(CL)„$Sm(C_5Me_5)_2$. This sequence represents as the B block in the ABA triblock copolymer. Exact ratio between m and n is unclear at present. Then L-LA or D,L-LA was reacted to afford the ABA type triblock copolymers (Scheme 2).

Reversed addition, i.e., addition of LA and then CL do not produce the desired BAB type triblock copolymer. Only, LA can react with this initiator to give $H[OCHCH_3(CO)]_m(PhC=C=C=CPh)[(CO)\ CHCH_3O]nH$. $Bu_2Sn(OCH_2CH_2CH_2O)$ (Sn2) was also used as a bifunctional initiator. First CL reacts with $Bu_2Sn(OCH_2CH_2CH_2O)$ to give cyclic $Bu_2Sn\ (OCH_2CH_2CH_2CH_2CH_2CO)_m(OCH_2CH_2CH_2O)$ $(COCH_2CH_2CH_2CH_2CH_2O)n$ species, which successively reacts with LA to lead to Bu_2Sn $(OCHCH_3CO)_l(OCH_2CH_2CH_2CH_2CH_2CO)_m(OC\ H_2CH_2CH_2O)(COCH_2CH_2CH_2CH_2CH_2O)n\ (CO\ CHCH_30)_o$. Reversed addition, i.e., LA and then CL, again did not give the desired species, due to the low reactivity of CL. Kricheldorf and Slicker [33] reported the similar cyclic structure by reaction of $Bu_2Sn(OCH_2CH_2CH_2O)$ with cyclic carbonates. Table 3 summarizes the results of triblock copolymerizations. We selected here three kinds of feed ratios, 80/20, 50/50 and 20/80, which generate 79-81/21-19, 39-50/61-50, and 15-19/85-81 molar ratio of LA/CL. Resulting molecular weights varies from 15.21 x 10^4 to 2.23 x 10^4 by changing the ratio of L-LA and

CL using both Sm2 and Sn2 catalysts, while M_n were nearly constant even by changing the D,L-LA/CL ratio in the case of D,L-LA/CL/D,L-LA triblock copolymerizations. L-LA/ CL/L-LA triblock copolymers show two T_m, derived from poly(L-LA) and poly(CL) sequences, while only one T_g was observed for L-LA/CL/L-LA (L-LA/CL = 80/20 feed ratio). Further increase of CL content resulted in the disappearance of T_g. Since homopoly(D,L-LA) is amorphous, resulting D,L-LA/CL/D,L-LA triblock copolymers do not show clear T_g.

Scheme 2.

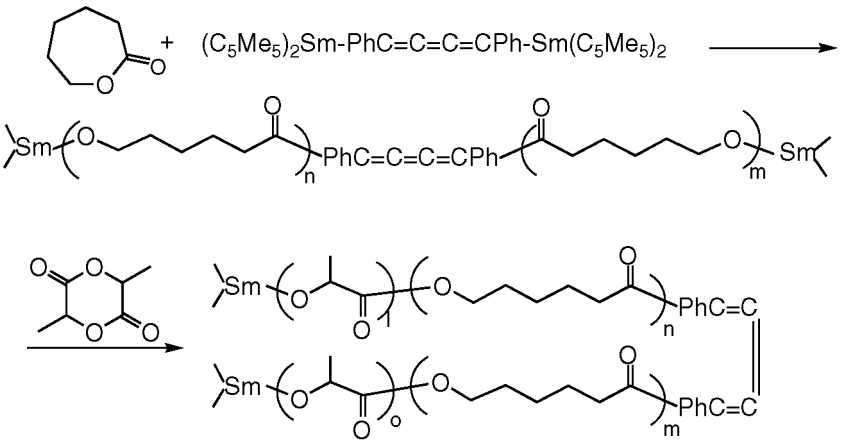


Table 3 : *Triblock copolymerizations of L-LA/CL/L-LA and D,L-LA/CL/D,L-LA with Sm2 and Sn2 compounds*

Catalyst	Polymer	LA fraction (mol %)		Yield (%)	M_n (10^4)	M_w/M_n	T_m(°C)	T_g(°C)	-ΔH_m (J/g)
		Feed	Found						
Sm2	Poly(L-LA-*b*-CL-*b*-L-LA)	80	79	91	15.21	1.39	163.5, 59.8	47.1	42.5, 23.5
Sm2		50	39	92	8.82	1.52	153.3, 58.7	-	45.9, 20.6
Sm2		20	15	94	2.23	1.64	168.5	-	78.5
Sn2		80	79	90	7.52	1.78	174.2, 52.5	56.3	43.3, 25.9
Sn2		50	48	91	6.35	1.81	166.5, 50.8	-	47.8, 26.8
Sn2		20	19	94	3.12	1.80	165.4, 49.8	-	77.9
Sm2	Poly(D,L-LA-*b*-CL-*b*-D,L-LA)	80	76	83	8.57	1.55	60.7		42.6
Sm2		50	42	85	7.76	1.35	62.3	-	58.2
Sm2		20	18	82	7.62	1.57	64.8	-	65.3
Sn2		80	79	90	5.21	1.67	65.9	-	45.6
Sn2		50	50	91	5.35	1.71	64.8	-	78.0
Sn2		20	19	89	4.95	1.75	64.5	-	76.8

Reaction conditions: Sm2 system, CL was reacted at 30 °C for 12 h in 4.0 ml toluene, followed by the addition of LA at 90 °C for 12 h; Sn2 system, CL was reacted at 90 °C for 12 h in 4.0 ml toluene, followed by the addition of LA at 110 °C for 12 h. Sm2, $(C_5Me_5)_2(PhC{=}C{=}C{=}CPh)(Sm(C_5Me_5)_2$, 0.1 mol% of monomer; Sn2, $SnBu_2(OCH_2CH_2CH_2O)$ 0.1 mol% of monomer.

3.3. Physical properties of random, diblock and triblock copolymers

All the polymers used in mechanical, degradation, and biocompatibility tests (vide infra) but not described in Tables 1-3 were prepared under the same conditions except for the monomer feed ratio, so they have similar molecular weights and molecular weight distributions to those of the polymers in Tables 1-3. Mechanical properties such as tensile strengths, tensile moduli and elongations at break were measured for random copolymers, poly{(L-LA or D,L-LA)-*ran*-CL}, and diblock copolymers, poly{(L-LA or D,L-LA)-*b*-CL} prepared with Sm1 and Sn1 catalysts (Table 4). Tensile strengths and tensile moduli for poly(L-LA-*b*-CL) are higher but the elongation is extremely lower than those of poly(L-LA-*ran*-CL), irrespective of the used catalysts. Poly(D,L-LA- *ran*-CL*)* revealed much smaller tensile strengths and high elongation because of the amorphousness of poly(D,L-LA) component, compared with both poly(L-LA-*ran*-CL) and a block copolymer, poly(L-LA-*b*-CL) even when the LA fraction is relatively high. Poly (D,L-LA-*b*-CL) also showed very small tensile strengths and small tensile moduli. Thus, poly(L-LA-*b*-CL) exhibits best mechanical property, although elongation is rather

small. Its tensile moduli exceed that of poly(L-LA).

Table 4: *Mechanical properties of copolymers of LA and CL prepared with Sml and Snl*

Cat	Polymer	LA fraction (%)	Tensile strength (MPa)	Tensile modulus (MPa)	Elongation at break (%)
Sm1	Poly(L-LA-*ran*-CL)	98	4.9	22.9	342
Sm1	Poly(D,L-LA-*ran*-CL)	96	1.3	-	1109
Sm1	Poly(L-LA-*b*-CL)	79	10.9	366.6	4.6
Sm1	Poly(D.L-LA-*b*-CL)	76	-	-	-
Sm1	Poly(L-LA)	100	17.2	308.5	283
Sn1	Poly(L-LA-*ran*-CL)	96	5.6	30.5	245
Sn1	Poly(D,L-LA-*ran*-CL)	96	2.5	-	895
Sn1	Poly(L-LA-*b*-CL)	79	12.5	402.1	10.5
Sn1	Poly(D.L-LA-*b*-CL)	81	0.9	4.5	2530

b means block.

Tensile strengths of triblock coplymers, poly(L-LA-*b*-CL-*b*-L-LA) (79/21-39/61), prepared with Sm2 catalyst is lower than that of the corresponding triblock copolymers prepared by Sn2, while the elongation at break of poly(L-LA-*b*-CL-*b*-L-LA) prepared with Sm2 is much larger than that obtained with Sn2, presumably due to the epimerization of LA in the former polymerization (Table 5). Thus, the triblock copolymers prepared with Sm2 species exhibit more flexible character than that obtained with Sn2. Triblock copolymers, poly(D,L-LA-*b*-CL-*b*-D,L -LA)s (79/21-76/24), obtained with both Sm2 and Sn2 exhibit excellent mechanical properties. Tensile moduli and elongations are high enough, although tensile strengths are a little smaller than that obtained for poly(L-LA) (Table 5).

3.4. Hydrolyses of random copolymers

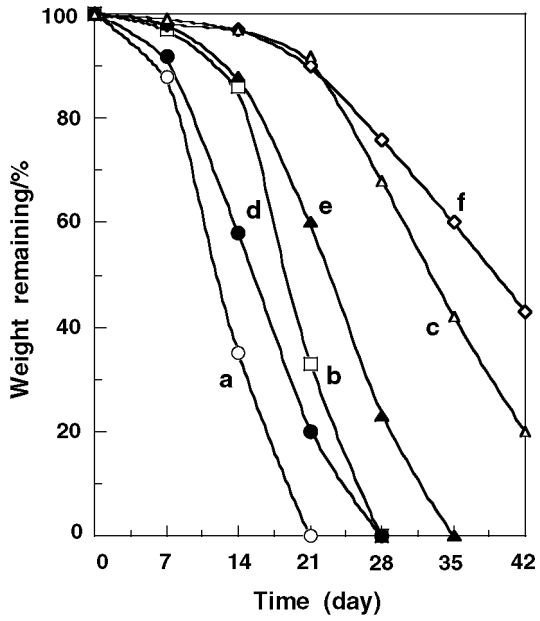
Hydrolyses of the resulting random copolymers together with homopoly(L-LA) prepared with Sm1 and Sn1 were carried out in Tricine buffer at 60 °C (Fig. 1). Poly(D,L-LA-*ran*-CL) (96/4) showed better degradability than poly(L-LA-*ran*-CL), irrespective of the used catalyst. These polymers exhibit higher degradability than homopoly(L-LA). Poly(D,L-LA-*ran*-CL) (96/4) and poly(L-LA-*ran*-CL) (92/8) obtained by Sm1 decompose completely after soaking the sample for 21 days and 28 days, respectively. On the other hand, poly(L-LA- *ran*-CL*)* and homopoly(L-LA) prepared with Sm1 show better degradability than those obtained by Snl, due to higher flexibility of the former. Poly(D,L-LA-*ran*-CL) (92/8) prepared with Snl showed nearly the same degradability with poly(L-LA-*ran*-CL) (92/8) prepared with Sm1, due to their identical crystallinities.

Table 5: *Mechanical properties of triblock copolymers*

Cat	Polymer	LA fraction (%)	Tensile strength (MPa)	Tensile modulus (MPa)	Elongation at break (%)
Sm2	Poly(L-LA-*b*-CL-*b*-L-LA)	79	8.2	134.6	625.5
Sm2	Poly(L-LA-*b*-CL-*b*-L-LA)	39	9.1	236.7	252.4
Sm2	Poly(D,L-LA-*b*-CL-*b*-D,L-LA)	76	11.3	186.8	450.3
Sm2	Poly(D,L-LA-*b*-CL-*b*-D,L-LA)	42	4.4	63.5	505.4
Sn2	Poly(L-LA-*b*-CL-*b*-L-LA)	79	11.8	156.6	16.7
Sn2	Poly(L-LA-*b*-CL-*b*-L-LA)	48	18.8	256.6	16.7
Sn2	Poly(D,L-LA-*b*-CL-*b*-D,L-LA)	79	12.3	191.1	388.3
Sn2	Poly(D,L-LA-*b*-CL-*b*-D,L-LA)	50	5.6	58.9	580.0

b means block.

Fig. 1: *Hydrolyses of poly{(L-LA or D,L-LA)-rαn-CL} prepared with Sml and Snl by Tricine buffer at 60 °C. (a) poly(D,L-LA- rαn-CL) (96/4, Sml); (b) poly(L-LA-ran-CL) (92/8, Sml); (c) poly(L-LA) (Sml); (d) poly(D,L-LA-rαn -CL) (92/8, Snl); (e) poly(L-LA-ran-CL) (91/9, Snl); (i) poly(L-LA) (Snl).*



3.5. Enzymatic degradation of random and dilock copolymers with proteinase K

Enzymatic degradations of random copolymers proceeded much faster than the degradation with Tricine buffer (hydrolysis) and compost at 60 °C (described later). Fig. 2 illustrates the plots of weight remaining using proteinase K in Tricine buffer against reaction time for poly(L-LA-*co*-TMC). Homopoly(L-LA) decomposes slowly than the random copolymers even when the sample was soaked for 200 h in the enzymatic solution. Poly(L-LA) prepared with Sml shows better degradability than that prepared with Sn1, due to the occurrence of the partial epimerization resulting more flexible polymer. In fact, poly(L-LA-*ran*-D,L-LA) (74/26) obtained with Snl revealed higher degradability as compared with poly(L-LA) (ca. 20 % weight remaining after 200 h, not shown in Fig. 2). Poly(L-LA-*ran*-CL) (84/16) a obtained by Sm1 exhibits a little higher degradability than poly(L-LA-*ran*-CL) (91/9) c obtained by Snl, and its degradability exceeds that of poly(L-LA-*ran*-CL) (65/35) because of the presence of appropriate crystallinity. Poly(L-LA-*b*-CL) (36/64-40/60) showed very little biodegradation due to its high crystallinity.

Fig. 3 illustrates the result of degradation for poly(L-LA-*ran*-CL), poly(D,L-LA-*ran*-CL), poly (L-LA-*b*-CL), and poly(D,L-LA-*b*-CL) prepared with Sm1 by a compost at 60 °C. poly(D,L-LA) and poly(D,L-LA-*ran*-CL) (95/5) exhibits relatively small degradability, while poly(L-LA-*b*-CL) (96/4) and poly(D,L-LA-*b*-CL) (93/7) have high degradability.

Fig. 4 describes the degradation with a compost for random and block copolymers prepared with Snl. Poly(L-LA) and poly(L-LA-*b*-CL) (46/54) exhibit low degradability. However, poly (D,L-LA-*b*-CL) (96/4), poly(L-LA-*ran*-CL) (92/8) and poly(L-LA-*b*-CL) (96/4) have excellent degradabilities. The degradability of poly(D,L-LA-*b*-CL) (96/4), poly(L-LA-*b*-CL) (96/4) and poly(D,L-LA) prepared with Sn1 are nearly identical with those prepared with Sm1, while poly(L-LA) exhibits much lower degradability than poly(D,L -LA) because of its high crystallinity.

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Fig. 2: *Degradation of poly(L-LA-ran-CL) with Sm1 and Sn1 by proteinase K at 37 °C. (a) poly(L-LA-ran-CL) (84/16, Sml); (b) poly(L-LA-ran-CL) (65/35, Sml); (c) poly(L-LA-ran-CL) (91/9, Snl); (d) poly(L-LA-b-CL) (78/22, Sml); (e) poly(L-LA) (Sm1); (f) poly(L-LA) (Snl); (g) poly(L-LA-b-CL) (36/64, Sml); (h) poly(L-LA-b-CL) (40/60, Snl).*

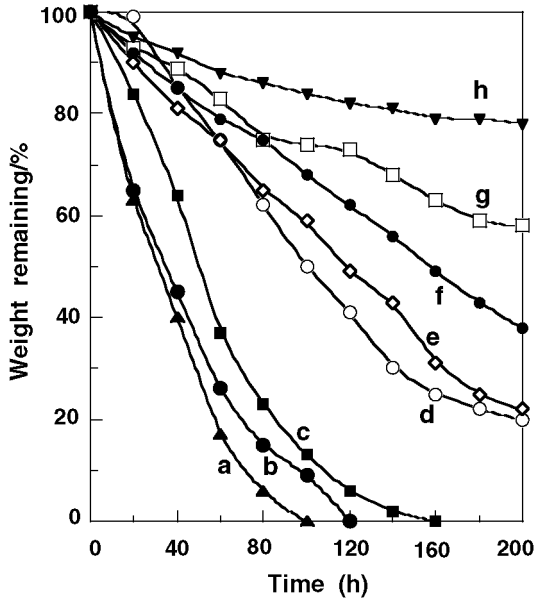


Fig. 3: *Degradation of poly(L-LA-b-CL) or poly(D,L -LA-b-CL) prepared with Sml catalyst with a compost containing 25 wt% of water at 60 °C. (a) poly(L-LA-b-CL) (96/4); (b) poly(D,L -LA-b-CL) (93/7); (c) poly(L -LA-b-CL) (92/8); (d) poly(D,L-LA-ran-CL) (95/5); (e) poly(D,L-LA).*

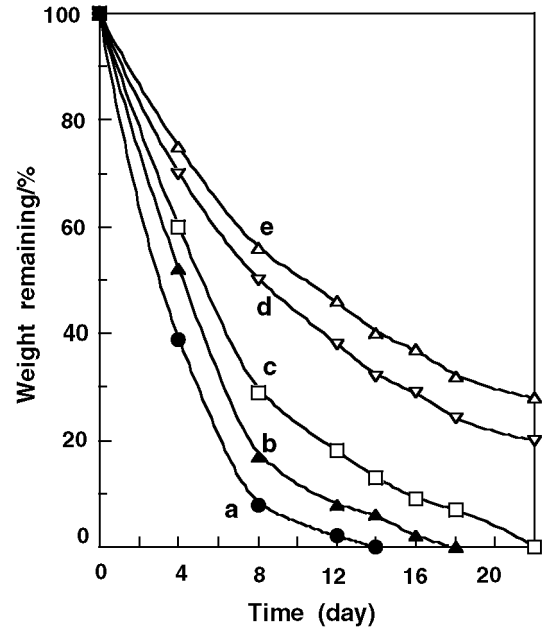
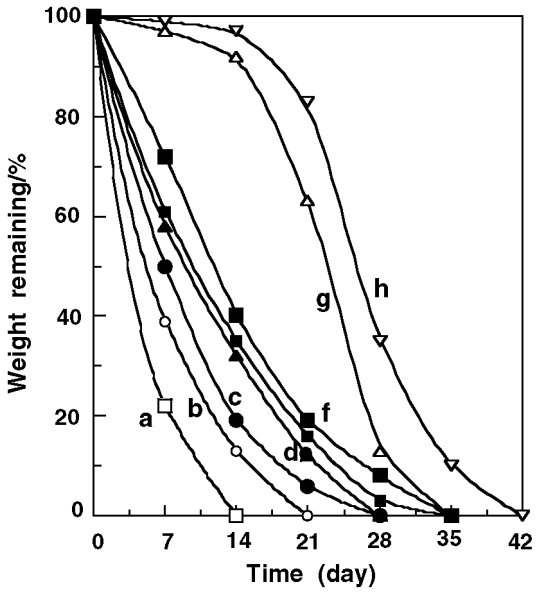


Fig. 4: *Biodegradations of poly(LA-co-CL) prepared with Sn1 by a compost at 60 °C. (a) poly(D,L -LA-b-CL) (96/4); (b) poly(L-LA-ran-CL) (92/8); (c) poly(L-LA-b-CL) (96/4); (d) poly(D,L -LA-ran-CL) (78/22); (e) poly(D,L-LA-ran-CL) (96/ 4,); (f) poly(D,L -LA); (g) poly(L-LA-b-CL) (46/54); (h) poly(L-LA).*



3.6. Hydrolysis of triblock copolymer

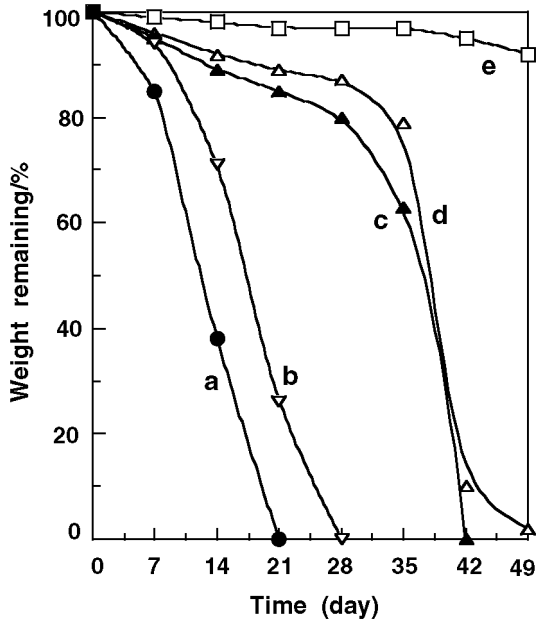
Hydrolysis of triblock copolymers with Tricine buffer at pH 8.0 is illustrated in Fig. 5. Degradation does not proceed so rapidly as enzymatic degradations. Among them, poly(L-LA-*b*-CL-*b*-L-LA) (L-LA/CL = 79/21) a synthesized with Sm2 shows much higher degradability than poly(L-LA-*b*-CL-*b*-L-LA) (L-LA/CL = 94/6, Sm2) c and poly(L-LA-*b*-CL-*b*-L-LA) (L-LA/CL = 92/8, Sn2) because of the presence of appropriate amount of crystalline part for the former. Poly(L-LA-*b*-CL-*b*-L-LA) (L-LA/CL = 76/24) b obtained by Sn2 exhibits less degradability than the a system, presumably due to the occurrence of partial epimerization for the a system, resulting more flexible polymer having better degradability. Poly(L-LA-*b*-CL-*b*-L-LA) (7/93) having excess of CL unit shows extremely low degradability by hydrolysis, because homopoly(CL) also shows very low degradability towards the hydrolysis (90% weight remaining after 49 days).

3.7. Enzymatic degradations of triblock copolymers with proteinase K

Enzymatic degradations of triblock copolymers composed of poly(L-LA-*b*-CL-*b*-L-LA) synthesized with Sm2 are illustrated in Fig. 6. Poly(L-LA-*b*-CL-*b*-L-LA) (L-LA/CL = 79/21) shows best degradability among them, and the increase of CL unit resulted in low degradability. Homopoly(CL) has almost no degradability in hydrolysis, and in fact poly(L-LA-*b*-CL-*b*-L-LA) in a 3/97 L-LA/CL ratio was also found to show almost no degradability even with proteinase K. Poly(L-LA-*b*-CL-*b*-L-LA) (L-LA/CL = 94/6) showed relatively low degradability, presumably due to high crystallinity. Its degradability is nearly the same level with those of poly(L-LA-*b*-CL-*b*-L-LA) (L-LA/CL = 48/ 52-15/85).

Fig. 7 illustrates the comparison of poly(D,L -LA-*b*-CL-*b*-D,L-LA) with poly(L-LA-*b*-CL-*b*-L-LA) prepared with Sn2 in degradability with proteinase K. The former samples exhibit higher degradability than the latter, irrespective of the molar ratio between LA and CL. When poly(L-LA-*b*-CL-*b*-L-LA) (94/6) synthesized with Sm2 (Fig. 6) was compared with those (96/4 and 79/21) synthesized with Sn2, the former exhibit much higher degradability, which is nearly the same degradability with random copolymers prepared with Sm1. However, mechanical properties of triblock copolymers exceeded those of random copolymers (Table 5). Therefore, triblock copolymers, poly(D,L-LA-*b*-CL-*b*-D,L-LA) (D,L-LA/ CL = 91/9-75/25) indicate the best biodegradable material exhibiting high degradability and relatively large tensile strength and tensile modulus. Triblock copolymers, poly(L-LA-*b*-CL-*b*-L-LA) (79/21) synthesized with Sm2 also exhibits relatively high mechanical properties.

Fig. 5: *Hydrolyses of poly(L-LA-b-CL-b-L-LA) prepared with Sm2 and Sn2 by Tricine buffer. (a) poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 79/21, Sm2); (b) poly(L-LA-b-CL-b-L-LA) (L-LA/ CL = 76/24, Sn2); (c) poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 94/ 6, Sm2); (d) poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 92/8, Sn1); (e) poly(L-LA-b-CL-b-L-LA) (L-LA/CL= 15/85, Sm2).*



3.8. Degradability of triblock copolymers by a compost

The biodegradability of triblock copolymers, poly(L-LA-*b*-CL-*b*-L-LA), synthesized by Sm2 was examined by using a compost (Fig. 8). The behavior of degradability differed from enzymatic degradation. The samples containing relatively low content of L-LA unit resulted in high degradability. Therefore, poly(L-LA-*b*-CL-*b*-L-LA) (79/21) sample is thought to be one of the best degradable copolymer. Corresponding triblock copolymers, poly(L-LA-*b*-CL-*b*-L-LA) (91/9-79/21), as well as poly(D,L-LA-*b*-CL-*b*-D,L-LA) (91/9-79/21) synthesized with Sn2 exhibit good degradability as compared with poly(L-LA). The degradability of these copolymers compares closely with those prepared with Sm2 species (Fig. 9).

3.9. SEM observation of poly(LA-co-CL) during degradation

Fig. 10 illustrates the scanning electron micrographic (SEM) analyses of the random copolymers after degradation with a compost at 60 °C. a shows the profile of poly(L-LA-*ran*-CL) (90/10) film after degradation for 6 days (weight remaining, 38.4%) and b shows poly(D,L-LA-*ran*-CL) (90/10) after degradation for 5 days (weight remaining 25.2%). Both polymers originally exhibit smooth surface with no cavities. After degradation with a compost, poly(L-LA-*ran*-CL) showed large notches. In the case of poly(D,L-LA-*ran*-CL), we can see fine cavities at around the polymer surface. The pore size is ca. 20 μm in diameter.

Fig. 11 shows the SEM images of poly(L-LA-*b*-CL-*b*-L-LA) synthesized with Sn2 after degradation by a compost, a shows the profile of a triblock copolymer containing L-LA/CL = 94/6 molar ratio (weight remaining 85%). Although we can see several clacks on the surface of a, the surface is still smooth, b is a copolymer exhibiting L-LA/CL ratio of 48/52 (weight remaining 89%) and we can see small cavities, c is that containing 7/93 molar ratio (weight remaining 59%). The surface turns unevenness by erosion. Thus, the sample c shows the largest degradability.

3.10. Compatibility of copolymers

To understand the compatibility of resulting copolymers, macrophage responses, specifically with regard to cytokine release, to lactic acid copolymers were examined. This research was focused on the release of tumor necrosis factor (TNF) from the murine macrophage cell line, RAW 264.7. Additionally, semi-quantitative RT-PCR was utilized to analyze the expression of interleukin-1-β (IL-lβ), another important proinflammatory mediator of the innate immune system. Macrophage response to LA copolymer films was determined by ELISA

and RT-PCR analysis. LA copolymers induced only background levels of TNF release from RAW 264.7 macrophages for all except system 1, 2, 3 and 16 as illustrated in Fig. 12. It should be noted that in the samples where TNF release was above background, the LA copolymer films were intact, producing insoluble particles that may induce a certain level of macrophage activation independent of the composition of those particles. Given the lack of response to the majority of LA copolymer film preparations, it is likely that the presence of oligomeric polymer is the reason for the observed TNF release. In fact, repeated dissolving of the sample 1 in chloroform followed by precipitation in methanol resulted the below background of TNF release. To confirm the viability of the RAW 264.7 cells, the cells were assayed utilizing the metabolic dye, MTS. These results indicate no significant decrease in viability based on the production of a soluble formazan product.

Fig. 6: *Enzymatic degradations of triblock copolymers prepared with Sm2 by proteinase K at 37 °C. (a) poly(L-LA) (Sm2); (b) poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 79/21, Sm2); (c) poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 94/6, Sm2); (d) poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 48/52, Sm2); (e) poly (L-LA-b-CL-b-L-LA) (L-LA/CL= 15/85, Sm2); (1) poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 6/94, Sm2); (g) poly(L-LA-b-CL-b-L-LA) (L-LA/CL=3/97, Sm2).*

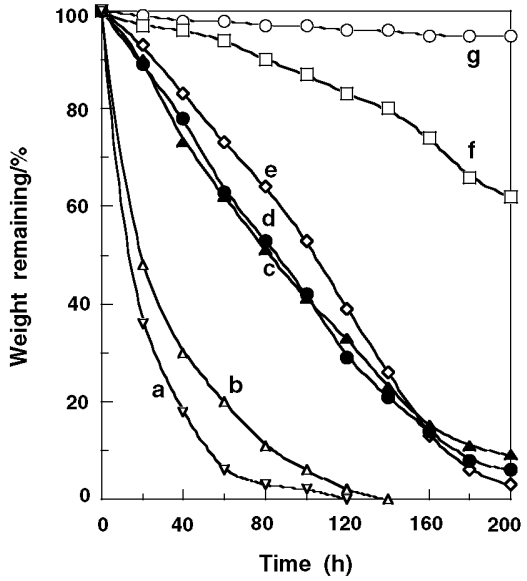


Fig. 7: *Enzymatic degradations of poly(LA-b-CL-b-LA) prepared with Sn2 by proteinase K at 37 °C. (a) poly(D,L-LA-b-CL-b-D,L-LA) (D,L-LA/CL = 91/9); (b) poly(D,L-LA-b-CL-b-D,L-LA) (D,L-LA/CL = 75/25); (c) poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 79/21); (d) poly(L-LA-b-CL-b-L-LA) (L-LA/ CL = 96/4).*

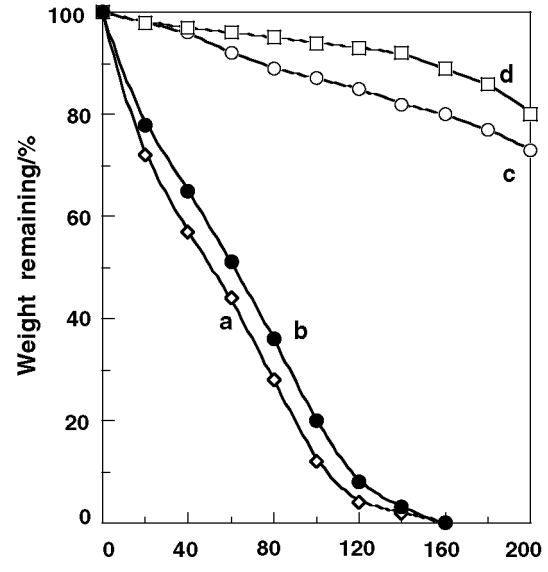


Fig. 8: *Biodegradations of triblock copolymers, poly(L-LA-b-CL-b-L-LA) prepared with Sm2 by a compost, (a) poly(L-LA-b-CL-b-L-LA) (L-LA/CL =15/85); (b) poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 39/61); (c) poly(L-LA-b-CL-b-L-LA) (L-LA/ CL = 79/21); (d) poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 94/6); (e) poly(L-LA).*

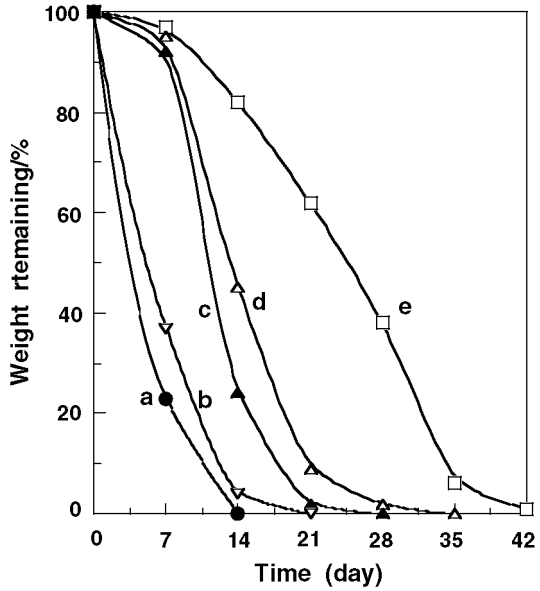


Fig. 9: *Biodegradations of triblock copolymers, poly{(L-LA or D,L-LA)-b-CL-b-(L-LA or D,L-LA) } prepared with Sn1 by a compost at 60 °C. (a) poly(D,L-LA-b-CL-b-D,L-LA) (L-LA/ CL = 91/9); (b) poly(L-LA-b-CL-b-L-LA) (L-LA/CL =91/9); (c) poly(D,L-LA-b-CL-b-D,L-LA) (D,L-LA/CL = 79/21); (d) poly(L-LA-b-CL-b-L-LA) (L-LA/CL =79/21); (e) poly(L-LA).*

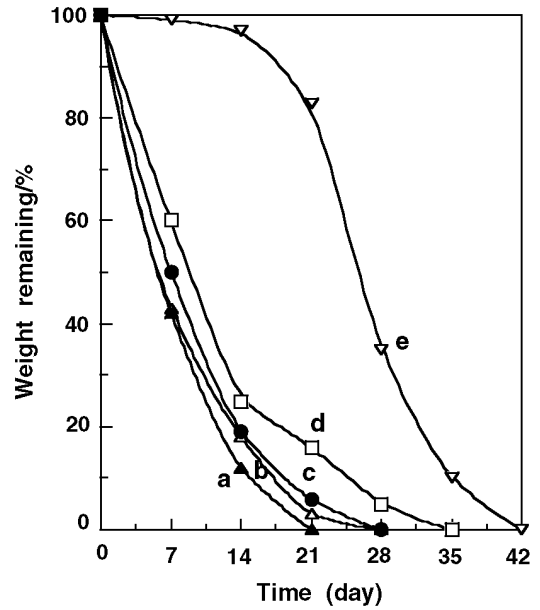
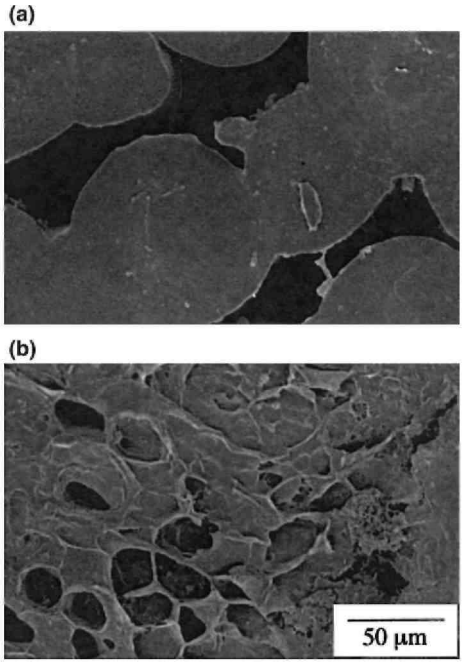


Fig. 10: *SEM profiles of random copolymers prepared with Sml after degradation by a compost: (a) poly(L-LA-ran-CL) (90/10) (weight remaining 38.4%) and (b) poly(D,L-ran-CL) (90/ 10) (weight remaining 26%).*



4. Discussion

In the random and block copolymerization of LA and CL, the Sm1 catalyst system shows similar activities to those of the Snl system at lower temperature to give copolymers with narrower molecular weight distributions than those for the Snl system. Sml afforded L-LA/CL copolymers with lower crystallinity than that of the Snl system, probably due to epimerization in the polymerization of L-LA with Sm catalysts. Thus, the Sm systems are good at control of molecular weight distribution and more susceptible to epimerization in comparison with the Sn systems.

Mechanical properties are highly depending on the polymer structure. It is notable that L-LA/CL/ L-LA triblock polymers show significantly higher elongation at break than that of the corresponding diblock polymers with keeping moderate tensile strength and modulus. In particular, the triblock copolymers obtained with Sm2 exhibit high elongation at break presumably due to the decreased crystallinity of the copolymers caused by the appropriate epimerization of L-LA units. The D,L-LA/CL/D,L-LA triblock copolymers are much more rigid than the corresponding diblock and random copolymers, although the reason is not clear.

The decreased crystallinity of the copolymers could enhance their degradability. In general, some crystalline or semicrystalline parts are necessary as a scaffold to endow the polymer samples with high biodegradability by enzymes [34,35]. Thus, completely crystalline polymers as well as completely amorphous polymers lack their enzymatic biodegradability. Thus, the samarium systems (e.g., Fig. 6b) tend to give more degradable copolymers in comparison with the corresponding stannous systems (e.g., Fig. 7c).

The degradabilities of the copolymers are also highly depending on their structures. In the enzymatic degradation of L-LA/CL copolymers (LA/ Cl ~90) prepared with the Sm systems, degradabilities of the copolymers are in the order of random copolymer (Fig. 2(a)) > triblock copolymer (Fig. 6(b)) > diblock copolymer (Fig. 2(d)). In sharp contrast, the compost degradability of the Sm systems is diblock copolymer (Fig. 3(a)) > triblock copolymer (Fig. 8(d)) ~ random copolymer (Fig. 3(d)). This could results from difference in the substrate specificity between pure proteinase K and the compost of complicated multiplicity. On the other hand, the enzymatic degradation of L-LA/CL copolymers (LA/C1~90) prepared with the Sn systems exhibited different preference, random copolymer (Fig. 4(b)) > triblock copolymer (Fig. 9(b)) ≥ diblock copolymer (Fig. 4(c)). This difference could come from lower susceptibility of the Sn systems to epimerization than the Sm systems. The use of D,L-LA instead of L-LA often improves degradability of the copolymers (e.g., Fig. 7). Especially, the D,L-LA/CL/D,L-LA triblock copolymers combine good mechanical properties and high degradabilities.

Fig. 11: *SEM profiles of poly(L-LA-b-CL-b-L-LA) prepared with Sn2 after degradation by a compost: (a) L-LA/CL = 94/6 (weight remaining 85%); (b) L-LA/CL = 48/52 (weight remaining 89%); and (c) L-LA/CL = 7/93 (weight remaining 59%).*

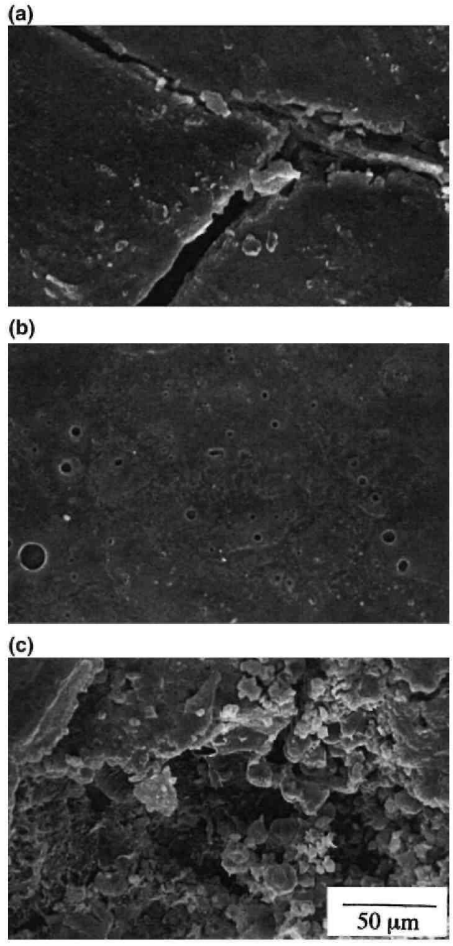
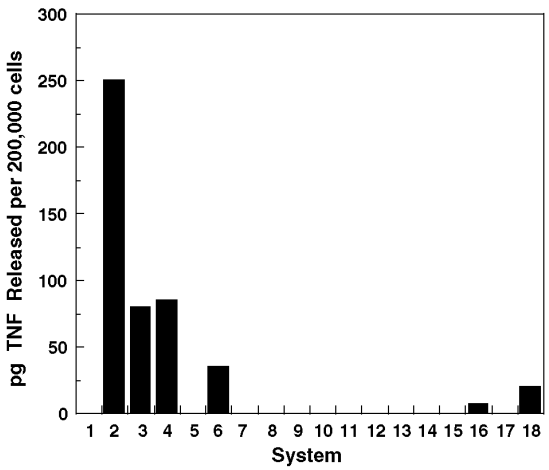


Fig. 12: *TNF release from RAW 264.7 cells for copolymers. 1, media; 2, LPS; 3, poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 96/4, Sm2); 4, poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 40/60, Sm2); 5, poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 15/85, Sm2); 6, poly(L-LA) (Sm1); 7, poly(L-LA-ran-CL) (L-LA/CL = 84/16, Sml); 8, poly(L-LA-b-CL) (L-LA/CL = 78/22, Sml); 9, poly(D.L-LA) (Sml); 10, poly(D,L-LA-ran-CL) (D,L-LA/CL = 81/29, Sml); 11, poly(D,L-LA-b-CL) (D,L-LA/CL = 50/50, Sml); 12, poly(CL) (Sml); 13, poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 79/21, Sn2); 14, poly(D,L-LA-b-CL-b-D,L-LA) (D,L-LA/CL = 79/21, Sn2); 15, poly(L-LA-ran-CL) (L-LA/CL = 91/9, Snl); 16, poly(D,L-LA-ran-CL) (D,L-LA/CL = 92/8, Snl); 17, poly(L-LA-b-CL-b-L-LA) (L-LA/CL = 90/10, SIT2); 18, poly(D,L-LA-b-CL-b-D,L-LA) (D,L-LA/CL = 91/9, Sn2).*



5. Conclusion

The comparison of $(C_5Me_5)2SmMe(THF)$ (Sml) and $[(C_5Me_5)_2Sm]2(PhC{=}C{=}C{=}CPh)$ (Sm2), with tin compounds, $Bu_2Sn(OMe)2$ (Snl) and $Bu_2Sn(OCH_2CH_2CH_2O)$ (Sn2), for the preparation of random and diblock copolymers composed of L-LA or D,L-LA and CL together with triblock copolymers composed of L-LA/CL/L-LA or D,L-LA/CL/D,L-LA was studied and the biodegradabilities of the resulting copolymers with proteinase K and a compost were examined. Poly(L-LA), poly(L-LA-*ran*-CL) and poly(L-LA-*b*-CL) prepared with Sml had better degradability than those synthesized with Snl using proteinase K. The degradability of poly(L-LA-*ran*-CL) is higher than that of poly(L-LA-*b*-CL) by proteinase K. Poly(LA-*ran*-CL) and poly(LA-*b*-CL) prepared with Sml revealed higher degradability than those obtained with Sn1 using a compost. Triblock copolymers, poly(L-LA-*b*-CL-*b*-L-LA), synthesized with Sm2 revealed nearly the same degradability with that obtained with Sn2 using a compost. The biocompatibility test examined using macrophage activation assay and metabolic viability assay tells us that almost all copolymers show good biocompatibility.

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