

Biodegradable Lactone Copolymers. II. Hydrolytic Study of ϵ -Caprolactone and Lactide Copolymers

M. MALIN, M. HILJANEN-VAINIO, T. KARJALAINEN, AND J. SEPPÄLÄ*

Helsinki University of Technology, Department of Chemical Engineering, Kemistintie 1, FIN-02150 Espoo, Finland

SYNOPSIS

Copolymers of ϵ -CL/L-LA and ϵ -CL/DL-LA were allowed to age in a buffer solution of pH 7 at 23 and 37°C. The effects of time and temperature on the rate of hydrolysis were examined by various techniques including weighing (water absorption and weight loss), SEC (molecular weight and polydispersity), and DSC (thermal properties). For comparison, the hydrolytic behavior of PLLA, PDLLA, and commercial PCL homopolymers was investigated by the same methods. SEC measurements showed that molecular weights of the copolymers and PLA homopolymers started to decrease during the first week of hydrolysis, but significant mass losses occurred only much later. As expected, there was no change in either molecular weight or mass of PCL during the hydrolysis study. The kinetic results for copolymers and homopolymers were calculated to study the degradation mechanism. During hydrolysis, the crystallinity of the initially semicrystalline copolymers increased and some crystallinity appeared in the initially amorphous L-LA-containing copolymers.

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INTRODUCTION

Hydrolyzable copolymers are an important group of materials, now finding an increasing number of applications. One of the critical properties of hydrolyzable copolymers is the rate of degradation, which is affected by the degree of crystallinity, molecular weight, and chemical composition. The percent crystallinity has proven to be an essential determinant of degradation behavior, and crystallinity, in turn, is strongly affected by monomer composition. However, changing the composition of a copolymer also changes its physical properties, and it may be difficult to achieve the desired combination of degradation and physical properties in a single material.

Probably the most widely used class of degradable polymers in the medical field is the aliphatic polyesters.¹⁻⁵ Polyesters degrade by hydrolysis, and the hydrolysis products are resorbed by the body with minimal reaction of the tissues.⁶ In the design of new biodegradable materials, tailor-made for specific

applications, it is important that the hydrolysis properties are well known and can be modified in a controlled way. One of the best ways of modifying properties is through copolymerization. P(CL/LA) copolymers exhibit a broad range of properties, including good mechanical strength, biocompatibility, biodegradability, and processability, which make them excellent materials for medical applications.⁷ Another interesting application would be to add small amounts of elastic P(CL/LA) copolymers to brittle polyesters to improve the impact strength.

In studies^{8,9} on the degradation of P(CL/DL-LA) copolymers, it has been noticed that actual mass loss does not begin until the molecular weight has decreased to about 5000 g/mol in PCL and 15,000 g/mol in PDLLA. The profile in degradation of P(CL/LA) copolymers shows a lag time where little degradation occurs followed by a rapid increase in the degradation process. P(CL/DL-LA) copolymers degrade much more rapidly than do their component homopolymers. P(CL/LA) copolymers reportedly degrade with a short induction period before water penetrates to the copolymer matrix. Despite a range of structures and morphologies, PDLLA and PCL and a number of copolymers degrade by a qualitatively similar mechanism. PDLLA and PCL are

* To whom correspondence should be addressed.

Table I Copolymer Compositions (¹³C-NMR), Molecular Weights, and Appearance of P(CL/LA) Copolymers and PLLA, PDLA, and PCL Homopolymers

Sample	Composition in Copolymer (Wt %)	Composition in Copolymer (Mol %)	After Processing		<i>D</i>	Appearance
			\bar{M}_n (g/mol)	\bar{M}_w (g/mol)		
P(CL80/L-LA20)	75/25	79/21	105,000	219,000	2.1	Plasticlike, waxy, elastic
P(CL80/DL-LA20)	73/27	77/23	107,000	231,000	2.2	Plasticlike, waxy, elastic
P(CL60/L-LA40)	49/51	55/45	103,000	215,000	2.1	Gummy, weak
P(CL60/DL-LA40)	49/51	55/45	75,000	176,000	2.3	Gummy, weak
P(CL60/DL-LA40) ^a	55/45	61/39	52,000	97,000	1.9	Gummy, weak
P(CL40/L-LA60)	33/67	39/61	74,000	145,000	2.0	Tough, elastic plastic
P(CL40/DL-LA60)	29/71	34/66	92,000	182,000	2.0	Gummy, weak
PLLA	—	—	50,000	114,000	2.3	Hard, brittle
PDLA	—	—	48,000	90,000	1.9	Hard, brittle
PCL	—	—	60,000	100,000	1.7	Tough

^a Polymerized with initiator.

bioerodible polymers and degrade with random chain scission by ester hydrolysis in a process autocatalyzed by the generation of carboxylic acid end groups. The rate of degradation of PCL is, however, almost three times slower.¹⁰ The first stage of the degradation involves a decrease in molecular weight produced by nonenzymatic, random hydrolytic scission of ester cleavage, and its duration is determined by the initial molecular weight of the polymer and its chemical structure. The second stage is characterized by mass loss and loss of mechanical strength and a change in the rate of chain scission.⁹

The two main mechanisms of chemical erosion can be described as being heterogeneous and homogeneous. Heterogeneous erosion occurs at the polymer surface only and is often referred to as surface erosion.¹¹ Homogeneous erosion, often but misleadingly called bulk erosion, causes degradation, at a constant rate, throughout the polymer matrix. Usually, the two mechanisms proceed simultaneously depending on the physical properties of the specific polymers.¹⁰

The degradation of PDLA has been found¹² to proceed more rapidly in the center than at the surface of the specimens, a feature, which has been related to a slower degrading outer layer, that entraps degrading macromolecules. In the case of initially amorphous PDLA, the degradation of polymer chains and the effect of this on chain relaxation, and perhaps on water uptake, allow the chains to undergo cold crystallization at 37°C in aqueous media. The crystalline structures obtained appear to be highly resistant to degradation and to contain multimodal molecular weight distributions due to

the preferential degradation of amorphous domains.¹³

The properties of P(CL/LA) copolymers can be modified over a wide range, from hard plastics to soft elastomers, by using different monomer ratios. The polymerization and some basic properties of copolymers of L- and DL-LA with ϵ -CL were examined in Part I of this series. In the work now described, the effects of time and temperature on the rate of hydrolysis of these copolymers were examined by various techniques including determination of water absorption and weight loss, molecular weight and polydispersity, and thermal properties. By way of comparison, the hydrolytic behavior of PLLA, PDLA, and commercial PCL homopolymers was tested in the same way. In this series of studies, we have used larger-scale polymerizations because our particular interest is the changes in the mechanical properties during hydrolysis, which will be reported in Part III.

EXPERIMENTAL

Materials

Copolymers (ϵ -CL/LA 80/20, 60/40, and 40/60 [wt %/wt % in feed], with both L-LA and DL-LA) were polymerized as described in Part I. PLLA and PDLA were obtained from Neste Chemicals and PCL (TONE P767E) was obtained from Union Carbide Co. The copolymers and homopolymers were used without further purification.

Table II Water Absorption of P(CL/LA) Copolymers and PLLA, PDLLA, and PCL Homopolymers as a Function of Hydrolysis Time at 23°C

Hydrolysis Time (Days)	P(CL80/ L-LA20) (Wt %)	P(CL80/ DL-LA20) (Wt %)	P(CL60/ L-LA40) (Wt %)	P(CL60/ DL-LA40) (Wt %)	P(CL60/ DL-LA40) ^a (Wt %)	P(CL40/ L-LA60) (Wt %)	P(CL40/ DL-LA60) (Wt %)	PLLA (Wt %)	PDLLA (Wt %)	PCL (Wt %)
1	3.3 ± 0.7	4.1 ± 0.5	4.2 ± 0.1	5.5 ± 0.8	2.2 ± 0.2	5.8 ± 0.6	4.6 ± 0.3	0.5 ± 0.2	0.4 ± 0.1	0.4 ± 0.2
2	3.8 ± 0.8	3.9 ± 0.5	4.7 ± 0.3	5.4 ± 0.9	2.9 ± 0.6	6.0 ± 0.6	3.4 ± 0.8	0.5 ± 0.1	0.5 ± 0.1	0.8 ± 0.1
3	3.2 ± 0.4	3.5 ± 0.3	4.4 ± 0.2	5.6 ± 0.8	2.0 ± 0.3	5.6 ± 0.6	3.7 ± 0.5	0.3 ± 0.1	0.6 ± 0.1	0.8 ± 0.1
7	2.1 ± 0.2	2.1 ± 0.1	3.4 ± 0.3	4.7 ± 0.6	2.5 ± 0.5	3.1 ± 0.2	9.2 ± 1.0	0.9 ± 0.2	0.8 ± 0.1	0.5 ± 0.1
14	1.0 ± 0.1	1.4 ± 0.1	2.8 ± 0.2	6.2 ± 0.6	3.1 ± 0.6	3.8 ± 0.2	19.8 ± 1.8	0.9 ± 0.1	2.1 ± 0.6	0.6 ± 0.1
21	0.7 ± 0.1	1.3 ± 0.2	3.1 ± 0.2	5.9 ± 0.7	2.6 ± 0.5	4.4 ± 0.3	^b	1.5 ± 0.2	2.8 ± 0.3	0.5 ± 0.1
28	0.9 ± 0.2	1.6 ± 0.2	2.7 ± 0.1	4.9 ± 0.4	3.6 ± 0.5	4.9 ± 0.3	29.9 ± 1.3	2.0 ± 0.2	4.6 ± 0.3	0.4 ± 0.1
42	1.0 ± 0.2	0.3 ± 0.2	2.4 ± 0.1	4.9 ± 0.5	2.6 ± 0.1	4.8 ± 0.4	16.6 ± 1.6	3.3 ± 0.4	9.5 ± 1.5	0 ± 0
56	0.3 ± 0.1	1.3 ± 0.2	2.9 ± 0.2	4.1 ± 0.5	2.7 ± 0.7	3.2 ± 0.3	19.7 ± 0.6	4.4 ± 0.8	11.2 ± 0.9	0 ± 0
70	0.3 ± 0.1	1.2 ± 0.2	1.1 ± 0.1	^c	^c	4.1 ± 0.2	^c	7.0 ± 0.6	15.0 ± 1.5	0 ± 0

^a Polymerized with initiator.^b Uncertain measurement.^c Not measurable.

Table III Water Absorption of P(CL/LA) Copolymers and PLLA, PDLLA, and PCL Homopolymers as a Function of Hydrolysis Time at 37°C

Hydrolysis Time (Days)	P(CL80/ L-LA20) (Wt %)	P(CL80/ DL-LA20) (Wt %)	P(CL60/ L-LA40) (Wt %)	P(CL60/ DL-LA40) (Wt %)	P(CL60/ DL-LA40) ^a (Wt %)	P(CL40/ L-LA60) (Wt %)	P(CL40/ DL-LA60) (Wt %)	PLLA (Wt %)	PDLLA (Wt %)	PCL (Wt %)
1	2.6 ± 0.3	2.8 ± 0.1	3.7 ± 0.2	5.2 ± 0.5	1.8 ± 0.2	4.2 ± 0.7	4.5 ± 0.6	0.7 ± 0.1	1.1 ± 0.2	0.4 ± 0.2
2	2.3 ± 0.3	1.8 ± 0.1	3.4 ± 0.1	4.5 ± 0.3	2.4 ± 0.6	^b	4.0 ± 0.3	1.1 ± 0.2	2.8 ± 0.3	0.8 ± 0.1
3	2.0 ± 0.1	1.4 ± 0.1	3.0 ± 0.2	4.6 ± 0.5	2.6 ± 0.3	^b	4.7 ± 0.4	1.7 ± 0.7	5.0 ± 0.5	0.8 ± 0.1
7	1.0 ± 0.2	0.6 ± 0.1	1.8 ± 0.1	^c	2.6 ± 0.3	2.9 ± 0.3	6.7 ± 0.5	4.7 ± 0.5	20.4 ± 1.9	0.5 ± 0.1
14	0.0 ± 0.1	0.7 ± 0.3	1.5 ± 0.1	^c	2.4 ± 0.4	3.2 ± 0.5	^c	13.3 ± 0.5	38.6 ± 2.5	0.5 ± 0.1
21	0.2 ± 0.1	0.7 ± 0.1	2.2 ± 0.2	^c	4.3 ± 0.2	3.8 ± 0.3	^c	15.0 ± 0.8	^c	0.5 ± 0.1
28	0.6 ± 0.1	1.4 ± 0.1	1.6 ± 0.1	^c	^c	3.5 ± 0.3	^c	16.2 ± 1.5	^c	0.5 ± 0.1
42	1.3 ± 0.1	0.5 ± 0.1	2.0 ± 0.1	^c	^c	^c	^c	16.1 ± 0.4	^c	0 ± 0
56	1.6 ± 0.4	3.2 ± 0.3	3.5 ± 0.4	^c	^c	^c	^c	16.9 ± 0.6	^c	0.1 ± 0.1
70	2.4 ± 0.4	3.0 ± 0.4	3.1 ± 0.6	^c	^c	^c	^c	18.3 ± 0.3	^c	0.1 ± 0.1

^a Polymerized with initiator.^b Uncertain measurement.^c Not measurable.

Table IV Mass Loss of P(CL/LA) Copolymers and PLLA, PDLLA, and PCL Homopolymers as a Function of Hydrolysis Time At 23°C

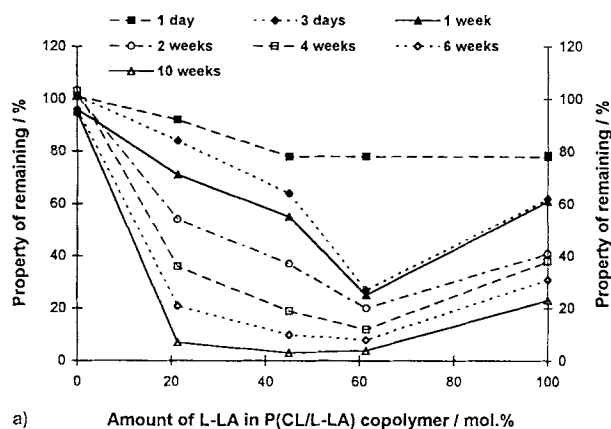
Hydrolysis Time (Days)	P(CL80/LA20) (Wt %)	P(CL80/DL-LA20) (Wt %)	P(CL60/LA40) (Wt %)	P(CL60/DL-LA40) (Wt %)	P(CL60/DL-LA40) ⁱ a (Wt %)	P(CL40/LA60) (Wt %)	P(CL40/DL-LA60) (Wt %)	PLLA (Wt %)	PDLLA (Wt %)	PCL (Wt %)
1	3.4 ± 0.9	4.5 ± 0.5	4.2 ± 0.1	5.3 ± 0.3	1.6 ± 0.2	4.1 ± 0.9	3.4 ± 0.4	0.6 ± 0.6	0.3 ± 0.2	0.2 ± 0.2
2	4.2 ± 0.7	4.7 ± 0.4	5.2 ± 0.3	6.2 ± 0.8	2.3 ± 0.6	4.2 ± 0.8	1.7 ± 0.3	0.5 ± 0.3	0.5 ± 0.4	0.5 ± 0.1
3	3.7 ± 0.5	4.8 ± 0.4	5.3 ± 0.3	6.0 ± 0.8	1.4 ± 0.3	3.9 ± 0.5	2.0 ± 0.2	0.4 ± 0.6	0.3 ± 0.3	0.5 ± 0.1
7	3.5 ± 0.4	4.5 ± 0.4	5.7 ± 0.4	7.1 ± 0.8	2.1 ± 0.1	3.0 ± 0.3	3.2 ± 0.2	1.3 ± 0.4	0.4 ± 0.4	0.3 ± 0.1
14	3.8 ± 0.4	5.1 ± 0.4	6.6 ± 0.1	7.4 ± 0.6	2.9 ± 1.5	4.5 ± 0.2	3.1 ± 0.9	0.7 ± 0.7	-0.2 ± 0.2 ^b	0.4 ± 0.1
21	3.5 ± 0.3	5.8 ± 0.3	7.4 ± 0.3	6.6 ± 0.7	2.1 ± 0.6	5.4 ± 0.7	3.3 ± 0.4	0.3 ± 0.3	-0.2 ± 0.6 ^b	0.3 ± 0.1
28	4.1 ± 0.5	6.4 ± 0.4	7.3 ± 0.1	6.0 ± 0.7	2.8 ± 0.3	7.1 ± 0.3	8.7 ± 4.6	0.1 ± 0.4	-0.7 ± 0.3 ^b	0.3 ± 0.1
42	4.6 ± 0.3	5.4 ± 0.1	7.7 ± 0.3	6.1 ± 0.6	2.5 ± 0.2	8.0 ± 1.1	1.8 ± 0.4	-0.5 ± 0.8 ^b	-0.7 ± 0.7 ^b	-0.3 ± 0.1 ^b
56	4.2 ± 0.4	7.0 ± 0.7	8.5 ± 0.3	6.2 ± 1.4	2.6 ± 0.4	8.9 ± 0.4	2.3 ± 0.4	-0.9 ± 0.1 ^b	-0.4 ± 0.7 ^b	-0.1 ± 0.1 ^b
70	5.5 ± 0.2	6.6 ± 0.4	8.1 ± 1.1	^c	^c	9.5 ± 0.2	^c	-0.2 ± 0.8 ^b	0.2 ± 1.3	-0.1 ± 0.1 ^b

^a Polymerized with initiator.^b Mass increase; might be due to chemically bonded water.^c Not measurable.

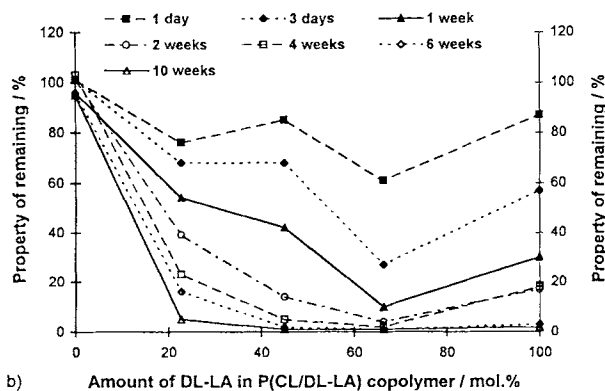
Table V Mass Loss of P(CL/LA) Copolymers and PLLA, PDLLA, and PCL Homopolymers as a Function of Hydrolysis Time at 37°C

Hydrolysis Time (Days)	P(CL80/LA20) (Wt %)	P(CL80/DL-LA20) (Wt %)	P(CL60/LA40) (Wt %)	P(CL60/DL-LA40) (Wt %)	P(CL60/DL-LA40) ⁱ a (Wt %)	P(CL40/LA60) (Wt %)	P(CL40/DL-LA60) (Wt %)	PLLA (Wt %)	PDLLA (Wt %)	PCL (Wt %)
1	3.4 ± 0.5	4.8 ± 0.3	4.9 ± 0.4	5.7 ± 0.4	1.5 ± 0.3	5.1 ± 1.7	3.2 ± 0.1	0.3 ± 0.2	0.4 ± 0.4	0.3 ± 0.2
2	3.8 ± 0.4	4.5 ± 0.2	5.4 ± 0.1	5.7 ± 0.1	2.0 ± 0.3	^b	2.4 ± 0.2	0.2 ± 0.2	0.3 ± 0.1	0.5 ± 0.1
3	4.5 ± 0.3	4.9 ± 0.3	6.0 ± 0.3	6.3 ± 0.6	2.2 ± 0.5	^b	3.0 ± 0.2	-0.3 ± 0.4 ^c	0.1 ± 0.1	0.5 ± 0.1
7	4.3 ± 0.6	5.5 ± 0.6	6.3 ± 0.1	^d	2.6 ± 0.1	7.0 ± 0.7	3.1 ± 0.2	-0.1 ± 0.2 ^c	0.6 ± 1.2	0.3 ± 0.1
14	4.4 ± 0.5	6.0 ± 0.2	8.3 ± 0.3	^d	2.2 ± 0.1	10.5 ± 0.5	^d	2.3 ± 2.2	-0.2 ± 0.3 ^c	0.4 ± 0.1
21	4.4 ± 0.6	6.5 ± 0.8	9.0 ± 0.5	^d	2.6 ± 0.9	11.2 ± 0.4	^d	4.2 ± 1.5	^d	0.5 ± 0.1
28	5.2 ± 0.3	7.5 ± 0.4	9.1 ± 0.2	^d	^d	11.5 ± 0.4	^d	5.0 ± 1.9	^d	0.5 ± 0.1
42	6.1 ± 0.4	6.7 ± 0.5	11.8 ± 3.7	^d	^d	12.7 ± 1.5	^d	6.7 ± 1.5	^d	-0.2 ± 0.1 ^c
56	5.9 ± 0.4	9.1 ± 0.2	13.4 ± 3.4	^d	^d	13.5 ± 1.8	^d	7.4 ± 0.7	^d	0.1 ± 0.1
70	9.7 ± 2.1	10.5 ± 1.3	13.0 ± 0.9	^d	^d	^d	^d	9.9 ± 0.1	^d	0.1 ± 0.1

^a Polymerized with initiator.^b Uncertain measurement.^c Mass increase.^d Not measurable.



a) Amount of L-LA in P(CL/L-LA) copolymer / mol.%



b) Amount of DL-LA in P(CL/DL-LA) copolymer / mol.%

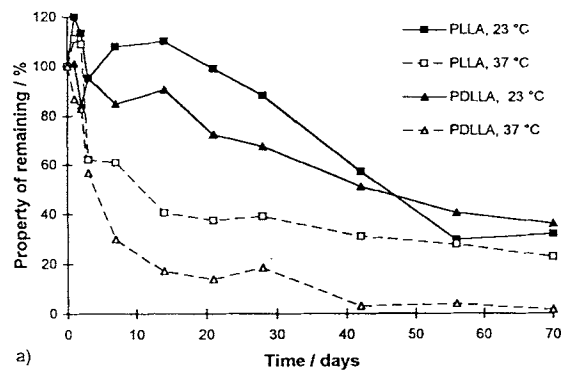
Figure 1 Effect of monomer composition on the weight-average molecular weight of (a) P(CL/L-LA) and (b) P(CL/DL-LA) copolymers at 37°C.

Molding

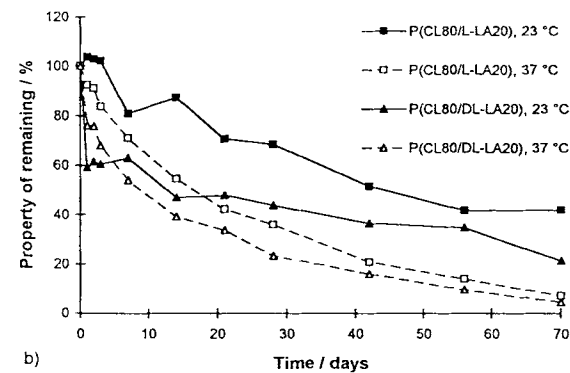
The copolymer samples for hydrolysis were prepared by compression molding (Fontijne TP 400) at different temperatures depending on the sample [P(CL80/L-LA20), P(CL80/DL-LA20), P(CL60/L-LA40), P(CL40/L-LA60): 160°C; P(CL60/DL-LA40): 140°C; P(CL60/DL-LA40)i: 130°C; P(CL40/DL-LA60): 120°C]. Test specimens were punched out from molded plates with an Elastocon EP 02 puncher. Homopolymer samples were injection-molded with Engel ES200/40 (PLLA, PDLLA: 200°C; PCL: 120°C).

Hydrolysis Tests

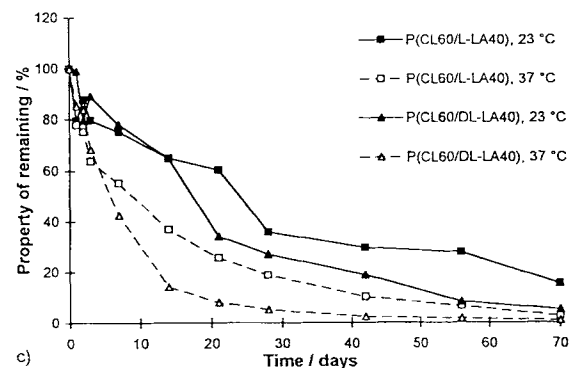
For each hydrolysis time, 10 weighed parallel test specimens were placed in test tubes immersed in 20–30 mL phosphate buffer solution of pH 7.0 at room temperature (five specimens) and at elevated temperature of 37°C (five specimens). The buffer solution was changed every other week. The gently



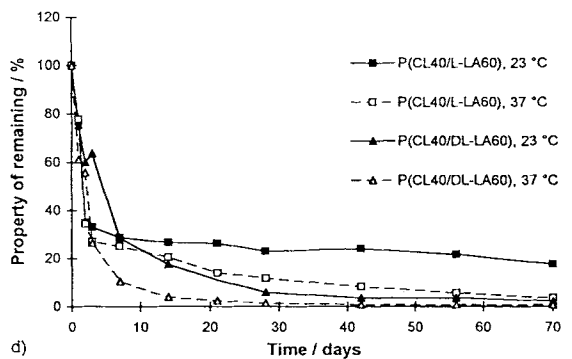
a)



b)



c)



d)

Figure 2 Loss of weight-average molecular weight of (a) PLLA and PDLLA, (b) P(CL80/L-LA20) and P(CL80/DL-LA20), (c) P(CL60/L-LA40) and P(CL60/DL-LA40), and (d) P(CL40/L-LA60) and P(CL40/DL-LA60), at 23 and 37°C.

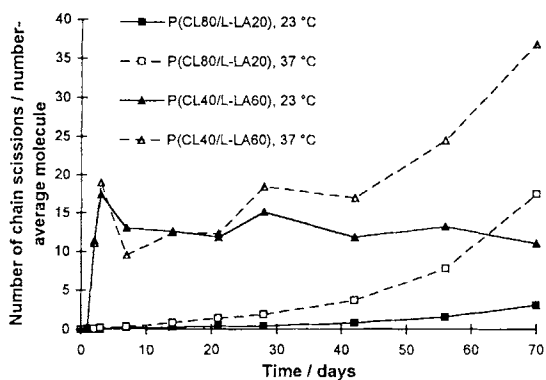


Figure 3 Number of chain scissions in P(CL80/L-LA20) and P(CL40/L-LA60) copolymers as a function of hydrolysis time.

mixed water baths (SALVIS SBK 25D) were established to maintain the set value of the temperature with an accuracy of 0.2°C. The test specimens were recovered from test tubes at different intervals and weighed, and tensile tests were made. Specimens were then vacuum-dried for 6 days at 40°C and stored in a desiccator for further analysis.

Molecular Weight Determination

Molecular weights were determined by room-temperature SEC (Waters system interface module, Waters 510 HPLC pump, Waters 410 differential refractometer, Waters 700 Satellite Wisp, and four linear PL gel columns: 10⁴, 10⁵, 10³, and 100 Å connected in series). Tetrahydrofuran was used as the solvent and eluent for copolymers and PCL and chloroform for PLLA and PDLA. The samples were filtered through a 0.5 μm Millex SR filter. The injected volume was 200 μL, and the flow rate, 1 mL/min. Monodisperse polystyrene standards were used for primary calibration, which means that the Mark-Houwink constants were not used.

Thermal Analysis

Glass transition and melting temperatures were measured by DSC (Polymer Laboratories). Nitrogen was used as a sweeping gas. Samples (5–10 mg) were heated twice, at a rate of 10°C/min, to ensure that their thermal histories were similar. The temperature range was between –100 and +200°C depending on the samples.

RESULTS AND DISCUSSION

The copolymers of ε-CL with L-LA and DL-LA were polymerized in compositions of 80/20, 60/40, and

Table VI Changes in the Polydispersity of P(CL40/L-LA60) and P(CL40/DL-LA60) Copolymers as a Function of Hydrolysis Time

Time (Days)	Polydispersity P(CL40/L-LA60)		Polydispersity P(CL40/DL-LA60)	
	23°C	37°C	23°C	37°C
0	2.0	2.0	2.0	2.0
1	2.0	1.9	1.9	2.0
2	8.5	8.1	1.9	1.9
3	11.9	10.6	2.2	6.2
7	7.9	5.2	7.6	5.2
14	7.1	5.4	6.6	3.5
21	6.6	3.7	6.7	2.5
28	7.2	4.5	4.0	1.9
42	6.0	2.9	4.2	1.6
56	6.0	2.8	3.2	1.5
70	4.2	2.6	2.5	1.4

40/60 (wt % in feed), in bulk, with stannous octoate used as the catalyst. Copolymer compositions determined by ¹³C-NMR, as well as molecular weights, molecular weight distributions, and physical appearances, are presented in Table I (partially also in Table I, Part I). The appearance of the copolymers is greatly influenced by the monomer composition and varied from plasticlike to gummy.

Water Absorption and Mass Losses

We needed to know the amount of water absorbed in order to evaluate the degree of swelling, which

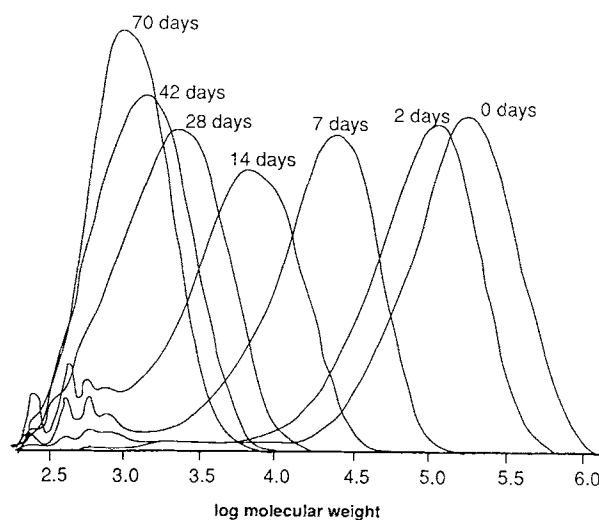


Figure 4 SEC curves of P(CL40/DL-LA60) copolymer as a function of hydrolysis time at 37°C.

Table VII Kinetic Data for the Hydrolysis of P(CL/LA) Copolymers and PLLA, PDLLA, and PCL Homopolymers at 23°C

Sample	Composition in Copolymer (Wt %)	Composition in Copolymer (Mol %)	Slope $k_1 \times 10^2$ (Days ⁻¹)	r , Correlation Factor	Slope $k_2 \times 10^6$ (Days ⁻¹)	r , Correlation Factor
P(CL80/L-LA20)	75/25	79/21	1.87	0.96	0.35	0.87
P(CL80/DL-LA20)	73/27	77/23	1.75	0.86	0.40	0.82
P(CL60/L-LA40)	49/51	55/45	2.69	0.95	0.89	0.80
P(CL60/DL-LA40)	49/51	55/45	5.18	0.93	4.47	0.94
P(CL60/DL-LA40) ⁱ ^a	55/45	61/39	2.89	0.93	1.55	0.75
P(CL40/L-LA60)	33/67	39/61	1.70	0.16	0.95	0.10
P(CL40/DL-LA60)	29/71	34/66	5.64	0.71	9.32	0.86
PLLA	—	—	2.00	0.81	0.76	0.69
PDLLA	—	—	1.84	0.88	0.91	0.81
PCL	—	—	—	—	—	—

^a Polymerized with initiator.

indicates the hydrophilicity of the polymer. Water absorption was calculated as the difference between the weight of the wet copolymer after hydrolysis and the weight of the dried copolymer, divided by the weight of the dried copolymer. Similarly, mass losses were calculated as the difference between the initial weight of the copolymer and the weight of the dried copolymer, divided by the initial weight of the copolymer.

Water absorption of P(CL/LA) copolymers and PLLA, PDLLA, and PCL homopolymers as a function of hydrolysis time at 23 and 37°C is presented in Tables II and III. The water absorption of copolymers varied from 2 to 6 wt % during the first few days of hydrolysis. With homopolymers, the corresponding values were much smaller and in-

creased toward the end of the hydrolysis period. Evidently, water molecules penetrate first into the amorphous zone of the semicrystalline structure of the material. The later decrease in the water absorption of some copolymers is assumed to be related to the degradation of amorphous parts in the copolymer. The increase again in the water absorption at 37°C is assumed to be due to the degradation of crystalline parts. In PLA homopolymers, the water absorption increased throughout the 70 day hydrolysis period and obtained much larger values than those for copolymers.

The mass losses during 70 days hydrolysis were within the limits of 10% for all samples at 23°C. The influence of copolymer composition on the mass changes was more pronounced at 37°C. The mass

Table VIII Kinetic Data for the Hydrolysis of P(CL/LA) Copolymers and PLLA, PDLLA, and PCL Homopolymers at 37°C

Sample	Composition in Copolymer (Wt %)	Composition in Copolymer (Mol %)	Slope $k_1 \times 10^2$ (Days ⁻¹)	r , Correlation Factor	Slope $k_2 \times 10^6$ (Days ⁻¹)	r , Correlation Factor
P(CL80/L-LA20)	75/25	79/21	3.98	0.99	1.90	0.81
P(CL80/DL-LA20)	73/27	77/23	4.45	0.99	2.72	0.78
P(CL60/L-LA40)	49/51	55/45	5.02	0.99	4.36	0.85
P(CL60/DL-LA40)	49/51	55/45	6.63	0.87	13.2	0.98
P(CL60/DL-LA40) ⁱ ^a	55/45	61/39	6.15	0.95	11.2	0.90
P(CL40/L-LA60)	33/67	39/61	3.16	0.43	5.0	0.74
P(CL40/DL-LA60)	29/71	34/66	5.79	0.60	17.8	0.92
PLLA	—	—	2.43	0.80	1.35	0.92
PDLLA	—	—	5.13	0.82	13.2	0.97
PCL	—	—	—	—	—	—

^a Polymerized with initiator.

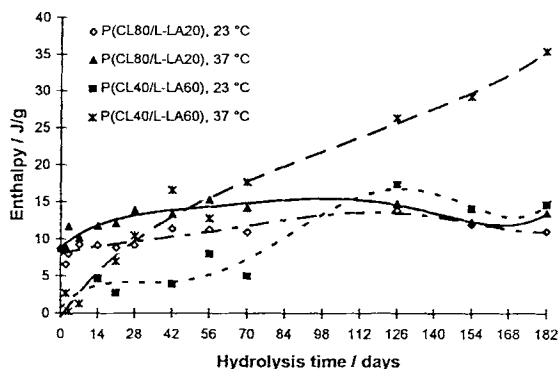


Figure 5 Changes in the melting enthalpy of P(CL80/L-LA20) and P(CL40/L-LA60) copolymers as a function of hydrolysis time at 23 and 37°C.

losses occurring at the beginning of the hydrolysis might be partly due to the withdrawal of the monomer residues in copolymers. Mass losses as a function of hydrolysis time at 23 and at 37°C are presented in Tables IV and V, respectively. Values for P(CL60/DL-LA40) and P(CL40/DL-LA60) copolymers could not be measured after 8 weeks at 23°C or after 1 week at 37°C because of the stickiness and viscosity of the samples. When the hydrolysis time was prolonged to 26 weeks, the mass losses of copolymers containing L-LA at 23°C appeared to stay below 10% or just barely exceed it [P(CL40/L-LA60)]. However, when the hydrolysis temperature was 37°C, the copolymers lost 30–50% of their mass, corresponding to the initial amount of L-LA in the copolymer.

Decrease in the Molecular Weights

The most sensitive parameters for studying degradation effects are molecular weight and molecular weight distribution. As is generally known, PLA degrades faster than does PCL. Our copolymers of PCL and PLA also degraded faster than did PCL and, depending on the composition of the copolymers, the hydrolysis was faster or about at the same level as the degradation of PLA (Fig. 1). It should be kept in mind that the initial molecular weights were slightly different (see Table I), which might have had an effect on the degradation rates. The molecular weights of the copolymers decreased faster with increasing amount of LA in the copolymer. In our experiments, the maximum degradation of P(CL/LA) copolymers was obtained with P(CL40/LA60) copolymers (i.e., composition L-LA 61 mol % and DL-LA 66 mol % in the copolymer).

The weight-average molecular weights remaining from the initial values for different copolymers and

PLLA and PDLA homopolymers at 23 and 37°C are presented in Figure 2. The molecular weights of all copolymers decreased dramatically during the first week *in vitro*, even though the mass losses were small. According to the literature, the molecular weight has to be reduced substantially to permit mass loss through solubilization.¹⁴ A large decrease in molecular weight at the beginning of hydrolysis is generally assumed to be indicative of random scission of the polymeric chains.⁹ Molecular weight losses of copolymers were faster for DL-LA than for L-LA especially at the beginning of the hydrolysis. The hydrolysis temperature had a clear effect on the decrease of molecular weights. There were no noticeable changes in the molecular weight of PCL during 10 weeks' hydrolysis.

To characterize copolymer molecular weight degradation, a kinetic model obtained from the literature^{15,16} for copolymers undergoing random chain scission was employed. According to this model, fractional molecular weight averages are related to X , the number of bond cleavages per initial number-average molecule. In eq. (1), the superscripts t and 0 refer to hydrolysis time t and time zero:

$$X = \frac{(\overline{M}_n^0 - \overline{M}_n^t)}{(\overline{M}_n^0)} \quad (1)$$

An example of the number of chain scissions per number-average molecule can be seen in Figure 3. In the case of P(CL80/L-LA20), no change was apparent in the rate of chain scission during hydrolysis at 23°C. However, at 37°C, the slope of the curve altered slightly between 42 and 56 days of hydrolysis. The corresponding number-average molecular weights were 22,000 and 12,000 g/mol. In the case of P(CL40/L-LA60), the number of chain scissions was much more extensive already at the beginning of hydrolysis. The slopes were steep and similar for the two hydrolysis temperatures during the first 3 days, but after this point, the number of chain scissions stayed at the same level at 23°C and increased at a slower rate at 37°C. A slowing of the decrease of molecular weight seemed to occur when the number-average molecular weight had reached a level of 7000–5000 g/mol.

Molecular weight distributions of P(CL80/L-LA20), P(CL80/DL-LA20), and P(CL60/L-LA40) changed only slightly during 70 days' hydrolysis. Random chain scission has taken place and evidently no small fragments exist. The molecular weight distribution of P(CL60/DL-LA40) became broader after 3 weeks of hydrolysis at 23°C due to

shorter-chain formulation and small fragments. This effect was not clear at 37°C owing to the marked decrease in molecular weight after 1 week. With P(CL40/L-LA60) and P(CL40/DL-LA60), the shorter-chain formulation and small fragments were noticed after few days of hydrolysis at both hydrolysis temperatures (Table VI). The molecular weight distribution became narrower again as the hydrolysis advanced, owing to disappearance of the high molecular weight fraction. The typical SEC curves of a copolymer where small fragments appeared during hydrolysis are presented in Figure 4.

Degradation Rate Constants

The mechanism of the hydrolysis reaction can be analyzed by determining the molecular weight and weight of the different copolymers as a function of time.¹⁷ In principle, the degradation may occur via either an autocatalyzed or an uncatalyzed reaction. The rate constant (k_1) for an autocatalyzed hydrolysis system can be calculated by eq. (2). The equation ($d[\text{COOH}]/dt = k_1[\text{COOH}]$) assumes that the carboxylic acid group is not ionized in the hydrophobic polymer bulk. The expression ($d[\text{COOH}]/[\text{COOH}]_0 = \exp(k_1 t)$) will hold until the loss of oligomers sufficiently reduces the carboxylic end group concentration of the polymer bulk. The rate constant (k_2) for an uncatalyzed system can be calculated by eq. (3)^{1,17}:

$$\ln(\overline{M}_n) = \ln(\overline{M}_n^0) - k_1 t \quad (2)$$

$$\frac{1}{\overline{M}_n} = \frac{1}{\overline{M}_n^0} + k_2 t \quad (3)$$

The kinetic results for the hydrolysis of copolymers at 23 and 37°C are presented in Tables VII and VIII. The autocatalyzed mechanism fitted better than did the uncatalyzed mechanism for P(CL80/LA20) and P(CL60/LA40). Experiments with P(CL40/L-LA60), in turn, showed poor adherence to both equations. This can be explained by the large drop in molecular weight during the first days of the hydrolysis, when the number-average molecular weight decreased to a value less than one-tenth of the initial one. As already seen in Figure 3, there was a marked change in the number of chain scissions per initial number-average molecule at this point, which perhaps was due to an increasing frequency of unzipping processes. The same behavior was noticed with P(CL40/DL-LA60). In general, the correlations were better at the higher hydrolysis temperature where the degradation was faster. The rate of hydrolysis

was faster for P(CL/DL-LA) copolymers than for P(CL/L-LA) copolymers and also for copolymers where the amount of LA relative to ϵ -CL was larger. In examining the kinetic data, it must be kept in mind that the initial molecular weight values were slightly different from each other, and this might have an effect on the degradation rate constants. The poor correlation coefficients could be partly explained in terms of low molecular weight values, which were possibly outside the linear range of the SEC calibration plot.

Changes in Thermal Properties

The thermal properties (melting enthalpy, glass transition, and melting temperatures) of the hydrolyzed samples were measured as a function of time *in vitro*. Differing from PLLA and PDLA, copolymers were hydrolyzed above their T_g values. Thermal investigations showed a lowering of T_g and T_m compared with the initial values for PLLA and a lowering of T_g for PDLA. The changes were attributed to a molecular weight decrease. The thermal properties of PCL did not change from the initial level. Negligible amounts of crystallinity appeared for amorphous PDLA during hydrolysis. The crystallinity of PLLA initially increased, but began to decrease after just 1 week. The lamella structures of crystalline areas may have been partly destroyed at that time. The crystallinity of PCL did not change during hydrolysis.

T_g values of copolymers decreased just few degrees during hydrolysis, while T_m values increased a few degrees despite the clear decrease in molecular weights. The caproyl units do not degrade in hydrolysis as fast as do the lactidyl units and this causes the changes in thermal properties. Eventually, after the molecular weight of the sample had decreased still farther, T_g could no longer be observed in the DSC curve.

The crystallinity of the semicrystalline P(CL80/L-LA20) and P(CL80/DL-LA20) copolymers increased during hydrolysis. In the case of the amorphous P(CL40/L-LA60), a marked increase in crystallinity appeared in 2 weeks at 23°C and in 2 days at 37°C (see Fig. 5). Amorphous P(CL60/L-LA40) appeared to have some crystallinity after 8 weeks at 37°C. This was due to the preferential degradation of amorphous domains leading to chain relaxations, although cold crystallization of chains in connection with water absorption cannot be excluded. As the hydrolysis advanced, the increase in crystallinity of the copolymer samples stopped, but, in most cases, only after 20 weeks. The time varied with the com-

position of the copolymer. The increase of crystallinity can, in part, be explained by a mass loss from the amorphous phase, but also to a lesser degree of entanglement of the chain fragments of the hydrolyzed amorphous regions and their ability to realign themselves into a more ordered crystalline state.

During the hydrolysis at 37°C, a double melting peak appeared for P(CL80/L-LA20) and P(CL80/DL-LA20) in 10 weeks, for P(CL60/L-LA40) in 8 weeks, for P(CL40/L-LA60) in 7 weeks, and for PLLA in 3 weeks. Macromolecular chains of different molecular weight tend to form crystallinities of different sizes.

CONCLUSIONS

Our experiments show that the hydrolytic degradation was significantly dependent on the composition of the copolymers, the stereoform of LA, and the conditions of the hydrolysis. The hydrolytic degradation of P(CL/LA) copolymers is rapid. SEC measurements showed a decrease in the molecular weights of the copolymers during the very first days *in vitro*. Especially at the beginning of the hydrolysis, molecular weight losses were faster for DL-LA than for L-LA. Mass losses during hydrolysis were within the limits of 10% for all the samples at 23°C. The influence of copolymer composition on the mass changes was more evident at 37°C. When the hydrolysis time at 23°C was prolonged to 26 weeks, the mass losses of copolymers containing L-LA appeared to stay below or just barely exceed 10%. However, when the hydrolysis temperature was 37°C, the copolymers lost 30–50% of their mass. With P(CL40/L-LA60) and P(CL40/DL-LA60), at both temperatures, a shorter-chain formulation and small fragments were noticed after only a few days. The autocatalyzed mechanism fitted better than did the uncatalyzed mechanism for the P(CL80/LA20) and P(CL60/LA40) copolymers. Experiments with P(CL40/L-LA60) showed poor adherence to both mechanisms. The amorphous and elastomeric copolymers were more sensitive to hydrolysis than were the solid and crystalline ones. The crystallinity of the semi-crystalline P(CL80/

L-LA20) and P(CL80/DL-LA20) copolymers increased during hydrolysis, and some crystallinity appeared in the amorphous P(CL40/L-LA60) and P(CL60/L-LA40) copolymers.

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