

# Biodegradable Lactone Copolymers. III. Mechanical Properties of $\epsilon$ -Caprolactone and Lactide Copolymers After Hydrolysis *in Vitro*

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## SYNOPSIS

Copolymers of  $\epsilon$ -CL/L-LA and  $\epsilon$ -CL/DL-LA and for comparison homopolymers PLLA, PDLA, and PCL were allowed to age in a buffer solution of pH 7 at 23 and 37°C and studied for the changes in the mechanical properties taking place as a function of hydrolysis time. Tensile modulus measurements showed the copolymers to retain their modulus much longer than did the PLA homopolymers. The copolymers became stiffer with hydrolysis, while the elongation at break decreased gradually. For the amorphous P(CL60/L-LA40) copolymer, the tensile modulus and yield stress values increased dramatically in hydrolysis. The initial copolymer was soft and tough but became more brittle during hydrolysis, and it exhibited a plasticlike rather than a rubberlike deformation, though the stress values were still very low. After a short period of decrease at the beginning of hydrolysis, the tensile modulus of P(CL80/L-LA20) and P(CL40/L-LA60) copolymers to some extent increased. Yield stress values for these copolymers decreased during hydrolysis. The tensile modulus of PLLA and PDLA began to decrease during the first days, i.e., the material became weaker. In the case of PCL, the tensile modulus remained almost the same during the 70 days of the test. The degradation was also studied by  $^{13}\text{C}$ -NMR. Caprolyl homopolymeric sequences did not degrade significantly during hydrolysis. © 1996 John Wiley & Sons, Inc.

## INTRODUCTION

Polymers that degrade through hydrolysis are an important group of materials with an increasing number of applications. Currently, new applications for degradable polymers are most actively being sought in biomaterials research.<sup>1,2</sup> The design of materials for specific applications demands a good understanding of the hydrolysis properties and the ability to modify these in a controlled way. Linear semicrystalline polyesters possessing microheterogeneous morphologies often display heterogeneous degradation patterns as the amorphous regions degrade faster than do the crystalline regions.<sup>3</sup>

Biodegradable polymers such as PLLA, PDLA, PCL, and their copolymers find wide use in surgery

primarily due to their hydrolyzability and biocompatibility. Semicrystalline PLLA has found applications mainly in temporary tissue and bone fixations where good mechanical strength is required. In contrast to PLLA, PDLA is an amorphous polymer and is used mainly for controlled drug release applications rather than tissue fixations.<sup>4</sup>  $\epsilon$ -CL has proven to be a suitable comonomer for the preparation of a diversified family of copolymers with mechanical properties ranging from elastomeric to rigid. These elastomeric copolymers have good elongation characteristics, which make them interesting for applications where both elasticity and degradability are required. Block copolymerization of  $\epsilon$ -CL and LA allows the great permeability of PCL segments to be combined with the rapid biodegradation of the PLA component. Crystalline domains consisting of long crystalline L-LA sequences account for the good mechanical strength, biocompatibility, and processability of very high molecular

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weight  $\epsilon$ -CL/L-LA copolymers and make them suitable for use as a strong, degradable biomedical elastomeric material.<sup>5,6</sup> In die-drawing studies,<sup>4</sup> a copolymer containing only 3 wt %  $\epsilon$ -CL has been found significantly to increase the flexibility of PLLA polymer at a room temperature when  $T_g$  and  $T_m$  lie below and above this temperature, without apparent loss in PLLA stiffness. Unlike pure PLLA cylinders, die-drawing was easily performed on this copolymer.

Since the mechanical and rheological properties of polymers are strongly dependent on the morphology of the samples, which, in turn, are a function of the way the test samples are prepared, test results in the literature are intrinsically variable and often not directly comparable. The changes occurring in the mechanical properties during hydrolysis are of current interest for the medical applications, but, at the moment, there is little information available on the changes in these properties in P(CL/LA) copolymers. Our interest in the present series of studies has been the hydrolytic degradation of  $\epsilon$ -CL/LA copolymers and PLLA, PDLLA, and PCL homopolymers: The changes in molecular weight, crystallinity, and mechanical properties occurring during hydrolysis. The polymerization and basic properties of the copolymers were examined in Part I and the mass losses and changes in molecular weight and thermal properties during hydrolysis in Part II. Now, in Part III, we report on the changes in the mechanical properties during hydrolysis.

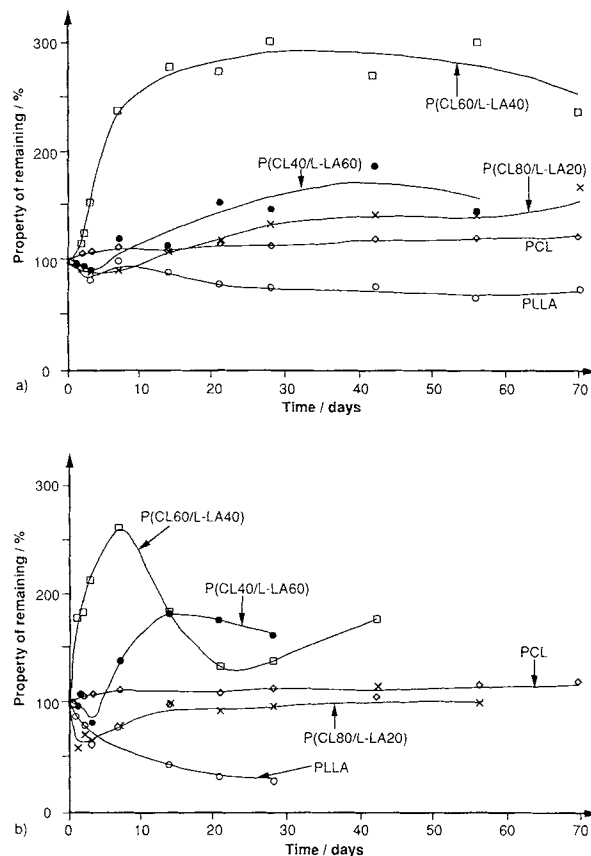
## EXPERIMENTAL

### Materials

Copolymers ( $\epsilon$ -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 PDLLA were obtained from Neste Chemicals and PCL (TONE P767E) was obtained from Union Carbide Co.

### Molding

The copolymer samples for hydrolysis were prepared by compression molding (Fontijne TP 400) with 5 min melting and 5 min pressing time 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



**Figure 1** Changes in the tensile modulus of P(CL/LA) copolymers and PLLA and PCL homopolymers during hydrolysis (a) at 23°C and (b) at 37°C.

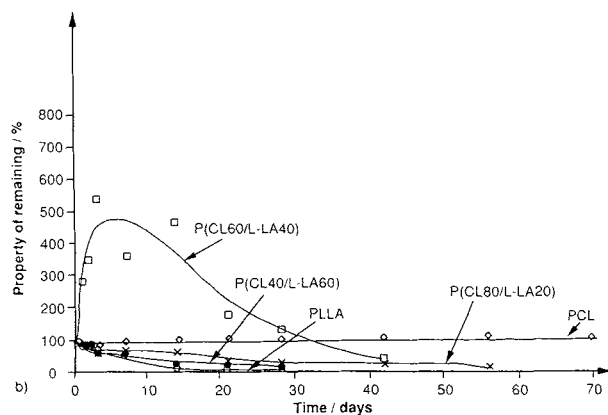
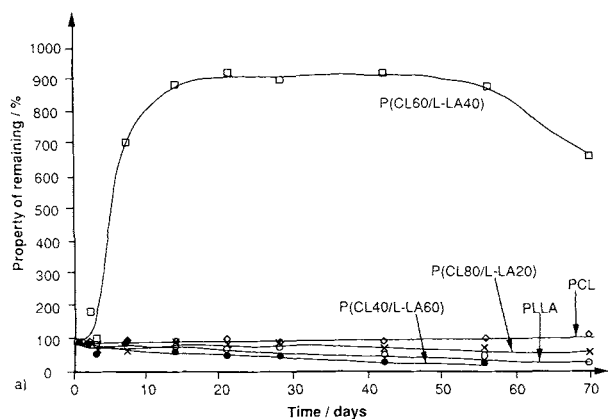
puncher. Homopolymer samples for tensile testing were injection-molded with an Engel ES200/40 (PLLA, PDLLA: 200°C; PCL: 120°C).

### Hydrolysis Tests

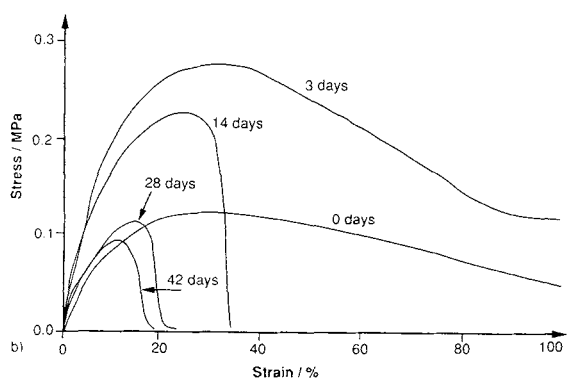
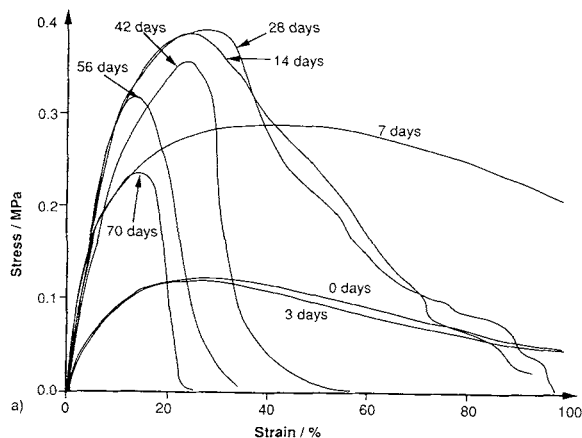
For each hydrolysis, times 10 weighted parallel test specimens were placed in test tubes immersed in 20–30 mL phosphate buffer solution of pH 7.0 at room temperature (five specimens) and at elevated temperature of 37°C (five specimens). The buffer solution was changed every other week. The gently mixed 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 tensile tests were made. For <sup>13</sup>C-NMR analysis, the samples were vacuum-dried for 6 days at 40°C.

### Tensile Testing

The tensile tests of the compression-molded copolymers (4 × 10 × 80 mm) and injection-molded



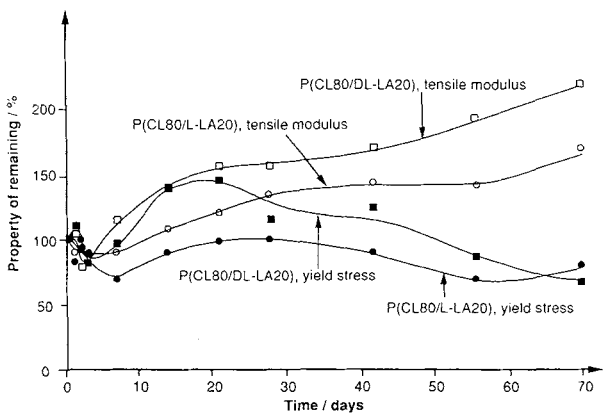
**Figure 2** Changes in the yield stress of P(CL/L-LA) copolymers and PLLA and PCL homopolymers during hydrolysis (a) at 23°C and (b) at 37°C.



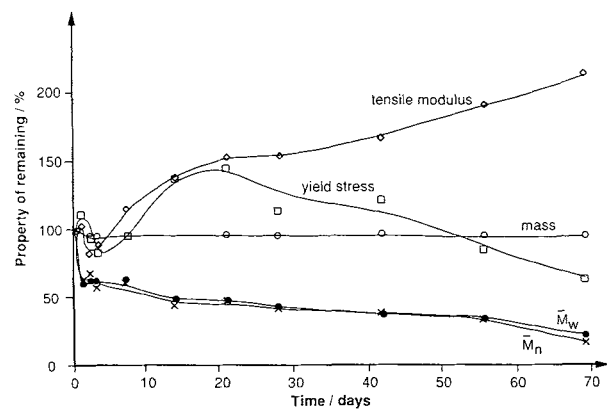
**Figure 4** Stress-strain diagrams of P(CL60/L-LA40) copolymer as a function of hydrolysis (a) at 23°C and (b) at 37°C.

homopolymers (4 × 10 × 110 mm) were done on an Instron 4204 tensile testing machine equipped with a computer adapting the standard ISO/R 527-

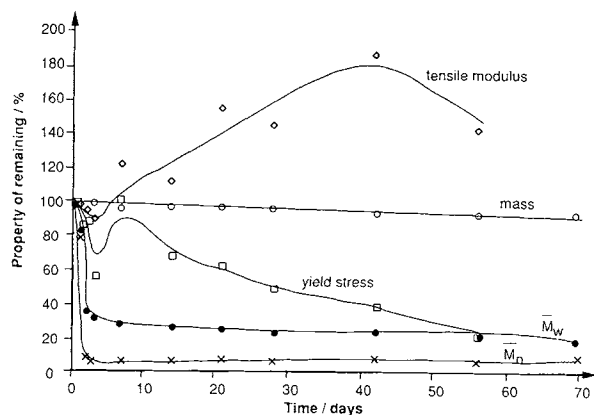
1966(E). The mechanical properties of the homopolymers and copolymers were measured using a tensile tester at a crosshead speed of 5 mm/min.



**Figure 3** Changes in the tensile modulus and yield stress of P(CL80/L-LA20) and P(CL80/DL-LA20) copolymers during hydrolysis at 23°C.



**Figure 5** Changes in tensile modulus, yield stress, mass, and molecular weights of P(CL80/DL-LA20) copolymer during hydrolysis at 23°C.



**Figure 6** Changes in tensile modulus, yield stress, mass, and molecular weights of P(CL40/L-LA60) copolymer during hydrolysis at 23°C.

The mechanical values were measured for five parallel wet specimens from hydrolysis.

### <sup>13</sup>C-NMR Measurements

The structures of copolymers were measured at 45°C with a Varian Unity 400 NMR spectrometer working at 100.577 MHz. Sample concentrations, in 5 mm tubes, were 10% by weight in chloroform-*d*<sub>1</sub>. The internal standard was tetramethylsilane, and chemical shifts were expressed in ppm. The hydrolyzed samples were not purified by precipitation.

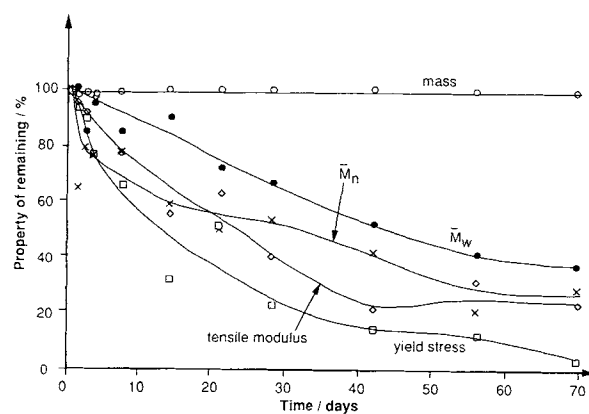
## RESULTS AND DISCUSSION

The copolymers of  $\epsilon$ -CL with L- and DL-LA were polymerized in compositions of 80/20, 60/40, and 40/60 (wt % in feed) in bulk with stannous octoate used as the catalyst. Monomer compositions in feed, copolymer compositions determined by <sup>13</sup>C-NMR, molecular weights, molecular weight distributions, and physical appearance were presented in Part I. The appearance of the copolymers was greatly influenced by the monomer compositions and varied from plasticlike to gummy. Hydrolysis tests were made on five parallel test specimens for each hydrolysis time and temperature. As reported in Part II, the molecular weights of the copolymers began to decrease within the first few days *in vitro*. The amorphous and elastomeric copolymers were more sensitive to hydrolysis than were the solid and crystalline ones.

### Changes in Mechanical Properties During Hydrolysis

The tensile properties of ( $\epsilon$ -CL/LA) copolymers and PLLA, PDLLA, and PCL homopolymers were determined immediately after the samples were taken from the buffer solution. The hydrolysis samples of P(CL60/DL-LA40) and P(CL40/DL-LA60) copolymers could not be tested mechanically because the copolymers became too viscous and sticky during the hydrolysis. For some copolymers, changes in the mechanical properties were unexpected. Figure 1 shows the changes in tensile modulus of the different P(CL/L-LA) copolymers and PLLA and PCL homopolymers during hydrolysis at 23 and 37°C. The tensile modulus of the copolymers in most cases increased during hydrolysis. Copolymers became stiffer and the brittleness increased slightly. The elongation at break decreased gradually. The tensile modulus of the P(CL60/L-LA40) copolymer increased during hydrolysis to as much as three times the initial value. That of PLLA and PDLLA started to decrease during the first few days, i.e., materials became weaker. In the case of PCL, the tensile modulus remained about the same for the entire 70 days. The measurements of the tensile modulus showed that the copolymers retained their modulus longer than did the PLA homopolymers. In interpreting the results, it must, nevertheless, be kept in mind that the initial values for tensile modulus and maximum stress were much higher for homopolymers than for copolymers (see Part I, Table V).

As reported in Part II, the molecular weight decreases faster with more LA in the copolymer. The  $\epsilon$ -CL/LA composition also clearly affects the mechanical behavior in hydrolysis. For the initially amorphous P(CL40/L-LA60), a marked increase



**Figure 7** Changes in tensile modulus, yield stress, mass, and molecular weights of PDLLA homopolymer during hydrolysis at 23°C.

**Table I** Experimental Average Lengths of Caproyl Units During Hydrolysis

Sample	Hydrolysis Time (Days)	Hydrolysis Temp (°C)	Sequence Length of $\epsilon$ -CL
P(CL80/L-LA20)	Initial		6.8
	21	23	6.2
	56	23	5.8
	21	37	6.9
	56	37	6.3
P(CL80/DL-LA20)	Initial		7.3
	21	23	4.8
	56	23	5.4
	21	37	7.6
	56	37	8.4
P(CL60/L-LA40)	Initial		4.0
	14	23	3.8
	42	23	3.9
	14	37	3.2
	42	37	4.2
P(CL60/DL-LA40)	Initial		4.0
	14	23	3.7
	14	37	3.7
	42	37	3.7
P(CL40/L-LA60)	Initial		2.4
	28	23	2.4
	7	37	2.8
	28	37	2.7
P(CL40/DL-LA60)	Initial		2.4
	28	37	2.5

in crystallinity occurred after 2 weeks at 23°C and after 2 days at 37°C (Part II), but the tensile modulus increased much less dramatically. By contrast, the initially amorphous P(CL60/L-LA40) appeared to have no crystallinity at 23°C and only some crystallinity after 8 weeks at 37°C, and its tensile modulus and yield stress values increased dramatically in the hydrolysis.

The changes in yield stress of the different P(CL/L-LA) copolymers and PLLA and PCL homopolymers during hydrolysis at 23 and 37°C are presented in Figure 2. While the yield stress value for the P(CL60/L-LA40) copolymer increased dramatically in the hydrolysis, the yield stress of P(CL80/L-LA20) and P(CL40/L-LA60) copolymers decreased slightly at 23°C and faster at 37°C.

The changes in tensile modulus and yield stress of P(CL80/L-LA20) and P(CL80/DL-LA20) copolymers during hydrolysis at 23°C are compared in Figure 3. The tensile modulus and yield stress values for P(CL80/LA20) copolymers did not change from the initial values as much for the co-

polymer containing L-LA as for that containing DL-LA. However, the initial value for the P(CL80/L-LA20) copolymer was slightly higher than for the P(CL80/DL-LA20) copolymer (see Part I). Molecular weight losses were faster, especially at the beginning of the hydrolysis, for copolymers of DL-LA than for copolymers of L-LA.

The stress-strain diagrams of the P(CL60/L-LA40) copolymer during hydrolysis are shown in Figure 4. The P(CL60/L-LA40) copolymer was initially soft and tough as reported in Part I. The material became more brittle during hydrolysis and exhibited plasticlike rather than rubber-like deformation, even though the stress values were still very low.

The changes in tensile modulus, yield stress, mass, and molecular weights as a function of hydrolysis at 23°C are shown in Figure 5 for the P(CL80/DL-LA20) copolymer, in Figure 6 for the P(CL40/L-LA60) copolymer, and in Figure 7 for the PDLLA homopolymer. Actually, for PDLLA, yield appeared just after the first week of hydrolysis

and the stress values until that point indicate maximum stress in Figure 7. As seen in the figures, the changes in mass were minor, but molecular weights decreased immediately. The mechanical properties of the copolymers persisted for a relatively long time.

### <sup>13</sup>C-NMR Analysis

The degradation was also studied by <sup>13</sup>C-NMR. Here, the hydrolysis times investigated were chosen on the basis of the changes in the mechanical values. The experimental average lengths of caproyl units, calculated as in Part I, remained at about the initial level (Table I), though none of the samples were measured after 56 days *in vitro*. It can be concluded that caproyl-containing sequences did not degrade very much during the periods investigated. The changes in structure are believed to occur mostly in lactidyl-containing sequences. The amount of random structure remained constant during the hydrolysis. Although the amount of lactide decreased slightly, no marked changes in the copolymer composition were seen by <sup>13</sup>C-NMR.

### CONCLUSIONS

The changes in the masses of the copolymers were minor, but molecular weights decreased immediately upon hydrolysis. However, the mechanical properties of copolymers persisted for a relatively long time. For most of the copolymers, the tensile modulus even increased during hydrolysis. The initial P(CL60/L-LA40) copolymer was soft and tough, but the material became more brittle in the course of hydrolysis, and it exhibited plasticlike rather than rubberlike deformation, even though the stress values were still

very low. While the yield stress value for P(CL60/L-LA40) increased dramatically in hydrolysis, the yield stress of P(CL80/L-LA20) and P(CL40/L-LA60) decreased slightly at 23°C and faster at 37°C. For copolymers, the elongation at break decreased gradually. The experimental average lengths of caproyl units of the copolymers remained more or less at the initial level. Tensile modulus and yield stress of PLLA and PDLA began to decrease during the first few days of hydrolysis. In the case of PCL, the mechanical properties remained almost the same during 70 days of hydrolysis.

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