

Influence of Molecular Structure on the Degradation Mechanism of Degradable Polymers: *In Vitro* Degradation of Poly(trimethylene carbonate), Poly(trimethylene carbonate-co-caprolactone), and Poly(adipic anhydride)

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SYNOPSIS

Relationships between molecular structure and the degradation mechanism of degradable polymers are of special interest for temporary medical applications. The *in vitro* degradation study of three aliphatic polymers—poly(trimethylene carbonate) (PTMC), poly(trimethylene carbonate-co-caprolactone) (PTMC-PCL), and poly(adipic anhydride) (PAA)—revealed that these polymers exhibit degradation times from several years (PTMC) to 1 day (PAA). PTMC degraded unexpectedly slow, accompanied by very small changes in weight loss, molecular weight (SEC), and in morphology (DSC, SEM). The degradation was independent of initial molecular weight, ionic strength of the water solution, temperature, and shaking motions. The copolymer PTMC-PCL showed a higher degradation rate compared to PTMC, with preferential degradation of amorphous parts leading to an increase in % crystallinity. The surprisingly rapid degradation of PAA showed characteristics typical for a surface-like eroding system in contrast to PTMC and PTMC-PCL. The degradation products corresponded to the repeating unit of the polymers. The hydrolysis rate increases in the order carbonate, ester, anhydride, and by combining different molecular structures we achieve specific degradation behavior. A change in hydrolysis rate of the labile bond is predicted by altering the electronegativity of groups near the carbonyl-oxygen region. © 1995 John Wiley & Sons, Inc.

INTRODUCTION

Aliphatic polyesters have found applications in the field of medicine as a temporary aid for time-limited biological dysfunctions. The crucial property of these polymers is the ability of the ester linkage to undergo a hydrolysis with chain cleavage as a consequence. Studies concerning degradable polymers are several, and deal with both synthesis and characterization of the chemical structure and degradation behavior. Most attention has been given to polymers based on lactic acid and glycolic acid,¹⁻⁴ but other polyesters like poly(ϵ -caprolactone)⁵ and poly(1,5-dioxepan-2-one)^{6,7} are also studied. The groups of

aliphatic polycarbonates and polyanhydrides are related to the aliphatic polyesters with respect to their structure.

The synthesis of aliphatic polyesters and similar structures for medical applications is generally done by ring-opening polymerization of the cyclic monomer corresponding to the repeating unit of the polymer. This is a convenient method to obtain the polymer, avoiding the drawbacks of the traditional condensation reaction like balancing equimolar amounts of monomer and removal of condensation product. The aliphatic polycarbonates can also be synthesized by copolymerization of epoxide and carbon dioxide. That method has the consequence of creating ether linkages in the chain due to decarboxylation. In the search for suitable polymers for medical applications, the method of copolymer-

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ization has been frequently used to reach a spectrum of properties such as degradation behavior and mechanical performance. We have recently reported the synthesis and characterization of poly(trimethylene carbonate-*co*-caprolactone), poly(1,5-dioxepan-2-one-*co*-lactide), poly(1,5-dioxepan-2-one-*block*-caprolactone), and poly(1,5-dioxepan-2-one-*co*-caprolactone).⁸⁻¹² By copolymerizing trimethylene carbonate with ϵ -caprolactone, we have shown that the morphology of the resultant material was strongly affected by the composition.⁸

On the scale of degradation rate, the polyanhydrides are the fastest. Most work concerning these polymers is done on the aromatic backbone structures.¹³ The aliphatic polyanhydrides do not frequently appear in the literature¹⁴⁻¹⁷ due to their presumed lack of applications. However, polyanhydrides exhibit good properties for drug delivery applications due to their degradation and release profiles and to their ability to form microspheres. From our work on synthesis, characterization, and degradation of aliphatic polyanhydrides¹⁸⁻²¹ we have shown the hydrolytic behavior of some polyanhydride structures. The present study characterizes the degradation of poly(adipic anhydride) that we use as a candidate matrix for ocular drug delivery.²²

Degradation studies of interest for materials aimed for medical applications are *in vitro* and *in vivo* (usually in rat) studies. There are few reports on the degradation behavior of poly(trimethylene carbonate) PTMC in the open literature, although trimethylene carbonate is used as a softening unit together with glycolide in a copolymer²³ used commercially as a degradable surgical suture.²⁴ Pitt and co-workers have studied the *in vitro* and *in vivo* degradation of poly(trimethylene carbonate),²⁵ and trimethylene carbonate/DL-lactide copolymer has been evaluated by Buchholz.²⁶ Previous studies concerning the degradation of aliphatic polycarbonates are mostly done on shorter homologs than poly(trimethylene carbonate).²⁷ The degradation of aliphatic polyester structures are recognized today to be dominated by a hydrolytic mechanism, but is also regarded to be promoted by enzymatic activity.^{25,28-31} The divergent opinions arose as a difference in degradation behavior that has been detected between *in vitro* and *in vivo* experiments for some polymers. The homogeneous hydrolytical degradation behavior of these materials is generally divided into two extreme cases, the bulk and the surface-eroding systems. The use of the terms degradation and erosion can cause confusion, but are used in this

context as a bond cleavage for the degradation and a depletion of the material for the erosion. In the ideal case of bulk erosion, the material is lost from the entire polymer volume, and in the ideal case of surface erosion, the material is lost only from the most outer parts of the sample. Factors like hydrophilicity and crystallinity are important in both cases. The surface erosion is proportional to the external surface area, and a larger area gives a faster erosion. The erosion of the materials is, in most cases, subsequent to the degradation of the polymer chains. Polyesters are recognized to be bulk degrading,³⁰ and the polyanhydrides are known to be surface eroding,¹³ although no ideal cases exist.

Degradation can also proceed by thermal actions, and for aliphatic polycarbonates it has been studied resulting in linear and cyclic degradation products, although the mechanisms are not clearly understood.³²⁻³⁶ The thermal degradation of these polymers is, however, of minor importance for medical applications of the material but has relevance in the preparation of the corresponding cyclic monomer by thermal decomposition of the prepolymers.

The goal of this article is to show the relation between molecular structure and degradation mechanisms of degradable polymers. This is illustrated by studying the *in vitro* degradation of poly(trimethylene carbonate) (**2**), the copolymer poly(trimethylene carbonate-*co*-caprolactone) (**4**), and poly(adipic anhydride) (**6**) (Fig. 1). The carbonate, ester, and anhydride functionalities as well as different lengths of methylene sequences are compared with respect to their contribution to the degradation.

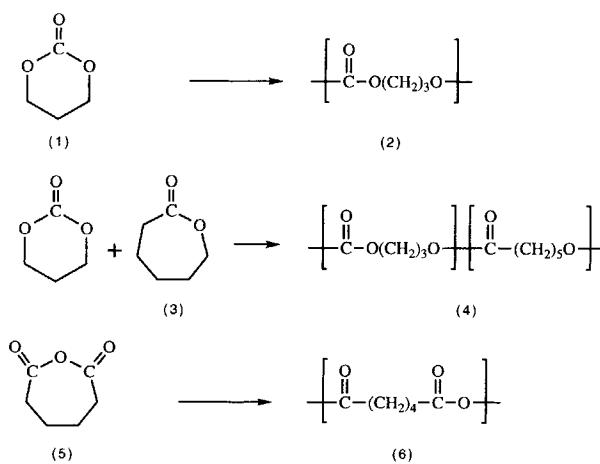


Figure 1 Schematic illustration of the polymerization from the monomers used.

EXPERIMENTAL

Materials

1,3-Propanediol (p.a.), adipic acid (p.a.), triethylamine Et_3N (p.a.), sodium hydride NaH (with 20% paraffin), and borontrifluoride etherate BF_3OEt_2 were used as received from Merck-Schuchardt, Germany. ϵ -Caprolactone (Merck-Schuchardt, Germany) was distilled from CaH_2 . Diethyl carbonate (p.a.) and stannous 2-ethylhexanoate were from Aldrich Chemical Co., USA. Acetic anhydride (p.a.) was from Riedel-de Haën AG, Germany. Solvents: methylene chloride (p.a.), methanol (p.a.), and petroleum ether (bp. 30–50°C) were used without further purification.

Synthesis of Monomers and Polymers

All polymers were synthesized by using ring-opening polymerization of the corresponding cyclic monomer structure (Fig. 1).

Monomers

1,3-Dioxan-2-one TMC (**1**) was synthesized from 1,3-propanediol and diethyl carbonate in equimolar portions and 5 mol % of stannous octanoate (transesterification catalyst). The mixture was refluxed for 8 h and the ethanol formed was distilled off. Vacuum distillation of the prepolymer gave 1,3-dioxan-2-one (bp 94°C at 0.8 mbar). Yield: 53%. $^1\text{H-NMR}$: (CDCl_3), $\delta = 2.15$ ppm (quint., $-\text{CH}_2-$, 2H), $\delta = 4.44$ ppm (t, $-\text{OCH}_2-$, 4H).

Oxepan-2,7-dione AA (**5**) was synthesized from a mixture of adipic acid and acetic anhydride (10-fold excess), which was refluxed for 3 h. Acetic acid was distilled off and the resulting prepolymer was vacuum distilled, giving a fraction of oxepan-2,7-dione (bp 85–88°C at ca 0.04 mbar). Yield: 70%. $^1\text{H-NMR}$: (CDCl_3), $\delta = 2.0$ ppm (m, $-\text{CH}_2-$, 4H), $\delta = 2.75$ ppm (m, $-(\text{CO})\text{CH}_2-$, 4H).

Polymers

All polymerizations were carried out in 25 mL septum vials with magnetic stirring bars sealed with a rubber septum. The monomer was added to the dried vessel, which was sealed and flushed with inert gas (Ar) through a syringe. The liquid initiator was added via syringe, and the bottle was placed in a thermostated oil bath stirrer.

Poly(trimethylene carbonate) PTMC (**2**):³⁷ three types of PTMC were synthesized: high HMW, medium MMW, and low molecular weight LMW.

PTMC-HMW was synthesized from 1,3-dioxan-2-one in the bulk by using borontrifluoride etherate BF_3OEt_2 (0.4 mol %) as initiator. The reaction temperature was 80°C, and the reaction time was 2 h. After polymerization, the polymer was dissolved in methylene chloride. The polymer was precipitated in methanol, filtered, and dried *in vacuo* (11 mbar) at 25°C to constant weight. Yield: 99%. $^1\text{H-NMR}$: (CDCl_3), $\delta = 2.0$ ppm (quint., $-\text{CH}_2-$, 2H), $\delta = 4.17$ ppm (t, $-\text{OCH}_2-$, 4H).

PTMC-MMW: 1,3-Dioxan-2-one was polymerized with BF_3OEt_2 (0.4 mol %) in toluene (5 mL/g monomer) at 80°C for 24 h. Workup as above. Yield: 78%. $^1\text{H-NMR}$: (CDCl_3), same as PTMC-HMW.

PTMC-LMW: 1,3-Dioxan-2-one was polymerized by sodium hydride NaH (0.4 mol %) at 80°C for 5 h. Workup as above. Yield: 37%. $^1\text{H-NMR}$: (CDCl_3), same as PTMC-HMW.

Poly(trimethylene carbonate-co-caprolactone) PTMC-PCL (**4**)⁸ was synthesized from a 12:88 molar ratio mixture of 1,3-dioxan-2-one and ϵ -caprolactone (**3**) by using stannous octanoate as catalyst (0.2 mol %) in the bulk at 120°C for 5 h. The polymer was isolated as described above. Yield: 90%. $^1\text{H-NMR}$: (CDCl_3), CL repeating unit; $\delta = 1.45$ ppm (m, $-\text{CH}_2-$, 2H), $\delta = 1.6$ –1.7 ppm (m, $-\text{CH}_2-$, 4H), $\delta = 2.35$ ppm (m, $-(\text{CO})\text{CH}_2-$, 2H), $\delta = 4.1$ ppm (m, $-\text{OCH}_2-$, 2H), and TMC repeating unit; $\delta = 2.0$ ppm (m, $-\text{CH}_2-$, 2H), $\delta = 4.17$ ppm (m, $-\text{OCH}_2-$, 4H).

Poly(adipic anhydride) PAA (**6**)²¹ was synthesized from oxepan-2,7-dione (**5**) in bulk at 25°C for 1 h by using triethylamine Et_3N (0.4 mol %) as the initiator. The polymer was recovered by dissolving the solid reaction product in methylene chloride and precipitating the solution in petroleum ether. After filtration, the polymer was dried to constant weight *in vacuo* (11 mbar). Yield: 92%. $^1\text{H-NMR}$: (CDCl_3), $\delta = 1.75$ ppm (m, $-\text{CH}_2-$, 4H), $\delta = 2.5$ ppm (m, $-(\text{CO})\text{CH}_2-$, 4H).

Preparation of Samples

For the hydrolysis tests, both circular discs and lumps of polymer were used in separate degradation series. Poly(trimethylene carbonate) and poly(trimethylene-co-caprolactone) were melt pressed to 0.5 mm thickness at 130 and 60°C, respectively. The films were cooled to room temperature under pressure. Circular discs (13 mm in diameter) were punched out from the films. Poly(adipic anhydride) as ground powder was compression molded at 25°C into circular discs (13

Table I Molecular Weights, M_n and M_w , and Molecular Weight Distributions, MWD, for the Different Polymers Used in the *In Vitro* Degradation Series

Polymer	Sample Series No.	M_n^a (g/mol)	M_w^a (g/mol)	MWD ^a
PTMC-HMW	1	75 100	118 700	1.6
PTMC-HMW	2	72 500	123 300	1.7
PTMC-MMW	3	57 300	95 400	1.7
PTMC-LMW	4, 5	4 600	15 500	3.4
PTMC-PCL	6	69 700	121 000	1.7
PAA	7	1 000	3 500	3.5

^a Measured by SEC in CHCl₃ at 25°C.

mm in diameter) with 0.7 mm thickness in a SPECAC manually operated hydraulic press P/N 15.011. The molecular weights (M_n and M_w) and molecular weight distributions ($MWD = M_w/M_n$) for the materials are shown in Table I.

In Vitro Hydrolysis

The circular samples (PTMC-HMW 58–84 mg, PTMC-PCL 61–79 mg, PAA 104–126 mg) and polymer lumps (PTMC-MMW 87–271 mg, PTMC-LMW 14–61 mg) were placed in individual vials with 0.06 M phosphate buffer solution PBS pH = 7.4 (Na₂HPO₄ and NaH₂PO₄ in 0.9% NaCl solution) or in distilled water. The vials were sealed with rubber septa and aluminum caps and placed in a thermostated chamber with or without shaking motions. Specific data for each sample series and abbreviations that are used in this article for the different polymers are listed in Table II.

Analysis and Measurements

Samples were withdrawn in duplicate or triplicate at each analysis time and dried by rapidly dipping the sample in ethanol 99.5% and placing the sample in a stream of nitrogen gas until the surface was visibly dry. The weight of the samples was recorded (wet weight) and further drying was done *in vacuo* (11 mbar) until the samples reached constant weight. The samples were characterized by measuring the wet and dry weight, molecular weight, and molecular weight distribution changes, morphological changes, and changes in composition. The water medium was analyzed with respect to pH changes and possible degradation products.

The weight loss was calculated from eq. (1).

$$\begin{aligned} \% \text{ remaining weight} \\ = \frac{\text{measured weight}}{\text{original weight}} \times 100 \quad (1) \end{aligned}$$

Table II Summary of Polymer Characteristics and *In Vitro* Test Parameters (Shapes, Hydrolysis Medium, and Hydrolysis Temperature) for the Different *In Vitro* Degradation Series

Sample Series No.	Polymer	Sample Shape	Hydrolysis Medium	Hydrolysis Temperature (°C)	Sample Series Code Name
1	PTMC-HMW	disc	PBS ^a	37	PTMC-HMW1 ^b
2	PTMC-HMW	disc	DI ^c	37	PTMC-HMW2
3	PTMC-MMW	lump	DI	60	PTMC-MMW3
4	PTMC-LMW	lump	PBS	37	PTMC-LMW4
5	PTMC-LMW	lump	PBS	60	PTMC-LMW5
6	PTMC-PCL	disc	PBS	37	PTMC-PCL6
7	PAA	disc	PBS	37	PAA7

^a PBS = phosphate buffer solution.

^b Sample series placed in a shaking chamber.

^c DI = deionized water.

Molecular Weight Measurements

A Waters size exclusion chromatography (SEC) equipment was used to measure the molecular weight. A Waters 6000A pump with five Ultrastyrigel® columns (10^5 , 10^4 , 10^3 , 500, and 100 Å pore sizes) and chloroform as eluent, with a flow rate of 1.0 mL/min, were used at 25°C with a Waters RI 401 refractive index detector. The SEC system was calibrated with polystyrene standards with narrow molecular weight distribution (MWD = 1.06).

Morphological changes were recorded by using a Perkin-Elmer differential scanning calorimeter DSC-7. Indium was used as standard for temperature calibration, and the analyses were made under a constant stream of nitrogen. The heating rate was 10°C/min and the cooling rate was 40°C/min. The melting endotherms were recorded on the first heating scan for PTMC-LMW and on the first and second scan for PTMC-PCL and PAA.

Topological changes were studied using a scanning electron microscope (SEM) Jeol JSM-5400. Samples were mounted on metal stubs and sputtered-coated with gold-palladium (Denton Vacuum Desc II).

Composition Analysis

A Bruker AC-250 nuclear magnetic resonance spectrometer (NMR) was used for composition analysis using the ^1H isotope. Samples were dissolved in deuteriochloroform CDCl_3 (Aldrich Chemical Co., USA) in 5 mm o.d. sample tubes.

Degradation Products

The pHs of the water solutions were measured with a Metrohm 704 pHMeter with a Metrohm combined glass electrode at 25°C. The gas chromatography-mass spectrometry (GC-MS) apparatus was used for detection and quantification of degradation products was a Perkin-Elmer 8500 connected to an ion trap detector, ITD mass spectrometer, with an Epsom data analysis system. The gas chromatograph was equipped with a WCOT fused silica DB-5 capillary column (30 m \times 0.32 mm i.d.) or a CB-19 column (25 m \times 0.32 mm i.d.). Helium was used as carrier gas. The phosphate buffer solutions were acidified by addition of HCl, extracted three times with CHCl_3 , and the combined organic phases were evaporated to dryness. The dry samples were derivatized by addition of 20 μL MTBSTFA, *N*-(*tert*-butyldimethylsilyl)-*N*-methyl trifluoroacetamide

(Fluka Chemie AG, Switzerland), and, subsequently, iso-butane (for PTMC-LMW4 series) or CHCl_3 with glutaric acid (for PAA7 series) was added. The extracts from PTMC-LMW4 series were injected using a Perkin-Elmer HS 101 Head-Space auto sampler.³⁸

RESULTS AND DISCUSSION

The degradation mechanism of degradable polymers has been studied in relation to molecular structure. Aliphatic polyesters and related structures are interesting for treatment of time-limited biological disorders. The hydrolytic degradation behavior should be well characterized before applying the material. We have studied the *in vitro* degradation of three different aliphatic polyester-related polymers, poly(trimethylene carbonate) PTMC, poly(trimethylene carbonate-*co*-caprolactone) PTMC-PCL, and poly(adipic anhydride) PAA, which contains the carbonate, ester, and anhydride functionality, respectively. The hydrolytic degradation of the polymers results in a molecular weight decrease (SEC measurements), weight loss, morphology changes (DSC), topological changes (SEM), and formation of degradation products (GC-MS). The intrinsic properties of the polymers affects the degradation resulting in different erosion mechanisms.

Molecular Weight Changes

Measuring the changes in weight and in molecular weight for the polymeric samples during degradation gives a good indication of the degradation rate and an initial measure on material deterioration. Molecular weight measurements on samples from PTMC, PTMC-PCL, and PAA series presented here are shown in Figures 2–4. The value of the molecular weight is not absolute, but relative to polystyrene standards. This is sufficient for this study, which is concerned with the change in molecular weight relative to the starting value to evaluate the degradation.

Figure 2 shows the molecular weight as a function of time for PTMC-HMW (series 1, 2) and PTMC-MMW (series 3) series. All of them exhibits the same slow degrading profile. The use of deionized water (series 2, 3) instead of a phosphate buffer solution (series 1) seems to have no effect. In the time scale of this experiment the higher temperature of 60°C used for PTMC-MMW3 instead of

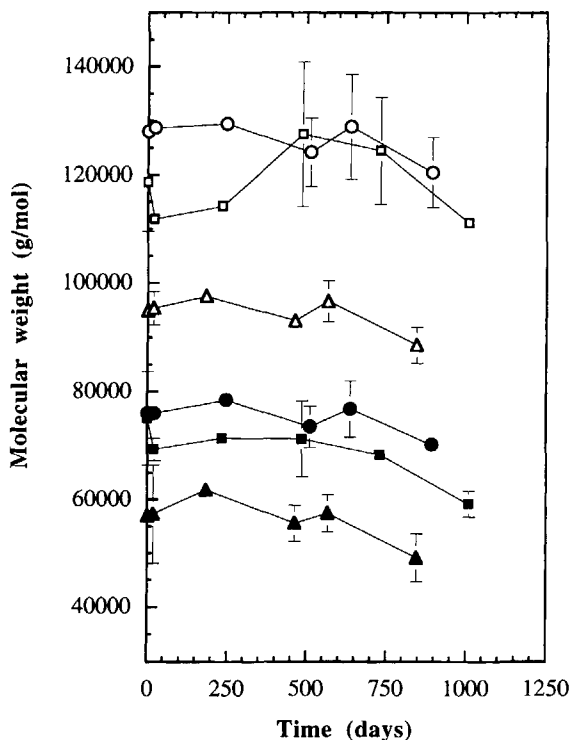


Figure 2 Molecular weight decrease, M_n (filled symbols) and M_w (open symbols), as a function of degradation time for PTMC-HMW1 (\square), PTMC-HMW2 (\circ), and PTMC-MMW3 (Δ) series.

37°C had no effect on degradation rate. By using poly(trimethylene carbonate) with a low molecular weight of 15 500 (weight average) the degradation could be expected to proceed faster, but that was not the case (Fig. 3). As for the higher molecular weight PTMC, a higher temperature had no effect on the molecular weight. Obviously, for poly(trimethylene carbonate), the molecular weight decrease is very slow starting after approximately 600 days of incubation. The resistance to chain cleavage up to 600 days is independent of type of aqueous medium, initial molecular weight of the samples, and the temperature during water exposure. Shaking of the sample vials may accelerate the transport of degradation products from the surface of the sample. This would be expected to lead to a faster erosion rate due to increased diffusion of degradation products from the bulk into the water. In this study, the PTMC-HMW1 series was subjected to shaking motions, but no effect was seen, although it may be significant when major degradation has started. The slow degradation of aliphatic polycarbonates has also been shown for poly(ethylene carbonate) and poly(propylene carbonate). *In vitro* studies of

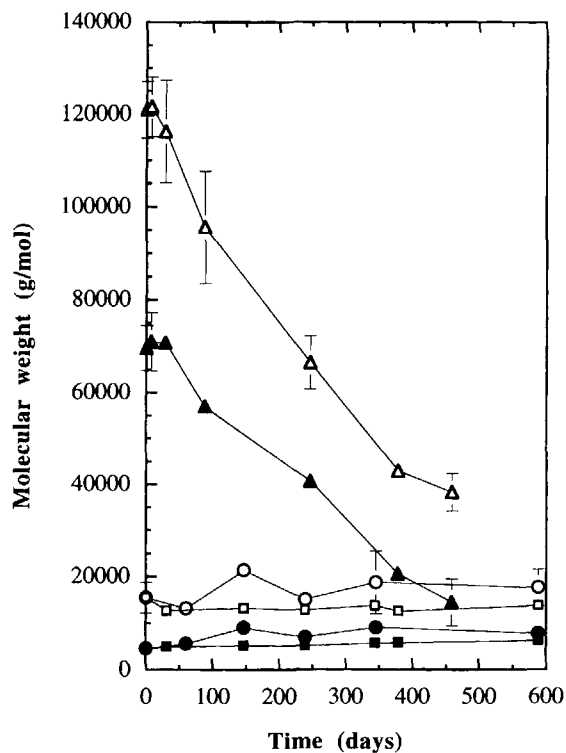


Figure 3 Molecular weight decrease, M_n (filled symbols) and M_w (open symbols), as a function of degradation time for PTMC-LMW4 (\square), PTMC-LMW5 (\circ), and PTMC-PCL6 (Δ) series.

the two polycarbonates show no degradation up to 40 days of exposure to a phosphate buffer. Poly(ethylene carbonate) is degradable *in vivo*, but

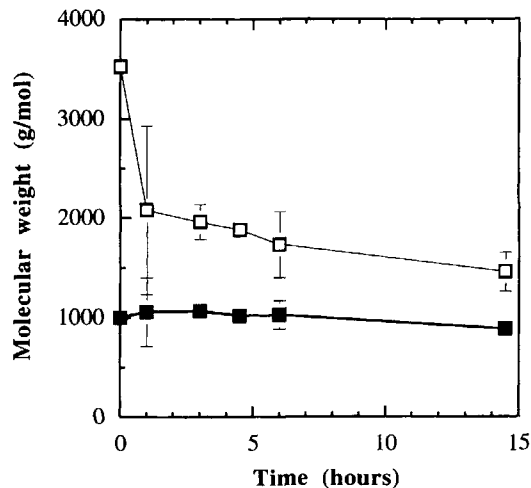


Figure 4 Molecular weight, M_n (filled symbols) and M_w (open symbols), as a function of degradation time for poly(adipic anhydride), PAA7 (\square) series.

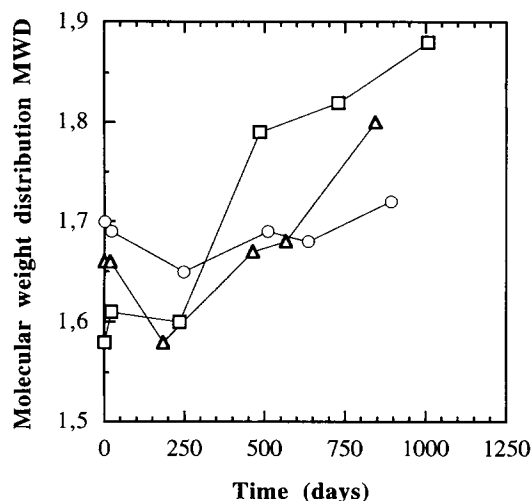


Figure 5 Molecular weight distribution, MWD, as a function of degradation time for PTMC-HMW1 (□), PTMC-HMW2 (○), and PTMC-MMW3 (△) series.

not the methyl substituted poly(propylene carbonate). The difference between *in vivo* and *in vitro* has been explained by enzymatic activity in the former case.²⁷ We have seen by *in vivo* (rat) study of PTMC samples from the same batch as PTMC-HMW1 series (Table I) that the material is not affected by the biological environment during an implantation time of 180 days. The molecular weight and molecular weight distribution were unchanged and, consequently, no weight loss was detected. These results are contradictory to the ones from Pitt and co-workers where a small change in weight and molecular weight was detected over a period of 30 days when the samples were subjected to a phosphate buffer solution. A molecular weight decrease and an increase in dispersity were recorded for PTMC samples subjected to *in vivo* environment over a period of 6 months and, hence, the authors suggests an enzymatic activated degradation.²⁵ The difference may, however, be an effect of other factors without direct involvement of enzymes,³⁰ and there is no single mechanism involved in polymer degradation *in vivo*.³¹ A biological system is a complex environment and differs within the same individual, depending on location.

Using the technique of copolymerization we have altered the degradation rate of poly(trimethylene carbonate) by randomly incorporating ϵ -caprolactone, where the homopolymer of ϵ -caprolactone is hydrolytically degradable²⁸ at a faster rate than PTMC (Fig. 2). A dramatic difference is seen in change of the molecular weight due to chain cleavage

where the copolymer drops 64% in M_w and 70% in M_n during 380 days (Fig. 3). The weight average molecular weight M_w of poly(adipic anhydride) PAA shows a greater change than the number average molecular weight M_n (Fig. 4). The overall tendency is a minor change in molecular weight contradictory to the expected behavior where the extremely water-sensitive anhydride linkage would be expected to cause a rapid decrease in the molecular weight. This behavior can be explained by surface erosion of the samples where the bulk is less affected by the water and retains the same molecular weight longer than the surface.

By looking at the molecular weight distribution, $MWD = M_w/M_n$, the insight in the degradation behavior increases. The distribution usually increases during polymer degradation due to cleavage of the chains, resulting in a larger fraction of lower molecular weight chains and ultimately oligomers and structures corresponding to the repeating unit of the polymer. The MWDs for the PTMC series 1–3 shows an overall increase in the distribution of the molecular weights due to chain cleavage (Fig. 5). The MWD is approaching the value 2, proving that random chain scission is dominant over unzipping from the chain ends. The faster decrease in M_w for PTMC-PCL samples is caused by the initial cleavage of long chains, leading to a decrease in molecular weight distribution, MWD, up to 28 days (Fig. 6). The MWD increases after the initial decrease. The low molecular weight PTMC series (4 and 5) have an opposite behavior to the higher molecular weight

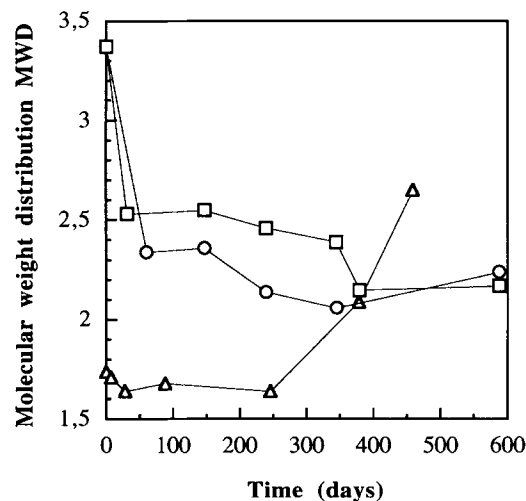


Figure 6 Molecular weight distribution, MWD, as a function of degradation time for PTMC-LMW4 (□), PTMC-LMW5 (○), and PTMC-PCL6 (△) series.

series in that they exhibit a noticeable decrease in the distribution (Fig. 3). This decrease in MWD in the early stages of water contact is caused by diffusion of a water-soluble oligomeric residue from the polymerization. The same behavior is seen in Figure 7 for PAA series.

The degradation of PTMC is unaffected by the initial molecular weight of the polymer, the ionic strength of the water, the degradation temperature, and shaking motions, and it starts to degrade at 600 days. This is to be compared to the copolymer PTMC-PCL, which degrades more rapidly. For the PAA series, the molecular weight shows a small change, and the decrease in the molecular weight distribution indicates the leach of substances and random chain scission. The differences in change of the molecular weight between the series indicates that different degradation mechanisms are involved for PTMC and PTMC-PCL compared to PAA.

Weight Loss

Weight loss experiment were carried out by weighing the samples after collection from the vials. The sample weight was recorded as wet weight immediately after collection and as dry weight after drying *in vacuo* to constant weight. The results are shown in Figures 8 and 9. PTMC-HMW series 2 [Fig. 8(b)] increases its water content with time, illustrated by the wet weight in contrast to series 1 [Fig. 8(a)], where the wet weight is approximately the same as the dry weight. The most prominent difference between the two series is that series 1 is performed in a phosphate buffer solution, PBS, and series 2 in deionized water, DI. The higher water uptake by samples from series 2 is due to osmotic effect caused by the lower ionic strength of the water. Raising the incubation temperature from 37 to 60°C [PTMC-MMW3, Fig. 8(c)] increases the water uptake in deionized water. However, the differences in water content of the samples has no effect on the chain cleavage and weight loss up to this point, shown in Figures 2 and 8. All amorphous samples became ball-like during the experiments due to higher mobility of the chains at elevated temperature in combination with the plasticising effect of the water. This change was not apparent from the rise in temperature alone for dry samples. The samples were translucent when stored in PBS, but became opaque in water with lower ionic strength due to high water uptake. At the higher temperature (60°C) discoloring appeared, indicating some thermal degradation, although se-

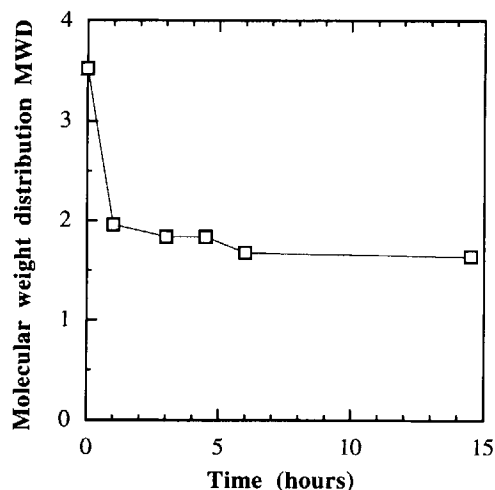


Figure 7 Molecular weight distribution, MWD, as a function of degradation time for poly(adipic anhydride), PAA7 (□) series.

vere chain cleavage only occurs at temperatures reaching 200°C.³²⁻³⁶

By incorporating ϵ -caprolactone into the trimethylene carbonate polymer chain, the structure of the backbone and the morphology changes. Poly(trimethylene carbonate) used in series 1-3 is amorphous and the copolymer between TMC and CL (12:88) is semicrystalline. The samples were stored in PBS, resulting in a low water absorption. Weight loss is usually accompanied by a decrease in molecular weight. No major weight loss can be seen in PTMC-PCL series, although significant chain cleavage has occurred (Fig. 3). This is caused by insolubility of the fraction of degraded polymer, which is still of relatively high molecular weight. This agrees with the results from molecular weight measurements showing that no low molecular fragments has been formed. ¹H-NMR analysis of PTMC-PCL samples shows no change in composition of the copolymer within the time of this experiment. Homopolymer PCL shows a weight loss when the molecular weight of the fraction has decreased to 5,000.⁵

Weight loss of PTMC-LMW series [Fig. 8(e-f)] deviates from the other ones by an instant decrease in dry weight to 85% of original sample weight. This is explained by the leaching effect mentioned above, where the low molecular weight fraction dissolves in the water. The wet weight of PTMC-LMW4 is higher than for PTMC-LMW5 series. The two low molecular weight series were initially equal in semicrystallinity. PTMC-LMW5 held at 60°C rearranged at the higher temperature and formed a to-

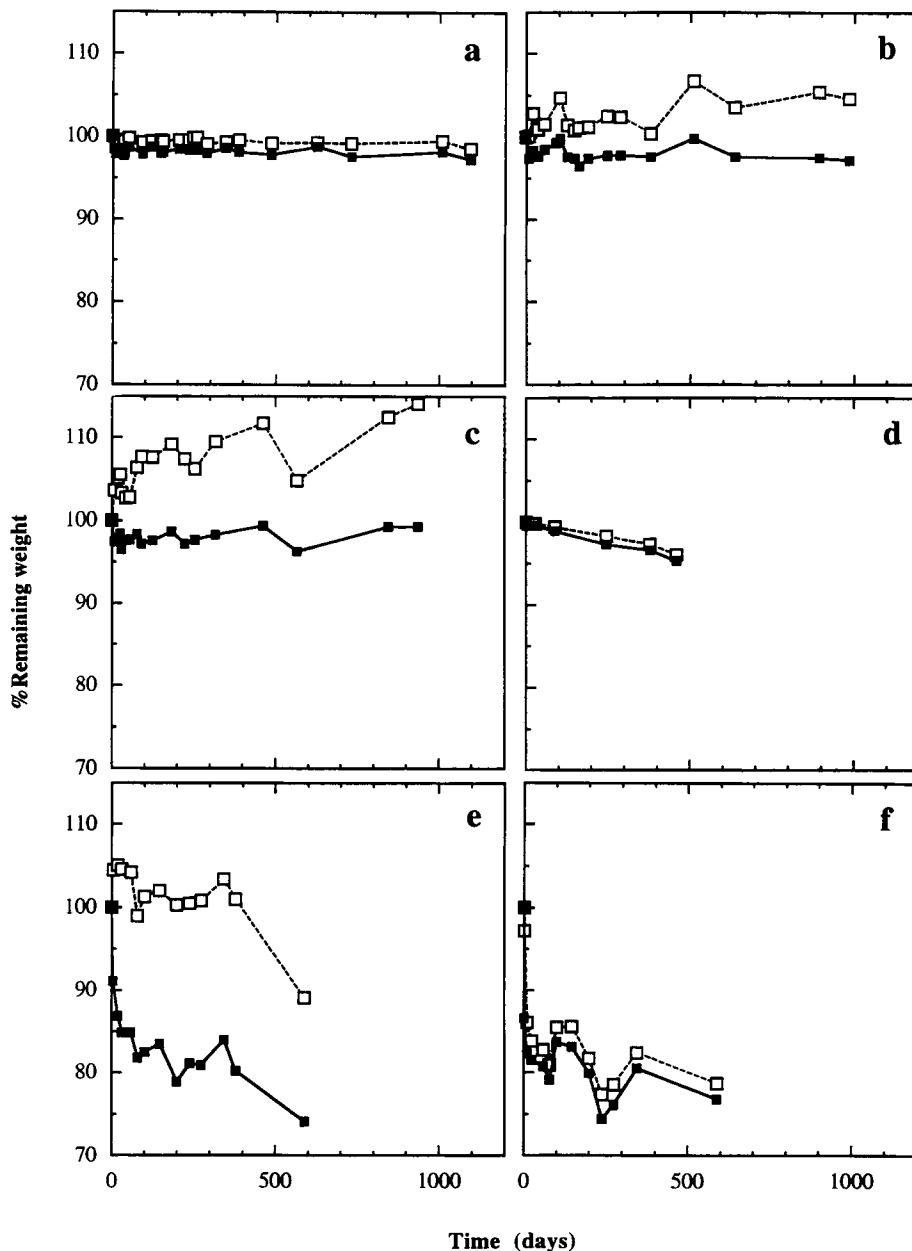


Figure 8 Percent remaining weight of polymer samples as a function of degradation time; dry weight (filled symbols) and wet weight (open symbols). (a) PTMC-HMW1, (b) PTMC-HMW2, (c) PTMC-MMW3, (d) PTMC-PCL6, (e) PTMC-LMW4, and (f) PTMC-LMW5.

tally amorphous material. The higher water uptake of the crystalline low molecular weight PTMC [Fig. 8(e)], compared to the amorphous [Fig. 8(f)], is probably due to the fact that the crystalline samples are more porous than the amorphous ones in this specific case, and the water is temporarily occluded in the sample. The higher water content of PTMC-LMW4 seems to have no major effect on the mo-

lecular weight and weight loss compared to the amorphous PTMC-LMW5 samples [Figs. 3, 8(e-f)]. In Figure 9, the weight loss of the PAA series is presented. The wet weight is constant in the beginning, whereas the dry weight of the samples decreases constantly by loss of material. The weight was decreasing rapidly after 6 h; however, the recording was complicated by fragmentation

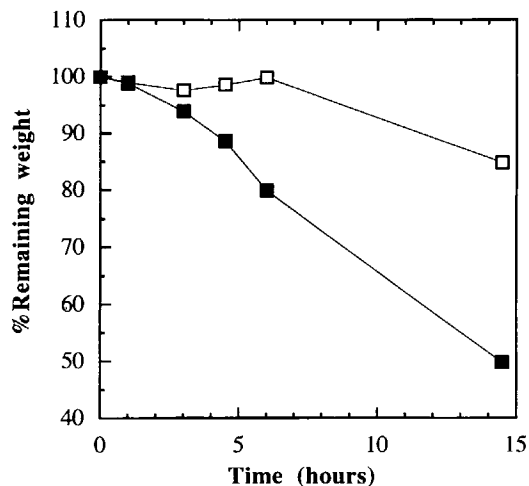


Figure 9 Percent remaining weight of polymer samples as a function of degradation time for poly(adipic anhydride), PAA7 series; dry weight (filled symbols) and wet weight (open symbols).

of the samples. The clear weight loss is not accompanied by a corresponding molecular weight change; this will be discussed under Degradation Mechanism.

Degradation Kinetics

The degradation rate can be expressed by the rate constant k , which can be calculated from the number average molecular weight M_n by using expressions derived from a kinetic model valid for chain cleavage by Pitt and Gu.³⁹ Two equations are derived for the autocatalyzed and the uncatalyzed hydrolysis reaction. The resulting equations are for the autocatalyzed case:

$$\ln(M_n) = \ln(M_n^0) - k_2 t \quad (2)$$

and for an uncatalyzed case:

$$1/M_n = 1/M_n^0 + k_3 t \quad (3)$$

where M_n^0 is the number average molecular weight before hydrolysis, k_2 and k_3 are the rate constants, and t is the degradation time. During the hydrolysis of an ester functionality it generally generates carboxylic end groups, which can further catalyze the hydrolysis due to their acidity. These equations assume several conditions, and their validity can be questioned, especially for PTMC in this study where the formation of carboxylic end groups is less probable upon hydrolysis of the polymer chain. However,

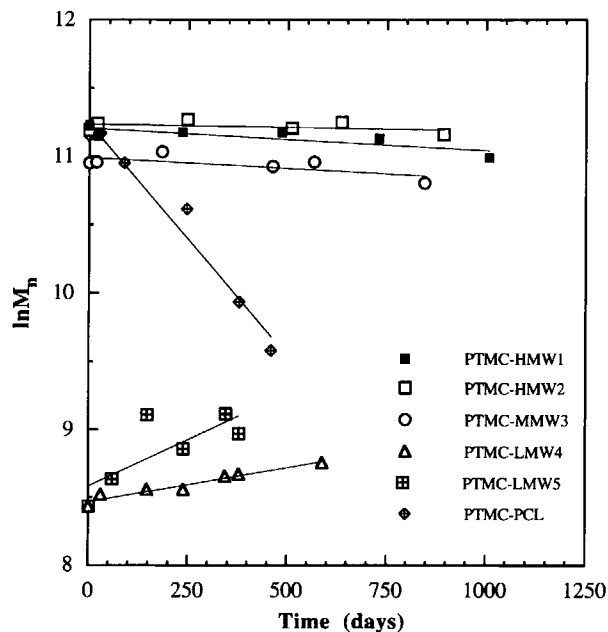


Figure 10 Degradation kinetics expressed by $\ln M_n$ as a function of degradation time [$\ln(M_n) = \ln(M_n^0) - k_2 t$] for PTMC and PTMC-PCL degradation series.

plots of $\ln(M_n)$ and $1/M_n$ as a function of time are generated from experimental data, giving a linear relationship in the initial phase of the degradation.³⁹ A linear fit of the curves in our study was done, and the dominating hydrolysis mechanism was elucidated by the best fit. The degradation rates of the series in this study are from 1 day (PAA) to several years (PTMC series 1–3), and this also shows in

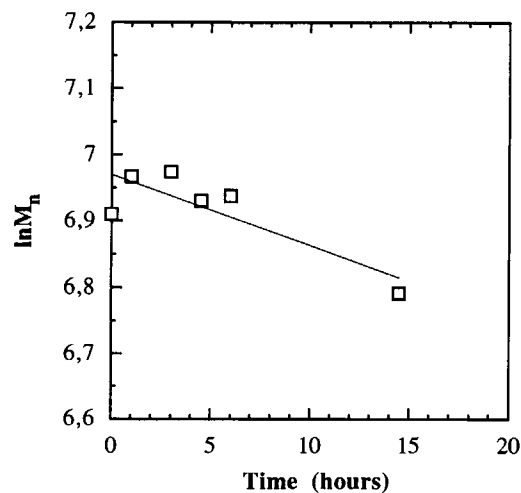


Figure 11 Degradation kinetics expressed by $\ln M_n$ as a function of degradation time [$\ln(M_n) = \ln(M_n^0) - k_2 t$] for poly(adipic anhydride), PAA7, degradation series.

Figures 10–11 where $\ln M_n$ is plotted against the degradation time. The slope of the curves is the rate constant k_2 , and it is $3.1 \times 10^{-3} \text{ days}^{-1}$ for PTMC-PCL6 series (curve fit $r = 0.98$) and $10.7 \times 10^{-2} \text{ h}^{-1}$ for PAA7 series (curve fit $r = 0.84$), which are the two series where a clear decrease in molecular weight is seen. There were no significant differences in the accuracy of curve fit for eqs. (2) and (3) for the two series, suggesting that the degradation mechanisms are not distinct. The slope of the curves in Figure 10 for the PTMC-LMW series are positive from an apparent increase in molecular weight and, as discussed earlier, these materials have water-soluble oligomers that diffuse from the bulk upon exposure to the aqueous phosphate buffer. This is probably the reason of the initial increase for PAA7 causing a poor curve fit. The diffusion effect is faster at 60°C than at 37°C for the PTMC-LMW series, due to the higher mobility of the polymer chains at higher temperatures.

In this study, the use of the Pitt and Chu approach for kinetic evaluation is limited, probably because some of the assumptions made do not apply to our system. As the erosion mechanisms not are distinct for many polymers, one cannot expect the hydrolysis to proceed as one or the other mechanism, thus, more probably by a combination.

Morphology Changes

The DSC measurements were made on vacuum-dried samples. The heat of fusion was recorded for the first heating scan to study the morphology resulting from the processing of the polymer and from the hydrolytic degradation in a phosphate buffer solution. A second heating scan were recorded for some of the samples immediately after the first scan, with a rapid cooling in between.

Poly(trimethylene carbonate), at higher molecular weights, is an amorphous polymer, but for molecular weights up to approximately 15,000, the polymer chains are able to crystallize on standing a week with a resulting melting point of 38.5°C measured by DSC. The crystallization is probably an effect of a reorganization of the chains facilitated by a low T_g ³⁷ compared to the storage temperature. The low molecular weight degradation series 4 and 5 were subjected to degradation at 37 and 60°C , respectively, which, in the latter case, resulted in a transformation from semicrystalline to an amorphous material. A study on the morphology changes during degradation was done for the PTMC-LMW4 series held at 37°C . The nondegraded material

showed one melting, but during exposure to the phosphate buffer solution at 37°C a second melting point arose, indicating a formation of a second type of crystalline fraction. The heat of fusion ΔH as a function of time for PTMC-LMW4 is shown in Figure 12. The samples were not able to crystallize in the DSC at a cooling rate of $40^\circ\text{C}/\text{min}$ and, hence, the recorded values of ΔH are from the first heating scan at $10^\circ\text{C}/\text{min}$.

The initial crystallinity decreases during the exposure to the phosphate buffer solution, and the peak melting point decreases from 38 to 32°C . The new formed crystalline regions of the material increases with time of exposure and has a steady value of the peak melting point of approximately 52°C . The higher melting crystalline domains are formed by recrystallization at 37°C , due to the higher mobility of the chains near the melting temperature. This recrystallization was not seen at 25°C , and the effect was independent of the PBS. The sum of the two heat of fusions increase with degradation time from 41.6 to 50.7 J/g , which mostly is an effect of the leach of low molecular compounds and oligomers and possibly degradation of the amorphous parts of the material. The morphology of PTMC-LMW4 (semicrystalline) and PTMC-LMW5 (amorphous) series seems to be of minor importance for the degradation up to this point, as the changes in molecular weight (Fig. 3) and in dry weight [Fig. 8(e–f)] are similar. Considering the higher water uptake of the semicrystalline samples [Fig. 8(e)], the degradation

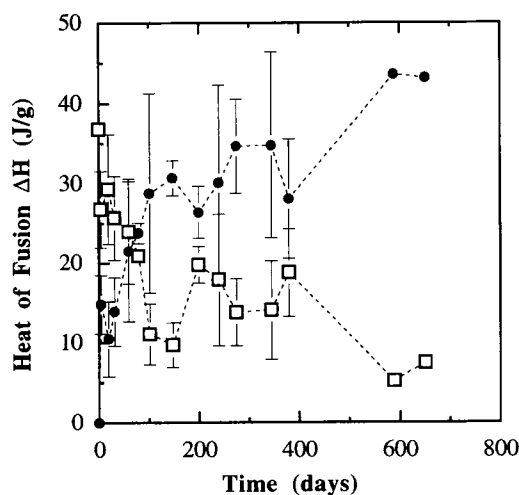
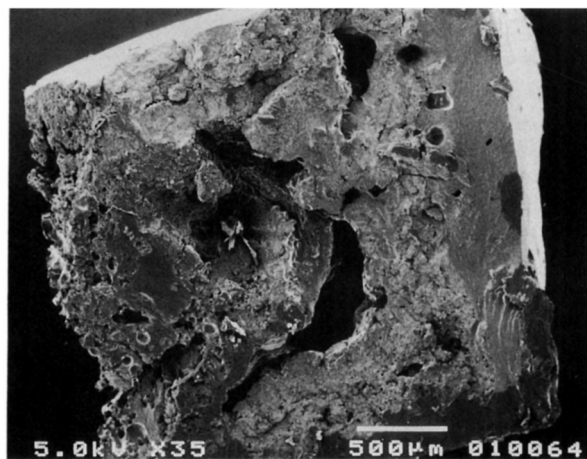
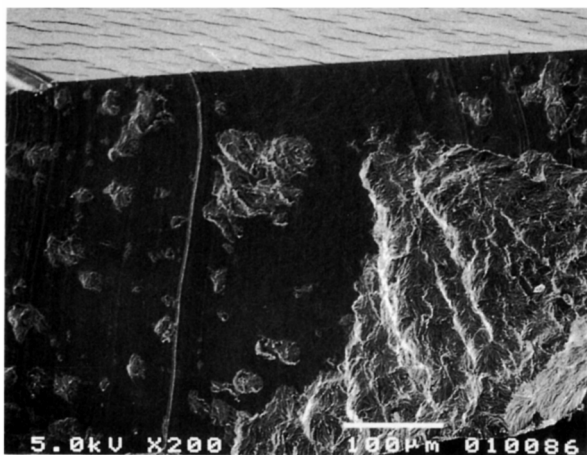


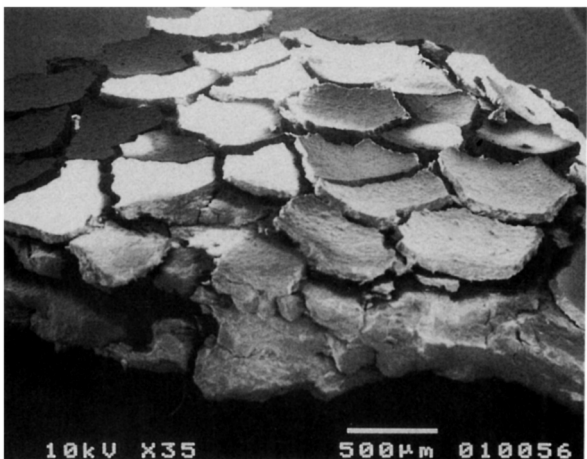
Figure 12 Heat of fusion, ΔH , as a function of degradation time for poly(trimethylene carbonate), PTMC-LMW4 series. Two melting endotherms were observed; $T_{m1} \approx 35^\circ\text{C}$ (open symbols) and $T_{m2} \approx 52^\circ\text{C}$ (filled symbols).



(a)



(b)



(c)

Figure 13 SEM micrographs from selected samples from (a) PTMC-LMW4 (cross section, 79 days of degradation), (b) PTMC-PCL6 (surface and cross section, 459 days), and (c) PAA7 (surface, 14.5 h) series.

of the amorphous parts is mostly a bulk phenomenon for the semicrystalline samples and most likely surface oriented in the amorphous samples as the sur-

face is more accessible. The SEM micrograph of a cross-section of a degraded PTMC-LMW4 sample [Fig. 13 (a)] shows a porous center with large holes surrounded of a more dense shell; the undegraded material showed a much less porous structure. This appearance resembles the results from the *in vitro* degradation of PLA samples in the study by Vert and co-workers.³ The structure in their study was created by a heterogeneous degradation involving carboxylic end groups in the center of the material causing an autocatalyzed degradation. The classic models of bulk or surface erosion did not explain this behavior, and it was described as a heterogeneous degradation. The autocatalyzed degradation is characterized by a fast internal degradation with a bimodal SEC chromatogram. The bimodality is caused by different degradation rates of the bulk and the outer layer. This heterogeneous degradation is dependent on the sample size. For PTMC-LMW samples in our study, no bimodal distribution were seen and no major decrease in molecular weight was detected, although the MWD decreased due to leach of oligomers. The extended hollow structure can be caused by interaction between the oligomeric components and the bulk.

The copolymer of TMC and ϵ CL, containing 88% of the latter component, has similarities with the homopolymer of ϵ CL. Both materials are semicrystalline, and as has been shown in this publication the copolymer degrades upon exposure to a phos-

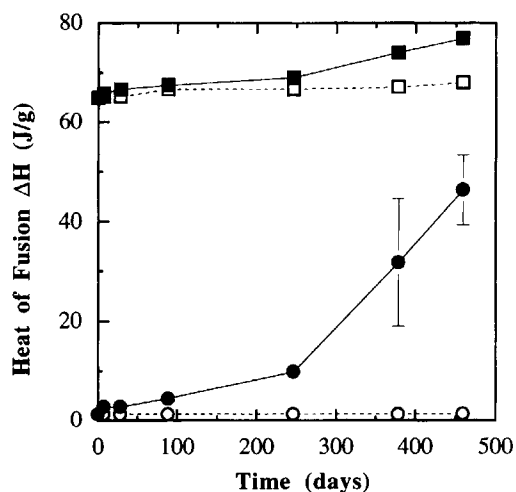


Figure 14 Heat of fusion, ΔH , as a function of degradation time for poly(trimethylene carbonate-*co*-caprolactone), PTMC-PCL6 series; first heating scan (■) and second heating scan (□). Calculated ΔH from the weight loss are shown with open symbols.

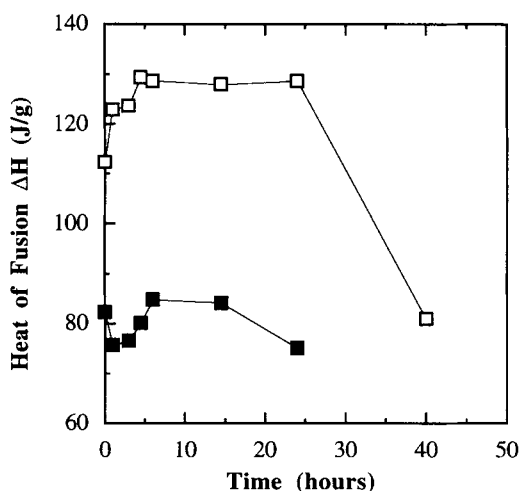


Figure 15 Heat of fusion, ΔH , as a function of degradation time for poly(adipic anhydride), PAA7 series; first heating scan (open symbols) and second heating scan (filled symbols).

phate buffer solution at 37°C. DSC analysis during the degradation shows a slow increase with degradation time in ΔH on the first heating scan (Fig. 14). On the second heating scan the initial heat of fusion is very low but increases with the degradation time. Copolymer, fresh from polymerization, shows a significantly higher heat of fusion on the second scan than the melt-pressed films used for the degradation series. Counting the cycles of heating and cooling for the two samples where both are subjected to the same DSC cycles (two heatings separated by a cooling), the melt pressed film has one heat/cool cycle more, including the processing of the films. The polymer is getting more unorganized as the number of heatings increases; hence, the ability to crystallize is reduced. However, upon *in vitro* degradation recrystallization can occur more easily due to the formation of lower molecular weight polymer chains, which partly explains the increase in enthalpy with time. A breaking point is observed at 248 days of degradation, and it coincides with an increase in the molecular weight distribution due to a faster formation of shorter chains. During the degradation process the amorphous regions of the material is degraded first, causing the proportion of crystalline material to increase. The calculated increase of ΔH is lower than the measured increase, which is expected from the discussion above. The peak melting temperature of the melting endotherm on the first heating scan increases from 54 to 58°C, whereas the peak melting temperature on the second

heating scan is almost constant at 45°C, resulting from a homogenous crystalline structure. By looking at a degraded PTMC-PCL sample by SEM [Fig. 13(b)] an interesting structure is seen. The cross-section has domains of another structure compared to the rest of the material, and no visible porosity is expected because no significant weight loss has been detected. The surface of the sample has microcracks all in one direction. The SEM results of the materials in this publication is part of work that will be published later on.⁴⁰

The rapidly degrading poly(adipic anhydride) PAA samples were also analyzed by DSC (Fig. 15). On the first heating scan the heat of fusion increases initially due to cleavage of the longest chains to form more easily crystallizable segments. The initial increase in enthalpy can also be attributed to the effect of annealing as the samples are introduced to the water and placed at 37°C, thus increasing the chain mobility and facilitating recrystallization of previously amorphous material. After a period of constant enthalpy, a dramatic decrease is seen after about 30 h of degradation time caused by a total collapse and

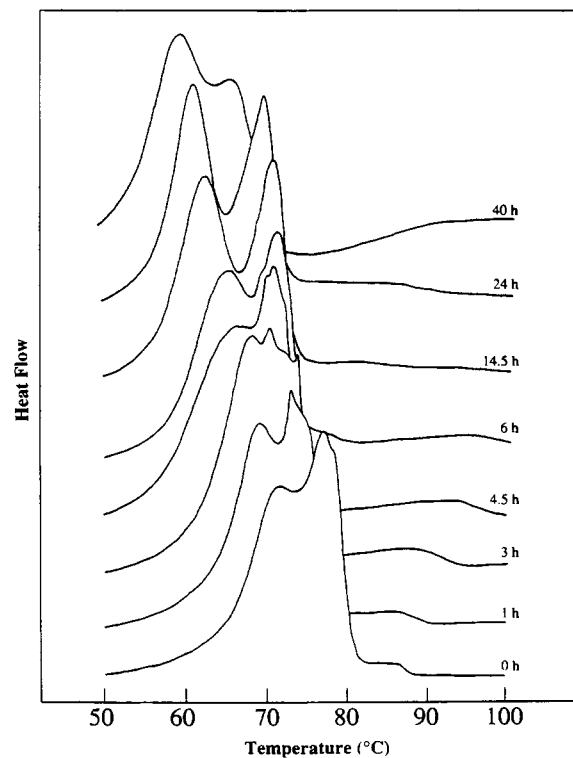


Figure 16 Melting endotherms, recorded by DSC at the first heating scan, for poly(adipic anhydride), PAA7 series, as a function of degradation time.

disintegration of the sample (Fig. 15). The DSC endotherms from the first heating scan are presented in Figure 16, and it is shown that the peak melting temperature is shifted towards lower temperature, and the ratio between the two peaks is changed. During the degradation process, the samples increase their water uptake shown by the wet weight recordings (Fig. 9). An SEM micrograph of a degraded PAA sample is shown in Figure 13(c). The initial smooth surface has cracked up, and flakes are covering the sample. This structure appeared when the samples were in the buffer solution. The cracking can be an effect of shrinkage of the material due to the crystallization in the initial phase of the degradation of the material. Further cracking appeared upon drying the samples. Upon exposure of a sample to water, the amount of water absorbed by the material depends mainly on the hydrophobicity of the polymer chain and the crystallinity of the material. As has been shown in earlier studies, materials like poly(lactide), poly(glycolide), and poly(caprolactone) are considered as bulk eroding materials where the bulk is penetrated by the water and a hydrolysis of the labile bonds takes place. Polyanhydrides are, however, accepted as surface eroding¹³ as the formed acidic degradation products inhibits further hydrolysis of the anhydride bonds in the bulk. The degradation is, therefore, mostly a surface phenomenon.⁴¹

PTMC is degraded by a bulk mechanism, as one can see for the low molecular weight crystalline samples used in this test. The effect will probably be more pronounced as the degradation proceeds. PCL are also bulk eroding, causing a decrease in molecular weight throughout the sample and which is shown here for PTMC-PCL where a decrease in molecular weight is detected, although no weight loss has taken place. PAA, on the other hand, is surface eroding, giving a molecular weight decrease on the surface but not the bulk, resulting in SEC results showing no major change in molecular weight.

Degradation Products and Degradation Mechanisms

As an obvious consequence of hydrolytic degradation of a polymer there will be degradation products with a chemical structure corresponding to the segment on either side of where the hydrolysis has taken place. By a qualitative analysis of the degradation products one can draw conclusions as to which degradation mechanism predominates. In this study, the identification and possibly quantification of low

molecular weight compounds in the water solutions was done by GC-MS analysis. The degradation products were derivatized and transferred to an organic solution to enable identification. GC-MS analysis of samples from PTMC-LMW4 series showed that 1,3-propanediol is present in the buffer solution. The amount of formed diol was approximately 25% of the measured weight loss of the polymer sample (Fig. 17). The agreement between amount of diol and weight loss is better for PTMC-LMW5 series where the diol formed is 71% of the weight loss. The difference between the two series can be attributed to the leached oligomers degrading in the water to a greater extent at the higher temperature.

The remaining weight loss is partly caused by evolution of CO₂ from the carbonate linkage and possibly undegraded oligomers. 1,3-Propanediol is one of the starting chemicals in the monomer synthesis. Purification of the monomer and further purification of the resulting polymer after polymerization minimizes the amount of the diol present in the sample for the degradation study. As the weight losses of the samples are not accompanied by a decrease in the molecular weight, the weight loss is probably due to soluble oligomers; 1,3-propanediol is formed by hydrolysis of these low molecular weight components. The hydrolysis of poly(trimethylene carbonate) eventually results in the formation of 1,3-propanediol and carbon dioxide (Fig. 18).

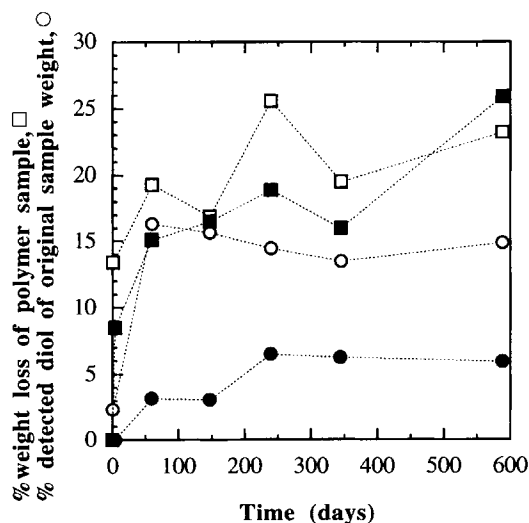


Figure 17 Percent weight loss (\square) and % detected diol of original sample weight (\circ) as a function of degradation time for PTMC-LMW4 (filled symbols) and PTMC-LMW5 (open symbols) series.

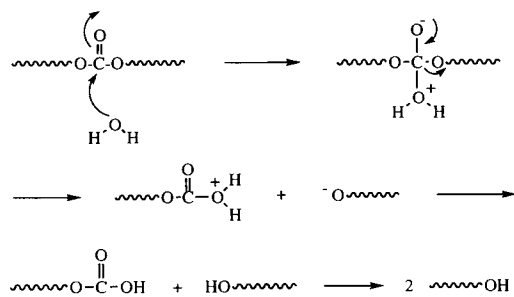


Figure 18 Proposed mechanism of the hydrolytic degradation of poly(trimethylene carbonate) PTMC.

The fastest degrading polymer in this study, poly(adipic anhydride), gives adipic acid as the degradation product, which was confirmed by GC-MS analysis. The amount of adipic acid detected in the buffer solution as a function of time is shown in Figure 19. The weight loss agrees well during the initial phase of the degradation. The weight loss could not be measured for degradation times over 15 h due to fragmentation of the heavily degraded samples. This is probably also causing the deviation between the measured weight loss and formed amount of acid. The increase in the amount of detected adipic acid is initially linear but declines as the degradation proceeds. From our study on the preparation and degradation of PAA microspheres we also saw a good correlation between the formed amount of adipic acid and the weight loss of the microspheres.²²

By measuring the pH of the aqueous solution, complementary information of the possible degradation products and, hence, the degradation mechanism is obtained. The pH of PTMC series are almost unchanged, indicating that no acidic end products are formed. Acidic intermediates are, however, formed (Fig. 18), probably causing a small bulk degradation of the samples [Fig. 13(a)]. For the PTMC-PCL series, the pH has a small but steady decrease from 7.4 to 7.2, probably caused by hydroxyacid compounds. It can be assumed that the pH is going to decrease further as the degradation proceeds. As expected, the pH of the solution from PAA series drops drastically due to the large amount of adipic acid that is formed during the rapid degradation and exceeding the buffer capacity (Fig. 20). The general degradation mechanism of the PCL units in the copolymer and of the PAA follow the traditional theory of ester hydrolysis.

It can be seen from our results that the effect of molecular structure is profound. The carbonate linkage resists hydrolysis for over a year but can be

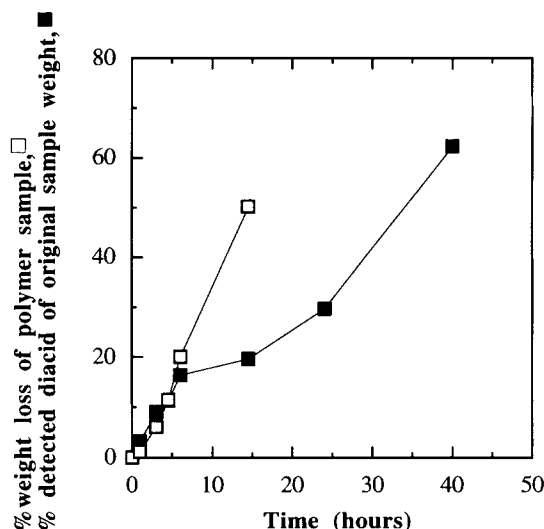


Figure 19 Percent weight loss (open symbols) and % detected diacid of original sample weight from GC-MS analysis (filled symbols) as a function of degradation time for PAA7 series.

noticeably changed by incorporating ester functionality into the chain. The degradation rate of the copolymer PTMC-PCL is comparable with poly(1,5-dioxepan-2-one),⁷ which has a repeating unit of the same length as poly(ϵ -caprolactone) but with an ether functionality in the backbone chain. Poly(tetramethylene adipate), an aliphatic condensation polyester with four methylene units between the ester bonds, has shown to be slowly degrading but faster than PTMC.⁴² Degradation times under a year can be achieved by using polyesters

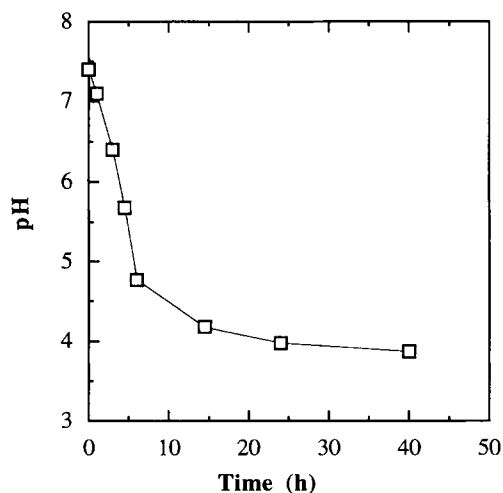


Figure 20 pH as a function of degradation time in the water solutions from PAA7 degradation series.

with a short methylene sequence between the ester bonds like poly(β -propiolactone)⁴³ and poly(lactide-co-1,5-dioxepan-2-one).⁴⁴ For the polyanhydrides, a longer methylene sequence, as in poly(dodecanoic anhydride) with 10 units, prolongs the degradation by several days compared to poly(adipic anhydride) with four units.²⁰ The degradation rate is, in many cases, dependent on initial molecular weight and morphology, but generally speaking, the hydrolysis rate increases in the order of carbonate, ester, and anhydride linkage. This implies that there are differences in the susceptibility of the linkages to nucleophilic attack of a water molecule. The carbonate is far more resistant to hydrolysis than expected compared to ester. The initial acyl-oxygen cleavage is slow and, hence, the rate-determining step in the hydrolysis. The decomposition of the intermediate oxygen-carboxylic moiety is fast, giving hydroxyl end group and carbon dioxide⁴⁵ (Fig. 18). By altering the substituents near the carbonyl oxygen we predict changes in hydrolysis rate.

CONCLUSIONS

Using long-term *in vitro* and *in vivo* degradation studies of aliphatic polyester-related structures we have shown the relationships between molecular structure and degradation mechanism. The degradation behavior is strongly dependent on the chemical structure. Upon degradation, the molecular weight distribution approaches 2; this suggests that random chain cleavage of the polymer chains is predominant. Poly(trimethylene carbonate) PTMC degrades unexpectedly slow, unaffected by initial molecular weight, ionic strength of the water, storage temperature, and shaking motions. A substantial increase in degradation rate was accomplished by incorporating ester functionality giving the statistical copolymer poly(trimethylene carbonate-co-caprolactone) PTMC-PCL. The *in vitro* study of poly(adipic anhydride) PAA revealed a surprisingly fast degradation, and the collected results supports the theory of a surface-eroding system. The mechanism of degradation is predominantly hydrolytic cleavage of the labile bonds, which results in the formation of harmless degradation products that correspond to the repeating unit of the polymers i.e., 1,3-propanediol and adipic acid. Using DSC, we have seen morphology changes in the crystalline materials during degradation and a correlation between change in enthalpy and change in molecular weight distribution. Formation of recrystallizable

fragments and loss of amorphous material caused an increase in % crystallinity.

This study shows that the rate of hydrolytic degradation increases in the order of carbonate, ester, and anhydride linkage governed by the inherent properties of the bonds. This implies that there are differences in the susceptibility of the linkages to nucleophilic attack of a water molecule. The carbonate is far more resistant to hydrolysis than expected compared to ester. By altering the electro-negativity of the groups near the carbonyl-oxygen region, we predict a change in hydrolysis rate.

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