Synthesis, Properties, and Biodegradation of Poly(1,3-trimethylene carbonate)

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ABSTRACT: Poly(1,3-trimethylene carbonate) (PTMC) was synthesized by diethylzinc-catalyzed ring-opening polymerization of 1,3-trimethylene carbonate. The polymer was characterized by measurement of its thermal and mechanical properties, permeability, and susceptibility to hydrolytic chain scission in vitro and in vivo. Molecular weights were determined by GPC using the universal calibration method. Mark-Houwink coefficients were derived from viscometry and GPC measurements: $K = 1.986 \times 10^{-4}$, $a = 0.789$ ($CHCl_3$); $K = 2.77 \times 10^{-4}$, $a = 0.677$ (THF). The rate of hydrolytic chain scission of solid PTMC in phosphate-buffered saline at 37 °C, pH 7.4, was approximately 20 times less than that of poly(ϵ-caprolactone); this rate difference was eliminated when the two polymers were compared in solution in aqueous THF. Degradation of PTMC implanted subcutaneously in rats was manifested by an increase in the molecular weight distribution at the implant surface, a decrease in the molecular weight, and substantial weight loss during a 6-month period. These observations, and the fact that the rate of chain cleavage in vivo was much more rapid than that observed in vitro, were indicative of an enzymatic degradation process.

Introduction

The in vivo enzymatic surface erosion of synthetic polymers is a relatively rare process, with only two examples reported in the literature.[1,2] As a result, the structural features that are responsible for the susceptibility of a polymer to enzymatic attack are not well defined. The in vivo enzymatic degradation of polyester elastomers derived from random copolymerization of δ-valerolactone and ϵ-caprolactone with the cross-linker 2,2-bis(ϵ-caprolacton-4-yl)propane has been attributed[2] to the flexibility of the polymer chain and ester linkage, manifested by a Young's modulus of less than 50 kg/cm^2. The low modulus is a reflection of the lack of crystallinity, low cross-link density, and low T_g of these elastomers. An increase in the cross-link density, which decreases the chain mobility and raises the modulus above 50 kg/cm^2, inhibits enzymatic erosion. Introduction of alkyl or hydroxy substituents slows but does not completely inhibit the enzymatic process.

Poly(ethylene carbonate) (PEC) is the second example reported to undergo rapid enzyme-mediated bioabsorption in vivo.[1,3] PEC has a T_g of 5 °C, and a modulus[4] of 21 kg/cm^2, compared with the values for poly(δ-valerolactone-*co*-ϵ-caprolactone) of −60 °C and 5–50 kg/cm^2, respectively.[2] PEC is apparently noncrystalline, for no T_m is reported. Introduction of a substituent methyl group, i.e., poly(1,2-propylene carbonate), completely suppresses enzymatic attack.[1] This loss of reactivity may be related to either the steric inhibition of access to the active site of the enzyme, or to the change in the physical properties of the polymer; poly(1,2-propylene carbonate)[4] has a higher T_g of 30 °C and a modulus of 30 kg/cm^2. To distinguish between the role of physical properties and chemical structure in determining enzymatic degradability, we have prepared and characterized the linear homologue, poly(1,3-trimethylene carbonate) (PTMC) and have studied its degradation under both in vitro and in vivo conditions.

Experimental Procedures

1,3-Trimethylene Carbonate. 1,3-Propanediol (76 g, 1.0 mol), diethyl carbonate (141 g, 1.19 mol), and sodium metal (0.1 g) were refluxed at 130 °C for 3 h. Ethanol and residual diethyl carbonate were distilled and the residue was dissolved in benzene, washed with water, and dried. Distillation afforded the crude product, bp 130–135 °C (5 Torr), yield 30–40%, which was purified by crystallization from ether: mp 46 °C (lit.[5] mp 45–47 °C); IR (KBr) 1750 cm^{-1} (>C=O).

PTMC. The purified monomer and catalyst (1% w/w) were heated in vacuo in a sealed glass tube at 60–100 °C for up to 24 h. The resulting polymer was purified by precipitation from chloroform with methanol and dried in vacuo: ^{13}C NMR (δ, $CDCl_3$) 28.05 (OCH_2CH_2), 64.3 (OCH_2CH_2), 154.9 ppm (C=O); ^{1}H NMR (δ, $CDCl_3$) 2.05 (t, J = 11 Hz, 2 H), 4.24 ppm (t, J = 11 Hz, 4 H); IR (KBr) 1750 cm^{-1} (>C=O).

Intrinsic viscosities were measured in chloroform or THF at 30.5 °C by using Ubelhodde viscometers; the single determination method of Solomon and Cinta[6] was applied after verifying its validity for PTMC samples. GPC was conducted using two size exclusion columns in series (μ-Styragel, molecular weight range 2000–4 000 000, Waters No. 10681), thermostated at 35 °C, and a differential refractometer (Waters Model 410).

Films, approximately 0.3-mm thickness, were prepared by casting a chloroform solution onto glass plates. Thermal analyses were conducted using a differential scanning calorimeter (Du Pont Model 910), a heating rate of 10 °C/min under nitrogen, and an indium standard. Water content was determined by thermogravimetric analysis (Du Pont Model 903 moisture evolution analyzer) of films that had been immersed in water at 37 °C for 10 weeks. Progesterone permeability was determined by immersion of the polymer film in water at 37 °C in a UV cuvette equipped with a mechanical stirrer; progesterone sorption was monitored by the change in absorbance at 250 nm.

Hydrolysis of the solid polymer in vitro was measured by immersion of films in phosphate-buffered saline, pH 7.4, at 37.5 °C; samples were recovered periodically and gravimetric weight loss and molecular weight changes (GPC) were determined. Hydrolysis in solution was measured by dissolution of the polymer in 5 or 10% aqueous THF at 37.5 °C, concentration 0.5% w/v; samples were withdrawn periodically and molecular weight changes were determined by GPC. In vivo degradation was measured in rats. Films, approximately 1 cm × 1.5 cm × 2 mm, were weighed and sterilized by dipping in isopropyl alcohol before implanting subdermally in adult male rats (Sprague–Dawley outbred, 201–223 g) in the scapular area lateral to the dorsal midline. At time intervals of 2, 4, and 6 months, single animals were sacrificed and the polymer was recovered. The rods were freed of adhering tissues by overnight immersion in 0.05 M sodium phosphate, 0.15 M NaCl, pH 7.2, containing 1% trypsin, 0.1% collagenase, and 0.1% elastase, then rinsed, and dried and the weight loss was determined gravimetrically. Molecular weight changes were determined by GPC. Control experiments estab-

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lished that this method of processing the recovered implants had no effect on their molecular weight.

In vitro enzymatic degradation was evaluated by immersing PTMC disks, 11-mm diameter, in phosphate buffer, pH 7.4, 37 °C, containing 1% of lipase (EC 3.1.1.3) or esterase (EC 3.1.1.1). The solutions were replaced every 48 h. Esterase (EC 3.1.1.1) from porcine liver (200 units/mg, in 3.2 M ammonium sulfate, pH 8) and lipase (EC 3.1.1.3) from wheat germ, porcine pancreas, and *Rhizopus arrhizus* (400 000 units/mg in 3.2 M ammonium sulfate and 10 mM potassium phosphate, pH 6.0) were purchased from Sigma Chemical Co.

Molecular Weight Determination. Viscosity average molecular weights (M_v) were determined by GPC and viscometry, using the procedure of Spatorico and Coulter[7] and Van Dijk and Smit[8] to derive the coefficients of the Mark–Houwink equation (1) relating M_v and the intrinsic viscosity. Five samples with an

$$[\eta] = KM_v^a \tag{1}$$

appropriate range of viscosity average molecular weights (6–110 kDa) and similar dispersities were characterized by measurement of their GPC traces and intrinsic viscosities in chloroform. The GPC columns (μ-Styragel, 2000–4 000 000) were calibrated by the universal method of Benoit et al.[9] using eight monodisperse polystyrene reference standards to establish the relationship $F(v)$ between M_v, $[\eta]$, and the elution volume v (eq 2). Equation 2 was

$$M_v[\eta] = F(v) \tag{2}$$

used in combination with eq 3, which expresses the relationship

$$\ln [\eta]_2 = a_2(1 + a_2)^{-1} \ln F(v) + (1 + a_2)^{-1} \ln K_2 \tag{3}$$

between $F(v)$, $[\eta]$, and the Mark–Houwink coefficients for polystyrene (K_1, a_1) and the unknown polymer (K_2, a_2). Values of K_1 and a_1 for polystyrene in chloroform were determined from best fit of eq 1 to the data for the polystyrene reference standards. The slope and intercept of a plot of $[\eta]_2$ versus $\ln F(v)$ using the data derived from the five PTMC samples afforded initial estimates of K_2 and a_2. These values were used with eq 4 to

$$\ln M_2(\text{PTMC}) = (1 + a_2)^{-1} \ln (K_1/K_2) + (1 + a_1)(1 + a_2)^{-1} \ln M_1 \tag{4}$$

calculate the M_v of each sample of PTMC. The values of M_v were then used in eq 3 to compute new values of K_2 and a_2. This process was repeated until the values of K and a converged. Five iterations were required before the values of K and a converged to 1.986×10^{-4} and 0.789, respectively.

These values were substantiated by the method of Mahabadi and Alexandru,[10] which utilizes a molecular weight average M_x based on the hydrodynamic volume, as in eq 5. These authors defined the Mark–Houwink equation in terms of M_x, which leads to eq 6. The slope of a plot of $\ln [\eta]$ versus $\ln M_x$ for all polymer samples allows one to determine the exponent a, while K is derived from eq 7

$$M_x = \sum \omega_i [\eta]_i M_i / \sum \omega_i [\eta]_i = \sum \omega_i J_i / [\eta]_i \tag{5}$$

where ω_i is the weight fraction of individual fractions of the GPC trace.

$$[\eta] = K_x(M_x)^a = K\delta(M_x)^a \tag{6}$$

and where

$$\delta = ((\sum \omega_i J_i^{a/a+1})^{a+1})/(\sum \omega_i J_i)^a$$

$$K = [[\eta]_1/(\sum \omega_i J_i^{a/a+1})]^{a+1} \tag{7}$$

This method yielded values of 1.968×10^{-4} and 0.783 for K and a, respectively, in good agreement with the values derived by the method of Van Dijk and Smit.[8]

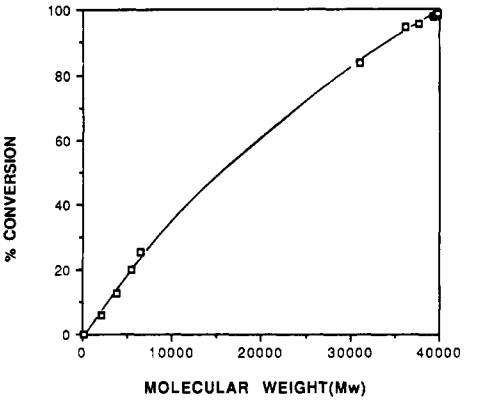

Figure 1. Relationship between the percent conversion and the molecular weight of PTMC prepared by ring-opening polymerization in the presence of diethylzinc.

The values of K and a for PTMC in THF were determined by measurement of the intrinsic viscosities of the same five PTMC samples in THF and correlation with the M_v values derived from the GPC measurements in chloroform. At least-squares fit of the data to eq 8 gave values of 2.77×10^{-4} and 0.677 for K and a, respectively.

$$\ln [\eta]_{THF} = \ln K + a \ln M_v \tag{8}$$

Results

Polymer Synthesis and Characterization. PTMC was prepared by ring-opening bulk polymerization of 1,3-trimethylene carbonate at 60–100 °C in the presence of coordination catalysts. Stannous chloride, stannous octoate, stannic bromide, and diethylzinc were all effective catalysts and afforded yields of 76% or greater after 18 h at 60–80 °C. Magnesium oxide and titanium tetrachloride were ineffective. Diethylzinc at 60 °C produced the highest yield (90%) and molecular weight (M_w 42 000); the molecular weight increased in proportion to the yield (Figure 1), consistent with a step-growth mechanism, and reached a maximum at 4 h. Polymerization occurred more slowly in chloroform (10% w/v) in the presence of diethylzinc and the conversion was 60% after 8 h at 60 °C.

The chemical structure of PTMC was confirmed by its infrared spectrum and ^{13}C and ^{1}H NMR spectra. PTMC is soluble in chloroform, methylene chloride, benzene, and THF, and insoluble in water, alcohols, and ether. These solubility properties are consistent with a solubility parameter of approximately 20 $J^{1/2}\cdot cm^{-3/2}$. The solubility parameters calculated from the group parameters of Fedor[11] and Van Krevelen[12] are 21.5 and 22.9 $J^{1/2}\cdot cm^{-3/2}$, respectively. The water content of films of the solution cast polymer was 1.8 ± 0.1% (n = 2) after immersion in water for 10 weeks.

The T_g of PTMC determined by DSC increased from −26 to −15 °C as the M_w increased from 7000 to 42 000. The T_g determined by a rheovibron was −14 °C (M_w = 42 100; M_w/M_n = 2.2). Only samples with a molecular weight of less than 12 000 showed any evidence of crystallinity, with a T_m of 36 °C and a heat of fusion that varied between 4.5 and 10 J/g (DSC). Higher molecular weight samples failed to crystallize, even on prolonged storage at room temperature. The tensile strength and Young's modulus of a noncrystalline sample were 5 and 30 kg/cm^2, respectively. The elongation at yield was 20% and the elongation at break was 160%.

The permeability of PTMC was assessed by measurement of the diffusion coefficient (D) of progesterone, a

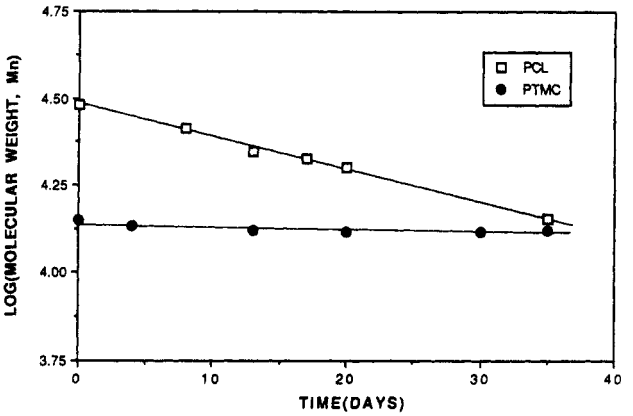

Figure 2. Semilog plots of the molecular weight (M_n) of PCL and PTMC films versus time in phosphate-buffered saline, pH 7.4, at 37 °C.

steroid that has been studied in combination with a number of other polymers used for drug delivery.[13] The method of Lee[14] was used, involving measurement of the kinetics of sorption by a slab of the polymer immersed in an aqueous solution of the solute at 37 °C. The kinetics are given by eq 9, where $\lambda = V/2KAa$, V is the volume of the aqueous

$$\tau = 0.75\lambda^2(\ln C + 0.5C^{-2} - 0.5) = Dt/a^2 \qquad (9)$$

solution, K is the polymer–water partition coefficient, A is the area of one side of the slab, a is half the slab thickness, and C is the fractional amount of solute in the aqueous phase at time t. The value of D, derived from the slope of a plot of τ vs time, was 3.26 (±0.10) × 10^{-9} cm^2/s (n = 3). The polymer–water partition coefficient of progesterone, determined from the same experiments, was 323 ± 7. The solubility of progesterone in PTMC, calculated from this partition coefficient and the reported aqueous solubility of progesterone of 14 μg/mL at 37 °C, is 4.5 mg/mL.

Polymer Degradation. The in vitro degradation of PTMC was measured by immersion of polymer disks in phosphate-buffered saline at 37 °C. Samples were recovered at intervals and hydrolytic chain scission was evaluated by measurement of molecular weight changes, while weight loss was determined gravimetrically. Poly(ε-caprolactone) (PCL) samples were evaluated under the same conditions. Over a 30-week time period, the weight of PTMC decreased by 9%, while its M_n decreased from 14 000 to 13 000. This rate of hydrolytic chain scission was much slower than the rate of PCL chain cleavage (Figure 2). Given the small change in molecular weight of PTMC, the observed weight loss must be attributed to slow diffusional loss of oligomers from the polymer bulk rather than to significant hydrolytic chain scission.

The role of polymer morphology versus the intrinsic reactivity of the ester and carbonate linkages in determining the relative rates of hydrolysis of PTMC and PCL was probed by measuring the rates of hydrolysis of samples in homogeneous solution in 5 and 10% aqueous THF at 37 °C. The results of these measurements are shown in Figure 3 as semilogarithmic plots of (DP − 1)/DP versus time, where DP is the degree of polymerization.

Enzymatic surface erosion was examined in vitro by immersing PTMC disks in phosphate buffer (pH 7.4, 37 °C) containing 1% of lipase or esterase. The solutions were replaced every 48 h. After 17 days no gravimetric weight loss was detected.

In vivo degradation was measured by implanting PTMC films subdermally in rats. Samples were recovered after 2, 4, and 6 months. The samples were recovered as balls rather than the originally implanted films. The molecular weight decreased with time, and, significantly, the molecular weight distribution of the recovered implants increased with time. Furthermore, the dispersity appeared to vary as a function of the depth from the implant surface. The low form stability and deformation of the samples recovered from rats prevented precise sampling of surface and bulk. Therefore, the recovered samples were extracted with $CHCl_3$ for 20 min to selectively separate the surface fraction. Control experiments with nondegraded polymer showed that $CHCl_3$, a poor solvent for PTMC, slowly dissolved the surface layer of the polymer and did not selectively leach oligomeric components. The results in Table I confirmed the much greater dispersity and lower molecular weight of the surface layer.

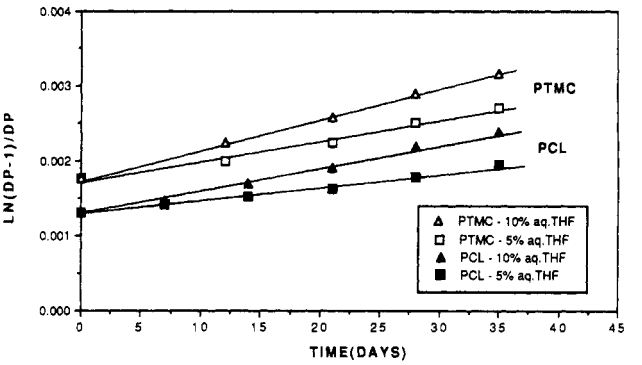

Figure 3. Semilog plots of (DP − 1)/DP versus time for PCL and PTMC in solution in 5 and 10% aqueous THF at 37 °C.

Table I
Molecular Weight and Molecular Weight Distribution of PTMC Samples[a] Recovered from Rats

A. Outer Surface

time, months	M_n	M_w/M_n
0	19100	2.20
2	8300 ± 100	3.85 ± 0.36
4	5900 ± 900	4.09 ± 0.38
6	6100	4.02

B. Polymer Bulk

time, months	wt loss,[b] %	M_n	M_w/M_n
0		19100	2.20
2	10.4 ± 3.8	13400 ± 300	2.74 ± 0.09
4	25.8 ± 16.5	9900 ± 1700	2.92 ± 0.40
6	21.1	8700	3.13

[a] Duplicate samples except at 6 months. [b] Weight loss refers to total implant mass (bulk plus surface).

Discussion

Aliphatic polycarbonates have been prepared by three methods: (1) by condensation polymerization of diols and carbonates, or diols and chloroformates;[15-17] (2) by ring opening of cyclic carbonates with nucleophilic[15,16] or cationic initiators;[5] and (3) by copolymerization of epoxides and carbon dioxide in the presence of diethylzinc–water or structurally related organometallic catalysts.[4,18,19] Only the third method was reported to afford a high molecular weight (>10 000) polymer. In our hands, high molecular weight PTMC was most easily prepared by ring-opening polymerization of 1,3-propylene carbonate, catalyzed by metalloorganics such as stannous octoate and diethyl zinc. The properties of the resulting polymer are compared with poly(ethylene carbonate) and the structurally similar polyesters PCL and poly(δ-valerolactone) (PVL) in Table II. All four polymers have low T_g's, reflecting the contribution of the polymethylene sequences in

Table II
Comparison of Properties of PTMC, PEC, and PCL

property/polymer	PTMC[a]	PEC	PCL
glass transition,[b] °C	−15	5	−60
mp, °C	36		57–60
modulus, kg/cm²	30	21	2770
% elongatn at break	160		750
tensile strength, kg/cm²	5	59	246
D(progesterone), cm²/s	3.26×10^{-9}		3.6×10^{-9}
C_s(progesterone), mg/cm³	4.5		16.9
water content, %	1.8	0.4–0.7	0.43

[a] PTMC values were derived by using a polymer of M_w of 42 100, $M_w/M_n = 2.2$, with the exception of the T_m for which a polymer of M_w 12 000 was used. [b] The reported glass transition and melting temperatures of poly(δ-valerolactone) are −67 and 59 °C, respectively.[25]

the main chains. In contrast to PCL and PVL, which are semicrystalline polymers, both PEC and higher molecular weight PTMC appear to be amorphous. The failure of higher molecular weight PTMC to crystallize may be a kinetic phenomenon, although the low T_g of PTMC would be expected to facilitate reorganization and crystallization of the polymer chains during storage for long periods at room temperature. The possibility that the lack of crystallinity of PTMC might be the result of disorder introduced by partial thermal loss of carbon monoxide during polymerization of PTMC was excluded by the ^{13}C and ^1H NMR spectra; there were no resonances other than those attributable to the $CH_2CH_2CH_2OC(=O)O$ repeat unit. This observation is in contrast to the polymerization of ethylene carbonate with metal alkoxides, which is reported[20] to occur with significant carbon dioxide loss and formation of poly(oxyethylene-*alt*-ethylene carbonate). The modulus and tensile strength of PTMC are greater than the values of its lower homologue, PEC, but less than the values of semicrystalline PCL. The diffusion coefficient of progesterone in PTMC is comparable to the value of PCL. The higher T_g of PTMC, relative to PCL, which would be expected to reduce the permeability, must be offset by the lack of crystallinity of PTMC, with the result that both polymers have similar free volumes.

Polymer Degradation. Measurements of the rate of hydrolysis of monomeric aromatic esters and carbonates in solution have shown that the carbonate group is intrinsically more reactive than the ester group.[21] This order of reactivity is not reproduced by PCL and PTMC in the solid state. A discussion of the basis for the observed reactivities requires an understanding of the mechanism of hydrolysis of the two polymers. Previous studies have shown that the bulk hydrolytic chain scission of polyesters is autocatalyzed by the carboxylic acid end groups and follows the kinetic law (eq 10).

$$-d[COOH]/dt = k[H_2O][ester][COOH] \quad (10)$$

By use of the two relationships between [COOH] and [ester]

$$[COOH] = W/(M_nV) = \rho M_n$$
$$[COOH] = [ester]/(DP - 1)$$

where W is the weight of the polymer sample, V is its volume, and ρ is its density, one obtains eq 11:

$$d[1/DP]/dt = k(\rho/M_n)[H_2O](DP - 1)DP^{-2} \quad (11)$$

Integration leads to eq 12

$$\ln [(1 - DP)/(1 - DP_0)] = -k't \quad (12)$$

where $k' = k[H_2O]\,\rho/M_n$ and DP and DP_0 are the degrees of polymerization at times t and zero, respectively. This equation will hold provided there is no weight loss and, provided DP ≫ 1, it may be simplified to eq 13.

$$\ln (DP/DP_0) = \ln (M_n/M_{n0}) = -k't \quad (13)$$

The accelerating role of the carboxylic acid function of polyesters has been substantiated by studies which showed that masking the carboxy end group retards hydrolysis[22,23] while the addition of low molecular weight carboxylic acids accelerates hydrolysis.[22] Dissociation of the carboxylic group in the polymer bulk is improbable, a conclusion supported by the dependence of the rate on the first power of [COOH] and not $[COOH]^{1/2}$. Hydrogen bonding between the ester and the carboxy end group is most likely responsible for the kinetic effect of the latter. Polycarbonates lack this mechanistic feature; the carbonic acid end group is a weaker acid (pK_a 6.5) than the carboxylic acid end group (pK_a 3–5) and is unstable (eq 14). In the

$$ROC(=O)OH \rightarrow ROH + CO_2 \quad (14)$$

absence of end group catalysis, the hydrolysis of polycarbonates can be expected to exhibit first-order kinetics (eq 15), where [carbonate] is the molarity of carbonate

$$-d[carbonate]/dt = k[H_2O][carbonate] \quad (15)$$

linkages in the polymer. Integrating leads to eq 16, where

$$\ln [carbonate]/[carbonate]_0 = k't \quad (16)$$

$k' = k[H_2O]$. The molarity of the carbonate groups in the solid polymer can be related to the density (ρ) and the degree of polymerization (DP) of the polymer and the molecular weight of the repeat unit (M_{mon}) by eq 17. Combining eqs 16 and 17, one may derive the kinetic expression eq 18 for the change in DP or molecular weight.

$$[carbonate] = \rho(DP - 1)/M_{mon} \quad (17)$$

$$\ln (DP - 1)/DP = \ln (DP_0 - 1)/DP_0 - k't \quad (18)$$

The change in the molecular weight of PTMC film immersed in phosphate-buffered saline for a 44-day period was too small to permit a distinction between the catalyzed and noncatalyzed processes represented by eqs 13 and 18, respectively. However, regardless of the kinetic analysis used, the order of the rate constants (k') is PCL > PTMC. This order cannot be attributed to the water concentration term $[H_2O]$, for the water content of PTMC is greater than that of PCL (Table II). It seems probable that the slower rate of hydrolysis of PTMC, relative to PCL, is at least partly due to the lack of the autocatalytic process.

The lower rate of in vitro hydrolysis of PTMC, relative to PCL and other aliphatic polyesters, is consistent with earlier studies of the relative rates of hydrolysis of the glassy aromatic polycarbonates and polyesters derived from Bisphenol A and *m*-hydroxybenzoic acid, respectively. Here it was shown that the rates of hydrolysis of the monomers were the reverse, e.g., diphenyl carbonate > phenyl benzoate,[21] of the polymer hydrolysis rates. In this case the relative rates of hydrolysis of the polyester and polycarbonate were attributed to the bulk properties of the glassy aromatic polymers.

The relevance of morphology to the hydrolysis of PTMC and PCL, both of which are in the rubbery state, was evaluated by comparing the hydrolysis rates of the two polymers as solutions in 5 and 10% aqueous THF at 37 °C. Under these conditions hydrogen bonding between

carboxylic acid end groups and ester groups in PCL is eliminated by the presence of the more basic solvent and the kinetics are expected to conform to eq 18.

Not surprisingly, chain cleavage in solution was much faster than in the solid state. Plots of the changes in (DP - 1)/DP versus time were linear (Figure 3) and the rate constants derived from the slopes of the plots showed that the rate of hydrolysis of PTMC was slightly greater than that of PCL: k' (5% aqueous THF), PCL 1.82×10^{-5} day^{-1}, PTMC 2.73×10^{-5} day^{-1}; k' (10% aqueous THF), PCL 3.19×10^{-5} day^{-1}, PTMC 3.98×10^{-5} day^{-1}. The observed rates of chain scission in aqueous THF can best be rationalized by assuming that the carbonate and ester groups have similar reactivities in solution, while the faster rate of cleavage of PCL in the solid state, relative to PTMC, is a result of the autocatalytic process involving the carboxylic end groups.

In Vivo Degradation. In contrast to the results in vitro, the molecular weight of PTMC films decreased during a 6-month period and substantial weight loss was observed. The molecular weight decrease was accompanied by an increase in the molecular weight distribution, M_w/M_n (Table I). The latter observation is not consistent with random hydrolytic chain scission, for which a dispersity of two is predicted;[24] rather, it is suggestive of enzymatic scission of the carbonate linkages. Enzymatic cleavage is necessarily restricted to the surface of the implant, because of the inaccessibility of the polymer bulk. As a consequence, enzymatic cleavage produces a reduction in the molecular weight at the surface, but not in the polymer bulk, and so increases the dispersity. The poor form stability of PTMC prevented a sharp distinction between the surface and the bulk. However, when partial separation was achieved by dissolution of the surface with chloroform, GPC analysis confirmed that the molecular weight of the surface layer was lower than the bulk (Table I). The contribution of an enzymatic process to the degradation of PTMC in vivo was also supported by the much greater rate of chain scission and mass loss, relative to in vitro degradation.

These results demonstrate the rate of enzymatic cleavage of PTMC is slower than that of PEC but much greater than that of poly(1,2-propylene carbonate). PEC is reported to be totally eroded in several weeks while poly(1,2-propylene carbonate) is not subject to enzymatic attack. This order of reactivity cannot be attributed to major differences in electronic effects, in the degree of hydration, or the chain flexibility as reflected by the modulus. Rather, it appears that the difference in rates of enzymatic attack must reflect the specificity of the active site of the enzyme(s) for the CCO(C=O)- part structure.

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Registry No. PTMC (homopolymer), 31852-84-3; PTMC (SRU), 50862-75-4; lipase, 9001-62-1; esterase, 9016-18-6; PCL (SRU), 25248-42-4; PCL (homopolymer), 24980-41-4; stannous octoate, 301-10-0; stannic bromide, 7789-67-5; diethylzinc, 557-20-0; stannous chloride, 7772-99-8.