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POLYMERIZATION AND DEGRADATION OF 1,5-DIOXEPAN-2-ONE

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ABSTRACT

1,5-Dioxepan-2-one was polymerized with stannous 2-ethylhexanoate as initiator and gave high molecular weight polymers, with MW > 150,000. The highest molecular weight was achieved at 110°C, and full conversion was reached after 20 hours. The polymerization rate increased with temperature. Transesterfication reactions and thermal degradation occurred above 130°C, which led to a decrease of the molecular weight. Polymerization with anion and cationic initiators led to low molecular weight polymers. Degradation of poly(1,5-dioxepan-2-one) took place by the hydrolysis of ester bonds, and the initial molecular weight decreased by 30% during 46 weeks, starting from MW = 45,000.

INTRODUCTION

Aliphatic polyesters are among the most frequently used polymers in medical applications. The design of tailor-made degradable materials is an interesting area mostly due to the possibility of controlling their degradability. Polyesters degrade by hydrolysis, and the hydrolysis products are absorbed by the body with a minimal reaction of the tissues. Synthetic polymers with a high absorptivity are represented by aliphatic polyetherester chains. The ether group in the backbone structure makes this type of polymer more flexible, which is an additional advantage.

Two polymers with a polyetherester chain have previously been synthesized by ring-opening polymerization of 1,4-dioxan-2-one [1] and 1,4,6-trioxaspiro-(4,4)nonane [2]. Polydioxanone, the polymer of 1,4-dioxan-2-one, has a tensile

strength and elasticity similar to that of human tissue [3]. In our laboratory, the monomer 1,5-dioxepan-2-one has now been used to make a polymer with a polyetherester chain. The polymer is amorphous with a T_g of about $-37°C$, in contrast to polydioxanone which is crystalline.

The polymerization of 1,5-dioxepan-2-one (DXO) was earlier studied for copolymerizations with ϵ-caprolactone, lactide, and glycolide [4–7]. We synthesized the homopolymer of poly-1,5-dioxepan-2-one (PDXO) [8], with a highest molecular weight of 50000. We also developed an improved procedure for the synthesis of DXO [8], where stannous 2-ethylhexanoate (SnOct) was used as the initiator. Organic tin compounds such as stannous 2-ethylhexanoate and dibutyltinoxide are known to be effective initiators for this polymerization. The use of SnOct can, however, give rise to secondary reactions like chain transfer, ester interchange, or even depolymerization at higher temperatures [9]. In the bulk polymerization of six- and seven-membered ring lactones, it was found that no relationship exists between initiator concentration and molecular weight [10]. Under the conditions for solution polymerization, on the other hand, ring-opening polymerization proceeded in a more predictable way [11]. In most cases where the polymerization of lactones has been initiated with metal salts, the polymerization mechanism has not been elucidated. Both nonionic insertion mechanisms and true anionic polymerizations may be initiated by metal salts and metal oxides. Unfortunately, in the case of Sn-initiators their usual unstable character hampers elucidation of the actual initiating species and the mechanism involved [9].

In-vitro degradation of biodegradable polymers is usually investigated in a saline solution (pH 7.4) at 37°C. The weight loss is important from the viewpoint of absorption and removal of the polymers from the body, but the most sensitive parameters for studying degradation effects are the molecular weight (MW) and the molecular weight distribution (MWD). The weight loss was expected to be slower than the decrease in MW because the MW can decrease to a considerable degree before any material can fragment and/or dissolve. Degradation is normally believed to be a surface phenomenon whereas infections cause bulk degradation. Surface erosion is characterized by a reduction in mass and a concomitant reduction in diameter, while the MW remains essentially unchanged. Bulk hydrolysis of the polymer was, however, characterized by random chain cleavage which resulted in a precipitous drop in MW [12]. The hydrolysis of the polymer is generally accepted as the main mechanism for the degradation of polyesters [13]. Hydrolysis can occur via the ester bond, resulting in the formation of alcohol and a carboxylic acid end group in the case of aliphatic polyesters. Weight loss became significant when the polymer chain had been degraded to a MW where the probability of random chain cleavage which produced diffusable oligomeric or monomeric units was sufficiently high. The rates of degradation for most aliphatic polyesters are substantially slower [14].

The objective of this paper was to investigate the synthesis of high molecular weight PDXO. The discussion is focused on the conditions for ring-opening polymerization with stannous 2-ethylhexanoate as initiator. It was also our objective to study the in-vitro degradation of PDXO. The degradation was monitored by measuring the decrease in MW, the weight loss, and the change in MWD. The degradation of PDXO is discussed in relation to the degradation of related polylactones.

EXPERIMENTAL

Materials

Aluminum trichloride (Merck) and ethylene gas (AGA ≥ 99.5%) were obtained commercially and used without further purification. 3-Chloropropionyl chloride (Aldrich), 3-chloroperbenzoic acid (Aldrich) and stannous 2-ethylhexanoate (Sigma) were used as received. Dibutyl tin oxide (Aldrich) was dried in vacuum at 120°C for one day prior to use. Iodometry was used to determine the active amount of peracid to 82%. Dichloro methane was distilled over P_2O_5 or calcium chloride and kept over Molecular Sieves (4Å).

Synthesis of Tetrahydro-4*H*-pyran-4-one

Tetrahydro-4*H*-pyran-4-one was prepared by Friedel–Craft acylation of ethylene with 3-chloropropionyl chloride followed by ring closure as described elsewhere [15].

Synthesis of 1,5-Dioxepan-2-one

Tetrahydro-4*H*-pyran-4-one, 55 g (0.55 mol), was added to a slurry of 160 g (0.75 mol) of 82% 3-chloroperbenzoic acid and 82 g (1 mol) sodium bicarbonate in 800 mL dry methylene chloride. The slurry was kept under constant stirring below 0°C in a ice/water/sodium chloride bath while tetrahydro-4*H*-pyran-4-one was added. The slurry was permitted to reach room temperature, and the reaction was maintained for 16 hours. The peracid was then removed by filtration, and the methylene chloride phase was first washed with 50 g (0.5 mol) sodium bisulfite in 400 mL water and then with some more sodium bicarbonate to eliminate any remaining peracid.

The methylene chloride phase was evaporated and gave a slightly yellow oil. Distillation under reduced pressure (68°C, 1 mbar) gave an 83% yield of 1,5-dioxepan-2-one.

Polymerization of 1,5-Dioxepan-2-one

Before the polymerization, 1,5-dioxepan-2-one was recrystallized twice in anhydrous diethylether under a nitrogen atmosphere. The polymerization was carried out in the following manner. The monomer and the initiator were added to a 20-mL serum bottle containing a magnetic stirrer. The reaction vessel was sealed with a rubber septum and purged with nitrogen (N_2) and placed on a thermostated oil bath. The polymer was dissolved in chloroform and precipitated in cold petroleum ether to remove the monomer residue and the metal catalyst. The polymer was isolated by filtration and dried at room temperature under vacuum.

Hydrolytic Degradation of Poly(1,5-Dioxepan-2-one)

The hydrolytic degradation of PDXO with MW 39,000 g/mol has been studied in a buffered salt solution (pH 7.4) at 37°C. Samples of 0.2 g of the polymer were placed in bottles which contained 20 mL buffered salt solution. The bottles were

placed in a thermostatically controlled shaking chamber and maintained at 37 ± 1°C. Prior to testing, two of the bottles were removed and their polymer was washed two times with deionized water. The samples were vacuum dried to constant weight at 0.1 mbar and 23°C for 1 day. The dry mass was measured prior to weight loss and molecular weight determinations.

The percentage mass loss was determined for each sample by comparing the dry weight (m_d) remaining at a specific time with the initial weight (m_0),

$$\% \text{ mass loss} = \frac{m_0 - m_d}{m_0} \times 100$$

Measurements

The IR spectra were recorded using a Perkin-Elmer FTIR model 1710 equipped with a 3600 data station. The polymer spectras were recorded on a thin film made from CH_2Cl_2 solution on NaCl crystals.

The polymer fraction was characterized by size exclusion chromotography (SEC). The system used was a Waters GPC system, run with THF in all measurements, equipped with a solvent delivery system (model 510), automatic injector (Wisp 710B), and a differential refractometer (Waters 410) as detector. The measurements were made at 30°C at a flow rate of 1 mL/min. Five μStyragel columns were used (500, 10^5, 10^4, 10^3, 100 Å). The calculation and recording were done on a Copam PC-501 Turbo unit.

Intensity light-scattering measurements were made using a photon counting device supplied by Hamamatsu. The light source was a 3 mW He-Ne laser (633 nm). The reduced scattering intensity, K_c/R_θ, was measured on polymer-THF solutions of various concentrations at an angle of 90°, 25°C. R_θ is the Rayleigh ratio obtained by calibration measurements with benzene. $K_c = 4\pi n_0(dn/dC)^2/N_A\lambda^4$ (optical constant for vertically polarized light), where n_0 is the solvent refractive index and dn/dC is the refractive index increment.

The initial polymerization was studied using ^{1}HNMR where the percentage conversion was calculated from the peak ratio between the methylene protons in the ring next to the ester bond and the corresponding protons in the ring-opened structure. A Bruker AC-250 FT-NMR spectrometer was used to obtain the ^{1}H-NMR spectra. All spectra were obtained from $CDCl_3$ solutions in 5-mm diameter sample tubes.

RESULTS AND DISCUSSION

Homopolymerization of 1,5-Dioxepan-2-one

The polymerization of 1,5-dioxepan-2-one to high molecular weight with transesterification initiators and the influence of reaction parameters, such as temperature, time, and initiator concentration, have been studied. Organometallic catalysts were by far the most effective initiators to achieve high molecular weight and high conversion of lactones. Organometallic catalysts are of the coordination type, and they involve a concerted insertion with concurrent cleavage of a covalent polymer–catalyst bond [16]. Polymerization is preferably done in bulk at high temperature.

Table 1 presents data for our coordination polymerization in bulk of DXO with common transesterification catalysts. The temperature, monomer ratio, and time were varied.

Tin(II) compounds are the most effective and also the most used compounds as transesterfication catalysts. In the polymerization of DXO, SnOct gave the highest molecular weight and the highest conversion. This initiator was used in most experiments.

The highest molecular weight was achieved with SnOct at a monomer–initiator [M]/[I] ratio of about 1000. A reduction in this ratio concentration did not affect the molecular weight, but at higher ratios the molecular weight decreased. This is probably because a small amount of initiator was partly inhibited by impurities. Although considerable care was taken to exclude such impurities as air and water, the possibility that small amounts of these impurities exist in these systems cannot be neglected. Impurities might hinder polymerization by early chain termination. In the presence of water, SnOct hydrolyzes to give the catalytically more active hydroxy derivative. Water can also act as a chain transfer agent [17]. An attempt to repeat the experiment at a given monomer/initiator ratio resulted in a considerable scatter ($\pm 20\%$) of the molecular weight.

Since the initiator ratio has no influence on the molecular weight, it can be said that tin(II) compounds act less as an initiator and more as a catalytic reagent,

TABLE 1. Coordination Polymerization in Bulk of DXO with Different Initiators, Mainly SnOct, with Variation in Temperature, Monomer Ratio, and Time

Sample	Initiator	[M]/[I]	Temperature, °C	Yield, %	Time, h	MW
1	$SnCl_2$	530	100	61	12	51,700
2	$SnCl_4$	500	100	25	15	3,000
3	DBTO	500	65	—	14	—
4	DBTO	280	100	80	12	68,300
5	DBTO	540	100	71	12	80,300
6	SnOct	500	65	—	16	—
7	SnOct	145	100	87	12	40,100
8	SnOct	320	100	82	12	102,300
9	SnOct	450	100	81	14	74,800
10	SnOct	970	100	86	12	178,400
11	SnOct	1,010	100	84	14	87,600
12	SnOct	1,500	100	46	17	67,700
13	SnOct	1,000	110	87	20	120,000
14	SnOct	1,300	110	83	14	121,200
15	SnOct	1,544	110	81	14	46,100
16	SnOct	3,000	110	64	20	86,900
17	SnOct	5,000	110	62	14	142,900
18	SnOct	500	160	16	10	4,500

as was observed in earlier work [10, 18]. This is also a strong indication that the insertion mechanism is nonionic.

The usual temperature for lactone polymerization is about 100°C, and this is also the best temperature for the polymerization of DXO. A lower temperature (65°C) gave no polymer and a higher temperature (160°C) involved degradation.

Tin(II) chloride and tin(IV) chloride both gave rather low yields and low molecular weights, especially tin(IV) chloride (MW = 3000) because of its high sensitivity to impurities and its low reactivity toward lactones. The complexation of tin(II) compounds with lactones is not very strong. This is in agreement with the significantly weaker Lewis acid character of tin(II) compounds [19]. This could be one of the reasons why tin(II) chloride is a more active catalyst than tin(IV) chloride. Tin(II) chloride gave a more moderate molecular weight (MW = 51,000), while dibutyl tin oxide (DBTO) gave a higher yield and a quite high molecular weight (MW = 80,300). SnOct gave high yields except at a low initiator concentration. It is also assumed that complexation occurs during the first step of initiation of lactones with tin(II) octanoate [20].

DXO needs a longer polymerization time than other lactones, such as glycolide and lactide, although the related ϵ-caprolactone also needs a quite long polymerization time. The molecular weight usually increases with time. The highest molecular weight (178,400) was achieved with SnOct and [M]/[I] = 970. The yield was also rather high, about 86%.

Table 2 shows data for the ionic and coordination polymerization of DXO in solution. The temperature, solvent, and time were varied.

The polymerization was rather unsuccessful in this case. None of the ionic initiators gave a polymer, only a low yield of oligomers. The SnOct worked only above 110°C and gave a polymer with a rather low molecular weight. Compared to bulk polymerization, the process was also very slow. In diglyme (2-methoxyethylether) a molecular weight of 9900 was obtained, and in tetrachloroethane the MW was 18,400. Both the yield and conversion were low and decreased with time. In toluene,

TABLE 2. Solution Polymerization of DXO with Different Solvents and Variation in Temperature and Time

Sample	Initiator	[M]/[I]	Temperature, °C	Solvent	Yield, %	Time, h	MW
1	SnOct		60	THF	–	20	–
2	SnOct		100	Toluene	–		–
3	SnOct		100	Toluene	82		40,500
4	SnOct	1000	110	Diglyme	Oligomer	39	Oligomer
5	SnOct	1000	130	Diglyme	66	39	9,900
6	SnOct	1000	130	Tetrakloretan	39	64	18,400
7	Ch_3Li		60	THF	–	24	–
8	*t*-BuLi	1000	60	THF	Oligomer	14	Oligomer
9	*t*-BuLi		100	Toluene	Oligomer	16	Oligomer
10	DBTO		60	THF	–		–

it was possible to reach higher molecular weights, up to 40,500. The polymer precipitated during polymerization. One reason for the relatively high molecular weight could be that the polymerization resembled bulk polymerization. Another possibility is that the polymerization took place in solution and the shell of the high molecular weight polymer prevents degradation.

Comparison of Tables 1 and 2 shows that SnOct in bulk polymerization gave a higher molecular weight than solution polymerization. Bulk polymerization is preferred to solution polymerization because high conversion and high molecular weight are easily obtained. As stated before, transesterfication initiators give the highest molecular weight. these initiators work best in bulk, and transesterfication between polymer chains is much larger in bulk than in solution. Tables 1 and 2 indicate that the polymerization temperature as well as the time has a tremendous effect on the molecular weight of PDXO.

Figure 1 shows the time/conversion curves for the bulk polymerization of 1,5-dioxepan-2-one at temperatures of 90, 110, 130, and 150°C. The bulk polymerization of DXO at 90 and 100°C is a slow process, reaching full conversion after about 30 hours for 90°C and after 20 hours for 100°C. As expected, the conversion is rather fast in the beginning, and 50% conversion is reached within 6-7 hours. After 20 hours the conversion is very slow, and after 30 hours less than 1% monomer is left. At 130°C, full conversion is obtained within 2 hours, and at 150°C, full conversion is obtained within 15 minutes.

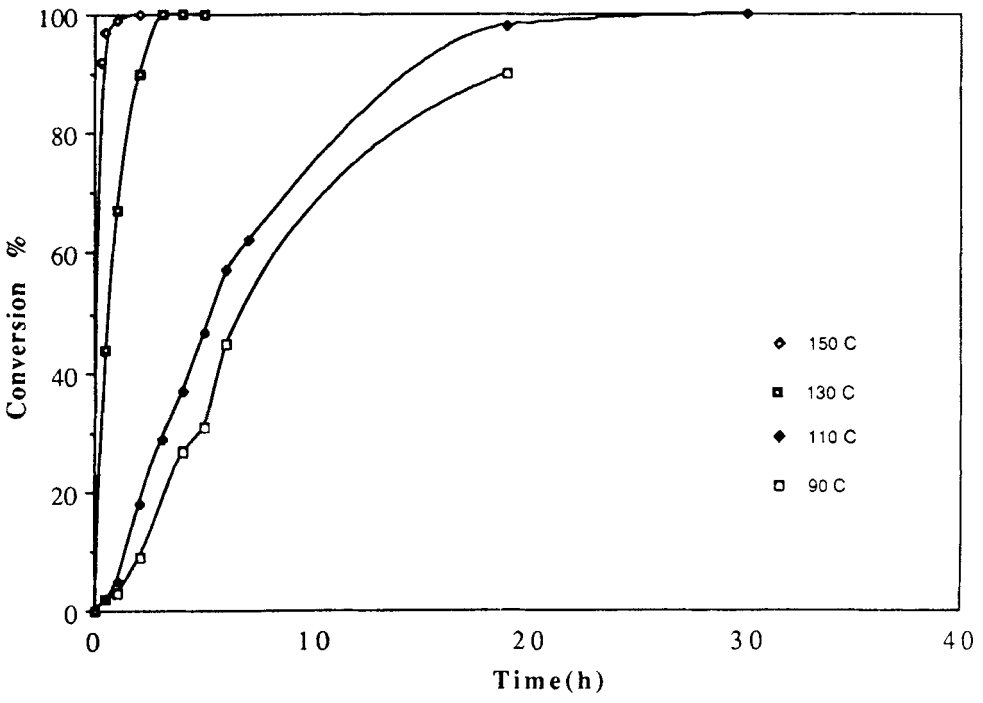

FIG. 1. Conversion curves as a function of time for the bulk polymerization of DXO with stannous 2-ethylhexanoate.

Figure 2 shows data for the change in molecular weight. At 90°C the molecular weight increased very slowly and even after 20 hours it was only 59,400. At 110°C the increase of the molecular weight was still rather slow, but the molecular weight after 20 hours was 172,000. At 130°C a high molecular weight was achieved at full conversion within 2 hours, giving a molecular weight of 133,400. Additional reaction time decreased the molecular weight, probably more because of transesterification than of degradation. At 150°C the highest molecular weight (50,400) was achieved within 1 hour. After that, the molecular weight decreased. At the same time, the polymer turned yellow. This is an indication of the predominance of thermal degradation and a lessening of transesterfication. the thermal degradation could also be referred to as a depolymerization at higher temperatures. In the case of transesterification, some chain transfer could also effect the molecular weight and the molecular weight distribution. It is known that tin(II) compounds catalyze depolymerization as well as polymerization. This drop in molecular weight at higher temperatures also occurs in the ring-opening polymerization of similar lactones, e.g., ϵ-caprolactone, lactides, and glycolides. After a certain time, the molecular weight decreases due to depolymerization processes.

The molecular weight distribution is shown as a function of time for the bulk polymerization of DXO in Fig. 3. At 150°C, as opposed to 90, 110, and 130°C, there is a broadening of the MWD, with an increase up to 4 hours and then a decrease. The broadening begins after full conversion was reached, i.e., after 15

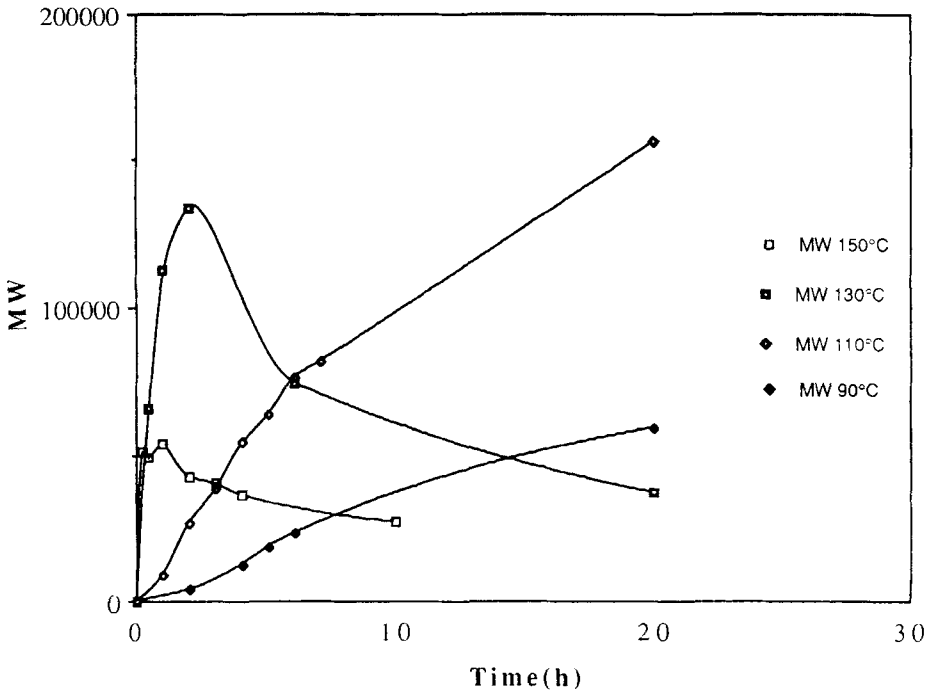

FIG. 2. MW curves as a function of time and temperature (90–150°C) for the bulk polymerization of DXO with stannous 2-ethylhexanoate.

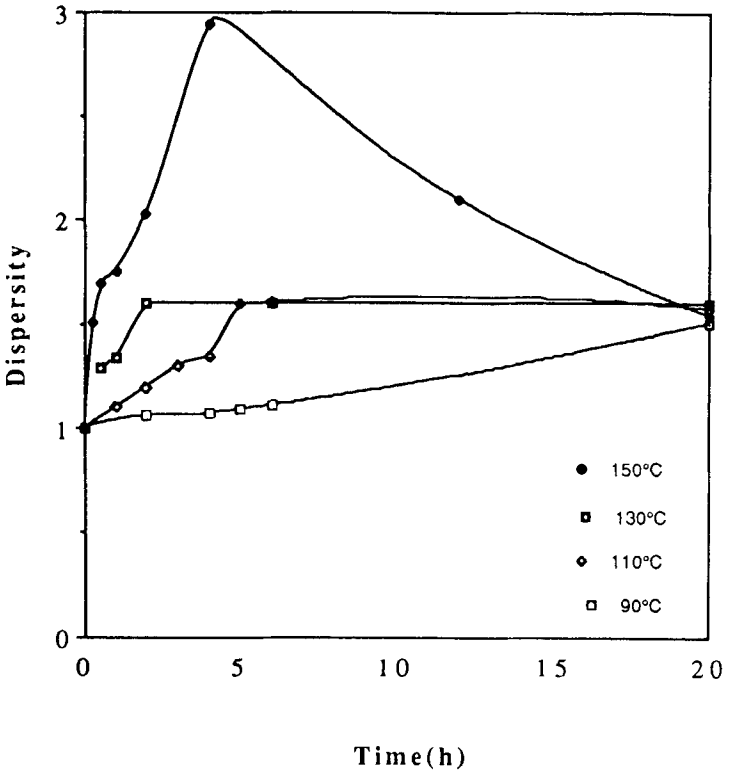

FIG. 3. Dispersity as a function of time and temperature (90–150°C) for the polymerization of DXO with stannous 2-ethylhexanoate.

minutes. The molecular weight decreases after the first hour. These observations demonstrate that transesterfication occurs and is the main reason for the decrease in molecular weight. In the latter stage, thermal degradation is the main cause of the decrease in molecular weight. The degradation reaction causes yellowing of the polymer after a few hours. According to Flory and other authors [21, 22], ester interchange equilibrium occurs in polylactones during polymerization or subsequent to polymerization. The initial polymerization distribution is considerably above 2, and that is when the subsequent ester interchange reactions should result in a decrease in molecular weight and when dispersity should reach a normal distribution. This agrees with our observation, for in our case we reached a normal distribution around 1.6, which is narrower than the most probable random distribution but broader than a Poisson distribution. At 110°C the polymerization is so slow that an ester interchange occurs and keeps the M_w/M_n at a normal distribution level. At higher temperatures (150°C), polymerization is very fast, leading to no ester interchange because this is kinetically less favorable. At 90°C, dispersity is close to unity during the first hours and the molecular weight is about 22,500. These data are in agreement with results obtained by Teyssie [11], who stated that he observed dispersity close to unity under mild reaction conditions. In our case, however, dispersity reached a ratio of 1.6 after a long polymerization time (20 hours).

TABLE 3. Comparison btween GPC Data and Light-Scattering Data

Sample	MW by GPC	MW by light-scattering
1	178,400	186,600
2	144,000	142,900
3	121,200	112,500

The polymers obtained were characterized by size exclusion chromatography (SEC). Since SEC does not give absolute values of the molecular weight, light scattering was used as a complementary method. The values from SEC were nearly the same as the absolute values from light scattering (Table 3). The deviation is less than 8% from the calculated SEC values.

Hydrolysis of Poly-1,5-dioxepan-2-one

The degradation of poly-1,5-dioxepan-2-one was studied in standard saline solution buffer at pH 7.4. The changes in mass and molecular weight (MW) are shown as a function of time in Figure 4. Mass loss and change in molecular weight began as early as the first week. The changes continued, but the molecular weight showed a more rapid decrease. The drop in the first weeks is due to diffusion of low molecular weight materials in the solution. After 10 weeks, the mass loss was slower when the low molecular weight fraction of the material decreased. After 20 weeks the molecular weight change increased due to chain cleavage as a result of backbone hydrolysis, but the rate of weight loss was fairly constant because no diffusion of low molecular compounds occurred. One reason for the higher degra-

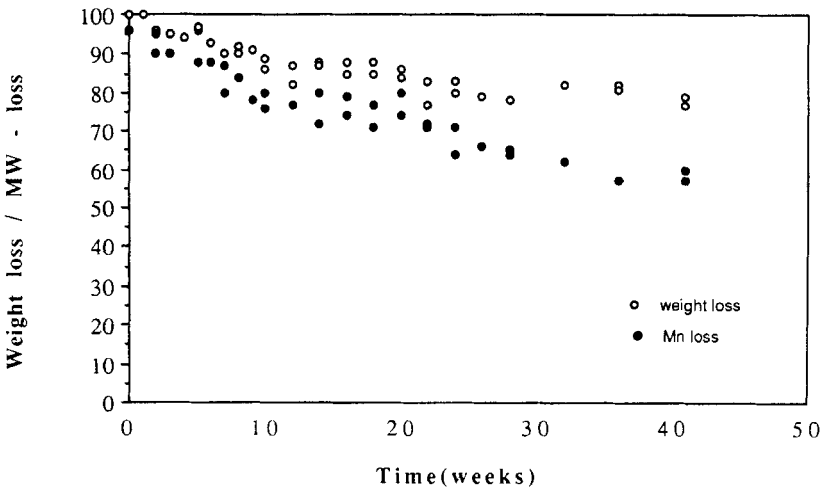

FIG. 4. Degradation of PDXOweight loss/MW loss (%) as a function of time (weeks).

dation rate after 30 weeks is probably because the generation of especially reactive ester end groups could affect the kinetics of the degradation process as well as the structure and composition of the remaining polymer.

Evidence that degradation did take place is demonstrated by a shift in the MWD. The plot of MWD versus time (Fig. 5) shows a drop at the beginning due to the diffusion of low molecular compounds to the water phase and later a slower drop that depends on random chain cleavage. In the later stages of degradation, the MWD is narrowed due to dissolution of the low molecular weight fraction.

In the first phase, in which the initial molecular weight decreased by 70% during 46 weeks from an initial molecular weight of 45,000, the degradation was similar to that of poly-ε-caprolactone (PCL) which is a semicrystalline polymer similar to PDXO (50,000 PCL). In a later stage, the degradation slowed down for PCL. The reason for this behavior is that the degradation first occurs in the amorphous region and that the crystallinity increases with time [23]. This seems to be attributed to recrystallization of partly degraded tie-chain segments connecting the separate crystalline domains. One of the reasons for the increase in M_w/M_n ratio for PCL and the decrease for PDXO is that in the case of PCL the recrystallization hinders diffusion of the oligomeric segments into the bulk. Poly(β-propiolactone) has nearly the same degradation properties as PCL [24]. For polytrimethylenecarbonate (PTMC), the rate of hydrolytic chain scission is much slower than for PDXO and PCL, probably because the carbonate group has a lower hydrolytic sensitivity than the ester group. The small change in molecular weight over a 30-week period

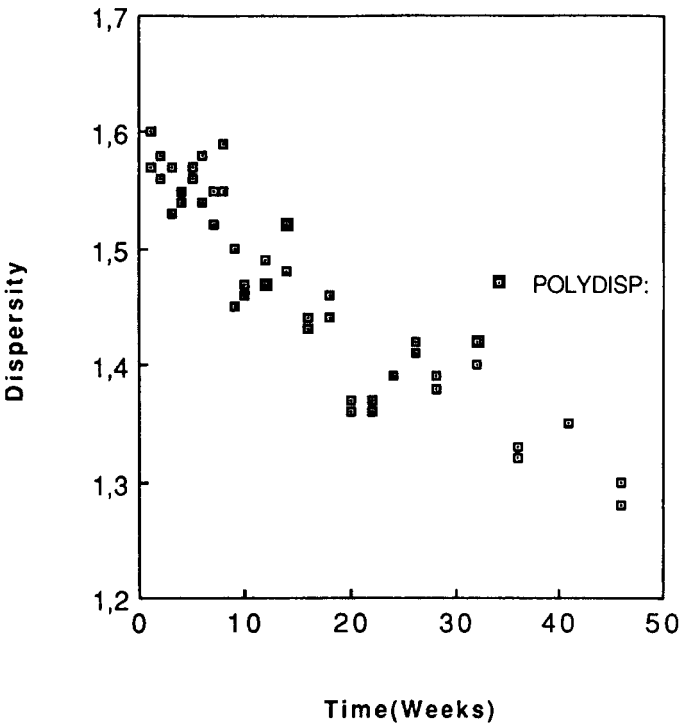

FIG. 5. Changes in dispersity during degradation of PDXO.

for PTMC is more probably due to a diffusional loss of oligomers from the polymer bulk than to hydrolytic chain scission [25]. Poly L-lactide (PLLA), which is one of the most used polymers in biomedical applications, totally degrades after 11 weeks, showing a degradation similar to PCL [26]. The reason for the fast degradation is due to the greater number of hydrolytic centers (ester groups).

CONCLUSIONS

The highest molecular weight of PDXO was achieved with SnOct in bulk at 110°C. Temperature has a tremendous effect on coordination polymerization. It causes faster conversion and leads to a high molecular weight in a shorter time period.

Oligomers, low molecular and high molecular compounds from the same monomer, have different properties. It is therefore of great interest to be able to control polymerization to achieve a desired molecular weight. PDXOs as homopolymer have poor mechanical properties, but their hydrolytic properties and biocompatibility are very good. Through copolymerization, block copolymerization, and crosslinking, it is possible to achieve a polymer with good mechanical and good biomedical properties.

PDXO has good degradation properties. It degrades rather slowly compared to other lactones. After 40 weeks, more than 50% of the molecular weight remains. This means that PDXO can be used for slow degradation applications, because the degradation time reflects changes in the initial molecular weight. PDXO has poor mechanical properties, but good elastic, degradation, and biomedical properties. Its copolymers can be used as low molecular compounds for drug delivery systems, and with crosslinks it can be made into a degradable elastic material suitable for several biomedical applications.

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