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Ring-opening polymerization of degradable polyesters

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SUMMARY: Medium to high molecular weight random copolymers of 1,5-dioxepan-2-one (DXO) and L-lactide (L-LA) or ε-caprolactone (ε-CL) of different compositions have been investigated. Polymerization was conducted in bulk at 110°C using stannous 2-ethylhexanoate as catalyst. Poly(DXO-co-L-LA) is a hydrolysable material with a glass transition temperature (T_g) ranging from -36 up to 58°C depending on the molar composition. The material exhibited crystallinity as long as the amount of DXO did not exceed 50 weight%. Reactivity ratios were determined to $r_{L\text{-}LA}$=10 and r_{DXO}=0.1, giving a more blocky structure than expected in a random copolymer. The copolymer between ε-CL and DXO was shown to be a truly random copolymer by ^{13}C NMR, as expected from the reactivity ratios, r_{DXO}=1.6 and $r_{\varepsilon\text{-}CL}$=0.6. T_g of the material was ranging from -64 up to -39°C. The ability of the poly(DXO-co-ε-CL) to crystallize was retained up to a DXO content of 40 weight%. The melting temperature and crystallinity of both copolymers decrease with increasing amount of DXO. Incorporation of semicrystalline comonomers, L-LA or ε-CL, into the amorphous poly(DXO) creates materials with adjustable properties depending on the molar composition.

Introduction

Increasing interest in the use of degradable polymers in medical applications have lead to the development of new types of materials in order to fulfill the demands one have on the properties with respect to its application. Polymer properties are readily controlled by their chemical composition and several approaches have been adopted in order to gain desired properties such as blending$^{1)}$ and copolymerization$^{2)}$, or by the use of macromolecular architecture giving e. g. star or comb$^{3,4)}$ polymers.

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The polylactones and polylactides represent a large group of hydrolytically degradable materials. Synthesis of these materials has traditionally been polycondensation, but generally ring-opening polymerization of the cyclic condensation product of the hydroxy acid is preferred. Polycondensation suffers from some major drawbacks such as long reaction times, high reaction temperatures, and very high monomer conversion are required in order to obtain high molecular weight polymers. In addition, this method provides a limited control over the structures of the end-groups of the prepared polymer. Ring-opening polymerization (ROP) is normally rid of these shortcomings and high molecular weight polymers can be formed under relatively mild conditions. ROP are normally carried out with no or limited number of side reactions taking place, making it possible to control properties like molecular weight and molecular weight distribution (MWD). ROP can be performed with a large number of different initiators to form high molecular weight products5). All types of polymerization mechanisms, e.g. cationic, anionic or coordinative, have been investigated in the literature in order to develop the method and produce as many different structures as possible6, 7, 8).

Degradation rate is a very important property which differs a great deal among the different classes of degradable materials. At one end of the spectrum we have aliphatic polyanhydrides which generally hydrolyze very quickly9) and on the other end we find the aliphatic polycarbonates which hydrolyze very slowly and hardly show any mass change even after 2 years in vitro10). Copolymers including one or several classes make an important contribution to already existing materials in that they combine the inherent properties of each homopolymer11). The degradation rate is in many cases the limiting property which determines what applications the materials can be used for.

The degradability of polylactones and polylactides and in many cases the low toxicity of their degradation products in vivo makes them interesting materials for medical applications. Poly(L- or D,L-LA) and poly(ε-CL) are two of the most common and well studied degradable materials on the market today. High molecular weight aliphatic polyesters of the poly(2-hydroxy acid) type were synthesized for the first time over 40 years ago12). These aliphatic polyesters undergo simple hydrolysis in vitro and in vivo, and poly(lactic acid) form natural metabolites as degradation products. The high strength and brittleness which characterize poly(lactic acid) can be substantially modified by copolymerization with e.g. DXO. The homopolymer of DXO is an amorphous material with a T_g of -36°C, interesting properties of this polymer led us to continue the research and explore the potentialities of this polymers as a component in a copolymer. The long degradation time of poly(ε-CL) is usually a disadvantage in medical applications and copolymerization is one approach to increase the degradation rate. The ether group in the backbone of DXO give the polymer chain a high degree of flexibility, which could be an advantage in developing a material with faster degradation rate. The good biocompatibility of L-LA and ε-CL are also characteristic for the homopolymer of DXO but also quite long degradation time[13)]. In the present work new copolymers of medium to high molecular weight were obtained and characterized. Copolymers between DXO and ε-CL or L-LA over the full range of compositions have been investigated.

Experimental

Materials

L-lactide (Boeringer GmBH, Germany) was recrystallized twice in dry toluene before use. ε-Caprolactone was obtained commercially (Aldrich, Germany) and purified by vacuum distillation over calcium hydride. 1,5-Dioxepan-2-one was synthesized by Baeyer-Villiger oxidation of tetra-4H-pyran-2-one (Fluka) as described earlier[12, 14)]. Before polymerization, DXO was distilled under reduced pressure and recrystallized twice in anhydrous diethyl ether to remove traces of 3-chlorobenzoic acid. Stannous 2-ethylhexanoate (Aldrich, Germany) was used as received.

Polymerization procedure

The catalyst, stannous 2-ethylhexanoate, and the purified DXO and L-LA or ε-CL were added to the previously flamed polymerization flask under an inert atmosphere (Ar). A magnetic stirring bar was added and the flask was sealed with a rubber septum and immersed into a thermostated oil bath. The obtained polymer was dissolved in $CHCl_3$ and precipitated in cold methanol or petroleum ether. The copolymer was isolated by filtration and dried under vacuum at room temperature.

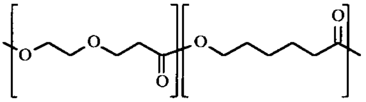
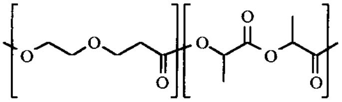
Measurements

The ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker AC-250 or AC-400 FT-NMR spectrometer. The samples were dissolved in deutero chloroform in 5 mm diameter sample tubes. The solvent was used as internal standard (δ=7.26 ppm). SEC measurements were made on a Waters model 510 apparatus equipped with an automatic injector (WISP 710B) and a differential refractometer (Waters 410) as detector. All measurements were made at 30°C with 5 μ-Styragel columns (500, 10^{3}, 10^{4}, 10^{5}, 100 Å) using THF as solvent with a flow rate of 1 ml/min. A Copam PC-501 Turbo unit was used to collect and process data. A Perkin-Elmer DSC-7 connected to a Perkin-Elmer 7700 computer was used for differential scanning calorimetric (D.S.C.) analysis. The temperature and heat capacity was calibrated with an indium sample (Tm=156.6°C). A heating and cooling rate of 10 K/min was used.

Result and discussion

This paper investigates the synthesis of the copolymers between DXO and L-LA or ε-CL (Tab. 1) and their thermal properties. The objective of the study was to produce materials with adjustable properties by changing the composition of the copolymers.

Tab. 1

Chemical structure	Chemical name
	poly(1,5-dioxepan-2-one-co-ε-caprolactone) poly(DXO-co-ε-CL)
	poly(1,5-dioxepan-2-one-co-L-lactide) poly(DXO-co-L-LA).

Organometallic initiators are the most effective type of initiators used to achieve controlled polymerization of lactones. Organic derivatives of metals such as aluminum, zinc and tin have been extensively studied by many laboratories worldwide as initiators in ring-opening polymerization of lactones and related compounds. An earlier study on coordination polymerization of DXO with transesterification catalysts showed that stannous 2-

ethylhexanoate (Sn(Oct)) is the most effective tin(II) catalyst giving high molecular weight polymers and high monomer conversions[14)], therefore this catalyst was selected to be used in this study.

Fig. 1 shows the results from the statistical bulk copolymerization between DXO and ε-CL or L-LA respective, using Sn(Oct) as catalyst at 110°C or 120°C. Conversion is plotted as a function of the polymerization time, and the monomer ratios for the reaction mixtures were selected to be equal in amount of DXO. This figure shows that DXO is consumed at a slightly faster rate when ε-CL is the comonomer. But the difference is small enough to expect that the formed polymers are truly of random nature. Full conversion was never reached, probably due to limited diffusion of the monomer in the formed polymer, since the polymerization was carried out in bulk.

Determination of the reactivity ratios using the method of Kelen and Tüdös resulted in values of $r_{DXO}=1.6$ and $r_{\varepsilon\text{-}CL}=0.6$[2)]. The random nature of the copolymers were confirmed by quantitative ^{13}C NMR. The opposite result was found when L-LA was copolymerized with DXO, in this case L-LA was consumed much faster than was DXO. A relatively large difference in reactivity ratios, $r_{DXO}=0.1$ and $r_{L\text{-lactide}}=10$, result in rather long initial blocks of poly(L-LA) being formed although these are expected to be redistributed by intermolecular transesterification reactions[11)]. Tab. 2 shows the average sequence lengths of DXO and L-LA in the copolymer from quantitative ^{13}C NMR measurements.

Tab. 2. Sequence lengths of DXO/L-LA copolymers

Sample (DXO/L-LA)	$\overline{L_D}^{a}$	$\overline{L_L}^{b}$	%DLD^{c}	Polym. time, h	Polym. temp., °C
35/65	3.6	3.5	0	9.25	115
50/50	4.1	2.6	0	24	120
50/50	2.8	1.6	7	20	140
25/75	2.6	4.3	1	20	120

a,b) average monomer sequence lengths of DXO and L-LA, respectively, in the copolymer

c) percent triad consisting of a half-lactide unit with a DXO unit on both sides

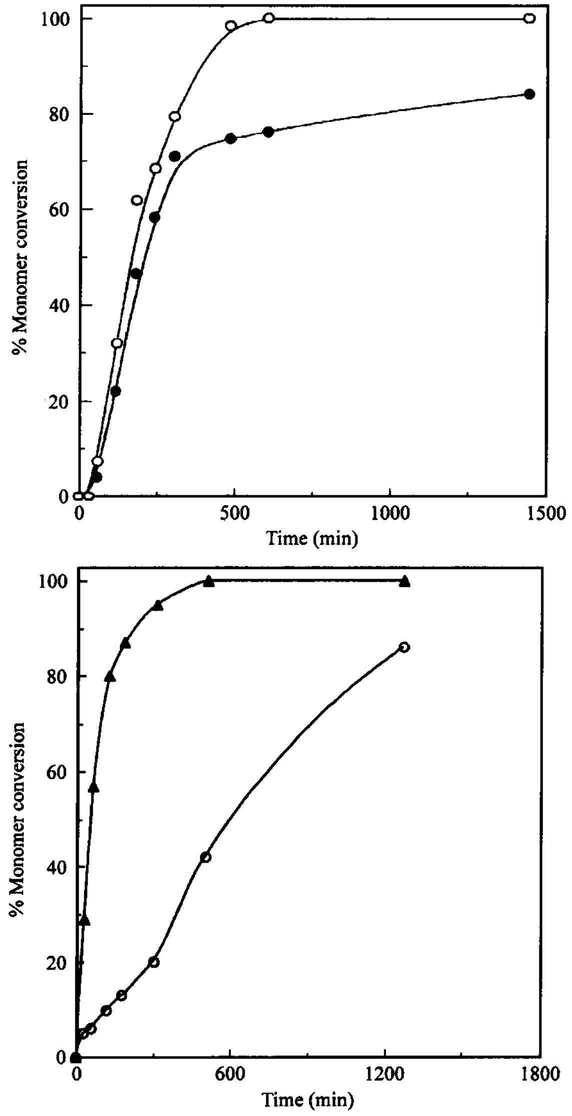


Fig. 1: The dependence of conversion on reaction time of Sn(Oct) initiated copolymerization of a) ε-caprolactone (●) and 1,5-dioxepan-2-one (O) b) L-lactide (▲) and 1,5-dioxepan-2-one (O).

The results indicate that L-LA is polymerized easier than ε-CL, when DXO is used as reference compound. This is in agreement with the investigation conducted by Schindler et al$^{15)}$, regarding copolymerization of lactide and ε-CL. Their study showed that the lactide monomer was consumed at a faster rate than the ε-CL monomer. L-LA preferentially polymerized with itself rather than with ε-CL, and the reactivity ratios were determined to be $r_{LA}=34.7$ and $r_{\varepsilon\text{-}CL}=0.24$. Also in this study the copolymers possess a blocky structure which might be randomized to some extent by transesterification reactions, as is the case when DXO is copolymerized with L-LA.

Fig. 2 shows the result from the SEC measurements for the copolymerization between DXO and ε-CL. As can be in this figure the number average molecular weight increases up to a reaction time of 500 min, up to almost complete monomer conversion, after this point the weight average molecular weight is increased mostly due to transesterification reactions which give an increase in the MWD. The results indicate that the transesterification reaction takes place in the reaction mixture mainly when very high monomer conversion is reached. The MWD of the prepared poly(DXO-co-ε-CL) varied between 1.1 at the beginning of the reaction and 1.7 at high monomer conversion.

The glass transition temperature, melting temperature and crystallinity are strongly affected by copolymerization. Large differences in T_g for the homopolymers, T_g(poly(DXO))≈-36°C, T_g(poly(L-LA))≈+55°C and T_g(poly(ε-CL)≈-65°C, result in copolymers with a wide range of intermediate properties. The series of copolymers prepared in this study were analyzed by D.S.C.. Fig. 3 shows the T_g-values for the copolymers as a function of their L-LA or ε-CL content. T_g decreased with increasing ε-CL content for the poly(DXO-co-ε-CL) and increased with increasing amount of L-LA for the poly(DXO-co-L-LA) as expected. A regular increase in T_g with the copolymer composition was observed, a behavior which is expected for a single phase system. The solid line represents the Fox equation$^{16)}$, which predicts the glass transition temperature for random copolymers. The deviation from the theoretical values are due to some limitations of this equation, it doesn't take into account factors like chemical structure or sequence effects, other methods have been presented$^{17)}$.

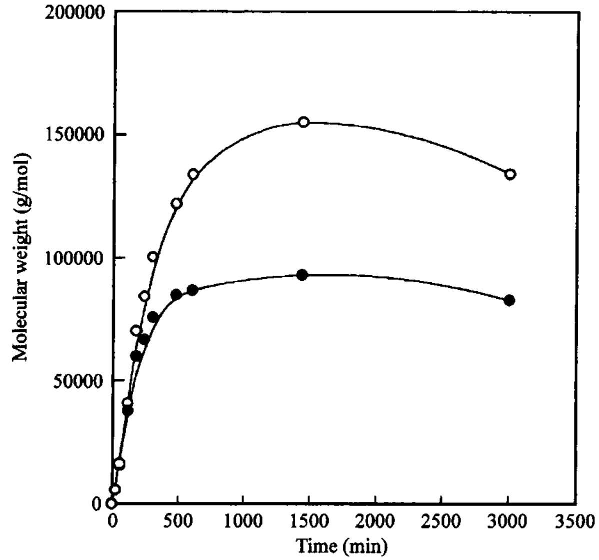


Fig. 2: Molecular weight dependence on reaction time for copolymerization of ε-caprolactone and 1,5-dioxepan-2-one, molar ratio: 80/20. Polymerization temperature 110°C. Mn: ●, Mw: ○.

Fig. 4 and 5 show the crystallinity determined by D.S.C. and X-ray diffraction measurements and meltingpoint as a function of the amount of DXO. The crystallinity and melting point of the resulting copolymers are conveniently varied between the respective homopolymer values depending on the molar composition as exemplified by the poly(DXO-co-ε-CL). The addition of DXO in small amounts to the comonomer ε-CL lead to a decrease in melting temperature and in crystallinity, and at DXO contents higher than 40% no crystallization occurs. The reported enthalpy of fusion of 139.5 J/g for a 100% crystalline poly(ε-CL) was used in the evaluation of the ΔH values obtained from D.S.C. measurements[18]. Copolymers between DXO and L-LA show the same behavior and it crystallizes as long as the amount of DXO is below 50%.

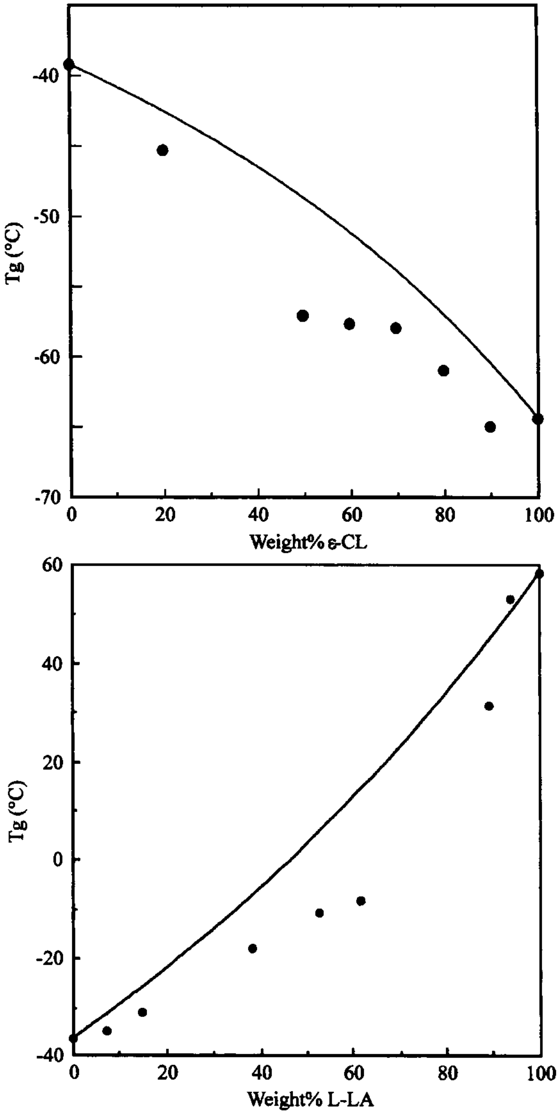


Fig. 3: Glass transition temperature of a) poly(ε-caprolactone-co-1,5-dioxepan-2-one) as a function of molar content ε-caprolactone b) poly(L-lactide-co-1,5-dioxepan-2-one) as a function of molar content L-lactide. The solid line corresponds to expected values calculated from the Fox equation.

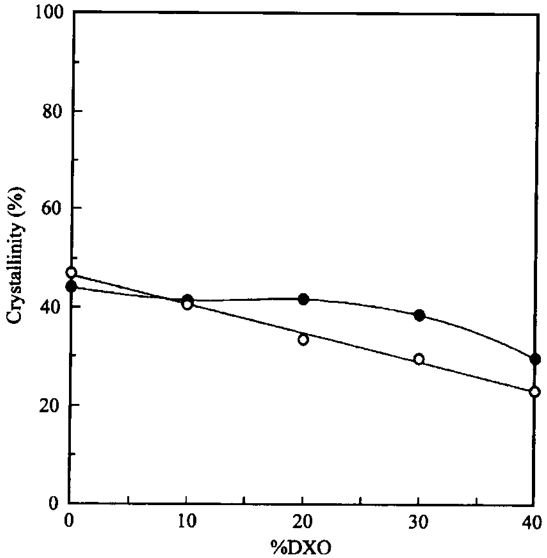


Fig. 4: Crystallinity as a function of amount 1,5-dioxepan-2-one in the ε-caprolactone/1,5-dioxepan-2-one copolymers. ●: crystallinity determined by X-ray diffraction measurements, O: crystallinity determined by DSC.

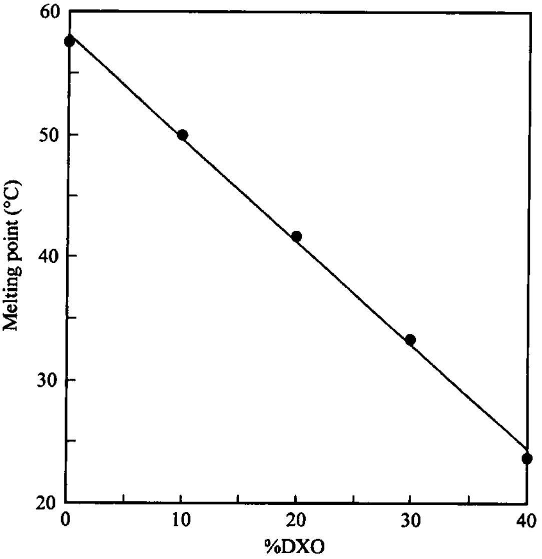


Fig. 5: Melting point of poly(ε-caprolactone-co-1,5-dioxepan-2-one) as a function of the amount 1,5-dioxepan-2-one.

Conclusion

In the search for new biodegradable polymeric materials we have prepared copolymers of 1,5-dioxepan-2-one, and ε-caprolactone or L-lactide. We have shown that random copolymers of medium to high molecular weight can be prepared using stannous-2-ethylhexanoate as catalyst. Truly random copolymers were prepared between DXO and ε-CL while polymers with a more blocky structure was obtained when copolymerizing DXO and L-LA.

Thermal properties changed with the molar ratio of the two monomers in the copolymers. Glass transition temperature decreased with increasing ε-CL content for poly(DXO-co-ε-CL) and increased with increasing amount of L-LA for poly(DXO-co-L-LA) as expected. Both copolymers showed a semicrystalline behavior as long as the DXO content was lower than 40 weight% respective 50 weight%.

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