BUTTERWORTH HEINEMANN

Polymer Vol. 36 No. 5, pp. 1009–1016, 1995

0032-3861/95/$10.00+0.00

Degradable high-molecular-weight random copolymers, based on ε-caprolactone and 1,5-dioxepan-2-one, with non-crystallizable units inserted in the crystalline structure

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(Received 31 August 1994)

High-molecular-weight copolymers of ε-caprolactone (CL) and 1,5-dioxepan-2-one (DXO) over the complete range of compositions have been synthesized and studied. Stannous 2-ethylhexanoate was used as a catalyst and the polymerization was carried out in bulk. Reactivity ratios were $r_{CL}=0.6$ and $r_{DXO}=1.6$, which give $r_1 r_2 = 1$, thus leading to an ideal copolymer. The copolymers exhibited crystallinity as long as the proportion of 1,5-dioxepan-2-one did not exceed 40%. The crystallinity and melting temperature of the copolymers decreased with increasing content of 1,5-dioxepan-2-one. Analysis of the melting-point depression data of the copolymers indicates that about 40% of the 1,5-dioxepan-2-one comonomer units are incorporated into the CL crystals.

(Keywords: ε-caprolactone; 1,5-dioxepan-2-one; degradable copolymer)

INTRODUCTION

Biomedical biodegradable polymers are a rapidly developing field, where there are still quite a lot of fundamental problems remaining unsolved. Thus it is still of great interest to achieve new polymers that fulfil all the demands that one has on biomaterials.

An ideal biodegradable polymer should have many different properties, such as adequate mechanical strength as well as good degradability. Often, the best way to achieve all the desirable properties is to copolymerize two different monomers.

Aliphatic polyesters are frequently used as both homopolymers and copolymers in different medical applications, such as temporary prostheses[1], surgical aids[2,3] and subdermal drug delivery systems[4]. We have previously reported on degradable polyesters[5], but also on related polymers such as poly(ether ester)s[6–9]. Interesting properties of poly(1,5-dioxepan-2-one) (PDXO) described earlier[6–9] made us continue research into this polymer as a component in a copolymer.

Poly(ε-caprolactone) (PCL) is a semicrystalline polymer ($T_m=63°C$, $T_g=-60°C$), which crystallizes very readily and cannot be quenched to a glass[10]. The relatively low crystallinity of PCL (40–50%), its low glass transition temperature (T_g) and its high permeability represent favourable properties for its use in biodegradable drug delivery systems[11,12], and PCL is therefore one of the most frequently used compounds in such applications. The mechanism of PCL degradation has also been thoroughly investigated[13,14].

One drawback is that PCL has a long degradation time (half-life time of one year *in vivo*)[4], which is usually a disadvantage in medical applications. Different approaches have been made to copolymerize PCL to increase the degradation rate.

Schindler *et al.* have investigated the rate of degradation of PCL and its copolymers with DL-lactide, DL-ε-decalactone and δ-valerolactone[15]. When the comonomer content was sufficient to reduce the melting point of ε-caprolactone sequences to body temperature, degradation occurred more rapidly, especially with increasing weight loss. Vion *et al.* have copolymerized DL-lactide and ε-caprolactone (CL) under different conditions, and have also studied copolymers between CL and substituted ε-caprolactones, such as ε-methyl-ε-caprolactone and δ,δ-methyl-ε-caprolactone[16]. Feijen *et al.* have increased the rate of degradability of PCL by copolymerizing it with cyclic ester amides[17].

Poly(1,5-dioxepan-2-one) is an amorphous poly(ether ester) with a T_g of approximately $-37°C$[6]. The ether group in the backbone gives the polymer chain a high degree of flexibility, which could be an advantage. PDXO has, however, insufficient mechanical strength and has to be either crosslinked or copolymerized. The homopolymer of DXO has, as well as PCL, very good biocompatibility and quite long degradation times, the initial molecular weight decreasing by 70% over a period of 46 weeks *in vitro*[6].

PDXO has earlier been copolymerized with lactide[8,9]

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and glycolide[18,19]. The copolymers were reported to exhibit crystallinity, but T_m decreased with increasing amount of DXO.

The copolymer between CL and DXO has earlier only been briefly mentioned in a note and a patent[20,21]. Copolymers with no more than 15% of DXO were prepared and the degree of crystallinity was reported to be maintained, even though the T_m was lowered. This was explained as being due to isomorphism.

Isomorphism is a phenomenon where two different species form mixed crystals over a certain range of concentration. Usually one divides isomorphism into three different categories. In the case of copolymerization between CL and DXO, the category where only one of the two types of repeating units is crystallizable is applicable. The other repeating unit is not capable of crystallization on its own, but shows isomorphism with the crystallizable repeating unit[22].

This paper gives a full investigation of the copolymerization of CL and DXO over the complete range of compositions. Both the conversion and the reactivity are studied, and the reactivity ratios are determined. Furthermore, the morphology and melting behaviour, especially the melting-point depression, have been investigated.

EXPERIMENTAL

Materials

ε-Caprolactone (CL) was obtained commercially (Aldrich) and purified by vacuum distillation over calcium hydride (CaH_2). Stannous 2-ethylhexanoate ($Sn(oct)_2$) (Aldrich) was used as received.

1,5-Dioxepan-2-one (DXO) was synthesized by Baeyer–Villiger oxidation of tetrahydro-4*H*-pyran-2-one (Fluka) as described earlier[7–9]. Before polymerization, the DXO was distilled under reduced pressure (0.1 mbar) and recrystallized twice in anhydrous diethyl ether.

Polymerization procedure

The purified DXO and stannous 2-ethylhexanoate were added to the polymerization flask under an inert atmosphere (Ar). The flask was equipped with a magnetic stirrer and sealed with a rubber septum. CL was added through a syringe. The polymerization flask was then immersed in a thermostated oil bath (110°C). The product obtained was dissolved in $CHCl_3$ and precipitated in cool petroleum ether. The polymer was isolated by filtration and dried *in vacuo* at room temperature.

Methods

The ^1H n.m.r. and ^{13}C n.m.r. spectra were obtained using a Bruker AC-250 *FT*n.m.r. All spectra were obtained from $CDCl_3$ solutions in 5 mm diameter sample tubes. Quantitative ^{13}C n.m.r. was carried out using the INVGATE sequence, covering the carbonyl region only. In the INVGATE sequence, the pulse width was set to 90°, the acquisition time to 11 s, and the delay time (D_1) plus acquisition time to 100 s.

S.e.c. measurements were made on a Waters g.p.c. system, equipped with a solvent delivery system (model 510), automatic injector (WISP 710B) and a differential refractometer (Waters 410) as detector. All measurements were made at 30°C with five μ-Styragel columns (500, 10^3, 10^4, 10^5, 100 Å). Tetrahydrofuran (THF) was used as solvent, with a flow rate of 1 ml min^{-1}. The data recording and calculations were made with a Copam PC-501 Turbo unit. Calibration was achieved using polystyrene standards that covered the molecular-weight range of 1000 to 2×10^6.

During the light scattering analysis, the g.p.c. was connected to a Wyatt model Dawn F MALLS photometer. The light source was a He–Ne laser operating at the wavelength $\lambda = 623.8$ nm. All data were treated using Wyatt Technology software. The refractive index increment (dn/dc) of PCL and the copolymers was estimated from the analysis data.

The d.s.c. used was a Perkin–Elmer DSC-7 with a Perkin–Elmer 7700 computer. The temperature and the heat capacity of the calorimeter were calibrated with an indium sample ($T_m = 156.6$°C). Heating and cooling rates were 10 K min^{-1}. Melting peaks (peak values) and ΔH values were recorded on the second scan.

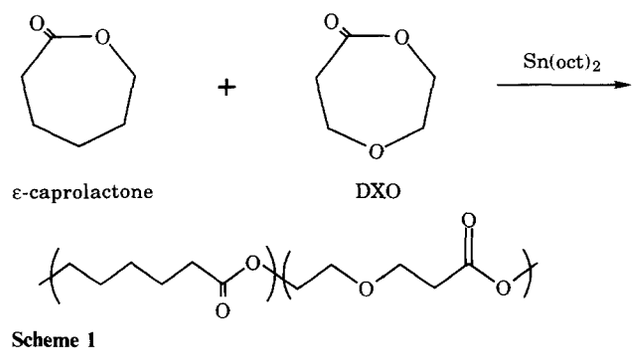
X-ray diffraction measurements were made with a Philips generator PW 1830 (Cu Kα radiation), a Warhus camera under vacuum and an image analysis system (Northern Light model B90 light table, Dage MTI70 series camera, DTK 486-33 MHz PC, Optimas software by Bioscan Inc., UN-Scorpion Framegrabber).

RESULTS AND DISCUSSION

Copolymers of ε-caprolactone (CL) and 1,5-dioxepan-2-one (DXO) with different compositions were made by random ring-opening polymerization according to *Scheme 1*. The results are summarized in *Table 1*. In all cases the polymerization temperature was 110°C and the polymerization time 24 h. The composition of the copolymers was determined by ^1H n.m.r. analysis.

Table 1 Results of the copolymerization of ε-caprolactone with DXO in bulk, catalysed by stannous 2-ethylhexanoate at 110°C

Expt No.	Mole ratio in feed, CL/DXO	[M]/[I]	Polym. compos., P(CL–DXO)	M_w	M_n	H
1	0/100	556	0–100	156000	112000	1.39
2	20/80	680	22–78	161000	98000	1.65
3	50/50	730	50–50	169000	100000	1.69
4	60/40	602	59–41	134000	84000	1.60
5	70/30	607	71–29	143000	86000	1.66
6	80/20	600	82–18	159000	100000	1.60
7	90/10	602	92–8	155000	90000	1.73
8	100/0	667	100–0	163000	92000	1.77



Scheme 1

The reaction parameters (monomer/initiator ratio, time and temperature) were chosen based on earlier studies of the homopolymerization of DXO[6]. The monomer/initiator ratio [M]/[I] has no significant effect on the molecular weight obtained, since stannous 2-ethylhexanoate acts as a catalyst rather than as an initiator. The true initiating species are small amounts of impurities in the monomer or the initiator. Traces of water are present in the purified monomer and impurities such as 2-ethylhexanoic acid, stannous hydroxide and water are always present in $Sn(oct)_2$ (ref. 23).

The molecular weights in *Table 1* are based on polystyrene (PS) standards. Using the two Mark–Houwink equations[24]:

$$\text{PS} \quad [\eta] = 0.932 \times 10^{-4} M^{0.740}$$
$$\text{PCL} \quad [\eta] = 1.395 \times 10^{-4} M^{0.786}$$

these data values can be converted into data based on PCL calibration. Molecular weights based on PCL calibration correspond fairly well with M_n data obtained from light scattering analysis, as shown in *Table 2*.

Conversion experiments were made with the molar compositions CL/DXO 80/20 and 50/50. Only results from the 80/20 composition are shown here. The composition of the reaction mixture was determined by the ^1H n.m.r. technique. Owing to extensive overlap of the monomer and polymer peaks, especially in the case of ε-caprolactone (see *Figure 1*), some simple mathematical calculations had to be made. At 1.7 ppm, a peak corresponding to six protons (H_b) from the monomer, CL, and four protons (H_{b*}) from the polymer, PCL, was identified. PCL also shows a peak with two protons (H_{c*}) at 1.4 ppm. By subtracting the latter from the first, one can calculate the amount of remaining monomer, CL, in the reaction mixture. The amounts of DXO and PDXO were calculated by comparing the peaks at 3.92 ppm (DXO) and 3.77 ppm (PDXO).

DXO was consumed slightly faster and after 10 h all the DXO had been polymerized (*Figure 2*). However, there was no great difference in conversion of the two

Table 2 Comparison of molecular weights obtained from g.p.c. with PCL calibration and from light scattering analysis

Polymer composition P(CL–DXO)	M_n[a] (s.e.c.)	M_n[b] (l.s.)
0–100	68 000	–
20–80	59 000	–
50–50	60 000	–
60–40	50 000	51 000
70–30	51 000	62 000
80–20	60 000	64 000
90–10	54 000	64 000
100–0	55 000	70 000

[a] Molecular weights obtained from s.e.c. measurements, recalculated to PCL calibration by using the Mark–Houwink equations
[b] Molecular weights obtained from light scattering analysis

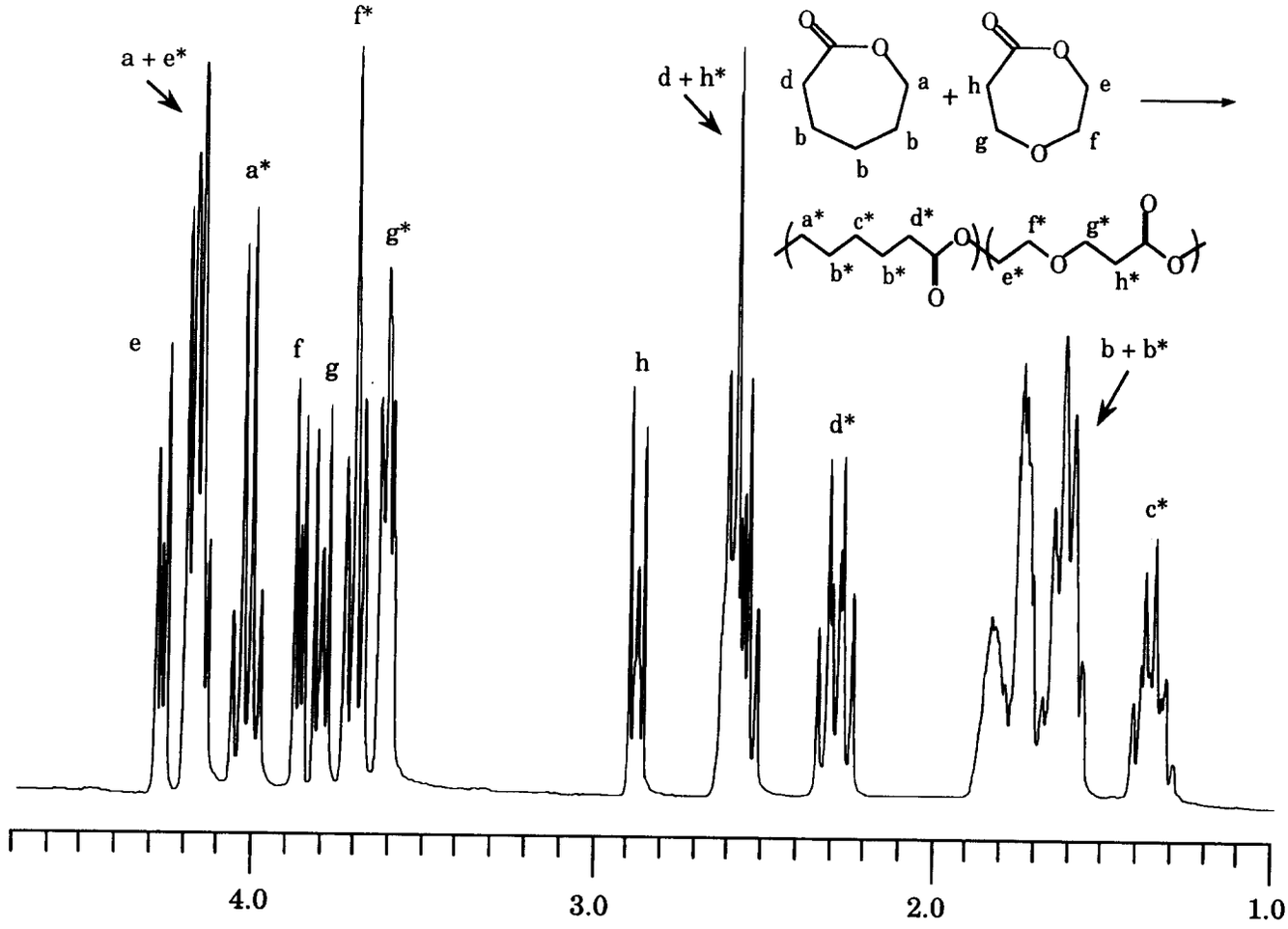


Figure 1 ^1H n.m.r. spectrum of P(CL-*co*-DXO) 50/50 with remaining monomer residues. Polymerization time 2 h; polymerization temperature 110°C

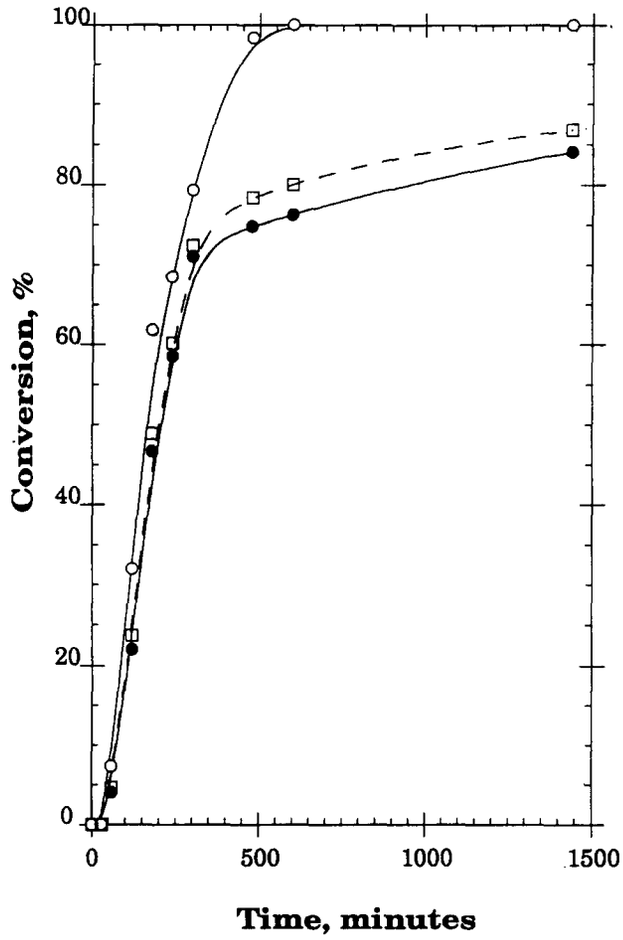


Figure 2 Conversion of CL and DXO as a function of time for P(CL-*co*-DXO) 80/20. Polymerization temperature 110°C. Symbols: (●) CL conversion; (○) DXO conversion; (□) total conversion

monomers, thus indicating that they had approximately the same reactivity. Full conversion was never reached, probably due to limited diffusion, since the polymerization was carried out in bulk.

Results from g.p.c. measurements on the copolymers from the conversion experiment are shown in *Figures 3* and *4*. The polydispersity is very narrow ($M_w/M_n \simeq 1.1$ after 120 min) at low monomer conversion, but increases up to 1.7 when the reaction is complete. The molecular weight increases constantly to reach a maximum after 24 h, which confirms that the chosen reaction parameters were correct.

These results indicate that, after the first 2 h, transesterification reactions occur, which increase both the molecular weight and the polydispersity. This is in complete agreement with earlier studies of $Sn(oct)_2$ (ref. 24).

The reactivity ratios were determined using the method of Kelen and Tüdös[25], which allows quite high conversions. The composition of the reaction mixture was determined as described above, and the conversion levels were below 40%. *Figure 5* shows the resulting plot of η against ξ for the CL/DXO system, where r_1 and r_2 are determined from the intercepts, $r_{CL}=0.6$ and $r_{DXO}=1.6$. These reactivity ratios show that the obtained polymers are ideal copolymers, since $r_1 r_2 = 1$. Furthermore, they indicate that the copolymers are truly of a random nature since both ratios are close to unity. Transesterification reactions will lead to an even more randomized structure.

Schindler *et al.*[15] determined the reactivity ratios in the copolymerization of dilactide and CL, under similar conditions (temperature and catalyst), and found that the reactivity of dilactide was significantly higher than that of CL ($r_{lactide}=34.7$, $r_{CL}=0.24$). In a recently published report[9] we have found the same large difference in reactivity ratios between dilactide and DXO ($r_{lactide}=10$, $r_{DXO}=0.1$). In both these cases, the copolymer obtained would possess a more blocky structure, but poly(CL-*co*-DXO) would have a completely random structure. The same random structure has been found by Vion *et al.*, who studied the copolymerization of CL and ε-methyl-ε-caprolactone[16].

Quantitative ^{13}C n.m.r. covering the carbonyl region of P(CL-*co*-DXO) 50/50 confirmed the randomized structure. Four different carbonyl peaks were identified, corresponding to the diads PCL–PCL, PCL–PDXO, PDXO–PDXO and PDXO–PCL. The homopolymer peaks (PCL–PCL and PDXO–PDXO) were only slightly separated from the copolymer peaks (PCL–PDXO, PDXO–PCL) owing to the similarity between the two monomers, and this therefore made integration difficult. However, it was clearly seen that all peaks were of the same magnitude, indicating a randomized structure.

The glass transition temperatures of the copolymers were determined by d.s.c. measurements. These experimental values were compared with the Fox equation (equation (1)), which predicts the glass transition temperatures of

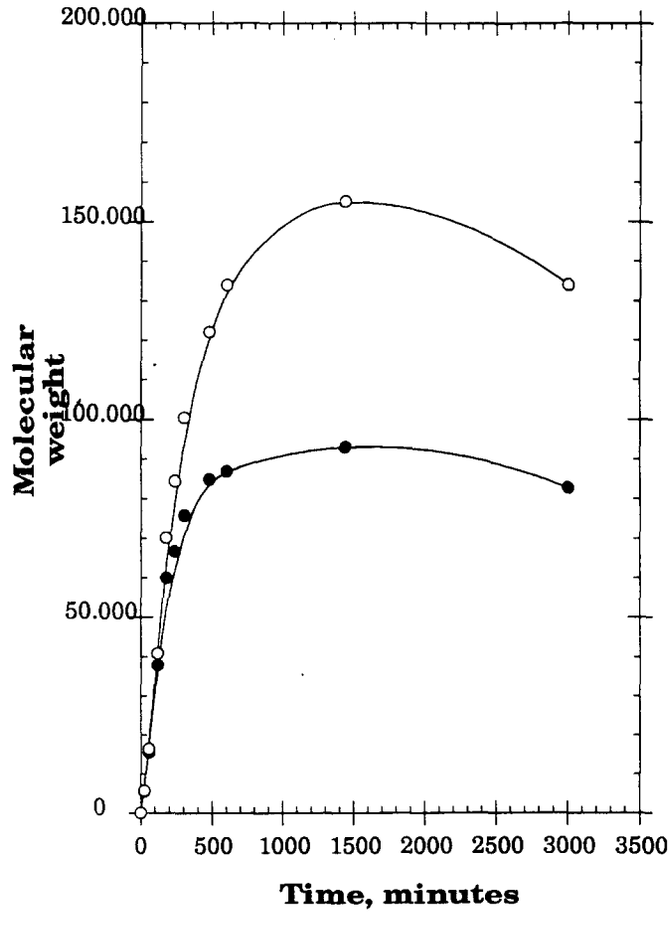


Figure 3 Molecular-weight dependence on polymerization time for P(CL-*co*-DXO) 80/20. Polymerization temperature 110°C. Symbols: (●) M_n; (○) M_w

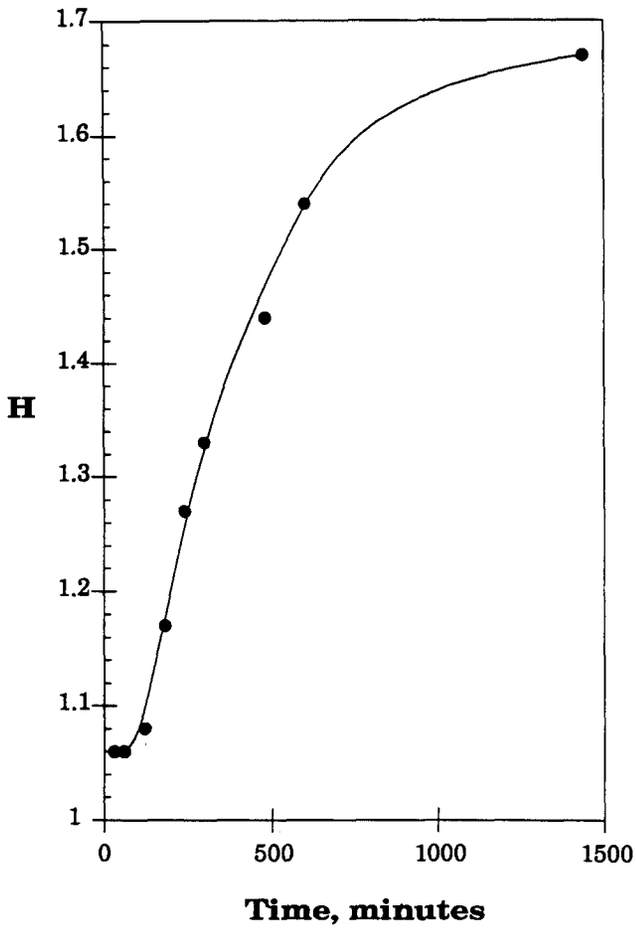


Figure 4 Polydispersity (H) dependence on polymerization time for P(CL-*co*-DXO) 80/20. Polymerization temperature 110°C

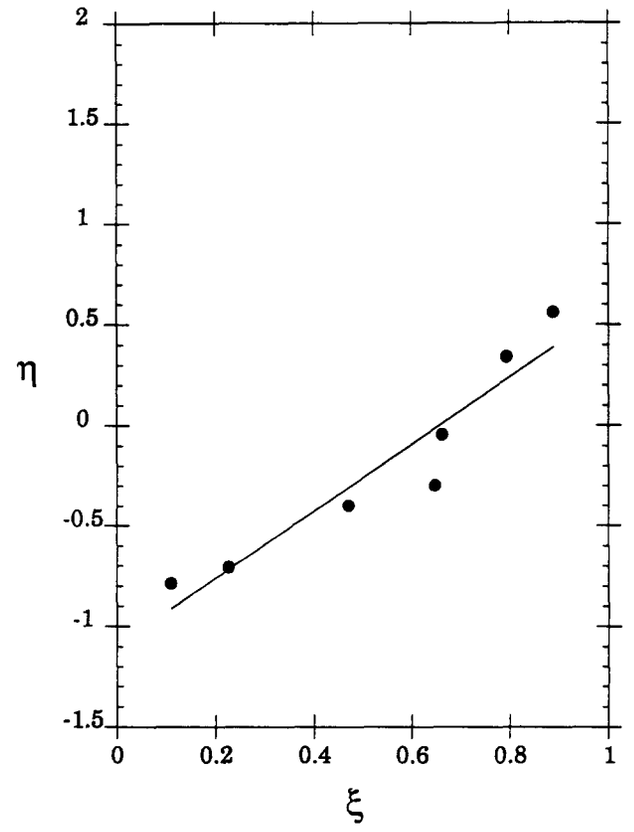


Figure 5 Reactivity ratio evaluation of the CL/DXO copolymer system. r_{CL} = intercept at $\xi = 1$, $-r_{CL}/\alpha$ = intercept at $\xi = 0$, where α is a constant dependent on the conversion

random copolymers[26]:

$$1/T_g = W_1/T_{g1} + W_2/T_{g2} \quad (1)$$

W_1 and W_2 are the weight fractions of the two monomers and T_{g1} and T_{g2} are the glass transition temperatures of the respective homopolymers.

As shown in *Figure 6* the experimental values are in general lower than the predicted values, even though they follow the same pattern of increasing T_g with increasing amount of DXO. The Fox equation is known to have limitations, since it does not account for factors like chemical structure and polymer chain mobility, and refinements of the equation have been presented[27].

The copolymers obtained were found to be opaque and to exhibit crystallinity as long as the amount of DXO did not exceed 40%. X-ray diffraction — and d.s.c. — measurements showed that crystallinity decreased with increasing DXO content (*Figure 7*). In the evaluation of the ΔH values obtained from d.s.c. thermograms, the reported enthalpy of fusion of 139.5 J g^{-1} for a 100% crystalline PCL was used[28].

These results are in agreement with earlier studies of other copolymers containing CL. Vion *et al.*[16] reported that for the random copolymer of CL and ε-methyl-ε-caprolactone the disappearance of crystallinity was observed at a ε-methyl-ε-caprolactone composition of 50%. In copolymers with a more blocky structure, e.g. poly(ε-caprolactone-*co*-L-lactide), the crystallinity also disappears when the concentration of the comonomer exceeds 40%. In both these cases the decrease in crystallinity is accompanied by a strong decrease in T_m.

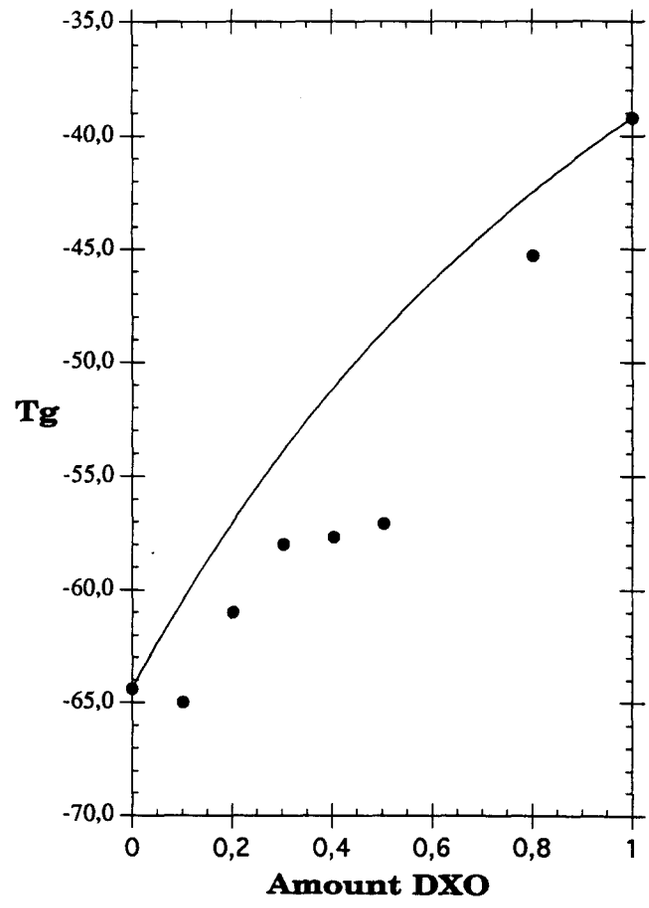


Figure 6 Glass transition temperature *versus* DXO content in the CL/DXO copolymer. The Fox equation is represented by the full curve

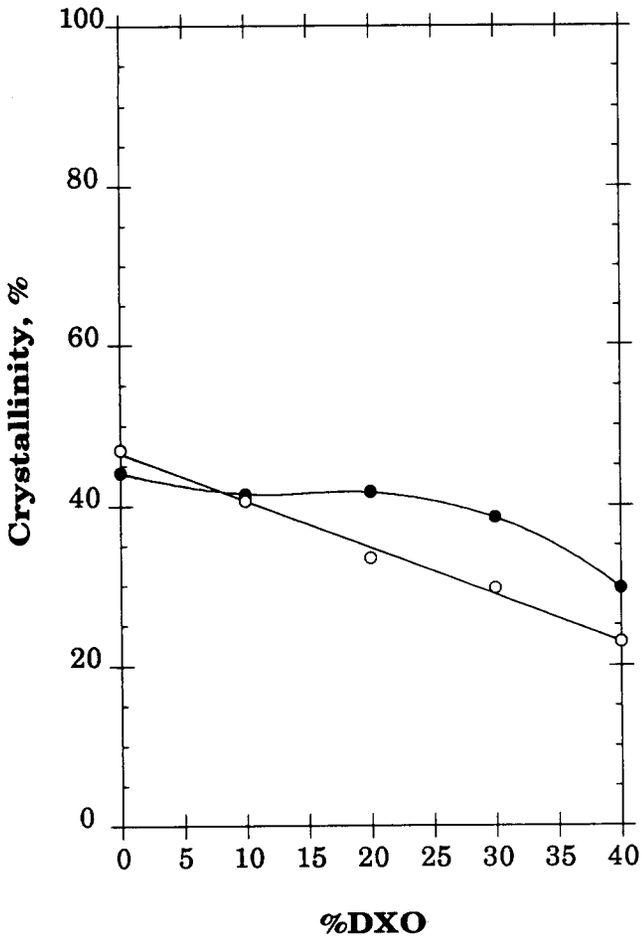


Figure 7 Crystallinity as a function of DXO content in the CL/DXO copolymers. Symbols: (○) crystallinity determined by d.s.c.; (●) crystallinity determined by X-ray diffraction measurements

The same decrease in T_m was also found with P(CL-*co*-DXO), as can be seen in *Figure 8*.

The copolymer containing 40% DXO showed quite a different thermogram, with an exotherm prior to the melting endotherm, possibly indicating recrystallization. All samples were cooled from the melt at a rate of 10°C min^{-1}, and then heated again at the same rate, but P(CL-*co*-DXO) 60/40 was the only sample showing this behaviour.

The decrease in crystallinity with increasing amount of DXO is not what has been reported earlier[20,21], although the assumption that the DXO units are being incorporated into the PCL crystals is correct, as will be shown in the next paragraphs. A decrease in crystallinity is also expected with this type of isomorphism, with only one crystallizable component. However, the decrease in crystallinity is expected to be more gradual than in the case of random copolymers incapable of forming mixed crystals[22].

The depression of the melting temperature T_m with increasing amount of DXO can be expressed by the Flory equation[29]:

$$1/T_m - 1/T_m^\circ = -(R/\Delta H)\ln x \qquad (2)$$

where T_m is the melting temperature of a random copolymer of mole fraction x, T_m° is the melting temperature of the corresponding homopolymer, R is the gas constant and ΔH is the enthalpy of fusion of the homopolymer crystal. According to Flory the copolymer is made of sequences of A units, which are able to crystallize, and sequences of B units, which do not crystallize under chosen conditions and which are completely excluded from the crystal. Equation (2) has been found to predict depressions of the melting temperature that are too low[30].

Baur has presented a refinement of the Flory equation[31], which takes the sequence length distribution into consideration:

$$1/T_m - 1/T_m^\circ = -(R/\Delta H)(\ln x - 1/\xi) \qquad (3)$$

where ξ is the average sequence length. For a random copolymer[30], ξ can be set to:

$$\xi = \frac{1}{2x(1-x)} \qquad (4)$$

If ξ is large, equation (3) gives the same results as equation (2), but with finite values of ξ a greater decrease in the melting temperature is observed. The Baur equation also assumes that the B units are rejected from the crystal, and this equation has been found to give satisfactory results for copolymers where one can guarantee exclusion of B units[30,31]. If this were the case, that the DXO units are completely rejected from the crystals, one would expect a better correlation between the experimental values and equation (3) than is obtained in *Figure 9*. Instead, the experimental data fall below those predicted by the Baur equation. This can be interpreted as indicating that some DXO units are incorporated in the PCL crystals.

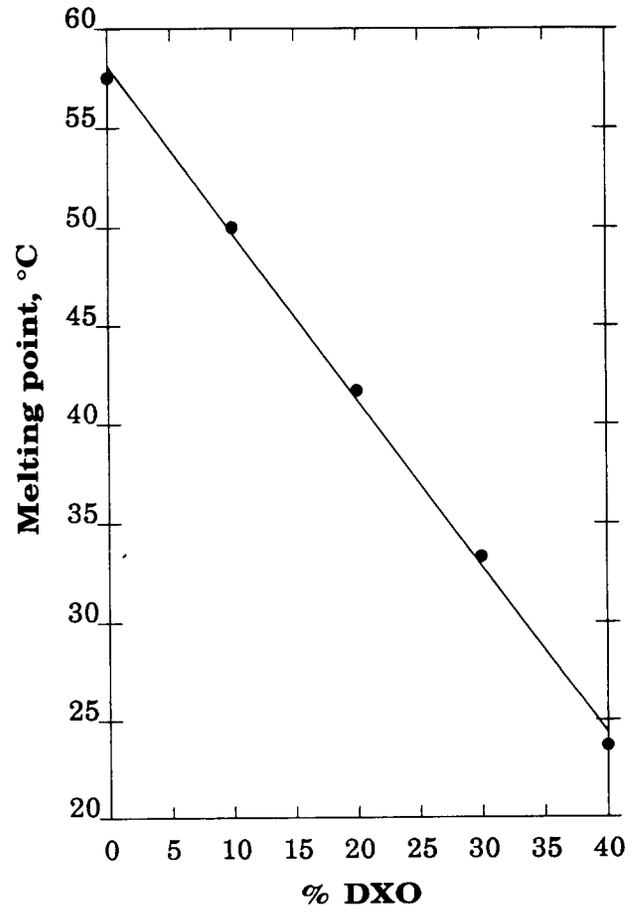


Figure 8 Melting temperature *versus* DXO content in the CL/DXO copolymers

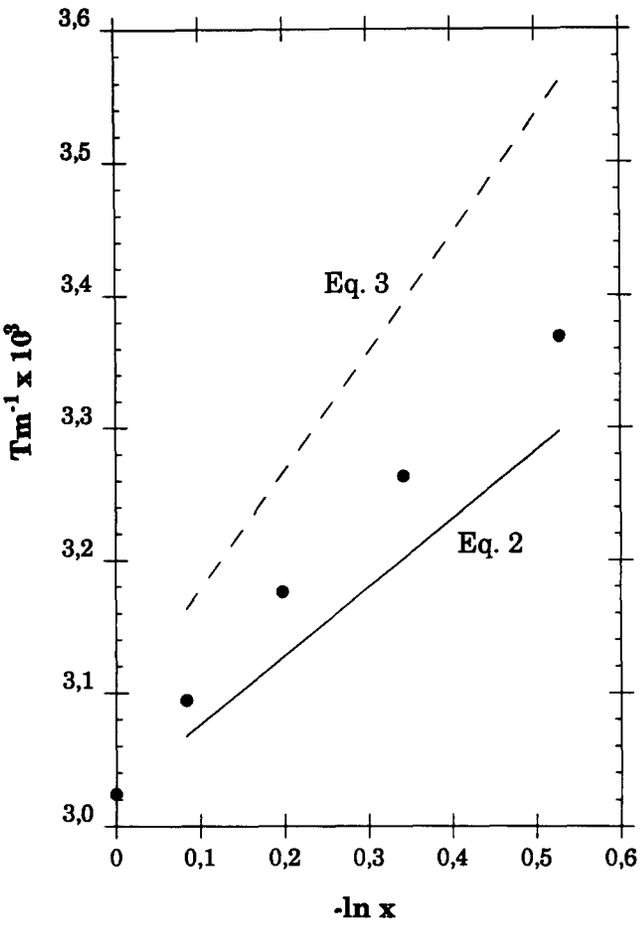


Figure 9 Analysis of the melting-point (T_m) data of P(CL-*co*-DXO) copolymers using equations (2) and (3), compared with experimental data (●). For both equations, ΔH was taken equal to 16.1 kJ mol^{-1} (ref. 28) and $R = 8.31$ J mol^{-1} K^{-1}

Table 3 Analysis of DXO insertion in the crystal structure

CL content (mole fraction)	T_m (exp) (K)	Crystallizable units (mole fraction)	DXO inserted in crystal (%)
0.920	323	0.954	42
0.820	315	0.897	43
0.710	306	0.832	42
0.590	297	0.748	39
		average	42

Eby has derived an expression for the depression of T_m, assuming a partial insertion of the non-crystallizable B unit[32,33]. Eby treated those incorporated B units as crystalline defects and an excess heat is therefore associated with the formation of such defects:

$$T_m = (1 - Ex_B)T_m^\circ \quad (5)$$

where $E = \Delta H_d/\Delta H_m$. The term ΔH_d represents the excess heat of transition associated with the formation of one defect per mole of B units and ΔH_m the enthalpy of fusion of the homopolymer per mole of A units. The best fit to the experimental data was obtained using an E value of 0.26, which seems to be a reasonable result. Goulet *et al.* reported a value of 0.21 for nascent samples of copolymers of CL and ε-methyl-ε-caprolactone, where 53% of the non-crystallizable component was inserted in the PCL crystals[34]. Generally, E increases with a decrease in the fraction of units inserted.

The Eby equation does not allow a quantitative determination of the fraction of DXO units inserted in the crystals. For this purpose the Baur equation was used instead, despite the fact that it is an exclusion model. This can be done, since the two monomers are similar and making the same assumptions made by Vion *et al.*[16] and Goulet *et al.*[34].

If this is done, the Baur equation can be used to calculate the mole fraction of crystallizable comonomer that would be required to account for the experimental T_m. The result of this analysis is reported in *Table 3*. It is shown that an average of 42% of the DXO units are incorporated into the PCL crystals.

It should be pointed out that the experimental values do not represent equilibrium melting.

Whether the copolymers obtained and their crystalline structure really should be treated as isomorphic is doubtful. Studies of the X-ray diffraction patterns of PCL and copolymers thereof indicate that the unit-cell dimensions do not change particularly with composition, since the positions and the number of peaks remain constant. A more accurate way of describing the copolymers is as PCL crystals, where the incorporated DXO monomer units act as impurities that form nuclei around which spherulites can grow. The larger the concentration of DXO, the larger the number of nuclei formed, which would lead to smaller average spherulite radii.

CONCLUSIONS

Random copolymers of ε-caprolactone and 1,5-dioxepan-2-one, P(CL-*co*-DXO), with high molecular weight, can be synthesized by ring-opening polymerization, using stannous 2-ethylhexanoate as a catalyst. The reactivity ratios in this copolymerization are $r_{CL} = 0.6$ and $r_{DXO} = 1.6$ at 110°C, leading to a true random structure since both reactivity ratios are close to unity. Transesterification reactions give an even more randomized structure.

When the amount of the amorphous component, DXO, does not exceed 40 mol%, the copolymer obtained exhibits crystallinity. Both crystallinity and melting temperature decrease with increasing amount of DXO. From the melting-point depression data and by using the Baur equation, it is concluded that about 40% of the DXO comonomer units of P(CL-*co*-DXO) are incorporated into the PCL crystals.

P(CL-*co*-DXO) could be a useful material in different medical applications, such as drug delivery systems. By copolymerization with DXO, one may overcome some of the disadvantages of PCL, e.g. the long degradation time. Reduction of the melting point below body temperature is known to enhance the rate of degradation of PCL[15]. By introducing flexible DXO units in the PCL crystal structure, one may expect further enhancement of the degradation rate.

ACKNOWLEDGEMENTS

MSc Torbjörn Lindberg is gratefully thanked for his help with the X-ray measurements. This work was financially supported by the Swedish Board for Technical Development (NUTEK).

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