## Polylactones. 13. Transesterification of Poly(*L*-Lactide) with Poly(Glycoude), Poly(β-Propio-Lactone), and Poly[ε -Caprolactone)

Hans R. Kricheldorf[a]; Ingrid Kreiser[a]

[a] Institut fur Technische und Makromoleculare Chemie, Hamburg 13, Federal Republic of Germany

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# POLYLACTONES. 13. TRANSESTERIFICATION OF POLY(L-LACTIDE) WITH POLY(GLYCOLIDE), POLY($\beta$-PROPIO-LACTONE), AND POLY($\epsilon$-CAPROLACTONE)

HANS R. KRICHELDORF and INGRID KREISER

Institut für Technische und Makromoleculare Chemie
D-2000 Hamburg 13, Federal Republic of Germany

## ABSTRACT

Homogeneous blends of poly(L-lactide) ($\bar{M}_n$ = 30 000 to 40 000) and poly($\beta$-propiolactone) or poly($\epsilon$-caprolactone) were prepared in solution. The solvent-free blends were subjected to transesterification catalyzed by means of methyl triflate, triflic acid, boron trifluoride, or tributyltin methoxide at 100 or 150°C. At 100°C, transesterification was barely detectable even after 96 h. When poly($\beta$-propiolactone) was used as the reactant at 150°C, degradation was faster than transesterification regardless of the catalyst. The same negative result was obtained for heterogeneous blends of poly(L-lactide) and poly(glycolide). In the case of poly($\epsilon$-caprolactone), copolyesters with slightly blocky sequences were obtained with tributyltin methoxide as catalyst, whereas the acidic catalysts caused rapid degradation. The copolyesters were characterized by means of ^{1}H-NMR spectroscopy with regard to their molar composition, by means of ^{13}C-NMR spectroscopy with regard to their sequences, and by means of differential scanning calorimetry with regard to crystallinity.

## INTRODUCTION

Copolyesters of lactic acid and glycolic acid or lactic acid and ε-hydroxy-caproic acid have found considerable interest and technical application as bio-degradable materials for various pharmaceutical or medical applications. In particular, copolyesters of lactic and glycolic acid proved to be useful as medical sutures [1, 3]. Such copolyesters are usually prepared by copolymerization of cyclic monomers, such as $L,L$-lactide, glycolide, and ε-caprolactone. An alternative approach might be transesterification of the corresponding homopolyesters. This approach is of interest, because the synthesis of low molecular weight poly($L$-lactide) by condensation of free lactic acid is less expensive than isolation and polymerization of $L,L$-lactide. The present work was therefore aimed at transesterification of poly($L$-lactide) with poly(glycolide), poly(β-propiolactone), and poly(ε-caprolactone).

## EXPERIMENTAL

### Materials

$L$-Lactide was a gift of Boehringer GmbH (Ingelheim, FRG). It was recrystallized from dry ethyl acetate and dried over $P_4O_{10}$ *in vacuo*. Poly(ε-caprolactone) with a melting point of 60°C was purchased from Aldrich Co. (St. Louis, Missouri, U.S.A.). By means of viscosity measurements [4], its $\bar{M}_w$ was found to be 30 000.

### Polymerization of $L$-Lactide

Dried and recrystallized $L$-lactide (0.5 mol) was mixed with 10 mmol tributyltin acetate in a 100-mL flask with a ground-glass joint. The flask was closed with a glass stopper and a steel spring and was thermostated at 150°C. After 2 days the reaction mixture was dissolved in 900 mL dichloromethane and poured into 10 L cold methanol. The polyester was isolated and dried at 40°C/1.2 kPa. The three batches prepared in this way had $\bar{M}_n$ in the range of 36 000 to 46 000, as determined by viscosity measurements [5].

### Transesterification

Poly($L$-lactide) (40 mmol) and poly(ε-caprolactone) (40 mmol) were dissolved in 60 mL dry dichloromethane. Freshly prepared 1 $M$ catalyst solution

in dry dichloromethane (0.5 or 0.2 mL) was added. The solvent was evaporated, and the reaction mixture was thermostated under nitrogen in a closed 100-mL flask. After a given time the reaction mixture was dissolved in 60 mL dichloromethane and poured into ~500 mL cold methanol. The transesterification product was isolated by filtration and dried at 60°C/1.2 kPa.

## Measurements

The $^{13}$C-NMR spectra were measured on a Bruker MLS-300 FT spectrometer in 10-mm o.d. sample tubes. The transesterification products (300 mg) were dissolved in CDCl$_3$ (2 mL) containing TMS as the internal shift standard. The pulse width was ~45° and the digital resolution 8K/5000 Hz. A relaxation delay of 2 s was used and up to 1600 transients were accumulated. The $^1$H-NMR spectra were measured on the same spectrometer in 5-mm o.d. sample tubes. For these measurements, solutions of 50 mg of the transesterification products in 1 mL CDCl$_3$ were used.

A Perkin-Elmer DSC-4 machine was used for the DSC measurements with a heating rate of 20°C/min and a cooling rate of -320°C/min.

The inherent viscosities in CHCl$_3$ were determined at 30°C by means of automated Ubbelohde viscometers.

The optical rotations were measured at 25°C on a Perkin-Elmer Polarimeter Md 243 in 1-mL sample tubes 10 cm long.

## RESULTS AND DISCUSSION

### Transesterification

Previous studies of the copolymerization of glycolide with various lactones [6, 7] demonstrated that cationic polymerization initiators are also good transesterification catalysts. Furthermore, tin alkoxides, which initiate the polymerization by nonionic insertion mechanisms, were found to be excellent transesterification catalysts [8, 9]. Therefore, tributyltin methoxide and three different cationic polymerization initiators were used in this work. Anionic polymerization initiators such as metal alkoxides, phenoxides, or carboxylates were avoided because they involve a high risk of racemization of poly(L-lactide) [10]. It is obvious that compounds that can bring about transesterification of polylactones can also bring about their degradation by "back-biting." For both kinetic and thermodynamic reasons, higher temperatures and lower concentrations favor the formation of cyclic oligomers at

the expense of linear polymers or copolymers. Hence, it is expected that successful synthesis of copolyesters via transesterification of homopolyesters requires high concentrations and low temperatures. The highest possible concentration is that of the pure polyesters. In order to obtain homogeneous blends of pure polyesters, the polyesters were dissolved and mixed in dichloromethane, and the solvent was removed *in vacuo* before transesterification. In the case of poly(glycolide), suspensions of finely powdered starting material in concentrated solutions of poly(L-lactide) or in molten poly(L-lactide) were subjected to transesterification, because high molecular weight poly(glycolide) is insoluble in all inert solvents.

The suspension of finely powdered poly(glycolide) in molten poly(L-lactide) was heated at 150°C with the following catalysts: triflic acid, methyl triflate, boron trifluoride etherate, or tributyltin methoxide. A molar ratio of monomer units and catalyst of 200:1 was used, and the reaction time was varied between 24 and 72 h. In all cases, complete degradation of poly(L-lactide) was observed whereas a part of the crystalline poly(glycolide) remained unchanged, evidenced by IR spectroscopy and differential scanning calorimetry (DSC). Copolyesters could never be isolated. Thus, it may be concluded that, in the absence of a suitable solvent, a satisfactory transesterification may not be expected for high molecular weight polyglycolide.

Further experiments were conducted with blends of poly(ε-caprolactone) and poly(L-lactide). Due to the relatively low melting point of poly(ε-caprolactone), the reaction temperature could be lowered to 100°C. The same catalysts and molar ratios of monomer units and catalysts were used. The lower temperature prevented rapid degradation of both polyesters, yet it also prevented transesterification. Blends of homopolyesters were recovered from all experiments with "yields" in the range of 88 to 96%. A clear-cut distinction between blends of homopolyesters and copolyesters was achieved by means of $^{13}$C-NMR spectroscopy and DSC measurements. As reported previously [6-8] and discussed below, the carbonyl signals in the $^{13}$C-NMR spectra of polylactones permit a straightforward characterization of the sequences of copolylactones. The DSC traces of blends of homopolyesters display the two characteristic melting endotherms.

When the reaction temperature was raised to 150°C, rapid degradation occurred when triflic acid or methyl triflate was used as the catalyst (Nos. 1-7, Table 1), so that copolyesters could never be isolated. Better results were obtained with boron trifluoride etherate (Nos. 8-11, Table 1). At reaction times of 48 and 72 h, copolyesters with relatively long blocks of lactidyl and ε-oxycaproyl units were isolated. However, longer reaction times again caused complete degradation of the polyesters, so that copolyesters with nearly random sequences were not obtained. Further progress

TABLE 1. Cationic Transesterification of Poly(L-Lactide) and
Poly($\epsilon$-Caprolactone) at 150°C

| No. | Catalyst | M/C[a] | Time, h | Yield, % | $\eta_{inh}$,[b] dL/g | $\bar{L}_{cap}$[c] |
|-----|----------|--------|---------|----------|-----------------------|--------------------|
| 1 | $CF_3SO_3H$ | 200 | 8 | 0 | — | — |
| 2 | $CF_3SO_3H$ | 200 | 24 | 0 | — | — |
| 3 | $CF_3SO_3H$ | 200 | 72 | 0 | — | — |
| 4 | $CF_3SO_3CH_3$ | 200 | 8 | 91 | 0.41 | |
| 5 | $CF_3SO_3CH_3$ | 200 | 24 | 88 | 0.36 | |
| 6 | $CF_3SO_3CH_3$ | 200 | 48 | 0 | — | — |
| 7 | $CF_3SO_3CH_3$ | 200 | 72 | 0 | — | — |
| 8 | $BF_3 \cdot OEt_2$ | 200 | 8 | 95 | 0.36 | |
| 9 | $BF_3 \cdot OEt_2$ | 200 | 48 | 86 | 0.32 | 11 |
| 10 | $BF_3 \cdot OEt_2$ | 200 | 72 | 80 | 0.16 | 6 |
| 11 | $BF_3 \cdot OEt_2$ | 200 | 120 | 0 | — | 0 |

[a]Molar ratio of monomer units to catalyst.
[b]Measured at 10 g/L in chloroform at 30°C.
[c]Average block lengths of $\epsilon$-hydroxycaproyl units calculated from the
^{13}C-NMR spectra according to Eq. (1).

in this direction could be made by means of tributyltin methoxide at 150°C
(Table 2). In this series of experiments a continuous decrease of the average
block length of the homogeneous blocks (calculated according to Eqs. 1 or 2
below) was detectable with increasing time. The lowest block length of $\epsilon$-oxy-
caproyl units ($\bar{L}_{cap}$ = 3.5), found after 96 h, comes close to the value of a
random sequence ($\bar{L}_{cap}$ = 2.0). The characterization of these copolyesters
is discussed below in more detail.

　　Finally, it is noteworthy that transesterification experiments conducted
with blends of poly(L-lactide) and poly($\beta$-propiolactone) under the condi-
tions of Tables 1 and 2 yielded either blends of homopolyesters (after short
times, <24 h) or resulted in complete degradation.

TABLE 2. Transesterification of Poly(*L*-Lactide) and Poly(ε-Caprolactone) with Tributyltin Methoxide at 150°C

| No. | M/C[a] | Time, h | Yield, % | $\eta_{inh}$,[b] dL/g | Lac/Cap[c] | $\bar{L}_{cap}$[d] | $[\alpha]_D^{20}$[e] |
|-----|--------|---------|----------|--------------|------------|-------------------|----------------------|
| 1 | 200 | 24 | 86 | 0.62 | 1.05 | 13.3 | 155.0 |
| 2 | 200 | 48 | 74 | 0.55 | 1.02 | 6.0 | 144.8 |
| 3 | 200 | 72 | 67 | 0.49 | 1.05 | 5.1 | 139.4 |
| 4 | 200 | 96 | 64 | 0.45 | 0.99 | 3.5 | 138.5 |

[a]Molar ratio of monomer units and catalyst.

[b]Measured at 2 g/L in chloroform at 30°C.

[c]Molar ratio of lactidyl and ε-hydroxycaproyl units in the isolated copolyester as determined by ^{1}H-NMR spectroscopy.

[d]Average block lengths of ε-hydroxycaproyl units.

[e]Measured at 10 g/L in chloroform at 25°C.

### Characterization of Lactide/ε-Caprolactone Copolyesters

The copolyesters obtained with tributyltin methoxide at 150°C (Table 2) were characterized with regard to their monomer composition by means of ^{1}H-NMR spectroscopy. As demonstrated in Fig. 1, the signals of lactidyl and ε-oxycaproyl units do not overlap in high-resolution ^{1}H-NMR spectra, so that accurate integration is feasible. The results indicate that the degradation process is not selective for one sort of polyester, so that the molar ratio of lactidyl and ε-oxycaproyl units in the isolated copolyesters is nearly identical to that of the starting material.

The analysis of sequences, and thus the evidence for transesterification, was obtained by ^{13}C-NMR spectroscopy. As demonstrated in a previous part of this series, the carbonyl signals are most sensitive to sequence effects and allow an easy distinction between a two-block copolyester and a random copolyester [8]. The signal pattern of Lac/Cap copolyesters is similar to that of the previously discussed Glyc/Cap copolyesters [6, 7]. Only the signals of the Cap-Lac-Lac and Lac-Lac-Cap triads display a more complex pattern and are difficult to distinguish. However, the carbonyl signals of the ε-oxycaproyl units show a dyad splitting with a fine structure due to triad effects (Fig. 2B). The signals of the homologous blocks (x and y in Fig. 2) can easily be assigned by comparison with the carbonyl signals of the corresponding homopolyesters.
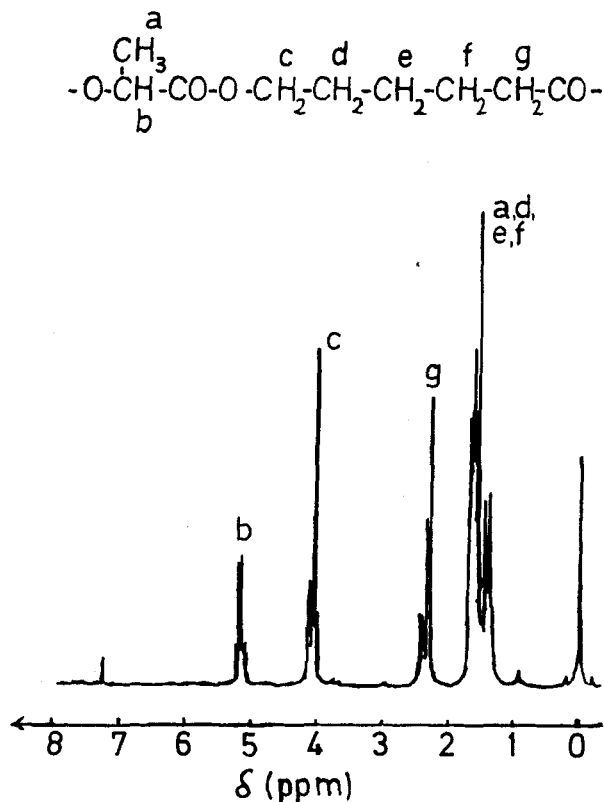
$$\overset{a}{\underset{\underset{b}{|}}{CH_3}}$$

$$-O\text{-}\overset{}{\underset{b}{CH}}\text{-}CO\text{-}O\ \overset{c}{-}CH_2\text{-}\overset{d}{C}H_2\text{-}\overset{e}{C}H_2\text{-}\overset{f}{C}H_2\text{-}\overset{g}{C}H_2\text{-}CO-$$



FIG. 1. 100 MHz $^1$H-NMR spectrum of the copolyester obtained by tri-butyltin methoxide-initiated transesterification of poly(L-lactide) and poly-(e-caprolactone) after 96 h at 150°C.

Thus, the average block lengths can be calculated according to Eq. (1) for $\epsilon$-oxycaproyl units or according to Eq. (2) for lactidyl units. As expected for a monomer ratio of 1:1, nearly identical $\bar{L}_{cap}$ and $\bar{L}_{lac}$ values were found.

$$\bar{L}_{cap} = \frac{I_{CC}}{I_{CL}} + 1 = \frac{I_y}{I_y{'}} + 1, \tag{1}$$

Lac-O-CH(CH$_3$)-$\overset{x}{C}$O-Lac

Cap-O-CH(CH$_3$)-$\overset{x'}{C}$O-Lac

Cap-O-(CH$_2$)$_5$-$\overset{y}{C}$O-Cap     Lac-O-CH(CH$_3$)-$\overset{x''}{C}$O-Cap

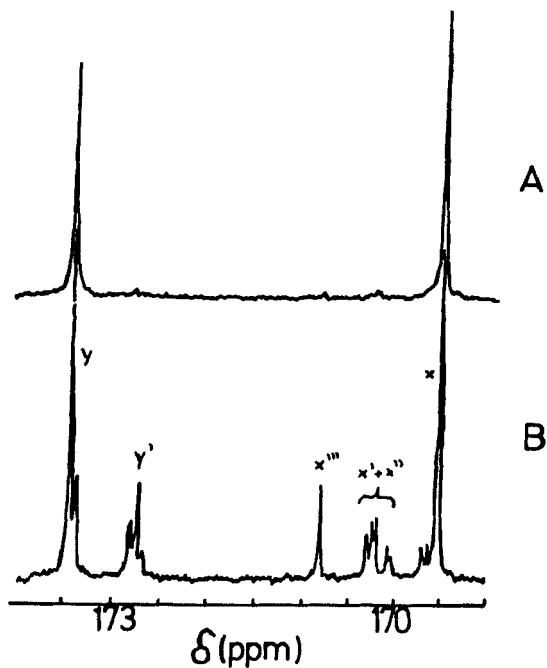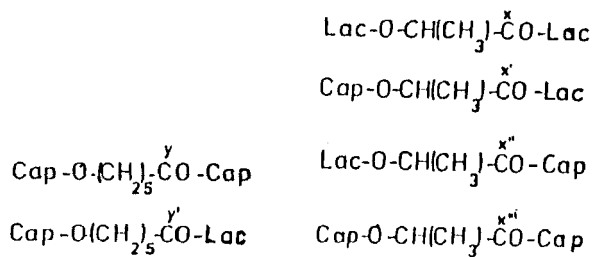Cap-O-(CH$_2$)$_5$-$\overset{y'}{C}$O-Lac     Cap-O-CH(CH$_3$)-$\overset{x'''}{C}$O-Cap



FIG. 2. 90.5 MHz $^{13}$C-NMR spectra (carbonyl signals of the copolyesters obtained by tributyltin methoxide-initiated transesterification of poly(L-lactide) and poly(ε-caprolactone): (A) after 24 h at 150°C (No. 1, Table 2); (B) after 96 h at 150°C (No. 4, Table 2).
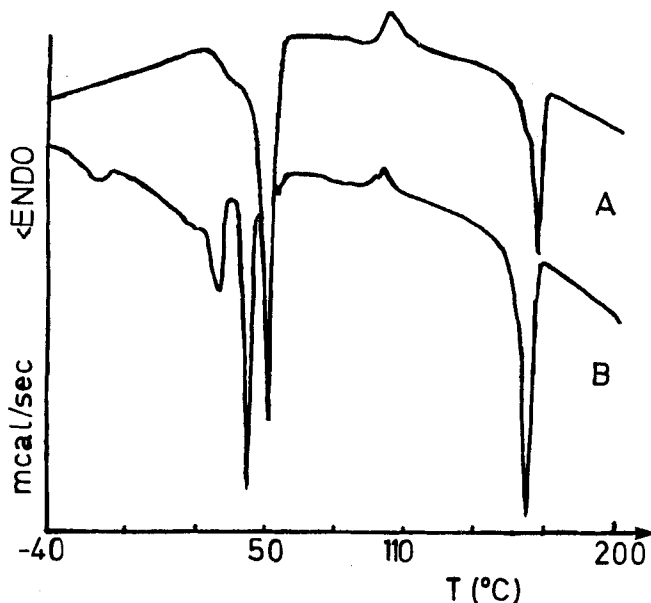
FIG. 3. DSC measurements (heating rate 20°C/min) of copolyesters obtained by tributyltin methoxide-initiated transesterification of poly(L-lactide) and poly(ε-caprolactone): (A) after 24 h at 150°C (No. 1, Table 2); (B) after 96 h at 150°C (No. 4, Table 2).

$$\bar{L}_{lac} = \frac{I_{LLL} + (I_{LLC} + I_{CLL})/2}{I_{CLC} + (I_{LLC} + I_{CLL})/2} + 1 = \frac{I_y + (I_{y'} + I_y'')/2}{I_y'' + (I_{y'} + I_y'')/2} . \tag{2}$$

The average block lengths thus obtained do not of course, give any information on block-length distribution or interchain chemical heterogeneity. Fractionation is the most useful approach to elucidate the extent of chemical heterogeneity. Unfortunately, the solubilities of poly(L-lactide) and poly-(ε-caprolactone) are nearly identical, so that fractionation based on chemical heterogeneity is difficult to achieve. However, when the samples of Table 2 were examined, DSC traces were found that display sharp melting endotherms both for crystallites built up by poly(ε-caprolactone) blocks and for crystallites built up by poly(L-lactide) blocks (Fig. 3). Such DSC traces do not fit in with a homogeneously transesterified material, but agree better with the
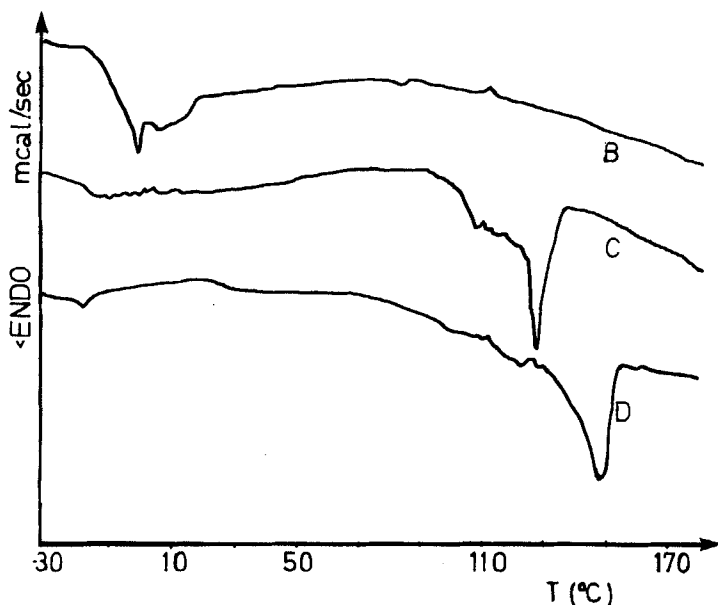
FIG. 4. DSC measurements (first heating, heating rate 20°C/min) of co-polyesters prepared by tributyltin methoxide-initiated copolymerizations of *L,L*-lactide and ε-caprolactone after 24 h at 120°C, (B) Lac/Cap = 2:1, (C) Lac/Cap = 4:1, (D) Lac/Cap = 8:1.

presence of relatively long homogeneous blocks (*DP* ≥ 10). This interpretation is supported by a comparison with Lac/Cap copolyesters prepared by tributyltin-methoxide-initiated copolymerization of *L,L*-lactide, and ε-caprolactone at 100°C. As demonstrated previously, perfectly random sequences are obtainable in this way. The DSC curves obtained from such random co-polyesters with Lac/Cap ratios of 1:1 and 2:1 show that melting endotherms are entirely absent in the first heating trace (Fig. 4, B) and also in the second heating traces (Fig. 5, A + B). The copolyesters with molar ratios of 4:1 and 8:1 display melting endotherms in their first heating trace (Fig. 4, C and D), yet these endotherms are broad compared to those of Fig. 3 and appear at lower temperatures. The endotherms are even absent in the second heating traces (Fig. 5, C + D), which are also interesting because they illustrate how the glass-transition temperature increases with the Lac/Cap ratio.
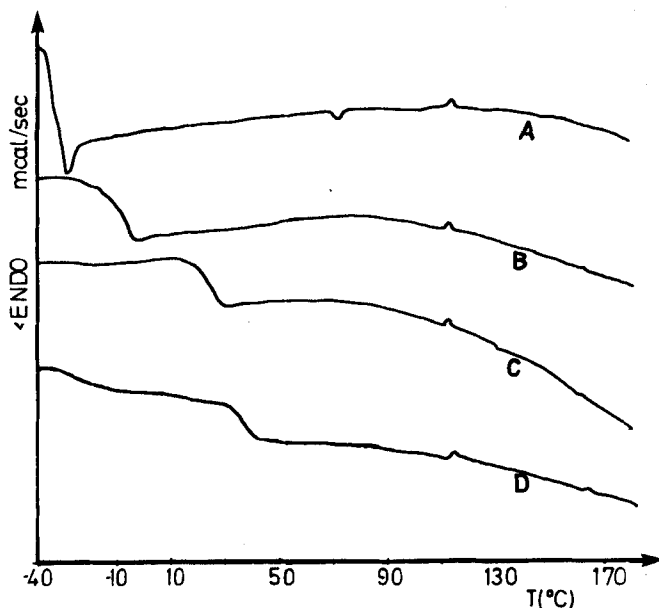
FIG. 5.  DSC measurements (second heating, heating rate 20°C/min) of copolyesters prepared by tributyltin methoxide-initiated copolymerization of $L,L$-lactide and $\epsilon$-caprolactone after 24 h at 120°C, (A) Lac/Cap = 1:1, (B) Lac/Cap = 2:1, (C) Lac/Cap = 4:1, (D) Lac/Cap = 8:1.

Thus, these results permit the conclusion that transesterification of poly-($L$-lactide) does not give an easy access to entirely random copolylactones. Yet, copolyesters with a certain degree of randomness and broad interchain heterogeneity can be synthesized in this way, and such copolyesters are diff-cult to obtain by copolymerization of $L,L$-lactide and other lactones. Thus, from a preparative point of view, transesterification of polylactones and co-polymerization of lactones are complementary methods rather than alter-natives.

## ACKNOWLEDGMENTS

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