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# DIRECT COPOLYCONDENSATION OF ϵ-CAPROLACTONE WITH δ-VALEROLACTONE IN THE ABSENCE OF CATALYSTS

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**Abstract**—Waxy and pasty copolymers of ϵ-caprolactone (CL) and δ-valerolactone (VL) with relatively low molecular weights were synthesized by direct copolycondensation without catalysts in the presence of water at 200° under nitrogen. This reaction proceeds by direct condensation between two linear monomers, i.e. linear 6-hydroxycaproic acid and linear 5-hydroxyvaleric acid produced by hydrolysis of the cyclic CL and VL, respectively. It was found by $^1$H-NMR that the molar ratio in the copolymer is markedly different from that in the initial monomer mixture; the CL contents in the copolymers are *ca* 92, 78, 71, 53 and 19 mol% for initial CL contents in the feed of 85, 70, 50, 30 and 15 mol%, respectively. The crystallinities of the copolymers were determined by differential scanning calorimetry and X-ray diffraction. Each homopolymer had relatively high melting point but it showed a marked decrease by copolycondensation, reaching a minimum for equimolar composition of copoly(CL/VL). This effect is closely related to the distortion of crystal structure because of a rapid decrease in block lengths of ϵ-oxycaproyl and δ-oxyvaleryl units in the copolymer, the so-called sequence effects.

## INTRODUCTION

The ring-opening homo-and co-polymerizations of lactones in the presence of various catalysts have been studied by many workers, giving high molecular weight polyesters [1–4]. We have synthesized low molecular weight polyesters by direct polycondensation in the absence of catalysts, using α-hydroxy acids and lactones, e.g.

copoly(D-lactic acid/L-lactic acid) [5];
copoly(L-lactic acid/ϵ-caprolactone) [6];
copoly(L-lactic acid/δ-valerolactone) [7, 8];
copoly(L-lactic acid/γ-butyrolactone) [9];
copoly(L-lactic acid/DL-mandelic acid) [10]; and
copoly(glycolic acid/lactones) [11].

These polyesters have found increasing interest for agricultural, medical and pharmaceutical applications, especially for application in drug delivery systems [12] because of low immunogeneity and biodegradability even in the human body. Such low molecular weight polyesters are characterized by easy processing without use of organic solvents and by good biocompatibility of the materials obtained by polymerizing in the absence of organic solvent and initiator. The most striking feature of such materials is easy control of biodegradation, in which the degradation pattern can be divided into three types, parabolic-type, linear-type and S-type.

For low molecular weight poly(lactones), the reaction generally proceeds by direct condensation of linear monomers produced by hydrolysis of the cyclic lactones. In this case, the balance between the rate of hydrolysis of lactones and the rate of condensation of the hydrolysis products may play an important role for the nature of polymer materials such as molecular weight, block length of each unit in the copolymer (sequence effect), molar ratio of the copolymer, crystallinity, biodegradability and morphologies (waxy, pasty and solid). However, in a copolycondensation between two lactones, the synthetic studies give very little information. In this study, we report the reaction mechanism for a copolymer for ϵ-caprolactone (CL: a seven-membered cyclic monomer) and δ-valerolactone (VL: a six-membered cyclic monomer) by direct copolycondensation in the absence of catalysts, deduced from results of studies by $^1$H-NMR, $^{13}$C-NMR, gel permeation chromatography (GPC), differential scanning calorimetry (DSC) and X-ray diffraction.

## EXPERIMENTAL PROCEDURES

### *Materials*

CL and VL were purchased from Tokyo Kasei Kogyo Co. Ltd. All other chemicals were special grades.

### *Synthesis of copolyesters*

The direct copolycondensation of CL and VL in the presence of water without catalysts was performed as follows. A mixture of 50 g of CL and VL, with desired composition, and 10 g of water was charged into a glass ampoule (25 mm i.d.) and then $N_2$ was bubbled into the monomer at a rate of 200 ml/min. The ampoule was then immersed in an oil bath at 200°. The resulting copolyesters were used without purification.

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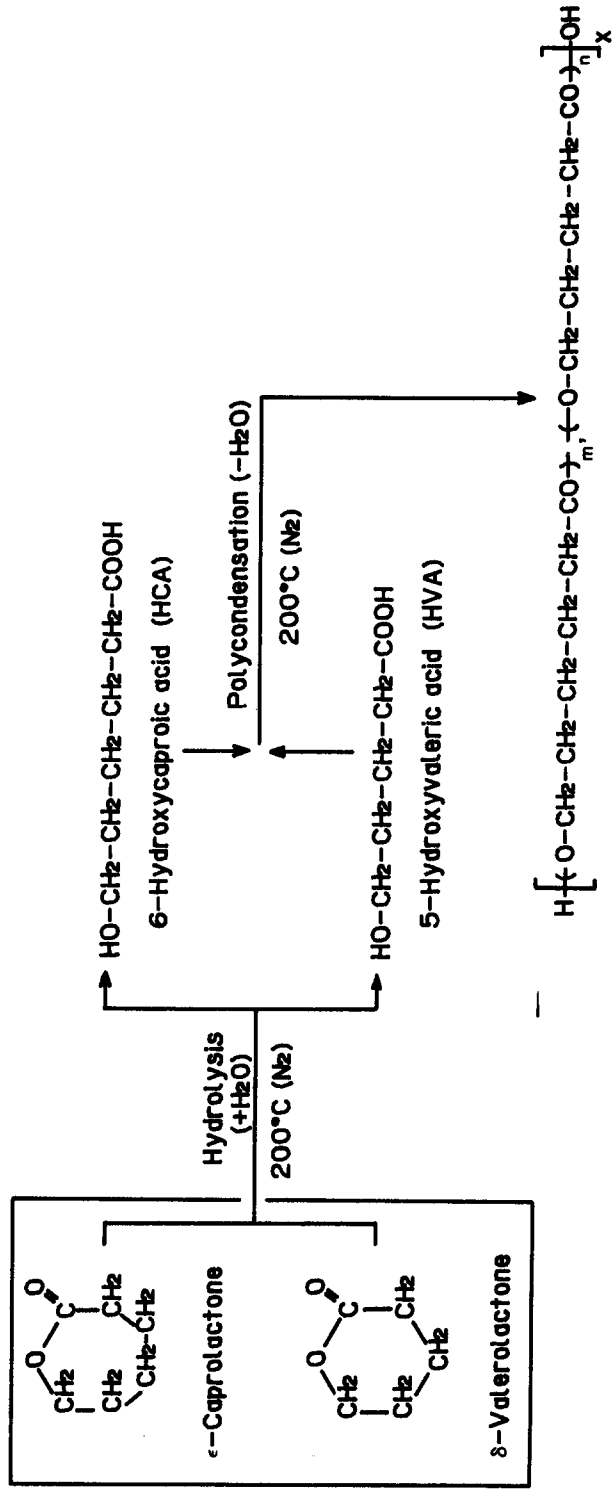



Fig. 1. Reaction scheme for direct copolycondensation of CL with VL in the presence of water without catalysts.

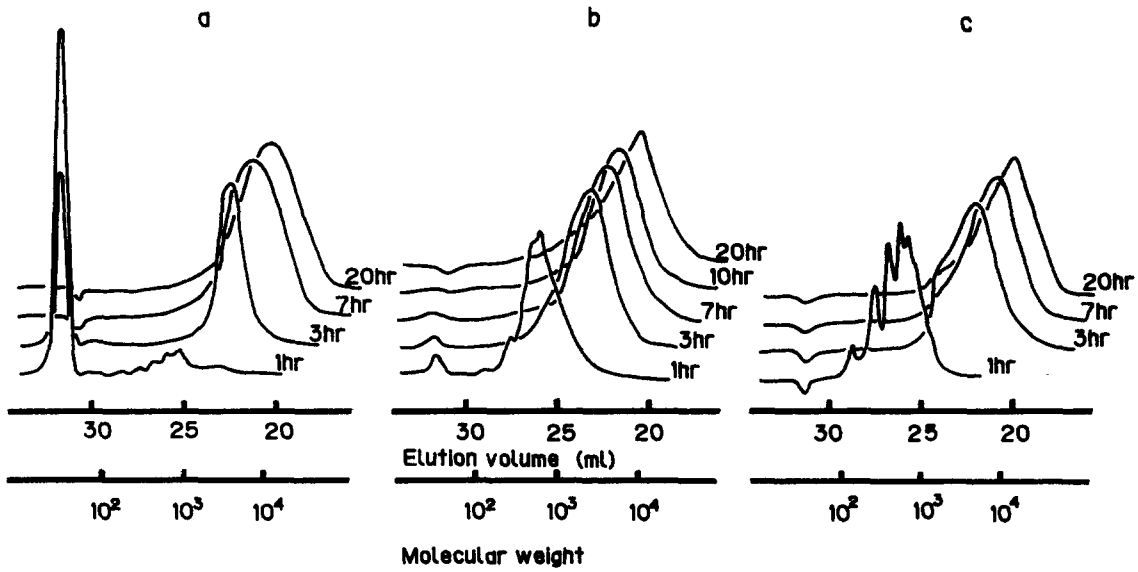



Fig. 2. GPC profiles of copoly(CL/VL) as a function of reaction time. The molecular weights refer to standard polystyrene. CL/VL monomer composition (mol%): (a) 100/0, (b) 50/50, (c) 0/100.

*Measurement of molecular weight*

The molecular weight of copoly(CL/VL) was measured by both terminal carboxyl group analysis and GPC. In the terminal carboxyl group analysis, the number-average molecular weight ($\bar{M}_n$) of copoly(CL/VL), dissolved in benzyl alcohol, was determined by titration using 0.025 N KOH in benzyl alcohol with phenolphthalein as indicator; $\bar{M}_n$ was calculated from

$$\bar{M}_n = \frac{1000W}{0.0025f(V - V_0)} \quad (1)$$

where $W$ is the weight of copolymer (g), $f$ is the titer of 0.025 N KOH solution (titrated solution), $V$ is the volume of titrated solution and $V_0$ is the blank volume of titrated solution, respectively.

In GPC, $\bar{M}_n$, weight-average molecular weight ($\bar{M}_w$) and polydispersity ($\bar{M}_w/\bar{M}_n$) were measured with a Waters ALC-244 high performance liquid chromatograph, at 25° at a flow rate of 1 ml/min through $10^2$, $10^3$ and $10^4$ Å Waters ultrastyragel columns in tetrahydrofuran; standard polystyrene was used for calibration.

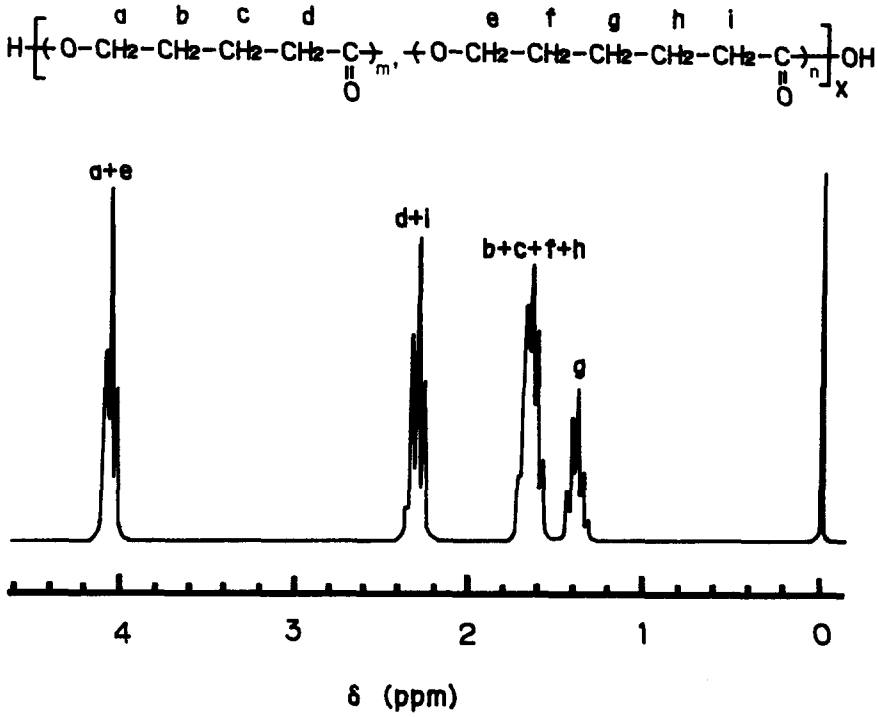



Fig. 3. Methylene signals in the 270 MHz $^1$H-NMR spectrum of a copoly(CL/VL) with a monomer composition of 70/30 mol% (No. 3 in Table 1).

*Instrumental analysis*

The molar composition of copoly(CL/VL) was determined from 270 MHz $^1$H-HMR spectra using a Jeol GSX-270 spectrometer. For this purpose, the copolymer was dissolved in $CDCl_3$ (5 wt% concentration) with internal tetramethylsilane (TMS) for shift reference. The sequence analysis of this copolymer, dissolved in $CDCl_3$ (20 wt% concentration), was obtained from 67.9 MHz $^{13}$C-NMR spectra (Jeol GSX-270 spectrometer) using internal TMS for shift reference.

The crystallinity of the copolymer was obtained using a Rigaku X-ray diffractometer with Ni-filtered CuK$\alpha$ radiation at 40 kV and 30 mA. The melting point (m.p.) was determined with a Perkin Elmer differential scanning calorimeter (DSC), Model DSC-7, at a heating rate of 10°/min.

## RESULTS AND DISCUSSION

### *Copolycondensability of CL and VL*

The reaction scheme for direct copolycondensation of a cyclic CL monomer with a cyclic VL monomer in the presence of water without catalyst at 200° under nitrogen is shown in Fig. 1. This reaction starts with hydrolysis of the cyclic monomers, followed by condensation of the resulting linear monomers, e.g. 6-hydroxycaproic acid (HCA) as a product from CL and 5-hydroxyvaleric acid (HVA) from VL.

The GPC profiles of copoly(CL/VL) as a function of reaction time are shown in Fig. 2. In a homopolymerization of VL, the monomer peak was completely missing after the first one hour period of converting the cyclic VL into the linear HVA, and the resulting plural peaks corresponding to the oligomers appeared. These peaks merged to a single peak with the passage of time because of the formation of higher molecular weight polymers, as seen clearly in Fig. 2c. In contrast, a longer period is required for the disappearance of the cyclic CL peak, which remains even after 3 hr of reaction (Fig. 2a). Possibly this effect is due to the difference in rate of hydrolysis between the two cyclic monomers. In a copolymerization of CL and VL, a small monomer peak assigned to the cyclic CL and VL remained after the first 7 hr period but subsequently disappeared completely; the product peaks gave a single peak with a right-side shift with time resulting from formation of higher molecular weight polymer. The molecular weight parameters, $\bar{M}_n$, $\bar{M}_w$, and $\bar{M}_n/\bar{M}_w$, are listed in Table 1.

The copolycondensability of CL and VL was evaluated by $^1$H-NMR considering the methylene signals in 270 MHz $^1$H-NMR spectra of copoly(CL/VL) are shown in Fig. 3. The $CH_2$ signals of the copolymer showed more peaks than both

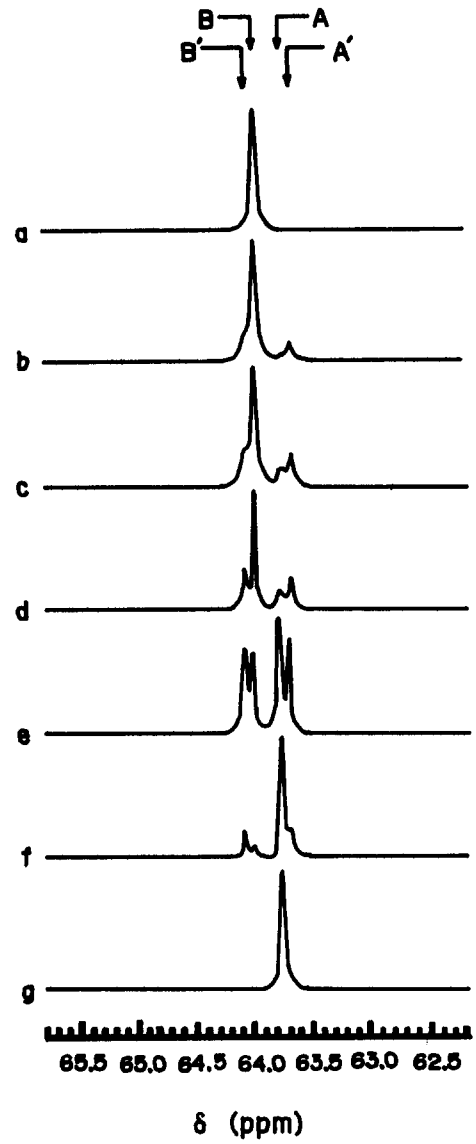



Fig. 4. Methylene signals in the 67.9 MHz $^{13}$C-NMR spectra of copoly(CL/VL) with monomer compositions of (a) 100/0 mol%, (b) 85/15 mol%, (c) 70/30 mol%, (d) 50/50 mol%, (e) 30/70 mol%, (f) 15/85 mol% and (g) 0/100 mol%.

Table 1. Direct copolycondensation of CL with VL in the absence of catalyst and properties of copolymers

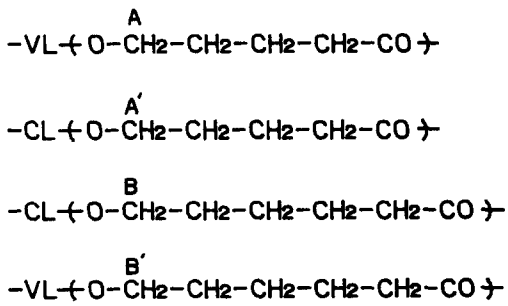
| | Synthetic conditions* | | | Properties of copolymer | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Monomer composition (mol%) | | Reaction time | | GPC | | | DSC m.p. | $^1$H-NMR Composition (mol%) | | |
| No. | CL | VL | (hr) | $\bar{M}_n$† | $\bar{M}_n$ | $\bar{M}_w$ | $\bar{M}_w/\bar{M}_n$ | (°C) | CL | VL | Appearance |
| 1 | 100 | 0 | 10 | | 5800 | 14800 | 2.55 | 61 | 100 | 0 | Waxy |
| 2 | 85 | 15 | 10 | | 5700 | 14200 | 2.51 | 49 | 92 | 8 | Waxy |
| 3 | 70 | 30 | 14 | $4500 \pm 300$ | 4700 | 13600 | 2.89 | 29 | 78 | 22 | Waxy |
| 4 | 50 | 50 | 14 | | 4500 | 14500 | 3.22 | 20 | 71 | 29 | Pasty |
| 5 | 30 | 70 | 10 | | 4600 | 13400 | 2.91 | 17 | 53 | 47 | Pasty |
| 6 | 15 | 85 | 10 | | 4200 | 13800 | 3.29 | 32 | 19 | 81 | Waxy |
| 7 | 0 | 100 | 10 | | 4100 | 14100 | 3.44 | 56 | 0 | 100 | Waxy |

*Reaction was carried out at 200° under nitrogen.
†Terminal carboxyl group analysis.

homopolymers [6, 7], suggesting that the polymer chain consists of CL and VL units. The molar compositions of the copolymers were calculated from the ratio of areas for peak (g) and peaks (a + e) or peak (g) and peaks (d + i); finally, it was found that the CL contents in the copolymers are *ca* 92, 78, 71, 53 and 19 mol% for initial CL contents in the feed of 85, 70, 50, 30 and 15 mol%, respectively. In any system, the CL content in copoly(CL/VL) is higher than that in the initial feed. This finding means that the CL unit is preferentially incorporated in the copolyester. The cause of low reactivity of VL is not clear, but it can be supposed that the balance between the rate of hydrolysis of cyclic lactone monomers and the rate of condensation of linear monomers produced by their hydrolyses plays an important role in the direct copolycondensation of CL and VL in the presence of water without catalysts.

*Sequence analysis of copoly(CL/VL)*

The sequence analysis of copoly(CL/VL) was investigated by $^{13}$C-NMR. The spectra of homopolymers of CL and VL are respectively composed of six and five signals which are singlets, in contrast to dyad splittings for the signals of $\delta$-methylene ($\delta$-oxyvaleryl unit: VL) and $\epsilon$-methylene group ($\epsilon$-oxycaproyl unit: CL) in the copolyester, because of the sequence effects. It can be seen clearly in Fig. 4, which shows the methylene signals in the 67.9 MHz $^{13}$C-NMR spectrum of copoly(CL/VL) as a function of monomer composition. The assignment of the dyad sequence represented in Scheme 1 is as follows.




Scheme 1

The peaks of the homogeneous bonds, for example peak A for the V–V sequence (V: $\delta$-oxyvaleryl unit) and peak B for the C–C sequence (C: $\epsilon$-oxycaproyl unit), were assigned by the $\delta$-values of each homopolymer (Fig. 4). The peaks A′ and B′ are assigned to the heterogeneous bonds, in which the peak A′ corresponding to the dyads V–C and C–V showed an upfield shift from peak A′, in contrast to a downfield shift for the peak B′ (dyads C–V and V–C). The relative peak intensity of each dyad is markedly influenced by change in monomer composition and, as a result, the dyad peak intensity of $\epsilon$-oxycaproyl units in the copolyester is approximately equal to that of $\delta$-oxyvaleryl units at 30/70 mol% CL/VL feed, leading to formation of equimolar copoly(CL/VL). This gives the results of polymer composition obtained by $^{1}$H-NMR spectra (Table 1).

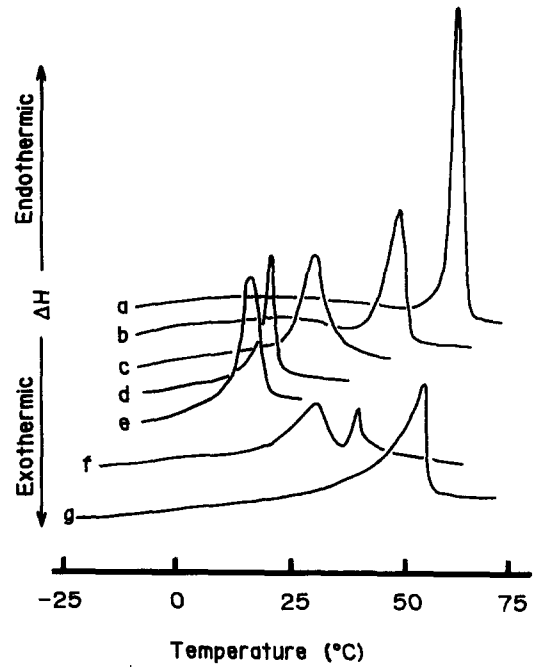



Fig. 5. DSC curves of copoly(CL/VL). Symbols refer to monomer compositions given in Fig. 4.

*Crystallinity of copoly(CL/VL)*

The DSC measurements were performed in order to check the crystallinity of copoly(CL/VL); results are shown in Fig. 5. The melting endotherms were observed not only in each homopolymer system but also in the copolymer system because of the formation of crystalline domains. In this case, the melting point of each homopolymer was relatively high e.g. 61° for a homopoly(CL) and 56° for a homopoly(VL). Such a melting point was markedly decreased by copolycondensation to an extent depending on monomer composition, reaching a minimum of 17° for equimolar copoly(CL/VL) (Fig. 5e). Possibly this effect is due to a rapid decrease in block lengths of $\epsilon$-oxycaproyl and $\delta$-oxyvaleryl units in the copolyester, in relation with distortion of the crystal structure. It can be seen clearly in Fig. 6,

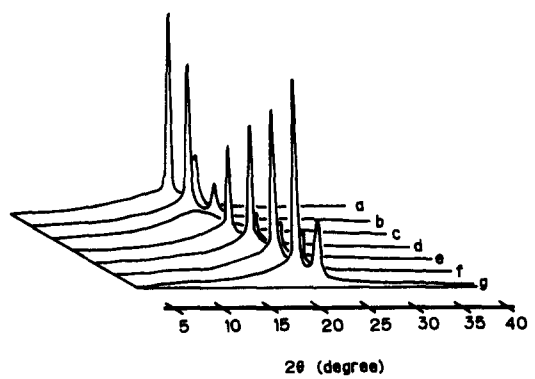



Fig. 6. X-ray diffraction diagrams of copoly(CL/VL). Symbols refer to monomer compositions given in Fig. 4.

which shows the X-ray diffraction patterns of co-poly(CL/VL) as a function of monomer composition. This result is in fair agreement with the DSC measurements.

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## REFERENCES

1. H. R. Kricheldorf, J. M. Jonte and R. Dunsing. *Makromolek. Chem.* **187,** 771 (1986).
2. H. R. Kricheldorf and M. Sumbel. *Makromolek. Chem.* **189,** 317 (1988).
3. R. Dunsing and H. R. Krichedorf. *Eur. Polym. J.* **24,** 145 (1988).
4. C. G. Pitt, M. M. Gratzl, G. L. Kimmel, J. Surles and A. Schindler. *Biomaterials* **2,** 215 (1981).
5. H. Fukuzaki, M. Yoshida, M. Asano and M. Kumakura. *Eur. Polym. J.* **25,** 1019 (1989).
6. H. Fukuzaki, M. Yoshida, M. Asano, M. Kumakura, T. Mashimo, H. Yuasa, K. Imai and H. Yamanaka. *Polymer* (in press).
7. H. Fukuzaki, M. Yoshida, M. Asano, Y. Aiba and I. Kaetsu. *Eur. Polym. J.* **24,** 1029 (1988).
8. H. Fukuzaki, M. Yoshida, M. Asano, M. Kumakura, T. Mashimo, H. Yuasa, K. Imai, H. Yamanaka, U. Kawaharada and K. Suzuki. *J. Controlled Release* **10,** 293 (1989).
9. H. Fukuzaki, Y. Aiba, M. Yoshida, M. Asano and M. Kumakura. *Makromolek. Chem.* **190,** 1553 (1989).
10. H. Fukuzaki, Y. Aiba, M. Yoshida, M. Asano and M. Kumakura. *Makromolek. Chem.* **190,** 2407 (1989).
11. H. Fukuzaki, M. Yoshida, M. Asano, Y. Aiba and M. Kumakura. *Eur. Polym. J.* **26,** 457 (1990).
12. M. Yoshida, M. Asano, H. Fukuzaki, I. Kaetsu, T. Mashimo, H. Yuasa, K. Imai and H. Yamanaka. Fundamental studies of a LH-RH agonist and several slow release materials. In *Prostate Cancer: The 2nd Tokyo Symposium* (edited by J. P. Karr and H. Yamanaka), pp. 288–292. Elsevier, New York (1989).