

# Cocrystallization of Random Copolymers of $\omega$ -Pentadecalactone and $\epsilon$ -Caprolactone Synthesized by Lipase Catalysis

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Random copolymers were prepared by *Candida antarctica* lipase B (Novozyme-435) catalyzed copolymerization of  $\omega$ -pentadecalactone (PDL) with  $\epsilon$ -caprolactone (CL). Over the whole composition range PDL–CL copolymers are highly crystalline (melting enthalpy by differential scanning calorimetry, above 100 J/g; crystallinity degree by wide-angle X-ray scattering, WAXS, 60–70%). The copolymers melt at temperatures that linearly decrease with composition from that of poly( $\omega$ -pentadecalactone) (PPDL; 97°C) to that of poly( $\epsilon$ -caprolactone) (PCL; 59 °C). The WAXS profiles of PCL and PPDL homopolymers are very similar, except for the presence in PPDL of the (001) reflection at  $2\theta = 4.58^\circ$  that corresponds to a 19.3 Å periodicity in the chain direction. In PDL–CL copolymers the intensity of this reflection decreases with increasing content of CL units and vanishes at 50 mol % CL, as a result of randomization of the ester group alignment and loss of chain periodicity. PDL–CL copolymers crystallize in a lattice that gradually changes from that of one homopolymer to that of the other, owing to comonomer isomorphous substitution. Cocrystallization of comonomer units is also shown by a random PDL–CL copolymer obtained in a polymerization/transesterification reaction catalyzed by *C. antarctica* lipase B (Novozyme-435) starting from preformed PCL and PDL monomer.

## Introduction

Recently enzyme catalyzed polymerizations have received much attention as a new methodology for polymer<sup>1–15</sup> and copolymer<sup>16–23</sup> synthesis. An important objective of enzymatic copolymerization reactions is the regulation of the repeat unit sequence distribution along the chain. Control over copolymer microstructure is critical to the ultimate goal of tailoring the physical, mechanical, and biological properties of the products.

The copolymerization of  $\omega$ -pentadecalactone (PDL) and  $\epsilon$ -caprolactone (CL) using immobilized lipase B from *Candida antarctica* (Novozyme-435) was recently reported.<sup>18</sup> PDL–CL copolymers with a high molar mass were prepared. In these lipase-catalyzed copolymerizations the reactivity of PDL was higher than that of CL.<sup>18</sup> It was also demonstrated that the lipase promotes enzymatic transesterification reactions and that, as a consequence, the repeating unit distribution changes with reaction time from blocky to close to random. Similar close-to-random distributions can also be obtained starting from preformed poly( $\epsilon$ -caprolactone) (PCL)

and PDL monomer<sup>20</sup> or alternatively from the two homopolymers and conducting the lipase-catalyzed reaction for a sufficient time.<sup>19</sup>

The homopolymer poly( $\omega$ -pentadecalactone) (PPDL) synthesized by Novozyme-435 has been recently characterized.<sup>24</sup> PPDL is a highly crystalline polyester that melts at about 100 °C and, because of its long methylene sequence, shows structural similarities to polyethylene. The crystal structure of PPDL has been thoroughly investigated,<sup>25</sup> and its unit cell was found to be pseudo-orthorhombic, with  $a = 7.49$  Å,  $b = 5.034$  Å,  $c$ (fiber axis) = 20.00 Å, and  $\alpha = 90.06^\circ$ .

This work reports on the solid-state characterization of lipase-catalyzed PDL–CL copolymers with the aim to illustrate the peculiar capability of these copolyesters to develop a high crystalline fraction over the entire composition range. This type of behavior is expected in random copolymers whose comonomer units undergo isomorphous substitution. The different types of isomorphism have been classified by Natta<sup>26</sup> and co-workers, and the subject was later reviewed by Wunderlich<sup>27</sup> and by Allegra et al.<sup>28,29</sup> Two main cases have been identified in random copolymers, namely, isomorphous and dimorphic substitution. When the homopolymers of the two repeating units have similar crystal structure, the copolymers form a crystal phase whose lattice parameters

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**Table 1.** Poly(PDL–CL) Synthesized from the Monomers

sample	feed PDL/CL (molar ratio)	reaction time	copolymer composition PDL/CL (mol %)	diads <sup>a</sup>				$M_n^b$ (g/mol)	$M_w/M_n^b$
				P–P	P–C	C–P	C–C		
A1	1:1	1 min	69:31	0.50 (0.48)	0.19 (0.21)	0.20 (0.21)	0.11 (0.10)	8410	2.50
A2	1:1	2 min	63:37	0.42 (0.40)	0.20 (0.23)	0.23 (0.23)	0.14 (0.14)	12 600	2.19
A3	1:1	5 min	60:40	0.37 (0.36)	0.23 (0.24)	0.21 (0.24)	0.19 (0.16)	14 600	2.37
A4	1:1	15 min	50:50	0.28 (0.25)	0.22 (0.25)	0.24 (0.25)	0.26 (0.25)	17 800	2.38
A5	1:1	45 min	50:50	0.24 (0.25)	0.26 (0.25)	0.22 (0.25)	0.28 (0.25)	19 300	2.28
A6	1:1	4 h	48:52	0.24 (0.24)	0.24 (0.25)	0.30 (0.25)	0.23 (0.26)	21 200	1.87
A7	1:1	6 h	48:52	0.24 (0.24)	0.24 (0.25)	0.26 (0.25)	0.26 (0.26)	22 300	1.97
A8	1:3	24 h	21:79	0.06 (0.04)	0.16 (0.17)	0.21 (0.17)	0.57 (0.62)	38 700	1.59

<sup>a</sup> P = PDL repeat units; C = CL repeat units. From <sup>13</sup>C NMR. Number in parentheses: calculated for random distribution. <sup>b</sup> From GPC in CHCl<sub>3</sub> (polystyrene standards calibration).

**Table 2.** Poly(PDL–CL) Synthesized from Preformed PCL and PDL Monomer

sample	feed PDL/CL (molar ratio)	reaction time	copolymer composition PDL/CL (mol %)	diads <sup>a</sup>				$M_n^b$ (g/mol)	$M_w/M_n^b$
				P–P	P–C	C–P	C–C		
B1	1:1	15 min	49:51	0.43 (0.25)	0.07 (0.24)	0.07 (0.25)	0.43 (0.26)	14 800	2.57
B2	1:1	30 min	55:45	0.44 (0.30)	0.11 (0.25)	0.12 (0.25)	0.33 (0.20)	17 700	2.4
B3	1:1	2 h	56:44	0.42 (0.31)	0.14 (0.25)	0.13 (0.25)	0.31 (0.19)	16 400	2.13
B4	1:1	6 h	52:48	0.36 (0.27)	0.16 (0.25)	0.18 (0.25)	0.30 (0.23)	16 300	2.04
B5	1:1	24 h	54:46	0.30 (0.29)	0.21 (0.25)	0.26 (0.25)	0.23 (0.21)	17 600	2.52

<sup>a</sup> P = PDL repeat units; C = CL repeat units. From <sup>13</sup>C NMR. Number in parentheses: calculated for random distribution. <sup>b</sup> From GPC in CHCl<sub>3</sub> (polystyrene standards calibration).

gradually change with composition from the unit cell of one homopolymer to that of the other (isomorphism). Conversely, when the reference homopolymers have different crystal structures, copolymers crystallize in either of the crystal lattices depending on composition (isodimorphism). It is the crystal lattice of the major monomer that hosts the minor comonomer units, and often both crystals coexist at some intermediate composition, where the change from one crystal phase to the other occurs.

Interest in cocrystallizing polymer systems has been recently revived by a number of papers in the literature.<sup>30–38</sup> The present work aims at contributing to this interesting subject by providing experimental evidence of isomorphism in random copolymers of PDL and CL, a system whose properties smoothly change with composition without loss of crystallinity.

### Experimental Section

**Materials.** The synthesis of PPDL<sup>10</sup> and of PDL–CL copolymers<sup>18</sup> was reported earlier. PDL–CL copolymers were also synthesized starting from preformed PCL homopolymer ( $M_n = 9200$  g/mol,  $M_w/M_n = 1.17$ ) and PDL monomer, using Novozyme-435 as the catalyst (1:10 w/w with respect to monomer/polymer), in toluene at 70 °C.

Table 1 summarizes the molecular characterization of the PDL–CL copolymers synthesized from the respective monomers (A-copolymers), whereas Table 2 lists the corresponding results for PDL–CL copolymers synthesized starting from preformed PCL homopolymer and PDL monomer (B-copolymers).

**Instrumental Methods.** Proton (<sup>1</sup>H) and carbon (<sup>13</sup>C) NMR spectra were recorded on a Bruker spectrophotometer model DPX300 at 300 and 75.13 MHz, respectively. The chemical shifts in parts per million (ppm) for the <sup>1</sup>H and <sup>13</sup>C NMR spectra were referenced relative to tetramethylsi-

lane and chloroform as an internal reference at 0.00 and 77.23 ppm, respectively. The assignment of <sup>1</sup>H and <sup>13</sup>C spectra of copolymers was reported elsewhere.<sup>18</sup> Molecular weights were determined by gel permeation chromatography (GPC) using a Waters HPLC system equipped with model 510 pump, Waters model 717 autosampler, and model 410 refractive index detector with 500, 10<sup>3</sup>, 10<sup>4</sup>, and 10<sup>5</sup> Å Ultrastaygel columns in series. Trisec GPC software, version 3 (from Viscotek Corp.), was used for calculations. Chloroform was used as the eluent at a flow rate of 1.0 mL/min. Sample concentrations of 0.2 (w/v) % and injection volumes of 100 μL were used. Molecular weights were determined on the basis of the conventional calibration curve generated by narrow molecular weight polystyrene standards obtained from Aldrich Chemical Co. Differential scanning calorimetry (DSC) was carried out using a TA-DSC 2910. The temperature scale was calibrated with high-purity standards. DSC scans were performed in the temperature range from –80 to +140 °C. The heating rate was 20 °C/min, and the cooling rate was 10 °C/min. The melting temperature ( $T_m$ ) and crystallization temperature ( $T_c$ ) were taken at the peak of the DSC endo- and exotherms, respectively. X-ray diffraction measurements were carried out at room temperature with a Bragg/Brentano diffractometer system (PhilipsPW 1050/81-PW1710), equipped with a graphite monochromator in the diffracted beam. The Cu anode was used as the X-ray source ( $\lambda_1 = 0.154 06$  nm,  $\lambda_2 = 0.154 43$  nm). For the wide-angle X-ray scattering (WAXS) data collection the instrument was equipped with 1°, 0.2 mm, 1° slits. The data were collected in the range 2.5–60° ( $2\theta$ ) counting for 3 s at each 0.1° step. The amorphous and crystalline contributions were calculated by fitting the experimental diffraction curve with the WinFit program.<sup>39</sup> The degree of crystallinity ( $\chi_c$ ) was evaluated as the ratio of the crystalline peak areas to the total area under the scattering curve, and the average crystal size was evaluated by means of the Scherrer equation.<sup>40</sup> X-ray

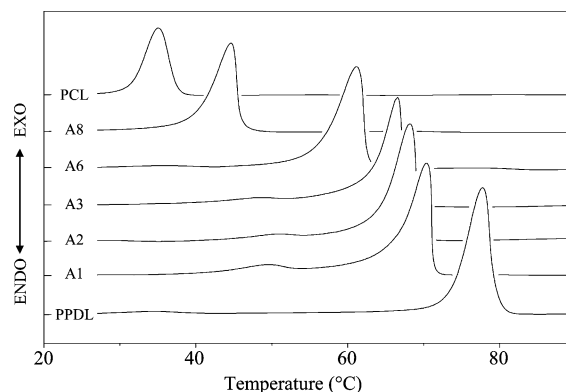
diffraction measurements in the range  $2.5\text{--}7.5^\circ$  ( $2\theta$ ) were acquired with a  $0.1^\circ$  step and 30-s counting time, using the set of slits  $0.5^\circ$ , 0.2 mm,  $1^\circ$ . The primary beam and air scattering contribution to the incoherent scattering was considered equal to the contribution of an empty sample holder recorded in the same conditions, which was, therefore, subtracted from the sample diffraction profile.

## Results and Discussion

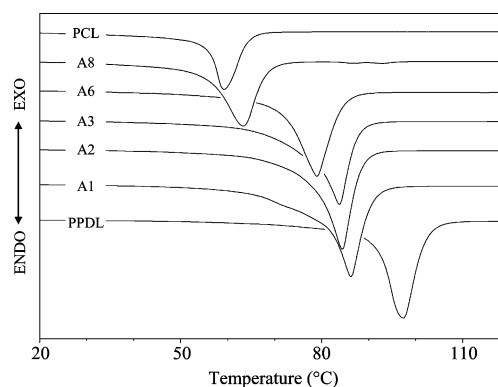
**Molecular Characterization.** Copolymers obtained by the Novozyme-435 catalyzed reaction of PDL with CL (A-copolymers) are listed in Table 1. PDL-CL copolymers A1-A7 were synthesized from an equimolar feed with increasing reaction time (1 min to 6 h). Proton ( $^1\text{H}$ ) NMR composition analysis of these copolymers (see ref 18) shows that the caprolactone molar content increases from 31 to 50% when the reaction time changes from 1 to 15 min. The composition of sample A4 equals that of the feed, and further increase of reaction time (samples A5-A7) causes only a limited molar mass increase and molecular weight distribution narrowing. An additional copolymer containing 79 mol % of CL units (A8 in Table 1) was obtained starting from a CL-rich feed (molar feed ratio PDL/CL = 1:3) after a 24 h reaction.

The diad content of PDL-CL copolymers determined by  $^{13}\text{C}$  NMR (see ref 18 for peak assignments) is compared in Table 1 with the calculated diad distribution (in parentheses) for random copolymers with the same overall composition. The agreement between the experimental and the calculated values is excellent, showing that the comonomer units are randomly distributed in all A-copolymers investigated. This result is consistent with earlier evidence<sup>18</sup> that, although the PDL monomer reactivity is 13 times higher than that of the CL monomer, Novozyme-435 actively promotes transesterification reactions that very rapidly randomize the comonomer unit distribution.

Another set of copolymers (B-copolymers) was obtained by Novozyme-435 catalysis from an equimolar feed of preformed PCL homopolymer and PDL monomer. The overall composition and diad distribution as a function of reaction time (from 15 min to 24 h) are given in Table 2. The composition of all B-copolymers is around 50:50, in agreement with the composition of PDL-CL copolymers synthesized from an equimolar mixture of the two monomers for times  $\geq 15$  min (A-copolymers, Table 1). However, unlike A-copolymers that are random after 1 min of reaction, the diad composition of the B-copolymers matches that calculated for random copolymers only in sample B5, that is, after extended reaction times (24 h). It is clear that in B-copolymers transesterification reactions progressively reshuffle the comonomer units along the polymer chain, going from essentially blocky copolymers (B1, B2) to copolymers with random co-unit distribution (B5). This result is consistent with earlier evidence that random copolymers can be obtained by the action of Novozyme-435 on preformed PCL and PPDL homopolymers and that the reaction time required to reach randomness depends on the molar mass of the starting polymers.<sup>19</sup>



**Figure 1.** DSC cooling curves ( $-10^\circ\text{C}/\text{min}$ ) of PDL-CL copolymers (A-copolymers) and of the reference PCL and PPDL homopolymers.



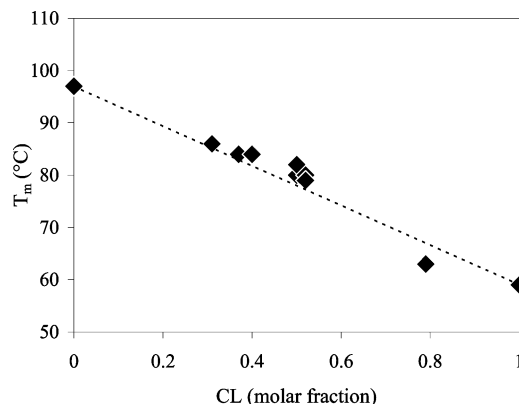
**Figure 2.** DSC heating curves ( $20^\circ\text{C}/\text{min}$ ) of PDL-CL copolymers (A-copolymers) and of the reference PCL and PPDL homopolymers, after cooling from the melt at  $10^\circ\text{C}/\text{min}$  (Figure 1).

**Table 3.** Calorimetric and X-ray Diffraction Data of Poly(PDL-CL) Copolymers and of the Homopolymers PPDL and PCL

sample	composition		$T_c^a$ ( $^\circ\text{C}$ )	$\Delta H_c^a$ (J/g)	$T_m^b$ ( $^\circ\text{C}$ )	$\Delta H_m^{b,c}$ (J/g <sub>tot</sub> )	$\chi_c^d$ (%)	c.s. <sup>e</sup> (nm)	$\Delta H_m^{b,f}$ (J/g <sub>cryst</sub> )
	PDL/CL (mol %)								
PPDL	100:0		78	134	97	140	65	12.6	215
A1	69:31		70	141	86	152	73	26.6	208
A2	63:37		68	128	84	143	72	22.1	199
A3	60:40		67	125	84	137	70	22.6	196
A4	50:50		62	117	81	130	67	21.1	194
A5	50:50		64	119	82	129	65	22.0	198
A6	48:52		62	119	80	127	66	20.2	192
A7	48:52		61	114	79	127	64	20.3	198
A8	21:79		45	91	63	102	61	15.0	167
PCL	0:100		35	66	59	74	56	10.3	132

<sup>a</sup> Cooling at  $10^\circ\text{C}/\text{min}$  from the melt. <sup>b</sup> Heating at  $20^\circ\text{C}/\text{min}$  (after cooling at  $10^\circ\text{C}/\text{min}$ ). <sup>c</sup> Melting enthalpy per gram of whole sample. <sup>d</sup> Crystallinity degree from WAXS ( $\pm 5\%$ ). <sup>e</sup> Average crystal size from WAXS. <sup>f</sup> Melting enthalpy per gram of crystal phase.

**Thermal Properties.** Figure 1 shows the DSC curves of PDL-CL copolymers (A-copolymers) during cooling from the melt. The thermograms obtained in a subsequent heating scan are collected in Figure 2. For the sake of clarity only selected curves, representative of the thermal behavior of all copolymers listed in Table 1, are reported. The DSC curves of the reference homopolymers (PPDL and PCL) are also shown for comparison in both Figures 1 and 2. The thermal data of the homopolymers and copolymers are collected in Table 3.



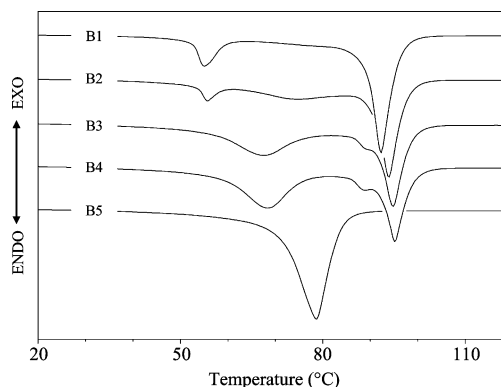
**Figure 3.** Composition dependence of the melting temperature of PDL-CL copolymers (A-copolymers).

All A-copolymers show a single crystallization (Figure 1) and melting process (Figure 2) at temperatures intermediate to those of the reference homopolymers. Both transitions systematically shift to lower temperatures with increasing content of CL units in the copolymer. The enthalpies associated with the crystallization and melting phenomena are very large (see  $\Delta H_c$  and  $\Delta H_m$  in Table 3), irrespective of copolymer composition.

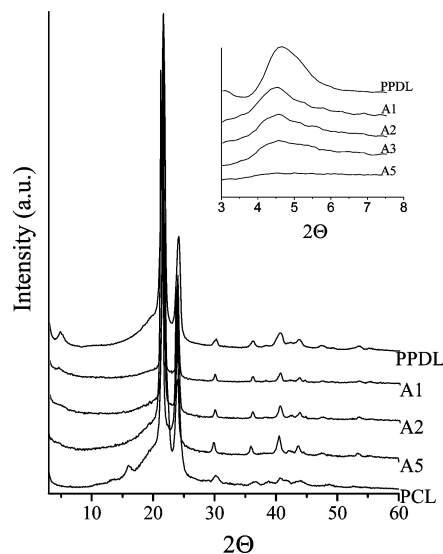
This result is quite uncommon in random copolymers. Usually, when the monomers of two crystallizable polymers are randomly copolymerized, crystallinity only develops if the content of one comonomer largely exceeds that of the other, because sequences of the major constituent crystallize while the minor comonomer is excluded from the crystal lattice. With increasing content of the latter monomer a sharp decrease of both the crystallinity and the melting temperature ( $T_m$ ) is usually observed. The melting temperature shows a minimum at intermediate copolymer compositions, and well-known equations<sup>41-43</sup> can be applied to describe the observed melting temperature depression.

Contrary to the "classical" behavior described above, Figure 3 shows that the melting temperature of the present PDL-CL copolyesters monotonically changes with composition and that the best fit to the experimental results is provided by a straight line connecting the melting temperatures of the two homopolymers. Similar behaviors are described in the literature for random copolymers where the two monomer species undergo isomorphic substitution, that is, enter a common crystal lattice.<sup>27,28</sup> The large melting enthalpy values in Table 3 also suggest that the PDL and CL units cocrystallize, giving rise to a conspicuous crystal phase.

Figure 4 shows the DSC curves of copolymers obtained from preformed PCL homopolymer and PDL monomer. The melting behavior of these B-copolymers is complex and differs from that of the A-copolymers discussed above, which displayed a single composition-dependent melting process. Copolymers B1-B4 show multiple melting endotherms attributed to fusion of the blocky structures present in these copolymers. Only after an extended reaction time (24 h) does sample B5 show a single melting endotherm at a temperature (around 80 °C) which matches that of the A-copolymers with a similar composition (see Table 3). This result is consistent with the presence of a randomly distributed comonomer



**Figure 4.** DSC heating curves (20 °C/min) of PDL-CL copolymers (B-copolymers).

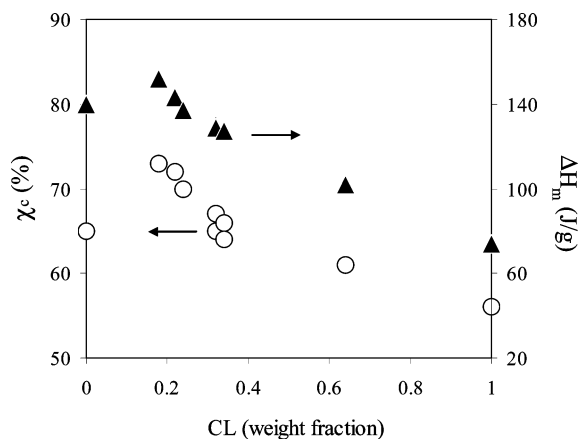


**Figure 5.** WAXS profiles of selected PDL-CL copolymers (A-copolymers) and of the reference PCL and PPDL homopolymers. Inset: magnification of the low-angle region.

sequence in copolymer B5, arising from repeated enzyme-mediated transesterification reactions.

**X-ray Diffraction.** A structural investigation of the crystal phase of random PDL-CL copolymers was carried out by WAXS. Figure 5 shows the diffraction profiles of selected PDL-CL copolymers (A-copolymers) together with the diffractograms of the reference homopolymers (PPDL and PCL). It was earlier pointed out<sup>25</sup> that the diffraction profile of PPDL in the range of diffraction angles  $2\theta > 10^\circ$  very closely resembles the diffractogram of both PCL and polyethylene. Peculiar to the PPDL pattern is the presence of the (001) reflection at  $2\theta = 4.52^\circ$ , corresponding to a 19.54 Å periodicity in the chain direction. The inset in Figure 5 shows a magnification of the profiles of PPDL and of the copolymers, in the range from  $2\theta = 3^\circ$  to  $2\theta = 7^\circ$ . With increasing content of CL units the (001) reflection intensity decreases and eventually vanishes in copolymer A5 containing 50 mol % of CL units. This result is the consequence of random insertion of CL units in the PDL sequences, which disrupts the regular ester group spacing of the PPDL homopolymer, responsible for the (001) reflection.

The X-ray diffraction profiles of all PDL-CL copolymers investigated contain sharp reflections, and the degrees of crystallinity derived from curve deconvolution in all cases



**Figure 6.** Composition dependence of (○) crystallinity degree by WAXS and (▲) melting enthalpy by DSC of PDL–CL copolymers (A-copolymers).

are high. For A-copolymers Table 3 lists the crystal fraction ( $\chi_c$ ) and average crystal size (c.s.) from WAXS. The latter data are the average of values calculated<sup>40</sup> from the half-width of the two most intense reflections in the diffraction pattern: (110) at  $2\theta = 21.5^\circ$  and (200) at  $2\theta = 23.9^\circ$ . It is interesting to note that the PDL–CL copolymers develop larger crystals than the homopolymers and unexpectedly high degrees of crystallinity. This latter point is highlighted in Figure 6, where  $\chi_c$  from WAXS and melting enthalpy ( $\Delta H_m$ ) from DSC are plotted as a function of composition (expressed on a weight basis because the result from both techniques depends on the analyzed sample mass). The experimental data are seen to fall above the additivity lines, confirming the exceptional crystallizing ability of random PDL–CL copolymers. Table 3 also lists the value of the melting enthalpy per gram of crystal phase, calculated as the ratio of  $\Delta H_m$  (per gram of whole sample, from DSC) to the fraction of crystallinity ( $\chi_c$ ) from WAXS. The enthalpy of fusion of the crystals tends to decrease with increasing CL comonomer content, as a result of the incorporation of foreign units in the PPDL crystal lattice.

Analysis of chain conformation and unit-cell parameters of the reference homopolymers can help rationalize the observed crystallization behavior. Both PPDL and PCL crystallize in an extended zigzag conformation, and their unit cells have very similar  $a$  and  $b$  parameters [PPDL,<sup>25</sup> pseudo-orthorhombic with  $a = 7.49 \text{ \AA}$ ,  $b = 5.034 \text{ \AA}$ ,  $c$  (fiber axis) =  $20.00 \text{ \AA}$ , and  $\alpha = 90.06^\circ$ ; PCL,<sup>44</sup> orthorhombic with  $a = 7.496 \text{ \AA}$ ,  $b = 4.974 \text{ \AA}$ , and  $c$  (fiber axis) =  $17.297 \text{ \AA}$ ]. The identity of chain conformation and close similarity of unit-cell lateral dimensions induce both polyesters to adopt polyethylene-like crystal structures, in agreement with early observations by Wunderlich<sup>27</sup> that the crystal structure of polymers with long methylene sequences is determined by the packing of polyethylene. Upon random copolymerization of PDL with CL, the chain packing remains practically undisturbed, while the only relevant effect from a structural viewpoint is the mentioned randomization of the ester group alignment with gradual loss of chain periodicity. We conclude, therefore, that PDL–CL copolyesters are an excellent example of random copolymers where the co-units are hosted in a common crystal lattice, that is, undergo isomorphous substitution.

We have recently reported on various cocrystallizing copolymer systems containing the very long pentadecalactone repeating unit. In block copolymers of PPDL with poly(ethylene glycol) (PEG), our groups showed that the PDL sequences have the unusual ability to induce crystallization of the covalently linked PEG block in the PPDL crystal lattice (i.e., in the planar zigzag conformation, uncommon to PEG).<sup>38</sup> Moreover, in copolymers of PDL with trimethylene carbonate (TMC) we have shown that sequences of alternate PDL–TMC units cocrystallize, forming a new crystal phase, with the fiber axis periodicity larger than that of PPDL and compatible with the length of the alternate diad.<sup>34</sup> To gain additional insights into cocrystallization of PDL copolymers, further studies are underway on random copolyesters of PDL with smaller lactones than CL and will be reported in due time.

## Conclusions

Random copolymers of PDL and CL are highly crystalline over the whole composition range, as a result of cocrystallization of the CL and PDL co-units. As expected in isomorphous copolymer systems, the crystal phase melts at a temperature ( $T_m$ ) that linearly changes with molar composition, from that of the PPDL homopolymer ( $97^\circ\text{C}$ ) to that of PCL ( $59^\circ\text{C}$ ).

Random PDL–CL copolymers constitute a system where the density of hydrolyzable ester groups can be freely changed with varying composition, without inducing dramatic changes of the material mechanical properties. This behavior has relevant practical consequences and represents an important advantage compared with common random copolymers, whose mechanical properties deteriorate upon changing composition owing to crystal phase depletion. In PDL–CL copolymers composition also controls the melting temperature and, hence, the applicability range of the material. The results of this work show that PDL–CL copolyesters with desired physical properties can be biosynthesized, based on the knowledge of microstructure–property relations and by careful selection of the reaction conditions.

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