APPENDICES

APPENDIX A

Theory of the Calorimetric Purity Method
(Standard Method of Calculation)

The determination of the purity of an organic compound by DSC is based upon the well known fact that the presence of even minute amounts of impurity in a material broadens its melting range and lowers the final melting point of the material from T_o, the melting temperature of an infinitely pure material, to a lesser temperature, T_m.

As the DSC theory predicts, as the impurity content increases, the melting point decreases and the range of melting broadens. Even minute differences in the impurity content of a sample result in distinct differences in the DSC melting peak shape and final melting temperature.

The quantitative assessment of the purity of an organic material requires the knowledge of three important sample parameters: melting point, heat of melting (ΔH_m) and analysis of the DSC melting peak shape.

Power-compensated differential scanning calorimeters provide both accurate temperature measurements and true calorimetric measurements, thus permitting the simple determination of each of these three important sample parameters from a single dynamic DSC experiment.

A true DSC measures directly the amount of energy absorbed or emitted by a sample, dq/dt, which can be expressed by the following simplified expression (Equation 1):

$$\frac{dq}{dt} = \frac{dT_s}{dt} \times \frac{dq}{dT_s} \qquad (1)$$

where

$\frac{dT_s}{dt}$ = scanning rate, degree/min

$\frac{dq}{dT_s}$ = heat capacity of the sample

The heat capacity term in this expression provides important information about the shape of a melting peak and, therefore, is the most important term here. From the Van't Hoff equation, which describes the rate of meting of a compound as a function of sample temperature, we can obtain a relationship describing the heat flow to or from a sample and the melting point depression of a sample due to the presence of an impurity. The relationships (Equations 2 and 3) are as follows:

$$\frac{dq}{dT_s} = \frac{\Delta q\,(T_o - T_m)}{(T_o - T_s)^2} \qquad (2)$$

where:

Δq = total heat of fusion of the sample, joules

T_o = melting point of a 100 % pure material

T_m = melting point of the sample

$(T_o\text{-}T_m)$ = melting point depression due to the impurity

T_s = sample temperature

The melting point depression due to an impurity (T_o-T_m) can be expressed as:

$$(T_o\text{-}T_m) = \frac{R\,T_o^2\,X_2}{\Delta H_m} \qquad (3)$$

where:

R = molar gas constant, 8.314 J/mole-K

X_2 = mole fraction of the impurity

ΔH_m = molar heat of melting, joules/mole

From these basic Van't Hoff relationships (Equations 2 and 3), the theory of the determination of the purity of a sample by DSC can now be derived. To do this, we must first integrate Equation 2. This results in an expression which describes the fraction of material reacted (melted in the case of an impurity) at any sample temperature on the melting curve (Equations 4 and 5):

$$F = \frac{T_o - T_m}{T_o - T_s} \qquad (4)$$

Rearranging this equation gives:

$$T_s = T_o - \frac{(T_o - T_m)}{F} \qquad (5)$$

where:

F = fraction melted
T_s = sample temperature

The theoretical discussion is now nearly complete. By substituting Equation 3, which defines the melting point depression due to an impurity, into Equation 5, we can obtain the now familiar linear equation for the determination of purity by DSC (Equation 6):

$$T_s = T_o - \left(\frac{RT_o^2 X_2}{\Delta H_m} \times \frac{1}{F}\right) \qquad (6)$$

Since Equation 6 is a linear equation, a plot of the sample temperature (T_s) versus the reciprocal of the fraction of material melted at that temperature (1/F) should give a straight line with a slope equal to the melting point depression (slope = $RT_o^2X_2 / \Delta H_m$) and a Y intercept T_o. This linear plot is referred to as a Van’t Hoff plot. The fraction of material at any sample temperature is determined directly from the dynamic DSC scan and is proportional to the peak area under the curve up to that temperature. By generating this Van’t Hoff plot from a series of sample temperatures and fraction melted results, in the range from approximately 5 to 60 percent melted, it is a relatively simple procedure to obtain values for T_o, the slope of the line, and finally, the direct determination of the mole fraction of impurity from Equation 6.

APPENDIX B

Supporting Works

1. **Poster Presentation** Pages 221-225

   W. Sangsuwan, S. Ruengdechawiwat, R. Molloy and A. Kleawkla, *"Synthesis and Characterization of a novel Tin(II) Poly(Propylene glycol) adduct for use as an Initiator in the Ring-Opening Polymerization of cyclic esters"* **Pure and Applied Chemistry International Conference 2013 (PACCON 2013)**, 23-25 January 2013, Chonbury Thailand.

2. **Poster Presentation** Pages 226-228

   S. Ruengdechawiwat, R. Somsunan, R. Molloy and J. Siripitayananon, *"Controlled Synthesis and Processing of a Poly(L-lactide-co-ε-caprolactone) Copolymer for Biomedical Use as an Absorbable Monofilament Surgical Suture"* **the 11th International Conference on Materials Chemistry (MC11)**, 8-11 July 2013, University of Warwick, UK.

3. **Poster Presentation** Pages 229-232

   S. Ruengdechawiwat, J. Siripitayananon, R. Somsunan, R. Molloy, P. D. Topham, B. J. Tighe, "*Synthesis, Processing and Tensile Testing of a Poly(L-lactide-co-ε-caprolactone) Monofilament Fibre for Potential Use as an Absorbable Surgical Suture*", **Macro 2014**, Chiang Mai Thailand.

4. **Poster Presentation** Pages 233-236

   A Kleawkla, T. Khawjanta, S. Ruengdechawiwat, R. Molloy, *"Synthesis of a Novel Tin(II) Ester Alkoxide Initiator for Use in the Ring-Opening Polymerization of ε-Caprolactone"*, **Macro 2014**, Chiang Mai Thailand.

5. **Poster Presentation** Pages 237-239

   P. Chairach, A. Kleawkla, R. Molloy and S. Ruengdechawiwat, *"Ring-Opening Polymerization of Cyclic Ester Monomers for the Synthesis of Biodegradable*

Polyesters" **Pure and Applied Chemistry International Conference 2013 (PACCON 2015)**, 21-23 January 2015, Bangkok, Thailand.

6. **Oral Presentation** Pages 240-245

   S. Ruengdechawiwat, R. Somsunan, R. Molloy, J. Siripitayananon, V. J. Franklin, P. D. Topham and B. J. Tighe, *"Controlled Synthesis and Processing of a Poly(L-lactide-co-ε-caprolactone) Copolymer for Biomedical Use as an Absorbable Monofilament Surgical Suture*" **the 4th International Conference on Advanced Materials Research 2014 (ICAMR 2014)**, 22-23 January 2014, Macau, China.

7. **Oral Presentation** Pages 246-247

   S. Ruengdechawiwat, J. Siripitayananon, R. Somsunan, R. Molloy, P.D. Topham, B.J. Tighe, *"Synthesis and Characterisation of a Poly(L-lactide-co-ε-caprolactone) Copolymer Using a Novel Tin(II) Alkoxide Initiator for Potential Use as an Absorbable Monofilament Surgical Suture"*, **the 27th International Symposium on Polymer Analysis and Characterization (ISPAC 2014)**, 16-18 June 2014, Geneva, Switzerland.

8. **Publications**

   W. Sangsuwan, S. Ruengdechawiwat, R. Molloy and A. Kleawkla, *"Synthesis and Characterization of a novel Tin(II) Poly(Propylene glycol) adduct for use as an Initiator in the Ring-Opening Polymerization of cyclic esters"* **Proceedings in Pure and Applied Chemistry International Conference 2013 (PACCON 2013)**, pp.1017-1020.

   S. Ruengdechawiwat, R. Somsunan, R. Molloy, J. Siripitayananon, V. J. Franklin, P. D. Topham and B. J. Tighe, *"Controlled Synthesis and Processing of Poly(L-lactide-co-ε-caprolactone) Copolymer for Biomedical Use as an Absorbable Monofilament Surgical Suture*" **Advanced Materials Research** Vol. 94 (2014) pp 172-176.

   A. Kleawkla, T. Khawjanta, S. Ruengdechawiwat, R. Molloy, *"Synthesis of a Novel Tin(II) Ester Alkoxide Initiator for Use in the Ring-Opening Polymerization of ε-Caprolactone",* **Proceedings in MACRO 2014**, pp. 307-309.

S. Ruengdechawiwat, J. Siripitayananon, R. Somsunan, R. Molloy, P. D. Topham, B. J. Tighe, *“Synthesis, Processing and Tensile Testing of a Poly(L-lactide-co-ε-caprolactone) Monofilament Fibre for Potential Use as an Absorbable Surgical Suture”*, **Macromolecular Symposia**.

PROCEEDINGS

PURE AND APPLIED CHEMISTRY INTERNATIONAL CONFERENCE 2013 (PACCON2013)

January 23-25, 2013
Bangsaen Beach
THAILAND

SYNTHESIS AND CHARACTERIZATION OF A NOVEL TIN(II) POLY(PROPYLENE GLYCOL) ADDUCT FOR USE AS AN INITIATOR IN THE RING-OPENING POLYMERIZATION OF CYCLIC ESTERS

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Abstract: Tin(II) alkoxides are commonly used as initiators in the ring-opening polymerization (ROP) of cyclic ester monomers to control the reaction kinetics and the molecular weight of the polyesters formed. Examples are poly(ε-caprolactone) and poly(L-lactide) which are used in various biomedical applications. This project has been concerned with the synthesis and characterization of a novel tin(II) poly(propylene glycol) initiator for use in ROP of cyclic ester, namely: ε-caprolactone. The tin(II) poly(propylene glycol) was synthesized via the reaction between anhydrous tin(II) chloride, poly(propylene glycol)400 (PPG400) and triethylamine at 20-16°C under a nitrogen atmosphere. After separation and purification, the product, $Sn(PPG400)_2$, was obtained as fine white powders with approximately 93% yield. The $Sn(PPG400)_2$ was characterized by a combination of analytical techniques such as Fourier-transform infrared spectroscopy (FT-IR), proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) and differential scanning calorimetry (DSC). It was found that polymers with controllable molecular weights could be produced, when $Sn(PPG400)_2$ was used as an initiator (0.1, 0.5 and 1.0 mol%) in the bulk ROP of ε-caprolactone at1 50 °C.

1. Introduction

Aliphatic polyesters are the most widely used biodegradable polymers in biomedical applications. These applications include absorbable sutures, nerve guides, bone fixation devices, drug delivery systems and 3-D scaffolds for tissue engineering [1]. The main method used in the synthesis of biodegradable polyesters is ring-opening polymerization (ROP) of the corresponding cyclic ester monomers. The polyesters formed are versatile polymers having good mechanical properties, hydrolyzability and biocompatibility. The synthesis of novel polymer structures through ROP has been studied for a number of years [2]. The polyesters which have so far found the most commercial importance are those derived from cyclic ester monomers such as glycolide, lactide (L, D and DL) and ε-caprolactone.

Poly(ε-caprolactone), PCL, has attracted particular attention because of its partial compatibility with a number of commercial polymers such as PVC and bisphenol A polycarbonate. It is of interest as a packaging material and in biomedical applications since it is degradable and its degradation products are non-toxic to the human body [3]. PCL is a synthetic biodegradable aliphatic polyester which has been attracting increasing research attention in recent years, notably in the specialist biomedical areas of controlled-release drug delivery systems and 3-D scaffolds for tissue engineering [4-6]. PCL is manufactured commercially via the ROP in bulk of ε-caprolactone, CL, as shown in Figure 1.

Tin(II) 2-ethylhexanoate, commonly known as tin(II) octoate or stannous octoate, $Sn(Oct)_2$, in combination with an alcohol ROH is employed as the initiating system at a temperature of, typically, 140-150 °C [3].

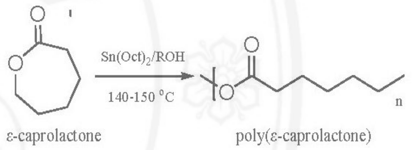


Figure 1. Ring-opening polymerization of ε-caprolactone as employed in its manufacture

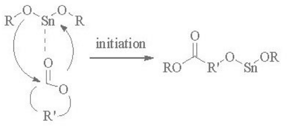
Stannous octoate, $Sn(Oct)_2$, is a frequently used initiator in the ROP of lactones and lactides. In combination with an alcohol, ROH, it is a very effective and versatile initiator which is easy to handle and is soluble in common organic solvents and lactones. It also has the advantage, as far as its use in the preparation of biomedical polymers is concerned, that the American Food and Drug Administration (FDA) has approved it as a food additive. However, $Sn(Oct)_2$ is also known to be an efficient transesterification agent which makes it difficult to synthesize controlled microstructures. Furthermore, it has now been established that $Sn(Oct)_2$ is not the true initiating species in the polymerization reaction. Instead, it has been shown that the $Sn(Oct)_2$ initiator and ROH coinitiator react together *in situ* to form the corresponding tin(II) monoalkoxide, Sn(Oct)(OR), and dialkoxide, $Sn(OR)_2$, which are the true initiators. The sequence of reactions is:

$$Sn(Oct)_2 + ROH \rightleftharpoons Sn(Oct)OR + OctH \quad (1a)$$

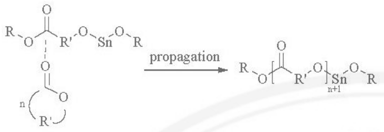
$$Sn(Oct)OR + ROH \rightleftharpoons Sn(OR)_2 + OctH \quad (1b)$$

where OctH is the octanoic acid by-product.

The generally accepted coordination-insertion mechanism of the ROP of a cyclic ester monomer by a tin(II) alkoxide, $Sn(OR)_2$, initiator is shown below in equations (2) and (3). This mechanism involves acyl-oxygen (CO-O) bond cleavage in the monomer followed by insertion into the tin-oxygen (Sn-O) bond of the initiator.



(2)



(3)

Since reactions (1a) and (1b) are interdependent equilibrium reactions, the actual [Sn(Oct)(OR)] and $[Sn(OR)_2]$ initiator concentrations are unknown throughout the polymerization. Thus, it is difficult to produce polymers with predictable and reproducible molecular weights and, in the case of copolymers, with consistent chain microstructures. It has therefore been in an attempt to overcome these uncertainties that this work has been focusing its attention on the synthesis of tin(II) alkoxides, $Sn(OR)_2$, so that they can be used directly in accurately known concentrations rather than have to be generated *in situ*.

The synthesis of tin(II) alkoxides, $Sn(OR)_2$, was first reported about 40 years ago by Morrison and Haendler [7]. It involves the reaction between anhydrous $SnCl_2$ and the corresponding alcohol ROH with triethylamine as HCl scavenger, as shown in equation (4) below.

$$SnCl_2 + 2ROH + 2(C_2H_5)_3N \longrightarrow Sn(OR)_2 + 2(C_2H_5)_3N{\cdot}HCl \quad (4)$$

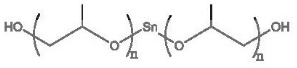
2. Materials and Methods

2.1 Initiator Synthesis

All chemicals used were purified by distillation. Since tin(II) alkoxides are both moisture and air-sensitive, their synthesis needs to be carried out using pure reagents in an inert atmosphere. Following the method of Morrison and Haendler [7], anhydrous tin(II) chloride was dissolved in poly(propylene glycol)400 (PPG400) and triethylamine added to cause a permanent precipitate. The reaction was stirred at 16-20 °C under a dry nitrogen atmosphere. The precipitate was filtered off, washed with methanol and dried under vacuum. This crude product was a mixture of the $Sn(PPG400)_2$ and the $(C_2H_5)_3N{\cdot}HCl$ by-product, as shown in reaction (5). They were separated by using chloroform to dissolve the hydrochloride after which the $Sn(PPG400)_2$ was purified and characterized.

$$SnCl_2 + 2HOROH + 2(C_2H_5)_3N \rightarrow Sn(OROH)_2 + 2(C_2H_5)_3NHCl \quad (5)$$

where HOROH = PPG400 = HO-$[CH_2(CHCH_3)O\text{-}]_n$-H
(average n ≈ 9-10)



$Sn(PPG400)_2$

The rationale behind the synthesis and use of the novel tin(II) alkoxide, $Sn(PPG400)_2$, as a coordination-insertion initiator in this work has been that, rather than being generated *in situ* in an indeterminate concentration, it could be synthesized separately and added directly into the system in an accurately known initial concentration. The main purpose of the long PPG400 substituents is to help make the initiator more soluble in cyclic ester monomers than conventional $Sn(OR)_2$ compounds synthesized from simple alcohols ROH which tend to be difficult to dissolve due to their tendency for molecular aggregation, $[Sn(OR)_2]_n$, as shown below. This insolubility greatly reduces the activity of the initiator since the Sn-O bonds, which are the active sites for polymerization, are only accessible on the surfaces of the initiator particles.

$n\ Sn(OR)_2$	→	$[Sn(OR)_2]_n$
non-aggregated		aggregated
soluble (homogeneous)		insoluble (heterogeneous)
active		less active

2.2 Bulk ROP of ε-Caprolactone

The bulk ROP of ε-caprolactone (CL) was carried out at 150 °C in a round-bottomed flask with magnetic stirring. $Sn(PPG400)_2$ initiator concentrations of 0.1, 0.5 and 1.0 mol % relative to the CL monomer were weighed accurately into the reaction flask in a glove box under dry nitrogen. After removing the flask from the glove box, it was immersed in a silicone oil bath at a constant temperature of 150 °C for 72 hrs. At the end of this period, the polymer was allowed to cool to room temperature. The crude PCL was purified by dissolving in chloroform, precipitating in ice-cooled methanol before finally drying in a vacuum oven at 45 °C to constant weight.

The purified polymers were characterized by a combination of analytical techniques, namely: Fourier-transform infrared spectroscopy (FT-IR) and proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) for structural confirmation, differential scanning calorimetry (DSC) for melting point and % crystallinity determinations, and dilute-solution viscometry for weight-average molecular weight, M_w, determination.

3. Results and Discussion

3.1 $Sn(PPG400)_2$ Initiator Characterization

The purified $Sn(PPG400)_2$ initiator product was obtained as a finely divided white powder in 93% yield. Solubility testing in a range of organic solvents showed that it was only partially soluble which indicated that, despite its long PPG400 substituents, it was still aggregated to a certain extent with only the lower aggregates being able to dissolve.

In order to confirm its chemical structure, the $Sn(PPG400)_2$ initiator was characterized initially by Fourier-transform infrared spectroscopy (FT-IR), as shown in Figure 2 below.

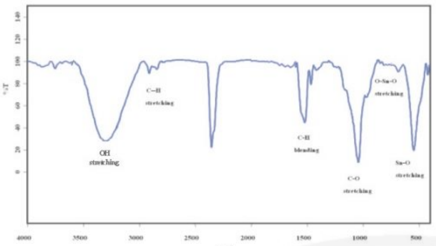


Figure 2. FT-IR spectrum of the $Sn(PPG400)_2$ initiator

The most prominent peaks in the FT-IR spectrum of $Sn(PPG400)_2$ are assigned to their respective bond vibrations as listed in Table 1 below. The appearance of these characteristic peaks is consistent with the chemical structure of $Sn(PPG400)_2$.

Table 1: Vibrational assignments in the FT-IR spectrum of the $Sn(PPG400)_2$ initiator.

Wavenumber (cm^{-1})	Vibrational Assignment
3506	O-H (stretching)
2932	C-H (stretching)
1520	C-H (bending)
1027	C-O (stretching)
676	O-Sn-O (stretching)
539	Sn-O (stretching)

The DSC thermogram of the $Sn(PPG400)_2$ initiator in Figure 3 shows a broad melting peak from 90-150 °C with a peak melting temperature (T_m) of 124.5 °C. The enthalpy of melting (ΔH_m), which is calculated from the area under the melting peak and is proportional to the % crystallinity, was 60.80 J/g.

The broad melting peak in Figure 3 is a further indication of the $Sn(PPG400)_2$ initiator's molecular aggregation and also the distribution in the degree of aggregation. Larger aggregates would be expected to have a higher T_m than smaller aggregates.

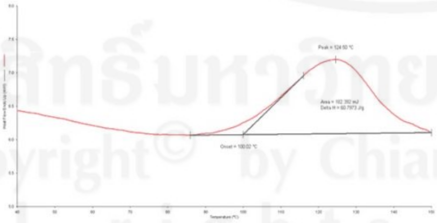


Figure 3. DSC thermogram of the $Sn(PPG400)_2$ initiator (Heating rate = 10 °C/min)

3.2 Polymerization of CL Monomer

In this work, bulk polymerization (CL monomer + $Sn(PPG400)_2$ initiator only) was the chosen method of polymerization since (a) it eliminated any complicating solvent effects and (b) biomedical polyesters are invariably synthesized by bulk polymerization in order to avoid potentially toxic trace amounts of solvent impurities remaining in the final product. The results obtained from the three polymerization experiments carried out here are summarized in Table 3 below.

The purified PCL was characterized by nuclear magnetic resonance spectroscopy (^1H-NMR) for structural confirmation as shown in Figure 4 and Table 2 below.

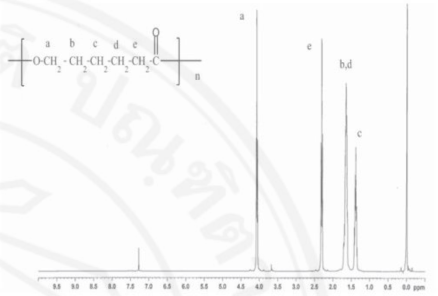


Figure 4. 400 MHz ^1H-NMR spectrum of PCL in deuterated chloroform ($CDCl_3$) as solvent.

Table 2: Chemical shifts of the peaks in the ^1H-NMR spectrum of PCL in Figure 4.

Proton Assignment		Chemical Shift (δ, ppm)
ε - CH_2	a	4.045
δ – CH_2	b	1.634
γ – CH_2	c	1.383
β – CH_2	d	1.634
α – CH_2	e	2.290

Table 3: Comparison of PCL properties obtained using various initiator concentrations.

[Initiator] % by mol	Yield %	T_m* °C	[η]** dl/g	M_w
0.1	73.8	65.7	0.629	2.82×10^4
0.5	83.8	64.3	0.378	1.53×10^4
1.0	89.5	66.5	0.336	1.32×10^4

* taken as the peak T_m from the DSC melting peak

** intrinsic viscosity measured in chloroform as solvent at 30 °C

Under the temperature/time conditions (150 °C / 72 hrs) employed, the various initiator concentrations gave high yields (>70%) and reasonably high weight-average molecular weights ($M_w > 10^4$). As expected, the M_w of the PCL decreased with increasing initiator concentration, as shown in Table 3. These M_w values were obtained from dilute-solution viscometry via the

Mark-Houwink Equation below for PCL in chloroform as solvent at 30 °C [4].

$$[\eta] = 1.298 \times 10^{-4} M_w^{0.828} \text{ dl/g}$$

Table 4 shows the DSC melting parameters and % crystallinities for the PCL samples. The values, which are comparable with those of commercial samples, are similar enough to suggest that, at a molecular weight level of $M_n > 10^4$, the thermal properties and semi-crystalline morphology of PCL are fully developed.

Table 4: DSC melting points, heats of melting and % crystallinities of the purified PCL products.

[Initiator] % by mol	Melting Point T_m (°C)*	Melting Parameters	
		ΔH_m (J/g)**	% Crystallinity***
0.1	65.7	107.8	75.9
0.5	64.3	136.9	96.4
1.0	66.5	87.0	61.3

* taken as the peak T_m from the DSC melting peak

** ΔH_m = heat of melting ($\propto$ area under T_m peak)

*** calculated from the equation:

$$\% \text{ crystallinity} = (\Delta H_m/\Delta H_m^*) \times 100\%$$

where, for PCL, $\Delta H_m^* = 142$ J/g [8]

$\Delta H_m^* = \Delta H_m$ of a 100% crystalline sample

Regarding initiator solubility, which has been one of the main focal points of this work, it was observed that, during the polymerization of the CL monomer at 150 °C, the $Sn(PPG400)_2$ initiator gradually but only partially dissolved. Dissolution continued until the system became so viscous that magnetic stirring was no longer possible. Thereafter, the polymerization had to continue in the viscous melt state. However, it can be said that the $Sn(PPG400)_2$ initiator was certainly more soluble than conventional $Sn(OR)_2$ initiators made from simple ROH alcohols.

4. Conclusions

The results presented here have shown that the $Sn(PPG400)_2$ initiator is effective in the bulk ROP of CL monomer and, by varying its concentration, can control the molecular weight of the PCL polymer formed. Moreover, it is easy to prepare and stable on storage in a desiccators. Since PPG alone is already used in biomedical applications, it would be expected to be non-cytotoxic.

However, the observation that the $Sn(PPG400)_2$ initiator did not completely dissolve in CL monomer during polymerization indicates that, despite its long PPG400 substituents, molecular aggregation in the solid state still occurred to a limited extent. Consequently, even though the initiator gave high yields and reasonably high molecular weights, its efficiency would have been slightly impaired by the fact that it was not completely soluble.

In conclusion, the use of a low molecular weight polymeric diol, PPG400, instead of a simple alcohol , ROH, in the synthesis of a tin(II) alkoxide, $Sn(OR)_2$, has succeeded in reducing, but not completely eliminating the tendency for molecular aggregation.

$$n\ Sn(OR)_2 \rightarrow [Sn(OR)_2]_n$$

Based on these results, it is reasonable to conclude that initiators such as $Sn(PPG400)_2$ have considerable potential for the use as initiators in the controlled ROP of cyclic esters, especially where the polymers are designed to be used in biomedical applications.

Acknowledgements

The authors gratefully acknowledge the Department of Chemistry, Faculty of Science, Maejo University and the Polymer Research Group, Department of Chemistry, Faculty of Science, Chiang Mai University, for provision of the research facilities.

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15 March 2013

11th International Conference on Materials Chemistry (MC11)
University of Warwick, UK   8-11 July 2013

NOTIFICATION OF POSTER ACCEPTANCE

Dear Miss Ruengdechawiwat,

This letter is notification that the abstract of your paper entitled:

Controlled Synthesis and Processing of a Poly(L-lactide-*co*-ε-caprolactone) Copolymer for Biomedical Use as an Absorbable Monofilament Surgical Suture

has been accepted for ***poster presentation*** in the Biomaterials Section of the 11th International Conference on Materials Chemistry (MC11) to be held at the University of Warwick, UK, from 8-11 July 2013.

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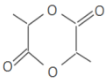
Controlled Synthesis and Processing of a Poly(L-lactide-*co*-ε-caprolactone) Copolymer for Biomedical Use as an Absorbable Monofilament Surgical Suture

Sujitra Ruengdechawiwat*, Runglawan Somsunan, Robert Molloy and Jintana Siripitayananon
Biomedical Polymers Technology Unit, Department of Chemistry, Faculty of Science,
Chiang Mai University, Chiang Mai, Thailand 50200

Abstract

The main objectives of this work are twofold: (1) to synthesize new soluble tin(II) alkoxide initiators for the controlled ring-opening polymerisation (ROP) of cyclic ester monomers and (2) to synthesize and melt spin purpose-designed copolyesters for use as monofilament absorbable surgical sutures. The chemical structures of the two cyclic ester monomers used: L-lactide (LL) and ε-caprolactone (CL), and the two initiators synthesized: tin(II) poly(propylene glycol) 400, $Sn(PPG400)_2$, and bis(tin(II) octoate) diethylene glycol, $[Sn(Oct)]_2DEG$, are shown below.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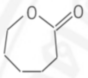
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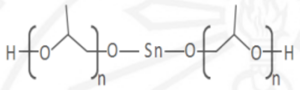
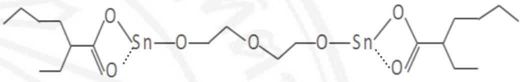
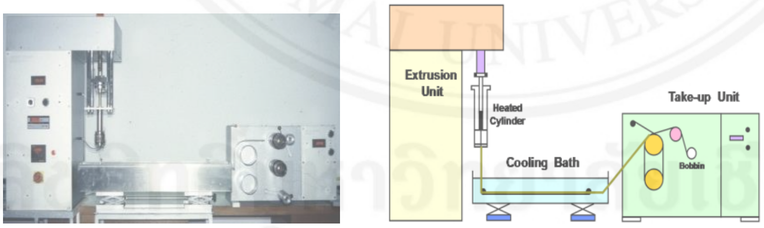

$Sn(PPG)_2$


$[Sn(Oct)]_2DEG$

Poly(L-lactide-co-ε-caprolactone), P(LL-*co*-CL), 75:25 mol % copolymers were synthesized via the bulk ROP of LL and CL at 130°C for 48 hrs using 0.02 mol % of initiator. The liquid $[Sn(Oct)]_2DEG$ initiator was found to be the more efficient due to its much easier and faster solubility than the solid $Sn(PPG400)_2$ initiator. Both copolymers were characterised and compared according to their molecular weights, monomer sequencing and thermal properties. Both P(LL-*co*-CL) copolymers could be melt spun into monofilament fibres of uniform diameter and smooth surface appearance. The required semi-crystalline morphology could be built into the as-spun fibres in a series of controlled off-line annealing and hot-drawing steps[1] resulting in tensile strengths in the region of 200-400 MPa. The small-scale melt spinning apparatus[2] and an example of the as-spun fibres obtained are shown below.



Photograph and schematic diagram of the small-scale melt spinning apparatus


Monofilament fibre

The underlying theme of this work is that it is only by understanding how the various synthesis and processing variables affect the copolymer's physico-chemical microstructure that fibres with consistent properties can be obtained. Microstructural control at the molecular level is very challenging and results so far have demonstrated that the nature and specificity of the initiator used in the ROP reaction is a key factor in achieving this.

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Biomedical Polymers Technology Unit, Department of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai, Thailand 50200

Introduction

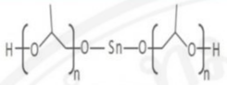
Biodegradable polymers are a class of biomaterials of growing technological importance. Cyclic esters such as L-lactide (LL), ε-caprolactone (CL) and glycolide (G) are widely used as monomers in polymer synthesis for medical applications because their co/terpolymers can degrade in the body through simple hydrolysis of the main chain ester bonds to non-toxic cleavage products.

Objectives

- To synthesize some novel, more soluble tin(II) alkoxide initiators for the controlled ring-opening polymerisation (ROP) of cyclic ester monomers
- To synthesize, melt spin and test the properties of some purpose-designed copolyesters for use as monofilament absorbable surgical sutures

INITIATOR Synthesis and Characterisation

$SnCl_2 + 2\,ROH + 2\,(C_2H_5)_3N \longrightarrow Sn(OR)_2 + 2\,(C_2H_5)_3N{\cdot}HCl$



Sn(PPG400)$_2$

PPG400 = polypropylene glycol, $\bar{M}n \approx 400$ (n ≈ 7)

$2\,Sn(Oct)_2 + DEG \longrightarrow [Sn(Oct)]_2DEG + 2\,OctH$

[Sn(Oct)]$_2$DEG

DEG = diethylene glycol = $HO\text{-}CH_2CH_2\text{-}O\text{-}CH_2CH_2\text{-}OH$

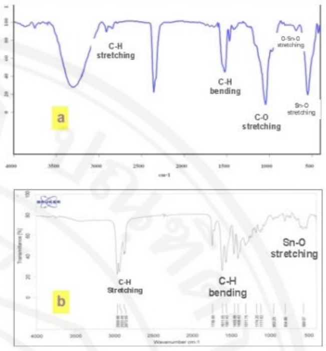
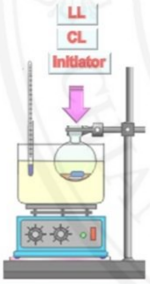
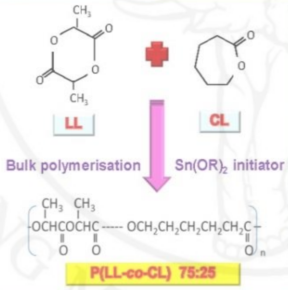


Fig. 1 FT-IR spectra of the novel initiators
(a) Sn(PPG400)$_2$ (b) [Sn(Oct)]$_2$DEG

POLYMER Synthesis and Characterisation





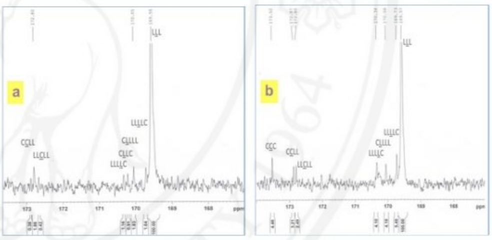
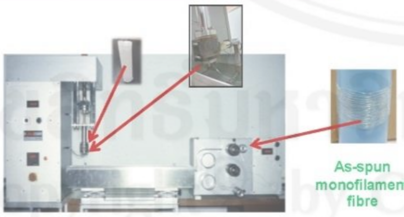


Fig. 2 ^{13}C-NMR expanded C=O regions of P(LL-*co*-CL) 75:25 using:
(a) Sn(PPG400)$_2$ (b) [Sn(Oct)]$_2$DEG
where C = caprolactone unit, LL = half L-lactide unit

FIBRE Processing and Testing



As-spun monofilament fibre

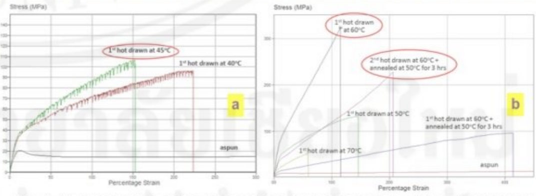


Fig. 3 Tensile testing of the fibres after controlled hot drawing and annealing from P(LL-*co*-CL) 75:25 obtained using:
(a) 0.02 mol % Sn(PPG400)$_2$ (b) 0.01 mol % [Sn(Oct)]$_2$DEG

Conclusions

The results have shown that the liquid [Sn(Oct)]$_2$DEG initiator is more efficient due to its much easier and faster solubility than the solid Sn(PPG400)$_2$ initiator. P(LL-*co*-CL) 75:25) obtained using the liquid [Sn(Oct)]$_2$DEG initiator gave the higher molecular weight (intrinsic viscosity η = 1.504 dl/g in chloroform at 30°C). Both random P(LL-*co*-CL) copolymers synthesized using 0.02 mol % Sn(PPG400)$_2$ and 0.01 mol % [Sn(Oct)]$_2$DEG could be melt spun into monofilament fibres. The mechanical strengths of the as-spun fibres could be improved by off-line annealing and hot-drawing steps. The results obtained showed that the fibre properties were strongly dependent on the matrix morphology (molecular orientation and crystallinity), draw ratio and fibre diameter.

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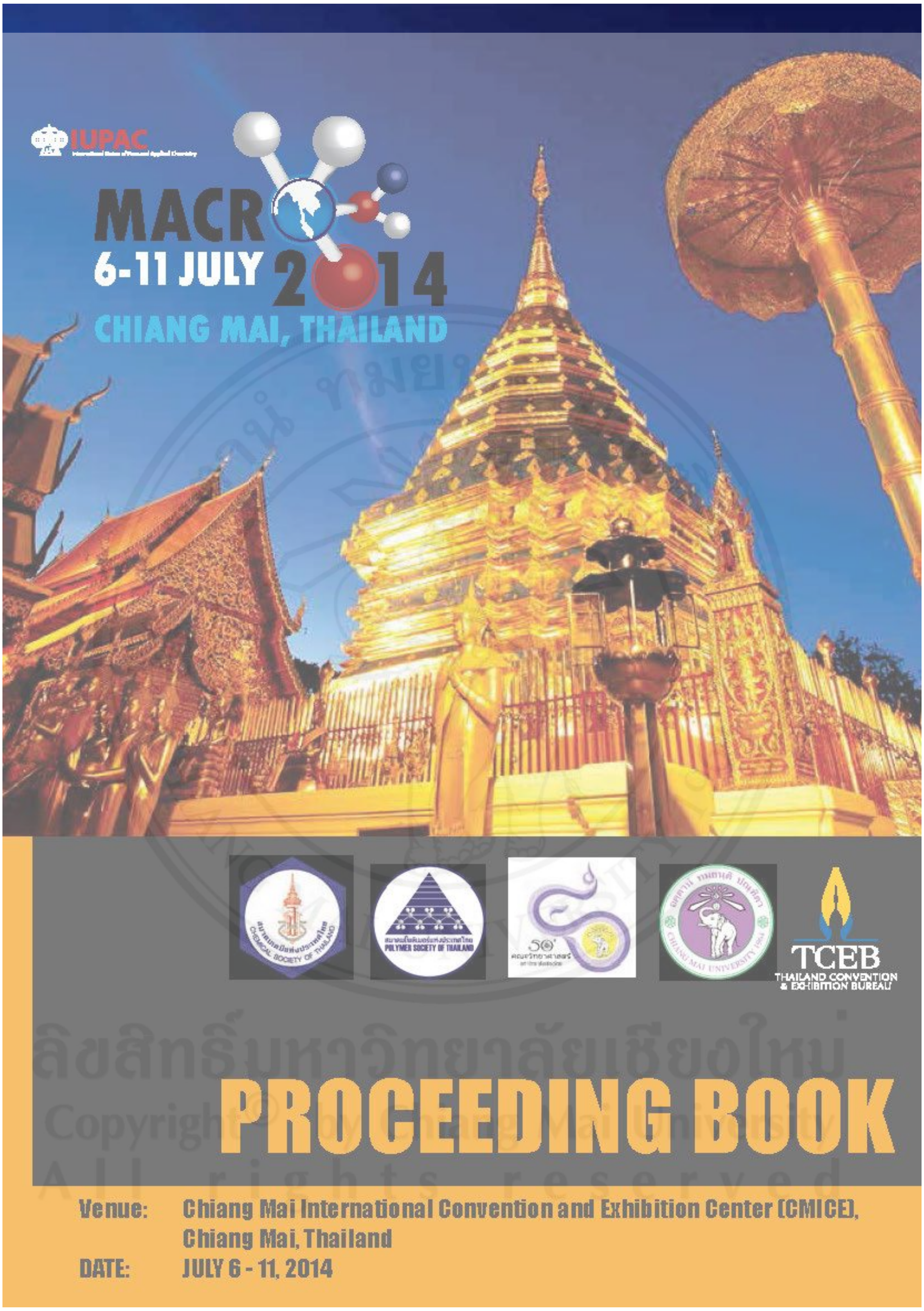
Acknowledgements

The authors wish to thank the Department of Chemistry, Faculty of Science, Chiang Mai University for providing the facilities used in this research and the National Metal and Materials Technology Center (MTEC), Thailand, for providing a research grant. The first–named author also thanks the Rajamangala University of Technology Lanna, and the Faculty of Science and the Graduate School, Chiang Mai University, for financial support.



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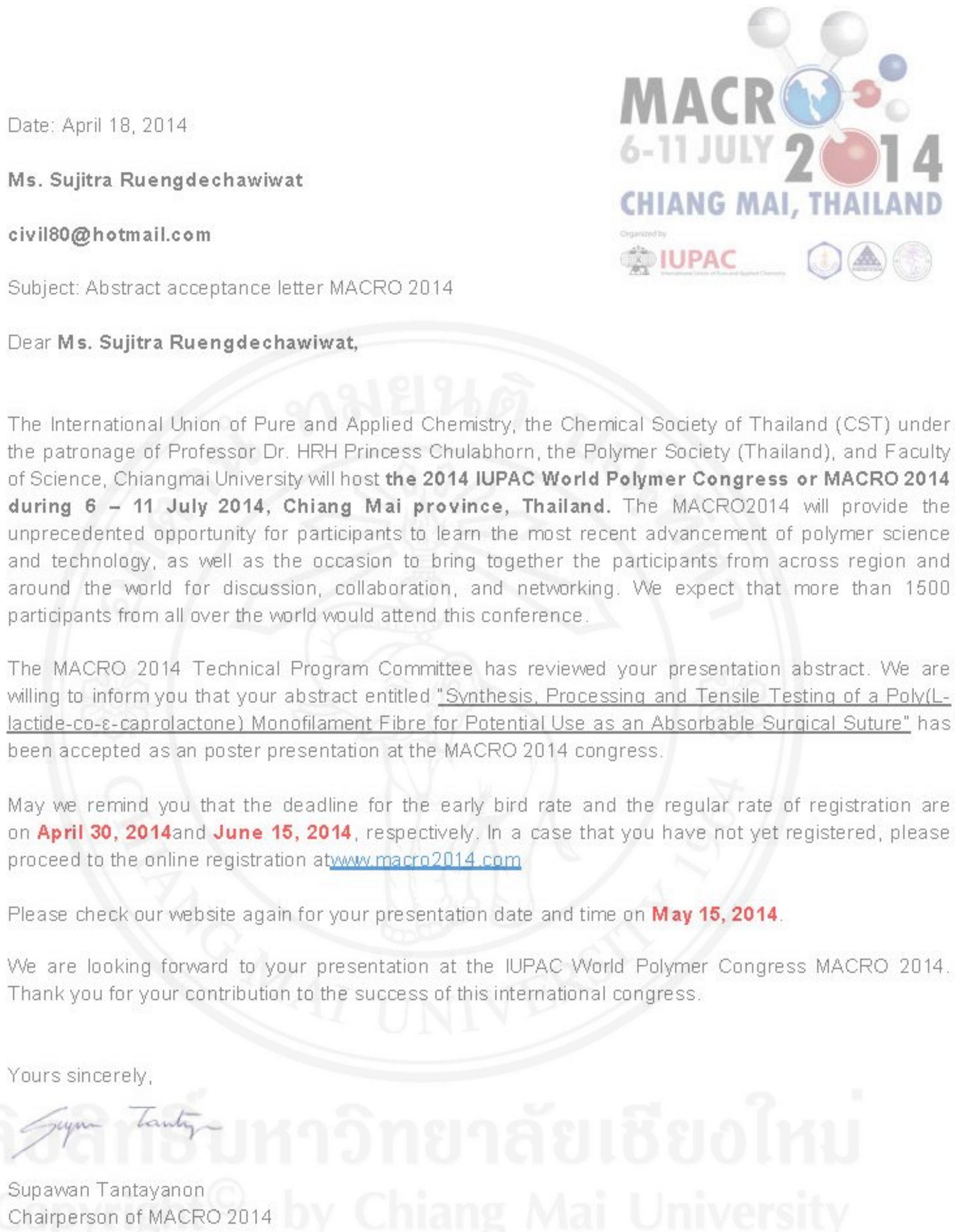

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Date: April 18, 2014

Ms. Sujitra Ruengdechawiwat

civil80@hotmail.com

Subject: Abstract acceptance letter MACRO 2014

Dear **Ms. Sujitra Ruengdechawiwat,**

The International Union of Pure and Applied Chemistry, the Chemical Society of Thailand (CST) under the patronage of Professor Dr. HRH Princess Chulabhorn, the Polymer Society (Thailand), and Faculty of Science, Chiangmai University will host **the 2014 IUPAC World Polymer Congress or MACRO 2014 during 6 – 11 July 2014, Chiang Mai province, Thailand.** The MACRO2014 will provide the unprecedented opportunity for participants to learn the most recent advancement of polymer science and technology, as well as the occasion to bring together the participants from across region and around the world for discussion, collaboration, and networking. We expect that more than 1500 participants from all over the world would attend this conference.

The MACRO 2014 Technical Program Committee has reviewed your presentation abstract. We are willing to inform you that your abstract entitled "Synthesis, Processing and Tensile Testing of a Poly(L-lactide-co-ε-caprolactone) Monofilament Fibre for Potential Use as an Absorbable Surgical Suture" has been accepted as an poster presentation at the MACRO 2014 congress.

May we remind you that the deadline for the early bird rate and the regular rate of registration are on **April 30, 2014**and **June 15, 2014**, respectively. In a case that you have not yet registered, please proceed to the online registration atwww.macro2014.com

Please check our website again for your presentation date and time on **May 15, 2014**.

We are looking forward to your presentation at the IUPAC World Polymer Congress MACRO 2014. Thank you for your contribution to the success of this international congress.

Yours sincerely,

Supawan Tantayanon
Chairperson of MACRO 2014

Synthesis, Processing and Tensile Testing of a Poly(L-lactide-*co*-ε-caprolactone) Monofilament Fibre for Potential Use as an Absorbable Surgical Suture

Sujitra Ruengdechawiwat[1], Jintana Siripitayananon[1], Runglawan Somsunan[1], Robert Molloy[1,2*],
Paul D. Topham[3], Brian J. Tighe[3]

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Abstract

A poly(L-lactide-*co*-ε-caprolactone), P(LL-*co*-CL), 75:25 mol % statistical copolymer was synthesized via the bulk ring-opening copolymerisation of L-lactide (LL) and ε-caprolactone (CL) at 130°C for 48 hrs. The initiator used was 0.02 mol % bis[tin(II) octoate] diethylene glycol, $[Sn(Oct)]_2DEG = Oct\text{-}Sn\text{-}OCH_2CH_2OCH_2CH_2O\text{-}Sn\text{-}Oct$, which had been synthesized via the reaction between $Sn(Oct)_2$ and DEG. The P(LL-*co*-CL) obtained was characterized in terms of its molecular weight (GPC: $M_n = 4.09 \times 10^4$, $M_w/M_n = 1.83$), copolymer composition (^{1}H-NMR), monomer sequencing (^{13}C-NMR) and thermal properties (DSC: $T_m = 155^oC$; TGA: $T_d = 240^oC$). For processing, the P(LL-*co*-CL) was melt spun into a monofilament fibre with fast cooling and minimal draw in order to produce a largely amorphous and unoriented as-spun fibre. The purpose of this was so that the required semi-crystalline morphology could be gradually built into the as-spun fibre and at the same time monitored in a series of controlled off-line annealing and hot-drawing steps. The final fibre, which combined a sufficiently high tensile strength with flexibility for use as a surgical suture, exhibited a tensile stress and strain at break of 344 MPa and 70 % respectively.

Keywords: L-Lactide, ε-caprolactone, ring-opening polymerisation, melt spinning, absorbable surgical suture

Synthesis, Processing and Tensile Testing of a Poly(L-lactide-*co*-ε-caprolactone) Monofilament Fibre for Potential Use as an Absorbable Surgical Suture

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Robert Molloy, Paul D. Topham, Brian J. Tighe
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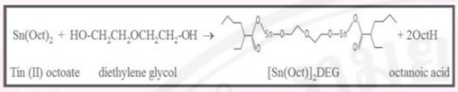
Biomaterials Research Unit, Department of Chemical Engineering and Applied Chemistry, Aston University, Birmingham B4 7ET, UK

Introduction

Biodegradable polymers, especially aliphatic polyesters, have been investigated worldwide as biomaterials for medical applications due to their biocompatibility and biodegradability. In this research, attention is focused on suture application. Attempt to synthesize a novel tin(II)alkoxide initiator for the controlled ring-opening polymerisation (ROP) of cyclic esters such as L-lactide and ε-caprolactone. Synthesized poly (L-lactide - *co* - ε - caprolactone) or PLLCL copolymer was melt spun into a monofilament fibre with suitable properties for use as an absorbable surgical suture.

NOVEL INTIATOR Synthesis and Characterisation



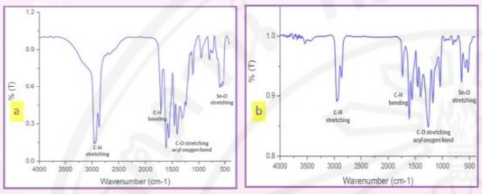


Fig. 1 FT-IR spectra of (a) Sn(Oct)$_2$ and (b) [Sn(Oct)]$_2$DEG initiators.

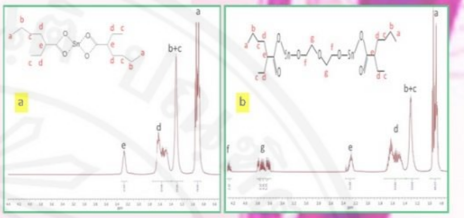
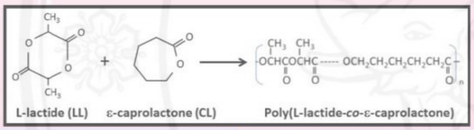


Fig. 2 ^{1}H-NMR spectra of (a) Sn(Oct)$_2$ and (b) [Sn(Oct)]$_2$DEG initiators.

POLYMER Synthesis and Characterisation



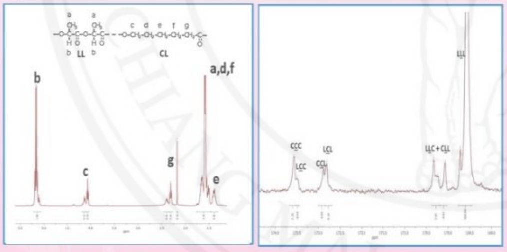


Fig. 3 ^{1}H- and ^{13}C- NMR spectra of PLLCL using [Sn(Oct)]$_2$DEG initiator

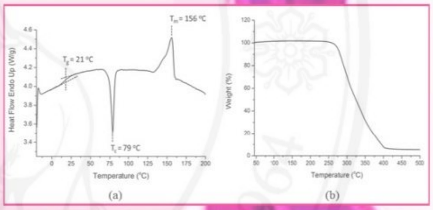


Fig. 4 DSC and TG thermograms of PLLCL using [Sn(Oct)]$_2$DEG initiator.

Table 1 Characterisation of PLLCL obtained from the two different initiators.

Initiator	Monomer composition LL:CL (mol%)	GPC	
		M_n (x 10^{-4})	PD (M_w/M_n)
Sn(Oct)$_2$	77 : 23	1.76	1.95
[Sn(Oct)]$_2$DEG	75 : 25	4.09	1.83

FIBRE Processing and Testing

Table 2 Values of stress and strain of PLLCL fibres using [Sn(Oct)]$_2$DEG initiator obtained at various stages.

Fibre Sample	Tensile Testing		
	Stress (MPa)	Strain (%)	Modulus (MPa)
As-spun	25	1363	157
First- draw	235	119	633
First-anneal	284	155	618
Second-draw	344	70	1173

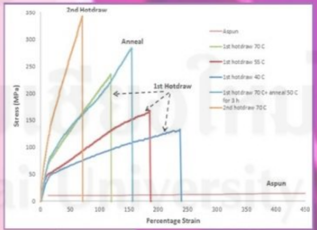


Fig. 5 Stress-strain curves of PLLCL fibres using [Sn(Oct)]$_2$DEG initiator obtained at various stages of fibre processing

Conclusions

In conclusion, the results presented here show that the novel [Sn(Oct)]$_2$DEG initiator is a more efficient initiator for the ROP of L-lactide and ε-caprolactone than the conventional Sn(Oct)$_2$ initiator, yielding a much higher M_n at the same initiator concentration of 0.02 mol %. In addition, P(LL-*co*-CL) copolymer has the potential to be developed further as an absorbable monofilament suture. The mechanical strengths of the as-spun fibres could be improved by a controlled sequence of off-line annealing and hot-drawing steps. This sequence of steps enabled the changes in mechanical properties after each step to be individually observed. The results obtained showed that the fibre properties were strongly dependent on the matrix morphology (molecular orientation and crystallinity). If this can be achieved, the copolymer could provide a viable lower-cost alternative to the current commercial monofilament absorbable sutures. It is towards this end that work in the Biomedical Polymers Technology Unit in Chiang Mai is continuing.

Acknowledgements

The authors wish to thank the National Metal and Materials Technology Center (MTEC) and the National Research University Project under Thailand's Office of the Higher Education Commission for financial support. The first-named author (S.R.) also thanks the Rajamangala University of Technology Lanna for the provision of a research grant.

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Synthesis of a Novel Tin(II) Ester Alkoxide Initiator for Use in the Ring-Opening Polymerization of ε-Caprolactone

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Introduction

The development of new biodegradable polyesters is an attractive area of research aimed at producing polymers that can be used in biomedical and pharmaceutical applications such as absorbable sutures, nerve guides, bone fixation devices and drug delivery matrices [1]. Biodegradable polymers can be either natural or synthetic. An important advantage of synthetic polymers as a class of material is that their physical and chemical properties can be varied over a wide range by, for example, advanced macromolecular architecture and copolymerization. Aliphatic polyesters prepared by ring-opening polymerization (ROP) are versatile polymers having good mechanical properties, hydrolyzability, and biocompatibility. The synthesis of novel polymer structures through ring-opening polymerization has been studied for many years [2]. The polyesters which have so far found the most commercial importance are those derived from cyclic ester monomers such as glycolide, lactide (L, D and DL) and ε-caprolactone.

Poly(ε-caprolactone), PCL, has attracted particular attention because of its partial compatibility with a number of commercial polymers such as PVC, poly(L-lactide), and bisphenol A polycarbonate. It is of interest as a packaging material and in biomedical applications since it is degradable and its degradation products are non-toxic to the human body [3]. PCL is a synthetic biodegradable aliphatic polyester which has been attracting increasing research attention in recent years, notably in the specialist biomedical areas of controlled-release drug delivery systems and 3-D scaffolds for tissue engineering [4-6]. PCL is manufactured commercially via the ROP in bulk of ε-caprolactone, CL, as shown in Figure 1. Tin(II) 2-ethylhexanoate, commonly known as tin(II) octoate or stannous octoate, $Sn(Oct)_2$, in combination with an alcohol ROH is employed as the initiating system at a temperature of, typically, 140-150 °C [3].

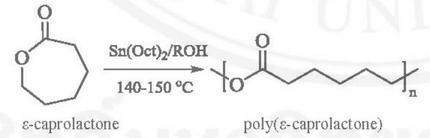


Figure 1. Ring-opening polymerization of ε-caprolactone as employed in its manufacture.

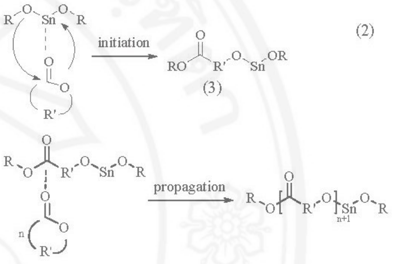
Stannous octoate, $Sn(Oct)_2$, is a frequently used initiator in the ROP of lactones and lactides. In combination with an alcohol, ROH, it is a very effective and versatile initiator which is easy to handle and is soluble in common organic solvents and lactones. It also has the advantage, as far as its use in the preparation of biomedical polymers is concerned, that the American Food and Drug Administration (FDA) has approved it as a food additive. However, $Sn(Oct)_2$ is also known to be an efficient transesterification agent which makes it difficult to synthesize controlled microstructures. Furthermore, it has now been established that $Sn(Oct)_2$ is not the true initiating species in the polymerization reaction. Instead, it has been shown that the $Sn(Oct)_2$ initiator and ROH coinitiator react together *in situ* to form the corresponding tin(II) monoalkoxide, Sn(Oct)(OR), and dialkoxide, $Sn(OR)_2$, which are the true initiators. The sequence of reactions is:

$$\mathbf{Sn(Oct)_2 + ROH \rightleftharpoons Sn(Oct)OR + OctH} \quad (1a)$$

$$\mathbf{Sn(Oct)OR + ROH \rightleftharpoons Sn(OR)_2 + OctH} \quad (1b)$$

where OctH is the octanoic acid by-product.

The generally accepted coordination-insertion mechanism of the ROP of a cyclic ester monomer by a tin(II) alkoxide, $Sn(OR)_2$, initiator is shown below in equations (2) and (3). This mechanism involves acyl-oxygen (CO-O) bond cleavage in the monomer followed by insertion into the tin-oxygen (Sn-O) bond of the initiator.



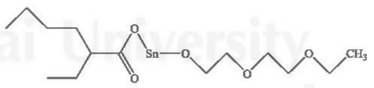
Since reactions (1a) and (1b) are interdependent reversible reactions, the actual [Sn(Oct)(OR)] and $[Sn(OR)_2]$ initiator concentrations are unknown throughout the polymerization. Thus, it is difficult to produce polymers with predictable and reproducible molecular weights and, in the case of copolymers, with consistent chain microstructures. It has therefore been in an attempt to overcome these uncertainties that this work has focused its attention on the synthesis of a novel tin (II) alkoxide, $Sn(OR)_2$, so that it can be used directly in an accurately known concentration rather than have to be generated *in situ*.

Experimental

Initiator Synthesis

All chemicals used were purified by distillation. Since tin(II) alkoxides are both moisture and air-sensitive, their synthesis needs to be carried out using pure reagents in an inert atmosphere. Tin(II) octoate was heated under vacuum with diethylene glycol monoethyl ether (DEGMEE) after which the (Oct)Sn(DEGMEE) product was characterized by Fourier-transform infrared spectroscopy (FT-IR) and proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) for structural confirmation.

$$Sn(Oct)_2 + DEGMEE \rightarrow (Oct)Sn(DEGMEE) + OctH \quad (4)$$



(Oct)Sn(DEGMEE)

The rationale behind the synthesis and use of this novel tin(II) alkoxide, (Oct)Sn(DEGMEE), as a coordination-insertion initiator in this work has been that, rather than being generated *in situ* in an indeterminate concentration, it is synthesized separately

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Synthesis of a Novel Tin(II) Ester Alkoxide Initiator for Use in the Ring-Opening Polymerization of ε-Caprolactone

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Introduction

The development of new biodegradable polyesters is an attractive area of research aimed at producing polymers that can be used in biomedical and pharmaceutical applications such as absorbable sutures, nerve guides, bone fixation devices and drug delivery matrices [1]. Biodegradable polymers can be either natural or synthetic. An important advantage of synthetic polymers as a class of material is that their physical and chemical properties can be varied over a wide range by, for example, advanced macromolecular architecture and copolymerization. Aliphatic polyesters prepared by ring-opening polymerization (ROP) are versatile polymers having good mechanical properties, hydrolyzability, and biocompatibility. The synthesis of novel polymer structures through ring-opening polymerization has been studied for many years [2]. The polyesters which have so far found the most commercial importance are those derived from cyclic ester monomers such as glycolide, lactide (L, D and DL) and ε-caprolactone**.**

Poly(ε-caprolactone), PCL, has attracted particular attention because of its partial compatibility with a number of commercial polymers such as PVC, poly(L-lactide), and bisphenol A polycarbonate. It is of interest as a packaging material and in biomedical applications since it is degradable and its degradation products are non-toxic to the human body [3]. PCL is a synthetic biodegradable aliphatic polyester which has been attracting increasing research attention in recent years, notably in the specialist biomedical areas of controlled-release drug delivery systems and 3-D scaffolds for tissue engineering [4-6]. PCL is manufactured commercially via the ROP in bulk of ε-caprolactone, CL, as shown in Figure 1. Tin(II) 2-ethylhexanoate, commonly known as tin(II) octoate or stannous octoate, $Sn(Oct)_2$, in combination with an alcohol ROH is employed as the initiating system at a temperature of, typically, 140-150 °C [3].

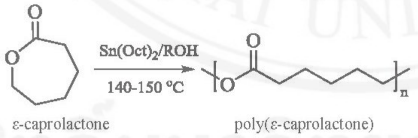


Figure 1. Ring-opening polymerization of ε-caprolactone as employed in its manufacture.

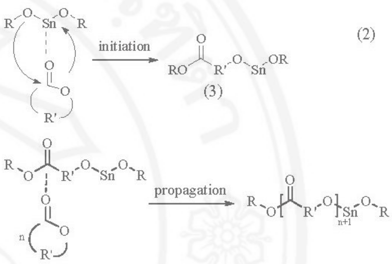
Stannous octoate, $Sn(Oct)_2$, is a frequently used initiator in the ROP of lactones and lactides. In combination with an alcohol, ROH, it is a very effective and versatile initiator which is easy to handle and is soluble in common organic solvents and lactones. It also has the advantage, as far as its use in the preparation of biomedical polymers is concerned, that the American Food and Drug Administration (FDA) has approved it as a food additive. However, $Sn(Oct)_2$ is also known to be an efficient transesterification agent which makes it difficult to synthesize controlled microstructures. Furthermore, it has now been established that $Sn(Oct)_2$ is not the true initiating species in the polymerization reaction. Instead, it has been shown that the $Sn(Oct)_2$ initiator and ROH coinitiator react together *in situ* to form the corresponding tin(II) monoalkoxide, Sn(Oct)(OR), and dialkoxide, $Sn(OR)_2$, which are the true initiators. The sequence of reactions is:

$$\mathbf{Sn(Oct)_2 + ROH \rightleftharpoons Sn(Oct)OR + OctH} \quad (1a)$$

$$\mathbf{Sn(Oct)OR + ROH \rightleftharpoons Sn(OR)_2 + OctH} \quad (1b)$$

where OctH is the octanoic acid by-product.

The generally accepted coordination-insertion mechanism of the ROP of a cyclic ester monomer by a tin(II) alkoxide, $Sn(OR)_2$, initiator is shown below in equations (2) and (3). This mechanism involves acyl-oxygen (CO-O) bond cleavage in the monomer followed by insertion into the tin-oxygen (Sn-O) bond of the initiator.



(2)

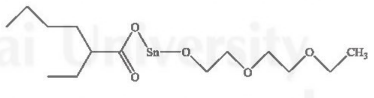
Since reactions (1a) and (1b) are interdependent reversible reactions, the actual [Sn(Oct)(OR)] and $[Sn(OR)_2]$ initiator concentrations are unknown throughout the polymerization. Thus, it is difficult to produce polymers with predictable and reproducible molecular weights and, in the case of copolymers, with consistent chain microstructures. It has therefore been in an attempt to overcome these uncertainties that this work has focused its attention on the synthesis of a novel tin (II) alkoxide, $Sn(OR)_2$, so that it can be used directly in an accurately known concentration rather than have to be generated *in situ*.

Experimental

Initiator Synthesis

All chemicals used were purified by distillation. Since tin(II) alkoxides are both moisture and air-sensitive, their synthesis needs to be carried out using pure reagents in an inert atmosphere. Tin(II) octoate was heated under vacuum with diethylene glycol monoethyl ether (DEGMEE) after which the (Oct)Sn(DEGMEE) product was characterized by Fourier-transform infrared spectroscopy (FT-IR) and proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) for structural confirmation.

$$Sn(Oct)_2 + DEGMEE \rightarrow (Oct)Sn(DEGMEE) + OctH \quad (4)$$



(Oct)Sn(DEGMEE)

The rationale behind the synthesis and use of this novel tin(II) alkoxide, (Oct)Sn(DEGMEE), as a coordination-insertion initiator in this work has been that, rather than being generated *in situ* in an indeterminate concentration, it is synthesized separately initiator concentrations gave high yields (> 80%) and reasonably high viscosity-average molecular weights ($M_v > 10^4$), as would be expected, it was found that the percentage yield increased while the molecular weight is decreased with increasing initiator concentration. These M_v values were obtained from dilute-solution viscometry via the Mark-Houwink Equation below for PCL in chloroform as solvent at 30 °C [4].

$$[\eta] = 1.298 \times 10^{-4} M_v^{0.828} \text{ dl/g}$$

Table 3 shows the DSC melting parameters and % crystallinities for the PCL samples. The values, which are comparable with those of commercial samples, are similar enough to suggest that, at a molecular weight level of $M_v > 10^4$, the thermal properties and semi-crystalline morphology of PCL are fully developed.

Table 3. DSC melting points, heats of melting and % crystallinities of the purified PCL products.

[Initiator] % mol	Melting Point T_m (°C)*	Melting Parameters	
		ΔH_m (J/g)**	% Crystallinity***
0.10	56.6	87.6	61.7
0.20	62.0	109.3	77.0

* Taken as the peak T_m from the DSC melting peak
** ΔH_m = heat of melting ($\propto$ area under T_m peak)
*** Calculated from the equation:

$$\% \text{ crystallinity} = [\Delta H_m / \Delta H^*_m] \times 100\ \%$$

where, for PCL, ΔH^*_m = 142 J/g (for a 100% crystalline sample) [7]

The bulk polymerization kinetic studies were carried out by dilatometry as shown in Figure 5-6 and Table 4. From the dilatometry data, it was found that the data fitted more closely to first-order kinetics with respect to monomer rather than zero-order kinetics with a first-order data constant, k_1, of 2.7×10^{-2} min^{-1}.

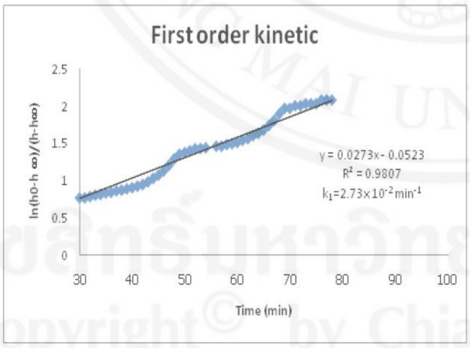


Figure 5. First-order kinetic plots of the bulk CL polymerization at 130 °C using 0.1 mol % initiator.

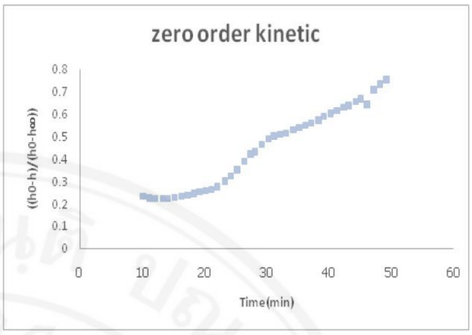


Figure 6. Zero-order kinetic plots of the bulk CL polymerization at 130 °C using 0.1 mol % initiator.

Table 4. Comparison of the zero-order, k_0, and first-order, k_1, rate constants of CL polymerization at 130 °C from dilatometry.

[Initiator] mol %	k_0 (min^{-1})	k_1 (min^{-1})	M_v
0.10	7.1×10^{-3}	2.7×10^{-2}	2.13×10^4
0.20	1.4×10^{-2}	3.2×10^{-2}	1.23×10^4

Conclusions

The results presented here have shown that the (Oct)Sn(DEGMEE) initiator is effective in the bulk ROP of CL monomer. Since it is the true initiator for coordination-insertion and can be added in an accurately known concentration, it can yield polymer with predictable and reproducible molecular weights. This is an important advantage for polymers which use in biomedical applications.

Acknowledgements

The authors gratefully acknowledge the Department of Chemistry, Faculty of Science, Maejo University and the Polymer Research Group, Department of Chemistry, Faculty of Science, Chiang Mai University, for provision of the research facilities.

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Synthesis of a Novel Initiator in Ring Opening Polymerization of ε-Caprolactone

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Introduction

Aliphatic polyesters are the most widely used biodegradable polymers in biomedical applications. These applications include absorbable sutures, nerve guides, bone fixation devices and drung delivery systems for tissue engineering [1]. The main method used in the synthesis of biodegradable polyesters is ring-opening polymerization (ROP) of the corresponding cyclic ester monomers. The polyesters formed are versatile polymers having good mechanical properties, hydrolyzability biocompatibility. The synthesis of novel polymer structures through ROP has been studied for a number of years [2]. The polyesters which have so far found the most commercial importance are those derived from cyclic ester monomers such as glycolide, lactide (L, D and DL) and ε-caprolactone.

Experimental

1.Initiator

Sn(Oct)+(DEG monoethyl ether) ⟶ Sn(Oct DEG monoethyl ether)2

Figure 1. synthesis of the Sn(Oct DEG monoethylether)2 Initiator

2. Bulk ROP of ε - Caprolactone

ε-caprolactone + Sn(Oct DEG monoethyl ether)$_2$*

130oC ↓ **48 hrs**

Poly (ε-caprolactone), PCL

*** [Initiator] : 0.02, 0.10, 0.20 mol%**

Figure 2. Bulk polymerization

Conclusions

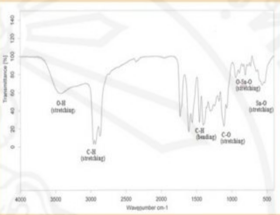
The results presented here have shown that the Sn(Oct DEG monoethyl ether)$_2$ initiator is effective in the bulk ROP of CL monomer and, by varying its concentration, can control the molecular weight of the PCL polymer formed.

Results and Discussion

1. Sn(Oct DEG monoethylethey)$_2$ Innitiator Characterization

The Sn(Oct DEG monoethylether)$_2$ initiator product was obtained as a finely divided white liquid in 98% yield.

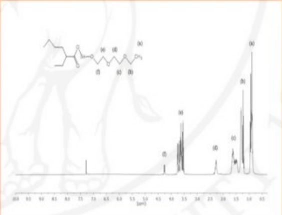
Fourier-transform infrared spectroscopy (FT-IR)



Wavenumber (cm^{-1})	Vibrational Assignment
3359	O-H (stretching)
2960	C-H (stretching)
1459	C-H(bending)
1110	C-O (stretching)
807	O-Sn-O (stretching)
568	Sn-O (stretching)

Figure 3. FT-IR spectrum of Sn(Oct DEG monoethylether)2 initiator

Nuclear magnetic resonance spectroscopy (^{1}H-NMR)



Proton Assignment	Chemical Shift (δ,ppm)
$-CH_3$ a	0.94
$-CH_2$ b	1.25
$-CH_2$ c	1.75
$-CH_2$ (-O-) d	2.25
$-CH_2$ e	3.50
$-CH_2$ f	4.25

Figure 4. 400 MH$_Z$ ^{1}H-NMR spectrum of Sn(Oct DEG monoethylether)$_2$

2. Polymerization of CL monomer

Table 1. Comparison of PCL properties obtained using various initiator concentrations

[Initiator] % by mol	Yield %	T_m °C	Melting Parameters		[η] dl/g	k_1	M_w**
			ΔH_m (J/g)	%Crystallinity*			
0.02	76.5	61.1	109.7	72.2	0.629		2.82×10^4
0.10	83.1	56.6	87.6	61.7	0.378	2.7×10^{-2}	1.53×10^4
0.20	89.3	62.0	109.3	77.0	0.336	3.2×10^{-2}	1.32×10^4

The (CL monomer + Sn(Oct DEG monoethylether)$_2$ initiator only) kinetic studies were carried out by dilatometry as shown in Figure 5.

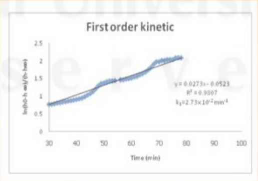


Figure 5 First order kinetic

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Ring-Opening Polymerization of Cyclic Ester Monomers for the Synthesis of Biodegradable Polyesters

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Biodegradable polymers are versatile materials with a wide range of applications including surgical sutures, scaffolds, matrix materials for tissue-engineering and regenerative medicine, biodegradable packaging and agriculture. The ring-opening polymerization of cyclic ester monomers such as L-lactide and Ɛ-caprolactone has been studied using novel organotin compounds as coordination-insertion initiators. In this research, a novel initiator was synthesized via the reaction between tin(II) octoate and diethylene glycol monoethyl ether at 130 °C under vacuum. After purification, it was obtained as a colourless liquid. The poly(L-lactide) and poly(Ɛ-caprolactone) products were characterized by a combination of analytical techniques such as fourier-transform infrared spectroscopy (FT-IR),thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC).The organotin initiator were used in concentration of 0.10, 0.20, 0.50 and 1.0mol% in the bulk ROP of Ɛ-caprolactone at 130°C and their efficiencies compared. The molecular weights of the poly(Ɛ-caprolactone) products were determined by dilute-solution viscometer. The results showed that an initiator concentration of 0.10 mol% gave the highest viscosity-average molecular weights 2.13×10^4.

Keywords Biodegradable polyesters; Ring-opening polymerization; Poly(L-lactide); Poly(Ɛ-caprolactone)

Ring-Opening Polymerization of Cyclic Ester Monomers for the Synthesis of Biodegradable Polyesters

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Abstract

Biodegradable polymers are versatile materials with a wide range of applications including surgical sutures, scaffolds, matrix materials for tissue-engineering and regenerative medicine, biodegradable packaging and agriculture. The ring-opening polymerization of Ɛ-caprolactone monomer has been studied using novel organotin compounds as coordination-insertion initiators. In this research, a novel initiator was synthesized via the reaction between tin(II) octoate and diethylene glycol monoethyl ether at 130 °C under vacuum. After purification, it was obtained as a colourless liquid. The poly(Ɛ-caprolactone) products were characterized by a combination of analytical techniques such as fourier-transform infrared spectroscopy (FT-IR), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and dilute-solution viscosity. The organotin initiator were used in concentration of 0.10, 0.20, 0.50 and 1.00 mol% in the bulk ROP of Ɛ-caprolactone at 130°C, 140°C and their efficiencies compared. The molecular weights of the poly(Ɛ-caprolactone) products were determined by dilute-solution viscometer. The results showed that an initiator concentration of 0.10 mol% gave the highest viscosity-average molecular weights.

Experimental

1. Synthesis of initiator :

$Sn(Oct)_2$ + Diethylene glycol monoethyl ether
(1 : 1)

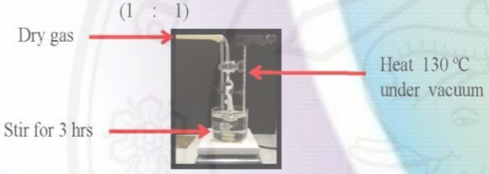
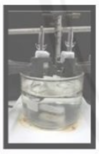


Figure 1. Synthesis of tin(II) octoate diethylene glycol monoethyl ether.

2. Polymerization of Ɛ-caprolactone :



Ɛ-caprolactone + Sn(Oct) DEGMEE

130 °C, 140 °C
for 48 and 72 hrs

Poly(Ɛ-caprolactone)

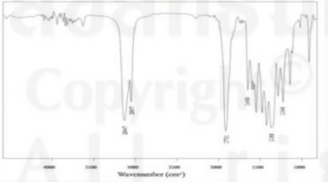
Figure 2. Bulk polymerization.

3. Analysis of poly(Ɛ-caprolactone) :

3.1 Fourier-transform infrared spectroscopy (FT-IR)
3.2 Dilute-Solution Viscosity
3.3 Differential Scanning Calorimetry (DSC)
3.4 Thermogravimetric Analysis (TGA)

Results and Discussions

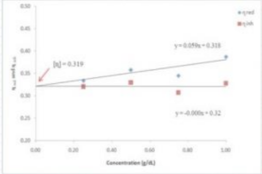
1. Fourier-transform infrared spectroscopy (FT-IR)



Wavenumbers (cm^{-1})	Vibration Assignment
2947, 2867	C-H (stretching)
1731	C-O (stretching)
1469	C-H (bending)
1189	C-O (stretching)
1046	C-O (stretching)

Figure 3. FT-IR spectrum of poly(Ɛ-caprolactone) using tin(II) Octoate diethylene glycol monoethyl ether 0.10 mol% as initiator, 130°C for 48 hrs.

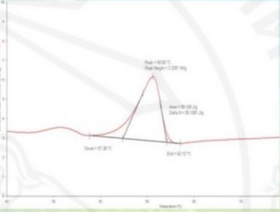
2. Dilute-Solution Viscosity



Molecular weights				
Temperature + Time / Concentration of Initiator (mol%)	130°C		140°C	
	48 hrs	72 hrs	48 hrs	72 hrs
0.10	1.39×10^4	1.24×10^4	1.98×10^4	2.13×10^4
0.20	1.37×10^4	1.21×10^4	1.82×10^4	1.15×10^4
0.50	1.07×10^4	1.16×10^4	1.42×10^4	1.14×10^4
1.00	1.00×10^4	1.01×10^4	1.18×10^4	0.89×10^4

Figure 4. Graph show relative between concentration and η_{red} and η_{inh} of poly(Ɛ-caprolactone) using tin(II) Octoate diethylene glycol monoethyl ether 0.10 mol% as initiator, 130°C for 72 hrs.

3. Differential Scanning Calorimetry (DSC)



Polymer	DSC Thermal Transition	Melting Parameter	
	T_m (°C)	ΔH_m J/g	Crystallinity (%)
PCL 130°C, 48 hrs	61.43	89.4048	62.96
PCL 130°C, 72 hrs	60.60	58.1081	40.92
PCL 140°C, 48 hrs	62.69	97.7006	68.80
PCL 140°C, 72 hrs	57.28	82.5466	58.13

Note : Polymer using 0.10 mol% initiator

Figure 5. DSC thermogram of poly(Ɛ-caprolactone) using tin(II) Octoate diethylene glycol monoethyl ether 0.10 mol% as initiator, 130°C for 72 hrs. (Heating rate = 10°C/min; N_2 pure gas)

4. Thermogravimetric Analysis (TGA)

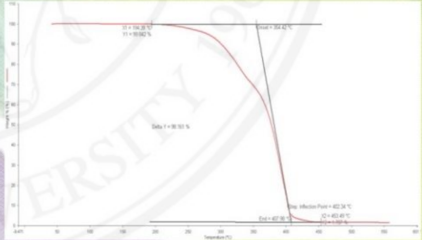


Figure 6. TGA thermogram of poly(Ɛ-caprolactone) using tin(II) Octoate diethylene glycol monoethyl ether 0.10 mol% as initiator, 130°C for 72 hrs.

Conclusions

FT-IR spectrum of poly(Ɛ-caprolactone) products can concern the structure. The results of dilute-solution viscosity showed that an initiator concentration of 0.10 mol% heated 140°C for 72 hrs gave the highest viscosity-average molecular weights 2.13×10^4. From DSC thermogram can relate to % crystallinity which have 40.92 – 68.80%. From TGA thermogram found that there is one step degradation.

Acknowledgements

The authors gratefully acknowledge Department of Chemistry, Faculty of Science, Maejo University and Polymer Research Group, Department of Chemistry, Faculty of Science, Chiang Mai University for provision of the research facilities.

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Acceptance Letter

2014 The 4th International Conference on Advanced Materials Research
(ICAMR 2014)
Macau, China, Jaunary22 - 23, 2014
www.icamr.org

Paper ID: R067

Paper Title: Controlled Synthesis and Processing of a Poly(L-lactide-co- ε-caprolactone) Copolymer for Biomedical Use as an Absorbable Monofilament Surgical Suture

Dear Sujitra Ruengdechawiwat, Runglawan Somsunan, Robert Molloy and Jintana Siripitayananon，

With heartiest congratulations I am pleased to inform you that based on the recommendations of the reviewers and the Technical Program Committees, your paper identified above has been accepted for publication and oral presentation by **2014 The 4th International Conference on Advanced Materials Research (ICAMR 2014).**

ICAMR 2014conference received over 140 submissions from countries and regions so far, reviewed by international experts; the acceptance ratio is controlled below40%. Your paper will be published in the Advanced Materials Research Journal after registration.

Herewith, the conference committee sincerely invites you to come to present your paper at ICAMR 2014 to be held in **Macau, China, Jaunary22 - 23, 2014.**

Yours sincerely,

ICAMR 2014 Organizing Committees
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Advanced Materials Research Vol. 894 (2014) pp 172-176
© (2014) Trans Tech Publications, Switzerland
doi:10.4028/www.scientific.net/AMR.894.172

Controlled Synthesis and Processing of a Poly(L-lactide-*co*-ε-caprolactone) Copolymer for Biomedical Use as an Absorbable Monofilament Surgical Suture

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Keywords: L-lactide, ε-caprolactone, ring-opening polymerisation, melt spinning, absorbable surgical suture, biomedical applications.

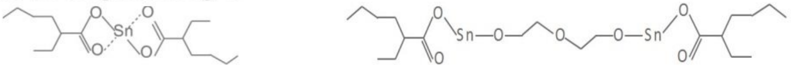
Abstract. Poly(L-lactide-*co*-ε-caprolactone) 75:25 % mol, P(LL-*co*-CL), was synthesized via bulk ring-opening polymerisation (ROP) using a novel tin(II)alkoxide initiator, $[Sn(Oct)]_2DEG$, at 130°C for 48 hrs. The effectiveness of this initiator was compared withthe well-known conventional tin(II) octoateinitiator, $Sn(Oct)_2$. The P(LL-*co*-CL) copolymersobtained were characterized using a combination of analytical technique including: nuclear magnetic resonance spectroscopy (NMR), differential scanning calorimetry (DSC), thermogravimetry (TG) and gel permeation chromatography (GPC). The P(LL-*co*-CL) was melt-spun into monofilament fibres of uniform diameter and smooth surface appearance. Modification of the matrix morphology was then built into the as-spun fibresvia a series of controlled off-line annealing and hot-drawing steps.

Introduction

Aliphatic polyesters have been investigated worldwide as biomaterials which are useful for biomedical and pharmaceutical applications such as absorbable sutures, nerve guides, bone fixation devices and drug delivery matrices [1-4].Biodegradable polymers break down in physiological environments by random chain scission into smaller fragments and ultimately into simple stable end-products. The main mechanism of degradation in the human body has been shown to be by simple hydrolysis of the main chain ester groups. This occurs by acyl-oxygen bond scission resulting ultimately in the release of low molecular weight products. These hydrolysis products are non-toxic and are eliminated from the body by the normal metabolic processes[5-6]. Most of these polymers have degradable backbones that are composed of esters, anhydrides, carbonates, urethanes and so forth. One of the most frequent applications of biodegradable polymers prepared from α-hydroxy acids(glycolic acid, lactic acid) and ε-caprolactone is in orthopeady [7-11]. The most widely used initiating system for research purposes and for the technical production of polylactides and related copolyestersis tin(II) octoate, $Sn(Oct)_2$, in combination with an alcohol to produce a tin(II) alkoxide*in situ* as the "true" initiating species [12-13]. However, the tin(II) alkoxide is produced in an unknown concentration and so attention has been focussed in this work on synthesizing a novel soluble tin(II) alkoxidewhich can be used directly rather than generated *in situ*. The ultimate objective is then to process the copolymer into amonofilament fibre with suitable properties for use as an absorbable surgical suture.

Experimental

Synthesis and Characterisationof Tin(II)Alkoxide Initiator. The two polymerisation initiators used in this work are tin(II)octoate,($Sn(Oct)_2$, systematic name: tin(II) bis(2-ethylhexanoate), and a novel tin(II)alkoxide, $[Sn(Oct)]_2DEG$,bis(tin(II) octoate) diethyleneglygol.Their molecular structures are compared in Fig. 1.



tin(II)octoate, $Sn(Oct)_2$ bis(tin(II) octoate) diethyleneglygol ($[Sn(Oct)]_2DEG$)

Fig.1 Molecularstructures of the polymerisation initiators used.

The $[Sn(Oct)]_2DEG$ initiator was prepared from the reaction between diethylene glycol (DEG), $HOCH_2CH_2OCH_2CH_2$-OH, and $Sn(Oct)_2$,as shown below. The product, $[Sn(Oct)]_2DEG$, was characterized by FT-IR and^{1}H-NMR to confirm its chemical structure, as shown in Fig. 2. The by-product of the reaction was octanoic acid (OctH).

$$2\ Sn(Oct)_2 + HO\text{-}CH_2CH_2OCH_2CH_2\text{-}OH \rightarrow [Sn(Oct)]_2DEG + 2\ Oct$$

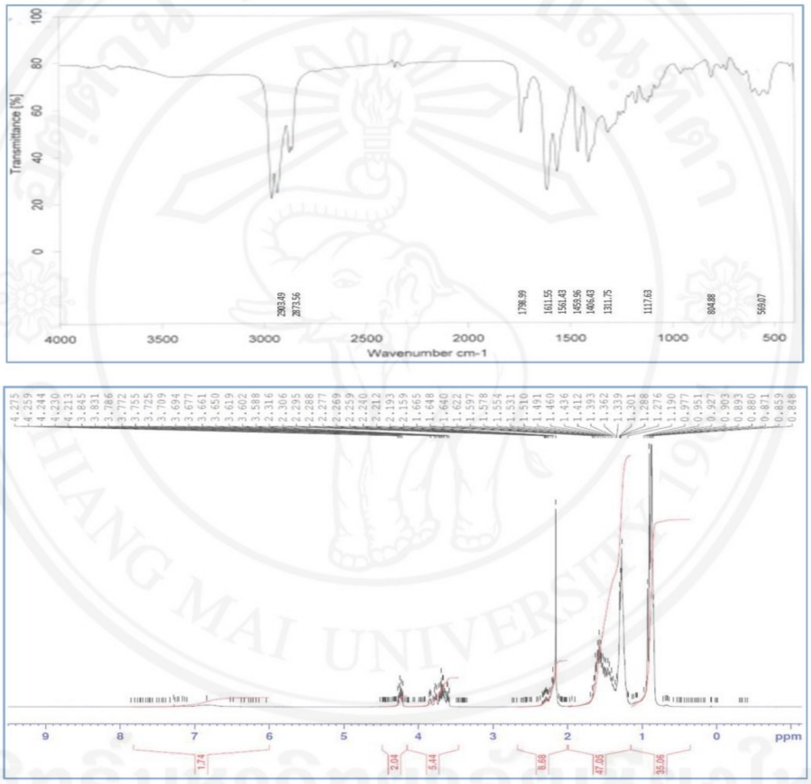


Fig. 2FT-IR and ^{1}H-NMR spectra of the synthesized initiator$[Sn(Oct)]_2DEG$.

Monomer Preparation.L-Lactidemonomerwas purified before use by recrystallisation from distilled ethyl acetate and dried to constant weight at 55°C in a vacuum oven. ε-Caprolactone monomer was purified by vacuum distillation. Purified ε-caprolactone was obtained as a clear colorless liquid and was stored over molecular sieves in a refrigerator in a tightly sealed container until required for use.

Polymerisation and Characterisation of Poly(L-lactide-co-ε-caprolactone). Poly(L-lactide-co-ε-caprolactone), P(LL-*co*-CL), with a mole % composition of LL:CL = 75:25 was obtained by ring-opening polymerisation (ROP) of L-lactide and ε-caprolactonein bulk under dry nitrogen at 130°C for 48 hrs, as shown in Fig. 3. The crude copolymer was purified by cutting into small pieces to increase its surface area and then drying to constant weight in a vacuum oven at 80°C to remove any trace amounts of residual monomers.

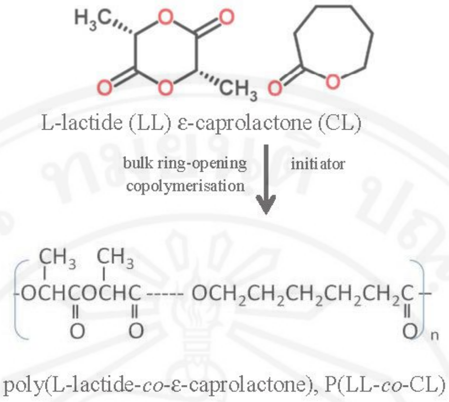


Fig.3Bulk ring-opening copolymerisation of L-lactide (LL) and ε-caprolactone (CL).

P(LL-*co*-CL) obtained using the two different initiators were characterized byDSC, TG and GPC. DSC and TG characterized the thermal properties while GPC gave the number-average molecular weights, M_n, and polydispersities, PD. The results are summarized in Table 1.

Table 1 Characterization of the P(LL-*co*-CL)copolymers obtained from the twodifferent initiators.

Initiator	Initiator Conc. (%mol)	DSC*		TG**	GPC***	
		T_m (°C)	ΔH_m (J/g)	T_d (°C)	Mn	PD
$Sn(Oct)_2$	0.02	143	19.7	234	17,658	1.9538
$[Sn(Oct)]_2DEG$	0.02	153	11.6	240	40,882	1.8263

* Tm and ΔHm were measured by DSC at a heating rate of 10 °C/min from 0 to 200 °C under dry nitrogen

** Thermal degradation was measured by TG at a heating rate of 20 °C/min from 50 to 450 °C under dry nitrogen

***GPC measurements were carried out using tetrahydrofuran (THF) as the solvent at a flow-rate 1 mL min^{-1}. The system, operating at 40 °C, was calibrated with narrow molecular weight distribution polystyrene standards.

As shown in Table 1, it was found that, under the temperature/time conditions (130 °C for 48hrs) employed, both the $Sn(Oct)_2$ and $[Sn(Oct)]_2DEG$ initiators at a 0.02 %mol initiator concentration gave reasonably high number-average molecular weights ($M_n > 10^4$)with the novel$[Sn(Oct)]_2DEG$ initiator giving the higher value. Copolymer compositions were determined from peak area integrations in the ^1H-NMR spectra andwere found to be very similar to the monomer feed ratio despite the different monomer reactivities (LL > CL). From ^1H-NMR, the copolymer compositions weredetermined asLL:CL = 76:24 and 75:25 % mol for the $Sn(Oct)_2$ and $[Sn(Oct)]_2DEG$ initiators respectively.

Fibre Processing. The P(LL-*co*-CL) copolymers weremelt-spun into monofilament fibres using a small-scale melt-spinning apparatus which was capable of processing as little as 10 g of material. The as-spun fibreswere of uniform diameter in the range of 0.6-0.8 mm and were of smooth surface appearance. On their emergence from the spinnerette, the as-spun fibres were cooled quickly with only minimal draw so that they would be largely amorphous and unoriented. The reason for this was so that the required semi-crystalline morphology and molecular orientation could be gradually built into the fibres off-line via a series of well-controlled hot-drawing and annealing steps.

For hot-drawing, both the temperature and draw rate needed to be carefully chosen, while for annealing, temperature and time were similarly important. These conditions and the sequence in which they were applied were critical in determining the degree of induced molecular orientation and crystallinity which, in turn, determined the mechanical properties. Sufficient tensile strength combined with sufficient flexibility (good handling properties) is essential for a monofilament fibre to be used as a surgical suture.

Tensile Testing. Fibre tensile strength was determined at ambient temperature using a Lloyds LRX+ Universal Testing Machineequipped with a 100 N load celland bollard grips. The initial gauge length of each fibre test sample was 40 mm and the test was carried out at a crosshead speed of 80 mm/min. The stress-strain curvesof the P(LL-*co*-CL) fibre, obtained using $[Sn(Oct)]_2DEG$ as the initiator, are shownin Fig. 4 and Table 2 at various stages of processing.

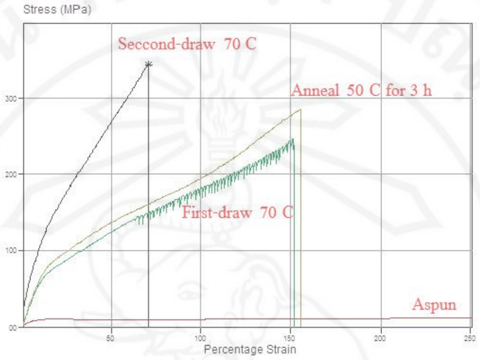


Fig.4Stress-strain curves of P(LL-*co*-CL) fibresusing $[Sn(Oct)]_2DEG$ as the initiator obtained at various stages of fibre processing

Table 2:Values of stress and strain at break from the curves shown above in Fig. 4.

Fibre Sample	Tensile Testing	
	Stress (MPa)	Strain (%)
As-spun	25	1368
First- draw	247	151
First-anneal	284	155
Second-draw	344	70

Conclusions

The copolymer synthesis results have shown that the novel $[Sn(Oct)]_2DEG$ initiator is a more efficient initiator for the ROP of L-lactide and ε-caprolactone than the conventional $Sn(Oct)_2$ initiator, yielding a much higher M_n at the same initiator concentration of 0.02 mol %. However, both initiators producedP(LL-*co*-CL) copolymers which were of sufficiently high M_n to be melt spun into monofilament fibres. The mechanical strengths of the as-spun fibres could be improved by a controlled sequence of off-line annealing and hot-drawing steps. This sequence of steps enabled the changes in mechanical properties after each step to be individually observed. The results obtained showed that the fibre properties were strongly dependent on the matrix morphology (molecular orientation and crystallinity).

Thus, the overall conclusion to be drawn from this work is that, in order to develop a polymer for use in such a specialist application as a surgical suture in which the property requirements are very stringent, it is essential to control each step of both the synthesis and processing procedures. While the synthesis procedure determines the copolymer's chemical microstructure, the processing stage determines the fibre's physical microstructure. Understanding the combination of the two and how they relate to properties is the key to the successful development of a new material.

Acknowledgements

The authors wish to thank the Department of Chemistry, Faculty of Science, Chiang Mai University for providing the facilities used in this research and the National Metal and Materials Technology Center (MTEC), Thailand, and the National Research University Project under Thailand's Office of the Higher Education Commission for financial support. The first-named author also thanks the Rajamangala University of Technology Lanna for the provision of a research grant.

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ISPAC 2014
15-18 June 2014

To whom it concerns,

I certified that the abstract proposed by Sujitra Ruengdechawiwat has been accepted for an **oral presentation** at the next ISPAC meeting (Les Diablerets, Switzerland).

The title of the presentation is "Synthesis and Characterisation of a Poly(L-lactide-*co*-ε-caprolactone) Copolymer Using a Novel Tin(II) Alkoxide Initiator for Potential Use as an Absorbable Monofilament Surgical Suture"

Grenoble, on April 3th 2014

Professor M.Rinaudo
Chairman of the ISPAC 2014

Abstract

Poly(L-lactide-*co*-ε-caprolactone) 75:25 mol %, P(LL-*co*-CL), initiated by either tin(II) octoate, $Sn(Oct)_2$, or bis[tin(II)(octoate)] diethylene glycol ($[Sn(Oct)]_2DEG$]), was synthesized via bulk copolymerization at 130°C for 48 hrs. The copolymers obtained were characterized by a combination of analytical techniques, namely: nuclear magnetic resonance spectroscopy (NMR), gel permeation chromatography (GPC), differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). For processing, the copolymers were melt spun into monofilament fibers and the required oriented semi-crystalline morphology developed via a series of controlled off-line annealing and hot-drawing steps. Depending on the draw ratio, the final fibers obtained had tensile strengths in the region of 200-400 MPa.

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