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Polymerization of ε-Caprolactone and its Copolymerization with γ-Butyrolactone using Metal Complexes

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Summary: Solution polymerization of ε-caprolactone (ε-CL) was performed using four different initiators namely: tin(II) octanoate ($Sn(Oct)_2$)/ethanolamine, aluminium Schiff's base complex-HAPENAlO^{i}Pr, lithium diisopropyl amide (LDA) and aluminium isopropoxide. The reaction conditions varied with the initiator used. LDA gave rise to the most rapid polymerization with the highest amount of cyclic species as detected by ^{13}C NMR. However, no cyclic species were detected when HAPENAlO^{i}Pr was used as initiator. The tin(II) octanoate/ethanolamine system lead to an α,ω-dihydroxy-polycaprolactone (PCL). The copolymerization of ε-CL was then performed with the hard to oligomerize γ-butyrolactone using the four initiators. GPC (Gel Permeation Chromatography) analyses showed the formation of copolymers. The highest incorporation of polybutyrolactone (PBL) in the copolymer was obtained using HAPENAlO^{i}Pr as evidenced by ^{1}H NMR. ^{13}C NMR indicated the presence of pseudoperiodic random copolymers with short blocks of PCL whose block length varied with initiator used. The longest and shortest block length were obtained using $Sn(Oct)_2$ and HAPENAlO^{i}Pr respectively as calculated from ^{13}C NMR. The reactivity ratios were determined using the Finemann-Ross method at low conversion with HAPENAlO^{i}Pr as initiator. The values obtained, $r_{CL} = 19.4$ and $r_{BL} = 0.11$, confirmed the presence of long blocks of CL units in the copolymer.

Keywords: copolymers; γ-butyrolactone; polycaprolactone; polyesters; reactivity ratio

Introduction

Polycaprolactone (PCL) is a polyester, which is very attractive due to a valuable set of properties such as high permeability, biodegradability and capacity to be blended with various commercial polymers or biopolymers. However, the high crystallinity and hydrophobicity of PCL result in long *in vivo* degradation times ranging from 1 to 2 years[1]. Previous studies have shown that the copolymerization with a second lactone monomer results in variation of degradation rates of PCL. For instance, copolymers of ε-caprolactone and γ-butyrolactone (70:30%) synthesized using direct ring-opening copolycondensation in the absence of a catalyst degrade 2.5 times faster than a PCL homopolymer[1].

The polymerization of ε-caprolactone (ε-CL) has been extensively studied, both via anionic and coordination-insertion pathways. Anionic polymerization of ε-CL has been carried out using ionic alkoxides such as ^{t}BuO$^-$K$^+$[2,3], ^{t}BuO$^-$Li$^+$[4], and RO$^-$K$^+$[5]. The polymerization was shown to proceed via a nucleophilic attack of the alkoxide anion (RO$^-$) onto the carbonyl group of ε-CL with subsequent acyl-oxygen bond cleavage. Anionic polymerization is usually accompanied by both inter- and intramolecular transesterification reactions. For instance, in the presence of ^{t}BuO$^-$K$^+$ only macrocycles were formed at monomer

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concentrations below 0.25 M[2–6] as evidenced by GPC[2]. The occurrence of side-reactions has been explained on the basis of the high reactivity of the anionic alkoxides.

Covalent metal alkoxides based on aluminium or zinc (e.g. $Al(O^iPr)_3$[7–12], $Br(CH_2)_2OAlEt_2$[9], $Br(CH_2)_2OAl(^iBu)_2$[9], $(C_2H_5)_2AlOCH_2CH_2Br$[10], $EtZnO(CH_2)_2$-Br[13], $Zn(O(CH_2)_2Br)_2$[13]) have also proved to be effective initiators for the polymerization of ε-CL. Polymerization was shown to proceed via a coordination-insertion mechanism which involves successive insertion of the monomer into the Al–O bond leading to an ester group at one chain end and an aluminium alkoxide at the other end. However, aluminium initiators were found to react at a slower rate as compared to ionic initiators[14]. For $Al(O^iPr)_3$, which has received most attention, it was found that only one isopropoxide group is active between 0° and 25 °C while all three groups become active above 100 °C. The polymerization was shown to exhibit living characteristics[7,15,16], i.e. linear variation of molar mass with time and close agreement between monomer to initiator ratio and DP_n. However, in some cases broadening of molar mass distribution was observed after prolonged reaction time. Polymerization was also performed in solvents having different polarities (toluene, DCM, THF) and it was found that polymerization rate decreases with increasing polarity of solvent[17].

Tin(II) octanoate/alcohol is the most often used initiator in the polymerization of ε-caprolactone. However, several initiation pathways have been proposed for these initiator systems[18–21]. In most cases, co-initiation with a hydroxyl group containing compound has been assumed. This mechanism has been thoroughly investigated by recent studies using NMR[22,23], MALDI-TOF MS[21] and kinetic data[24]. It is argued that OctSnOR species are formed reversibly during the initiation step and is actually the initiator for the polymerization.

On the other hand, γ-Butyrolactone with its small ring strain does not homopolymerize under usual polymerization conditions. Duda *et al.*[25] have shown that oligomers (decamers) could be synthesized using $Al(O^iPr)_3$-trimers as initiator. They have also performed copolymerization of ε-caprolactone with γ-butyrolactone in toluene at 20 °C [25,26]. Polymerization of an initial 50:50 monomer feed, resulted in a pseudoperiodic copolymer consisting of PCL/PBL in the ratio of 89:11.

In this paper we report on the copolymerization of ε-caprolactone and γ-butyrolactone in the presence of tin(II) octanoate, aluminium Schiff's base complex - HAPENAlO^iPr, and lithium diisopropylamide (LDA) as initiators. A thorough understanding of the mechanisms of polymerization using these initiators is essential to explain the differences in incorporation ratios. This paper will thus discuss new insights into the microstructure of copolymers using reactivity ratios and calculated block lengths.

Results and Discussions

Homopolymerization of ε-caprolactone

In the first part of this study, the polymerization of ε-caprolactone was closely investigated using $Sn(Oct)_2$/ethanolamine (I), HAPENAlO^iPr (II), LDA (III) and $Al(O^iPr)_3$ (IV) as initiators. Table 1 summarizes the polymerization results. In the presence of LDA the polymerization reached completion in a few minutes while $Sn(Oct)_2/NH_2CH_2CH_2OH$ reached only 40% monomer conversion after 42 hours in dioxane. Polymerization in the presence of the Al initiators were relatively faster compared to the Sn system.

We reported previously that, the polymerizations of lactides in the presence of HAPENAlO^iPr and LDA proceeded via classical coordination-insertion[27,28] and anionic mechanisms[29] respectively. The polymerization of ε-CL was thus assumed to proceed similarly.

A more detailed study of the $Sn(Oct)_2$/ethanolamine system was undertaken using NMR via a model reaction. In a first

Table 1.
Polymerization of ε-caprolactone using initiators (I), (II), (III) and (IV). Conversion = 100%[a)]

	Initiator	[M]/[I]	Solvent	Time (h)	$M_n^{calcb)}$	$M_n^{1H\ NMR}$
P1	I	50	dioxane	42[c)]	2280	2400
P2			toluene	21	5700	—
P3	II	10	DCM	1.5	1140	1100
P4		50		3	5700	6600
P5	III	10	dioxane	5 mins	1140	2000
P6		50		5 mins	5700	—
P7	IV	10	toluene	1.5	1140	1600
P8		50		3	5700	6500

a) determined from ^{1}H NMR.
b) $M_n^{calc} = 114 \times [M]/[I] \times (conversion/100)$.
c) conversion = 40%.

instance, the octanoate (Figure 1B)/ethanolamine (Figure 1A) mixture (ratio 2:1) was analyzed by ^{1}H NMR spectroscopy. Figure 1(C) shows the occurrence of shifts in the signals upon probable complexation of ethanolamine on $Sn(Oct)_2$. The $–NH_2$ end group of ethanolamine has shifted from 2.14 ppm to 6.30 ppm which is an indication of deshielding and thus complexation through electron donation. In addition integration of the signals at 3.8 and 2.9 ppm corresponding to the $NH_2C\underline{H_2}–$ and $OHC\underline{H_2}–$ of ethanolamine in the complex, yielded a ratio of 1:1. The ^{13}C NMR spectrum of the mixture revealed the presence of only one carbonyl peak compared to two peaks present in the original spectrum of $Sn(Oct)_2$. These results suggested that both the OH and NH_2 groups are linked to the Sn center forming a new complex (Scheme 1).

ε-CL was then added to the mixture and evolution of the NMR signals was followed (Figure 1 D). The OH end group attached to CL was detected (3.65 ppm) but the NH_2 signal decreased drastically in intensity in ^{1}H NMR spectrum. ^{13}C NMR spectrum of the product showed five signals in the carbonyl region which have been assigned as follows: 173 ppm CO-main chain PCL;

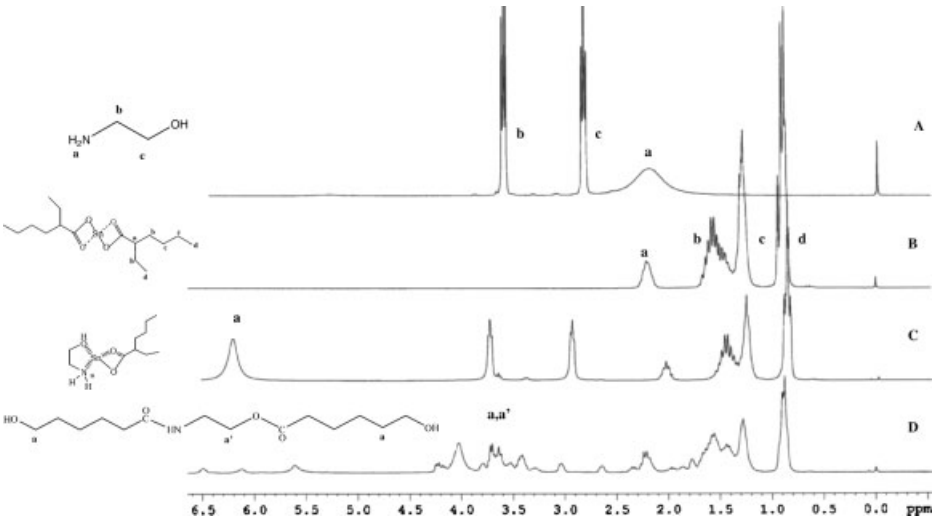
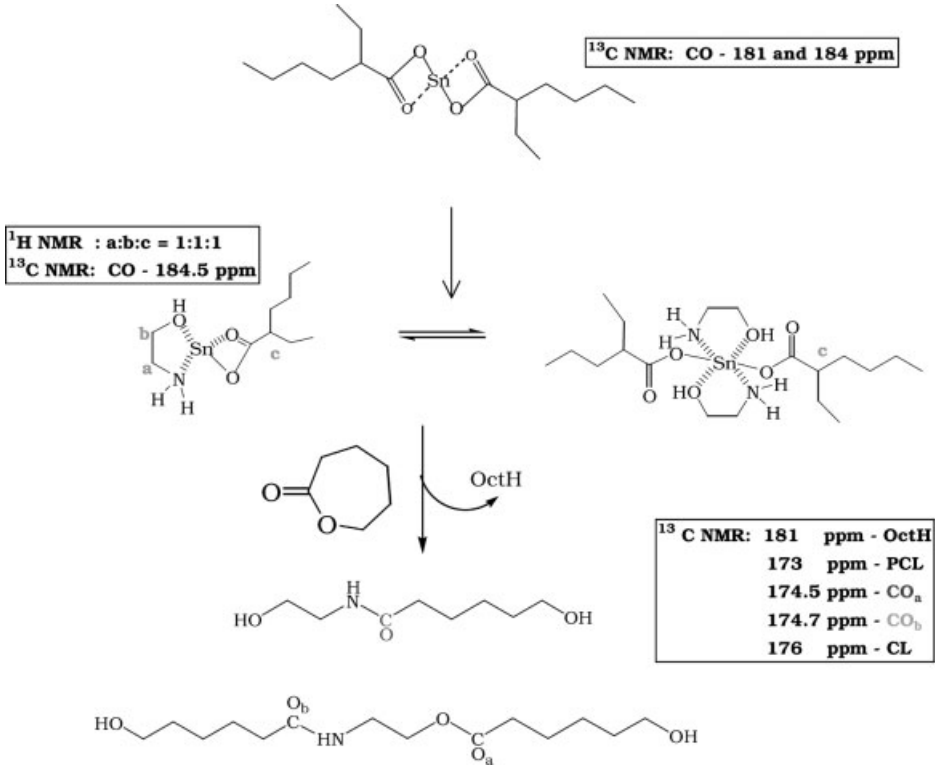


Figure 1.
^{1}H NMR spectra of (A) ethanolamine (B) $Sn(Oct)_2$ (C) $Sn(Oct)_2$/ethanolamine mixture (D) product of model reation with ε-CL.



Scheme 1.
Proposed mechanism using $Sn(Oct)_2$:ethanolamine:ε-CL (1:2:2).

174.5 and 174.7 ppm CO_a-ester linkage/CO_b-amide linkage; 176 ppm CO-ε-CL, and 181 ppm CO-octanoic acid (Scheme 1).

The model study has thus revealed that the polymerization proceeded first through a complexation of both the OH and NH_2 groups of ethanolamine on $Sn(Oct)_2$ (Scheme 1). Both functional groups can then initiate polymerization of ε-CL yielding α,ω-dihydroxy-PCL.

Study of The Occurrence of Side Reactions in Homopolymerization

In the present study we have also attempted to examine the occurrence of side reactions using ^{13}C NMR spectroscopy focusing on the carbonyl region. Crude polymers obtained with initiators **(I)–(IV)** at [M]/[I] = 50 present a single signal at 173.6 ppm characteristic of the carbonyl in the main chain. At this polymer to initiator ratio, end-group signals are not observed and it is therefore not possible to discuss whether side-reactions are occurring or not. Low-molar-mass polymers synthesized at higher initiator concentration ([M]/[I] = 10) were analyzed by ^{13}C NMR spectroscopy. Figure 2 shows an expansion of the carbonyl region of these polymers. The signals at 173.6 (CO main chain) and 173.8 (CO penultimate group) ppm are common to all three spectra. In addition, **P3** and **P7** exhibit a peak at 173.1 ppm. The latter has been assigned to the end chain isopropoxy carboxylate group (COO^{i}Pr) thereby supporting the coordination-insertion mechanism of the polymerization. Finally, the peak at 173.5 ppm is present in both **P3** and **P5**, but is more intense in the latter which has been obtained via the anionic route. From MALDI TOF MS characterization, we propose that this signal be assigned to the carbonyl group of cyclic oligomers. The crude polymers were precipitated in

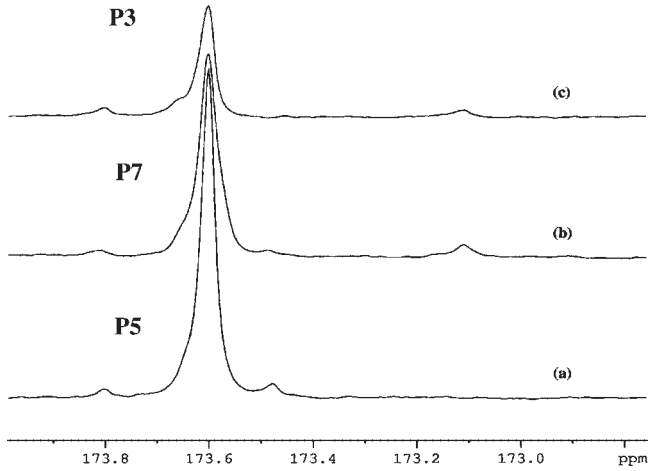


Figure 2.
Carbonyl region of polymers (a) P5 (b) P7 (c) P3.

methanol and again analyzed by ^{13}C NMR spectroscopy. The signal at 173.5 ppm present in crude **P5** is no longer present, which implies that the cyclic oligomers have been eliminated by precipitation.

Copolymerization of ε-caprolactone and γ-butyrolactone

Copolymerization of ε-CL and γ-BL was performed using HAPENAlO^{i}Pr, LDA and $Sn(Oct)_2/HOCH_2CH_2NH_2$ as initiators. The reaction conditions (solvent and temperature) depended upon the initiator used but the [M]/[I] ratio was kept constant ([M]/[I] = 50). The polymers were analyzed using NMR after complete consumption of ε-CL. Figure 3 shows typical ^1H NMR spectra of ε-CL, γ-BL, copolymer before and after precipitation in methanol. ε-CL is completely consumed as it follows from the absence of a triplet at 4.25 ppm due to the $OCOC\underline{H}_2$ in the monomer. A new peak was obtained at around 2.2 ppm for the crude copolymer. This peak was persistent after precipitation in methanol and was assigned to β-$C\underline{H}_2$ of butyrolactone in the copolymer. Integration of this peak was used to calculate the mol% incorporation of BL units in the copolymer. Table 3 shows the results obtained. It was also found that conversion of γ-BL leveled off after consumption of ε-CL. This result can be explained by the fact that γ-BL cannot homopolymerize.

GPC analysis of the copolymers gave monomodal distributions and the patterns obtained indicated that the composition of the copolymers is different (Figure 4).

Calculation of Block Length

Analysis of the ^{13}C NMR spectra of the precipitated polymer show the presence of triads in the carbonyl region (Figure 5). The triad intensities were calculated and are listed in Table 4[25].

The triad intensities indicated that the copolymers had a pseudoperiodic pattern. The values were used to calculate the block length of PCL (L_1) in the random copolymer at [M]/[I] = 50 according to equation 1 (a)[30]. The block length of PBL (L_2, equation 1 b) could not be calculated due to overlapping of triads CLBLCL and BLBLCL, CLBLBL and BLBLBL. The following results were obtained: HAPENAlO^{i}Pr = 4; LDA = 5, and $Sn(Oct)_2$ = 9.5. The block length gives a good indication of the percentage of BL units incorporated in the copolymer. $Sn(Oct)_2$ has the longest block length of PCL and the lowest incorporation of BL units (16%). LDA and HAPENAlO^{i}Pr have quite similar CL block length and incorporation of BL units

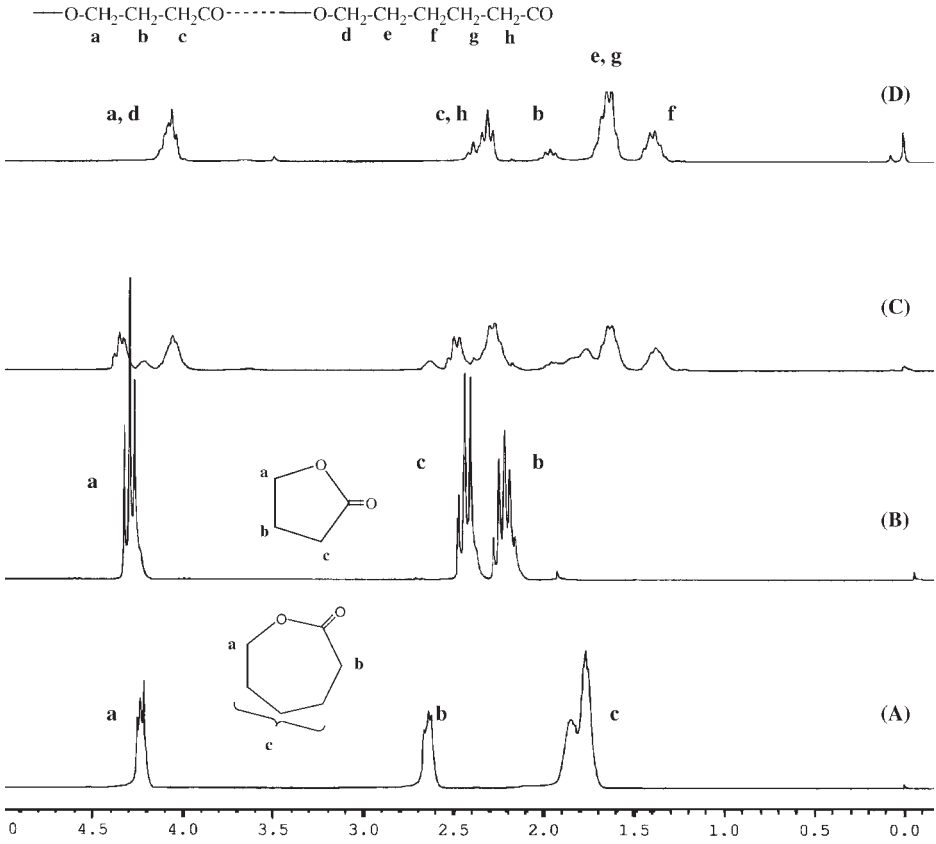


Figure 3.
^{1}H NMR spectra of (A) ε-CL (B) γ-BL (C) crude copolymer (D) precipitated copolymer synthesized using HAPENAlO^{i}Pr.

in the copolymer (26%).

$$\overline{L}_1 = \frac{(I_{111} + I_{211})}{(I_{112} + I_{212})} + 1 \qquad (1a)$$

$$\overline{L}_2 = \left[\frac{I_{222}(I_{221} + I_{122})/2}{(I_{221} + I_{122})/2 + I_{121}} + 1\right]\frac{1}{2} \qquad (1b)$$

Table 3.
Mol% incorporation of BL units in the copolymer calculated using ^{1}H NMR.

Initiator	Mol% of γBL in monomer feed	Mol % BL in copolymer
HAPENAlO^{i}Pr	25	11
	50	26
LDA		26
Sn(Oct)$_2$/ $HOCH_2CH_2NH_2$	50	16
Al(O^{i}Pr)$_3$ – trimer*		11

* Obtained from Ref. 25.

Determination of Reactivity Ratios

The reactivity ratios of the monomers were determined for HAPENAlO^{i}Pr initiated polymerizations conducted at low co(monomer) conversion (15%), using the Finemann-Ross method (Figure 6). The calculated values $r_{CL} = 19.4$ and $r_{BL} = 0.11$ show that the copolymer consists of long blocks of CL units. These values are to be handled with care as the copolymerization in the presence of HAPENAlO^{i}Pr is solvent dependent.

Conclusion

In this paper, we have shown that copolymers containing varying amounts of γ-butyrolactone and ε-CL can be synthesized using different types of initiators operating

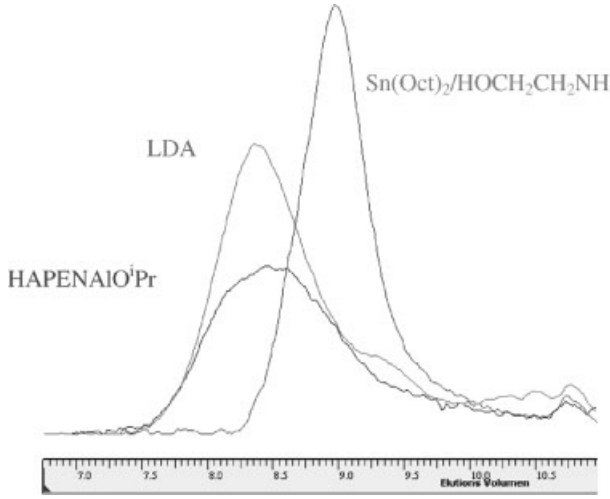


Figure 4.
GPC chromatograms of copolymers using different initiators, [M]/[I] = 50.

via different polymerization mechanisms. Calculation of average block lengths of copolymers based on ^{13}C NMR data combined with determination of reactivity ratios have given a better insight of the microstructure of the copolymers synthesized.

Copolymers containing relatively higher proportions of γ-butyrolactone are expected to biodegrade faster than caprolactone homopolymer and they could prove to be useful materials as polymer scaffolds.

Experimental

Materials

ε-caprolactone, γ-butyrolactone, lithium diisopropylamide, $Al(O^{i}Pr)_3$, $Sn(Oct)_2$

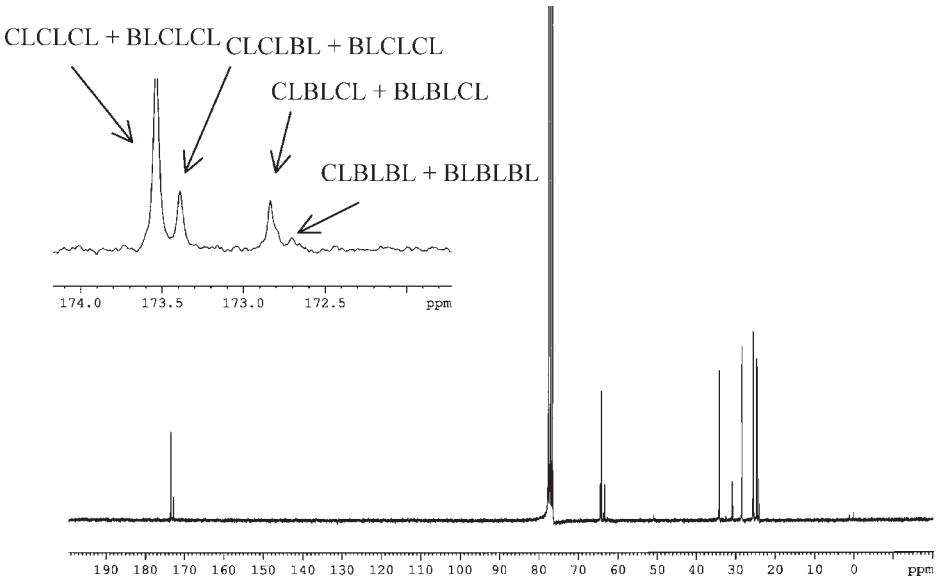


Figure 5.
^{13} C NMR spectrum of random copolymer

Table 4.
Triad intensities of random copolymer

Initiator	Monomer feed (ε-CL:γ-BL)	Triad intensities (%) – carbonyl peak			
		CLCLCL + BLCLCL	CLCLBL + BLCLBL	CLBLCL + BLBLCL	CLBLBL + BLBLBL
HAPENAlO^{i}Pr	75:25	86	10	4	—
	50:50	61	20	16	3
	10:90	66	15	—	19
LDA	50:50	73	17	8	2
$Sn(Oct)_2/HOCH_2CH_2NH_2$	50:50	85	10	5	—

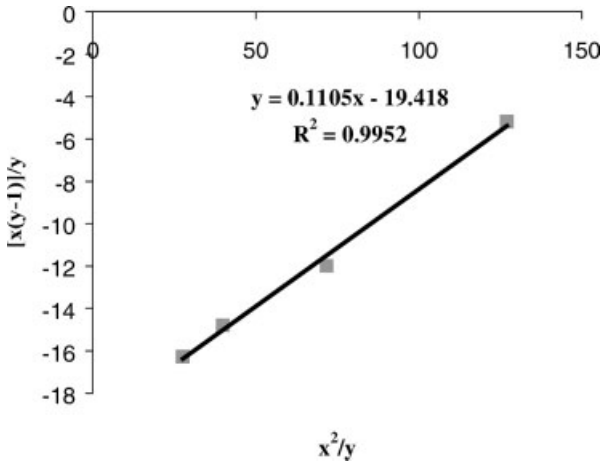


Figure 6.
Determination of reactivity ratios using Finemann-Ross method.

and ethanolamine were used as received from Aldrich. Toluene was first refluxed, then distilled with sodium under nitrogen and kept under argon. Dichloromethane was first refluxed and distilled twice over CaH_2 under nitrogen and stored under argon. Dioxane sealed under nitrogen was used as purchased from Aldrich.

Synthesis of Initiators

HAPENAlO^{i}Pr was synthesized according to the procedure given in ref. 28.

Polymerization

Polymerization/copolymerization with HAPENAlO^{i}Pr in dichloromethane, lithium diisopropylamide in dioxane and $Al(O^{i}Pr)_3$ in toluene were carried out under stirring in glass tubes at 25 °C under argon in a glove box. The initiator, solvent and monomer(s) were introduced in the tubes inside the glove box. After the desired time of polymerization the solvent was removed under vacuum and the percentage conversion was determined by ^{1}H NMR. Polymerization with $Sn(Oct)_2$ was performed at 110 °C. The monomer, solvent and initiator were loaded inside a glove box in Schlenk tubes. The tubes were then placed in an oil bath at 110 °C under vacuum.

Measurements

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using an FT Bruker 250 MHz spectrometer at 25 °C. GPC chromatograms were recorded using a PSS (WGE Dr. Bures Q 1000) apparatus. PSS SDV PC column 1 was used at a flow rate of 1ml/min, pressure: 10 bar and temperature 23 °C. Polystyrene was used as standard and THF as eluent. MALDI-TOF spectrometry was performed at the Université Pierre et Marie

Curie (Paris) using a PerSeptive Biosystems Voyager Elite (Framingham, MA) time-of-flight mass spectrometer.

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