Novel functionalization routes of poly(ε-caprolactone)

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Abstract: The aluminum alkoxide mediated ring opening polymerization of functional lactones, such as γ-ethylene ketal-ε–caprolactone (TOSUO), γ-(triethylsilyloxy)-ε–caprolactone (SCL) and γ–bromo-ε–caprolactone (γBrCL), is a versatile route to polyesters containing ketal, ketone, alcohol and bromide groups. As result of living polyaddition mechanism, random and block copolymerization of εCL and γBrCL has been successfully carried out. The reactivity ratios are quite similar (1.08 for ε-CL, and 1.12 for γBrCL). These random copolymers are semicrystalline when they contain less than 30 mol% of γBrCL, otherwise they are amorphous. No transesterification reaction occurs during the sequential polymerization of ε-CL and γBrCL leading to block copolymers. Reaction of poly(εCL-co-γBrCL) with pyridine provides quantitatively a polycationic polyester. Furthermore, the reaction of this random copolymer with 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) is a route to unsaturated polyesters, whose the non conjugated double bonds can be quantitatively converted into epoxides by reaction with m-chloroperbenzoic acid (mCPBA). No chain degradation is detected during these derivatization reactions of poly(εCL-co-γBrCL).

Introduction

Nowadays, a steadily increasing attention is paid to biodegradable polyesters for their potential in agriculture, waste management of plastics, medicine and surgery.[1]

Over the last 20 years, CERM has been involved in a research program dealing with the macromolecular engineering of polylactones and polylactides.[2] Aluminum alkoxides [$Al(OCH_2CH_2X)_3$] carrying a functional group (X=Br, CH_2NEt_2, $CH_2CH=CH_2$, $OCOC(Me)=CH_2$,...) or not (X = H) have been used as efficient initiators for the ring opening polymerization (ROP) of lactones, lactides, glycolide and cyclic anhydrides. Hydrolysis of the active aluminum alkoxide bond leads to the formation of an asymmetric telechelic polyester, the end groups being X and OH, respectively. The mechanism proceeds through the coordination of aluminum to the exocyclic carbonyl oxygen of ε-caprolactone (εCL), followed by the acyl-oxygen cleavage of the monomer and insertion into the Al-O bond of the initiator (Scheme 1). These polymerizations are living and they have been exploited for the macromolecular engineering of polyesters and polyanhydrides, including the tailoring of block copolymers and more complex architectures.

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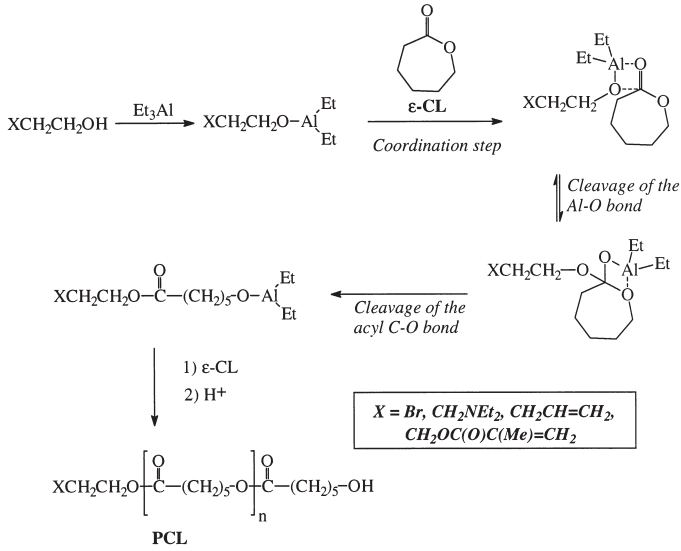


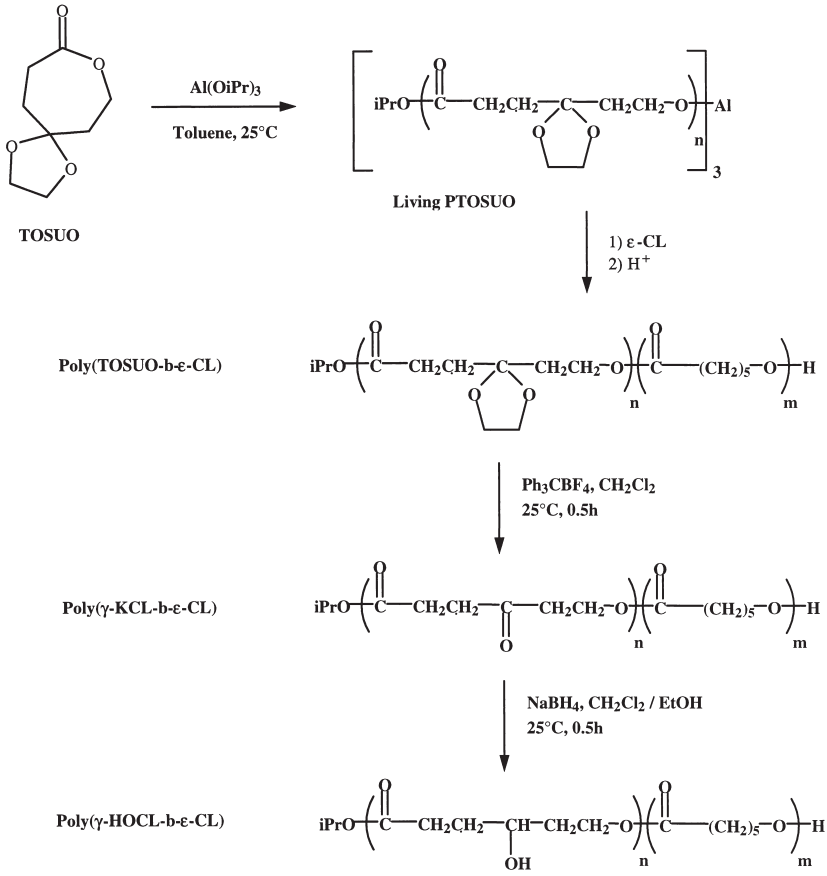
Scheme 1 : Mechanism for the aluminum alkoxide mediated ring opening polymerization of εCL.

Poly(ε–caprolactone) (PCL) shows a remarkable sets of characteristic features, such as biocompatiblity, permeability and miscibility with a wide range of polymers, e.g., PVC bisphenol A polycarbonate. Nevertheless, depending of the envisioned applications, some properties, such as hydrophilicity, biodegradation rate, and mechanical properties, have to be optimized. The εCL copolymerization with glycolide and lactides is a first tool to tailor the PCL properties. An alternative pathway relies on the synthesis and (co)polymerization of functional derivatives of εCL, so leading to polymers with functional pendent groups which are highly desirable for attaching drugs, tuning biodegradation rate, improving biocompatibility and promoting bioadhesion. The functional groups have to be protected or chosen in such a way that they do not interfere with the polymerization mechanism. A few years ago, synthesis of a few functional εCL's was known, although it was usually tedious and the polymerization was ill-controlled. [3]

γ-ethylene ketal-ε–caprolactone and γ-silyloxy-ε–caprolactone

More recently, we reported on the synthesis of γ-ethylene ketal-ε–caprolactone (TOSUO).[4,3] The TOSUO polymerization was initiated by aluminum alkoxide in toluene at 25°C and found to be living, which allowed for the controlled synthesis of poly(TOSUO-b-εCL) copolymers of narrow molecular weight distribution (Scheme 2).[5] No transesterification

reaction occurred as proved by ^{13}C-NMR analysis. The end-group analysis agreed with the coordination-insertion mechanism previously reported for the εCL polymerization (Scheme 1). Random copolymerization of εCL and TOSUO was also carried out, and the reactivity ratios were measured by ^{13}C-NMR, being 1.3 for εCL and 1.0 for TOSUO. [6]

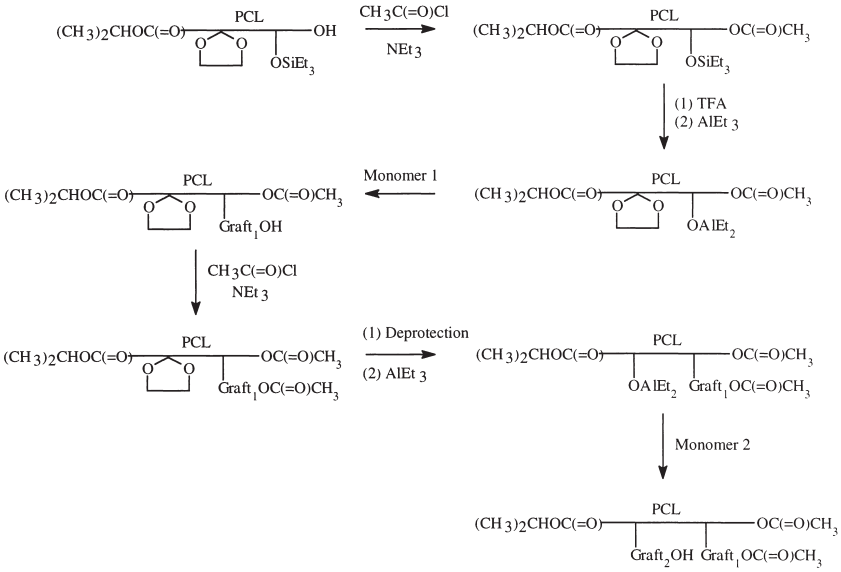


Scheme 2 : Synthesis of poly(εCL-b-TOSUO) copolymer and deprotection of the ethylene ketal pendent groups into ketones and alcohols, respectively.

The ethylene ketal pendent groups of the PTOSUO block were successfully deacetalized into ketones, which were further reduced into hydroxyl groups (Scheme 2). Therefore, PCL with well-defined content of ketone and hydroxyl pendent groups could be made available. It is worth pointing out that poly(2-oxepane-1,5-dione) (poly γ–KCL) prepared by deprotection of the homo PTOSUO is a highly crystalline modified poly(ε–caprolactone) with a high melting

temperature of ca. 150°C.[7] Remarkably, the pendent hydroxyl groups can be reacted with triethylaluminum with formation of macroinitiators for ROP of lactones, lactides and glycolide. Complex molecular architectures, e. g., comb-shaped[4], graft[4], hyperbranched [8] and dendrigraft [9] polyesters, were accordingly synthesized.

An alternative pathway to polyesters containing hydroxyl pendent groups was also investigated based on γ-(t-butyldimethylsilyloxy)-ε-caprolactone (SCL) [10] and γ-(triethylsilyloxy)-ε–caprolactone (TeSCL) [11]. For instance, the poly(εCL-co-TOSUO-co-TeSCL) terpolymer was prepared with a predictable molecular weight and a narrow molecular weight distribution. The silanolate groups were selectively deprotected into hydroxyl groups, then converted into aluminum alkoxides, and the macroinitiator was used to synthesize graft copolymer. The subsequent conversion of the ethylene ketal groups into aluminum alkoxides followed by lactide ROP proved to be a valuable route to hetero-graft aliphatic copolyesters, as shown below (Scheme 3).[11]



Scheme 3 : Synthesis of hetero-graft polyester from poly(εCL-co-TOSUO-co-TeSCL).

γ–Bromo-ε–caprolactone

Since bromine containing compounds are easily converted into a wide range of organic functions by well-known reactions of organic chemistry, e. g. elimination and substitution reactions, we have been interested in the synthesis and polymerization of γ–bromo-

ε–caprolactone (γBrCL). The synthesis of this monomer has been reported elsewhere.[12] The γBrCL polymerization has been initiated by $Al(OiPr)_3$ in toluene at 0°C. All the molecular characteristic features of the polymer agree with a living polymerization process according to the same coordination-insertion mechanism as εCL and TOSUO. Differential Scanning Calorimetry (DSC) shows that PγBrCL is an amorphous polyester with a Tg of -16.5°C, which makes it comparable to PTOSUO (Tg = -11°C) but different from PCL which is typically semi-crystalline (Tg = -60°C and Tm=60°C).

Although the copolymerization of γBrCL and εCL mixtures was reported, the structure of the copolymer was not investigated in detail. A series of random copolymers of different composition has been prepared by changing the molar fraction of γBrCL in the comonomer feed (f_B), as shown in Table 1. The molar fraction of γBrCL (F_B) in the copolymer and the number-average molecular weight ($M_{n,\ ^1H\text{-}NMR}$) have been measured by ^{1}H-NMR and found in agreement with the expected values f_B and $M_{n,th}$. The molecular weight distribution is narrow in line with a living polymerization.

Table 1. Molecular characteristics of random copolymers of εCL and γBrCL.[a]

f_B[b]	$F_{B,\ ^1H\text{-}NMR}$[c]	Conv. (%)	$M_{n,\ th}$[d]	$M_{n,\ ^1H\text{-}NMR}$	$M_{n,SEC}$[e]	M_w / M_n
0.1	0.09	100	17,000	17,000	25,500	1.17
0.3	0.28	100	17,000	16,500	23,500	1.16
0.5	0.49	100	17,000	16,000	20,700	1.18

a) Conditions: toluene, 2h, 0°C

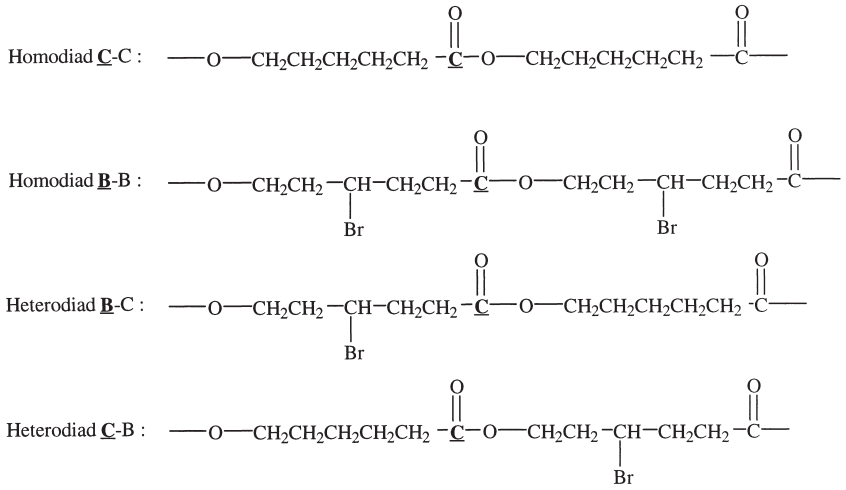
b) molar fraction of γBrCL in the comonomer feed

c) molar fraction of γBrCL in the random copolymer

d) $M_{n,\ th} = (114 * [\varepsilon CL]_0 / [Al(OiPr)_3]_0) + (193 * [\gamma BrCL]_0 / [Al(OiPr)_3]_0)$

e) $M_{n,SEC}$ based on calibration valid to polystyrene.

As reported in the scientific literature, the carbonyl resonances observed by ^{13}C-NMR of the aliphatic polyesters are sensitive to the sequence effect (Scheme 4).[3]



Scheme 4 : Homodiads and heterodiads observed by ^{13}C-NMR.

Figure 1 shows the spectra of the carbonyl region for the homopolyesters and the random copolyester. Although only one resonance is observed for the carbon of the carbonyl in PCL (Figure 1a) and PγBrCL (Figure 1b), respectively, four resonances are observed for the random copolymer (Figure 1c). By comparison with the carbonyl chemical shift in PCL and PγBrCL,the resonances at 173.5 ppm and at 172.4 ppm are typical of the homodiads C-C and B-B, respectively. In the C-B heterodiad, the bromine atom triggers an upfield resonance at 173.2 ppm. In the case of the second heterodiad B-C, a downfield shift occurs at 172.6 ppm.

When the copolyester composition is changed, only the relative intensity of the four resonances changes, in contrast to the number and position of the carbonyl resonances which remain unmodified. In binary copolymers (C and B comonomers), the average lengths L_C and L_B can be calculated from the integration of the diad signals in the case of quantitative ^{13}C-NMR, according equations (1) and (2) where I stands for the integral of the diad under consideration.[6]

$$L_C = I_{CC} / [(I_{CB} + I_{BC}) / 2] + 1 \qquad (1)$$

$$L_B = I_{BB} / [(I_{CB} + I_{BC}) / 2] + 1 \qquad (2)$$

Table 2 shows that the F_B values determined by ^{1}H-NMR and ^{13}C-NMR are in good agreement within the limits of the NMR experimental errors, which confirms the assignment of the ^{13}C-NMR spectra.

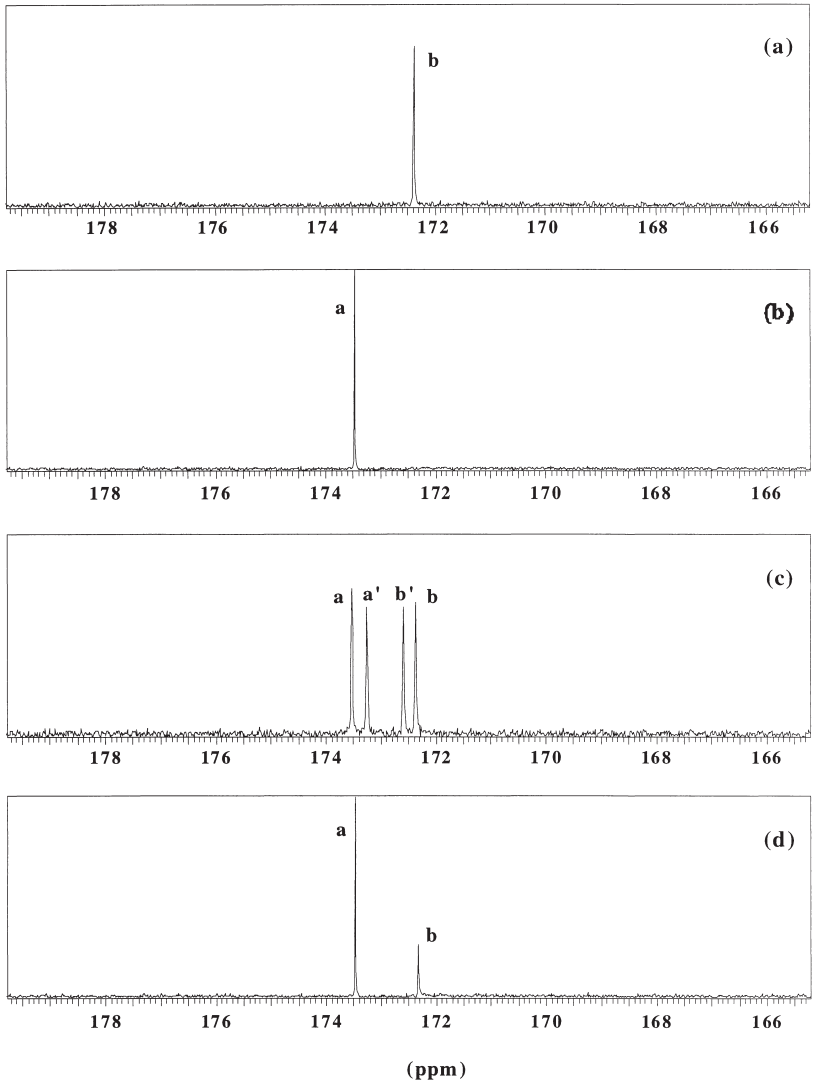


Figure 1 : ^{13}C-NMR spectra in the carbonyl region for PCL (a), PγBrCL (b), poly(γBrCL-co-εCL) (c) and poly(γBrCL-b-εCL) (d).

Table 2 : ^{1}H-NMR and ^{13}C-NMR data for poly(εCL-co-γBrCL).

Entry	F_B (^{1}H-NMR)	L_C	L_B	F_B (^{13}C-NMR)
1	0.09	10.77	1.08	0.09
2	0.28	3.18	1.58	0.33
3	0.49	2.15	2.09	0.49

$$F_B = L_B / (L_B + L_C) \qquad (3)$$

A linear relationship is observed when the sequence length is plotted against $A = [\varepsilon Cl]_0 / [\gamma BrCL]_0$ (Figure 2a) or against $A^{-1} = [\gamma BrCL]_0 / [\varepsilon CL]_0$ (Figure 2b). The reactivity ratios, r_C and r_B, have been calculated from the slope of the straight line, according to the equations (4) and (5). R_C=1.08 and r_B=1.12.

$$L_C = (A \,.\, r_1) + 1 \qquad (4)$$
$$L_B = (r_2 / A) + 1 \qquad (5)$$

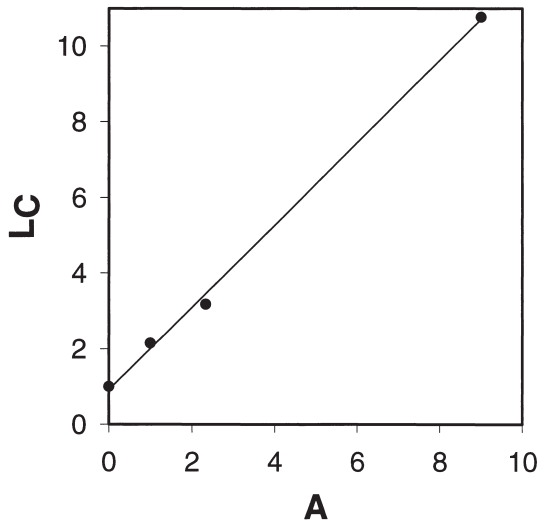


Figure 2a : Linear relationship of L_C versus A

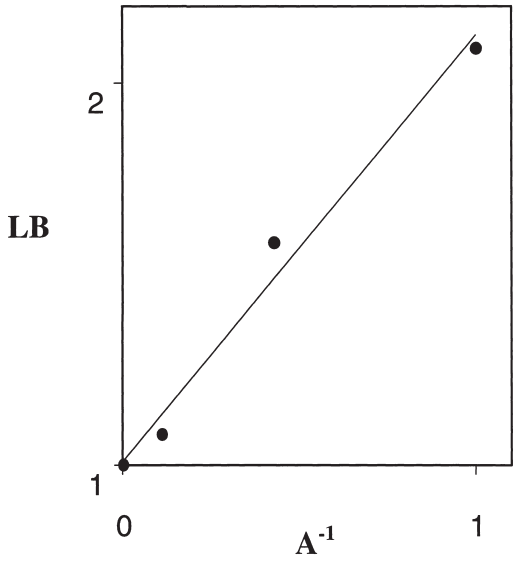


Figure 2b: Linear relationship of L_B versus A^{-1}

Although transesterification reactions can be responsible for errors in the L_C and L_B values, and thus in the r_C and r_B values, no reaction of this type is detected when the γBrCL polymerization is initiated by PCL macroinitiators in toluene at 0°C. Indeed, the blocky structure of the poly(εCL-b-γBrCL) copolymer is confirmed by the absence of the two heterodiad signals in the ^{13}C-NMR spectrum (Figure 1d). The narrow molecular weight distribution (M_w/M_n =1.2) of poly(εCL-co-γBrCL) and poly(εCL-b-γBrCL) is an additional evidence that no transesterification occurs during the sequential polymerization.

The thermal transitions of the poly(εCL-co-γBrCL) have been determined by DSC. The melting temperature of PCL decreases as the γBrCL content is increased until F_B of ca. 0.3 (Figure 3), consistently with the decreased average block length of the εCL units (L_C), reported in Table 2. At $F_B > 0.3$, L_C is indeed too small for crystallization to occur. The unique Tg which is observed increases with F_B as it could be anticipated from the higher Tg for PγBrCL compared to PCL (Tg=-60°C).

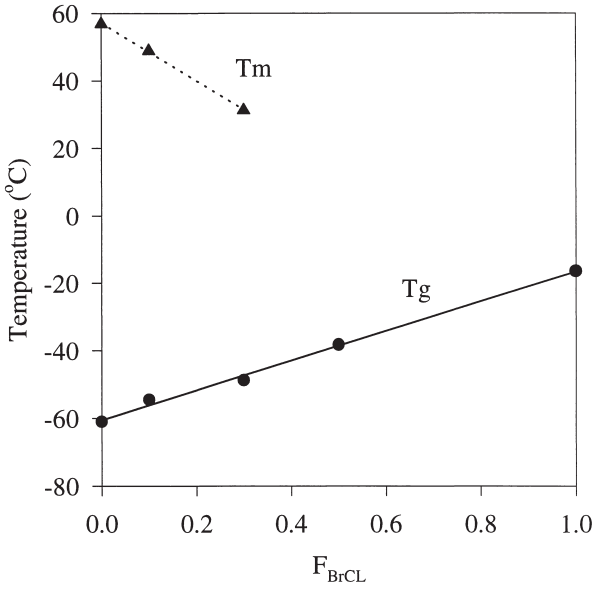
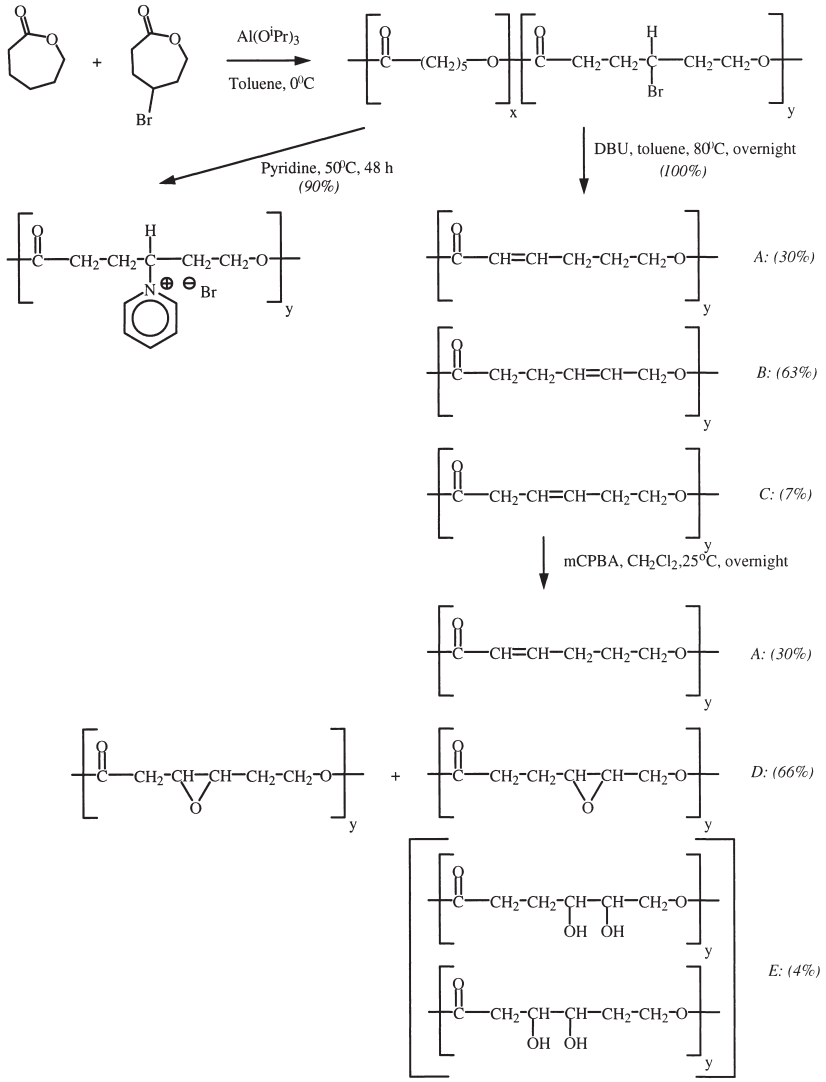


Figure 3 : Phase diagram for poly(CL-co-γBrCL)

Functionalization of PγBrCL

Reactivity of the γ–bromo substituent allows for new functional polyesters to be prepared. A polycationic polycaprolactone has been made available by reaction of pyridine and poly(εCL-co-γBrCL) (M_w/M_n = 1.2 ; $M_{n,\ ^1H\text{-}NMR}$ = 16,500 ; F_B = 0.28) at 50°C (Scheme 5).[13] The quaternization is close to completeness (>90%) after 48 h. No olefinic proton is detected by ^{1}H-NMR, indicating that no elimination reaction has occurred. The average degree of polymerization calculated by ^{1}H-NMR before and after derivatization remains unchanged which is evidence that chains have not been degraded. This functionalization opens the way to the synthesis of hydrosoluble polyesters and to amphiphilic diblock copolymers. Further studies are in progress in this field.

The reaction of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) with poly(εCL-co-γBrCL) (M_w/M_n = 1.2 ; $M_{n,\ ^1H\text{-}NMR}$ = 17,000 ; F_B = 0.09) in toluene at 80°C leads to unsaturated polyester (Scheme 5).[13] The elimination reaction is not selective since a mixture of non-conjugated and conjugated olefinic units is formed. The molecular weight distribution remains narrow (M_w/M_n = 1.2), which is evidence of lack of degradation.



Scheme 5 : Quaternization and elimination of bromine in poly(εCL-co-γBrCL).

The quantitative epoxidation of the non conjugated double bonds has been carried out overnight at room temperature with m-chloroperbenzoic acid (mCPBA) in dichloromethane (scheme 5).[13] The conjugated double bonds remain untouched under these conditions. A low content (4%) of diol results from the acidic catalyzed hydrolysis of the epoxides. It must be

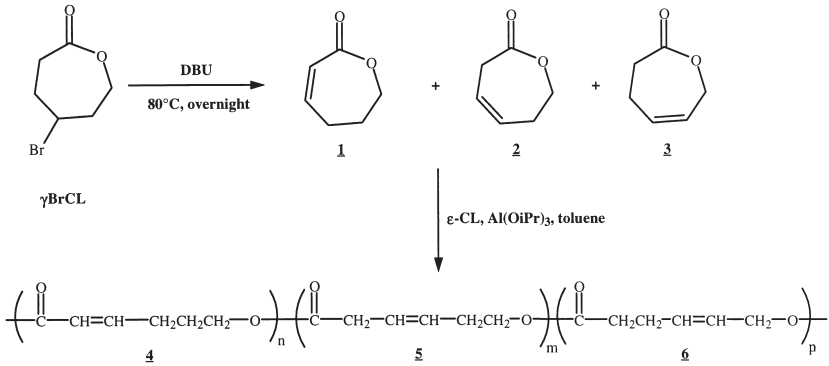
noted that the epoxidation reaction does not lead to chain degradation and provides versatile intermediates for further functionalization of the polyester backbone. The non-epoxidized double bonds are also available to crosslinking reactions, which might be a way to prepare gels with tunable properties.

Unsaturated Lactones

Finally, an alternative pathway to unsaturated polyesters is proposed in Scheme 6, based on the reaction of γ–bromo-ε–caprolactone with DBU. Preliminary results show that the elimination reaction is not selective, leading to a mixture of three unsaturated lactones.
We are currently investigating a more selective synthesis of these new monomers. It must be noted that the double bond containing lactone could be polymerized by Ring Opening Metathesis Polymerization (ROMP) as a new route to unsaturated polyesters. This opportunity, including copolymerization with monomers typically polymerizable by ROMP, e.g. norbornene derivatives, will be studied in the near future.
ROP of the mixture of the unsaturated lactones has been initiated by $Al(OiPr)_3$ at room temperature (Scheme 6 ; Table 3). The first lactones mixture (Table 3, entry 1) has been polymerized almost quantitatively within 2 h. The second mixture (Table 3, entry 2), which contains 90% of lactone 1, has also been polymerized. Clearly, the polymerization is slower, which confirms that the conjugated double bonds in lactone 1 decrease the reactivity towards aluminum alkoxide. The experimental number-average molecular weights calculated by ^{1}H-NMR agree with the theoretical values ($M_{n,th}$) calculated from the initial monomer to initiator molar ratio. Furthermore, the polydispersity of the terpolymers is not exceedingly broad.

Table 3: ROP of mixtures of unsaturated lactones

Entry	Monomers 1 / 2 / 3	Time (h)	Yield (%)	$M_{n,th}$	$M_{n,^1H\text{-}NMR}$	$M_{n,SEC}$	M_w / M_n
1	26 / 24 / 50	2	94	11,000	11,000	14,000	1.35
2	90 / 5 / 5	14	60	4,000	3,500	3,000	1.4



Scheme 6 : Elimination of bromine from γBrCL, and ROP of the unsaturated lactones

Conclusions

The controlled polymerization of functional ε-caprolactones is a versatile route to polyesters containing alcohol, ketone, bromo, olefinic and epoxy functions. Although some progress is needed to improve the selectivity of some derivatization reactions, a new set of polymers and copolymers is now available, whose the most representative properties will be investigated in the near future.

Acknowledgment

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