Preparation of highly pure cyclo-polylactides by optimization of the copper-catalyzed azide-alkyne cycloaddition reaction

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In memory of Prof. Dr Andrzej Duda

Abstract: This work reports on the preparation of highly pure cyclo-polylactides ($\overline{M}_n \approx 4\ 000\ g \cdot mol^{-1}$) by the optimization of the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction applied on α-azide-ω-alkyne linear polylactide (PLA) precursors. By adjusting parameters such as the rate of reactant addition and the catalyst loading, monocyclic PLA's with a degree of purity of 93 % are obtained in few minutes. Highly pure monocycles (purity as high as 99.9 %) are also possibly prepared in few hours.

Keywords: lactide, ring-opening polymerization, copper-catalyzed azide-alkyne cycloaddition, cyclization.

Otrzymywanie cyklopolilaktydów o wysokiej czystości poprzez optymalizację katalizowanej miedzią cykloaddycji azydek-alkin

Streszczenie: Opisano optymalizację syntezy cyklopolilaktydów w katalizowanej miedzią(I) reakcji cykloaddycji azydku do alkinu (CuAAC), której celem było uzyskanie polimerów o wysokiej czystości i średnim ciężarze cząsteczkowym $\overline{M}_n \approx 4\ 000\ g \cdot mol^{-1}$. Do reakcji użyto prekursorów, którymi były liniowe α-azydo-ω-alkinowe polilaktydy (PLA). Dobrano warunki syntezy, takie jak szybkość dodawania reagenta oraz ilość używanego katalizatora, które pozwalają na otrzymanie w ciągu kilku minut monocyklicznego PLA o stopniu czystości 93%. Prowadząc syntezę w ciągu kilku godzin można otrzymać monocykliczny polimer o czystości do 99,9%.

Słowa kluczowe: laktyd, polimeryzacja z otwarciem pierścienia, cykloaddycja azydek-alkin katalizowana miedzią, cyklizacja.

Due to intriguing characteristics issued from their endless topology, cyclic structures have been the subject of an intensive research [1–5]. It quickly came out that to take advantage of their properties, macrocycles should have been cleared of any linear by-products, most of the time obtained due to the non-efficiency of the chemical process used to perform the cyclization. To date, two main routes to generate cyclic structures are known as ring-expansion and ring-closure techniques [1]. Among the ring-closure (RC) techniques available, the copper-catalyzed azide-alkyne cycloaddition (CuAAC) has rapidly become one of the most popular [5]. It actually responds to the definition of a "click process" as reported by Kolb *et al.* in 2001 [6] demonstrating an exceptional coupling efficiency as well as a high compatibility allowance in regards to various functional groups [7].

Following the pioneering work of Laurent and Grayson [8] who produced near-quantitatively cyclic polystyrene (c-PS) *via* the CuAAC methodology, other cyclo-polymers were produced so far [9–17]. If a high efficiency as well as a technical simplicity have been deservedly gained, not

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fully quantitative preparation of macrocycles has always been observed because of the presence of poisoning impurities including unreacted linear chains, interconnected chains or possible catenanes. Although the work of Lonsdale *et al*. [18] allowed to prepare c-PS in a more rapid way by taking advantage of the Jacobson-Stockmayer theory, apparent contamination of the monocyclic product was again visible even at 23 °C.

Herein, we report the study dedicated to the optimization of the conditions used to perform the intramolecular CuAAC cyclization of α-azide, ω-alkyne polylactide (PLA) chains. Parameters such as injection rate, catalyst loading and dilution were examined in order to ultimately make perfect the intramolecular cyclization process and get rid of any contaminants. The high efficiency of cyclization was confirmed by traditional experimental techniques including proton nuclear magnetic resonance (^{1}H NMR) and size exclusion chromatography (SEC) analyses and was also attested by ion-mobility spectrometry-mass spectrometry (IMS-MS).

EXPERIMENTAL PART

Materials

All reagents were purchased from Aldrich and used without further purification, unless otherwise noted. L-Lactide (L-LA, ≥99 %) was purchased from Galactic, recrystallized from dried toluene three times and stored in a glove box under dry nitrogen atmosphere (O_2 < 3 ppm, H_2O < 1 ppm) prior to use. CH_2Cl_2 was dried over CaH_2 for 48 h at room temperature, distilled under reduced pressure and stored in a glove box under dry nitrogen atmosphere. 1,8-Diazabicyclo-[5.4.0]undec-7-ene (DBU) was purchased from Fluka, dried over BaO, distilled and stored in a glove box. Copper(I) bromide was purified by washing with acetic acid. 11-Azido-1-undecanol was synthesized as reported in the literature [19] and dried over anhydrous $MgSO_4$ prior storage in the glovebox. 4-Pentynoic anhydride was also synthesized as reported in the literature [20].

Methods of testing

^{1}H NMR spectra were recorded in $CDCl_3$ at a concentration of 20 mg/0.6 cm^3 on a Bruker AMX500 (500 MHz), with shift reported in part-per-million downfield from tetramethylsilane used as internal reference.

Size exclusion chromatography (SEC) was performed in tetrahydrofuran (THF, with 2 % triethylamine added) at 35 °C using a Polymer Laboratories liquid chromatograph equipped with a PL-DG802 degasser, an isocratic HPLC pump LC 1120 (flow rate = 1 cm^3/min), a Marathon autosampler (loop volume = 0.2 cm^3, solution conc. = 1 mg/cm^3), a PL-DRI refractive index detector and three columns: a PL gel 10 μm guard column and two PL gel Mixed-B 10 μm columns [linear columns for separation of poly(styrene) molecular weight ranging from 500 to 10^6]. Poly(styrene) standards were used for calibration.

Positive-ion MALDI-Mass Spectrometry (MALDI-MS) experiments were recorded using a Waters QToF Premier mass spectrometer equipped with a Nd:YAG (third harmonic) operating at 355 nm with a maximum output of 65 μJ delivered to the sample in 3 ns pulses at 50 Hz repeating rate. Time-of-flight mass analyses were performed in the reflectron mode at a resolution of about 10 000. All the samples were analyzed using *trans*-2-[3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]malononitrile (DCTB) as a matrix. This matrix was prepared as 40 mg/cm^3 solution in $CHCl_3$. The matrix solution (1 mm^3) was applied to a stainless steel target and air-dried. Polymer samples were dissolved in THF to obtain 1 mg/cm^3 solutions and 50 mm^3 of 2 mg/cm^3 NaI solution in acetonitrile has been added to the polymer solution. Therefore, 1 mm^3 of this solution was applied onto the target area already bearing the matrix crystals, and air-dried. For the recording of the single-stage MS spectra, the quadrupole (rf-only mode) was set to pass all the ions of the distribution, and they were transmitted into the pusher region of the time-of-flight analyzer where they were mass analyzed with 1s integration time. Data were acquired in continuum mode until acceptable averaged data were obtained.

Ion-mobility spectrometry-mass spectrometry (IM-MS) experiments were performed using a Waters Synapt G2-Si mass spectrometer. Polymer solutions were prepared at a final concentration of 15 μM in acetonitrile. 10 mm^3 of sodium iodide solution (13 mM in acetonitrile) was added to the polymer solution. The so-obtained solution was directly infused in the ESI source with a typical flow rate of 5 mm^3/min with a capillary voltage of 3.1 kV, a source temperature of 100 °C and a desolvation temperature of 150 °C. Ion mobility spectrometry was carried out with nitrogen as the drift gas at a pressure of 289 Pa, an ion-mobility wave velocity of 800 m/s and wave height of 40 V.

Preparation of linear α-azide-ω-hydroxy P(L-LA)

In a glovebox under nitrogen pressure (O_2 < 5 ppm, H_2O < 1 ppm), a vial was charged with L-LA (1.00 g, 6.9 mmol). CH_2Cl_2 (10.0 g) was added, followed by the addition of 11-azido-1-undecanol (60 mm^3, 0.28 mmol) and DBU (43 mm^3, 0.28 mmol). Initialy L-LA/11-azido-1-undecanol/DBU mole ratio was 25/1/1. After 2.5 min under stirring, benzoic acid (50 mg, 0.4 mmol) was added. The DBU catalyst and residual L-LA were removed by precipitation into cold methanol to give α-azide-ω-hydroxy poly(L-LA). Representative results of analysis are given below.

^{1}HNMR($CDCl_3$, δ, ppm): 1.27 [m, 14, $N_3(CH_2)_2(CH_2)_7(CH_2)_2O$-), 1.57 [m, 4, $N_3CH_2CH_2(CH_2)_7CH_2CH_2O$-), 1.57 (d, 6n, -[$COCHCH_3O]_{2n}$-), 3.25 [t, 2, $N_3CH_2(CH_2)_{10}O$-], 4.11 [m, 2, $N_3(CH_2)_{10}CH_2O$-], 4.36 (m, 1, -$COCHCH_3OH$), 5.15 (m, 2n, -[$COCHCH_3O]_{2n}$-). $Conv^{1H\ NMR}$ > 99 %; $\overline{M}_n^{1H\ NMR}$ = 4280 g/mol.

MS (MALDI-ToF): $\overline{M}_n^{MALDI}$ = 3940 g/mol, $Đ_M$ = 1.05. SEC: $\overline{M}_n^{SEC,\ app}$ = 7000 g/mol, $Đ_M$ = 1.11.

Preparation of linear α-azide-ω-alkyne P(L-LA)

Linear α-azide-ω-hydroxy P(L-LA) ($\overline{M}_n^{SEC}$ = 4000 g/mol, $Đ_M$ = 1.11) (0.500 g, 0.13 mmol) was dissolved in dichloromethane (30 cm^3). 4-Pentynoic anhydride (30 mm^3, 0.17 mmol) and 4-dimethylaminopyridine (0.020 g, 0.17 mmol) were added to the solution. The solution was allowed to stir at room temperature for 24 h. The reaction was followed by MALDI-MS until completion. The crude reaction mixture was extracted three times from saturated aqueous $NaHCO_3$ into dichloromethane and three times from saturated aqueous $NaHSO_4$ into dichloromethane. The organic phase was dried on $MgSO_4$, filtered and concentrated in a rotary evaporator prior to precipitation from dichloromethane into cold methanol to give α-azide-ω-alkyne P(L-LA). Representative analysis results are given below.

^{1}HNMR ($CDCl_3$, δ, ppm): 1.27 [m, 14, $N_3(CH_2)_2(CH_2)_7(CH_2)_2O$-], 1.57 [m, 4, $N_3CH_2CH_2(CH_2)_7CH_2CH_2O$-], 1.57 (d, 6n, -$[COCHCH_3O]_{2n}$-), 1.97 [t, 1, -$CO(CH_2)_2CCH$], 2.52 (td, 2, -$COCH_2CH_2CCH$), 2.64 (t, 2, -$COCH_2CH_2CCH$), 3.25 [t, 2, $N_3CH_2(CH_2)_{10}O$-], 4.11 [m, 2, $N_3(CH_2)_{10}CH_2O$-], 5.15 (m, 2n, -$[COCHCH_3O]_{2n}$-). $Conv^{1H\ NMR}$ > 99 %; $\overline{M}_n^{1H\ NMR}$ = 4280 g/mol.

MS (MALDI-TOF): $\overline{M}_n^{MALDI}$ = 4020 g/mol, $Đ_M$ = 1.05. SEC: $\overline{M}_n^{SEC,\ app}$ = 7000 g/mol, $Đ_M$ =1.11.

Preparation of cyclic P(L-LA)

In a glovebox under nitrogen pressure (O_2 < 5 ppm, H_2O < 1 ppm), a first flask was charged with linear α-azide-α-alkyne P(L-LA) ($\overline{M}_n^{SEC}$ = 4000 g/mol, $Đ_M$ = 1.11) (0.250 g, 0.06 mmol) dissolved in THF (10 cm^3). In a second flask, Cu(I)Br (450 mg, 3.1 mmol), THF (25 cm^3), *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA) (1.3 cm^3, 6.2 mmol), a stirring bar and molecular sieve were then added. The flasks were then taken out of the glovebox but kept under nitrogen pressure. A syringe and a syringe pump were used to transfer the polymer solution to the rapidly stirring CuBr/PMDETA solution at a rate of 0.75 mm^3/h. After complete addition of the polymer solution, the reaction mixture was allowed to stir for an additional 5 h. The solvent was evaporated in a rotatory evaporator before solubilization of the crude product in 20 cm^3 of CH_2Cl_2. Then, the medium was extracted from an aqueous solution of ethylenediaminetetraacetic acid (50 mM, adjusted to pH 7 using $NaHCO_3$) until getting a colorless aqueous phase. The organic phase was dried on $MgSO_4$, filtered and concentrated in a rotary evaporator prior to precipitation from dichloromethane into cold *n*-heptane to give cyclo-P(L-LA).

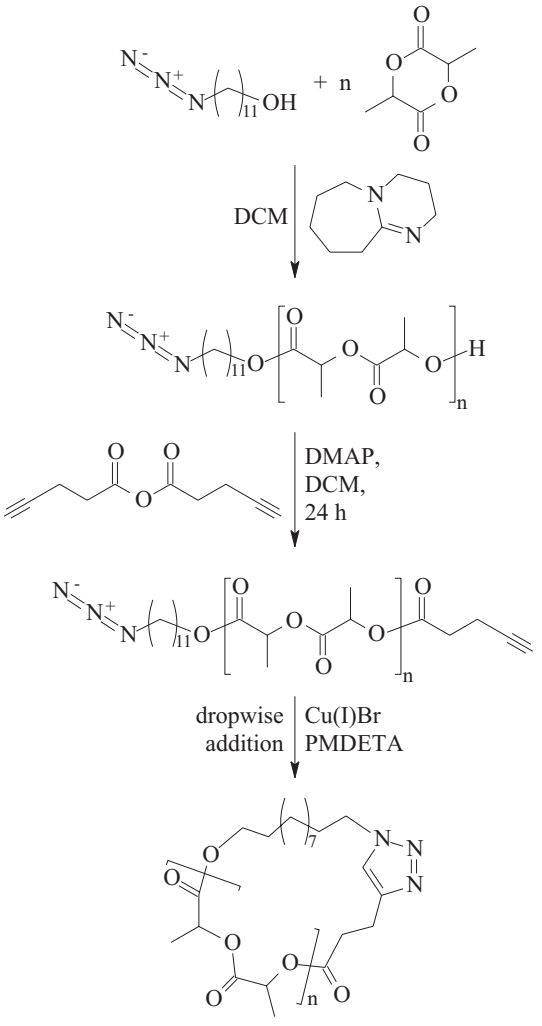
Representative results of analysis are given below.

^{1}H NMR ($CDCl_3$, δ, ppm): 1.27 [m, 14, $N_{triazole}(CH_2)_2(CH_2)_7(CH_2)_2O$-], 1.57 [m, 4, $N_{triazole}CH_2CH_2(CH_2)_7CH_2CH_2O$-], 1.57 (d, 6n, -$[COCHCH_3O]_{2n}$-), 2.80 (t, 2, -$COCH_2CH_2C_{triazole}$), 3.07 [t, 2, $N_{triazole}CH_2(CH_2)_{10}O$-], 4.12 [m, 2, $N_{triazole}(CH_2)_{10}CH_2O$-], 4.28 (t, 2, -$COCH_2CH_2C_{triazole}$), 5.15 (m, 2n, -$[COCHCH_3O]_{2n}$-), 7.38 (s, 1, -$N_{triazole}CHC_{triazole}$-). $Conv^{1H\ NMR}$ > 99 %, $\overline{M}_n^{1H\ NMR}$ = 4280 g/mol.

MS (MALDI-TOF): $\overline{M}_n^{MALDI}$ = 4020 g/mol, $Đ_M$ = 1.05. SEC: $\overline{M}_n^{SEC,\ app}$ = 4800 g/mol, $Đ_M$ = 1.12.

RESULTS AND DISCUSSION

The synthetic pathway for the preparation of cyclopolylactide (c-PLA) is illustrated in Scheme A. 11-Azido-1-undecanol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were used as ring-opening polymerization initiator and catalyst, respectively, affording PLA samples with terminal hydroxyl functionality [21]. An initial L-LA/initiator/DBU molar ratio of 25/1/1 ($[LA]_0 \approx 1$ mol/dm^3) has been selected.



Scheme A

In such experimental conditions, the polymerization was extremely fast, yielding quantitative monomer conversion in less than 5 minutes. To minimize the occurrence of deleterious transesterification reactions, kinetic study of the homopolymerization has been performed and results are given in Table 1.

T a b l e 1. Molecular parameters of c-PLA obtained using various polymerization times

Entry	Polymerization time, min	Conversion[a], %	$\overline{M}_n$ [b] (SEC)	$Đ_M$ [b] (SEC)	$\overline{M}_n$ [a] (NMR)	$\overline{M}_n$ (MALDI)	$Đ_M$ (MALDI)
1	10	>99	6700	1.23	4000	3500	1.12
2	5	>99	6800	1.17	3900	3550	1.08
3	4	>99	6725	1.16	3825	3600	1.06
4	3	>99	6750	1.16	3825	3600	1.05
5	2.5	>99	7000	1.11	4280	3940	1.05

[a] As determined by ^{1}H NMR based on signal integration.

[b] As determined by SEC in THF at 35 °C using a refractive index detector; calibration with polystyrene standards.

Since the Mark-Houwink parameters cannot be applied to the macrocyclic topology, the as-reported size-exclusion chromatography (SEC) molecular weights are relative to polystyrene standards and therefore over-predict the absolute average molecular weights. Nevertheless, $\overline{M}_n$ values determined by both ^{1}H NMR and MALDI-ToF analyses were found in good agreement. The results are presented in Figs. 1 and 2. Obviously, the best degree of control over the molecular parameters was achieved for a polymerization carried out for 2.5 min. The quantitative initiation by 11-azido-1-undecanol was estimated using ^{1}H NMR by comparison of the methylene end-group protons (Ha) with the characteristic hydroxymethine end-group protons (He′) of c-PLA (Fig. 1a).

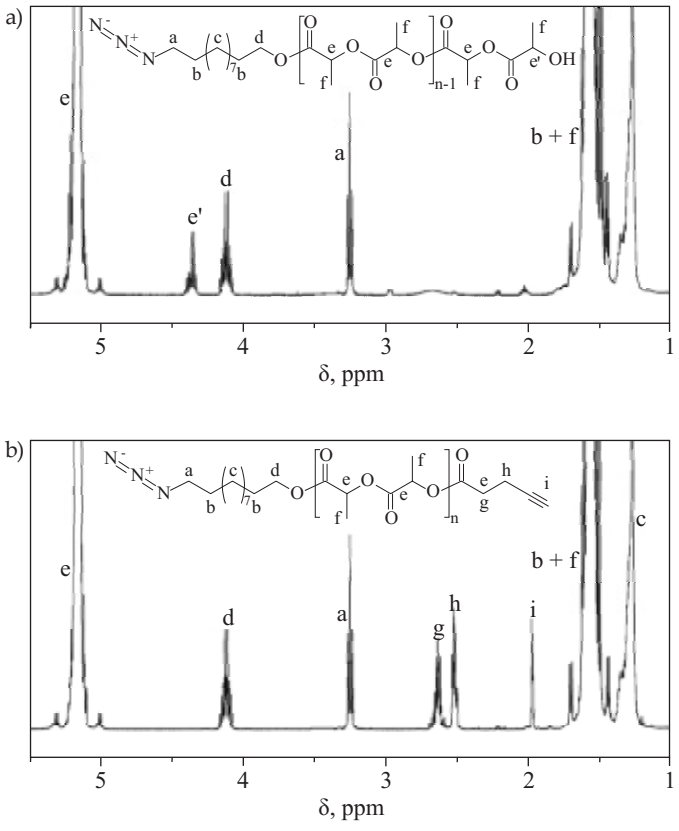


Fig. 1. ^{1}H NMR spectra of the α-azido-ω-hydroxyl P(L-LA) (a) and the α-azido-ω-alkyne P(L-LA) (b); He′ refers to the hydroxymethine proton of the terminal monomer unit

The subsequent reaction of the hydroxyl end-group of PLA with pentynoic anhydride yielded the linear α-azido-ω-alkyne PLA (l-PLA) [14]. ^{1}H NMR spectrum revealed the quantitative disappearance of the hydroxyl end-group resonance initially present at δ = 4.36 ppm (He′ in Fig. 1a) and the appearance of a new set of resonances at δ of 2.64, 2.52 and 1.97 ppm (Hg, Hh and Hi, respectively), corresponding to the alkynyl chain-end protons (-$CH_2CH_2C{\equiv}CH$) (Fig. 1b). The complete transformation is additionally confirmed by MALDI-MS analysis, where the main distribution is shifted by 80 mass units to higher *m/z* (Fig. 2).

As far as the CuAAC intra-molecular cyclization reaction is concerned, troubles in explaining the near-quantitativity of the method may origin from either the premature deactivation of the Cu(I)Br catalyst in inactive Cu(II) derivatives or by application of inappropriate experimental conditions (catalyst loading, dilution, injection rate). Since the oxidation of Cu(I) is caused by the inopportune presence of both oxygen and water, all of our cyclization tests were carried out in a glove box ([H_2O] < 1 ppm; [O_2] < 3 ppm) to minimize as much as possible this deleterious effect. In 2010, Lansdale *et al.* [18] concluded that the fraction of monocyclic species during a CuAAC-based cyclization is attributed to the probability of an azide chain-end being within the capture volume with the complementary alkyne end-group carried by the same polymer chain to diminish the probability of intermolecular reaction. The effect is that the injection rate and the concentration of the linear polymer in the catalytic solution are of prime importance. They, however, concluded that the amount of catalyst does not really matter on the efficiency of the process (at least in toluene). Since the type of solvent used during a CuAAC reaction dictates the kinetics of ligand exchange and the aggregation of copper species [22], and because the l-PLA intracyclization is here performed in THF, the effect of the catalyst loading has also been taken into account in our experiments. The CuAAC reactions were then realized in pseudo-high diluted conditions by a continuous dropwise addition of the l-PLA precursor (in solution in deoxygenated THF; $[\text{l-PLA}]_0 = 6.6 \cdot 10^{-3}$ mol/dm^3) into a deoxygenated solution of THF containing various amounts of CuBr catalyst and a pentamethyldiethylenetriamine (PMDETA) ligand ($[\text{PMDETA}]_0 \approx 2[\text{Cu(I)}]_0$). Table 2 gathers all experimental conditions and reports the percentage of monocycles obtained for each reactions. Those values have been

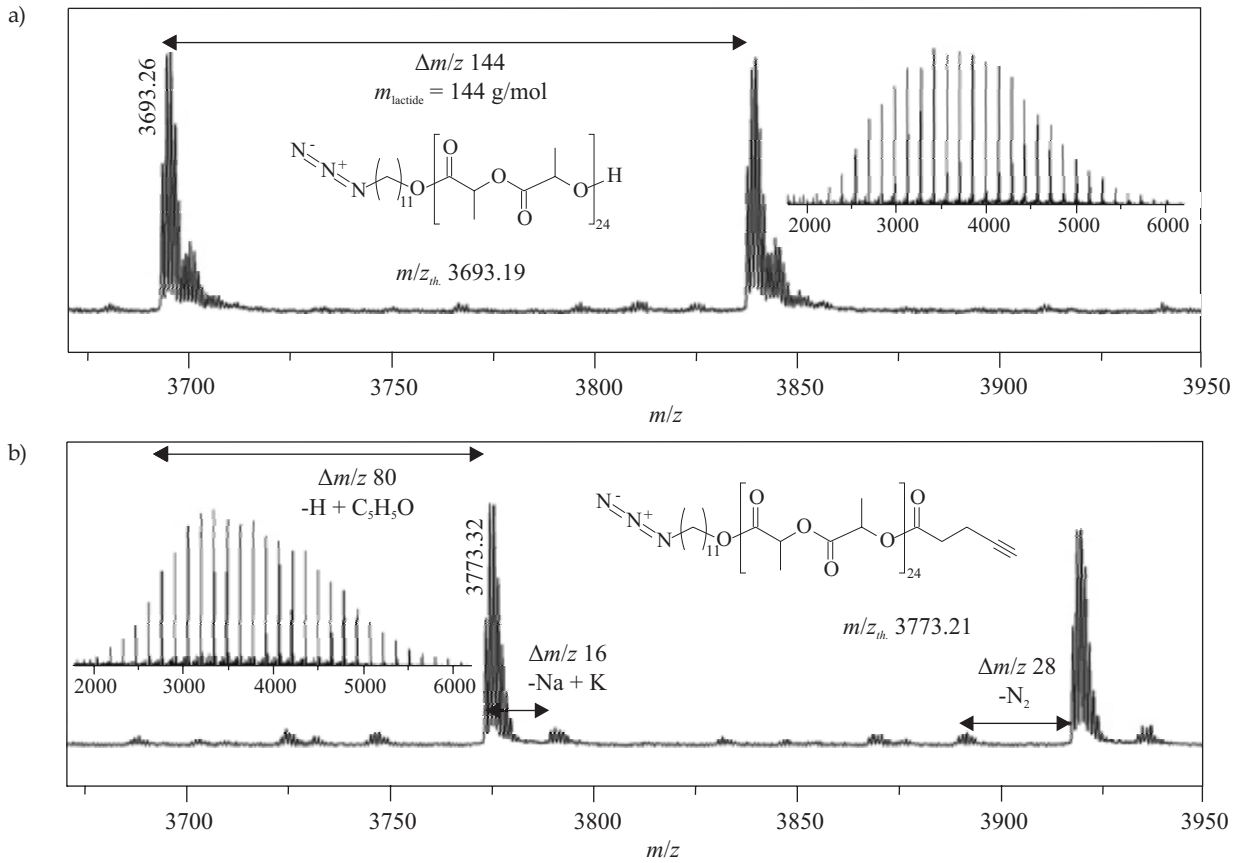


Fig. 2. MALDI-MS spectra of the α-azido-ω-hydroxyl P(L-LA) (a) and the α-azido-ω-alkine P(L-LA) (b)

obtained by a deconvolution method applied to the SEC chromatograms (refractive index detector).

Influence of the reactant injection rate on cyclization reaction

The size-exclusion chromatograms recorded for PLA samples obtained after 5, 15 and 25 min of continuous addition of the l-PLA solution on a 25-fold excess of copper catalytic complex (entries 1, 3 and 5 in Table 2) are compared in Fig. 3.

Being connected with an effective macrocyclization, an important proportion of interconnection is clearly visible in the low elution volume part of all three SEC chromatograms. This effect is even more pronounced for a very quick addition of l-PLA (entry 1) reinforcing the conclusion of a "diffusion-controlled" process [23].

T a b l e 2. Experimental conditions used to perform the intra-molecular cyclization of a l-PLA in THF in presence of Cu(I)Br and PMDETA ($[l\text{-PLA}]_0 = 6.6 \cdot 10^{-3}$ mol/dm^3, THF, 21 °C, initial molar ratio PMDETACu(I) = 2/1)

Entry	t[a] min	Initial molar ratio Cu(I)/l-PLA	$[l\text{-PLA}]_t$[b] mmol/dm^3	The percentage of purity of synthesis monocycle[c] %
1	5	25	2	59.6
2	5	50	2	74.6
3	15	25	2	77.2
4	15	50	2	84.5
5	25	25	2	84.7
6	25	50	2	92.1
7	25	50	0.85	93.0

[a] t – polymerisation time.

[b] $[l\text{-PLA}]_t$ – concentration of l-PLA after time t.

[c] Obtained by SEC chromatogram deconvolution of the refractive index response.

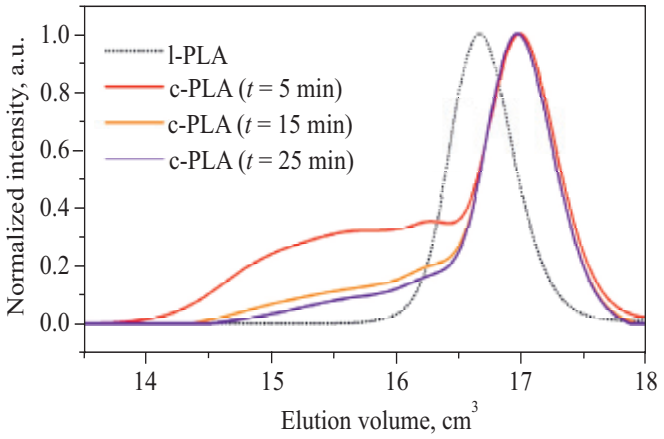


Fig. 3. SEC traces of crude c-PLA obtained after polymerization times of 5, 15 and 25 min (conditions of cyclization: $[l\text{-PLA}]_0 = 6.6 \cdot 10^{-3}$ mol/dm^3, 21 °C, initial molar ratio l-PLA/CuBr/PDMETA = 1/25/50)

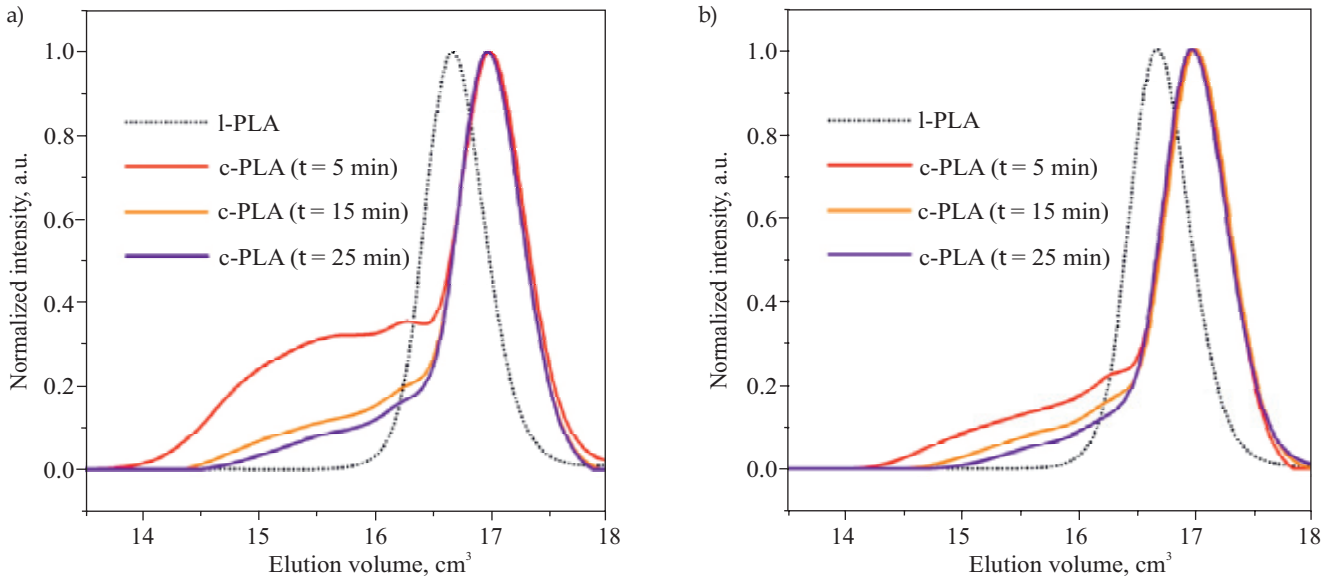


Fig. 4. SEC traces of crude c-PLA obtained after polymerization times of 5, 15 and 25 min either in presence of 25 (a) or 50 equivalents of CuBr (b) (conditions of cyclization: $[l\text{-PLA}]_0 = 6.6 \cdot 10^{-3}$ mol/dm^3, 21 °C, initial molar ratio CuBr/PDMETA =1/2)

Influence of the catalyst loading on cyclization reaction

As compared to the Monteiro's observation [18], increasing the quantity of catalyst (compared to the linear precursor molar content) improves the control over the intra-molecular cyclization. This has been confirmed for both low and high reactant injection rates as it is shown in Fig. 4. This observation tends to foster the hypothesis that if both complemental chain-ends of the l-PLA need to be in a capture volume, the probability of presence of the copper and therefore its amount as compared to the complemental end-groups is also essential for the intracyclization efficiency.

Influence of the dilution on cyclization reaction

If the proportion of copper as compared to the l-PLA precursor is of importance, neither the $[l\text{-PLA}]_t$ nor the $[Cu(I)]_t$ concentrations play an important role on the minimization of the interconnectivity reactions. This effect has been highlighted by comparison of SEC results for the samples shown in the entries 6 and 7 of Table 2 as well as in Fig. 5.

In accordance to the Monteiro's conclusion [18], it seems indeed possible to perform an intramolecular cyclization in few minutes and obtain a high degree of purity product (93 % in 25 min). As far as the formation of c-PLA is concerned, the effect of the catalyst loading is very important. This experimental condition needs, however, to be associated with a low reactant injection rate (high addition time) in order to diminish as much as possible the possibility of contamination. To verify this fact, the l-PLA has finally been cyclized by CuAAC ~~by~~ using a 50-fold excess of Cu(I) but for an addition time of 13.5 h (injection rate ~ 0.75 cm^3/h). As expected, the deconvolution of the SEC chromatogram, shown in Fig. 6, indicates a quanti-

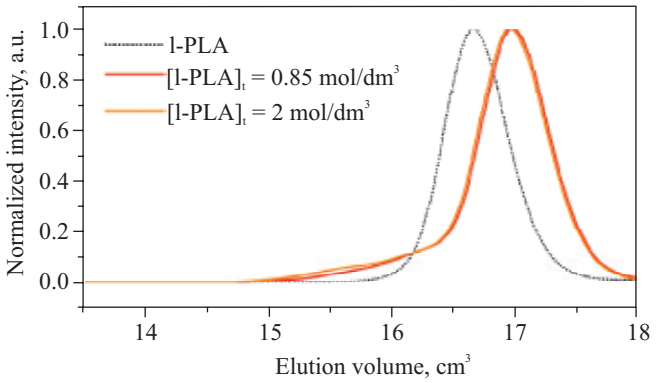


Fig. 5. SEC traces of crude c-PLA obtained after polymerization time t = 25 min for a $[l\text{-PLA}]_t$ of 0.85 and 2 mmol/dm^3 (conditions of cyclization: $[l\text{-PLA}]_0 = 6.6 \cdot 10^{-3}$ mol/dm^3, 21 °C, initial molar ratio l-PLA/CuBr/PDMETA = 1/50/100)

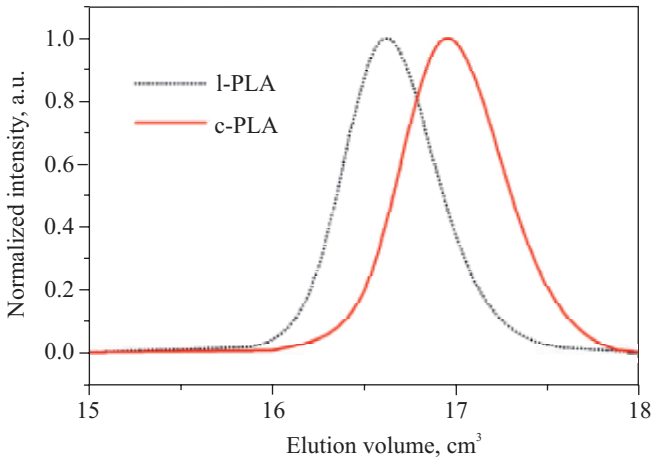


Fig. 6. SEC traces of both l-PLA and c-PLA (condition of cyclization: $[l\text{-PLA}]_0 = 6.6 \cdot 10^{-3}$ mol/dm^3, 21 °C, time of addition 13.5 h with speed rate ~ 0.75 cm^3/h, initial molar ratio l-PLA/CuBr/PDMETA = 1/50/100)

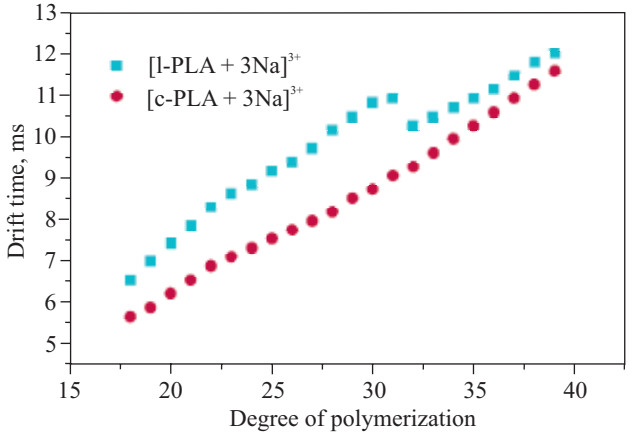


Fig. 7. Evolution of the drift time versus the degree of polymerization for triply charged linear polylactides (■) and triply charged cyclic polylactides (●)

tative reaction by determining a percentage of purity as high as 99.9 %.

In order to confirm the cyclization efficiency, the polymer sample has been characterized by using ion-mobility spectrometry-mass spectrometry (IMS-MS). This analytical technique has already proved its efficiency to discriminate linear from cyclic polymer ions [24]. Therefore, linear and cyclo polylactides were submitted to IMS-MS experiments. The evolution of the drift time depending on the degree of polymerization is shown in Fig. 7. As expected, the linear ions are characterized by a longer drift time while the cyclic ions are drifted quickly. The comparison of two mobilograms for m/z = 1081 ions, corresponding respectively to linear and cyclic ions is presented in Fig. 8. The good separation as well as the perfect symmetry of the cyclic ion signal clearly confirms the absence of linear precursor in the cyclic sample, at least in the limit of detection.

CONCLUSIONS

This work highlights the key role of experimental conditions in the preparation of highly pure cyclo-polylactides synthesized by CuAAC reaction applied to well-controlled α-azide-ω-alkyne linear PLA precursors. The rate of reactant addition/injection and the catalyst loading proved to be important parameters. Interestingly, highly pure PLA monocycles, *i.e.* with a purity as high as 99.9 %, have been produced and easily recovered.

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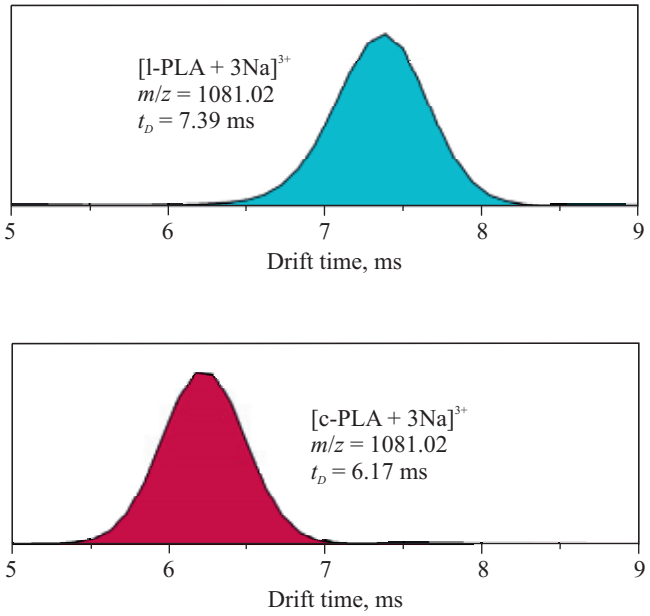

Fig. 8. Mobilograms for m/z = 1081.02 ions linear triply charged polylactides (a) and cyclic triply charged polylactides (b)

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