Controlled Cationic Polymerization of Lactide

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ABSTRACT: The combination of trifluoromethanesulfonic acid (as a catalyst) and a protic reagent (such as water, 2-propanol, or 1-pentanol as an initiator) efficiently initiates the cationic polymerization of lactide in dichloromethane solution at room temperature. Polylactides (PLAs) with molar masses up to 20 000 were obtained via an activated-monomer mechanism. ^{1}H NMR spectroscopy and electrospray-ionization mass spectrometry of PLA oligomers demonstrated the quantitative incorporation of the protic initiator in the polymer chains and showed that transesterification reactions did not occur to a significant extent. The controlled character of the polymerization was indicated by the linear relationships of the number-average molar mass vs monomer conversion and monomer-to-initiator ratio. Kinetic measurements revealed a first-order dependence on monomer concentration. Moreover, no noticeable epimerization of the stereogenic carbon atom was observed in these polymerization conditions, as deduced from ^{1}H NMR analysis of a poly(L-lactide) sample.

Introduction

Because of their biodegradability, biocompatibility, and ready availability from inexpensive renewable resources, polylactides (PLAs) are attracting growing interest as environmentally friendly substitutes for petrochemical-based polymers. Accordingly, these synthetic polyesters have given rise to a broad range of practical applications in packaging, surgery (tissue and bone repairing and engineering), and pharmacology (controlled release of active ingredients).[1] PLAs are usually prepared by ring-opening polymerization (ROP) of lactide via a coordination−insertion mechanism involving a metal complex.[2] The numerous well-defined complexes investigated over the past 15 years toward lactide polymerization have contributed significantly to a better understanding of the factors that govern the polymerization, and spectacular improvements have thereby been achieved in terms of catalytic activity as well as polymerization control. Taking into account the biomedical interest of PLAs, special interest has been devoted to initiators containing biocompatible metals, particularly Li,[3] Mg,[4] Ca,[5] Fe,[6] Zn,[3b,4,7] and lanthanides.[8] Moreover, Hedrick et al. recently reported the first metal-free systems for the living polymerization of lactide, using nucleophilic organocompounds (namely 4-aminopyridines, phosphines, and *N*-heterocyclic carbenes) in association with an alcohol as an initiator.[9−11]

Comparatively, the acid-catalyzed ROP of lactide has been much less developed. Kricheldorf et al. demonstrated the feasibility of this cationic route in the late 1980s, but the polymerization was far from living even in the optimum conditions.[12] So far, controlled cationic polymerizations have only been achieved for δ-valero- and ϵ-caprolactones, using HCl or an organic acid as a catalyst.[13] Here we report that cationic polymerization of lactide can be efficiently achieved in solution at room temperature combining trifluoromethanesulfonic acid (HOTf) and a protic reagent. Special attention has been paid to demonstrate the controlled character of this alternative metal-free polymerization.

Experimental Section

Materials. All reactions were performed under an inert atmosphere of argon, using standard Schlenk techniques. Solvents were dried and distilled prior to use: toluene (>99.9%) over sodium, pentane (>99%) over calcium dihydride, and dichloromethane (>99.95%) over phosphorus pentoxide. L-Lactide (99.5%) and DL-lactide (99.5%) (PURAC) were purified by recrystallization in toluene and stored under argon. Trifluoromethanesulfonic acid (99%, Aldrich) was used as received and stored under argon. 1-Pentanol (99+%) and 2-propanol (99+%) were dried over sodium and distilled before use.

Characterizations. ^{1}H NMR measurements were used to determine the monomer conversion and the chain end groups. Spectra were recorded in $CDCl_3$ on Bruker AC 200 MHz and Avance 400 and 500 MHz spectrometers at room temperature, and ^{1}H chemical shifts are reported in ppm relative to Me_4Si as an external standard. Monomer conversion was determined from the relative intensities of the methyl signals for the monomer (doublet at δ 1.61 ppm) and polymer (multiplet at δ 1.58 ppm).

The number-average and weight-average molar masses (M_n and M_w, respectively) and polydispersity indexes (M_w/M_n) of the PLA samples were determined by size exclusion chromatography (SEC) at 35 °C with a Waters 712 WISP high-speed liquid chromatograph equipped with a R410 refractometer detector. Tetrahydrofuran (THF) was used as the eluent, and the flow rate was set up at 1.0 mL/min. A SHODEX precolumn (polystyrene AT806M/S M_w = 50 000 000 g/mol) and two STYRAGEL columns (HR1, 100−5000 g/mol, and HR 4E, 50−100 000 g/mol) were used. Calibrations were performed using polystyrene standards (400−100 000 g/mol). For end-capped oligomers prepared with 2-propanol and 1-pentanol initiators, the molar masses M_n deduced from SEC analyses were in good agreement with those deduced from ^{1}H NMR spectroscopy (by the relative integration of the signals for the lactate units and chain ends).

Electrospray-ionization mass spectra (ESI-MS) were performed on a Perkin-Elmer Sciex API-365 spectrometer operat-

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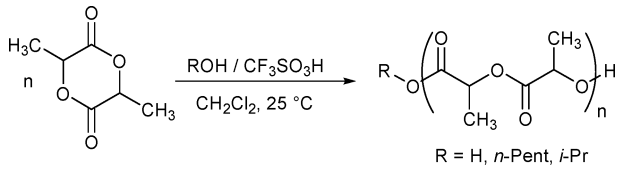
Table 1. Polymerization of DL-Lactide (LA) with the CF_3SO_3H/ROH System[a]

run	ROH	$[LA]_0/[ROH]$	time (min)	conv[b](%)	$M_{n(th)}$ [c]	M_n [d]	M_w/M_n [d]
1	H_2O	10	180	>96	1458	1760	1.48
2	H_2O	27.8	360	>96	4020	5460	1.33
3	H_2O	125	480	>96	18060	16360	1.18
4	*i*-PrOH	10	150	>96	1500	1660	1.25
5	*i*-PrOH	20	180	>96	2940	3060	1.35
6	*i*-PrOH	50	600	>96	7260	7790	1.37
7	*i*-PrOH	76.5	720	>96	11076	11300	1.15
8	*i*-PrOH	100	1680	>96	14460	14790	1.47
9	*i*-PrOH	75[e]	720	>96	10860	9120	1.26
10	*n*-PentOH	10	150	>96	1528	1660	1.13
11	*n*-PentOH	15	300	>96	2248	2300	1.14

[a] Polymerizations of 1 M solutions of DL-lactide in CH_2Cl_2 were carried out at 25 °C with an initiator-to-catalyst ratio of 1. [b] Obtained from ^{1}H NMR spectroscopy. [c] Calculated from the molar mass of lactide (144 g/mol) × $[LA]_0/[ROH]$ plus the molar mass of the initiator (ROH). [d] Number-average molar mass (M_n) and polydispersity index (M_w/M_n) obtained from size exclusion chromatography (in tetrahydrofuran, THF) using polystyrene standards. [e] L-Lactide.

Scheme 1



ing in positive ion mode. Samples were dissolved in acetonitrile, doped with traces of ammonium hydroxide, and infused with a syringe pump at 5 mL/min.

General Polymerization Procedure. Lactide (LA) (6.04 g, 42 mmol, 20 equiv) was dissolved in dichloromethane (41.6 mL, [LA] = 1 M). The initiator, 2-propanol (0.16 mL, 2.1 mmol, 1 equiv), and the catalyst, trifluoromethanesulfonic acid (0.18 mL, 2.1 mmol, 1 equiv), were successively added. The reaction mixture was stirred at 25 °C for 3 h (until the complete consumption of lactide monitored by ^{1}H NMR spectroscopy). The mixture was then treated with basic alumina in order to eliminate the catalyst and concentrated under vacuum. The polymer was precipitated with excess pentane and dried under vacuum. Conversion: >96%; yield: 70%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.20−4.95 (m, 44 H, OC*H*CH_3 and C*H*$(CH_3)_2$), 4.33 (q, J = 6.8 Hz, 1 H, HOC*H*CH_3), 3.63 (s br, 1 H, *H*OCHCH_3), 1.60−1.40 (m, 130 H, OCHC*H*$_3$), 1.24 and 1. 22 (two d, J = 6.0 and 6.5 Hz, 6 H, CH(C*H*$_3)_2$). DP_{NMR} = 21. SEC (THF): M_n = 1660, M_w/M_n = 1.25.

Procedure for Kinetic Studies. Polymerization was carried out at 25 °C in $CDCl_3$ solution (85 mL) with a lactide concentration of 1 M (12.00 g, 83.3 mmol of DL-lactide), and a lactide/2-propanol/trifluoromethanesulfonic acid molar ratio of 40/1/1 (0.16 mL, 2.1 mmol of 2-propanol and 0.18 mL, 2.1 mmol of trifluoromethanesulfonic acid). Aliquots (0.5 mL) were taken at different times during the polymerization and filtered over basic Al_2O_3. Lactide conversion was determined by ^{1}H NMR spectroscopy (400 MHz). After evaporation of $CDCl_3$ under vacuum, the PLA samples were analyzed by SEC in THF solution.

Results and Discussion

Various Brönsted acids have been investigated as catalysts for DL-lactide polymerization in the presence of a protic reagent (ROH) as an initiator. HOTf is the only catalyst active in dichloromethane at room temperature,[14] the complete polymerization of 10 equiv of lactide requiring 150−180 min with 1 equiv of water, 2-propanol, or 1-pentanol (Scheme 1, Table 1). Notably, the monomer conversion reached only 23% after 120 min in the absence of a protic initiator, and the combinations of 2-propanol with weaker acids such as $HCl.Et_2O$ or CF_3CO_2H are completely inactive after 120 min under the same conditions. Therefore, lactide is far less reactive toward cationic polymerization than δ-valero-

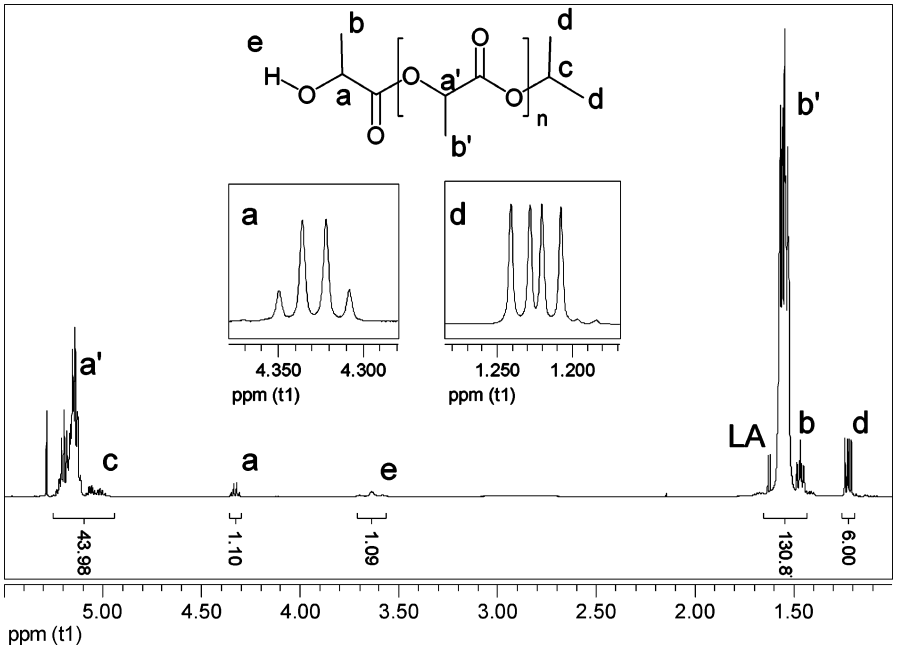


Figure 1. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of a polylactide sample obtained by polymerization of DL-lactide (LA) with *i*-PrOH as initiator (CH_2Cl_2, 25 °C, $[LA]_0/[i\text{-PrOH}]_0/[CF_3SO_3H]_0$ 20/1/1, $[LA]_0$ = 1 M).

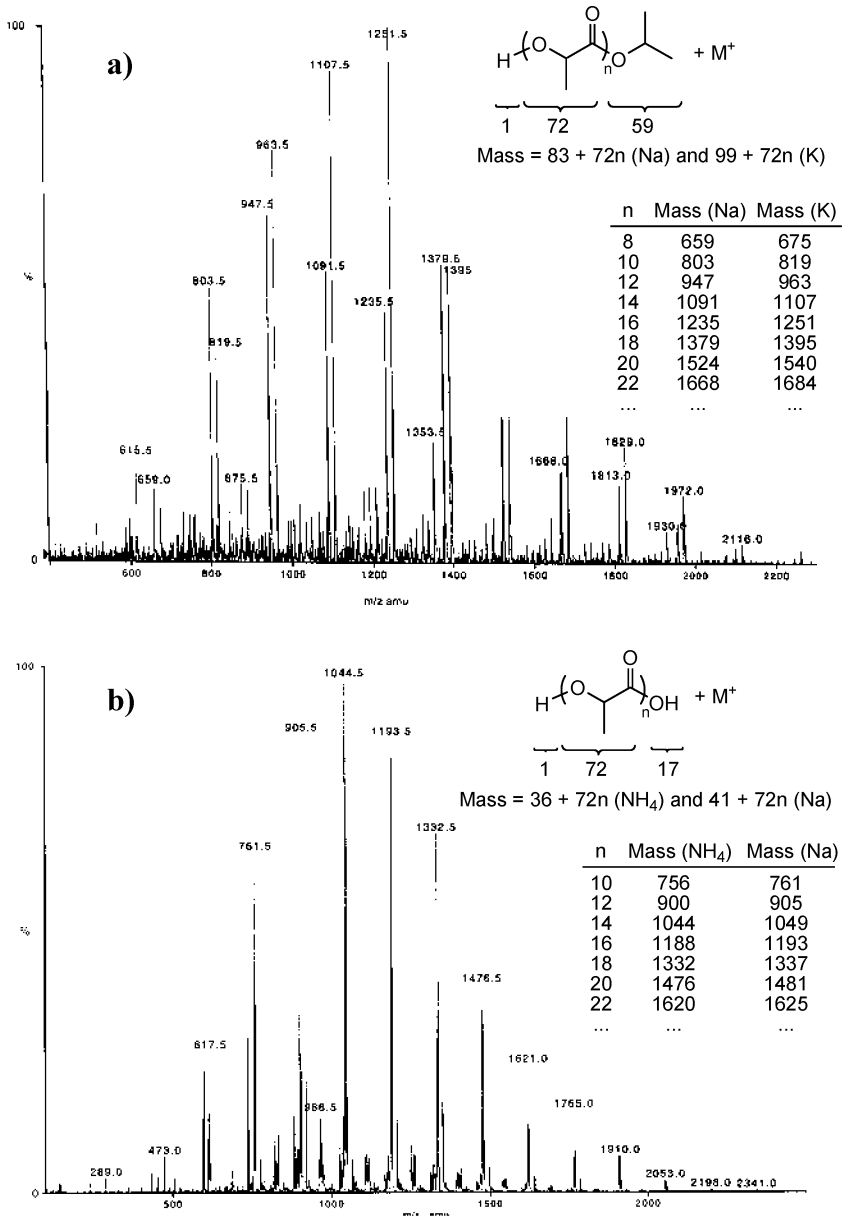


Figure 2. Electrospray-ionization mass spectra (region *m/z* 400−2200) of polylactide oligomers prepared by polymerization of DL-lactide (LA) with (a) 2-propanol (CH_2Cl_2, 25 °C, $[LA]_0/[i\text{-PrOH}]_0/[CF_3SO_3H]_0$ 10/1/1, $[LA]_0 = 1$ M) and (b) water (CH_2Cl_2, 25 °C, $[LA]_0/[H_2O]_0/[CF_3SO_3H]_0$ 10/1/1, $[LA]_0 = 1$ M).

lactone and ϵ-caprolactone, which are both efficiently polymerized with HCl at room temperature.[13]

Characterization of the PLAs. Spectroscopic analyses revealed the quantitative incorporation of the protic initiator in the PLAs prepared with the HOTf/ROH combination. Figure 1 shows the ^{1}H NMR spectrum of a PLA resulting from the polymerization of 20 equiv of lactide with 2-propanol as the initiator. The multiplet at 1.60−1.40 ppm is typically associated with the methyl (b + b′) protons of the lactate units. The related methine protons (a and a′) appear as two distinct signals: a multiplet at 5.20−5.05 ppm (a′) and a quartet at higher field (4.34 ppm) for the terminal methine (a) that bears a free hydroxyl group instead of an ester moiety. In addition, three signals were observed for the chain ends. The broad signal at 3.6 ppm (e) is associated with the O-terminal hydroxyl moiety. The multiplet at 5.03 ppm is attributed to the methine (c) of the isopropyl group, and two doublets at 1.24−1.20 ppm are observed for the corresponding methyl groups (d) that are diastereotopic due to the presence of a stereogenic center at the adjacent lactate unit. Notably the chemical shift for (c) clearly indicates the presence of an ester chain end. Moreover, the signals (d) and (a) integrated in a ratio 6/1. This demonstrates that all polymer chains had been initiated by the isopropyl alcohol, and therefore, they are all capped with the corresponding ester moiety.

Mass spectra analysis of a related *i*-PrOH-initiated oligomer corroborated the exclusive incorporation of the protic reagent in the polymer chains. Indeed, the spectrum obtained by electrospray-ionization exhibited only signals corresponding to oligomers of the formula $i\text{-PrO(COCHMeO)}_n\text{H}\cdot\text{M}^+$ (M = Na, K) (Figure 2a). The presence of carboxylic chain ends in the H_2O-initiated samples was established in a similar way, the corresponding spectrum exhibiting only signals associated with oligomers of the formula $\text{HO(COCHMeO)}_n\text{H}\cdot\text{M}^+$ (M = Na, NH_4) (Figure 2b). Notably, the presence of only even numbers of lactate units in both cases demonstrated that transesterification reactions did not occur

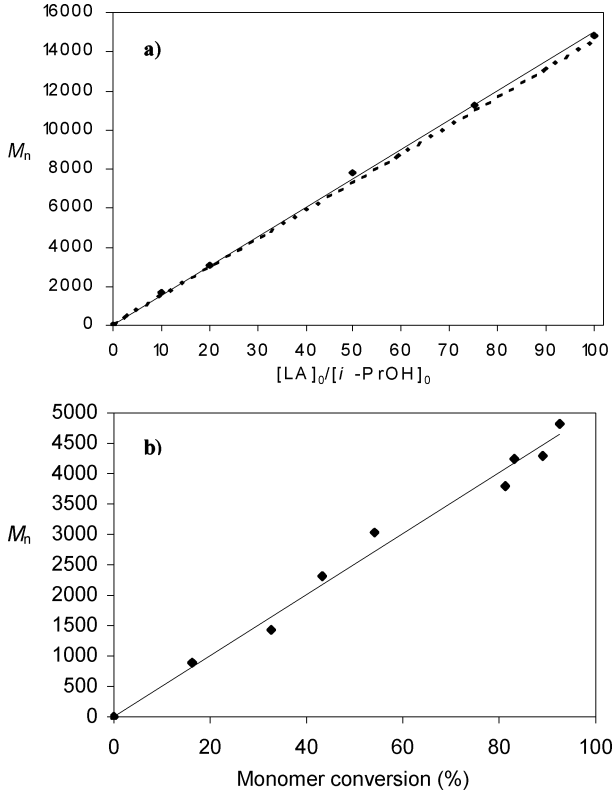


Figure 3. (a) Plot of number-average molar mass M_n (estimated by size exclusion chromatography SEC) vs DL-lactide (LA) to initiator ratio (solid line) (CH_2Cl_2, 25 °C, [*i*-PrOH]$_0$/[CF_3SO_3H]$_0$ = 1, [LA]$_0$ = 1 M). Broken line shows the $M_{n(th)}$ values calculated from the molar mass of lactide (144 g/mol) × [LA]$_0$/[*i*-PrOH] plus the molar mass of 2-propanol (60 g/mol). (b) Plot of M_n (estimated by SEC) vs DL-lactide conversion (estimated by ^{1}H NMR spectroscopy) ($CDCl_3$, 25 °C, [LA]$_0$/[*i*-PrOH]$_0$/[CF_3SO_3H]$_0$ 40/1/1, [LA]$_0$ = 1 M).

to a significant extent under these conditions. Indeed, such side reactions (intermolecular redistribution and intramolecular backbiting) could involve any of the ester functionalities of the polymer chain and would therefore lead indiscriminately to oligomers with even and odd numbers of lactate units.

Controlled Character of the Cationic ROP. The cationic ROP of lactide with the HOTf/ROH system was evaluated for different monomer-to-initiator ratios (Table 1). PLAs with molar masses up to 20 000 g/mol and relatively narrow molar mass distributions (M_w/M_n < 1.5) were obtained. The experimental M_n values (determined by SEC analysis) vary linearly with the monomer-to-initiator ratio (Figure 3a, correlation coefficient R^2 = 0.999) and agree well with those calculated from the monomer feed. The M_n values also vary linearly with the monomer conversion (Figure 3b, correlation coefficient R^2 = 0.986). These linear relationships demonstrate the controlled character of these cationic polymerizations. In contrast, the polymerization was only poorly controlled when Kricheldorf et al. used methyl triflate alone, as indicated by the very similar viscosities (0.15−0.27 dL/g) measured for polymer samples prepared from a span of monomer-to-initiator ratios varying from 50 to 400 (precise data concerning the molar masses are not available). This comparison highlights the critical influence of the protic initiator on the control of the cationic polymerization.

Furthermore, the living character of the polymerization was supported by a second-feed experiment. A PLA

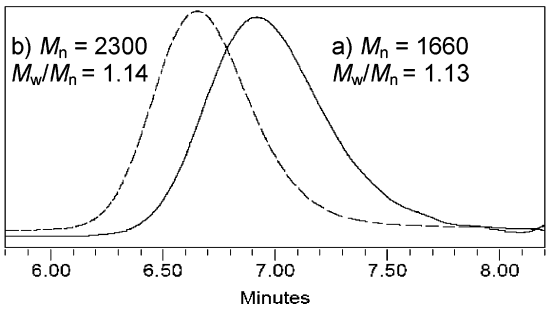


Figure 4. Superposed size exclusion chromatography (SEC) traces for the polylactide samples: (a) obtained after the first feed of DL-lactide (LA) (CH_2Cl_2, 25 °C, [LA]$_0$/[*n*-PentOH]$_0$/[CF_3SO_3H]$_0$ 10/1/1, [LA]$_0$ = 1 M) and (b) after a second feed of 5 equiv of DL-lactide.

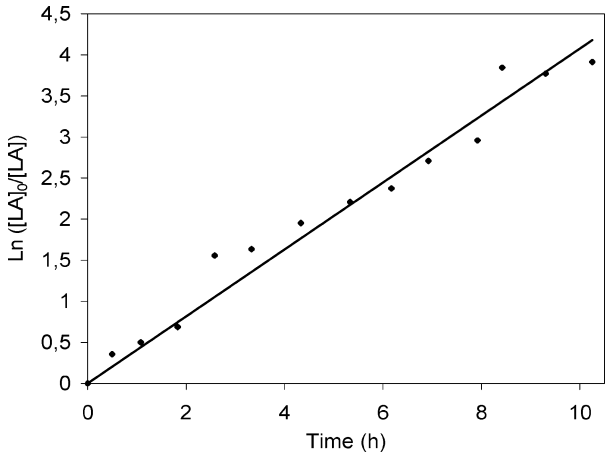


Figure 5. Semilogarithmic plot of DL-lactide (LA) conversion (estimated by ^{1}H NMR spectroscopy) vs time in $CDCl_3$ at 25 °C ([LA]$_0$ = 1 M, [LA]$_0$/[*i*-PrOH]$_0$/[CF_3SO_3H]$_0$ 40/1/1).

with M_n = 1660 g/mol and M_w/M_n = 1.13 was first prepared by complete polymerization of 10 equiv of DL-lactide with HOTf/*i*-PrOH (1/1). Polymerization was then restarted by subsequent addition of 5 equiv of DL-lactide to afford a PLA with M_n = 2300 g/mol and M_w/M_n = 1.14 (Figure 4).

Kinetic Study and Mechanism of the Cationic ROP. The polymerization of 40 equiv of DL-lactide ([LA]$_0$ = 1 M) in the presence of HOTf/*i*-PrOH ([*i*-PrOH]$_0$ = [HOTf]$_0$ = 25 mM) was monitored by ^{1}H NMR in $CDCl_3$ at 25 °C in order to establish the reaction order in monomer. The plot of ln([LA]$_0$/[LA]) vs time revealed a linear relationship (Figure 5, correlation coefficient R^2 = 0.967). The polymerization proceeds with a first-order dependence on DL-lactide concentration with a k_{obs} of 6.8×10^{-3} min^{-1} at room temperature. According to this value, the HOTf/ROH combination clearly does not compete with the most active systems reported to date (k_{obs} up to 100−700 min^{-1} for a few metallic complexes[4a,7c,d] and *N*-heterocyclic carbenes[7e]). However, trifluoromethanesulfonic acid seems at least as active as 4-(dimethylamino)pyridine, for which polymerization proceeds only at 35 °C and requires longer reaction times.[9a]

All the observations accumulated regarding the cationic polymerization of lactide (incorporation of the protic initiator, controlled character of the polymerization, and first-order kinetic dependence on monomer) support an activated-monomer mechanism.[15] This most probably involves protonation of lactide and its subsequent ring opening by nucleophilic addition of either the

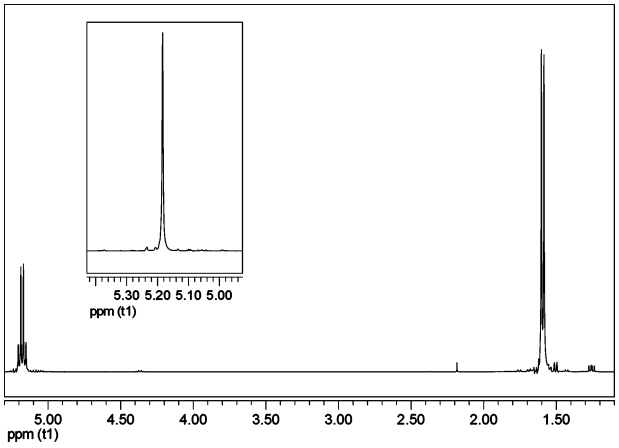
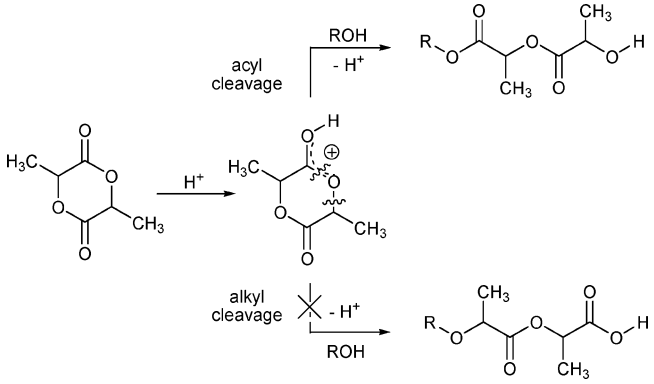


Figure 6. Normal and homonuclear decoupled ^{1}H NMR spectra ($CDCl_3$, 400 MHz) of a sample prepared by polymerization of L-lactide (L-LA) (CH_2Cl_2, 25 °C, $[L\text{-LA}]_0/[i\text{-PrOH}]_0/[CF_3SO_3H]_0$ 75/1/1, $[L\text{-LA}]_0 = 1$ M).

Scheme 2



initiating protic agent or the growing polymer chain (Scheme 2). In this regard, the acidic catalyst preferentially and selectively activates the monomer compared with the polymer chain, as deduced from the limited extent of undesirable transesterification reactions established above. Moreover, the presence of isopropyl ester chain ends (as deduced from NMR characterizations) demonstrates that the chain growth proceeds via acyl cleavage rather than alkyl cleavage (that would lead to isopropyl ether chain ends).

Finally, the influence of the strong acid (HOTf) on the monomer stereochemistry was investigated by polymerizing L-lactide under the same conditions (Table 1, run 9). According to homonuclear decoupled ^{1}H NMR spectroscopy (Figure 6),[16] a perfectly isotactic L-PLA has been obtained indicating that epimerization of the stereogenic carbon atom did not occur to a noticeable extent.

Conclusion

The HOTf/ROH system initiates and controls the cationic polymerization of DL-lactide via an activated-monomer mechanism. This readily accessible and easily removed[17] acid catalyst affords an alternative metal-free entry to PLAs of tailored properties. Current efforts focus on extending the initiator pool in order to elaborate variously capped PLAs[18] including block copolymers.[19]

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