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Poly(L-lactide) Epimerization and Chain Scission in the Presence of Organic Bases

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Abstract: Organocatalysis for polymer chemistry has become a subject of significant interest in the last two decades. In this contribution, we have studied the evolution of the microstructure of poly(L-lactide) in solution in toluene at 105 °C in the presence of various organocatalysts. Weak bases such as triethylamine and DMAP (4-dimethylaminopyridine) lead to a low extent of epimerization and a chain scission reaction. The DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) amidine induces in turn important extents of both epimerization (up to 37% D-stereoisomer formation) and chain scission. This has been tentatively attributed to a nucleophilic mechanism. Cinchona alkaloids lead to only a modest amount of epimerization. Phosphazene bases are in turn rather active, especially for high catalytic loadings (>1 mol %). The chain scission observed in this case is proposed to occur via a base-catalyzed hydrolysis mechanism. Finally, it is shown that combining an organic base with an acid can lead to a synergistic effect regarding notably the chain scission reaction.

Keywords: polylactide; organocatalysis; epimerization; chain scission; hydrolysis

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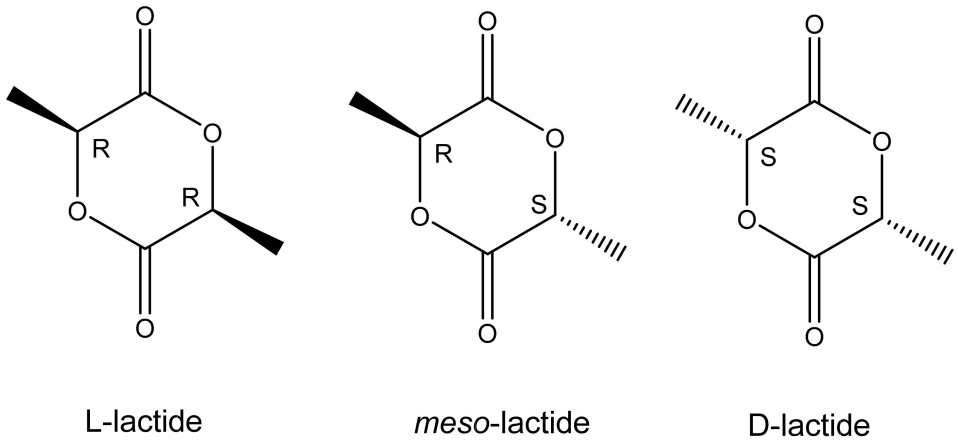
1. Introduction

Research toward biopolymers is a field in continuous expansion due to the depletion of fossil resources and the environmental concerns. In this context, polylactide (PLA), a biodegradable and biocompatible polymer, is one of the bio-based aliphatic polyesters with the most promising potential. It is produced at the industrial scale for competitive biomedical and packaging applications notably. It is usually obtained by the ring-opening polymerization of lactide, which is a cyclic ester produced via the oligomerization and cyclization of lactic acid. Organocatalysts are becoming more and more studied as an efficient alternative to metal-based catalysts, as they afford PLA without residual metal contaminates [1–3]. Since the discovery of the first organocatalyzed living polymerization using 4-dimethylaminopyridine (DMAP) [4], nitrogenous bases such as, e.g., amidines [5–7], guanidines [5,8,9] and phosphazenes [10–13] have received huge interest in the field. This is notably to be ascribed to the possible occurrence of different mechanisms for amidines and guanidines, as the nitrogen atom can activate a protic co-initiator and react with the lactide monomer directly by nucleophilic attack [7,9,14–17]. Nitrogenous catalysts bases are also known to allow the depolymerization of polylactide in combination with protic compounds, leading to alkyl lactates and control molecular weight oligomers [18,19].

The lactide monomer presents two asymmetric carbons, which lead to three diastereoisomers, i.e., L-, D- and *meso*-lactide (Scheme 1). In the presence of a base, several side reactions can occur such as transesterification, chain scission and epimerization on the lactyl moieties. Different studies have reported the stereochemical inversion of the lactide monomer. The optical purity of lactide is a major factor for the material properties of polylactide. The incorporation of a small amount of *meso*-lactide units into the structure of

poly(L-lactide) can deteriorate the polymer properties by reducing the crystallinity, thermal properties and biodegradation rate [20]. The conversion of L-lactide to *meso*-lactide was observed at high temperature (T > 180 °C) without catalyst in bulk conditions [21]. The racemization of *meso*-lactide into L- and D-lactides was also reported in toluene with an equimolar amount of *N*-heterocyclic bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and imidazole [22]. The combination of DABCO with the $B(C_6F_5)_3$ Lewis acid has been reported to epimerize quickly and quantitatively *meso*-lactide into *rac*-lactide, a mixture of D- and L-lactides, with only 20 ppm catalyst loading [23]. The subsequent kinetic resolution polymerization was performed to access an optical purity of poly(L-lactide) and poly(D-lactide). Epimerization was also reported during the ring-opening polymerization of L-lactide catalyzed by various metal carbonates, carboxylates and oxides [24].



Scheme 1. The three diastereoisomers of lactide.

The aforementioned studies were realized starting from the lactide monomer or in the course of a polymerization reaction. It is only recently that epimerization was thoroughly studied in the presence of an organic base starting directly from polylactide polymers [25]. Among various motivations, such works can have implications in macromolecular synthesis (e.g., what happened at the end of a polymerization reaction when all monomers have been consumed), upon storage or high temperature analysis if residual catalyst is still present [26], or for polylactide recycling. In this frame, the evolution of the microstructure of polylactide in the presence of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) at 105 °C in toluene has been studied [25]. The racemization rate was found to depend on the catalyst loading and the reaction time. As an example, 46% D-lactidyl units can be formed starting from poly(L-lactide) in the presence of 5 mol% TBD. An important chain scission reaction was also found to occur, leading to hydroxyl and carboxylic acid end-capped oligolactides. In this contribution, we report on the epimerization and chain scission of poly(L-lactide) in the presence of various organic bases, including an alkylamine, a pyridine derivative, an amidine and two phosphazenes, some of them being well-known organocatalysts for the ring-opening polymerization of lactide.

2. Materials and Methods

2.1. Materials

Poly(L-lactide)s (PLLA) were kindly supplied by Corbion (L105, M_n = 35,400 g/mol) and Natureworks (4032D Biopolymer Ingeo, M_n = 61,300 g/mol). The catalysts used in this study were purchased from Acros Organics (triethylamine (99%), 4-dimethylaminopyridine (DMAP) (99%), 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) (98%), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (98%)) or Sigma Aldrich (1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (98%), 1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2λ5,4λ5-catenadi(phosphazene) (*t*-BuP_4,

0.8 M in hexane), quinidine (98%), quinine (98%), cinchonidine (96%), cinchonine (98%), diphenylphosphate (99%)) as well as acyl chloride (98%). All catalysts were used as received without supplementary purification. Diethylether was purchased from Fisher Chemical. Toluene and THF (Aldrich) were purified through an alumina column (Mbraun SPS).

2.2. Typical Epimerization Reactions

Poly(L-lactide) (0.5 g–6.94 mmol considering a 72 g/mol repeating unit) and the catalyst (1 mol%, 69.4 µmol) were inserted in a Schlenk flask and dried under vacuum (10^{-2} mbar, 25 °C) during 6 h. Experiments using phosphazenes were prepared in a glove box.Purified toluene was added under argon atmosphere. The reaction was let at 105 °C during the desired time. At the end of the reaction, the solution was precipitated in ethanol, and the product was filtered and dried for 48 h. In the case of low molecular weight polylactides, the solution was put under vacuum to remove toluene.

2.3. Synthesis of Acetate End-Capped Poly(L-lactide) PLLA

Hydroxyl-ended PLLA (1.075 g, 15 mmol) was dissolved in 70 mL of anhydrous THF at 60 °C. Triethylamine (2.25 mL, 15 mmol) was then added at 25 °C. Acetyl chloride (1.25 mL, 17 mmol) was added dropwise to the stirred THF solution at 0 °C. The solution was let at ambient temperature overnight. The product was precipitated in cold methanol and filtrated. The PLLA was dissolved again in THF. The ammonium salt was removed by filtration through silica gel. The filtrate was concentrated. The acetate end-capped PLA was precipitated in diethyl ether, filtrated and dried under vacuum.

2.4. Characterization

^{1}H NMR spectra were recorded on an AVANCE III HD 300 Bruker spectrometer at room temperature with $CDCl_3$ (0.5 mL). The M_n NMR number-average molecular weight in Table 2 was calculated from the number-average degree of polymerization, which was determined by the integration of the proton of the -C*H* group and the proton of C*H*-OH end groups of polylactide, which are at δ = 5.2 and 4.4 ppm respectively (see e.g., Figure S3 in the SI section).

The number-average molecular weights (M_n) and the molar mass dispersities ($Đ_M$) were determined by Size Exclusion Chromatography (SEC). The SEC apparatus (Agilent Technologies) is equipped with Styragel HR1, HR3 and HR4 separative columns and a refractive index detector. Polystyrene (PS) standards were used for calibration by using THF as the eluent at a 1 mL/min flow rate at 40 °C. To determine the most reliable M_n for polylactide samples, a correction factor of 0.58 was applied [27].

Polarimetry data were obtained with Perkin Elmer (343) in chloroform (0.020 g of polylactide in 2 mL of solvent) at T = 20 °C with the D-line of the sodium lamp (λ = 598 nm). Equation (1) (from Biot law) was applied to determine the specific optical rotation.

$$\text{Equation (1)}: \ [a]_D^{20} = \frac{a_{obs}}{c * l} \quad (1)$$

where α_{obs} corresponds to the observed optical rotation angle, c is the concentration of the solution (g/mL), and l is the length of the tube in decimeters.

Equation (2) was used to determine the rate of isomer D [28].

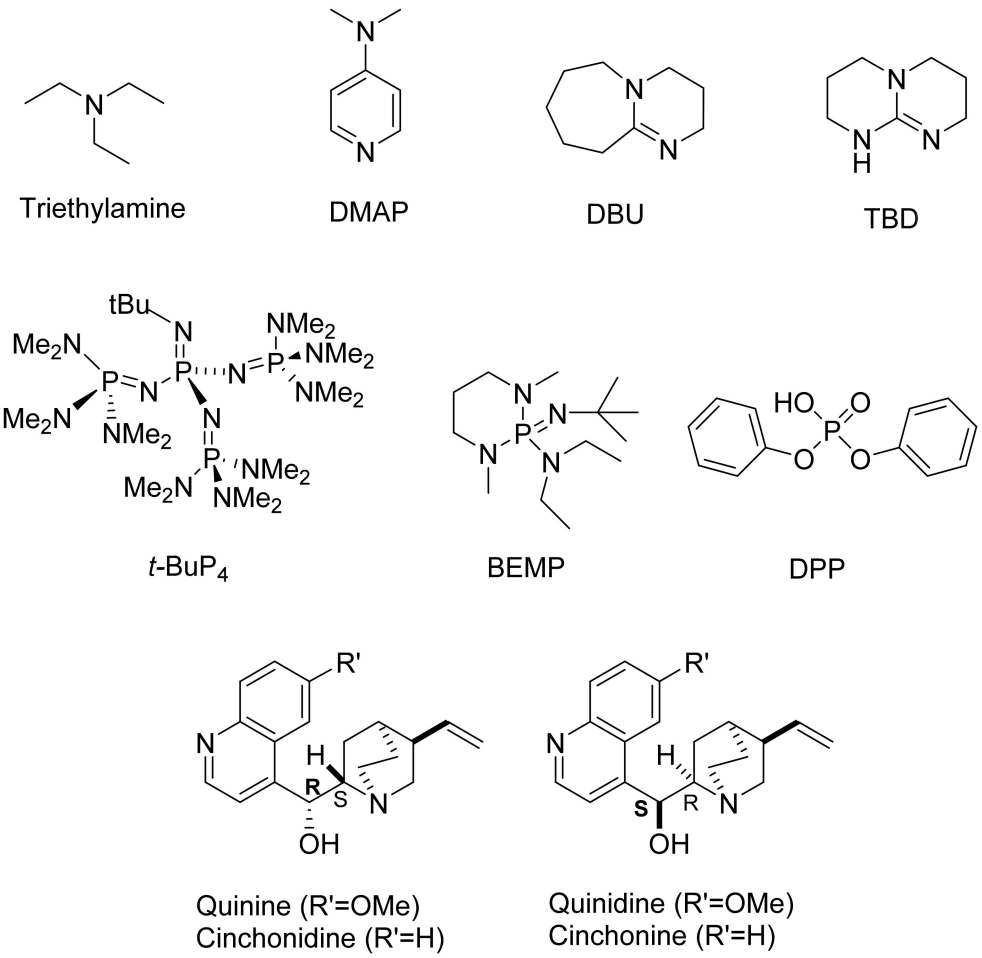
$$\text{Equation (2)}: \ D\ (\%) = \frac{\left([a]_D^{20}\right)\text{PLLA} - \left([a]_D^{20}\right)\text{PLA after reaction}}{2* \left([a]_D^{20}\right)\text{PLLA}} \times 100 \quad (2)$$

The poly(L-lactide) (M_n = 35,400 g/mol) optical rotation angle (α_{obs}) was measured eight times, and the calculated specific optical rotation values varied from $-159°$ to $-165°$ with an average of $-162.3°$ (standard deviation = 2.3°). The corresponding standard deviation on the epimerization rate (D %) was 0.6%. This specific rotation was in accordance with the data of the literature [29] (chloroform, 25 °C, λ = 598 nm).

Positive-ion Matrix assisted LASER Desorption/Ionization-Mass Spectrometry (MALDI-MS) experiments were performed using a Waters QToF Premier mass spectrometer equipped with a Nd:YAG laser operating at 355 nm (third harmonic) with a maximum output of 65 μJ delivered to the sample in 2.2 ns pulses at 50 Hz repeating rate. Time-of-flight mass analysis was performed in the reflectron mode at a resolution of about 10 k (m/z 569). All samples were analyzed using trans-2-[3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]malononitrile (DCTB) as a matrix. Polymer samples were dissolved in THF to obtain 1 mg.mL^{-1} solution. Additionally, 40 μL of 2 mg·mL^{-1} NaI solution in acetonitrile was added to the polymer solution.

3. Results and Discussion

Various catalysts were selected for this study: triethylamine as a simple trialkylamine, DMAP, DBU and two phosphazenes, which are known as polymerization catalysts for the ring-opening polymerization of lactide, and cinchona alkaloids as chiral bases. Their structures are given in Scheme 2. The microstructure of poly(L-lactide) initially drying at 25 °C, 10^{-2} mbar for 6 h, after 48 h at 105 °C in toluene in the presence of 1 mol% of these bases is presented in Table 1. The yield is higher than 95% in all cases. The use of a non-purified solvent as a case study for a higher content of water, as well as the azeotropic distillation of PLLA prior to the experiment is discussed in the SI section for selected cases.



Scheme 2. Structure of the catalysts investigated in this study. DMAP is 4-dimethylaminopyridine, DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene, TBD is 1,5,7-triazabicyclo[4.4.0]dec-5-ene, *t*-BuP$_4$ is 1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2λ5,4λ5-catenadi(phosphazene), BEMP is 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine and DPP is diphenylphosphate.

Table 1. Epimerization of poly(L-lactide) in the presence of an organic base as catalyst [a].

Entry	Catalyst	pK_{aH} [b]	$[a]_D^{20}$(°) [c]	Epimerization D (%) [d]	$M_{n\ corrected}$ (g/mol) [e]	$Đ_M$ [e]
	Starting PLLA	-	−162.3	0	35,400	1.7
1	No catalyst	-	−159.4	0.9	33,500	1.8
2	NEt_3	18.8 CH_3CN [30]	−152.0	3.2	31,400	1.8
3	DMAP	17.9 CH_3CN [30] 9.7 H_2O [31]	−154.5	2.4	19,200	1.8
4	DBU	24.3 CH_3CN [30] 11.9 H_2O [31]	−43.5	36.6	5800	1.5
5	TBD	26.0 CH_3CN [30]	−64.9	30	6000	1.6
6	Quinine	8.6 H_2O [32]	−158.2	1.3	13,200	1.8
7	Quinidine	8.6 H_2O [32]	−151.0	3.4	12,100	1.9
8	Cinchonidine	8.4 H_2O [32]	−155.9	2.0	11,500	2.0
9	Cinchonine	8.4 H_2O [32]	−151.2	3.4	12,000	1.9
10	BEMP	27.6 CH_3CN [33]	−149.9	3.8	10,600	1.8
11	*t*-BuP_4	42.7 CH_3CN [34]	−142.8	6.0	8300	2.1

[a] 1 mol% of catalyst, 0.5 g PLLA (M_n = 35,400 g/mol), 48 h, T = 105 °C, anhydrous toluene (3 mL, 2.3 mol/L); [b] in acetonitrile or water. For comparison, see the values for DMAP and DBU; [c] Specific optical rotation determined by polarimetry (chloroform, 20 °C, λ = 598 nm, standard deviation ± 2.5°); [d] Determined with equation 2 (standard deviation ± 0.6%); [e] M_n corrected = $M_{n\ SEC}$ × 0.58, $Đ_M$ is the dispersity, SEC (THF, standard PS, 40 °C).

Triethylamine (entry 2) and DMAP (entry 3) lead to a modest amount of epimerization in these conditions, with the formation of 2 to 3% of D-stereoisomer. This is only slightly higher than that obtained from a blank reaction conducted without catalyst (D = 0.9%, entry 1). A decrease in the number-average molecular weight can in turn be noticed, as observed previously in the presence of TBD [25]. This chain scission reaction is significant for DMAP, with a number-average molecular weight of 19,200 vs. 35,400 g/mol for the poly(L-lactide) precursor.

The use of DBU as catalyst leads to an even more important decrease in the molecular weight (5800 g/mol, entry 4), which is similar to that observed with TBD in similar conditions (6000 g/mol, entry 5). The epimerization is also very important, with a percentage of D-stereoisomer close to 37%. This result prompted us to perform a kinetic study, which is represented in Figure 1 in comparison with TBD. It is shown that the cleavage reaction reaches its maximum within a few hours, while epimerization is continuously increasing over the time. MALDI ToF analysis (given in the SI in Figure S1) shows that the polylactide is composed of linear macromolecules with carboxylic acid and hydroxyl end groups together with macrocyclic species. This microstructure is the same as that observed using TBD as the catalyst [25]. These similarities between DBU and TBD suggest that the catalytic mechanism is probably of the same type. A nucleophilic mechanism was proposed for TBD [25], and it may also apply for DBU. The mechanism of chain scission presented in Scheme 3 may be advanced for DBU on the basis of (i) the aforementioned behavior and (ii) the mechanism reported in the literature for the ring-opening polymerization of lactide in the presence of DBU without protic co-initiators [6,7]. The latter involves a zwitterionic acyl amidinium intermediate resulting from a nucleophilic attack of DBU on the lactide monomer. From these studies, we propose the following mechanism. The first step is a nucleophilic attack of the imine nitrogen of DBU on the carbonyl moieties, leading first to an acyl-amidinium intermediate and finally to an acyl-DBU. The latter is hydrolyzed by water molecules present in the reactive medium and/or at the end of the reaction by the quench, releasing a carboxylic acid end-capped polylactide.

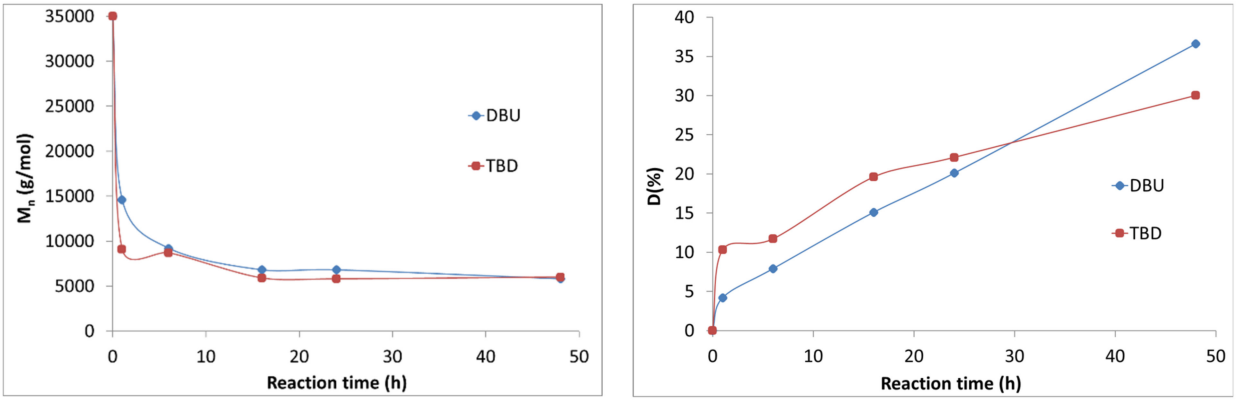
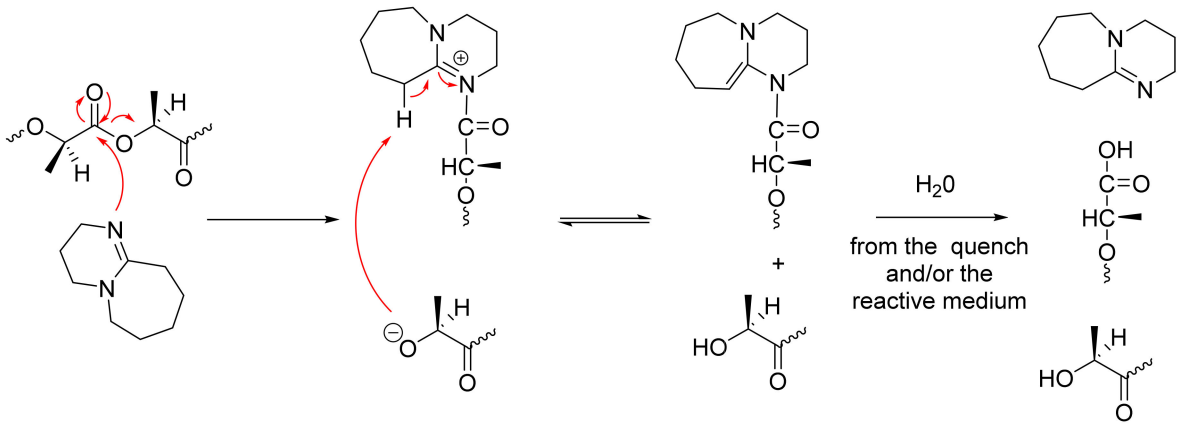


Figure 1. Number-average molecular weight (**left**) and D stereoisomer percentage of polylactide (**right**) as a function of the reaction time at 105 °C in the presence of 1 mol% DBU or 1 mol% TBD.



Scheme 3. Nucleophilic mechanism proposed for the chain scission with DBU as the catalyst.

We further assessed cinchona alkaloids (entries 6–9) as chiral bases in order to see if an effect could be evidenced. Although the epimerization reaction occurs at a modest extent (D < 3.4%), we can observe a slight influence of the configuration of the bases. The epimerization increases when the asymmetric carbon linked to the hydroxyl group of the chiral base and asymmetric carbon of poly(L-lactide) have the same configuration (S). With these bases, the chains scission is significant (M_n < 13,000 g/mol). This could be explained by the presence of nitrogen included in the cycles of chiral bases, which could have a nucleophilic action and promote chain scission.

BEMP and *t*-BuP_4 phosphazene bases were then assessed in similar experimental conditions. The resulting epimerization rate was found to be modest, with only 6% D stereoisomer after 48 h (entries 10–11). The chain scission was in turn found to be important, with M_n in the 8300–10,600 g/mol range in the experimental conditions of Table 1. As a matter of fact, regarding all the bases assessed in this work, there is no clear correlation between the pKa of the bases and the extent of epimerization (pKa given in Table 1, and a graph is provided in the SI section as Figure S5).

Additional reactions were performed with *t*-BuP_4 by varying the reaction time and catalyst loading, starting from a poly(L-lactide) of higher number-average molecular weight. The results are presented in Table 2, entries 12–20. For a catalyst charge of 0.25 mol % (entry 13), the epimerization is very low, and the molecular weight is divided by 4 in 48 h, confirming an important activity of phosphazenes for chain scission. Increasing stepwise the catalyst loading up to 3 mol % (entries 15;17;20) leads to an increase in both the epimerization and the chain scission extents, up to 41% D stereoisomer and 1000 g/mol,

respectively. The extent of the reactions over time can be seen for 1 h and 6 h according to the catalyst loading (entries 14, 16, 18–19).

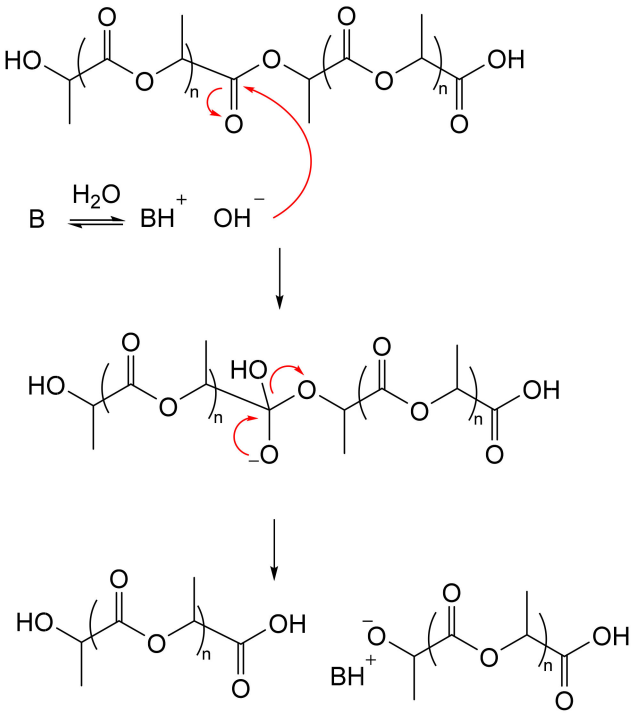
Table 2. Epimerization poly(L-lactide) in the presence of *t*-BuP_4 as catalyst [a].

Entry	Amount of Catalyst (mol%)	Time (h)	$[a]_D^{20}(^\circ)$ [b]	Epimerization D (%) [c]	M_n NMR [d] (g/mol)	$M_{n\ corrected}$ SEC (g/mol) [e]	$Đ_M$ [e]
Starting PLLA	-	-	−153.3	0	nd	61,000	1.6
12	0	48	−152.0	0.3	nd	61,000	1.6
13	0.25	48	−148.1	1.6	16,800	16,000	1.7
14	0.65	6	−138.6	4.7	15,600	17,000	1.9
15	0.65	48	−128.5	8.0	10,000	10,100	1.8
16	1	6	−137.7	5.0	13,000	12,000	1.8
17	1	48	−127.8	8.3	5000	7200	1.6
18	3	1	−142.0	3.7	13,800	12,000	2.1
19	3 [f]	6	−59.4	30.6	2400	3200	1.6
20	3 [f]	48	−27.2	41.1	900	1000	1.8

[a] 0.5 g PLLA, T = 105 °C, anhydrous toluene (3 mL, 2.3 mol/L), prepared in a glove box; [b] Specific optical rotation determined by polarimetry (chloroform, 20 °C, λ = 598 nm, standard deviation ± 2.5°); [c] Determined with Equation (2) (standard deviation ± 0.6%); [d] Number-average molecular weight determined by ^{1}H NMR (see experimental part); [e] M_n corrected = $M_{n\ SEC} \times 0.58$, $Đ_M$ is the dispersity, SEC (THF, standard PS, 40 °C); [f] The reaction product was recovered by evaporation of the solvent.

Phosphazene bases possess a strong basic character without being nucleophilic; thus, a nucleophilic attack of the catalyst for the chain scission is highly unlikely. Among possible mechanisms, it is known that the depolymerization of polylactide in basic medium can occur via a backbiting reaction starting by the deprotonation of the hydroxyl chain ends [35,36]. To assess this hypothesis, we realized experiments after acetylation of the hydroxyl chain end of the polylactide precursor. The results presented in Table S1 in the SI are similar to those obtained starting from the hydroxyl end-capped polylactide in the same experimental conditions. Thus, such a mechanism seems not to be operating for the phosphazene. In addition, intensive intramolecular transesterification is also not observed here, as the MALDI ToF analysis of a typical sample (given in Figure S2 in the SI) shows a very low amount of macrocyclic species in addition to linear polylactide bearing carboxylic acid and hydroxyl end groups. An anionic/enolate mechanism may also be considered based on the literature. Indeed, an initiation of the ring-opening polymerization of lactide catalyzed by a phosphazene was shown to occur via an enolate form resulting from deprotonation of the lactide monomer [37]. Transposing this mechanism to polylactide as a starting material would lead to branched/grafted polylactide (see Figure S4 in the SI), which would not lead to the observed decrease in the molecular weight. In addition, the resulting branched PLA would present a hydrodynamic volume that is different from that of a linear polymer, and thus, the number-average molecular weight measured by SEC using PS standards and Mark–Houwink correction should be different from the "true" M_n. We check by NMR, and this is not the case (see the NMR and SEC M_n columns in Table 2).

We propose that a base-catalyzed hydrolysis mechanism may occur. Indeed, although the polylactide precursor has been dried under vacuum for 6 h, there is probably still a significant amount of water molecules. The phospazene catalyst would deprotonate a water molecule, leading to an OH^- anion that can make a nucleophilic attack on the ester bond, as presented in Scheme 4. The resulting alkoxide chain end may be stabilized by the BH-conjugated acid. This could also explain why the epimerization extent is rather modest for a low amount of phosphazene, as the catalyst would in this case interact preferentially with water molecules rather than the C-H moieties of the polylactide.



Scheme 4. Base-catalyzed hydrolysis mechanism proposed for the chain scission in the presence of phosphazene.

Acid–base conjugates are known as catalysts for both the polycondensation of lactic acid [38] and the ring-opening polymerization of lactide [39–44]. Regarding the latter, the acid base conjugation presents several advantages, such as reducing the extent of transesterification, and/or increasing the activity, and/or improving the control over the molecular weight. It was shown recently that a DMAP/methanesulfonic acid combination leads to a ring-opening polymerization of lactide in the bulk at 130 °C with extremely few epimerization, yielding great potentialities for industrial applications [45]. From Table 1, it can be seen that among catalysts performant for the ROP of lactide such as amidine, guanidine and phosphazene, DMAP leads to the lower extent of epimerization in our experimental conditions (105 °C in toluene). We wanted to assess the use of an acid-base conjugate starting from a base that induces a more important extent of epimerization. TBD was selected for this purpose, and also considering its wide use, while diphenylphosphate was selected as the acid. The results presented in Table 3 show that the acid leads to a lower amount of epimerization than the base (4 vs. 8% D stereoisomer after 48 h for 0.5 mol %, entry 22 vs. 21), as expected. Chain scission is observed for both cases. When the two catalysts are combined, the epimerization does not exceed 4.7% (entry 23). The basic character of TBD is lowered in the presence of the acid. There is in addition a synergistic effect regarding the chain scission reaction, which is half as important for the conjugate vs. the single catalysts. This may be attributed to the lower nucleophilic character of TBD in the acid/base conjugate than alone.

Table 3. Epimerization of poly(L-lactide) in the presence of TBD, diphenyl phosphate (DPP) and their conjugate [a].

Entry	Catalyst	mol % vs. PLA	$[a]_D^{20}(^\circ)$ [b]	Epimerization D (%) [c]	$M_{n\ corrected}$ (g/mol) [d]	$Đ_M$ [d]
21	TBD	0.5	−136.3	8.0	11,000	1.8
22	DPP	0.5	−149.3	4.0	12,100	1.9
23	TBD/DPP	0.5/0.5	−147.0	4.7	25,600	1.9

[a] 0.5 g PLLA (M_n = 35,400 g/mol), T = 105 °C, 48 h, anhydrous toluene (3 mL, 2.3 mol/L); [b] Specific optical rotation determined by polarimetry (chloroform, 20 °C, λ = 598 nm, standard deviation ± 2.5°); [c] Determined with Equation (2) (standard deviation ± 0.6%); [d] M_n corrected = $M_{n\ SEC}$ × 0.58, SEC (THF, standard PS, 40 °C).

4. Conclusions

The epimerization of poly(L-lactide) was conducted in the presence of organic base catalysts in anhydrous toluene at 105 °C. It was found to be very low (D < 3.4% after 48 h) with weak bases such as triethylamine or DMAP and increased significantly with stronger bases such as, e.g., DBU (up to 37% D-stereoisomer). During the epimerization, chain scissions of PLA occurred certainly due to a nucleophilic attack of DBU on the PLA carbonyl. It was shown with a kinetic study that the cleavage reaction occurred faster (in a few hours) than epimerization, which is increasing over several days. Cinchona alkaloids were assessed as chiral bases, with little effect in the range of our experimental conditions. In the presence of phosphazene bases, a low epimerization rate was observed for low catalysts loadings, but there was a significant chain scission reaction. A base-catalyzed hydrolysis mechanism was proposed in this case. A synergistic effect is finally observed by combining an acid with a base, leading to a significant reduction in both epimerization and chain scission.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/macromol2020016/s1, Figure S1: MALDI Tof analysis of entry 4 (DBU as catalyst), Figure S2: MALDI ToF analyses of the PLLA precursor (A, blue) and a PLA after epimerization (entry 11, B, green) with *t*-BuP_4 as the catalyst, Figure S3: ^{1}H NMR spectra of PLLA-OH, and acetate end-capped PLLA before and after purification in CDCl3, 300 MHz, Figure S4: Hypothetical anionic/enolate mechanism, Figure S5: Influence of the pKa on the epimerization rate, Table S1: Reaction of OH end-capped PLLA and acetate end-capped PLLA with a phosphazene, Table S2: Epimerization of poly(L-lactide) in the presence of an organic base as catalyst. Influence of solvent purification.

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