



ARTICLE

High molecular weight poly(L-lactide) via ring-opening polymerization with bismuth subsalicylate–The role of cocatalysts

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Abstract

The catalytic potential of bismuth subsalicylate (BiSub), a commercial drug, for ring-opening polymerization of L-lactide was explored by variation of cocatalyst and polymerization time. Various monofunctional phenols or carboxylic acids, aromatic ortho-hydroxy acids, and diphenols were examined as potential cocatalysts. 2,2'-Dihydroxybiphenyl proved to be the most successful cocatalyst yielding weight average molecular weights (uncorrected M_w values up to 185,000) after optimization of reaction time and temperature. Prolonged heating (>1-2 h) depending on catalyst concentration) caused thermal degradation. In polymerization experiments with various commercial Bi(III) salts a better alternative to BiSub was not found. By means of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry a couple of unusual and unexpected transesterification reactions were discovered. Finally, the effectiveness of several antioxidants and potential catalyst poisons was explored, and triphenylphosphine was found to be an effective catalyst poison.

KEYWORDS

catalysts, polycondensation, polyesters, ring-opening polymerization

1 | INTRODUCTION

In addition to certain derivatives of starch or cellulose, polylactides are the most widely used and produced bio-sourced and biodegradable polymer.^{1–5} Since the pollution of nature with “immortal” plastics rapidly increases, their substitution by biosourced, hydrolytically degradable polymers is an important contribution to the reduction of environmental pollution with large plastic articles and microplastic. In addition to the substitution of immortal plastics homo- and copolymers of lactic acid have found numerous applications in medicine and

pharmacy.^{6–9} This situation justifies to explore new methods and catalysts useful for the preparation of high molecular polylactides and to explore their chemical and physical properties in more detail.

In contrast to the classical polymer chemistry, mainly based on polymers of α -olefins and vinyl monomers, the production of biodegradable environmentally friendly polymers makes only sense when the catalysts used for their production possess a low toxicity. Commercial polylactides are all produced by ring-opening polymerization (ROP) of L-lactide (sometimes containing also D-units) by means of tin(II) 2-ethylhexanoate (SnOct₂) as catalyst in

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combination with an alcohol as initiator. This tin(II)salt, like all other tin compounds, possess a considerable broad cytotoxicity, which concerns all kind of animals including microorganism. Since its toxicity against humans is rather low, SnOct₂ had been accepted by the American FDA as antifouling food additive. Nonetheless, for medical and pharmaceutical applications the tin content of polylactides is a matter of concern and thus, a less toxic substitute was desirable, at least for certain applications.

Over the past 20 years an increasing number of research groups has focused its work on ROPs of L-or D,L-lactide catalyzed by metal-free organo-catalysts, claiming that they are less toxic than metal-based catalyst.^{10–15} The following statement might be characteristic “Such organo-catalysts present lower toxicity than their organo-metallic counterparts and can, for the most part, be safely used in biomedical and electronic applications and be easily removed from the final PLLA material.”¹² This comment is at least misleading, not to say wrong, for the following reasons. First, none of those authors, who have advocated organo-catalysts, have published toxicity data of their catalysts. Thus, any comment claiming that their toxicity is lower than that of metal-based catalysts is not justified. Second, several metals, such as Mg, Zn, and Bi, are far less toxic than Sn, in as much as Mg and Zn belong to the human nutrition and play a role in the human metabolism. Hence, organocatalyst cannot be less toxic. Bismuth is the least toxic heavy metal, even slightly less toxic than zinc.^{16,17} In the United States, bismuth subsalicylate (BiSub) has been an over-the-counter drug for more than 100 years (e.g., under the trade mark “Peptobismol”).¹⁸ It has been demonstrated (and reviewed) that various bismuth(III) salts combined with

alcohols enable syntheses of linear homo and copolymers of lactide and glycolide.¹⁹ Recently, BiSub-catalyzed syntheses of low molecular weight polylactides initiated by aliphatic diols were described by Baez and coworkers.²⁰ Also quite recently, the authors have reported that the combination of BiSub and salicylic acid also allows for a racemization-free synthesis of cyclic poly(L-lactide) under optimized reaction conditions.²¹ In this context, the present work had the purpose to find out to what extent other “cocatalysts” influence the effectiveness of BiSub as catalyst for ROPs or REPs of L-lactide in bulk with a focus on three aspects. First, it should be found out which catalyst favors syntheses of polylactides having (uncorrected) weight average molecular weights (M_w 's) above 100,000 (the threshold for good mechanical properties). Second, it should be elucidated which type of cocatalysts favors formation of cyclic polylactides. Third, how does the reactivity of BiSub compare to that of other commercial Bi(III) salts.

2 | EXPERIMENTAL

L-Lactide, a product of Carbon Purac was kindly supplied by Thyssen-Uhde AG (Berlin, Germany). It was recrystallized from toluene (99.89% extra dry, AGROs Chem. Geel, Belgium). BiSub was purchased from Sigma–Aldrich (Taufkirchen, Germany) and used as received. Salicylic acid, 2-hydroxyphenylacetic acid, 2-hydroxyphenoxyacetic acid, 2,2'-dihydroxybiphenyl, catechol, 4-cyanoacatechol, 2-ethylhexanoic acid, phthalic acid and 4-hydroxybenzotrile, α -tocopherol and 1-hydroxymethyl naphthalene were all purchased from Alfa Aesar (Karlsruhe, Germany) and used as received.

TABLE 1 BiSub-catalyzed polymerizations of L-lactide in bulk at 170°C/2 h with variation of bifunctional carboxylic acids or phenols as cocatalyst (Lac/Cat = 1000/1, Coc/Cat = 1/1)

Exp. no.	Cocatalyst	M_n^a	M_w^a	Predominant topology ^b
1	—	23,500	57,000	Cyc <2500 Da
2	Salicylic acid	37,000	79,000	Cyc <4000 Da
3	2-Hydroxyphenyl acetic acid	38,000	84,000	Cyc + lin
4	2-Hydroxyphenoxy acetic acid	19,000	45,000	Lin
5	4-Cyanocatechol	31,000	98,000	Cyc <6000 Da
6	2,2'-Dihydroxy1,1'-biphenyl	41,000	132,000	Cyc <6000 Da
7	Bisphenole-A	36,000	110,000	Cyc + lin
8	Phthalic acid	— ^c	—	—
9	Phthalic anhydride	18,000	61,000	Cycl + lin.

Abbreviation: BiSub, bismuth subsalicylate.

^aUncorrected molecular weights obtained by SEC with polystyrene calibration.

^bAs indicated by MALDI TOF MS below m/z 10,000.

^cLow conversion.

TABLE 2 BiSub-catalyzed polymerizations of L-lactide in bulk at 170°C/2 h: Variation of monofunctional carboxylic acids and phenols (Lac/Cat = 1000/1)

Exp. no.	Cocatalyst	Co/Cat	t (h)	M _n ^a	M _w ^a	Predominant topology
1	2-Ethyl-hexanoic acid	1/1	2	Low conversion		Cyc. <3000
2A	4-Hydroxy-benzonitrile	1/1	2	31,000	69,000	Cyc. <3000
2B	4-Hydroxy-benzonitrile	1/1	3.5	33,000	74,000	Cyc. <3000
3A	4-Hydroxy-benzonitrile	2/1	2	44,000	82,000	Cyc. <3000
3B	4-Hydroxy-benzonitrile	2/1	3,5	33,000	81,500	Cyc. <3000
4A	α-Tocopherol	1/1	2	39,000	72,000	Lin
4B	α-Tocopherol	1/1	3.5	28,000	92,000	Lin
5A	α-Tocopherol	2/1	2	36,000	74,000	Lin
5B	α-Tocopherol	2/1	3,5	27,000	85,000	Lin

Abbreviation: BiSub, bismuth subsalicylate.

^aUncorrected molecular weights obtained by SEC with polystyrene calibration.

TABLE 3 BiSub-catalyzed polymerizations of L-lactide in bulk at 170°C cocatalyzed with catechol (Cocat/cat = 1/1)

Exp. no.	Lac/cat	t (h)	M _n ^a	M _w ^a	Color
1	1000/1	1.0	Low melt viscosity	—	Brownish
2	1000/1	2.0	24,000	75,000	Brown
3	1000/1	3.5	24,000	83,500	Brown
4	2000/1	1.0	Low melt viscosity	—	Brownish
5	2000/1	2.0	50,000	92,000	Brown
6	2000/1	3.5	53000	122,000	Brown

Abbreviation: BiSub, bismuth subsalicylate.

^aUncorrected molecular weights obtained by SEC with polystyrene calibration.

TABLE 4 BiSub-catalyzed polymerizations of L-lactide in bulk cocatalyzed with 2,2'-dihydroxybiphenyl: Optimization of the reaction conditions

Exp. no.	Lac/cat	Cocat/cat	T (°C)	T (h)	M _n ^a	M _w ^a	Color
1 ^b	1000/1	1.0/1	160	2.0	48,000	122,000	Sl. yellow
2 ^b	1000/1	0.5/1	170	1.0	97,000	160,000	Sl. yellow
3 ^b	1000/1	1.0/1	170	1.0	99,000	164,000	Sl. yellow
4 ^b	1000/1	1.5/1	170	1.0	93,000	155,000	Sl. yellow
5 ^b	2000/1	1.0/1	170	2.0	98,500	165,000	Yellow
6A ^b	2000/1	1.0/1	180	1.5	50,000	126,000	Yellow
6B ^c	2000/1	1.0/1	180	2.5	73,000	185,000	Yellow

Abbreviation: BiSub, bismuth subsalicylate.

^aUncorrected molecular weights obtained by SEC with polystyrene calibration.

^bSame batch of lactide was used.

^cAnother batch of lactide was used.

2.1 | Polymerizations

2.1.1 | With various cocatalysts in bulk at 170°C

BiSub (0.05 mmol), the cocatalyst (0.05 mmol) and L-lactide (50 mmol) were weighed under a blanket of

argon into a 50 ml flame-dried Erlenmeyer flask and a magnetic bar was added. The reaction vessel was immersed into an oil bath preheated to 170°C; finally, part of the reaction product was removed with spatula and pincer and characterized without purification (Tables 1-4, 7, and 8).

2.1.2 | With various Bi(III) salts at 170°C

The catalyst (0.05 mmol) and L-lactide (50 mmol) were weighed into a flame-dried 50 ml Erlenmeyer flask under a blanket of argon. After addition of a magnetic bar, the reaction vessel was immersed into a preheated oil bath and the reaction product was finally isolated by means of spatula and pincer.

2.1.3 | With addition of a catalyst poison at 170°C

The catalyst (0.05 mmol), the cocatalyst (0.05 mmol), and triphenylphosphine (0.05 mmol) were weighed into a 50 ml Erlenmeyer flask and L-lactide (50 mmol) was added under a blanket of argon. The polymerization was performed as described under Section 2.1.1.

2.2 | Measurements

The 400 MHz ¹H NMR spectra were recorded with a Bruker Avance 400 in 5 mm sample tubes. CDCl₃

TABLE 5 BiSub-catalyzed ROPs of L-lactide in bulk cocatalyzed with bisphenol-a: Optimization of the reaction conditions (lac/cat = 2000/1, Cocat/cat = 1/1)

Exp. no.	T (°C)	T (h)	M _n ^a	M _w ^a	Color
1	180	1	36,000	91,000	Sl. yellow
2	180	2	35000	97,000	Ocre
3	180	3	39,000	117,000	Ocre

Abbreviations: BiSub, bismuth subsalicylate; ROPs, ring-opening polymerizations.

^aUncorrected molecular weights obtained by SEC with polystyrene calibration.

Exp. no.	Catalyst	Lac/cat	T (°C)	t (h)	M _n ^a	M _w ^a
1A	Bi ₂ O ₃	1000/1	170	2	13,000	33,000
1B	Bi ₂ O ₃	1000/1	170	3.5	10,000	38,000
2	BiAc ₃	1000/1	170	3	22,000	44,000
3	BiOct ₃	400/1	170	2	26,000	45,000
4	BiOct ₃	1000/1	170	4	39,000	54,000
5	BiF ₃	1000/1	170	2	No polymerization	—
6	BiCl ₃	1000/1	170	2	No polymerization	—
7	BiCl ₃	100/1	160	48	200	3300
8	BiCl ₃	200/1	160	48	8500	20,000
9	BiBr ₃	1000/1	170	2	No polymerization	—
10	Bi-Triflate ₃	1000/1	170	2	Black tar	—

Abbreviation: ROPs, ring-opening polymerizations.

^aUncorrected molecular weights obtained by SEC with polystyrene calibration.

containing TMS served as solvent and shift reference. The 150 MHz ¹³C NMR spectra were recorded with a Bruker Avance III 600 MHz FT NMR spectrometer in 5 mm sample tubes, so that at least 4000 scans were accumulated. Matrix-assisted laser desorption/ionization time-of-flight (MALDI TOF) mass spectrometry was performed using an autoflex maX (Bruker Daltonik GmbH, Bremen) equipped with a Nd-YAG laser (355 nm). Trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene] malononitrile dissolved in chloroform (20 mg ml⁻¹) was doped with potassium trifluoroacetate and served as matrix. Matrix solution was premixed with the analyte solution (chloroform, 4 mg ml⁻¹) in a ratio of 5/1 (vol/vol). A volume of 1 μL of the resulting solution was deposited on the sample target. At least 2000 single spectra recorded at different positions within the spots were accumulated in the linear positive mode. The instrument was previously calibrated with PEO standards.

For the GPC experiments a modular system running at 40°C with chloroform as mobile phase (isocratic pump, 1 ml min⁻¹, refractive index detector, RI-501 -Shodex) was applied. Samples were manually injected (100 μl,

TABLE 7 BiSub-catalyzed ROPs of L-lactide in bulk at 170°C cocatalyzed with 2,2'-dihydroxybiphenyl: Variation of time

Exp. no.	t (h)	M _n ^a	M _w ^a	Color
1	1	81,000	153,000	Sl. yellow
2	2	62,000	141,000	Yellow
3	4	54,000	127,000	Brownish
4	9	42,000	122,000	Brown
5	24	27,000	99,000	Dark brown

Abbreviations: BiSub, bismuth subsalicylate; ROPs, ring-opening polymerizations.

^aUncorrected molar masses obtained by SEC measurements with PS calibration.

TABLE 6 ROPs of L-lactide at 170°C in bulk catalyzed by various Bi(III) salts

TABLE 8 Comparison of antioxidants and potential catalyst poisons in BiSub-catalyzed ROPs at 170°C/2 h cocatalyzed with 2,2'-dihydroxybiphenyl

Exp. no.	Catalyst poison	M_n^a	M_w^a	Color
1	Triphenylphosphine	No polymer	—	—
2	Tris(4-nonylphenoxy)-phosphite	31,000	97,000	Brownish
3	Phenylphosphonic acid	38,000	76,000	Faint yellow
4	Diphenylphosphonic acid	17,000 ^b 71,000	25,000 ^b 83,000	Yellow
5	N, N'-diphenyl-thiourea	47,000	95,000	Brown

Abbreviations: BiSub, bismuth subsalicylate; ROPs, ring-opening polymerizations.

^aUncorrected molecular weights obtained by SEC measurements with PS calibration.

^bThese products were isolated after crystallization.

2–4 mg ml⁻¹). For instrument control and data calculation, the Clarity software (GPC extension, DataApex) was used. The calibration was performed using polystyrene standard sets (Polymer Standards Service – PSS, Mainz, Germany). For the determination of the Mark-Houwling-Sakurada (MHS) relationship a viscometer (Viscostar, Wyatt, Germany) and a multiangle laser light scattering detector (Dawn EOS, Wyatt, Germany) were used. The Astra 6.1 software (Wyatt) served for calculating the MHS curves.

3 | RESULTS AND DISCUSSION

3.1 | Optimization of the molecular weight

A first series of polymerizations was designed to study the influence of difunctional compounds as potential cocatalysts on topology and molecular weights of the resulting poly(L-lactide)s. In previous studies of ROP and REP of L-lactide with cyclic tin catalysts^{22–25} or with BiSub in combination with salicylic acid²¹ it was found that reaction times <4 h are beneficial to avoid thermal degradation and racemization, when reaction temperatures >160°C were used. Since BiSub-catalyzed ROPs and REPs had shown that this catalyst system is somewhat less reactive than most cyclic tin catalysts studied before, this first series was conducted at 170°C and the reaction time was limited to 2 h. For all the polymerizations summarized in Table 1 the ¹H NMR spectra revealed that 2 h were indeed long enough to achieve conversion around 97%, the thermodynamic equilibrium of L-lactide. The MALDI TOF mass spectra revealed complete cyclization was never achieved as discussed below. In agreement with previous results obtained from combinations of BiSub with salicylic acid,²¹ it was also observed that the weight average molecular weights (M_w 's) of most poly-lactides were below 100,000. Only two experiment, based on 2,2'-dihydroxybiphenyl or bisphenol-A as cocatalyst, gave M_w value above 100,000. Since these values were

slightly higher than the best M_w achieved previously, with addition of free salicylic acid, further experiments were performed with the purpose to optimize the cocatalyst and the reaction conditions. The results obtained with monofunctional cocatalysts under the reaction conditions of Table 1 are compiled in Table 2. These results demonstrate that all monofunctional cocatalysts were somewhat inferior to 2,2'-dihydroxybiphenyl or bisphenol-A. Therefore, the optimization of the reaction conditions was performed with the three most promising diphenols. Instead of the relatively poisonous 4-cyanocatechol, unsubstituted catechol was used, because it can be found in numerous plants (although in small quantities). Thus, it belongs to the human nutrition, whenever salads or vegetables are consumed. The first piece of information, which could be learned from these experiments compiled in Table 3, was the finding that the rate of polymerization was slowed down compared to experiment No. 5 in Table 1 so that longer reaction times were needed. These longer times in combination with catechol had the consequence that the resulting poly-lactides showed a strong brownish discoloration, and thus, were not attractive for further studies and a potential production.

Variation of time and temperature proved to be considerably more successful when 2,2'-dihydroxybiphenyl was used as cocatalyst as illustrated by the experiments summarized in Table 4. At a Lac/Cat ratio of 1/1 a shorter reaction time of 1 h proved to be beneficial for higher molecular weights and experiment No. 3, which was the first the authors have conducted, a M_w above 150,000 was achieved for the first time. The additional experiments evidenced that M_w 's above 150,000 could be achieved under more than one set of reaction conditions. When a Lac/Cat ratio of 2000/1 was used, finally a M_w of 185,000 was obtained. As published previously, commercial poly(L-lactide)s designed for injection molding typically have M_w 's in the range of 100,000–150,000 and thus, the results obtained here with 2,2'-dihydroxybiphenyl demonstrate for the first time, that poly(L-lactide)s suited

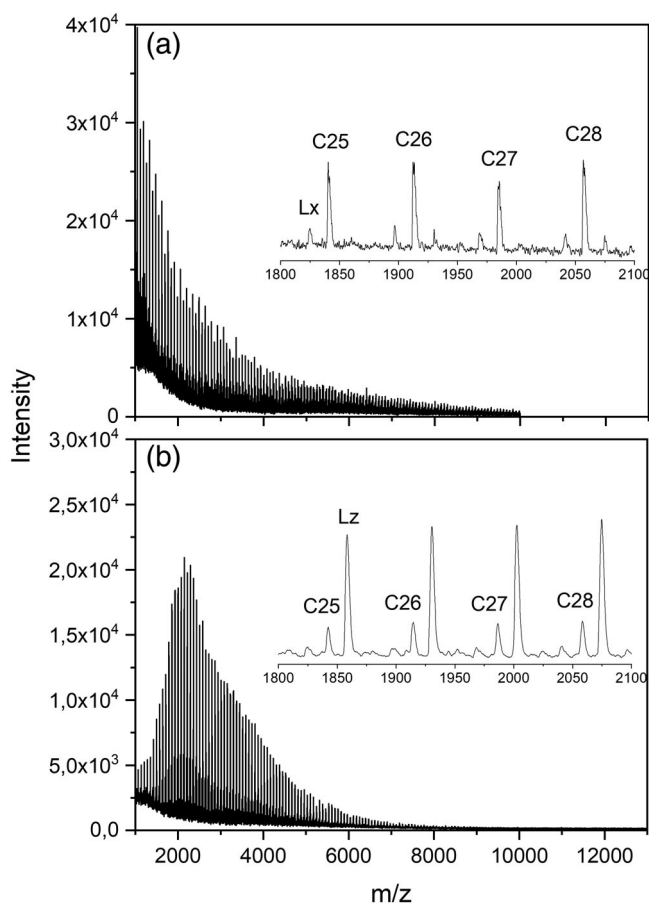


FIGURE 1 Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectra of poly(L-lactide)s prepared with (a) bismuth subsalicylate (BiSub) and 4-cyanoacatechol (no. 5, Table 1); (b) BiCl_3 (no. 7, Table 6)

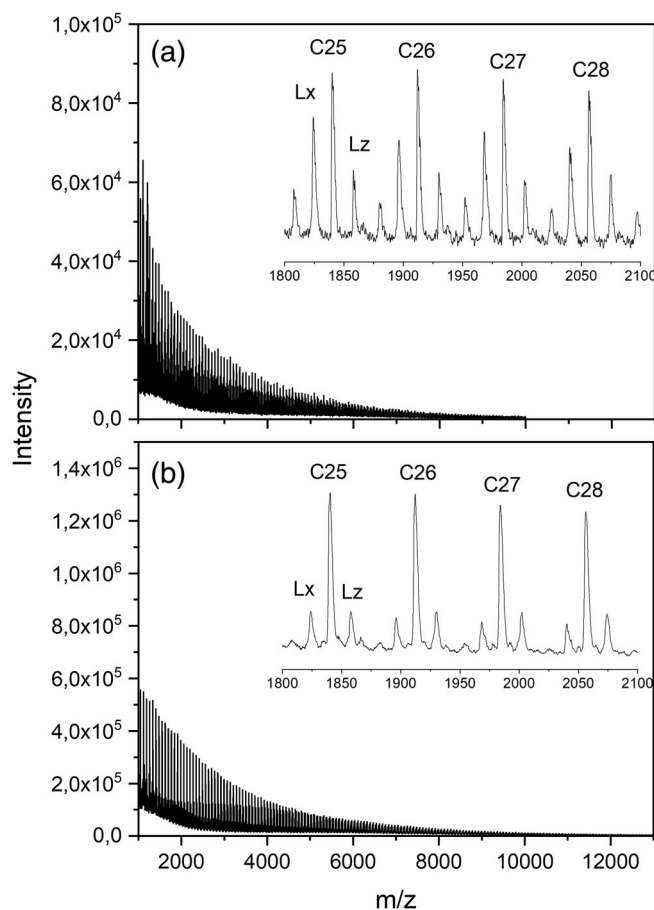


FIGURE 2 Matrix-assisted laser desorption/ionization time-of-flight (MALDI TOF) mass spectra of poly(L-lactide)s prepared with bismuth subsalicylate (BiSub) and 2,2'-dihydroxybiphenyl at 170°C (a) after 2 h /no. 1, Table 7) and (b) after 24 h (no. 5, Table 7)

toxicity. In the case of tin-based catalysts it is well known that organotin compounds may be several orders of magnitude more toxic than Sn(II) salts, such as Sn(II) 2-ethylhexanoate or SnCl_2 . Since Bi like Sn has a considerably “affinity” to sulfur and may easily react with SH groups of enzymes, it is imaginable that the toxicity of lipophilic organo-bismuth compounds is again much higher than that of Bi(III) salts.

Finally, it should be mentioned that quite recently a study about methanolytic degradation (and recycling) of used polylactide articles catalyzed by various Bi(III) salts was published.³³ There, it was found that BiSub was the most effective transesterification catalyst of all Bi(III) salts used in that study.

3.3 | Topology and MALDI TOF mass spectrometry

In a previous publication it was reported that addition of salicylic acid to BiSub-catalyzed polymerizations

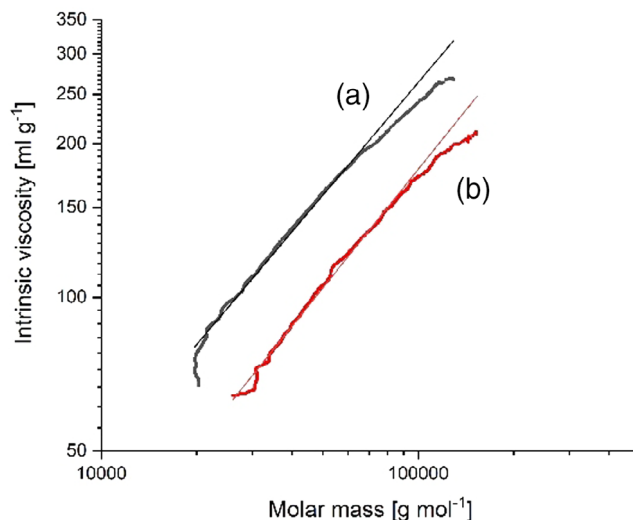


FIGURE 3 Comparison of intrinsic viscosities (Mark-Houwink-Sakurada [MHS] measurements) of (a) commercial linear polylactide, Purapol L105); (b) sample no. 5, Table 1, prepared with 4-cyanoacatechol as cocatalyst [Color figure can be viewed at wileyonlinelibrary.com]

conducted in bulk at 160°C and primarily at 180°C in yielded poly(L-lactide)s predominantly consisting of cycles even in the high molecular weight region above 50,000.²¹ However, careful optimization of the reaction conditions was necessary, and in the vast majority of the experiments, the MALDI TOF mass spectra displayed peaks of linear chains accompanying the cycles. In the present work MALDI TOF mass spectra of all samples were recorded. A significant predominance of cycles in the observable mass range up to m/z 10,000 was only found for two experiments, namely for the 4-cyanoatechol-cocatalyzed polymerization No.5, Table 1 (Figure 1(a)) and, to a somewhat lesser extent, for one 2,2'-dihydroxybiphenyl-cocatalyzed sample No. 5, Table 7 (Figure 2(b)). In the case of sample No. 5, Table 1, the intrinsic viscosity was measured and compared with that of commercial linear poly(L-lactide) (Purapol L105). As demonstrated by Figure 3, the intrinsic viscosity of sample No. 5 was lower to an extent suggesting that 80–90% of the product consisted of cycles, a result which is in good agreement with the mass spectrum of Figure 1(a). Compared with similar experiments using salicylic acid as co-catalyst; however, experiment No. 5, Table 1, does neither represent a progress with regard to higher molecular weight nor with regard to a higher extent of cyclization. Nonetheless, the formation of rather large amounts of cycles in almost all samples catalyzed by BiSub suggests that part of the polymerization process proceeded via ring-expansion polymerization as illustrated by Scheme 1.

Cyclic catalyst structure involving 4-cyanoatechol or 2,2'-dihydroxybiphenyl may also be involved. This hypothesis is supported by the observation that the content of cycles extremely low, when BiCl₃ served as catalyst (Figure 1(b)). Two peaks of linear chains were observed in almost all mass spectra with largely varying intensity ratios, as illustrated by Figures 1,2 and 3 and by Figures S1-S3 in the supporting information. Peak Lx is characterized by a mass of 16 Da below that of the next cycle and Lz is characterized by a mass of 16–18 Da above that of the next cycle. In principle, one may explain Lx by unintended doping with Na ions, but intentional doping with sodium iodide proved that only part of the Lx intensity results from doping with Na. The Lz peaks may, in principle, be explained by initiation or transesterification with water introduced via BiSub. However, several observations are in contradiction to this explanation. First, the authors were of course careful with exclusion of moisture and Lz peaks were also observed in hundreds of mass spectra of polylactides catalyzed by tin compounds. Thus, these peaks are not characteristic for Bi(II)-catalyzed polymerizations. Second, in certain tin-catalyzed polymerizations it was found that

the intensities of Lz peaks increase with time and temperature suggesting an origin by degradation reactions. Third, in this work the opposite trend was observed as illustrated by Figure 2(a),(b) for the experiments of Table 7. The intensities of both, Lx and Lz peaks decreased with time. Such a trend has never been observed before and is in contradiction to proceeding hydrolysis. A more detailed study of structures behind these peaks and their hypothetical origin was outside the scope of this study but will follow in the near future. Another unexpected trend was revealed by MALDI TOF mass spectrometry, namely formation of a new maximum around m/z 3000 in the number (mass) distribution of several samples (Figures S1A, S2A,B and S4A,B). With 4-hydroxybenzotriazole as cocatalyst this maximum vanished upon prolonged heating (Figure 1). Formation of a new maximum around m/z 5000 was also found in several REPs of L-lactide catalyzed by cyclic tin compounds under conditions where crystallization occurred. The maxima were explained by preferential crystallization of chains or cycles having a length favorable for crystallization. Yet, the experiments of this work were all performed under reaction conditions preventing crystallization. Therefore, the authors must again concede that they were unable to offer a reasonable explanation. Figure S3 is shown to demonstrate that in all experiments with bisphenol-A (like in all experiments with 2,2'-dihydroxybiphenyl) formation of a distinct new maximum above m/z 2000 did not occur. In summary, it may be said that the BiSub-catalyzed polymerizations of L-lactide involve a complex transesterification chemistry which is, at least partially, different from that of tin-catalyzed polymerizations.

3.4 | Mechanistic discussion

Unfortunately, the BiSub-based catalyst systems are unfavorable for a straightforward elucidation of the polymerization mechanism. BiSub is initially insoluble in molten L-lactide like in almost all organic solvents. It slowly dissolves, when the Lact/Bi ratio is around or above 1000/1. When refluxed with equimolar or double molar amounts of 4-cyanoatechol or 2,2'-dihydroxybiphenyl in dioxane, chlorobenzene or dichlorobenzene again no dissolution occurred, so that formation of well-defined complexes was not observable. Considering the large number of reports of numerous research groups on metal alkoxide or phenoxide initiated polymerization of lactide and lactones, a coordination-insertion mechanism formulated in Schemes 1 and 2 is the most probable scenario. The Bi—O—CH end group formed by the initiation step is the most nucleophilic and most reactive species in the

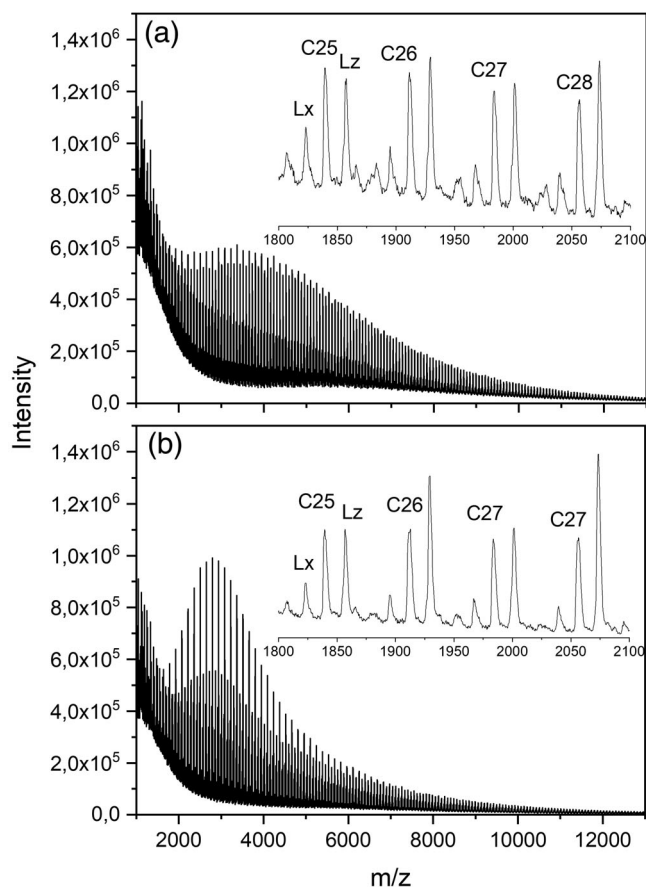


FIGURE 4 Matrix-assisted laser desorption/ionization time-of-flight (MALDI TOF) mass spectra of poly(L-lactide)s prepared with bismuth subsalicylate (BiSub) and 2,2'-dihydroxybiphenyl at 180°C (a) after 1 h (no. 6A, Table 4) and (b) after 2 h (no.6B, Table 4)

reaction mixture and thus followed by rapid chain growth. As already mentioned above, formation of cycles, above all, large cycles having masses above m/z 5000 are best explained by a REP mechanism (Scheme 1). Yet, when monofunctional phenols are used as catalyst or when a bisphenol is attaches to a Bi atom by only one Bi—O—C bond, the polymerization may proceed according to Scheme 2. However, it is hard to explain why peaks of linear chains having phenylester end groups (La in Scheme 2) are absent in almost all mass spectra.

Since the MALDI TOF mass spectra indicate equal or nearly equal quantities of even and odd species including formation of cycles (see Figures 2-4), the polymerization process certainly involves back-biting and other transesterification reactions.

3.5 | Thermostability

Variation of the time in the experiments of Table 4 suggested that longer reaction times than 1 h the catalyst

may cause degradation for instance by formation of smaller cycles, when a Lac/Cat ratio of 1/1 is used. At a Lac/Cat ratio of 2000/1 the optimum time may be shifted to 2 h. To shed more light on this aspect, a series of polymerizations was conducted with 2,2'-dihydroxybiphenyl at 170°C under variation of the time. The M_n and M_w data listed in Table 7 confirmed indeed that at a Lac/Cat ratio of 1000/1 the optimum time is around 1 and 2 h or longer times cause degradation of the molecular weights. Furthermore, the discoloration became more intensive with longer times. From SnOct₂-catalyzed ROPs of L-lactide it is known that the degradation occurring at longer times is mainly caused by the catalyst and not so much by non-catalyzed chain scission. Therefore, the technical production of polylactides based on SnOct₂ is performed in such a way that a catalyst poison is added at the end of the polymerization before removal of unreacted monomer and extrusion of the melt from the reactor. This scenario prompted the authors to perform a preliminary study of potential catalyst poisons for BiSub. The results summarized in Table 8 indicate that only one of the “additives” prevented the BiSub-catalyzed polymerization completely, namely triphenyl phosphine. This result is not trivial, because no poisoning effect was found, when SnOct₂-catalyzed polymerization was performed under quite similar reaction conditions. In contrast diphenylphosphinic acid proved to be a good poison for SnOct₂ but failed to poison BiSub (Table 8). Hence, these experiments prove that good catalyst poisons for Sn(II) and Bi(III) salts are not necessarily identical.

3.6 | Optical purity

In a previous study of the first author numerous salts of 14 metals were compared with regard to their propensity to racemize L-lactide at higher temperatures. In addition to tin only bismuth was found to avoid racemization under the given reaction conditions.³⁴ The low propensity of Bi(II) salts to racemize L-lactide was confirmed in a recent study dealing with ROPs of lactide catalyzed by the combination of BiSub and salicylic acid.²¹ Nonetheless, four samples of the present work were subject to a test of their optical purity. From samples No 2 to 4 (Table 4), which were prepared under optimum conditions, high resolution ¹³C NMR spectra were measured with a signal-to-noise ratio > 150/1. Sharp and perfectly symmetrical CO signals were found indicating an optical purity >99% (Figure S4). The sensitivity of the CO signal of polylactide to different stereo-sequences has been documented in the literature several times.^{35,36} Furthermore, these samples were annealed at 120°C for 24 h and subject to DSC measurements. Melting points (DSC minima) in the range of 176.8–177.2 were found after

annealing at 120°C for 1 day which indicate again an optical purity around or above 99% (Figure S5A). This interpretation is supported by a previous DSC measurement of an optically pure commercial poly(L-lactide), Purapol L105, which after annealing at 120°C/1 d showed a T_m of 177.5°C.²⁴ However, when the polymerization was performed at 180°C for 2 h (No. 2, Table 5) a lower T_m of 174.2 was found (Figure S5B) indicating that under these harsher conditions slight racemization has occurred (optical purity ~98%). In other words, a temperature around 170°C and a polymerization time < 1.5 h seem to be the optimum conditions with regard to molecular weight, racemization and discoloration.

3.7 | Molecular weights and distribution

It is known from publications of numerous research groups that SEC calibrated with polystyrene standards overestimate the molecular weights of most aliphatic polyesters because the hydrodynamic volume of polystyrene is smaller. In the case of polylactide a correction factor of 0.68 has been published for solutions in dichloromethane.³⁷ The M_w data listed in the Tables 1-8 were not corrected to allow for direct comparison with the data of commercial poly(L-lactide)s.²⁶ However, when the M_w 's listed in this work are multiplied with the aforementioned correction factor the highest values are still above 100,000 and justify the classification as high molecular weight polylactides.

Furthermore, it should be mentioned that the M_n values listed above are somewhat higher than the real values (even after correction), because they were calculated from 1000 onwards, and thus the oligomers <1000 were not included in this calculation. This fact has almost not influence on M_w , but it lowers the dispersities. For polycondensates free of cycles Flory has calculated a dispersity of 2.³⁸ When cycles are present, the typical range of dispersities is 3–5 as calculated and experimentally verified by Niehaus and Jackson for Nylons and poly(ethylene terephthalate).³⁹ More than 90% of the dispersities found in this work fall into the range of 2–3 indicating that they are somewhat too low, and this conclusion certainly concerns the few values below 2. Over the past 20 years numerous research groups have published polymerization methods yielding dispersities <1.3, and these results were hailed as an important success of the method. This view may be justified from a theoretical, academic point of view, but it is not justified when potential applications requiring processing from the melt come into play (e.g., injection molding, extrusion, bottle blowing, fiber spinning). For such applications a broad dispersity is advantageous, because broadly dispersed polymers possess a better balance of moderate melt viscosity and

good mechanical properties. From this point of view, the high dispersities obtained in this work are an advantage and not a shortcoming, in as much, as applications of polylactides requiring dispersities <1.3 are not in sight.

4 | CONCLUSIONS

The experimental results of this work allow for the following conclusions. First, by means of BiSub and a suitable cocatalyst, such as 2,2'-dihydroxybiphenyl, poly(L-lactide)s having M_w values in the range of 120,000–185,000 can be prepared. Such M_w 's can rival with those of commercial poly(L-lactide)s produced by means of SnOct₂. Second, BiSub is the best catalyst for the preparation of high molecular weight polylactides, when compared with other Bi(III) salts. Third, the lower catalytic acidity of BiSub and 2,2'-dihydroxybiphenyl relative to SnOct₂ has not only the negative consequence of a slower ROP, it has also the positive effect that the rate of thermal degradation is reduced. Fourth, addition of phenylphosphonic acid reduces the yellowish discoloration characteristic for Bi(III)-catalyzed polymerizations of lactide, and addition of triphenylphosphine prevents polymerization and thus, triphenylphosphine may be used as catalyst poison if necessary. In summary, it may be concluded that BiSub + cocatalyst may be an attractive alternative to produce optically pure poly(L-lactide)s, wherever the toxicity of SnOct₂ is a matter of concern.

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