

# Synthesis of Cyclic Poly(L-lactide) Catalyzed by Bismuth Salicylates—A Combination of Two Drugs

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**ABSTRACT:** L-lactide was polymerized in bulk at 160 or 180°C with mixtures of bismuth subsalicylate (BiSub) and salicylic (SA) as catalysts. The SA/Bi ratio and the monomer/Bi ratio were varied. The highest molecular weights (weight average,  $M_w$ ) were achieved at a SA/Bi ratio of 1/1 ( $M_w$  up to 92 000 g mol<sup>-1</sup>). L-Lactide was also polymerized with combinations of BiSub and silylated SA, and  $M_w$  values up to 120 000 g mol<sup>-1</sup> were achieved at 180°C. MALDI-TOF mass spectrometry and Mark-

Houwink-Sakurada measurements proved that under optimized reaction conditions the resulting polylactides consist of cycles. © 2019 The Authors. *Journal of Polymer Science Part A: Polymer Chemistry* published by Wiley Periodicals, Inc. *J. Polym. Sci., Part A: Polym. Chem.* 2019

**KEYWORDS:** bismuth; cyclization; Polylactide; salicylic acid; toxicity; ring-opening polymerization

**INTRODUCTION** Polylactides are biodegradable polyesters that have found numerous applications in medicine, agriculture, packaging, and so forth. Their technical production is based on ring-opening polymerization (ROP) initiated by an alkanol and catalyzed by tin(II)-2-ethylhexanoate (SnOct<sub>2</sub>) and thus this catalyst system has been studied by numerous research groups in much detail.<sup>1–21</sup> This catalyst system yields linear polylactides and has several advantages. It is highly efficient and at temperatures around or above 160°C polymerizations are complete within 1 h even when the catalyst concentration is low (Lac/Cat >1 000). The molecular weight may be roughly controlled via the lactide/alcohol ratio (more precisely at lower temperatures).<sup>16,17</sup> These ROPs are free of racemization and yield colorless polylactides. Furthermore, the toxicity of alcohol-SnOct<sub>2</sub> combination is relatively low and SnOct<sub>2</sub> is admitted by the American FDA as food additive. Nonetheless, tin (II) and tin(IV) ions or compounds are more or less cytotoxic, because they tend to bind to the SH groups of proteins. Therefore, less toxic alternatives were and are of great interest, but difficult to find. Frequently found comments, that metal-free organic catalysts are advantageous over organometallic catalysts are for several reasons misleading.<sup>22,23</sup> First, the toxicity of almost all of these organic catalysts is unknown, second amines and phosphines tend to racemize L-lactide, when applied at temperatures >100°C for polymerizations in bulk.

Potential candidates for nontoxic organometallic catalysts are bismuth compounds, (above all, bismuth subsalicylate) because bismuth(III) is the least toxic heavy metal ion,<sup>24,25</sup> and the tendency of bismuth salts to cause racemization of L-lactide at high temperatures is as low as that of tin salts.<sup>26</sup> Zinc salts or compounds that represent another nontoxic alternative to Sn salts are more basic and tend to racemize L-lactide when used for polymerizations in bulk at higher temperatures (>140°C).<sup>26</sup>

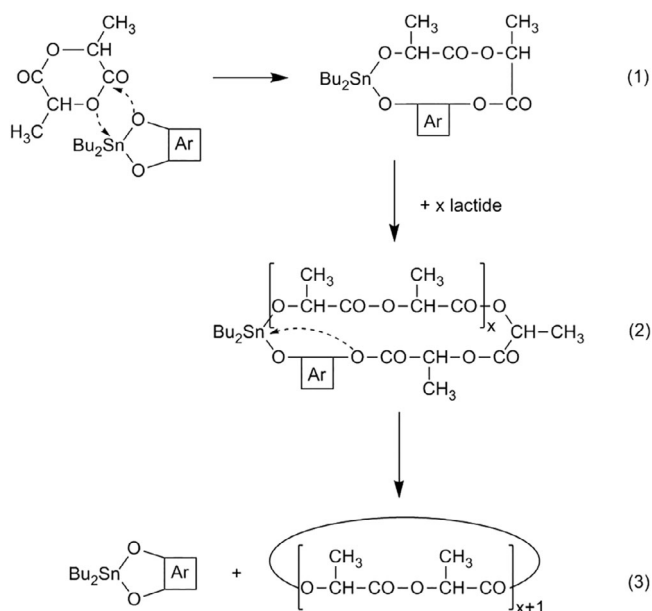
Over the past 15 years, syntheses and properties of cyclic polylactides have attracted increasing interest.<sup>27–33</sup> Cyclic poly(L-lactide) may possess several advantages over linear polylactides, such as lower melt viscosity due to a lower hydrodynamic volume, a slightly higher thermostability, and a higher hydrolytic stability, because one cleavage of the ring does not reduce the molecular weight, and because hygroscopic COOH end groups, which may catalyze hydrolysis, are absent.<sup>27</sup> However, a comprehensive study of the properties of high molar mass cyclic poly(L-lactide) and comparison with linear chains of similar molar mass is still lacking, because a convenient synthetic procedure suitable for upscaling and technical production was missing.

Quite recently, it has been found that certain cyclic dibutyltin compounds catalyze ring-expansion polymerization of L-lactide,<sup>34–37</sup> whereupon optically pure poly(L-lactide)s having

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**SCHEME 1** Simplified scheme of a REP catalyzed by a cyclic dibutyltin bisphenoxide.

Mw's up to 190 000 g mol<sup>-1</sup> were obtained (Scheme 1).<sup>34</sup> However, with regard to technical application, these new catalysts have the disadvantage that their toxicity is unknown. In this context, it was the purpose of this work to find out, if bismuth subsalicylate alone or in combination with salicylic acid might be a suitable catalyst, because the toxicity of both compounds is extremely low. Salicylic acid is the main component of the most widely used drug of the humankind, acetylsalicylic acid (SASS, Aspirin), and BiSub is known in the United States for more than 100 years as an OTC drug against stomach problems, for example under the trade mark "Pepto-bismol".<sup>38</sup> However, in addition to a low toxicity, a successful catalyst must meet the following requirements: The resulting poly(lactides) should have (a) weight average molecular weights (*M<sub>w</sub>*) > 50 000 or better >100 000 g mol<sup>-1</sup>, (b) high extent of

cyclization (>90%), (c) racemization free polymerization in bulk at temperatures up to 180°C, (d) no or little discoloration. Finally, it should be mentioned that 1,4-butanediol-initiated, BiSub-catalyzed homo- and copolymerizations of L-lactide, glycolide and ε-caprolactone have been published under conditions excluding formation of cyclics.<sup>39</sup>

## EXPERIMENTAL

### Materials

L-Lactide was kindly supplied by Thyssen-Uhde AG (Berlin). According to DSC measurements with a heating rate of 5 K min<sup>-1</sup>, it had a melting temperature (*T<sub>m</sub>* defined as maximum of the endotherm) around 98.4(+/-0.1)°C. After recrystallization from "Toluene 99.99%, extra dry" of ACROS Organics (Geel, Belgium), it had a *T<sub>m</sub>* of 98.6(+/-1)°C. With exception of the experiments 1X, 2X, 3X, and 5X in Table 1, all polymerizations were performed with recrystallized Uhde L-lactide. For the "X-experiments" recrystallized L-lactide of Carbion Purac was used. Its recrystallization was performed as described above. In a previous publication, it was demonstrated that once-recrystallized Uhde and PURAC lactides may yield poly(lactides) with high molecular weight (*M<sub>w</sub>* > 200,000).<sup>40</sup> Furthermore, the <sup>1</sup>H NMR signal of CH<sub>2</sub>-OH endgroups (4.35 ppm) typical for contamination with linear oligolactides was not detectable in the 400 MHz <sup>1</sup>H NMR spectra. Salicylic acid and bismuth subsalicylate (BiSub) were purchased from Sigma-Aldrich (Steinheim, Germany) and used as received. Salicylic acid was at first silylated with trimethylchlorosilane and trimethylamine according to the literature,<sup>41</sup> but refluxing with an excess of hexamethyldisilazane in toluene followed by distillation is a more convenient procedure. Xylene (mixture of isomers) was distilled over P<sub>4</sub>O<sub>10</sub> in vacuo and used for dilution of silylated salicylic acid (SiSA), so that a 0.5 M solution was obtained.

### Polymerizations

#### With the Addition of Salicylic Acid (SA)

SA (No. 2, Table 2) SA (0.05 mmol), BiSub (0.05 mmol), and L-lactide (50 mmol) were weighed into a flame-dried 50 mL

**TABLE 1** Polymerizations of L-Lactide Catalyzed by BiSub + SA at 160°C in Bulk (Conversions Around 97% According to <sup>1</sup>H NMR in All Experiments)

Experiment Number	Lac/Bi	SA/Bi	t (h)	<i>M<sub>n</sub></i>	<i>M<sub>w</sub></i>	Đ
1X	500/1	0/1	1.3	28 000	55 000	1.9
2X	500/1	1/1	1.0	35 000	80 000	2.2
3	1 000/1	0/1	2.5	24 500	52 000	2.1
3X	1 000/1	0/1	2.5	25 500	58 000	2.3
4	1 000/1	0.5/1	2.0	46 000	92 000	2.0
5	1 000/1	1/1	2.0	41 000	81 000	2.0
5X	1 000/1	1/1	2.0	35 500	77 000	2.2
6	1 000/1	2/1	2.0	30 500	60 000	2.0
7	1 000/1	4/1	2.0	21 000	41 500	2.0
7 <sup>a</sup>	2 000/1	0/1	4.0	27 000	59 000	2.2
8	2 000/1	1/1	4.0	25 000	65 000	2.6
9	2 000/1	2/1	4.0	26 000	66 000	2.6

<sup>a</sup> Lactide of Uhde was used (instead of TCI for others).

**TABLE 2** Polymerizations of L-Lactide Catalyzed by BiSub + SA at 180°C in Bulk (Conversions Around 97% According to <sup>1</sup>H NMR in All Experiments)

Experiment Number	Lac/Bi	SA/Bi	t (h)	M <sub>n</sub>	M <sub>w</sub>	Đ
1	1 000/1	0/1	1.0	26 000	58 500	2.2
2 <sup>a</sup>	1 000/1	1/1	1.5	24 500	58 000	2.3
	1 000/1	1/1	1.5	22 500	57 500	2.5
3	1 000/1	2/1	2.0	23 000	62 000	2.6
4	2 000/1	0/1	3.5	32 500	67 000	2.1
5	2 000/1	1/1	3.0	43 000	89 000	2.1
6 <sup>b</sup>	2 000/1	2/1	3.0	40 000	85 000	2.1
	2 000/1	2/1	3.5	38 500	81 000	2.1

<sup>a</sup> Repetition with the same batch of L-lactide and catalyst.

<sup>b</sup> With another batch of L-lactide.

Erlenmeyer flask under a blanket of argon. The reaction vessel was placed into an oil bath preheated to 160°C. The viscous reaction product was removed from the reaction vessel with a spatula and/or pincer and characterized without purification.

For the polymerizations performed with a Lac/BiSub ratio of 2000/1, a quantity of 100 mmol of L-lactide was used. The experiments of Table 1 were conducted analogously with an oil bath preheated to 182°C, which was cooled to 180°C after 10 min.

#### With the Addition of Silylated Salicylic Acid (SiSA)

(No. 2, Table 3) Lactide (50 mmol) and BiSub (0.05 mmol) were weighed into a flame-dried 50 mL Erlenmeyer flask under a blanket of argon and 0.1 mL of a 0.5 M solution of SiSA (no. 2, Table 3) in xylene were injected. The reaction vessel was placed into an oil bath preheated to 160°C. The viscous reaction product was removed from the reaction vessel with a spatula and/or pincer.

#### Measurements

The 400 MHz <sup>1</sup>H NMR spectra were recorded with a Bruker Avance 400 in 5-mm sample tubes. The DSC measurements were performed on a Mettler-Toledo DSC-1 equipped with Star-Software

11.00 at a heating rate of 5 K min<sup>-1</sup> for monomeric species and 10 K min<sup>-1</sup> for polymers. MALDI TOF mass spectrometry was performed using an Autoflex III (Bruker Daltonik GmbH, Bremen) equipped with a Nd-YAG laser (355 nm). Trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene] malononitrile (DCTB) dissolved in tetrahydrofuran (10 mg mL<sup>-1</sup>) was doped with potassium trifluoroacetate and used as matrix.

Matrix solution was premixed with the analyte solution (chloroform, 4 mg mL<sup>-1</sup>) in a ratio of 5/1(v/v). One microliter of the resulting solution was deposited on the sample target. At least 2000 single spectra recorded at different positions (linear positive mode) within the spots were accumulated. The instrument was previously calibrated with PEO standards.

For the GPC experiments, a modular system kept at 40°C (isocratic pump, 1 mL min<sup>-1</sup>, refractive index detector, RI-501-Shodex) was applied. Samples were manually injected (100 µL, 2–4 mg mL<sup>-1</sup>). For instrument control and molecular weight 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

**TABLE 3** Polymerizations of L-Lactide Catalyzed by BiSub + Silylated SA at 160 and 180°C in Bulk (Conversions Around 97% According to <sup>1</sup>H NMR in All Experiments)

Experiment Number	Lac/Bi	SA/Bi	T (°C)	t (h)	M <sub>n</sub>	M <sub>w</sub>	Đ
1	1 000/1	0.5/1	160	2.5	17 000	65 500	3.8
2	1 000/1	1/1	160	2.5	19 000	60 000	3.3
2X <sup>a</sup>	1 000/1	1/1	160	2.5	22 500	64 000	2.8
3	1 000/1	2/1	160	2.5	17 000	57 000	3.5
3X <sup>a</sup>	1 000/1	2/1	160	2.5	19 500	60 000	3.1
4	2 000/1	1/1	160	5.0	32 500	82 000	2.5
5	2 000/1	2/1	160	5.0	33 500	97 500	2.9
6 <sup>b</sup>	2 000/1	1/1	180	3.0	42 000	102 000	2.4
	2 000/1	1/1	180	3.5	44 000	101 000	2.3
7	2 000/1	2/1	180	3.0	57 000	122 000	2.2

<sup>a</sup> Lactide of TCI Chemicals was used.

<sup>b</sup> Repetition with another batch of L-lactide.

multiangle laser light scattering (MALS) detector (Dawn EOS, Wyatt, Germany) were used. Astra 6.1 software (Wyatt) served for calculating the MHS curves.

UV Spectra were recorded in chloroform at a scan rate of  $1 \text{ nm s}^{-1}$  in a range 250–380 nm using a UV/Vis spectrophotometer (Cary 5000, Varian).

## RESULTS AND DISCUSSION

### Polymerizations with Addition of SA

A temperature of  $180^\circ\text{C}$  is the highest temperature, which has been used for the technical production of poly(L-lactide)s because higher temperatures induce rapid degradation, racemization, and discoloration. However, a temperature above the melting temperature ( $176\text{--}178^\circ\text{C}$ ) prevents crystallization and enables extrusion of the melt from the reactor. A temperature of  $160^\circ\text{C}$  has the advantage that it still prevents crystallization for several hours, and the risk of racemization and side reactions is significantly reduced compared to  $180^\circ\text{C}$ . Hence, this temperature was selected as standard polymerization temperature in all our recent studies of ring-opening or ring-expansion polymerizations of L-lactide, and therefore, the first series of polymerization conducted in the present work was also performed at  $160^\circ\text{C}$ .

The results of these polymerizations were summarized in Table 1 and revealed the following trends. First, all polymerizations were at least by a factor of two slower than analogous polymerizations performed with Sn(II) octanoate in combination with alcohols or salicylic acid.<sup>42</sup> Second, addition of salicylic acid to BiSub slightly accelerates the rate of polymerization. Third, a salicylic acid/Bi ratio of 2/1 gives similar results as the 1/1 ratio with a tendency toward slightly lower molecular weights. However, a still higher ratio such as 4/1 (No. 5, Table 1) is clearly unfavorable for the resulting molar mass. Fourth,  $M_w$  values above 90 000 were not obtained, and a Lac/Cat ratio of 2000/1 did not yield higher molecular weights than the Lac/Cat ratio of 1 000/1 in agreement with a ring-expansion polymerization.

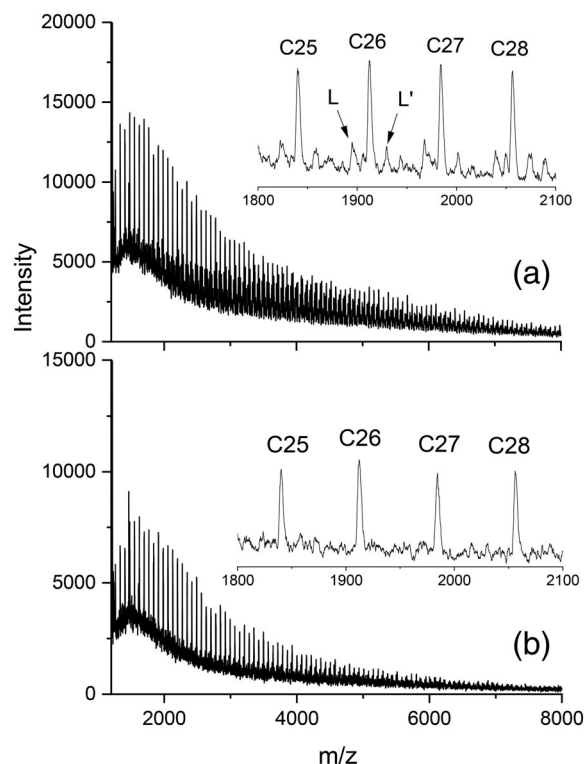
Since the molecular weights achieved at  $160^\circ\text{C}$  were all below 90 000 and since relatively long reaction times were needed to achieve the maximum conversion (97% for thermodynamic reasons), a second series of polymerizations was performed at  $180^\circ\text{C}$  (Table 2). At this temperature, a slight shortening of the reaction time was feasible, but a significant reduction was only achieved in the experiment with neat BiSub as a catalyst at a Lac/Cat ratio of 2 000/1 (see No. 5, Table 1 and No. 4, Table 2). In contrast to the experiments of Table 1, the  $M_w$  values obtained with a Lac/Cat ratio of 2 000/1 were higher than those obtained at a ratio of 1 000/1, but even the best values did not exceed 90 000. From this point of view, the polymerizations conducted at  $180^\circ\text{C}$  were not advantageous over those performed at  $160^\circ\text{C}$ . Repetition of experiments Nos. 5 and 6, Table 2, with L-lactide from another source (Thyssen Uhde) confirmed these results.

The MALDI TOF mass spectra gave the following results. None of the samples prepared at  $160^\circ\text{C}$  gave a satisfactory mass

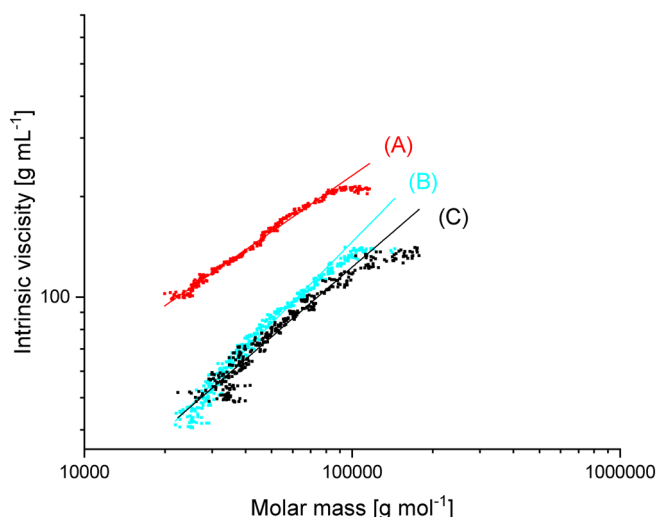
spectrum, meaning a spectrum exclusively displaying peaks of cycles. In this regard, better results were obtained at  $180^\circ\text{C}$ . Another trend was the observation that those samples prepared with a Lac/Bi ratio of 1 000/1 displayed tiny peaks of linear chains in their spectra as demonstrated by Figure 1A, whereas these peaks were absent in the mass spectra of the samples prepared with a Lac/Bi ratio of 2000/1 (Fig. 1B). However, the mass spectra limited to masses up to  $m/z$  8 000, it did not say much about the extent of cyclization in the high molar mass fraction ( $>30\ 000$  Da).

Therefore, Mark-Houwink-Sakurada (MHS) measurements were performed, which correlate intrinsic viscosity and molar mass of numerous fractions obtained by SEC. This correlation is sensitive to the hydrodynamic volume, and it is theoretically and experimentally established for numerous polymers, including polylactides<sup>28–31</sup> that the hydrodynamic volume of cyclic polymers is significantly lower than that of linear polymers according to a ratio of 2/3 (0.66). Figure 2 presents a comparison of samples No. 5 and 6(b), Table 2 with a commercial linear poly(L-lactide), "Purapol L105," which proves that the polylactides prepared with the combination of SA and BiSub at a Lac/Bi ratio of 2 000/1 possess indeed an intrinsic viscosity, which amounts to 2/3 of that of Purapol Interestingly, the SA/Bi ratios of 1/1 and 2/1 gave nearly identical results.

Therefore, it may be concluded that cyclic poly(L-lactide)s having a degree of cyclization certainly above 90%, and most likely even above 95%, can be reproducibly prepared at  $180^\circ\text{C}$ .



**FIGURE 1** MALDI-TOF mass spectra of poly(L-lactide)s cocatalyzed with SA at  $180^\circ\text{C}$ : (A) No. 2, Table 2; (B), No. 5, Table 2.

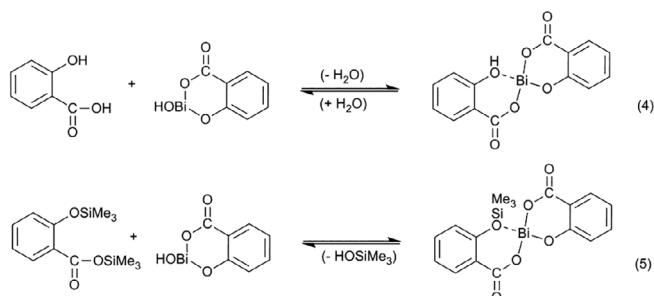


**FIGURE 2** MHS measurements of poly(L-lactide)s: (A) Purapol L105; (B) No. 5, Table 2; (C) No. 6(c), Table 2. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

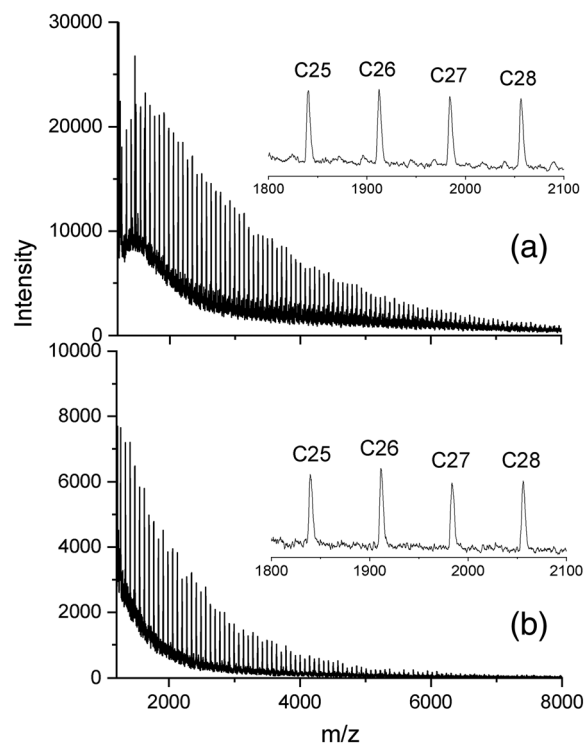
### Polymerizations with Addition of Silylated Salicylic Acid (SiSA)

A third series of polymerizations was performed at 160°C with addition of silylated salicylic acid (SiSA) instead of neat salicylic acid. SiSA was used for three reasons. Firstly, the number of acidic protons that may catalyze side reaction should be reduced. Secondly, it should be found out, if SiSA has an influence on the course of the polymerization, for example, by reaction with BiSub according to eq. (5) in Scheme 2. Thirdly, SiSA is a liquid, which can easily be mixed with various inert solvents, and these solutions allow for a more precise dosage of salicylic acid in small-scale experiments. The reaction conditions of the experiments listed in Table 3 parallel those compiled in Table 1, so that direct comparison and evaluation of the results is feasible.

In principle, the same trends were found as observed for polymerization cocatalyzed by free SA. Firstly, cleaner MALDI TOF mass spectra were obtained at 180°C (Nos. 6, 7, Table 3) than at 160°C as demonstrated by Figure 3. Secondly, all mass spectra of samples prepared with Lac/Bi ratios of 1 000/1 (Nos. 1–3) displayed tiny peaks of linear chains that were absent in spectra of samples prepared with a Lac/Bi ratio of



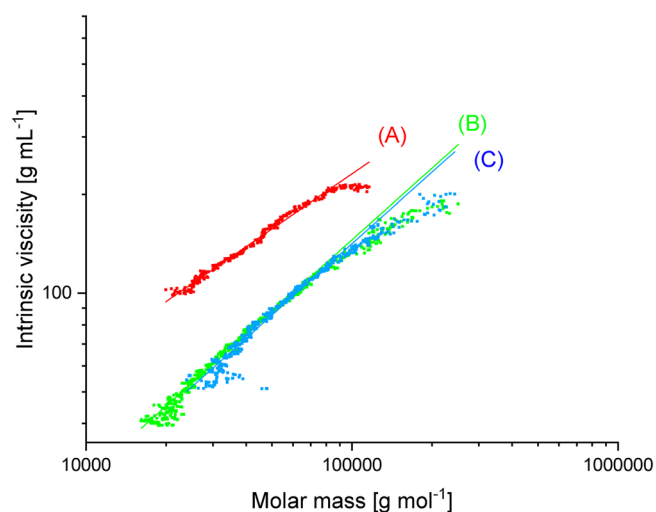
**SCHEME 2** Hypothetical reaction of SA or SiSA with BiSub.



**FIGURE 3** MALDI-TOF mass spectra of poly(L-lactide)s cocatalyzed by SiSA: (A) No. 5, Table 3; No. 6(b) Table 3.

2 000/1, but it must be admitted that the signal-to-noise ratio of these mass spectra is not satisfactory. For the samples with the best mass spectra, Nos. 5 and 6 (Table 3), MHS measurements were performed, which proved that their hydrodynamic volume amounted to 2/3 of the commercial linear polylactide (Fig. 4).

When the polymerizations Nos. 6 and 7 were repeated with another batch of L-lactide, both mass spectra and MHS



**FIGURE 4** MHS measurements of poly(L-lactide)s: (A) Purapol L105; (B) No. 7, Table 3; (C) No. 6(c), Table 3. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

measurements proved to be reproducible. In other words, the experiments with SiSA confirmed the results obtained with free SA, but somewhat higher molecular weights were achieved. Concerning the  $M_w$  values, it should be added that commercial linear poly(L-lactide)s designed as engineering plastics for injection molding, such as Purapol L105 or Nature Works 3001D or 3251D possess  $M_w$  values around 110 000–150 000.<sup>43</sup> Since cyclic poly(lactides) possess a lower hydrodynamic volume,  $M_w$ 's around 100 000–120 000  $\text{g mol}^{-1}$  correspond to  $M_w$ 's of linear poly(L-lactide)s in the range of 140 000–160 000  $\text{g mol}^{-1}$ . Hence, the highest molecular weights achieved in this work can rival with those of commercial linear products.

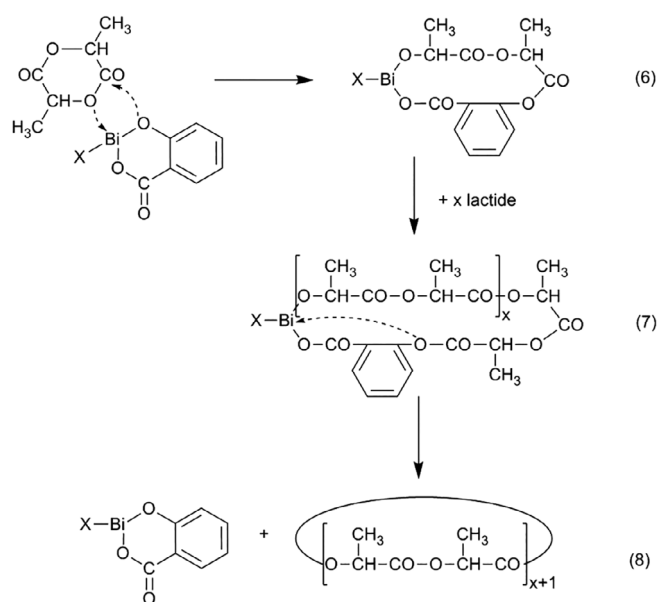
Finally, it should be mentioned that the optical purity of the sample No. 5, Table 2 and Nos. 5, 6, and 7, Table 3, was checked in two ways. First these samples were precipitated into ligroin and annealed at 160°C for 1 day. Afterward melting temperatures in the range of 176–177.5°C (DSC maxima at 10  $\text{K min}^{-1}$ , Supporting Information) were found for samples No 5, Tables 2 and 6, 7, Table 3, as expected for poly(L-lactide)s with optical purity around 99.5%.<sup>44–47</sup> This interpretation was confirmed by optical rotation measurements that yielded  $\alpha$ -values in the range of 154.5–156°. In other words, no significant racemization occurred when the time at 180°C was limited to 3.5 h. These results agree with aforementioned previous studies of metal salt-catalyzed racemization of L-lactide.<sup>26</sup> However, when the reaction time was extended to 5 h at 160°C (No. 5, Table 3) the  $T_m$  dropped to 175.2°C (Supporting Information) and the optical rotation dropped to 152+/-0.5°. These values are compatible with an optical purity around 98%, but possibly indicate beginning racemization.

### Mechanistic Aspects

Although the present work is focused on the preparative aspects of the new catalyst system and not meant as a mechanistic study, a couple of fundamental findings concerning the polymerization mechanism should be shortly discussed. The formation of high-molecular-weight cyclic poly(L-lactide)s suggests the existence of a REP, as pointed out in Scheme 3, which is combined with intracircular backbiting like all REPs based on tin catalysts (Scheme 4).

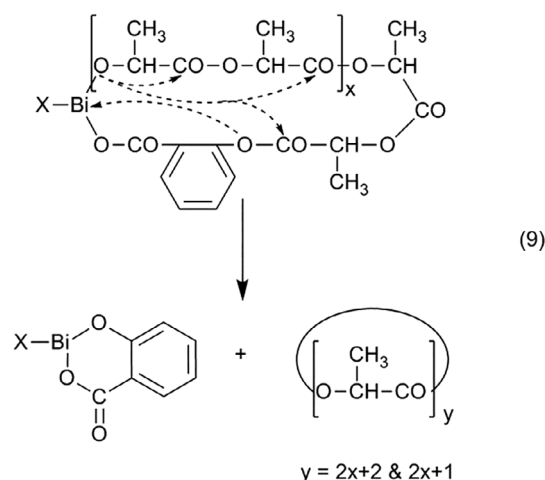
An alternative mechanism might be a combination of simultaneous ROP and polycondensation (ROPPOC) partially outlined in Scheme 5. The first stage of this mechanism is ROP-yielding linear chains and the combination of backbiting and end-to-end cyclization (see Scheme 5) finally yields cyclics as the stable end products. The success of this mechanism requires a reactive electrophilic end group and a salicylate end group including an internal H-bond might play this role.

However, all studies with various ROPPOC catalysts have shown, that the best results (high molecular weights and high degree of cyclization) were obtained at low Lac/Cat ratios such as 100/1. The results obtained in this work present exactly the opposite trend. Since BiSub alone can catalyze polymerizations of L-lactide, the interesting question concerns

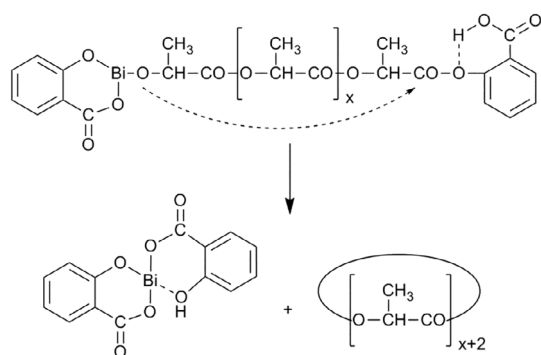


**SCHEME 3** Simplified scheme of a REP catalyzed by a bismuth salicylate.

role and advantages of added salicylic acid or its trimethylsilyl derivative. The formula of BiSub presented in Scheme 2 can be found in publications, chemical catalogs, and internet, but the insolubility of BiSub in all inert solvents indicates that either strong donor-acceptor interactions between O and Bi atoms exist yielding a 3D network or clusters based on  $\mu$ -oxo bridges are formed. Therefore, the role of additional SA or SiSA might mainly consist in breaking up of these O-Bi bonds (or interactions), so that molecularly dispersed, catalytically active Bi-salicylate molecules are formed. However, a systematic comparison of polymerizations with and without addition of SA (e.g., No. 1–3, Table 2) revealed that complete dissolution of BiSub in the molten lactide requires Lac/Cat



**SCHEME 4** Scheme of intracircular “back-biting” transesterification yielding odd- and even-numbered rings.



**SCHEME 5** Formation of cyclics by end-to-end cyclization in a ROPPOC process.

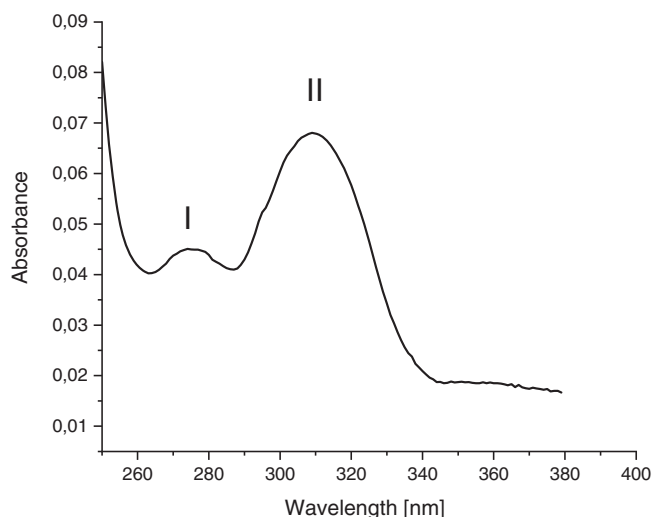
ratios around or above 1 000/1 regardless whether SA is added or not. This observation agrees with model experiments that had the purpose to study the reaction of BiSub with equimolar or double molar amounts of SA. Such experiments were performed in boiling dioxane or chlorobenzene, in DMF at 150°C and in *o*-dichlorobenzene at 170°C. Yet regardless of solvent, temperature, and time and regardless if free or silylated SA was added, no reaction was detectable and thus, no evidence for the reactions formulated in Scheme 2 was obtained.

Nonetheless, the addition of SA has a positive influence on the entire polymerization process, which can be subdivided into four aspects. First, SA slightly reduces the extent of discoloration (see below). Second, it slightly enhances the resulting molecular weights. Third, it slightly enhances the extent of cyclization. Fourth, it accelerates the polymerization by approximately a factor of 1.5. This effect does not exist for silylated SA. Hence, one might speculate that other weak acids might have a similar or even better effect. Yet, a detailed study in this direction was outside the scope of this work and it does not make sense to replace SA by a more toxic additive. All these effects are weak, but their sum is decisive for a successful synthesis of cyclic poly(*L*-lactide)s having *M<sub>w</sub>*'s around 100 000.

### Discoloration

Poly(*L*-lactide) is known to undergo a brownish discoloration regardless if a catalyst is present or not, when it is heated to temperatures around or above 180°C. Since the technical production includes extrusion of the molten polylactide from the reactor at temperatures up to 210°C and since such temperatures are also needed for processing from the melt, stabilizers and antioxidants are added at the end of the polymerization process to suppress or reduce discoloration and thermal degradation. In small-scale experiments, a homogeneous admixture of additives is difficult to achieve within a short time, and therefore the properties of the virgin reaction products obtained in this work should be reported.

BiSub has the tendency to impart a yellowish discoloration the intensity of which increases with time and temperature quite analogous to the brownish discoloration typical for polylactides



**FIGURE 5** UV spectrum of sample No. 8 (Table 1) recorded in chloroform.

with tin catalysts. Experiments with reaction times above 1.5 h or with temperatures around 180°C all yielded a yellowish discoloration. Furthermore, it was found that addition of salicylic acid slightly reduces rate and extent of discoloration. Moreover, it was found that the origin, and thus, the purity of the monomer also play a minor role. The weakest discoloration was found in experiments 1X, 2X, 3X, and 5X of Table 1, for polylactides prepared from PURAC *L*-lactide, whereas all other polymerizations were performed with recrystallized Uhde *L*-lactide. For example, colorless polylactides were obtained in the experiments 1X and 2X of Table 1, and a nearly colorless sample in experiment 3X, whereas a deep yellow color was obtained after long reaction times at in experiments Nos. 7–9, Tables 1, 7–10, Tables 2 and 4–7, Table 3. A yellowish color may be acceptable for medical, pharmaceutical, and agricultural applications, because the extremely low toxicity of the catalyst is the more important aspect, and because the polylactides used for many of such applications are. Furthermore, it was found that the absorption in the violet region of the visible light spectrum is combined with an intensive absorption in the near UV range. Several samples gave almost identical UV spectra, which are exemplarily illustrated by Figure 5. The weak maximum around 275 nm, labeled I, is due to salicylic acid units, but there is also a broad, far more intensive absorption between 280 and 350 nm (II). This absorption most likely results from dihydroxybenzophenones, which are condensation products of salicylic acid, because the commercial 3,4-dihydroxybenzophenone shows quite similar spectroscopic properties. Regardless, if this interpretation is correct, this UV absorption helps to protect vitamins, hormones, flavors, and drugs against damage by UV light when such polylactides are used for drug delivery, food packaging or films for plant protection in agriculture.

### CONCLUSIONS

The results elaborated in this work demonstrate that the combination of two widely used drugs, salicylic acid, and bismuth

subsalicylate, is an effective catalyst for the polymerization of L-lactide and yields optically pure cyclic poly(L-lactides) even at high temperatures with weight average molecular weights in the range of 50 000–120 000 g mol<sup>-1</sup>. Higher molecular weights may be achieved with cyclic tin catalysts (study in progress), but tin salts and compounds are considerably more toxic than bismuth salts. The main advantage of the Bi-SA system is its extremely low toxicity, which cannot be under matched by other metal catalysts, because even zinc ions are somewhat more toxic than bismuth against kidney tubuli<sup>48</sup> and because magnesium salts cause partial racemization at temperatures above 100°C<sup>15</sup> and organo-magnesium compounds such as Bu<sub>2</sub>Mg and Mg alkoxides cause racemization even at 20°C.<sup>49</sup> Furthermore, nontoxic, metal-free organo-catalysts yielding high molar mass cyclic polylactides have not been reported so far.

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