DOI: 10.1002/cssc.201501695

Lactide Synthesis and Chirality Control for Polylactic acid Production

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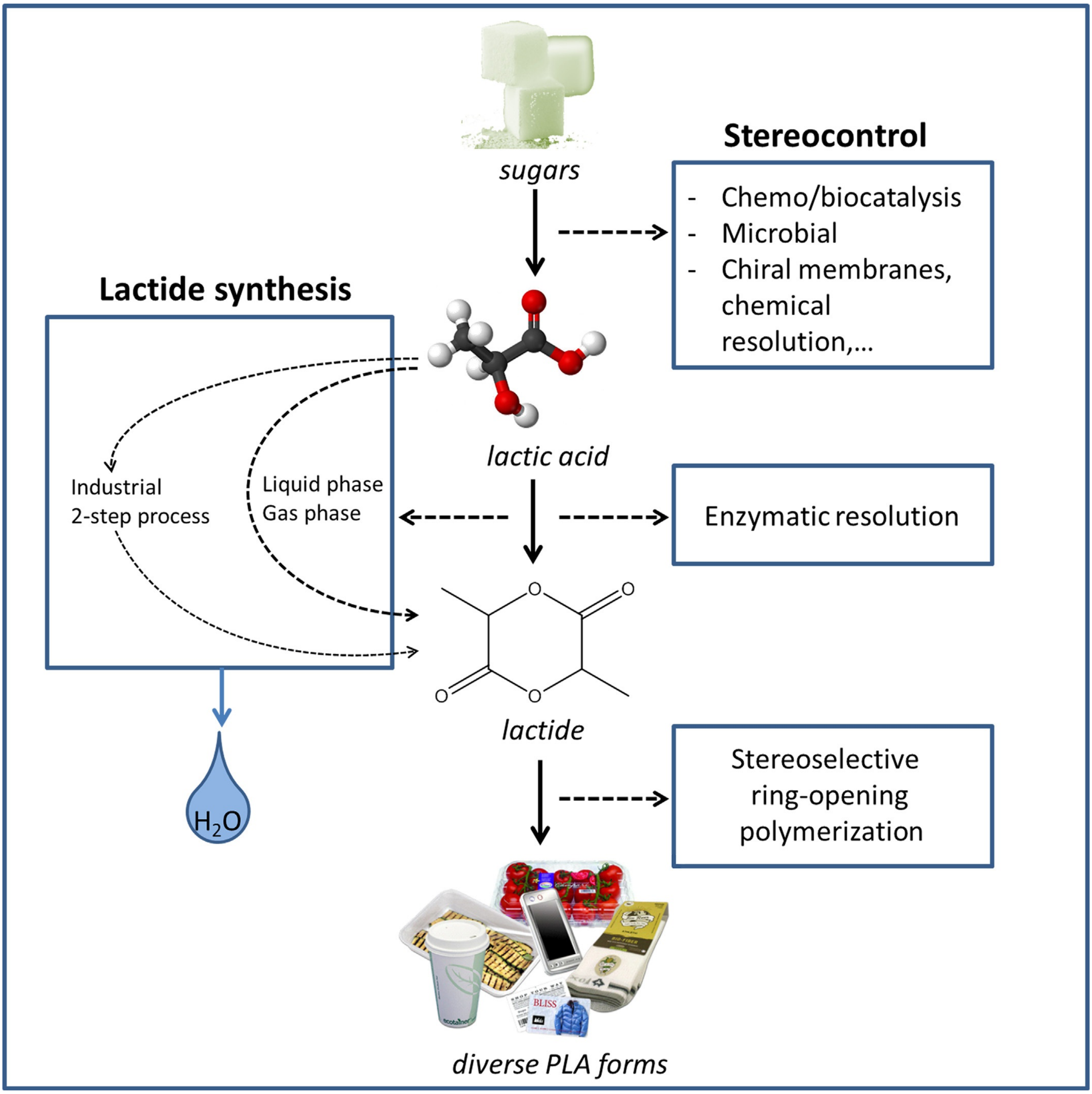

Polylactic acid (PLA) is a very promising biodegradable, renewable, and biocompatible polymer. Aside from its production, its application field is also increasing, with use not only in commodity applications but also as durables and in biomedicine. In the current PLA production scheme, the most expensive part is not the polymerization itself but obtaining the building blocks lactic acid (LA) and lactide, the actual cyclic monomer for polymerization. Although the synthesis of LA and the polymerization have been studied systematically, reports of lactide synthesis are scarce. Most lactide synthesis methods are described in patent literature, and current energy-intensive, aselective industrial processes are based on archaic scientific literature. This Review, therefore, highlights new methods with a technical comparison and description of the different approaches. Water-removal methodologies are compared, as this is a crucial factor in PLA production. Apart from the synthesis of lactide, this Review also emphasizes the use of chemically produced racemic lactic acid (esters) as a starting point in the PLA production scheme. Stereochemically tailored PLA can be produced according to such a strategy, giving access to various polymer properties.

1. Introduction

Limitations in the use of fossil resources and plastic pollution in our oceans are major driving forces in the search for biodegradable and renewable materials. The growing production trend of both lactic acid (LA) and polylactic acid (PLA) clearly demonstrates the potential of PLA as a useful plastic in a variety of applications (Figure 1).[1] The global PLA market was estimated to be around 360 800 tons in 2013 (more or less the starting point of the graph) while a growth of 18.8 % is expected, reaching over 1.2 million tons in 2020.

Today, most PLA is produced for single-use applications in packaging. Still, perspectives from academia and industry show that PLA can also be successfully used in more durable applications. Aside from the potential for replacing traditional fossil-based polymers by renewable and/or biodegradable polymers, PLA has interesting characteristics that render it suitable for specialty applications. Due to its biocompatibility, PLA-based materials are well suited in biomedical in vivo applications such as bone fixations, tissue engineering, and drug delivery systems.[2] Inkjet printing of PLA for the production of functional materials (example: coating of drugs) is another area gaining increasing attention.[3] LA, a high-potential biomass-derived platform molecule,[4] is the building block of PLA.

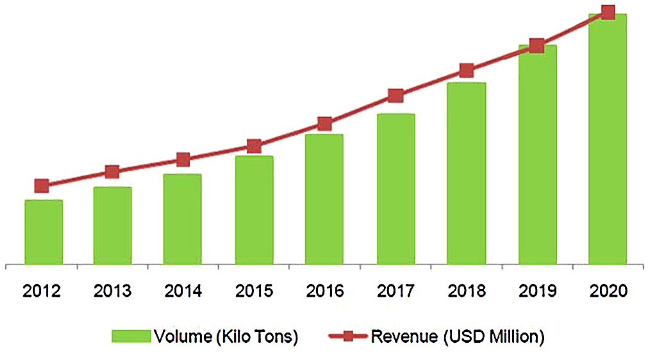

Figure 1. Global PLA market prospects (2012–2020), adapted from [1].

The intuitive route for producing PLA is through the polycondensation of LA owing to the presence of both the α-hydroxyl and carboxyl function in LA. This polymerization is mostly carried out in the absence of a solvent while applying high temperatures and vacuum for the removal of water from the aqueous feedstock and the condensation reaction.[5] Equilibrium issues are the limiting factor in this type of polymer synthesis as water removal in the later phase is challenging due to the increasing viscosity of the polymer melt.[6] In addition, side reactions occur such as intramolecular transesterifications within a polymer chain. Another drawback is racemization, that is, the transformation of L-LA in D-LA during the process [when poly-L-lactic acid (PLLA) is targeted from pure L-LA] causing stereoirregularities in the polymer that result in inferior or undesired properties.[7] Chen et al. were able to synthesize PLA with a molecular weight up to 130 000 $g\,mol^{-1}$ through polycondensation by continuously decreasing the pressure in a controlled manner.[8] The use of a Brønsted acid co-catalyst in melt polycondensation is also beneficial for increasing the molecular weight of the polymer.[9] Another strategy for making PLA via polycondensation comprises the use of a solvent and a soluble (mostly Lewis acid) catalyst such as $SnCl_2$, Sn(octanoate)$_2$ but also scandium(III) trifluoromethanesulfonate and scandium(III) trifluoromethanesulfonimide [Sc(OTf)$_3$ and Sc(NTf)$_3$, respectively] In such setups, water removal can occur at milder conditions, resulting in less racemization; however, this has proven to be solvent and catalyst dependent. The removal of water during such reactions occurs through azeotropic distillation whereas a molecular sieve can also be applied to remove small fractions of dissolved water in the organic phase. The maximum molecular weight of PLA synthesized as such is still low: around 30 000 $g\,mol^{-1}$, a typical value in LA polycondensation reactions.[9b, 10] These examples demonstrate multiple difficulties associated with the polycondensation strategy. Moreover, polycondensation does not give access to high-quality PLA with a controlled molecular weight, high optical purity, and low polydispersity. Therefore, industrially manufactured PLA is produced via a cyclic intermediate, that is, lactide. This cyclic dimer of LA can be converted via ring-opening polymerization (ROP) into PLA in a very controlled manner, result-

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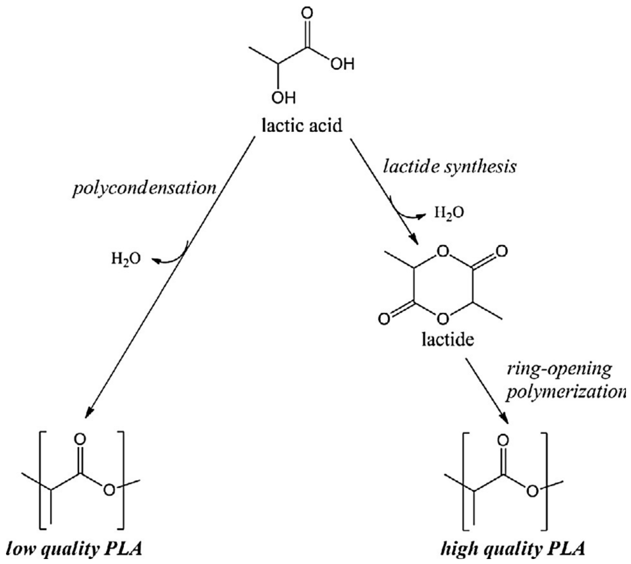
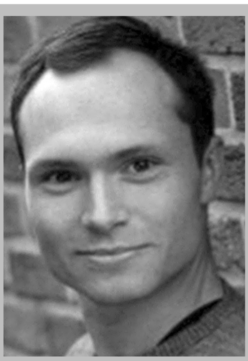
ing in monodisperse PLA with a higher molecular weight (Scheme 1).[11]

The production scheme for industrial PLA synthesis can be summarized as a three-step process: the synthesis of LA from sugars, the transformation of LA into its cyclic dimer, and ROP of lactide. When analyzing the contribution of each of these steps to the overall PLA synthesis cost, roughly 50 % can be attributed to the synthesis of LA, including the feedstock cost. The synthesis of lactide from LA contributes 30 % of the PLA cost whereas only 20 % of the total cost is due to the polymerization step.[12] LA synthesis is intensively studied nowadays in academic literature as the economics and the large waste amount of the current industrial fermentative production is still the main bottleneck. Recent reviews summarize the efforts and advances in catalytic[4,13] and fermentative LA production.[14] ROP of lactide is also broadly reported in literature. On the other hand, literature reports on lactide synthesis are scarce and mostly encountered in patents. Therefore, this Review will provide a complete discussion of different methods of lactide synthesis as well as a concise overview on LA production and ROP of lactide.



Scheme 1. Overview of PLA synthesis starting from LA.



Pieter Van Wouwe obtained his Master's degree in Catalytic Technology (Bioscience Engineering) at the Catholic University of Leuven in 2011. He did his master thesis under the supervision of Prof. Sels at the Center for Surface Chemistry and Catalysis and started his Ph.D. in the same group. Currently, he is in the process of finishing his Ph.D thesis. During his doctoral research he focused on enantioselective reactions with α-hydroxy compounds and, in collaboration with Total, he explored alternative routes for the synthesis of PLA.

Evelien Vanleeuw obtained her master's degree in Catalytic Technology (Bioscience Engineering) at KU Leuven (Belgium) in 2014. She did her master thesis at the Center for Surface Chemistry and Catalysis, where she examined the synthesis of lactide through shape-selective biomass conversion. She recently started a Ph.D. also under the guidance of Prof. Sels. Her research focuses on the synthesis of lactic acid by biocatalysis and sustainable bio-/chemocatalytic routes to building blocks for functional bio-based polymers.

Michiel Dusselier has a MSc in engineering and catalysis (KU Leuven, 2009) and studied in part at the Technische Universität München. He obtained his Ph.D. in 2013 under the guidance of Profs. Sels and Pierre Jacobs on the topic of tailoring catalytic routes toward lactic acid and bio-based plastics. He was awarded the ACS Dr. J. Breen memorial award in 2013. In 2014–15, he performed postdoctoral work with Prof. Mark Davis at Caltech, studying the synthesis of small-pore zeolites for methanol conversion and deNOx catalysis. He is an honorary fellow of the Belgian American Educational Foundation and has personal FWO funding. His current interests reside in zeolite synthesis.

Bert F. Sels, currently full professor at the KU Leuven, obtained his Ph.D. in 2000 in the field of heterogeneous oxidation catalysis. He was awarded the DSM Chemistry Award in 2000, the Incentive Award by the Societè Chimique Belge in 2005, and the Green Chemistry Award in 2015. He was recently elected co-chair of the IZA Catalysis Commission and is international board member of ChemSusChem. He heads a research group in the Centre for Surface Chemistry and Catalysis, designing heterogeneous catalysts for future challenges in industrial organic and environmental catalysis. His expertise includes heterogeneous catalysis in biorefineries and the spectroscopic and kinetic study of active sites for small-molecule activation.

2. Lactic-Acid Synthesis

2.1. Current fermentative production

The majority of LA is produced through microbial fermentation of all types of sugar sources, ranging from pure monosaccharides to more complex polysaccharides found in molasses, whey, and beet extracts, and even cellulosic materials.[15] Glucose and sucrose are most frequently used. Mainly homofermentative bacteria such as *Lactobacillus delbrueckii* or *amylophilus* are used, as they make two LA molecules from one hexose and thus provide the highest atomic efficiency.[16] As the price of the starting source is also a determining factor in LA production, there is a recent focus on cellulosic raw materials. Typical problems here are necessary expensive pretreatments as these substrates are generally not suited for direct fermentation. Although the use of several types of micro-organisms could offer a solution for some substrates, a topical subject of interest is the development of genetically adapted micro-organisms, which can convert such raw substrates directly into LA.[14,17] The fermentative production of LA is mainly a batch process although (semi-)continuous systems are also reported.[18] The current industrial fermentative process has several drawbacks, the major bottleneck being the co-generation of a stoichiometric amount of gypsum ($CaSO_4$) waste, that is, 1 ton per ton of LA. $CaSO_4$ originates from a neutralization process: as the LA bacteria are pH sensitive, the broth needs continuously buffering with bases such as $Ca(OH)_2$. Calcium lactate is then formed, and to obtain the free acid, H_2SO_4 is added, resulting in gypsum production. For further purification of LA from the fermentation broth, an esterification is necessary to perform final purification by distillation, after which the ester is hydrolyzed back to the acid. In addition, volumetric productivity of this fermentation is generally low. As a solution for the waste generation, a strategy was developed in which the lactate salts were split using electrodialysis systems.[18a, 19] Still, from an economic point of view, this might be less interesting as it further complicates the process. Another approach consists of using adapted pH-tolerant micro-organisms.[20] Still, such a fermentative approach proved to be difficult. As PLA production is further growing, the demand for LA will further increase and, with current bottlenecks in fermentative production, other synthesis routes could become necessary.

A remark that should be made concerns the chirality: generally, microbial fermentation results in the production of L-LA as it is the naturally more abundant isomer. Because the properties of PLA can be tuned by playing with the L and D fraction and stereoregularity in the polymer, a lack of sufficient D-LA could limit the variability of accessible PLA varieties. For example, stereocomplexed PLA, as discovered by Tsuji and Ikada and which consists of racemic crystallites of poly-L-lactic acid and poly-D-lactic acid (PLLA and PDLA, respectively), has excellent thermomechanical properties compared to each of the individual homopolymers.[21] Introducing a certain amount of D-LA in a PLLA chain can also make the polymer appropriate for a specific application (e.g., in biomedics) as it increases biodegradability. Generation of both enantiopure L- and D-LA isomers could be critical for a broader application of PLA polymers.

2.2. Alternative methods for the production of LA

2.2.1. Chemocatalytic production of LA

Chemocatalysis can be used as a tool to convert trioses,[22] hexoses,[23] cellulose,[24] and also glycerol[25] into LA (or its esters). Homogeneous and heterogeneous catalysis, provided with appropriate Lewis and Brønsted acidities, have proven to be useful for the selective synthesis of lactate esters in alcoholic media.[26] The synthesis of esters of LA in alcoholic media is generally easier than synthesizing the free acid in water. Furthermore, lactate esters are more convenient with respect to purification procedures. Although hexoses are clearly more interesting substrates than trioses with respect to cost and availability, yields are significantly lower: using heterogeneous catalysts, a near quantitative yield can be reached starting from trioses,[26a] whereas the highest reported yield from hexoses (in fact from disaccharide sucrose) is 75 %, using stannosilicates and an added alkali salt.[27] On the other hand, inedible abundant cellulose is the most interesting substrate and recent reports show high yields (up to 90 %) and volumetric productivities (up to 17.7 $g\,L^{-1}\,h^{-1}$); however, a heterogeneous catalytic system is not established yet.[24,28] In a recent report in which $ErCl_3$ is used as the catalyst, the homogeneous Lewis acid can be recovered using a simple extraction procedure.[28] Glycerol, the main byproduct from biodiesel production and, more importantly, the soap industry, is another interesting substrate for LA synthesis. From a chemical point of view, the conversion of cellulose, hexoses, and glycerol into LA provides 100 % atomic efficiency with preservation of the overall chemical functionality.[13] A recent report emphasizes the economic potential of routes starting from trioses and glycerol through bio-/chemo-catalysis compared with the traditional fermentation pathway.[29]

2.2.2. Alkaline production of lactates

Plaxica, a technology-licensing company and spin-off from Imperial College London, produces LA using a non-fermentative technology. In their patents, they use stochiometrically added metal or ammonium hydroxide compounds such as $Ba(OH)_2$ (see [30]) or butyl ammonium hydroxide to convert aqueous saccharides (mostly glucose) at 80 °C into a lactate complex.[31] The highest lactate yields in their examples are between 55 and 60 % whereas volumetric productivities are low, that is, 2.6 $g\,L^{-1}\,h^{-1}$. Note that such an alkaline conversion strategy can also be carried out starting from glycerol.[32] Further processing/purification strategies are also given in the patents. Ba-lactate could for example be converted in the presence of an amine and CO_2 pressure into an insoluble LA–amine complex and $BaCO_3$, providing the purified lactate in one phase of a biphasic system. $BaCO_3$ precipitates and can be calcined, resulting in BaO, which forms $Ba(OH)_2$ in aqueous medium. Another option discussed is the release of BaCl and LA by stoichiometric addition of HCl to Ba-lactate.[31c]

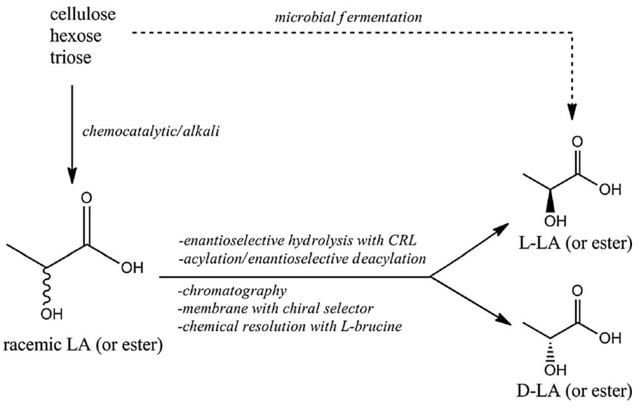
2.2.3. Enantioseparation of racemic lactate streams

Non-fermentative routes to LA or its esters (Section 2.2.1 and 2.2.2.)result in racemic mixtures. . In principle, this feed has the desired composition as both enantiomers are valuable for polyester chemistry. Further processing of such a racemate to lactide and PLA, however, results in an amorphous polymer. To control the stereoselectivity of the final polymer, which has a large impact on the properties, a separation of both enantiomers is often necessary.

Traditional enantiomeric separation methods are chromatography[33] or chemical resolution of racemates of LA using L-brucine.[34] Another report describes the use of membranes containing a chiral selector, which will trap one of the enantiomers. These methods are, however, characterized by a low general efficiency and difficulty to scale up.

An approach proposed by Plaxica to separate the enantiomers of racemic LA starts from an acylated form of lactate ester, which can be synthesized by esterification of the α-hydroxy group with a carboxylic acid. Next, this acylated ester can be deacylated by enantioselective alcoholysis using *Candida antarctica* lipase B in an ether or ketone solvent. This enantioselective action results in a nearly enantiopure LA ester and an acylated ester form of the other enantiomer, with an ester also being generated as a side product of the deacylation.

We recently reported a more straightforward method to create both enantiopure L- and D-LA from racemic lactate esters using enzymatic catalysis. *Candida rugosa* lipase (CRL) was found to catalyze the enantioselective hydrolysis of L-alkyl lactates in water at ambient conditions, providing easily separated and processable mixtures of L-acid and D-ester. This route aligns well with chemocatalytic production routes that showed high alkyl lactate yields in alcoholic media.[35] An overview of LA syntheses including enantiomeric separation is presented in Scheme 2.



Scheme 2. Overview of LA synthesis and enantiomeric resolution methods.

3. Synthesis of Lactide

In general, three types of processes for the synthesis of lactide from LA are described in literature. The most common and industrial practiced method is the production of lactide via a two-step process, which is widely described in patent literature. Other patents describe the gas-phase synthesis of lactide usually over packed solid catalyst beds. Finally, we describe the recently reported one-step liquid-phase conversion of LA to lactide. Apart from the synthesis of lactide starting from commercial L-LA, some recent patents also describe the synthesis of L- and D-lactides from racemic lactate using an enzymatic strategy.

3.1. Two-step synthesis of lactide (industrial process)

3.1.1. Chemocatalytic production of LA

Chemically seen, lactide is the cyclic dimer of LA. LA itself contains a chiral center, resulting in three existing stereoisomers of lactide: L-lactide (with 2 times the L-configuration), D-lactide (with 2 times the D-configuration), and *meso*-lactide (with both the L- and D-configuration). The isomers are presented in Figure 2. In general, aqueous L-LA is the substrate for lactide synthesis.

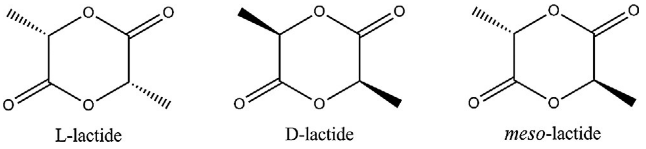
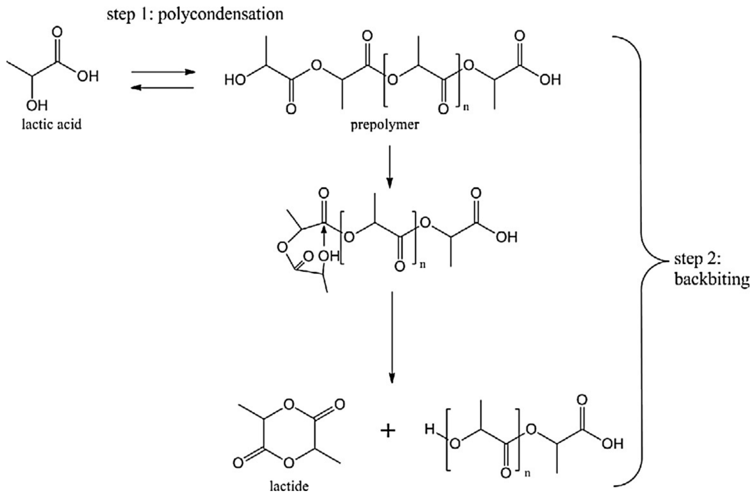


Figure 2. Stereoisomers of lactide: L-lactide, D-lactide, and *meso*-lactide.

The first report of the two-step lactide synthesis dates back to 1878, when Wislicenus detected lactide by first applying a temperature of 130 °C during LA polycondensate formation before increasing the temperature to 150 °C.[36]

This polymerization–depolymerization strategy is depicted in Scheme 3.

The molecular weight of the prepolymer is a determining factor. Shorter prepolymers have a low viscosity, resulting in faster heat transfer for the depolymerization step and a faster transfer of the lactide out of the prepolymer mass.[37] A sufficiently low pressure and high temperature (180 °C) are necessary for achieving an efficient water removal in the first stage, and in the second stage as well, for a fast reaction and the recovery of lactide by distillation. This also limits the time necessary for the preprolymer to be subjected to severe conditions, which causes unwanted racemization. On the other hand, too high temperatures (240 °C) will also cause racemization (see Section 3.1.4.), leading to *meso*-lactide formation.



Scheme 3. Two-step reaction for the synthesis of lactide.

3.1.2. Catalysts

The first reported catalyst, applied in the backbiting step, was ZnO.[38] Sn dust was used for the first time in a publication of 1959 and proved to be a more active catalyst as well as resulting in less racemization.[39] Until today, Sn compounds, such as Sn(octanoate)$_2$ and SnO, are still the schoolbook examples of the backbiting catalyst and are used in multiple patents and publications, likely due to their high activity and solubility in the polymer mass.[11a,40] Another reported type of catalyst are Pb-oxides, used for both the polycondensation step and backbiting. These catalysts seem more water robust than the classical homogeneous Sn compounds, although they are not favorable from a toxicity point of view.[41] Futerro, which is a joint venture of Total (polymer specialist) and Galactic (LA specialist), focuses on phosphite catalysts such as SnHPO$_3$ in WO2009077615 to improve the synthesis of lactide. Kinetically, lactide formation is improved whereas these phosphite catalysts are also more stable and minimize racemization compared with typical backbiting catalysts such as SnO and Sn(octanoate)$_2$.[42] Rare-earth metal catalysts form a last class of catalysts. These compounds can be used for the synthesis of the oligomers as well as for the backbiting step. Clear advantages are that these catalysts are generally non-toxic, while they allow synthesis of prepolymers with relatively low molecular weights in a controlled manner.[37a] Nevertheless, racemization is stimulated by rare-earth metal catalysts.[37b]

3.1.3. Condition and feedstock variations

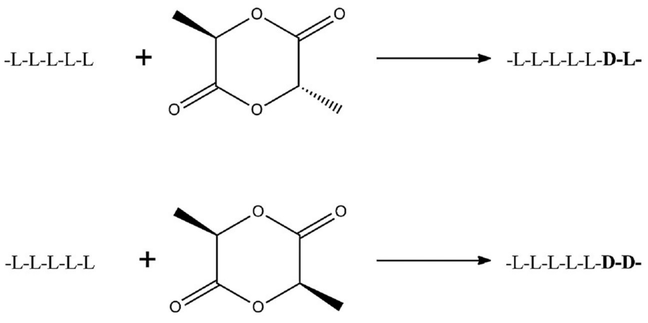
As LA derived from fermentation is a 10–20 wt% solution in water, water removal through evaporation in a separate step, before the polycondensation, is an option. Hereby the volume of the prepolymerization reactor can be greatly reduced. As the vapor of the prepolymer-reactor contains some LA, this can be easily recovered and reintroduced in the evaporation reactor.[40a]

A patent from 1970[41a] and two recent publications[40c,41b] address the use of LA esters as a feed for lactide synthesis, which are also converted according to the polycondensation/backbiting mechanism. An advantage of starting from the ester feedstock is that it avoids the last hydrolysis step from the current workup of fermentation-derived LA. Moreover, esters can be fed fully concentrated to the prepolymer reactor. Interestingly, the recent developments in alkyl lactate synthesis from sugars might further stimulate such an approach.

3.1.4. Racemization

The production of *meso*-lactide (Figure 2) was patented in US5214159.[40b] Still, this isomer is generally undesired. If the synthesis of high-quality PLA is targeted, racemization should be minimized as much as possible; thus, starting from L-LA, enantiopure L-lactide should be obtained. Over the years, methods were explored to minimize racemization by changing the catalyst and the reaction conditions. This is demonstrated in multiple patents.[37b,40a] Coszach et al. introduced SnHPO$_3$ as catalyst and *meso*-lactide formation could be limited to 3.3%, instead of $>10\%$ with Sn(octanoate)$_2$ under the same conditions.[42] O'Brien et al. adapted the conditions during the polycondensation step, aiming for a shorter contact time at high temperature and could limit the *meso*-lactide percentage to just below 5%.[37b]

NatureWorks, today's largest PLA-producing company, even specifically reported an approach to deal with the racemization problem by patenting a process with continuous *meso*-lactide recycling (R.D. Benson, US 8674056 B2, 2014). If D-lactide is introduced in pure PLLA, an L-polymer chain is interrupted by two D-LA units whereas in the case of *meso*-lactide, the interruption consists of only one D-unit (Scheme 4).



Scheme 4. Introduction of *meso*-lactide (upper case) and D-lactide (lower case) in PLA.

Even though interrupting the stereoregularity of PLLA results in changed properties, similar changes in crystallinity and thermomechanical properties are noticed with a D,L- or a D,D-interruption. Therefore, in the patent by Benson et al., a method is proposed in which *meso*-lactide is recycled via hydrolysis and subsequently reintroduced in the prepolymerization reactor.[43] This results again in the formation of *meso*-, D-, and L-lactide.

Yet, the fraction of D-lactide will be higher than in the first cycle. Finally, interruptions in the PLLA chain will appear mostly as D,D-sequences, meaning that for a given amount of racemization (and D-unit formation) only half as much interruptions (D,D) are introduced than in the case of pure *meso*-interruptions (D,L).

3.1.5. An integrated process example

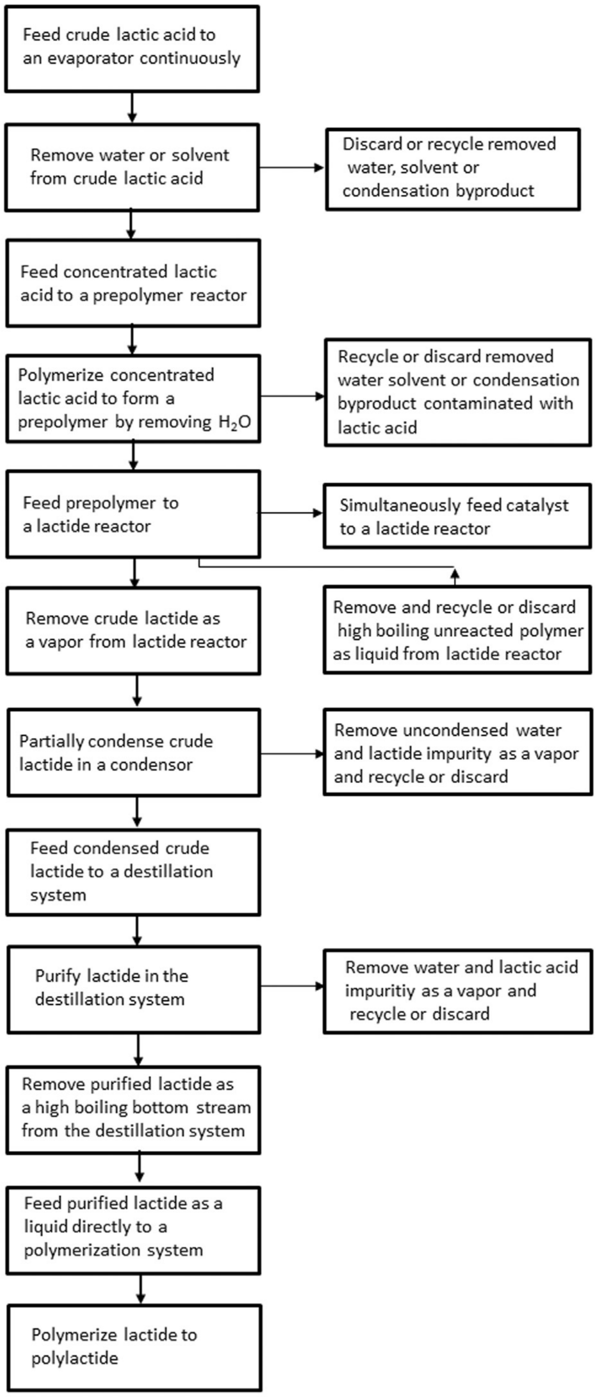
The largest amount of patents concerning lactide production is assigned to NatureWorks, with origins in Cargill's research, aimed at the development of a new starch-based product. In some of these applications, an entire process for PLA production is described. It includes lactide production as well as purification strategies.

In Scheme 5, a flow scheme of Cargill's patented process is depicted.[44] Note that a completely solvent-free process is proposed, including a "bulk" lactide polymerization in which the catalyst is dissolved in the melt.[11a] For the synthesis of lactide, the inventors first applied a water-removal stage (evaporation) to concentrate LA to 85–99 wt% before its conversion into a prepolymer (polycondensation). This evaporation stage is carried out under vacuum to minimize temperature-induced racemization. An essential factor in the LA feed is the amount of cationic impurities as these stimulate the percentage of racemization and thus the formation of *meso*-lactide. Next, the concentrated LA stream is converted into a prepolymer with molecular weights around 400–2500 $g\,mol^{-1}$. This step is carried out under vacuum at 200°C–220°C without the use of a catalyst. While water is being removed, small amounts of LA also evaporate. This can be reintroduced in the evaporation reactor. Next, the prepolymer, is converted via the backbiting reaction catalyzed by SnO, resulting in a vapor-phase lactide stream. Higher molecular weights of the prepolymer result in higher amounts of *meso*-lactide. The amount of catalyst should also be limited to 0.1 wt% as otherwise racemization percentages are too high. Starting from the prepolymer, they reach crude lactide yields of up to 75%.[40a,44]

Further purification of the vapor stream is performed by distillation: lactide is separated from water and LA that are also present in the crude vapor. The separated LA can be reintroduced at some point more upstream in the process. Next, the pure lactide is fed into the polymerization reactor in molten state as the reaction temperature for ROP is 180–210°C.

3.1.6. Specific variations on the two-step process

Several patents describe optimizations/variations on different aspects of the two-step process.. Du Pont proposes an optimization of the depolymerization step: to minimize the time that the prepolymer is subjected to the severe conditions (which lowers the selectivity), a multi-stage column process, with a specific temperature program, is elaborated.[45] Another option to limit the contact time of the prepolymer is described by O'Brien et al.[37b] To enhance water removal in the polycondensation step, the surface area of the polymer mass is increased, by using high-pressure spraying devices.



Scheme 5. Flow chart of the continuous process from NatureWorks for the production of PLA based on Ref. [44]

To facilitate purification of lactide and minimize racemization by working at lower temperatures, Kim et al. introduce an ionic liquid in the reaction system. A typical two-step procedure is reported, viz. a polymerization followed by a depolymerization step, with a ZnO catalyst (among others) in the 2nd stage. The ionic solvent leads to a higher mobility of the reactant and allows the use of lower temperatures as heat transfer seems to be more efficient in such solvent systems. At the same time, the ionic liquid absorbs moisture, which protects the lactide from hydrolysis.[46]

3.2. Gas-phase synthesis of lactide

Gas-phase catalytic processes have been proposed as an alternative strategy to overcome some of the drawbacks associated with the two-step process for lactide synthesis. In short, Bellis et al.[47] proposed a process in which LA (or its ester) is vaporized and reacted over a (plug-flow) catalyst bed. An inert carrier gas stream is used during the process. Proposed catalysts are, for example, SnO and other oxides containing metals from group III, IV, V, or VIII. High-SiO_2-content SiO_2–Al_2O_3 materials are particularly suitable. Faster reaction times are one of the main advantages compared with the traditional two-step process. As a consequence, degradation and racemization reactions are less pronounced. As this gas-phase process operates at atmospheric pressures instead of very low pressures, investment costs are estimated to be lower than in the two-step process.[47] Benecke et al. describe a very similar process (i.e., a lactic acid feed is vaporized and passed over a catalyst bed together with an inert carrier gas). Though, a more specific feed is described. As the composition of an aqueous LA solution is concentration dependent,[49] the authors focused on a feed mainly composed of LA and its dimer. Furthermore, the authors reported clear catalyst trends by means of examples, but show that the reaction can also be conducted in absence of a catalyst. The advantage of the latter is that typical side products, such as CO and acetaldehyde, do not form as such. With a catalyst, the conversions are boosted, resulting in higher yields but lower selectivities. Al_2O_3-containing catalysts, for example, are very effective: at a space time of around 0.8–3 s^{-1} and a catalyst bed temperature of 220 °C, a maximum yield of 44.6% can be reached. About 4% CO was formed as decomposition product. The weight of the catalyst increased significantly, which was attributed to oligomer formation. The use of typical acidic catalysts such as phosphoric acid (on Kieselguhr) or amberlyst ion-exchange resin results in higher CO formation. Still, the highest reported yield in their examples is only 44%.[49]

As one of the leading PLA producers in Europe, Uhde Inventa Fischer holds a patent for continuous lactide synthesis directly from concentrated LA.[50] A one-step strategy is described in which a concentrated LA is passed in an inert gas stream over a heated reaction zone (containing a heterogeneous catalyst such as an aluminiumoxide or a zeolite) at reduced pressure. Although this is theoretically a gas-phase approach, given the discussed pressure–temperature range the system could be closer to liquid-phase conditions. Lower pressures and higher temperatures increase the lactide yield as it stimulates the evaporation of oligomeric LA species. The highest reported yield is 40% using γ-Al_2O_3 at 240 °C and 150 mbar. The reaction mechanism is discussed, and it seems that lactide cannot be synthesized directly from monomeric LA but only from oligomeric LA species. This is also deducted from the examples, as higher lactide yields are reached when starting from more concentrated LA solutions as these are typically more enriched in oligomers.[48] In this scenario, the lactide yield is restricted by the LA feed and only concentrated solutions well above 50 wt% are interesting.

In Figure 3 the oligomer percentage, that is, the non-monomeric LA species, is given as a function of wt% LA based on an equilibrium study performed by Vu et al.[48] Please note that the amount of LA can be above 100 wt% if the water formed during esterification has been removed from the solution. These oligomer percentages indicate thus the maximum lactide yields that can be reached using the synthesis strategy according to Uhde Inventa Fischer.[50]

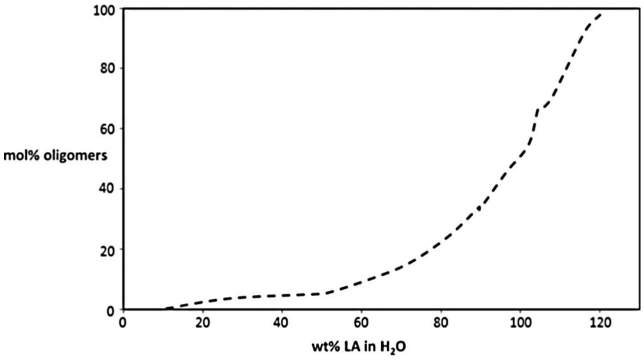


Figure 3. Mol% oligomers in an aqueous LA feed as a function of wt% LA in H_2O, based on data from Vu et al.[48]

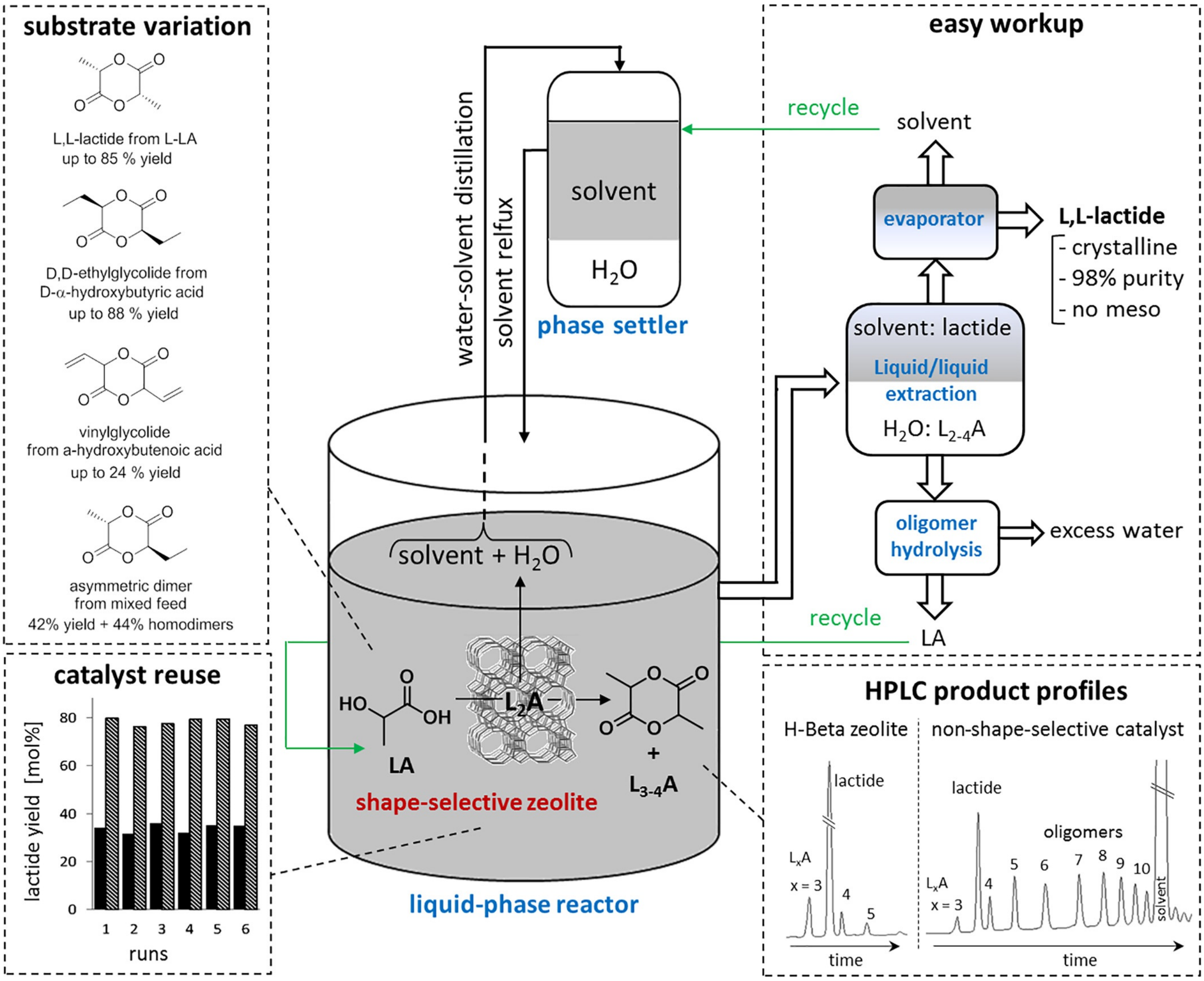
Fermentatively produced LA generally occurs as an aqueous solution below 20 wt%.[40a] In such diluted aqueous solutions, LA oligomers are not present. Consequently, a water-removal step needs to be performed prior to fermentation to achieve intermediate lactide yields when using the above approach. Differences in catalyst morphologies and acidity are discussed, although no clear trends are visible. The authors also state that catalysts with a higher Lewis acidity than Brønsted acidity are preferred, although this is not demonstrated in the examples. The claim that racemization is limited (<9%) is emphasized in the invention, but not supported by examples. In addition, for every 1% of racemization, the melting temperature (T_m) of homopolymeric PLA decreases with 3 °C, which also affects the crystallization rates.[51] Producing high-purity lactide for high-quality PLA requires more severe restrictions on the racemization percentage. The most recent gas-phase approach was described in a Korean patent.[52] Sn oxides were used as catalysts in a fixed-bed reactor while an inert gas stream was used to dilute the aqueous LA feed. Although very high yields could be reached (70%–90%) and racemization percentages were low, the reported volumetric productivities (weight hourly space velocity-dependent) were very low (<0.05–1 $g_{lactide} L^{-1} h^{-1}$).

3.3. One-step liquid-phase process for the synthesis of lactide

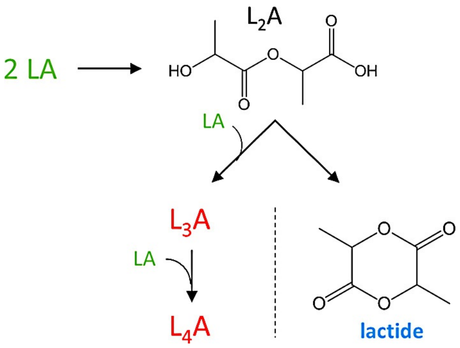
Recently, we reported a new approach to synthesize lactide.[53] A uniquemethodology was used, and unlike in the two-step synthesis, water removal takes place during the ring-closing reaction; thus, lactide is synthesized directly from an aqueous LA solution though condensation rather than through transesterification. In this approach, a water- removal setup based on reactive distillation (e.g., using *o*-xylene as a reaction solvent) is used (see Scheme 6).

Zeolites (microporous aluminosilicates), well-known heterogeneous catalysts in petrochemistry, are introduced to bioplastic synthesis. More specifically, H-Beta-zeolites are used, resulting in lactide yields of more than 80%. Stereoselectivity is $>99\%$; thus, the unwanted *meso*-lactide isomer is not produced, which is contrast to the two-step process. In analogy to multiple examples in refining and petrochemical catalysis, zeolite-based shape-selective reaction chemistry is exploited, but now in the synthesis of biomass-derived molecules, and in the liquid phase.[53] In this approach, lactide (a smaller cyclic molecule) is favorably synthesized in the presence of confined Brønsted acid sites rather than larger LA oligomers (L_4A, L_5A, and so on). The reaction path is depicted in Scheme 7. The shape selectivity can also be recognized when comparing HPLC product profiles (HPLC panel in Scheme 6) of H-Beta with a non-shape-selective condensation catalyst. In a heterogeneously catalyzed process, full reusability of the catalyst is an important measure: the zeolite could be regenerated by calcination and showed no decline in activity or selectivity in both productive and initial (kinetic) conditions (catalyst reuse panel in Scheme 6).[53]

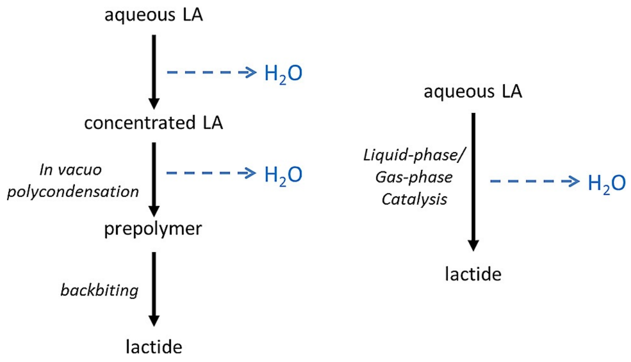
Process integration of such a reaction, including recovery and regeneration of products and catalyst, is relatively straightforward. Lactide is soluble in *o*-xylene (or other aromatic solvents), whereas the aqueous phase of a water/solvent liquid–liquid extraction step right after reaction allows full recovery of unreacted LA and the small amount of short oligomer side products (L_xA with $x=2$–4, Scheme 7). As all lactide resides in the aromatic phase after extraction, solvent removal by evaporation of this phase results in spontaneous crystallization of



Scheme 6. Proposed process scheme and setup for one-step liquid-phase lactide synthesis.



Scheme 7. Reaction path of lactide synthesis during condensation. L_xA denotes an oligomer of x lactic-acid units.



Scheme 8. Water removal in the industrial two-step lactide process (left) and in the gas-phase or liquid-phase approach (right).

lactide (98 % pure) and easy solvent recovery. The oligomers in the aqueous phase can be hydrolyzed and recycled in the catalytic reaction (workup panel in Scheme 6). Additionally, the shape-selective reaction can be extended to synthesize dimers of other LA-like molecules such as α-hydroxy butyric acid and vinyl glycolic acid. The synthesis of asymmetric dimers is also possible using this approach (substrate variation panel in Scheme 6). Some of these alternative acidic feedstocks have been selectively prepared from biomass sugars[55] since they were discovered as byproducts in chemocatalytic routes towards lactates (Section 2.2.1).[23a, 26a, 27]

3.4. Discussion of different lactide synthesis approaches

Although the synthesis of lactide is only scarcely reported in academic literature, the increasing amounts of patents in recent years indicates that alternative synthesis strategies are highly desired to enhance the production of bioplastic PLA. The differences between the three discussed strategies are summarized in Table 1.

In the conversion of LA towards lactide, one of the key energy-consuming aspects is the removal of water, both originating from the aqueous diluted feed and the reaction. Scheme 8 indicates the location of the stage(s) of water removal for the different lactide synthesis strategies.

Clearly, in the current industrial process, water removal and the final lactide formation step occur at different stages. From an equilibrium point of view this is an interesting strategy as in a water-free environment, lactide cannot undergo hydrolysis back to LA. A drawback, however, is the multiple stages of this approach. As can be seen, a concentration step (i.e., water removal of the aqueous fermentatively produced LA feed) is necessary, before the actual ring-closing reaction can occur, as LA oligomers/polymers are the starting point for this depolymerization procedure. This water removal is mostly carried out in 2 steps, (i.e., removal of most of the water originating from the aqueous fermentation stream up to 85–99 wt % of LA, and secondly, water removal coming from the polycondensation step of lactic acid).[40a] In both the one-step liquid approach as well as gas-phase synthesis, water removal and lactide formation occur at the same stage. This means it comes down to the economics of energy input necessary for water removal. In this respect, the one-step liquid-phase process seems interesting as energy input is minimal: the reaction is carried out at atmospheric pressure, mild temperatures, that is, the boiling point of the solvent (i.e., $<150\,^{\circ}C$ for xylenes). The cost of water removal in the gas-phase approach is difficult to estimate. In the industrial process, the diluted aqueous LA feed is concentrated in an initial water- removal step by evaporation under vacuum. The subsequent polycondensation step is performed at very low pressures and high temperatures and is thus also an energy-demanding step. In the current industrial two-step process, a low molecular weight PLA is synthesized initially, that is then converted to lactide to finally resynthesize the high mo-

Table 1. Comparison of the different lactide production processes.

Parameter	Process		
	industrial	gas phase	liquid phase
number of steps	2	1	1
water removal methods	vacuum distillation	vapor in inert gas stream	reactive distillation
T and p	180–240 °C at 0–50 mbar	190–260 °C at atmospheric pressure[47b, 49b] 150–240 °C at 150 mbar-atmospheric pressure[50] 170–280 °C at atmospheric pressure[52]	110–150 °C at atmospheric pressure
feedstock	LA or esters	LA or esters	LA
yield and volumetric productivity	55–60 %[a]	$<45\%$ at $0.06\ g\,L^{-1}\,h^{-1}$[47b, 49b] 50 % at $0.95\ g\,L^{-1}\,h^{-1}$[50] 70–93 % at $0.05–1\ g\,L^{-1}\,h^{-1}$[52]	$>85\%$ at $150–300\ g\,L^{-1}\,h^{-1}$

[a] Productivity values are hard to estimate in these patents due to the two-step nature and lack of detailed information.

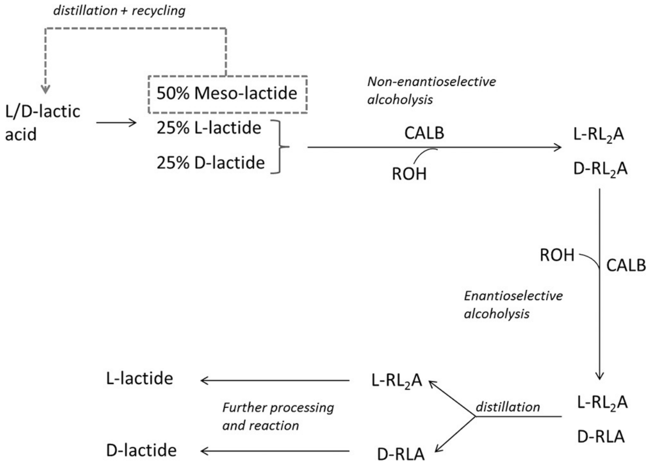
lecular weight polymer. Alternatively, a one-step lactide synthesis approach seems more straightforward from a chemical point of view. Moreover, in the discussed liquid-phase approach, an initial concentration step of the diluted LA is not necessary as the water originating from the feed can be removed during the shape-selective condensation reaction. In addition, compared with both the industrial and gas-phase approaches, all reaction compounds are kept in the solvent (liquid phase), indicating that the heat of evaporation of the organic reaction species should never be invested.

When it comes down to the catalyst, the backbiting procedure is catalyzed by a non-recoverable metal (mostly Sn) salt whereas in the one-step approach (both in gas phase and liquid phase) heterogeneous catalysts can be applied. A returning issue in PLA synthesis is the isomeric purity as incorporation of the *meso*-lactide in PLA will have detrimental effects on its properties. Although racemization is not occurring at all in the liquid-phase approach (because of the mild conditions) and less pronounced in the gas phase (owing short residence times), it is still a major obstacle in current industrial lactide synthesis. More specific patents are dealing with this problem in the two-step process by introducing other catalysts and further optimizing parameters.[37b,42,43,46]

Gas-phase synthesis of lactide is interesting due to the one-step approach, lower racemization, and use of heterogeneous catalysts. A drawback thus far is the limiting yields (highest yields are around 40 %). However, the method patented by Chang et al. of the Korean Research Institute of Chemical Technology results in high yields.[52] Nevertheless, the volumetric productivity is very low due to the high dilution of the LA that is fed to the Sn oxide catalyst in a N_2 flow. In our belief, new approaches such as the liquid-phase processes are particularly interesting: knowledge and catalysts from traditional petrochemical processes are transferred to an aqueous biomass feed composed of functionalized molecules such as LA. Use of heterogeneous catalysts, including zeolites, in the synthesis of LA from sugars,[4] as discussed in Section 2.2, together with their shape-selective behavior in the production of lactide, emphasizes the successful introduction of these affordable and robust catalytic materials into the PLA scheme.

3.5. Enantioseparation of lactide isomers

When using commercial L-LA as feedstock, L-lactide is usually the desired product. For the synthesis of, for example, stereocomplexes of PLA consisting of PLLA and PDLA chains , L- and D-lactides should be both accessible. Therefore, one could either start from separate streams of L- and D-LA (as discussed in Section 2.2.3) and convert these molecules separately into their respective cyclic dimers or convert a LA racemate into a mixture of lactides. Such mixtures should statistically have an isomeric composition of around 50 % *meso*-lactide and 25 % L-lactide and D-lactide each. Plaxica holds multiple patent applications concerning the enantiomeric purification and separation of the lactide products.[56] As *meso*-lactide is a diastereomer of L-and D-lactide, it has a lower boiling point than both enantiomers; thus, the main strategy to isolate *meso*-lactide is through distillation. This isomer should then be recycled towards LA to avoid low overall yields and the need to discard a large part of the product. A strategy to separate enantiomeric L- and D-lactide through an enzymatic kinetic resolution was also proposed. Such a strategy was first reported by Jeon et al., who performed an enantioselective enzymatic alcoholysis in a THF/hexane solvent system, which gave rise to enantiopurities of > 97 % enantiomeric excess (*ee*).[57] Contacting both lactides with an alcohol and *Candida antarctica* lipase B (CALB) results initially in the generation of both L- and D-alkyllactyllactates. Secondly the D-dimeric ester (D-RL_2A) form undergoes a subsequent alcoholysis that is catalyzed by the enantioselective enzyme, which leaves the L-alkyllactyllacate (L-RL_2A) untouched. Plaxica describes an identical strategy, but here the reaction is performed in a ketone solvent.[56a] The monomeric and dimeric ester form can then be separated by fractional distillation (Scheme 9). Hydrolysis of both separated compounds results in enantiopure (> 99 % *ee*) L- and D-LA isomers, which can be converted into the corresponding lactides.



Scheme 9. Separation of lactide isomers by enzymatic kinetic resolution. R = alkyl; ROH = alcohol.

Synthesis of the lactides might also start directly from the monomeric or dimeric LA esters.[56a,b,d] The strategy is depicted in Scheme 9. Note that this strategy results in very enantiopure product streams. On the downside, around 50 % lactide, that is, *meso*-lactide, should be continuously recycled and the desired L- and D-lactides have to be synthesized twice according to this approach.

4. Ring-Opening Polymerization of Lactide

4.1. General polymerization mechanisms and procedures

Depending on the type of catalyst, ROP of lactide can occur according to three mechanisms: anionic, cationic, or through a coordination–insertion mechanism. Numerous reviews and scientific reports have been published with respect to the polymerization mechanisms of lactide and a detailed discussion is outside the scope of this Review and can be found in

Refs. [11,51b, and 58]. In the patented industrial process of NatureWorks,[44] ROP is performed without a solvent (i.e., in the lactide melt) and thus represents a type of bulk polymerization. Tin(octoate)$_2$ (Sn(oct)$_2$) can be used here as a catalyst because of its high solubility in lactide and its high catalytic activity. This type of catalyst operates through the coordination–insertion mechanism.

4.2. Stereoselective polymerization of lactide isomers

The last option to introduce chirality in PLA synthesis is to perform stereoselective polymerization. The discussion of the catalysts, kinetics, and mechanistic studies of this type of polymerizations is beyond the scope of this Review and can be found elsewhere.[59] As already mentioned, the polymer's properties can be tailored by tuning the stereocomposition of the polymer. For the synthesis of stereocomplex PLA, a stereoselective catalyst is not used, and an inexpensive catalyst such as Sn(oct)$_2$ can be used to synthesize the homopolymers, after which stereocomplexation can take place in melt or solution.[21a,60] In Table 2 an overview of the different stereochemical forms of PLA is given.

Table 2. Overview of stereochemical PLA forms.

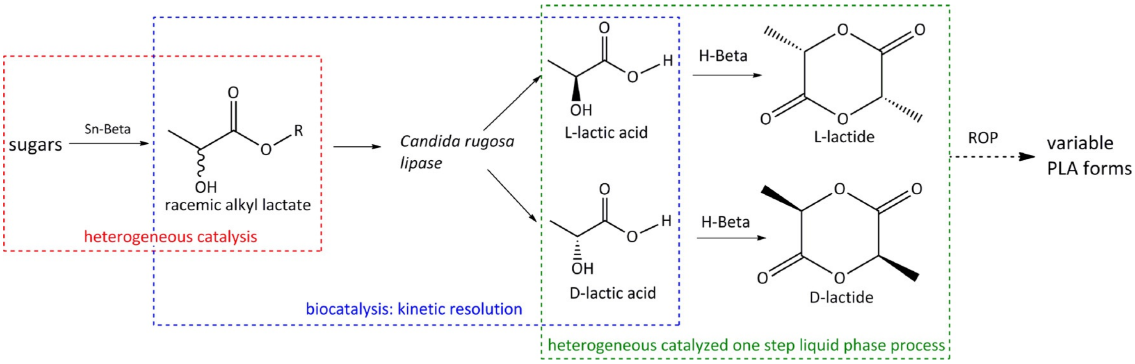
PLA type	Tacticity	Lactide feed	Crystallinity
isotactic PLLA	-L-L-L-	L-lactide	semicrystalline
isotactic PDLA	-D-D-D-	D-Lactide	semicrystalline
syndiotactic PLA	-L-D-L-D-L-D-	*meso*-lactide	semicrystalline
heterotactic PLA	-L-L-D-D-L-L-	*meso* or racemic	amorphous
stereocomplex PLA	L-L-L- and -D-D-D-	PLLA and PDLA	semicrystalline
atactic PLA	random	*meso* and/or racemic	amorphous

Isotactic PLLA is the commercially most abundant form of PLA and has a melting point (T_m) around 165 °C. The properties of PDLA are identical. Stereocomplexes usually composed of 1:1 mixtures of PLLA and PDLA have a T_m around 235 °C, and the chain interaction is based on hydrogen bonding. In principle, block co-polymers, consisting of isotactic L- or D-sequences, can also co-crystallize but not to the same extent as stereocomplexes, resulting in lower melting points. Syndiotactic PLA is synthesized from *meso*-lactide, crystallizes, and has a lower T_m of 152 °C. Heterotactic PLA, consisting of alternating L,L- and D,D-sequences, is an amorphous polymer and can be synthesized from both *meso*- or racemic lactide. Atactic PLA, lacking any form of stereoregularity, is an amorphous polymer and can be formed from *meso*- and/or racemic lactide or mixtures thereof with L- and/or D-lactide.[51b] Research is nowadays mainly focused on improving the activity and enantioselectivity of the catalyst; although this type of reactions are examples of a particular polymerization chemistry, it starts from lactide feedstocks that are currently not accessible on a large scale.[59a,61] L-, D-, racemic, and *meso*-lactide should thus be available for making all these types of PLA. While the L-isomer of lactide is commercially produced, other forms could become accessible if started from a racemic LA feed. A large potential thus lies in the implementation of chemocatalytic methods for the production of racemic LA (and its esters). From this racemic feed L-,D-, and *meso*-lactides can become available. L- and D-lactide can be separated from *meso*-lactide by for instance distillation, resulting in racemic lactide and *meso*-lactide. The lactides can then be converted by an appropriate (whether or not stereoselective) catalyst towards different types PLA (Table 2).

5. View on Enantioselectivity

The enantioselectivity in PLA structures has an enormous impact on the physical properties. It is clear that chirality in the final PLA can be adjusted at different points in the process scheme. Stereoselective polymerizations are nice examples of how polymers with different tacticity (and physical properties) can be produced. However, the critical parameter in the PLA production scheme is the need for a source of D-lactide. Racemic LA could be of high significance in this scheme as then *meso*-lactide and racemic lactide could be directly synthesized by the current industrial backbiting method. These isomers can be converted into multiple PLA forms by stereoselective polymerization.

Alternatively, we propose the route shown in Scheme 10. Based on our progress in the chemocatalytic conversion of sugars into racemic alkyl lactates,[4,26a,62] the enzymatic resolution of this racemate[35] and the one-step synthesis of lactide from LA, we are convinced of the potential of this route. First,



Scheme 10. Alternative synthesis route starting from sugars towards various PLA forms.

the Sn-Beta zeolite seems especially interesting for producing racemic ethyl lactates from sugars, backed by the reported high catalytic productivity.[23a,62,63] A following enzymatic resolution by enantioselective hydrolysis with *Candida rugose* lipase is very straightforward and commercially attractive,[35] providing the pure enantiomeric acid for the one-step zeolite-catalyzed (liquid-phase) lactide synthesis. Note that avoiding racemization during lactide synthesis is critical in this scheme, as L- and D-LA (or esters) were already produced and separated in a prior enantioselective step. From the resulting L- and D-lactide isomers, PLA can be synthesized; depending on the desired polymer properties, the polymerization feed can be composed of both cyclic dimers.

In contrast to our strategy, which relies on the introduction of enantioselectivity at the level of the acid and a racemization-free lactide production, another option could be the enantiomeric resolution of lactides, as proposed by Plaxica (Scheme 9).[56a] The latter strategy seems cumbersome, as *meso*-lactide will be a largely undesired product, and L- and D-lactide are separated by a subsequent degradation–resynthesis procedure.

6. Conclusions and Outlook

Renewable and biodegradable polymers continue to attract a lot of attention, both in industry and academia. Fact-based studies (life cycle analysis, …) and reports are necessary to truly show the benefits of some of these plastics as a convincing route forward to a more sustainable economy.[64] From such studies, polylactic acid (PLA) has come forward as a high-potential polymer and it is currently the most commercially available synthetic biobased polymer.[65] Moreover, prices of fossil resources will likely further increase while PLA production keeps on becoming more economically attractive through technological advances. Bioplastics are mainly used in packaging applications and estimates foresee a continuous increase of PLA use in this area. Due to their close contact with these products, consumers seem well aware of the sustainability issues. On the other hand, applications in the biomedical field are of interest due to the biocompatibility of PLA. Because of its suitable properties, PLA already replaces metallic materials in bone fixation devices to some extent.[66] Drug delivery particles made from PLA are also particularly interesting. Related to this type of applications, adaptable forms of PLA could be interesting as the polymer can then covalently bind drugs or antimicrobial agents.[67] Therefore, the development of chemocatalytic routes towards new types of renewable building blocks with functional side chains is essential but ongoing.[55]

The focus in PLA synthesis is diverse: academically, lactic acid synthesis and ring-opening polymerizations (ROPs) are highlighted, whereas in industry the focus (cfr. patents) seems to be more on lactide synthesis and processes. To close this gap and avoid misunderstanding, it would be beneficial to aim for further progress in PLA production through a joint effort between industry and academia. One could, for instance, question the purpose of further academic research in stereoselective ROPs in the light of the availability of the different lactide isomers (and especially D-lactide). Moreover, by using the appropriate isomeric lactide feed, PLA with tailored properties can be synthesized by inexpensive and traditional ROP catalysts without the need for expensive and (air/water) sensitive stereoselective catalysts.

The potential role of racemic LA is clear as it can be synthesized by chemocatalytic methods and provides both L- and D-LA, which can lead to a range of PLA products (Scheme 9). Moreover, chemically synthesized racemic LA is also a promising feedstock for the synthesis of other chemicals such as 2,3-pentanedione, acrylates, 1,2-propanediol, and green solvents for which the enantioselectivity is not of any importance.

Synthesis of lactide is nowadays still done using an energy-intensive process based on observations dating back to the 19th century. A recent increase in patent applications, describing different methods for alternative lactide production processes, proves the need for a more economically attractive method. Racemization, low selectivity, and high energy costs are the main issues in the current industrial two-step process. One-step gas-phase methods have been explored and, in general, result in lower racemization percentages. Although high yields can be reached, volumetric productivities are very low as the feed is highly diluted in an inert gas stream. Our recent one-step liquid phase approach seems to combine the best of both worlds as high yields and very high productivities are attained while racemization does not occur because of the nature of the catalysts and the mild conditions. Moreover, it nicely illustrates how zeolite catalysts, well known from petrochemistry and refining, can be very apt for designing new production technologies, that is, converting LA in a direct liquid-phase process alternative to an archaic two-step process. An upcoming and interesting challenge in the shape-selective zeolite-catalyzed process lies in the exploration of other and more sustainable solvents that still allow water removal and product extraction.

The diverse range of properties of PLA can only be fully exploited if both D- and L-lactides are accessible. Therefore, we envision a new synthesis route towards stereoselective and property-tailored PLA. It starts with a Lewis acidic Beta zeolite-catalyzed synthesis of racemic alkyllactates. Then, this heterogeneous catalytic step can be followed by a biocatalytic enantioselective resolution, resulting in L- and D-LA (or ester), which can be further processed into the respective lactides by using the racemization-free Brønsted acidic Beta zeolite-catalyzed liquid-phase process.

Acknowledgements

The authors acknowledge The Research Council of the KU Leuven (IDO 3E090504 and IOF KP/14/003). Total S.A. is also gratefully thanked. M.D. thanks Research Foundation Flanders FWO for his postdoctoral grant.

Keywords: chirality · enzymes · polylactic acid · renewable polymers · zeolites

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Received: December 27, 2015