PART I

CHEMISTRY AND PRODUCTION OF LACTIC ACID, LACTIDE, AND POLY(LACTIC ACID)

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PRODUCTION AND PURIFICATION OF LACTIC ACID AND LACTIDE

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1.1 INTRODUCTION

Natural polymers, biopolymers, and synthetic polymers based on annually renewable resources are the basis for the twenty-first-century portfolio of sustainable, eco-efficient plastics [1]. These biosourced materials will gradually replace the currently existing family of oil-based polymers as they become cost- and performance-wise competitive. Polylactide or poly(lactic acid) (PLA) is the front runner in the emerging bioplastics market with the best availability and the most attractive cost structure. The production of the aliphatic polyester from lactic acid, a naturally occurring acid and bulk produced food additive, is relatively straightforward. PLA is a thermoplastic material with rigidity and clarity similar to polystyrene (PS) or poly(ethylene terephthalate) (PET). End uses of PLA are in rigid packaging, flexible film packaging, cold drink cups, cutlery, apparel and staple fiber, bottles, injection molded products, extrusion coating, and so on [2]. PLA is bio-based, resorbable, and biodegradable under industrial composting conditions [1, 3, 4].

PLA can be produced by condensation polymerization directly from its basic building block lactic acid, which is derived by fermentation of sugars from carbohydrate sources such as corn, sugarcane, or tapioca, as will be discussed later in this chapter. Most commercial routes, however, utilize the more efficient conversion of lactide—the cyclic dimer of lactic acid—to PLA via ring-opening polymerization (ROP) catalyzed by a Sn(II)-based catalyst rather than polycondensation [2–6]. Both polymerization concepts rely on highly concentrated polymer-grade lactic acid of excellent quality for the production of high molecular weight polymers in high yield [2–4, 7].

Purification of lactic acid produced by industrial bacterial fermentation is therefore of decisive importance because crude lactic acid contains many impurities such as acids, alcohols, esters, metals, and traces of sugars and nutrients [4].

The lactide monomer for PLA is obtained from catalytic depolymerization of short PLA chains under reduced pressure [4]. This prepolymer is produced by dehydration and polycondensation of lactic acid under vacuum at high temperature. After purification, lactide is used for the production of PLA and lactide copolymers by ROP, which is conducted in bulk at temperatures above the melting point of the lactides and below temperatures that cause degradation of the formed PLA [4].

Processing, crystallization, and degradation behavior of PLA all depend on the structure and composition of the polymer chains, in particular the ratio of the L- to the D-isomer of lactic acid [2, 4, 6, 8, 9]. This stereochemical structure of PLA can be modified by copolymerization of mixtures of L-lactide and *meso*-, D-, or *rac*-lactide resulting in high molecular weight amorphous or semicrystalline polymers with a melting point in the range from 130 to 185°C [3, 4, 6–10].

Isotactic PLLA homopolymer—comprising L-lactide only—is a semicrystalline material with the highest melting point, while PLA copolymers with higher D-isomer content exhibit lower melting points and dramatically slower crystallization behavior, until they finally become amorphous at D-contents higher than 12–15% [8–10].

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For decades, ROP has been the preferred route to PLA for biomedical applications with small production volumes. PLLA and copolymers with *rac*-lactide, glycolide, and ε-caprolactone for resorbable biomedical applications have been produced by, for example, PURAC, previously known as CCA, since the 1970s [5]. Since the 1990s, the ROP concept is also used for high-volume production of PLA grades for other end uses.

Large-scale production of PLA, copolymers of L- and *meso*-lactide, was started in 2002 by a joint venture of Cargill and Dow under the name NatureWorks LLC. Nowadays, since July 1, 2009, NatureWorks LLC is again wholly owned by Cargill and has a production capacity of 140 ktpa for its Ingeo PLA grades in Blair, Nebraska [11].

The attractive price and commercial availability of lactic acid were important reasons why PLA became the first mass-produced bio-based polyester. The critical success factor for a final breakthrough of all green chemicals and plastics based on annually renewable materials is economic sustainability. Thus, the very basis of cost-competitive PLA is an industrial fermentative production process for lactic acid with efficient use of carbohydrates followed by excellent purification technology with minimum generation of by-products.

An important impulse for the expanding bioplastics market is the commercialization of lactide monomers for PLA by PURAC in 2008. Solid D- and L-lactides are now available in bulk quantities and can be polymerized into a whole range of tailor-made polylactides by continuous melt polymerization processes, like the technology based on static mixing reactors that was jointly developed by Sulzer and PURAC.

PLA offers an unprecedented market potential to lactic acid producers all over the world, but not all potential players can succeed, because PLA production poses stringent demands to lactic acid quality and price. The chemistry and physics of today's fermentative production and industrial-scale purification of lactic acid and lactide are the subject of this chapter.

1.2 LACTIC ACID

1.2.1 History of Lactic Acid

Lactic acid was discovered in 1780 by the experimental chemist Carl Wilhelm Scheele, who isolated "acid of milk" from sour whey [12, 13]. A further description of the history of lactic acid by Holten and Benninga shows that industrial production of lactic acid started in the United States in the 1880s [14, 15]. Avery patented and applied a process of fermentation of vegetable sugars [16]. The actual application was the use of a mixture of calcium lactate and lactic acid as baking powder. Unfortunately, this application was not a big success, but other applications in food and textile dyeing were developed.

(*S*)-Lactic acid
L-(+)-Lactic acid

(*R*)-Lactic acid
D-(–)-Lactic acid

FIGURE 1.1 Two enantiomeric forms of lactic acid: (*S*)- and (*R*)-2-hydroxypropionic acid.

In 1950, the first commercial production of synthetic lactic acid started in Japan [15]. Lactonitrile was produced from acetaldehyde and hydrogen cyanide and hydrolyzed in the second stage to lactic acid. For some decades, synthetic lactic acid competed with lactic acid obtained by fermentation, but currently almost all lactic acid is produced by fermentation.

1.2.2 Physical Properties of Lactic Acid

Lactic acid (2-hydroxypropanoic acid) is the simplest 2-hydroxycarboxylic acid (or α-hydroxy acid) with a chiral carbon atom and exists in two enantiomeric forms (Figure 1.1).

The chirality of lactic acid often results in confusion regarding nomenclature. A number of different names are used in the literature. This confusion is the result of mixing the molecular structure and a physical property (optical rotation). (*S*)-Lactic acid (or L-lactic acid) has a slightly positive specific optical rotation and is frequently named L-(+)-lactic acid [14]. However, a concentrated solution of (*S*)-lactic acid at equilibrium contains lactic acid oligomers, which results in an overall negative optical rotation. Therefore, it is advised to use the structural *R*/*S* notation or the older notation of L and D and avoid the + and − of the optical rotation (Table 1.1).

1.2.3 Chemistry of Lactic Acid

The lactic acid molecule has a hydroxyl and an acid functional group, which may result in intermolecular and intramolecular esterification reactions. The first step is the formation of a linear dimer (lactoyl lactic acid). This condensation reaction can proceed to higher oligomers and is promoted by removal of water. Also a cyclic dimer, lactide, is formed in small amounts. Lactide can be formed by intramolecular esterification of lactoyl lactic acid or by breakdown of higher oligomers. All reactions are equilibrium reactions (Figure 1.2).

Due to these reactions, a solution of lactic acid at equilibrium consists of monomeric lactic acid, dimeric lactic acid or lactoyl lactic acid, higher oligomers of lactic acid, and

TABLE 1.1 Physical Properties of Lactic Acid [14]

Property	Value	Reference
CAS number	General: 50-21-5 (*S*)-Lactic acid: 79-33-4 (*R*)-Lactic acid: 10326-41-7	
Molecular weight (g/mol)	90.08	
Formula	$C_3H_6O_3$	
Melting point (°C)	18 (racemic)	[17]
	53 (chiral pure)	[18]
Crystal structure	(*S*)-Lactic acid: orthorhombic, space group $P2_12_12_1$	[19]
Solid density (g/mL)	1.33 (solid, 20°C)	[20]
Solubility in water (wt%)	86 (20°C, monomeric (*S*)-lactic acid)	[20]
Heat of fusion (kJ/mol)	(*S*)-Lactic acid: 16.8	[21]
Boiling point (°C)	122 (at 14 mmHg)	[22]
Liquid density (g/mL, 20°C)	1.224 (100% undercooled liquid)	[22]
	1.186 (80.8% solution in water)	[23]
Viscosity (mPa s)	28.5 (85.3% solution in water, 25°C)	[23]
pK_a	3.86	[24]
Specific heat (J/(g K) at 25°C)	Crystalline (*S*)-lactic acid: 1.41	[25]
	Liquid lactic acid: 2.34	[26]

lactide. The ratios between all substances depend on the amount of water present; for example, a 90.1% lactic acid solution (total acidity) contains about 59.3% of monomeric lactic acid and 27.3% of lactoyl lactic acid and higher oligomers [14].

The condensation reactions are also the reason that it is quite difficult to obtain pure, solid, and enantiopure lactic acid. This can only be achieved by crystallization [27, 28]. The kinetics of the condensation reactions determine the stability of a solution of monomeric lactic acid and have a large influence on the stability of solid lactic acid.

1.2.4 Production of Lactic Acid by Fermentation

Almost all lactic acid available on the market is produced by fermentation. During fermentation, a suitable carbohydrate is converted to lactic acid by microorganisms. Although some of the microorganisms used, such as the mold *Rhizopus*, need oxygen for growth, the actual conversion of sugars to lactic acid is carried out without oxygen. As a matter of fact, the complete oxidation of a sugar to carbon dioxide and water is energetically much more favorable, so lactic acid is mainly formed under anaerobic conditions. Indeed, most lactic acid producing microorganisms are inactive when oxygen is continuously present in high amounts [29]. Upon entering the cell, the sugar is first converted to pyruvate by several enzymatic steps. This conversion yields chemical energy in the form of ATP (adenosine triphosphate) and reducing equivalents (NADH); see the reaction in Figure 1.3.

In order to recycle these reducing equivalents, microorganisms convert the pyruvate into the more reduced lactic acid; see the reaction in Figure 1.4.

In other words, lactic acid is mainly produced to keep the cellular processes going [30]. The chemical energy obtained is used by several processes elsewhere in the cell, for example, cell growth, maintenance, and sometimes even motility.

The reaction in Figure 1.3 takes place in the so-called homofermentative lactic acid bacteria (LAB). Homofermentative bacteria have almost exclusively lactic acid as a

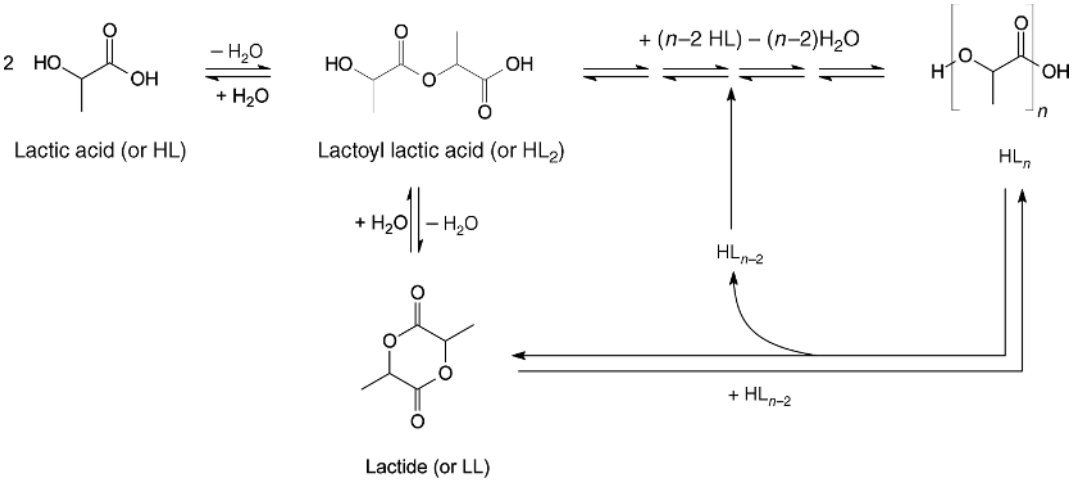

FIGURE 1.2 Lactic acid condensation reactions: interchange between lactide, oligomers, and poly(lactic acid).

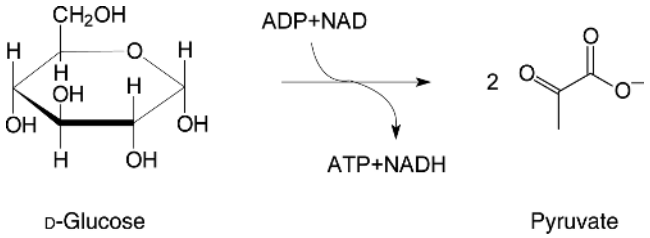

FIGURE 1.3 During conversion of glucose to pyruvate, chemical energy (ATP) is generated as well as reducing equivalents (NADH).

fermentation product, in contrast to heterofermentative bacteria that produce a mixture of lactic acid, acetate, CO_2, and acetate or ethanol [31]. Heterofermentative bacteria were believed to use exclusively the so-called phosphoketolase pathway, and homofermentative bacteria were believed to use exclusively the glycolysis (Figure 1.3) that splits C_6 into two C_3 molecules [31].

The phosphoketolase pathway is a route where a C_6 is transformed to a C_5 sugar (and CO_2) and split into a C_2 and a C_3 molecule. The C_3 molecule is then converted to lactic acid whereas the C_2 molecule is converted to acetate or ethanol. In the same traditional view, C_5 sugars were regarded as leading to this heterofermentative metabolism, which is less interesting from the point of view of industrial production as a lot of acetic acid or ethanol is produced simultaneously. Although some bacteria seem to fit well in this paradigm, more recent literature has shown that this view is oversimplified and somewhat obsolete for a number of reasons.

- Some heterofermentative bacteria are shown to have both pathways active at the same moment and produce mostly lactic acid under certain circumstances [32, 33].
- Pentoses can lead exclusively to lactic acid as a fermentation product [34].
- Lactic acid producing organisms that do not have a phosphoketolase pathway can still produce acetate or ethanol, formed by the usual mixed acid fermentation, via pyruvate. This is the case for, for example, *Lactococcus lactis* [35].

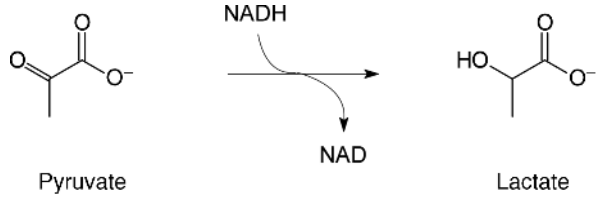

FIGURE 1.4 Lactic acid formation from pyruvate: reoxidation of NADH and NAD takes place; NAD can be used again in the reaction of Figure 1.3.

The reason why even heterofermentative bacteria prefer to produce mostly lactic acid is related to the fast generation of chemical energy and thus fast growth and acidification of the environment [32, 36, 37]. The fast growth and acidification gives lactic acid bacteria a competitive advantage and that is exactly why lactic acid bacteria are so troublesome in ethanol fermentations [38]. Lactic acid production is certainly not restricted to bacteria or fungi. Higher organisms, including humans, also use lactic acid formation for fast supply of energy in muscles when needed [39].

The uniformity in this biochemistry is in sharp contrast with the degrees of freedom one has in choosing the microbes, the acid-neutralizing agent, nutrients, and carbohydrates needed for industrial lactic acid fermentation. Only delicate weighing of the pros and cons of every possibility leads to an economically feasible fermentation.

1.2.4.1 The Microbes There are several important features a microorganism used for the production of lactic acid must have in order to be industrially attractive:

- high productivity to reduce fermentation time,
- high conversion yield to reduce carbohydrate costs,
- ability to use cheap sources of nutrients to reduce nutrient costs,
- high end concentration to reduce evaporation costs,
- low amount of by-products to increase purification yield, and, of course,
- the organisms must be robust with regard to contamination and infections.

Every microorganism has its own benefits and drawbacks, but lactobacilli (present in many food fermentations) and *Rhizopus* (a fungus) are the most reported [40]. Besides lactobacilli and *Rhizopus*, *Streptococcus*, *Pediococcus*, *Sporolactobacillus inulinus*, *Bacillus coagulans*, and several yeasts are mentioned in the excellent overview by Vaidya et al. [41].

Lactobacilli generally have high productivity, but special and often expensive nutrient requirements. *Rhizopus* needs much less nutrients, but has a lower yield, needs oxygen, and its morphology is sometimes difficult to handle. Of course, via genetic manipulation, researchers have tried to make an ideal lactic acid producing microorganism.

1.2.4.2 Stereochemical Purity In order to make semicrystalline, high-melting PLA, stereochemically pure lactic acid is needed. Not all microorganisms yield such stereochemically pure lactic acid and some even produce a racemic mixture [29]. Therefore, a strain must be chosen that meets the quality demands. Finding such a strain that produces L-lactic acid in an economically feasible manner is relatively easy. Producing D-lactic acid by bacterial fermentation on an industrial scale is far more difficult.

Several natural D-lactic acid producing bacterial species exist; *Sporolactobacillus inulinus*, *Sporolactobacillus laevolacticus* (previously *Bacillus laevolacticus*), and *Lactobacillus delbrueckii* are among these bacteria [29, 42, 43]. Also, patents have been filed claiming the production of D-lactic acid by a genetically modified microorganism. Several different species such as *Kluyveromyces* and *Escherichia coli* have been claimed so far [44, 45].

1.2.4.3 Nutrients The most well-known lactic acid producing organisms, such as *Lactobacillus* and *Lactococcus* species, are members of the taxonomic order of Lactobacillales, also commonly referred to as lactic acid bacteria. These lactic acid bacteria have their really complex nutrient need in common [29]. Vitamins and peptides need to be added to the medium to enable growth. This can be done by adding peptones, yeast extract, or corn steep liquor, but this is expensive. Nutrients for lactic acid production can also be derived from nutrient-rich waste streams such as rice bran, fish waste, or vinification lees [46–48].

1.2.4.4 Neutralization Lactic acid fermentation inevitably leads to a drop in pH, and without neutralization the microorganism is quickly unable to continue the fermentation, as the environment becomes too acidic. Several bases can be used to neutralize the acidity during fermentation, and the choice of the base will determine the nature of the downstream processing (DSP). Most industrial lactic acid plants use $Ca(OH)_2$ or $CaCO_3$, which results in the production of a large amount of gypsum as a by-product.

A major challenge in lactic acid production is to find or construct an efficient microorganism that can produce at such a low pH that the fermentation does not require neutralization. Lactic acid bacteria are usually able to grow at low pH, but it is difficult to find an organism capable of producing lactic acid in reasonable amounts at pH close to the pK_a of lactic acid [49]. Another solution is to construct a lactic acid producing yeast but organisms like this still suffer from low productivities (amount of lactic acid produced per hour) and low final concentrations, leading to the requirement for large fermenter volumes and high amounts of water evaporation [50].

Some basic hurdles have to be overcome in order to improve the low-pH fermentation by yeasts. Although yeasts are very resistant to low pH, the export of lactate from the yeast cell to the outside medium costs them as much energy as they get from lactic acid production by fermentation. For this reason, lactic acid producing yeasts need reasonable amounts of oxygen in order to generate enough energy to survive [51]. In contrast, traditional lactic acid bacteria use another way to transport lactic acid across the membrane and even gain extra energy by exporting lactic acid to the medium [52].

1.2.4.5 Carbohydrates for Lactic Acid Production In principle, any carbohydrate source containing pentoses (C_5 sugars) or hexoses (C_6 sugars) can be used for the production of lactic acid, although it is very rare that any particular microorganism is able to use all possible and available C_5 and C_6 sugars. Pure sucrose from sugarcane or sugar beets and glucose from starch are available in large amounts and readily fermentable. Polysaccharides such as cellulose or starch are more complex and need special pretreatment. When using less pure sources such as raw sugar beet juice, the impurities must be removed somewhere in the total lactic acid production process [53]. This can be done before, during, or after the fermentation. This often leads to special adaptations in the production plant. Last but not least, the local price and availability of the carbohydrate source determine the raw material of choice for industrial fermentation. Another usable disaccharide is lactose present in whey, as was used by Scheele when he discovered lactic acid in 1780 [12].

1.2.4.6 Starch Starch occurs in discrete granules and is usually a mixture of two homopolymers of glucose, amylopectin and amylose. Starch can be derived from corn, wheat, potato, or tapioca [54]. Although some microorganisms are able to degrade and ferment starch directly to lactic acid, most lactic acid producing microorganisms cannot hydrolyze starch themselves. A solution is to hydrolyze the starch to glucose prior to fermentation with the commercially available enzymes, α-amylase and glucoamylase. This can be done in a separate process, so no incompatibilities are present between the optimal pH and temperatures of the enzymes on one hand and the optimal pH and temperature of the microbes on the other. However, if the right combination of enzymes, microorganisms, pH, and temperature is carefully chosen, the hydrolysis and fermentation can be carried out in one reactor. This process is generally called SSF (simultaneous saccharification and fermentation) [55]. Prior to SSF, the starch granules usually must be gelatinized at high temperature by cooking. However, even a cooker is optional nowadays as commercial enzymes are becoming available that are able to attack and hydrolyze the granules efficiently and fast enough at relatively low temperatures.

1.2.4.7 Lignocellulose Sucrose and starch have in common that they are used for food and nowadays, with oil wells drying out and prices rising, also for biofuels. A decrease in the availability of fossil fuels is envisaged for the future, and with increasing population, more food is needed at reasonable prices. Therefore, the ideal raw material for biofuels and bioplastics is carbohydrates that are not edible. Such material is abundantly available around the globe as lignocellulose, like in corn stover or wheat straw. Lignocellulose consists of the glucose homopolymer cellulose, the heteropolymer hemicellulose, and lignin. Hemicellulose consists of hexoses

and pentoses. In all, lignocellulose contains roughly 80% fermentable sugars, but this largely depends on the source [54]. The remainder, lignin, is a phenolic polymer that is difficult to degrade and is not directly usable for lactic acid production. It may be used for energy production though, which can be returned to the lactic acid plant.

A purer source of cellulose without lignin is waste paper that can be used for lactic acid production at lab scale [56]. Thus, even this book can eventually be converted into PLA!

Complete utilization of cellulose and hemicellulose requires selection or genetic modification of an organism that is able to ferment pentoses. In order to obtain monosaccharides from the raw material, several pretreatments and/or separations are required. First, the lignocellulosic material is mechanically treated and then delignified (pulped) by strong alkali or acid treatment. The (hemi)cellulose part becomes more accessible for enzymes at the same time. Subsequent enzymatic treatment mainly yields glucose and xylose and some arabinose. The enzymatic treatment and subsequent fermentation can be done in separate reactors or in one fermenter, in an SSF concept similar to starch SSF [57].

1.2.4.8 Batch versus Continuous Fermentation A process can be run in batch or continuous mode. In continuous mode, there is a constant flow of fermented sugar out of the reactor that is equal to a continuous flow of fermentation medium into the reactor. During batch fermentation, there can be an inflow of medium, but there is no outflow [58]. Batch fermentation needs to be inoculated with a starter culture every time, whereas this is not needed in a continuous fermentation setup. However, in case of problems, the continuous fermentation needs to be restarted, so an infrastructure for starter cultures is needed anyway. A high volumetric production rate can be achieved when combining continuous fermentation with biomass retention, leading to smaller fermenter size [59]. It must be stated that the lactic acid concentration is lower compared to batch culture [58]. The concentration of lactic acid influences the water balance in the production plant.

In all scenarios, microorganisms produce an aqueous lactic acid solution, comprising mainly lactate and counterions from the base, impurities from raw materials or fermentation by-products, residual sugars and polysaccharides, and the microorganism itself.

1.2.5 Downstream Processing/Purification of Lactic Acid

When Scheele discovered lactic acid, he recovered and purified the lactic acid from sour whey by saturation with lime, filtering off the crude calcium lactate, acidifying the crystal mass with "acid of sugar" (oxalic acid), filtering off the calcium oxalate, and evaporating to obtain a crude viscous lactic acid [12, 13]. Basically, this process with a calcium-based neutralized fermentation and sulfuric acid instead of oxalic acid is the same process used in industry today for the production of crude lactic acid. Drawbacks are the continuously rising costs of lime/chalk, sulfuric acid, and other chemicals and the disposal of large quantities of gypsum ($CaSO_4 \cdot 2H_2O$), as an unavoidable side product of this technology.

In such a process also the first down stream processing (DSP) step, biomass removal by filtration, can be accomplished relatively easily in a (mild) liming step, in essence quite similar to the traditional liming step to remove protein in sugar beet or sugarcane processing in sugar mills. A simplified block scheme of the traditional lactic acid production process including fermentation is shown in Figure 1.5.

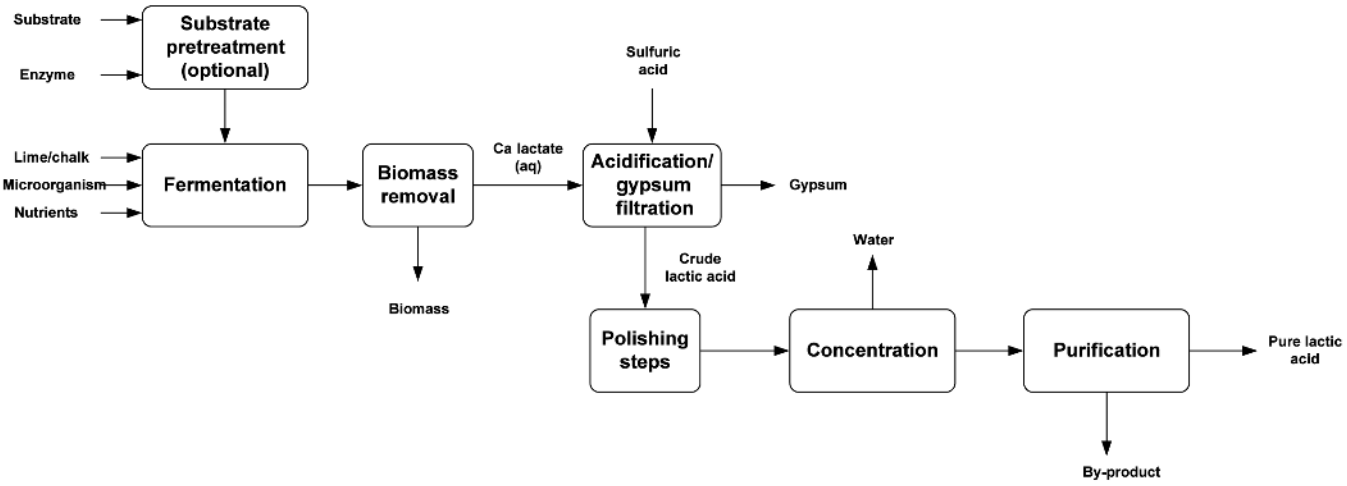

FIGURE 1.5 Simplified block scheme of traditional lactic acid production process.

TABLE 1.2 Summary of Lactic Acid Purification Methods

Lactic Acid Purification Method	Advantages	Disadvantages
Crystallization [27, 28]	Highly pure lactic acid product	Amount of mother liquor by-product, scalability
Esterification/distillation [52]	Highly pure acid, scale-up	Relatively high utility cost, amount of residue as by-product
Lactic acid distillation [27, 28, 53]	Good splitting for heavy compounds	Amount of residue as by-product
Extraction [54, 55]	Potentially high yield	Complex (e.g., for emulsion, entrainment issues), extractant cost

1.2.5.1 Purification Methods for Lactic Acid Crude lactic acid, which may be upgraded by simple active carbon treatment and/or ion exchange to remove impurities and salts, can be directly used in a large number of food applications. Traditionally, taste, smell, and heat stability for color formation have been used to express lactic acid quality. The presence of acids (e.g., acetic acid and pyruvic acid), alcohols (e.g., methanol and ethanol), and esters can directly influence taste and smell [4]. The presence of residual sugar and nitrogen compounds greatly influences heated color, that is, browning of the liquid upon heating. The formation of color upon heating prohibits the use of crude acid in foods that need to undergo pasteurization/sterilization. Over the decades, the demand for purer lactic acid with improved color stability upon heating has increased, as exemplified by the need for ultrapure lactic acid as a sodium lactate base in pharmaceutical infusion products. At present, a chemical engineer can choose from a number of mature industrial methods to purify lactic acid. Table 1.2 lists their relative advantages and disadvantages.

Choices in an overall process are governed by raw material costs, utility costs, and, last but not least, outlets for by-products.

The purification methods described above each involve considerable technological know-how:

- *Esterification/Saponification*. Esterification of lactic acid with methanol/ethanol yields systems with good separation characteristics to separate many impurities with different boiling points [60]. However, the energy demand of a full reaction/distillation route from crude acid to pure acid is high.
- *Crystallization*. Crystallization can yield an excellent lactic acid grade, but the yield is low.
- *Lactic Acid Distillation*. Industrial equipment is available to distill lactic acid at low vacuum. Higher molecular weight components such as sugar and protein will leave the system as a residue. Heat-stable lactic acid is obtained as the top product. In the stages of dewatering the crude lactic acid prior to distillation, the formation of oligomers will limit an overall high distillation yield.
- *Extraction*. An extraction/back-extraction process, for example, with the well-described tertiary amine systems, is a suitable way to purify lactic acid [61, 62]. The possible combination of extraction with low-pH fermentation yields an elegant concept to arrive at a gypsum-free process.

For future large-scale, low-cost lactide/PLA production, lactic acid DSP will need to meet new challenges:

- *Use of Low-Cost and Nonedible Substrates*. Whereas production of lactic acid from sucrose or glucose syrup is well established, crude sources (starches, sugars, or future lignocellulose hydrolysates) will form the next hurdle as they contain much more impurities and possible fermentation inhibitors.
- *Gypsum-Free Processing*. For large-scale, sustainable PLA production, a fermentation process that does not coproduce a mineral salt is a must.

1.2.5.2 Gypsum-Free Lactic Acid Production Gypsum-free lactic acid production can be briefly categorized as follows:

- *Low-pH Fermentations Coupled to In Situ Product Removal*. As discussed in Section 1.2.4, fermentations can be carried out without neutralization at pH 2–3 with genetically modified yeast or at pH 4 with LAB with partial neutralization [50]. When a separation method to recover the undissociated acid is integrated with fermentation, a process route can be designed in which no gypsum is produced. In the literature, a number of separation methods are described with an emphasis on extraction [63]. Cost efficiency in the fermentation (e.g., nutrients, yield) and the practical processing of large dilute streams need breakthroughs for economical processing.
- *Electrochemical Splitting of a Neutral Lactate Salt*. Numerous articles have described the splitting of a lactate salt, notably sodium lactate, into lactic acid and the original base [64]. With this principle, a gypsum-free process can be designed, with electrodialysis

separate from or integrated with fermentation. The use of electrodialysis with new bipolar membranes is straightforward, but a large-scale commercial breakthrough as in the 1980s and 1990s with monopolar membranes for the chloro-alkali process is still pending. Electrodialysis involves relatively high electricity costs and a huge membrane area, but these costs may be managed in biorefinery concepts with integrated energy production.

- *Chemical Salt Splitting of a Lactate Salt*. Lactate salts can be split with the help of auxiliary chemicals and the regeneration of these chemicals. A patent by Baniel et al., for example, describes a method in which a sodium lactate solution is acidified with CO_2 under pressure, and simultaneously undissociated lactic acid is extracted and insoluble sodium bicarbonate ($NaHCO_3$) is formed [65].

Another patent describes the splitting of ammonium lactate by esterification with butanol while liberating ammonia [66]. In the distillation process, the butyl lactate can be hydrolyzed with water to liberate lactic acid. This is an interesting option, but the energy consumption and side reactions such as the formation of lactamide and racemization require attention.

Chemical salt splitting processes with the recycle of chemicals can be complex, but it is a challenge to develop a system with straightforward chemistry, high yield, low energy consumption, and good scaleability.

1.2.5.3 Modern Industrial Methods In overall process development, knowledge about dealing with impurities will be important. Residual sugar in the broth and sugar degradation products play a role throughout the process at the various levels of temperature and acidity. Color may be formed at any step from low- to high-boiling color precursors. Volatile acids such as acetic acid and formic acid will partition throughout DSP and their concentration in recycle streams must be prevented.

In the design of a modern lactic acid plant, mathematical models are indispensable. For example, the kinetic model of oligomerization of lactic acid and the right thermodynamic model for the gas/liquid equilibria are important in design for the concentration of lactic acid by evaporation as well as for prepolymerization in the lactide route.

Lactic acid solutions and vapors are quite corrosive and knowledge of the material of construction is a must for a low-maintenance plant. Also, wastewater treatment is an integral part of a lactic acid plant. Aerobic systems are state of the art, but anaerobic systems are increasingly used to treat acid-containing wastewater streams. The biogas can then be profitably used for steam production. While a plant using sucrose has a net intake and net purge of water, future plants using crude, low-cost, water-rich substrates will need to pay more attention to the water balance and wastewater treatment.

Although the fermentation industry can be considered traditional, new technologies may quickly find uses. The rapid commercial application of filtration techniques such as in membrane bioreactors in wastewater treatment and the fast introduction of nanofiltration for making process water from river water are examples. The discovery of ionic liquids with high distribution coefficients for lactic acid in dilute solutions may lead to breakthroughs [67]. New steam boiler concepts that can handle residues can drastically change DSP layout in energy-efficient integrated biorefineries.

1.2.6 Quality/Specifications of Lactic Acid

The dehydration of lactic acid to make the prepolymer should start with an $-$OH to $-$COOH ratio of 1:1. All other components with $-$OH and $-$COOH functionality disrupt the stoichiometric balance and may be incorporated as comonomers during prepolymerization, which limits the final lactide production yield from lactic acid. Little public information is available on the technical and economic relationship between lactic acid quality and lactide synthesis. Only a few patents mention the effect of metal impurities on racemization [68, 69]. Stereochemical purity is one of the key parameters determining lactic acid purity.

Lactic acid purified by crystallization may be taken as the benchmark in lactide manufacture, but the expected unfavorable economics of making crystalline acid in relation to mother liquor processing may prevent its commercial use for lactide/PLA. The next level of quality with the right commercial relevance is heat-stable lactic acid. Heat stability puts constraints on the content of sugar, and thus on the DSP method used in the process. It is unlikely that suitable acid for making lactide will contain sugar because of the high temperatures involved (see the next section) and the well-known practical decomposition problems when sugars are cracked. In practice, this means that color, or actually heated color (color after heating of the acid), is an important indicator for the suitability of the acid for lactide/PLA production [6, 70]. The appeal for lactic acid with little or no sugar and the DSP methods mentioned in practice lead to demands for separation methods that are similar for sugar and other heavy components such as proteins, amino acids, and polysaccharides.

It is expected that the desired quality of lactic acid for making lactide/PLA will evolve, with overall process yields and economics as the criteria.

1.3 LACTIDE

1.3.1 Physical Properties of Lactide

The dehydrated, cyclic dimer of lactic acid is commonly called lactide (3,6-dimethyl-1,4-dioxane-2,5-dione). Due to

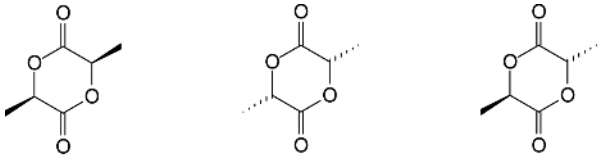

FIGURE 1.6 The three diastereomeric structures of lactide (3,6-dimethyl-1,4-dioxane-2,5-dione).

the two asymmetric carbon atoms in the molecule, lactide exists in three different forms (Figure 1.6).

In addition to the three diastereomeric structures mentioned above, also a racemate of D-lactide and L-lactide exists: *rac*-lactide or DL-lactide (Table 1.3).

1.3.2 Production of Lactide

The synthesis of lactide was first described by Pelouze in 1845 [71]. He investigated the self-esterification of lactic acid by heating and driving off water and obtained a prepolymer that was no longer fully miscible with water. Upon continued heating of the prepolymer, he noticed that in a certain distillate fraction nice crystals were formed. He was able to deduce the chemical formula and gave the name "lactid" to the substance. An improved procedure was described in a patent by Gruter and Pohl in 1914 [72]. Lactic acid was self-esterified at 120–135°C, and air was drawn in to remove the water. Next, zinc oxide was added as a catalyst and lactide was distilled off under vacuum at 200°C. In practice, modern industry cannot dispense with this concept of thermal catalytic depolymerization for lactide production. A major step forward was the use of a tin catalyst, a frequently used coordinating catalyst in polymerizations, in the process. The general scheme of lactide manufacture including the purification is shown in Figure 1.7.

In the past two decades, several papers have appeared on lactide manufacture [73, 74]. A main underlying problem in understanding all information is that the reaction from oligomer to lactide is an equilibrium reaction. In order to pull the reaction toward the right, lactide must be withdrawn from the system. In reaction engineering terms, this means that the chemical kinetics of the reaction cannot be understood without consideration of the method and efficiency of lactide removal. In terms of know-how described in patents, this means that reported lactide production rates depend to a large extent on the geometry of the equipment in which lactide synthesis is performed and that provides for removal of lactide vapor from the reaction zone.

In modern chemical technology, one of the goals is to fully understand a given system, capture the knowledge in models to describe experimental work, and ultimately use these models to design, optimize, and debottleneck large-scale

TABLE 1.3 Physical Properties of the Lactides

	Unit	D-Lactide	L-Lactide [6]	*meso*-Lactide	*rac*-Lactide
CAS number		13076-17-0	4511-42-6	13076-19-2	116559-43-4
Molecular weight	g/mol	144.12	144.12	144.12	
Melting point	°C	96—97	96	53 [64]	125 [6]
Boiling point	°C				142 (20 mbar) [64]
Heat of fusion	J/g		146	128 [64]; 118 [6]	185 [6]
Heat of vaporization	kJ/mol		63		
Solid density	g/mL		1.32–1.38	1.32–1.38 [6]	
Liquid viscosity	mPa s		2.71 (110°C); 2.23 (120°C); 1.88 (130°C)		

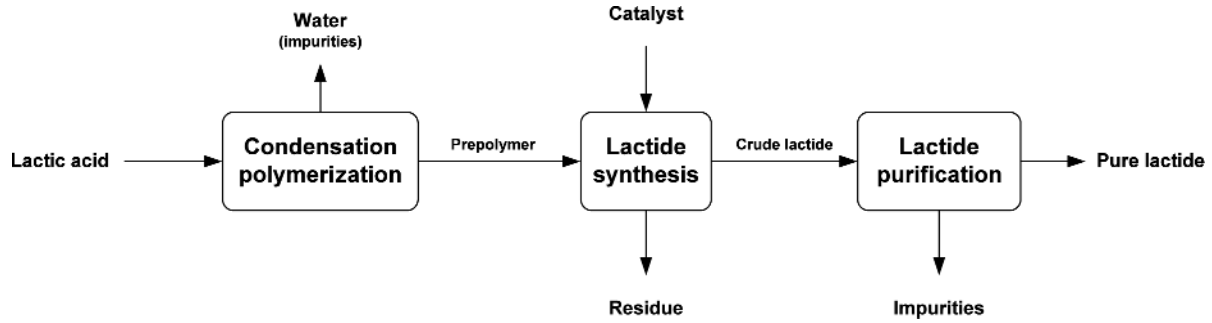

FIGURE 1.7 Schematic illustration of lactide manufacture by thermal catalytic depolymerization of lactic acid oligomers.

equipment. For the present system, this means that one must develop process know-how on chemical kinetics and thermodynamics of lactide and HL oligomers, and on physical phenomena related to equipment design.

These aspects will be relevant for both the prepolymerization and the synthesis of lactide, as these chemical systems are highly similar. In practice, however, lactide synthesis is more complex as chemistry, recovery and type of equipment are intertwined, and the viscous nature of reaction mixtures requires special attention.

With these aspects in mind, the information on the lactide synthesis that can be found in the literature is summarized below.

1.3.2.1 Prepolymerization A general procedure for batch prepolymerization is described in a patent by O'Brien et al. [75]. Typically, vacuum pressures of 70–250 mbar and temperatures up to 190°C are used to dewater lactic acid to a prepolymer with an average degree of polymerization (DP) of around 10 in a batch process time of 6 h. For lab-scale equipment, it was also found that thin film and rotating flask vacuum equipment showed faster reaction times than a stirred tank, indicating the importance of mass transfer of water in the already viscous prepolymer.

Continuous prepolymerization has also been described in a number of patents, for example, in stirred tanks in series or in evaporator-type equipment [68, 76, 77]. Usually patents describe prepolymers with a DP of 7–20 as feed to the lactide synthesis. Using modern HPLC methods, it has been shown that in oligomeric systems up to DP 10, an equilibrium is present with constant equilibrium constants between the oligomers [6, 72].

1.3.2.2 Lactide Synthesis During Prepolymerization Because the composition of a mixture comprising lactic acid oligomers and lactide is governed by chemical equilibria, a prepolymerization exhibits relatively high concentrations of lactide (HL_2–H_2O–L_2 equilibrium) around DP 2. Sinclair et al. distilled these fractions to recover lactide, but the crude lactide was quite impure, which may prevent economical processing [73]. In hindsight, the patent describes trials to optimize Pelouze's original lactide synthesis without catalyst [71].

1.3.2.3 Basic Research on Batch Lactide Synthesis and the Catalysts Used Noda and Okuyama reported on the batch synthesis of lactide from DP 15 prepolymer with various catalysts at 4–5 mbar and 190–245°C [74]. In a batch synthesis with 50 g of oligomer in a stirred flask, the evolution rate of crude lactide is rather constant and then starts to decline and the conversion levels off at 80–90%. The tin catalyst performed best compared to other catalysts and showed the lowest levels of racemization. Tin octoate (stannous 2-ethylhexanoate) is a liquid catalyst that can be handled easily, is food grade, and is widely available.

Thinking in terms of mechanisms, the equilibrium concentration of lactide in an oligomer mixture is 5% or less, and it will boil off at low vacuum [6, 68]. The catalyst increases the rate of lactide formation by facilitating lactide formation by backbiting from hydroxyl chain ends of oligomers [4, 74]. In a batch experiment, the rate is initially constant, but during synthesis esterification also occurs, and the DP of the polyester rises concomitantly. The melt viscosity of the reaction mixture increases accordingly and at the end of a batch process, mixing the highly viscous residue becomes very difficult, which limits the extent to which the residue can be depleted of lactide.

In engineering terms, this means that mass transfer of lactide from the liquid to the gas phase decreases as viscosity increases. The balance between lactide production and lactide removal plays a role in all experiments that one might want to investigate on lab scale. For example, catalyst concentrations of 0.05–0.2 wt% tin(II) octoate are mentioned in the literature, but traditional experiments to verify the order of the reaction for the catalyst are difficult because of the influence of mass transfer limitations.

1.3.2.4 Continuous Synthesis In 1992, Gruber et al. [68] described a continuous lactide synthesis in which prepolymer is fed continuously to a reactor, crude lactide is evaporated under vacuum, and residue is removed. Typical operating conditions for the reactor were residence time around 1 h, vacuum pressure 4 mbar, temperature 213°C, and catalyst amount 0.05 wt% tin(II) octoate on feed. The conversion per pass was around 70%, and the overall yield was increased by recycling the residue to the lactic acid section of the process, where the oligomers are hydrolyzed again.

Especially in the patent literature, several different reactor types are described for continuous lactide synthesis:

- Stirred tank reactor with different stirrer types [76]. On a bench scale, the reactor is jacketed for heating.
- Stirred reactor with a distillation section on top of the reactor to fractionate the product [50].
- Thin film evaporator with a typical conversion of 80% on pilot scale [70].
- Horizontal wiped film evaporator. In a patent by Kamikawa et al. [77], the use of horizontal wiped film is described. In the horizontal mode, the residence time of the reaction mixture can be controlled and a conical form is used in which wipers transport the viscous residue.
- Distillation column. In a patent by O'Brien et al. [75], a distillation column with perforated plates and optional use of packing material and heating on the stage are described. In an experiment with a single tray, a DP 10 feed was fed to the top, and N_2 was used to strip the

lactide from the liquid. At different residence times, the conversion on the tray could be as high as 93% at 210–215°C. In other patents, the use of N_2 gas as a stripping agent is mentioned, but it is to be expected that in large-scale equipment the processing of large amounts of inert gases will be less economical compared to the use of vacuum systems.

Reviewing the literature provides a list of process aspects that need consideration in the design of a solventless synthesis operated with vacuum equipment.

- *Temperature*. Intrinsic reaction rates increase with temperature. At higher temperature also, the vapor pressure of lactide above the reaction mixtures increases. The reaction rate of racemization will also increase with temperature. In Witzke's Ph.D. study, information on activation energies can be found [6].
- *Pressure*. Pressures of 10 mbar or less are used. At higher pressures, the driving force for lactide evaporation will be lower, and the overall reaction rate will be lower. Low pressures will require detailed considerations of equipment size, vacuum systems, condensers, and so on.
- *Feed DP*. The feed DP has two effects. First, a low DP feed will contain more monomer lactic acid that boils at a lower temperature than lactide, and this will contaminate the crude lactide distilled off from the reactor. Also, monomer lactic acid can be released from DP 3 with the catalyst, leading to more acidity in the crude lactide. Second, it is to be expected that at a higher feed DP the residue in the reactor will have a higher DP and viscosity with consequences for equipment design. The influence of prepolymer DP on the *meso*-lactide level formed during lactide synthesis was discussed by Gruber et al. [69]. Increasing feed DP clearly resulted in a decrease in the lactic acid concentration in the crude lactide. A drawback is that the *meso*-lactide concentration also increased significantly.
- *Catalyst Concentration*. More catalyst will increase the overall reaction rate. In practice, this effect may not be linear, since next to kinetics mass transfer in the equipment will play a role.
- *Racemization*. In the production of stereochemically pure lactide, formation of the other lactic acid enantiomer and *meso*-lactide is unwanted. Higher temperatures, longer reaction times, and increased catalyst levels result in increased rates of racemization [4, 6, 69]. Since temperature and catalyst influence the rate of lactide formation as well, controlling the racemization rate can become quite complex.
- *Impurities*. Data in the literature on the role and fate of impurities from the feed in the synthesis are scarce. Some metal cations such as sodium and potassium in the feed increase racemization risk, while other metals (Al, Fe) are catalytically active in transesterification, resulting in competitive polylactide formation [68, 69]. Through corrosion, metals may be released in the residue and will build up there [6, 75]. Some patents discuss the presence of acid impurities in the process [6, 7, 67, 78]. Mono- and dicarboxylic fermentation acids are responsible for stoichiometric imbalance in the lactic acid polycondensation reaction. Consequently, the composition of the obtained lactic acid oligomer chains can differ from pure PLA, resulting in impeded and incomplete catalytic depolymerization of the oligomers into lactide. In PLA manufacture, degradation reactions play a role, mainly via *intramolecular chain scission*, and this may also affect lactide synthesis.

On the one hand, it can be concluded that the lactide synthesis is straightforward in the sense of making a prepolymer and releasing lactide by thermal catalytic depolymerization at low pressure. On the other hand, it can be concluded that the scale-up from a lab-scale process to an economical, large-scale process with high yield and no compromises on stereochemical purity is a complex multifaceted task.

1.3.3 Purification of Lactide

A lactide synthesis reactor invariably produces a crude lactide stream that contains lactic acid, lactic acid oligomers, water, *meso*-lactide, and further impurities. The specifications for lactide are stringent mainly for free acid content, water, and stereochemical purity. Basically, two main separation methods, distillation and crystallization, are currently employed for lactide purification:

- *Distillation*. Splitting the multicomponent mixture consisting of lactide, water, lactic acid, and its oligomers into pure fractions requires considerable know-how on kinetics and operation of vacuum equipment. Distillates and bottoms may be recycled, but the accumulation of impurities from the feed or the production of *meso*-lactide during the process requires careful fine-tuning of temperatures and residence times. Distillation is well described in the patent by Gruber et al. in 1993 [68]. The crude lactide from the synthesis is distilled in the first column to remove the acids and water, and then *meso*-lactide is separated from lactide in the second column. As the boiling points of all compounds are in the range of 200–300°C, low pressures are used. Since the difference in boiling temperature of lactide and *meso*-lactide is quite small, this distillation requires a lot of theoretical stages (>30). The Cargill/NatureWorks distillation uses a series of distillation

columns and is performed continuously [4]. Part of the distillation can also be integrated with the reaction [79].

- *Solvent Crystallization*. A commonly used laboratory method for lactide purification is recrystallization from mixtures of toluene and ethyl acetate [4]. Lactide of extremely high purity can be obtained by repeated crystallization with different toluene/ethyl acetate ratios. Several patents also mention the use of solvents for the crystallization of lactide, but for large scale, melt crystallization without the use of solvents is preferred.
- *Melt Crystallization*. Lactide crystallizes easily and several patents describe how crystallization can yield lactide with required specifications regarding lactic acid content, oligomers, *meso*-lactide, and water. An early patent describes such a crystallization method and includes some information on the thermodynamic equilibria (eutectica) of the lactide/lactic and the lactide–*meso*-lactide system, which define the maximum yield as a function of these impurities in the feed [80]. In patents, the use of different types of equipment is mentioned: static equipment, falling film crystallizers, vertical column with scraper to remove crystal mass from the cooled wall, and scraped heat exchanger coupled to a wash column [70, 80, 81]. For large scale, it is a challenge to design and scale-up the crystallization equipment with respect to the needed heat transfer areas and hydrodynamics, and the possible increase of viscosity of mother liquor by oligomerization of lactide and residual acid.

The choice between distillation, crystallization, or novel separation methods such as absorption or membrane separation is determined by the desired stereochemical purity of the product. Crystallization yields highly pure lactide, suitable, for example, for high-melting PLLA homopolymer of high molecular weight. Affordable distillation equipment does not fully remove all *meso*-lactide, and consequently, a lactide monomer mixture for PLA copolymers with other thermal properties is obtained upon ring-opening polymerization.

The design of the separation system relies on detailed knowledge of the thermodynamic properties of the compounds and the kinetics of the reactive system. Obtaining such know-how requires sophisticated analytical methods for lactic acid and its oligomers, lactides, and residues. Impurities can also be formed in lactide synthesis, similar to PLA degradation reactions, and gas chromatography (GC) methods are needed to identify these compounds and determine their fate in the process.

1.3.4 Quality and Specifications of Polymer-Grade Lactide

The specifications and allowed impurity levels of lactide monomer for PLA are defined by the polymerization mechanism and the applied catalyst. PLA is commercially produced by ROP of lactides in bulk. The tin(II)-catalyzed process offers good control over molecular weight and reaction rate provided that it is performed in the absence of impurities such as water, metal ions, lactic acid, or other organic acids. Purification of crude lactides is therefore indispensable for the industrial manufacture of high molecular weight PLA ($M_w > 100$ kg/mol). In fact, lactide is the ultimate form of lactic acid, in its dehydrated and purest form.

1.3.4.1 Role of the Catalyst and Initiator in Lactide Polymerization The theoretical description of the $Sn(Oct)_2$-catalyzed ROP of cyclic esters has been studied by many authors, but there does not appear to be a theory that consistently explains all experimental results of the coordination–insertion polymerization [3, 4, 82–84]. Different polymerization mechanisms may dominate, depending on polymerization conditions, catalyst and initiator concentration, and the presence of a solvent.

Here it is assumed that lactide is polymerized in bulk with $Sn(Oct)_2$—a Lewis acid—and that the mechanism follows the model proposed by Kowalski et al. [84]. Since lactide is a cyclic ester, its ring can be opened by nucleophilic attack on the ester bond to start polymerization. Suitable initiators (nucleophiles) are water and alcohols, including the hydroxyl group of lactic acid. One ester linkage of a lactide ring is cleaved by reaction of the OH group of the initiator R-OH, creating a new R-O-C(O)- ester end group and an OH end group (Figure 1.8).

Every initiating molecule is covalently bonded as an end group to each polymer chain [84]. Via transesterification

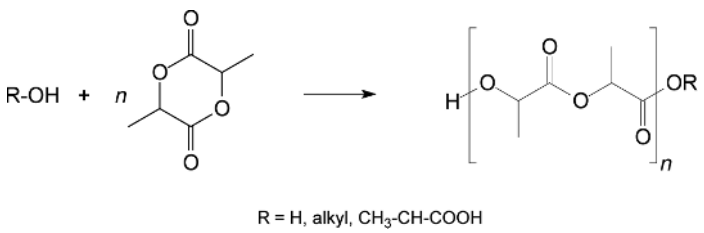

FIGURE 1.8 Ring-opening polymerization of lactide to PLA initiated by an alcohol.

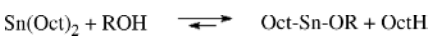

FIGURE 1.9 Equilibrium reaction of tin octoate with alcohol initiator or impurities to form catalytically active tin alkoxide bonds Sn-O-R [76].

reactions, the 2-ethylhexanoate ligands of the $SnOct_2$ catalyst will also end up as octanoic ester groups in the polymer. In some papers, the Sn(II) catalyst is indicated as the initiator, presumably because lactide also polymerizes upon addition of that substance, and the effect of impurities is overlooked. An initiator—or *coinitiator*—is a substance that can start polymerization, in the case of lactide by opening the lactide ring, and thus offers control over molecular weight. This has to be a nucleophile and cannot be the Sn catalyst itself, as supported by the excellent work of Kowalski et al. who proved that $SnOct_2$ needs activation with R-OH (Figure 1.9) [84].

In a nutshell, the total hydroxyl content, including R-OH initiator and lactic acid impurities, determines the maximum attainable M_n (number-average molecular weight) [4, 6]. The rate of polymerization is controlled by factors such as temperature and catalyst content, with the remark that a tin (II) octoate catalyst requires traces of the initiator to become active.

1.3.4.2 Alcohols If water is the initiator, R equals H and hydrolysis of lactide produces lactoyl lactic acid (HL_2). Propagation with lactide in the presence of a polymerization catalyst produces PLA with a hydroxyl and one carboxylic acid end group, as if the PLA was obtained by polycondensation of lactic acid.

If the hydroxyl group of lactic acid acts as an initiator, PLA with one hydroxyl end group and a lactic acid end group ($HOOC\text{-}CH(CH_3)\text{-}O\text{-}C(O)\text{-}$) is obtained.

If the initiator itself is polymeric in nature, for example, polyethylene glycol (PEG), lactide can polymerize from the hydroxyl end group(s) of PEG resulting in PEG–PLLA diblock or triblock copolymers.

The molar ratio of monomer to initiator (M/I)—where initiator can also be read as total hydroxyl content—basically controls the final, average molecular weight (M_n) of the PLA. A high amount of initiator produces short polymer chains, and a low amount of initiator produces high molecular weight polymer. The lower the amount of potentially initiating hydroxyls in the lactide monomer, the higher the maximum attainable degree of polymerization [69]. Since water and lactic acid can both cause ring scission of the lactide and initiate polymerization, their amounts in the lactide must be low and should be specified.

1.3.4.3 Carboxylic Acids Carboxylic acids are poor initiators, but they are believed to interfere with the commonly used Sn(II) polymerization catalyst. According to Kowalski, carboxylic acids may suppress the rate of polymerization by shifting the equilibrium between ROH and $Sn(Oct)_2$ to the inactive $Sn(Oct)_2$ side [83, 84]. Consequently, longer polymerization times are needed to achieve the desired molecular weight, accompanied by unavoidable degradation caused by the extra residence time at high temperature in the presence of a catalyst [84].

The effect of carboxylic acids on lactide polymerization rate was published in 1993 in patents by Ford and O'Brien [78, 85]. The results clearly show the dramatic rate-decreasing effect of organic acids: according to O'Brien, melt polymerization slows down by a factor of 2 upon increasing free acidity from less than 2 to between 2 and 4 meq/kg [85].

Witzke, however, states that the presence of lactic acid did not negatively influence polymerization rate [4, 6]. Lactic acid is therefore a practically used initiator that is already present in lactide as an impurity.

Lactic acid and its oligomers have a hydroxyl group and a carboxylic acid group. Consequently, a free acidity of 10 meq/kg—that is, 900 ppm expressed as lactic acid equivalents—in lactide corresponds to a hydroxyl concentration that limits M_n to 100 kg/mol. Free acidity of 4 meq/kg sets a theoretical limit of 250 kg/mol to M_n.

Free acid and water content specifications are essential for any lactide grade; the lower the amount of hydroxyl impurities, the better the storage stability and product properties of the lactide.

1.3.4.4 Metals Metal cations such as Sn, Zn, Fe, Al, and Ti not only accelerate polymerization, but can also affect hydrolysis, oxidation, racemization, or other degradation mechanisms of PLA and lactides [4, 6]. Consequently, the lactic acid used for lactide preparation should be very low (ppm) in metal cations in order to avoid considerable racemization during lactide synthesis.

O'Brien has shown that the formation of dark color of lactide was a direct function of the iron content of the material in which the lactide was in contact [86]. Other examples in the patent (Examples 7 and 8) demonstrate the desirability of having low alkali (e.g., sodium) content and minimizing the depolymerization temperature.

Cationic impurities such as sodium ions have no direct effect on lactide production rate, but the sodium content has a direct correlation with the *meso*-lactide content in the crude lactide [67, 87].

1.3.4.5 Stereochemical Purity The higher the stereochemical purity of the lactide monomer, the higher the stereochemical purity of the obtained PLA, which controls material properties such as melting point, crystallinity and crystallization rate, and mechanical strength [8, 9, 88].

The strong dependence on D-isomer content presents an opportunity to control polymer properties. NatureWorks

Ingeo PLA is easily processable and suitable as amorphous biopackaging material as a result of its relatively high *meso*-lactide content. The downside is the poor resistance to elevated temperatures (low *heat distortion temperature*, HDT) during transportation, storage, and use of articles produced from this bioplastic. *meso*-Lactide—which contains an L- and a D-isomer—is an unavoidable side product of lactide production and must be separated from L- and D-lactides of high stereochemical purity.

Kolstad [9] investigated the crystallization behavior of copolymers of L-lactide and *meso*-lactide. He found that every 1% of *meso*-lactide comonomer—or D-isomer—causes a 3°C reduction in the melting point of the PLA copolymer. With 3% *meso*-lactide in PLA, crystallization is more than two times slower than PLLA under the same conditions. With 6% *meso*-lactide incorporation, the difference can be up to 10 times!

This underlines the need for a low *meso*-lactide content in the monomer mixture for semicrystalline PLA, because *meso*-lactide formation by racemization cannot be avoided during melt polymerization of lactides. According to Gruber and coworkers, racemization, which lowers the stereochemical purity of the PLA, is believed to be driven by factors such as temperature, pressure, time at a given temperature or pressure, the presence of catalysts or impurities, and relative concentrations of the two enantiomers at any given time during the polymerization process [88].

PLA grades for more demanding applications that require better heat resistance are achievable by stereocomplexation with PDLA [89]. This is only effective with PLA grades of high stereochemical purity. In order to prepare high-quality PLA, it is necessary to start with lactide monomers with the highest possible stereochemical purity, that is, the lowest *meso*-lactide content that is technically and economically achievable by purification.

D-Lactide can be obtained if one has the appropriate biochemistry to produce the D-enantiomer of lactic acid by fermentation of carbohydrates. Copolymerization of controlled mixtures of L- and D-lactides subsequently offers the advantage of precise control over PLA properties. Moreover, D-lactide is the monomer for the production of poly(D-lactide), which is able to form high-melting stereocomplex PLA via 1:1 racemic cocrystallization with P(L)LA, as will be discussed in Chapter 5 [89].

1.3.5 Concluding Remarks on Polymer-Grade Lactide

In conclusion, the most important quality specifications for lactide monomers are those of free acidity, water, metal ion content, and stereochemical purity.

- *Free acidity*, for example, lactic acid or lactoyl lactic acid, slows down the rate of polymerization and limits the achievable degree of polymerization. According to the patent literature, free acidity of polymer grade lactide should be <10 meq/kg, and preferably no more than 5 meq/kg.
- *Water* causes hydrolysis of lactide and also limits the attainable degree of polymerization of PLA.
- *Metal ions* need to be specified in low quantities, because Sn, Zn, Fe, and Al cations accelerate polymerization, but may also affect hydrolysis, oxidation, or other degradation mechanisms. Sodium in particular causes racemization even in ppm amounts.
- *Stereochemical purity* expresses the sum of *meso*-lactide and D-lactide in L-lactide and vice versa. The higher the stereochemical purity of the lactide monomer, the higher the stereochemical purity of the obtained PLA, which controls material properties such as melting point, crystallinity, and mechanical strength.

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