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Ring-Opening Polymerization Strategies for Degradable Polyesters

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7.1 Introduction

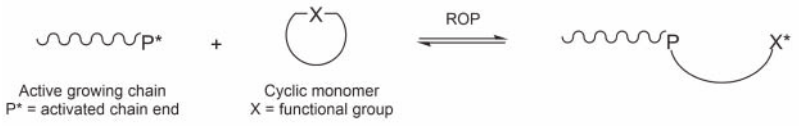
Polymer synthesis by ring-opening polymerization (ROP) dates back to the early 1900s when Leuchs (1906) described the synthesis of *N*-carboxyanhydride, which could be polymerized by ROP to prepare polypeptides [1]. Later (1918), ROP was applied in the synthesis of polysaccharides starting from anhydro sugars [2]. In 1932, Carothers et al. [3] described the first ROP of lactide (LD) to obtain what is now one of the most prominent polyester bioplastics on the market, poly(lactic acid) (PLA). In 1954, this method was patented by Du Pont [4] and, until the late 1970s, mainly used in the context of biomedical applications, due to its particularly costly production at the time [5]. In addition to the synthesis of PLA and other polyesters such as poly(ε-caprolactone) (PCL) and poly(glycolic acid) (PGA), contemporary ROP is used to supply industry with a number of other essential polymer materials, including polyethers (such as poly(oxy methylene), poly(ethylene glycol), or poly(tetrahydrofuran)), polysiloxanes, polyphosphazenes, poly(cyclooctene), poly(norbornene), poly(ethylene imines) made from aziridine or oxazoline monomers and several polylactams, such as Nylon 6 [6, 7].

ROP is a chain-growth polymerization reaction in which a cyclic monomer is added to a growing polymer chain by ring-opening the monomer via a reaction with the active terminal group of this polymer (Figure 7.1a). The type of cyclic monomer, as well as the catalyst/initiator system used, will determine the nature of the resulting active end-group of the growing chain. The nature of the resulting end-group then determines the type of mechanism through which the polymerization reaction will take place. The most important ROP mechanisms include radical, ionic (cationic or anionic), coordination–insertion, metathetic, and enzymatic [8].

A wide variety of cyclic molecules can react via one or more ROP mechanisms. Some general structures that are amenable to ROP include cyclic alkanes and alkenes as well as molecules containing heteroatoms in the ring, such as oxygen

Biodegradable Polymers in the Circular Plastics Economy, First Edition.
Edited by Michiel Dusselier and Jean-Paul Lange.

(a)



(b)

Oxygen		Nitrogen		Sulfur		Phosphor	
Function	—X—	Function	—X—	Function	—X—	Function	—X—
Ether	—O—	Amine	—NH—	Thioether	—S—	Phosphine	—P(R)—
Acetal	—O—C(R,R)—O—	1,3-Oxaza	—O—C(H,H)—N(H)—	Thiolactone	—S—C(=O)—	Phosphinate	—P(R)(=O)—O—
Lactone	—O—C(=O)—	Lactam	—N(H)—C(=O)—	Thionolactone	—O—C(=S)—	Phosphonite	—O—P(R)—O—
Carbonate	—O—C(=O)—O—	Urea	—N(H)—C(=O)—N(H)—	Thiocarbonate	—O—C(=S)—O—	Phosphite	—O—P(OR)—O—
Anhydride	—C(=O)—O—C(=O)—	Imide	—C(=O)—N(H)—C(=O)—	**Silicium**		Phosphonate	—O—P(=O)(R)—O—
		N-carboxy-anhydride	—N(H)—C(=O)—O—C(=O)—	**Function**	**—X—**	Phosphate	—O—P(=O)(OR)—O—
				Silane	—Si(R,R)—	Phophazene	—N=P(R,R)—N=
				Silaether	—Si(R,R)—O—		
				Siloxane	—O—Si(R,R)—O—		

Figure 7.1 (a) The general mechanism of ring-opening polymerization, (b) Functional groups (–X–) of cyclic monomers used in ROP.

(ethers, acetals, esters [lactones and carbonates], and anhydrides), nitrogen (amines, amides [lactams], urea, imides, *N*-carboxyanhydrides, and 1,3-oxaza derivatives), sulfur (thioethers, thioesters [thiolactone, thionolactone], and thiocarbonates), phosphorus (phosphines, phosphinates, phosphonites, phosphites, phosphonates, phosphates, and phosphazenes) [9], or silicon (siloxanes, silaethers, and silanes) (Figure 7.1b) [10].

In contrast to some prominent industrial polymerizations (e.g. polyolefins), ROP enables the incorporation of heteroatoms within the polymer backbone, leading to materials with some unique properties, such as (bio)degradability. Moreover, the reversible nature of ROP reactions permits in certain cases for easy depolymerization and thus chemical recycling. This chapter primarily focuses on ROP for the synthesis of polyesters, containing ester linkages in their chains. At certain conditions, these ester linkages can make a polymer material amenable to (bio)degradation (e.g. via (a)biotic hydrolysis), offering the potential to create environmentally benign plastics. Although various polyesters can be obtained through condensation polymerization of diols with diacids or of hydroxy acids, ROP holds several advantages over this polymerization method. Compared to addition polymerizations, such as ROP, condensation polymerization involves repeated condensation reactions between two complementary functional groups (step-growth polymerization) and results in the production of by-products (i.e. condensates). When by-products are not efficiently removed from the reaction, they may promote depolymerization (equilibria), resulting in limited chain lengths and poor mechanical properties as a consequence. In addition, condensation polymerizations are often carried out at high temperatures (>200 °C) and are generally more difficult to control. Moreover, they only lead to high degrees of polymerization at very high conversions (>99%), whereas dispersity

(i.e. M_w (weight-average molar mass)/M_n (number-average molar mass), i.e. a measure for the uniformity of chain lengths of a polymer) is often broad [11]. Nevertheless, many factors may have an impact on the course of a ROP, such as ring structure (size, number and position of substituents, functional groups), reaction conditions (e.g. temperature, solvent, monomer concentration), the catalyst system, and side reactions due to transesterification (i.e. chain transfer, backbiting, end-to-end biting). Therefore, ROP can be highly complex and sensitive to external factors [12]. In addition, it has to be mentioned that polymer structures obtained via polycondensation of hydroxy acids can often also be obtained via ROP of lactones, while the chain structures created by polycondensation of diacids with diols cannot be synthesized via ROP.

This chapter will first discuss several key ROP mechanisms and the associated thermodynamics and kinetics, followed by an overview of the most important degradable (or potentially degradable) polyesters obtained by ROP. A classification of the different polyesters will be made based on the ring size of their corresponding cyclic monomers.

7.2 Ring-Opening Polymerization Mechanisms

In the following sections only the most essential ROP mechanisms for the synthesis of aliphatic polyesters will be elaborated (cationic, anionic, coordination–insertion, and enzymatic). Although radical ROP can give rise to certain (bio)degradable polyester structures, research is relatively limited and will not be further discussed here. For more information on radical ROP the reader is referred to some excellent reviews [13, 14]. Ring-opening metathesis polymerization (ROMP) converts an unsaturated cyclic monomer into a polymer chain by means of metathesis. However, ROMP for the synthesis of degradable polyesters has only been described through polymerization of multifunctional macrocyclic monomers [15, 16] or macrocyclic unsaturated lactones [17, 18]. As such, further discussions on ROMP are not included in this chapter.

7.2.1 Cationic Ring-Opening Polymerization

Cationic ring-opening polymerization (cROP) occurs through the formation of a positively charged intermediate. Positive charges typically originate from addition of electrophilic/acidic initiators, such as Brønsted acids, carbenium ions, or onium ions. Typical Brønsted acids include HCl, H_2SO_4, $HClO_4$, or heteropolyacids ($H_nX_mM_zO_y$ with X = P, Si, and M = Mo, W, V) of which $H_3PMo_{12}O_{40}$ and $H_3PW_{12}O_{40}$ are extensively described in literature. In addition, more recently described derivatives of phosphoric acid [19, 20] (e.g. diphenylphosphate [DPP]) and triflic acid (CF_3SO_3H) have become more prominent. Lewis acids, of which the most important ones in cROP include BF_3 and PF_5, typically require a co-initiator such as water or alkyl halides, resulting in Brønsted acidic catalyst systems. Examples of cROP-initiating carbenium ions include $(C_6H_5)_3C^+$, $(C_6H_5)_2CH^+$, $(C_6H_5)CH_2^+$,

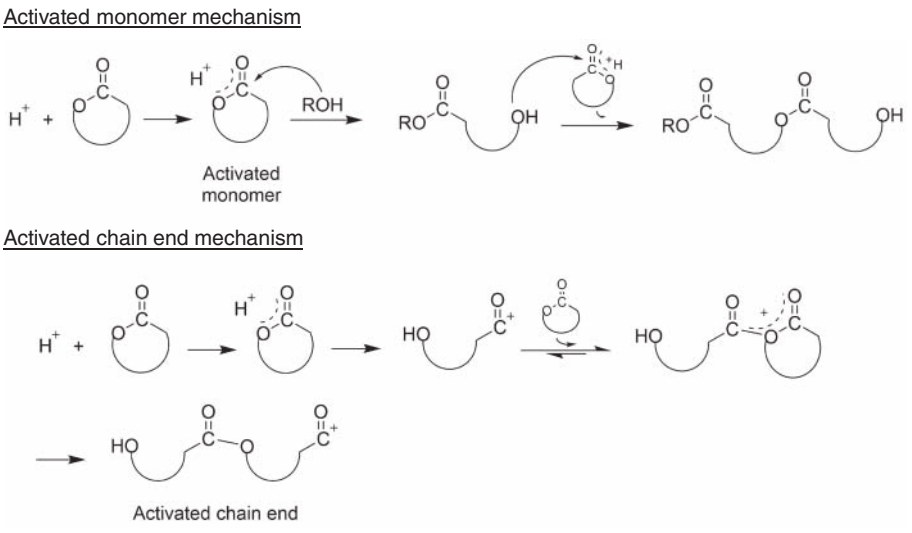


Figure 7.2 The activated monomer (AM) and activated chain end (ACE) mechanisms for cROP of lactone monomers. Source: Figure adapted from Kaluzynski et al. [23].

$H_2C{=}CH{-}CH_2^+$, $(CH_3)_3C^+$, etc., while trialkyl oxonium is an often-used onium ion initiator [6, 21, 22].

cROP can proceed via two main mechanisms: an activated chain-end (ACE) mechanism or an activated monomer (AM) mechanism, as depicted in Figure 7.2 for lactone monomers [12, 23, 24]. Typical monomers that can be polymerized via a cationic mechanism include cyclic ethers, sulfides, imines, amines, acetals, lactones, siloxanes, phosphazenes, oxazolines, etc.

The ACE mechanism is most common in cROP, while the number of monomers polymerizing via the AM mechanism is rather limited [25]. The ACE mechanism proceeds via a nucleophilic attack of the cyclic monomer on the positively charged onium ion at the growing chain-end of the polymer. The AM mechanism proceeds via a nucleophilic attack of the growing polymer chain on the positively charged, AM molecule [6, 12, 24, 25].

cROPs can undergo various termination reactions. In certain cases, living polymerization can be conducted, in which termination is limited. Since the ACE mechanism proceeds via a nucleophilic attack of the monomer on the ACE, other nucleophiles present in the reaction mixture could interact with the growing polymer chains and terminate the reaction. Typical terminating nucleophiles are counter-anions of the initiator or heteroatoms present in the growing chains. Counter-anions can transform the active chain-end into an uncharged system. Depending on the nucleophilicity of the initiating system, this covalent interaction can be permanent, reversible, or even negligible. Heteroatoms present in a polymer chain can interact with the active chain end of their own polymer molecule or of another chain. Both reactions can be either reversible or irreversible. In the former case, branched structures are created, while in the second case cyclic structures

can be obtained. If in the latter case termination is reversible, cyclic oligomeric molecules can arise [24].

7.2.2 Anionic Ring-Opening Polymerization

Anionic ring-opening polymerization (aROP) proceeds via a nucleophilic initiator cleaving a cyclic monomer with high electrophilicity. While during cROP a protonated ring structure is opened, aROP proceeds through the cleavage of an uncharged cyclic monomer. Since the latter reaction requires more energy than the first, the number of monomers that can be polymerized through aROP is more limited compared to cROP [12]. Cleaving uncharged bonds is not evident and therefore needs activating agents, typically nucleophilic compounds. Examples of some common catalysts capable of aROP initiation include alkyl metals (alkyl lithium, alkyl magnesium bromide [Grignard reagent], alkyl aluminum, alkyl zinc, etc.), metal amides, alkoxides, phosphines, amines, thiols, alcohols, and water.

Monomers that can efficiently be polymerized via an aROP mechanism include (thio)esters, (thio)carbonates, amides, urethanes, phosphates, etc. Less electrophilic cyclic molecules, such as (thio)ethers or amines, can only be polymerized via aROP when the ring-strain in the molecules is sufficiently high such as in three-membered rings (epoxides, episulfides, aziridines, etc.) [12, 26].

The general (ACE) mechanism of aROP is depicted in Figure 7.3. Through ring-opening, a negatively charged structure is formed which represents a new nucleophilic species. This new nucleophile can attack a second molecule to form a dimer. The nucleophilic attack can, depending on the monomer, both occur on the carboxyl carbon (leading to acyl–oxygen bond cleavage) and on the alkoxide carbon (leading to alkyl–oxygen bond cleavage) (Figure 7.3) [6]. This repeating procedure will eventually provide a polymer chain. As is the case for cROP, aROP can occur via both an ACE and/or an AM mechanism. However, in aROP the AM mechanism

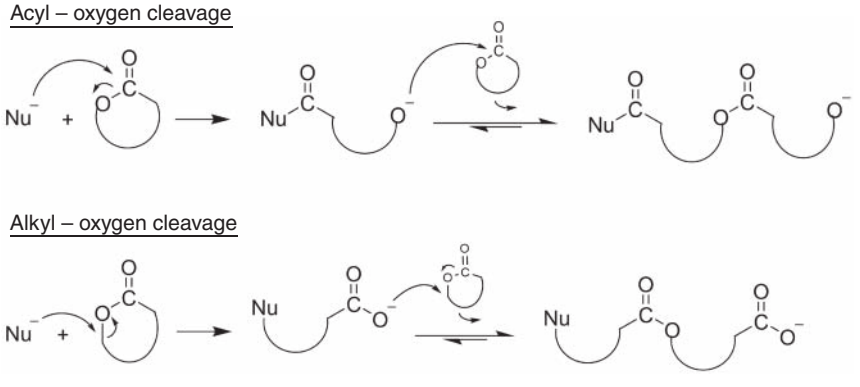


Figure 7.3 General mechanism of aROP: the monomer ring breaks via a nucleophilic attack of the initiator on the carboxyl carbon (acyl–oxygen cleavage) or the alkoxide carbon (alkyl–oxygen cleavage).

is only achieved when deprotonation of the functional group in the monomer by the nucleophile is possible, such as in the case of lactam polymerization [25].

Termination of aROP can occur by similar termination reactions as described for cROP through the presence of electrophilic compounds.

In addition to the catalytic systems for ionic ROP mentioned above, organic catalysts have gained more attention lately. These type of catalysts include amines (triethylamine, 4-dimethylaminopyridine [DMAP], 4-pyrrolidinopyridine [PPY], etc.), phosphines, N-heterocyclic carbenes [NHCs], amidines (1,8-diazabicyclo[5.4.0] undec-7-ene [DBU]), guanidines (1,5,7-triazabicyclo[4.4.0]dec-5-ene [TBD]), etc. For more information on organocatalysts for ROP the reader is referred to the review by A. Dove [27].

7.2.3 Coordination–Insertion Ring-Opening Polymerization

Coordination–insertion-based ring-opening polymerization (ciROP) starts with the interaction of a cyclic monomer with a catalytic system, without the formation of charges or radicals. The polymer chain is built up by successive insertion of monomers at the activated catalyst-bound chain. The mechanism of these types of ROP depends on the cyclic monomer and the specific catalytic system. Most catalytic systems are metal-based complexes.

ciROP is widely used in the polymerization of lactones. A generic ROP of lactones by a coordination–insertion mechanism is depicted in Figure 7.4. In this mechanism, the organometallic species (typically a metal alkoxide) initiates the reaction by coordinating with the carbonyl group of the monomer. This step is followed by cleavage of the acyl–oxygen bond to open the ring structure and simultaneous insertion of the monomer into the metal alkoxide bond [28, 29].

The two most widely used metal complexes for ROP of cyclic esters (also used in polycondensation) are Sn(II) 2-ethylhexanoate ($Sn(Oct)_2$) and aluminum alkoxides such as aluminum isopropoxide (Figure 7.5) due to their high selectivity and high control over the final molar mass (MM) of the polyesters. By reaction with alcohols

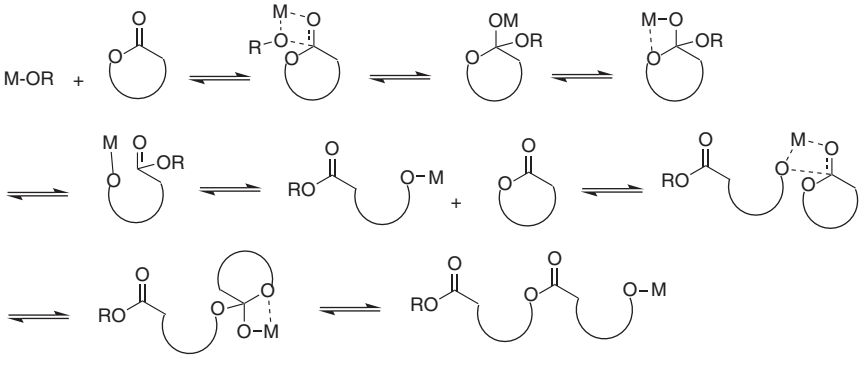


Figure 7.4 Ring-opening polymerization of lactones by coordination–insertions with metal alkoxides (M-OR). Source: Figure adapted from Jérôme and Lecomte [28].

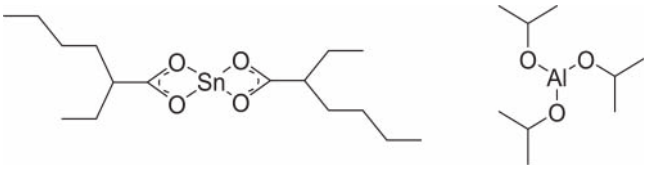


Figure 7.5 Structures of Sn(II) ethylhexanoate (left) and Al isopropoxide (right).

or other protic impurities, $Sn(Oct)_2$ is converted into the corresponding tin alkoxide, which acts as the active initiator. Every active initiator will theoretically create one growing polymer chain (when side reactions, such as transesterification, are neglected). As a consequence, by controlling the amount of alcohol added to the ROP reaction, the molar mass of the final polymer can be predicted.

An extremely wide range of other metals and complex structures have been investigated in the field of cyclic ester polymerization. Some extensively studied metal complexes and derivatives mainly contain rare earth metals (mainly La, Ln, Y, Sc, Nd, Sm, etc.) [30], alkali metals (Li, Na, K) [31–33], alkaline earth metals (Mg, Ca, Sr, Ba, Zn) [32–34], group 4 metals (Ti, Zr, Hf) [35–37], group 13 metals (Al [38], Ga, In) [33, 39], Sn, etc.

7.2.4 Enzymatic Ring-Opening Polymerization

Enzymatic ring-opening polymerization (eROP) can be defined as a ROP reaction induced by enzymatic activity. The most widely studied lactones in eROP include ε-caprolactone (ε-CL), ω-pentadecanolide, and LD, while lipases are the main class of enzymatic catalysts [40]. For a complete overview of all lactones and derivatives polymerizable by eROP the reader is referred to the review by Engel et al. [40]. Although eROP is much less discussed than the other ROP methods described in this chapter, enzymes have some important advantages over chemocatalysts. Enzymes can exhibit very high selectivities, while being active in mild reaction conditions and potentially also in greener reaction media, such as water, ionic liquids, or supercritical fluids. In addition, no toxic compounds remain after polymerization, making it especially suitable for biomedical applications. However, the main challenge in eROP is the rather low molar masses that are currently obtained [40].

7.3 ROP-Based Polyesters

7.3.1 Lactones

ROP to create polyesters most often takes place starting from lactone monomers. Lactones are ring-shaped molecules containing an ester function as part of their ring structure. Both monolactones and dilactones exist in ROP in which the ring contains one or two ester groups, respectively. Monolactones are usually not called by their IUPAC name, but the rings are based on the name of their hydroxy acid

precursor, in which the Greek letter refers to the position of the hydroxy group relative to the acid function (e.g. β-propionic acid → β-propiolactone [β-PL]). In the name of the lactone, the letter thus often indicates the ring size of the molecule (e.g. β-lactone = four-membered ring and γ-lactone = five-membered ring) [11]. For the sake of consistency, this nomenclature will be used throughout this chapter. Naturally occurring lactones are mainly γ- and δ-lactones (five- and six-membered lactones), due to their high stability resulting from their low ring strain. However, more stable rings translate to more challenging polymerizations. Whether a lactone can undergo ROP is determined by polymerization thermodynamics and kinetics. The following section will give a basic introduction to the thermodynamics and kinetics of ROP.

7.3.2 Thermodynamics and Kinetics

The general ROP reaction can be written as a reaction between a cyclic monomer (M) and a growing polymer chain consisting of n monomer (M_n^*) units (with * representing the activated end-group) resulting in a chain with $n+1$ units (M_{n+1}^*) (Eq. (7.1)).

$$M_n^* + M \underset{k_d}{\overset{k_p}{\rightleftharpoons}} M_{n+1}^* \tag{7.1}$$

$$r_p = k_p \left[M_n^*\right][M] \qquad r_d = k_d \left[M_{n+1}^*\right]$$

$$K = \frac{k_p}{k_d} = \frac{\left[M_{n+1}^*\right]}{\left[M_n^*\right][M]} \tag{7.2}$$

The parameters k_p and k_d are the rate constants of polymerization and depolymerization, respectively. The rates of polymerization (r_p) and depolymerization (r_d) are both dependent on the rate constants and concentrations of monomer ([M]) and growing polymer ($\left[M_n^*\right]$). At equilibrium r_p and r_d are equal, which is expressed by the equilibrium constant K, as shown in Eq. (7.2).

Polymerization can only take place if the Gibbs free energy of polymerization (ΔG_p) is negative, i.e. when the polymer has a lower free energy than the monomer. ΔG_p is determined by the enthalpy (ΔH_p) and entropy (ΔS_p) of polymerization (Eq. (7.3)) with T being the absolute temperature.

$$\begin{aligned}\Delta G_p &= G_{polymer} - G_{monomer} \\ &= H_{polymer} - H_{monomer} - T\left(S_{polymer} - S_{monomer}\right) \\ &= \Delta H_p - T\Delta S_p\end{aligned} \tag{7.3}$$

Since polymerization results in the enchainment of a large number of monomers in macromolecular chains, the degrees of freedom decrease, and therefore ROP (and other polymerization types) is most often entropically unfavored (i.e. $\Delta S_p < 0$). As such, ROP is often an enthalpy-driven process ($\Delta H_p < 0$) in which ΔH_p is strongly dependent on ring strain. Ring strain is dependent on the conformation, repulsion, and angle strain of the molecule, and therefore ring size and degree of substitution play a critical role in ROP thermodynamics. Small lactone rings (four to seven

membered rings) often exhibit sufficient strain to enthalpically drive ROP ($\Delta S_p < 0$, $\Delta H_p < 0$), whereas the ROP of larger rings (nine membered rings or larger) can become entropically driven ($\Delta S_p > 0$, $\Delta H_p > 0$) [41, 42]. Since this chapter will focus on small lactone rings, the rest of this section will focus on enthalpically driven ROP.

Although entropic changes are generally limited compared to enthalpic changes, the positive entropic term in Eq. (7.3) ($T\Delta S_p$) becomes more dominant when the temperature (T) at which ROP is performed is high. This indicates, from a purely thermodynamic point of view, that ROP is preferably performed at lower temperatures, particularly when $\Delta S_p < 0$.

ΔG_p can also be written as the sum of the standard free energy of polymerization (ΔG_p^0) and a term related to the equilibrium constant K with R the gas constant (Eq. (7.4)). As shown in Eq. (7.2), K is related to the concentrations of monomer and growing polymers, which results in Eq. (7.5).

$$\Delta G_p = \Delta G_p^0 + RT \ln K \tag{7.4}$$

$$\Delta G_p = \Delta G_p^0 + RT \ln \frac{\left[M_{n+1}^*\right]}{\left[M_n^*\right][M]} \tag{7.5}$$

When the polymer chains are sufficiently long, one can assume that the reactivity of an active center on the polymer molecule does not depend on the degree of polymerization. Following this assumption, Eq. (7.5) can be written according to Eqs. (7.6) and (7.7) [10, 43].

$$\Delta G_p = \Delta H_p^0 - T\Delta S_p^0 - RT \ln [M] = \Delta H_p^0 - T\left(\Delta S_p^0 + R \ln [M]\right) \tag{7.6}$$

$$T = \frac{\Delta H_p^0 - \Delta G_p}{\Delta S_p^0 + R \ln [M]_{eq}} \tag{7.7}$$

$$T_c = \frac{\Delta H_p^0}{\Delta S_p^0 + R \ln [M]_0} \tag{7.8}$$

Equation (7.8) shows that at equilibrium (when $\Delta G_p = 0$) a critical temperature exists at which no net polymerization takes place ($r_p = r_d$). This temperature is called the ceiling temperature (T_c). According to IUPAC, T_c is defined as "*the temperature at or above which the concentration of monomer in equilibrium with its polymer becomes essentially equal to the initial monomer concentratio*n" [44]. Therefore, Eq. (7.8) can be written with the starting monomer concentration ($[M]_0$) instead of $[M]_{eq}$. This essentially means that to promote polymerization the reaction should be performed at a temperature below T_c, while above T_c depolymerization will take place.

Since T_c is strongly dependent on the initial monomer concentration, this value is typically determined at either a monomer concentration of 1 M or in neat monomer (bulk). It is noteworthy that different monomers have intrinsically different bulk concentrations due to variations in MM and density of the monomers [42, 44].

In a lot of literature, it has been described that changes in concentration or solvent only result in changes in entropy, assuming enthalpy and thus ring strain is not affected by concentration or solvent. Nevertheless, this is not completely true,

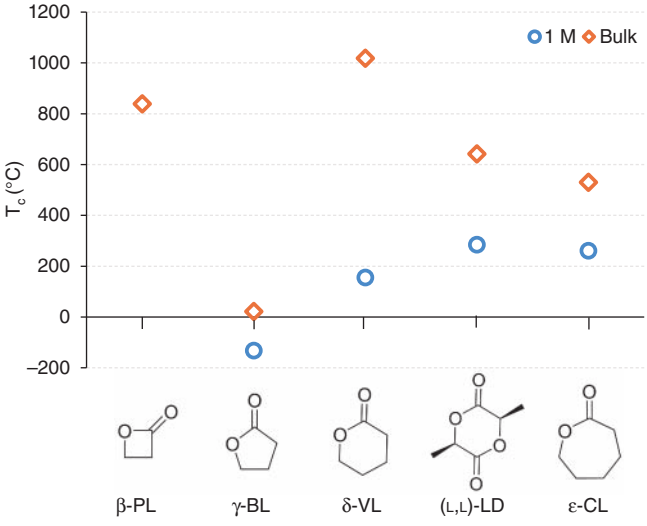


Figure 7.6 Ceiling temperature (T_c, °C) for different lactones at an initial monomer concentration ($[M]_0$) of 1 M or in bulk (10–13 M). Source: Data obtained from Duda and Kowalski [10] and Olsén et al. [42].

since ring strain can be affected by interactions of the monomer with the solvent depending on, among others, concentration, and polarity [42]. Finally, it should be stressed that enthalpy and entropy of polymerization are affected by the aggregation states of both monomer and polymer during polymerization, resulting from the corresponding phase transition (e.g. melting and crystallization) enthalpies and entropies. Therefore, one should be careful when comparing the values of enthalpy and entropy in literature [10].

The thermodynamic properties of different lactones, as summarized by the T_c value, are shown in Figure 7.6. For lactones of small ring size, thermodynamics of ROP are most favorable for four-membered (β-PL), six-membered (monolactone: δ-valerolactone [δ-VL], dilactone: LD), and seven-membered (ε-CL) rings, mainly resulting from the high ring strain of these molecules. Five-membered rings (γ-butyrolactone [γ-BL]), however, exhibit very stable ring structures with low ring strains, reflected in the exceptionally low T_c values of ROP.

7.3.3 Functionalization

The polyesters obtained from the ROP of simple lactones only have an ester bond which is susceptible to hydrolysis and biodegradation. However, certain applications require further tuning of degradability through, for example, increasing hydrophilicity and decreasing crystallinity. Introducing additional functional groups is an essential strategy to increase (bio)degradation capabilities. Attributes such as hydrophobicity can severely limit biodegradation (see Chapter 2). One way to increase the hydrophilicity is the direct ROP of ether-lactones, thus adding ether bonds into the polymer backbone. Some prominent examples of

poly(ether-lactones) are mentioned in further detail in Section 7.3.5.4, 7.3.6.4, 7.3.7.3.

Additionally, functionalities can also be introduced in the polymer backbone in the form of pendant functional groups. In this way, the hydrophilicity can be increased by incorporating polar functional pendants, including small groups such as $-NH_2$, –COOH, –OH, and –C=O [45, 46]. These functionalities can be introduced either through ROP of substituted, functional lactone monomers or through post-polymerization modification and grafting onto the polyester backbone.

7.3.3.1 ROP of Functional Lactones

There are a multitude of examples in which ROP has been performed on functionalized lactones, including halide, ester, and acetyl functional groups. Direct ROP of cyclic lactones bearing, e.g. hydroxyl groups, needs to be bypassed because these groups can undergo undesirable transesterification reactions and, unprotected, those lactones would act as inimers, i.e. act as both monomers and initiators alike, resulting in hyperbranched structures [47, 48]. Therefore, protective groups are used or the lactones are first polymerized with a suitable functional group and replaced post-polymerization by the desired group.

The benefit of using functionalized lactones is the possibility of purification before polymerization. Possible disadvantages include multiple steps for monomer synthesis as well as difficulties related to the choice of the protective group. If too labile the polymerization is impeded, but stronger groups (e.g. $-OSiEt_3$) require more stringent conditions for deprotection, risking degradation of the polymer [28]. Dilactones such as benzoyloxymethyl glycolide can be polymerized using conventional ROP catalysts and readily deprotected to yield the corresponding polyester with pendant OH-groups [28, 49]. An additional reason for the protection of carboxylic acid groups in the form of esters is their incompatibility with common metallic ROP catalysts [48].

7.3.3.2 Post-polymerization Functionalization

ROP of certain functionalized lactones takes place forming a precursor polymer which is subsequently modified to obtain the desired functionality. Halogenated lactones are an interesting group of such precursor monomers as the resulting functionalized polyesters can be derivatized in a number of ways, while the halogen groups do not disrupt the polymerization. This is demonstrated here by the derivatization of poly(α-Cl-ε-CL) from the ROP of α-chloro-ε-caprolactone (α-Cl-ε-CL) in Figure 7.7.

After polymerization, the chlorinated groups can be quantitatively replaced by azido pendants, which can then undergo so-called click reactions with alkynes to graft the desired functional groups onto the polymer [28, 47]. The advantage of click reactions compared to deprotection reactions is that they can readily take place under mild conditions, ensuring that degradation is minimized. For certain applications, the toxicological drawbacks of copper catalysts for these reactions make them unsuitable [50].

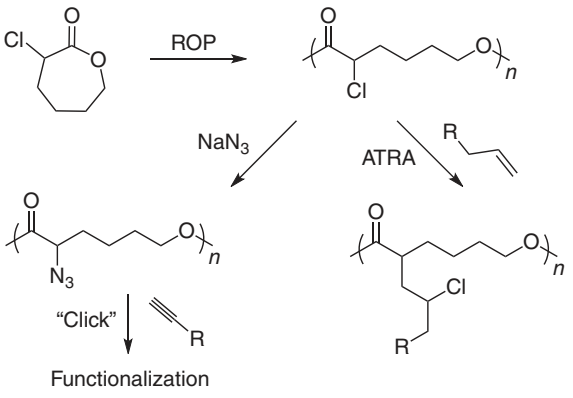


Figure 7.7 Derivatization pathways of chlorinated PCL from ROP of α-Cl-ε-CL: (left) derivatization to azido moiety with sodium azide followed by click reaction with an alkyne, (right) ATRA reaction with a functional alkene.

A second possibility is via so-called atom transfer radical addition (ATRA), see Figure 7.7 (right). The halogen atom is activated by the adjacent ester function and can react with functional alkenes (e.g. 3-buten-1-ol) in the presence of organometallic catalysts. Here, the copper catalyst required can be of concern for toxicological reasons, especially since it is typically used in stoichiometric amounts and some cases require elevated temperatures leading to polymer degradation [28].

Polyesters with pendant allyl groups or unsaturated backbones are another group of possible intermediates for the creation of more hydrophilic polymers. Reported post-polymerization functionalizations for such unsaturated polyesters include (di)hydroxylation, halogenation, epoxidation, hydrosilylation, thiol-ene reaction, and crosslinking and cross-metathesis reactions with functionalized alkenes [51–55]. Examples of polyesters with halogenated or unsaturated functional groups and their post-polymerization modifications can be found in Sections 7.3.4.4, 7.3.5.2, 7.3.6.2, and 7.3.7.2.

7.3.3.3 Grafting

In grafting, side chains or groups are added onto preformed polymer chains. An example of grafting with functional groups onto a polyester backbone can be seen in Figure 7.8. A precursor is formed via an anionic reaction using lithium diisopropylamide (LDA). The benefit of this strategy is that this precursor acts as a template for several different functionalized polyesters, as is illustrated here with some examples [28].

7.3.4 Four-Membered Lactones

Four-membered lactones or β-lactones are widely described as useful monomers for the ROP of some interesting, biodegradable polyesters.

The two structurally most simple β-lactones are β-PL and β-butyrolactone (β-BL), which are industrially synthesized through cycloaddition of ethenone with an aldehyde (formaldehyde for β-PL, acetaldehyde for β-BL) (Figure 7.9) and are therefore most often non-renewable [56]. Another synthesis method includes the carbonylation of epoxides [57, 58].

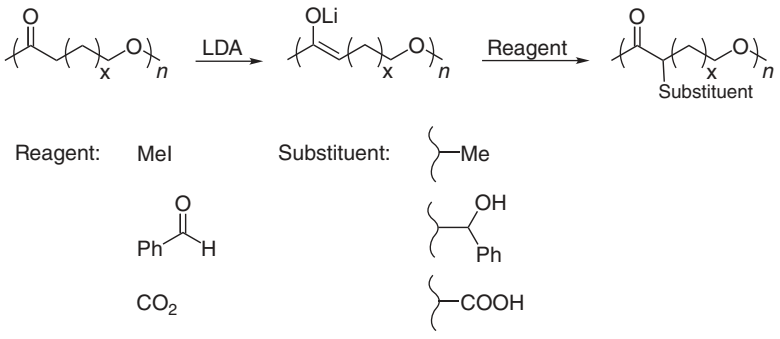


Figure 7.8 Grafting reaction onto polyesters with lithium diisopropylamide (LDA) and selection of reagents and substituents.

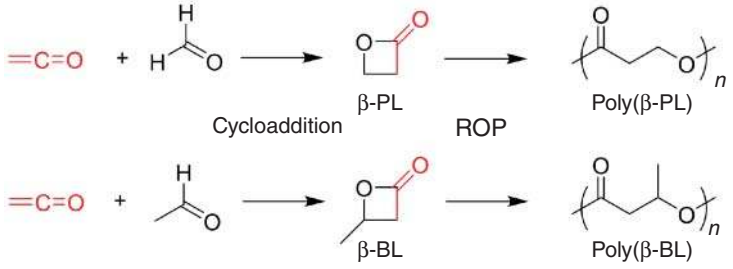


Figure 7.9 Industrial synthesis method of β-propiolactone (β-PL) and β-butyrolactone (β-BL) and their corresponding ROP-based polyesters.

Due to their very high internal ring strain and high polarity, β-lactones exhibit notably different polymerization behavior than their larger counterparts. Whereas larger lactone structures most often proceed through acyl-cleavage, creating alkoxide end groups, β-lactones regularly undergo both acyl- and alkyl-cleavage (see Section 7.2.2 on ROP mechanisms). While acyl-cleavage will ensure the preservation of the monomer stereochemistry, alkyl-cleavage will invert the stereochemistry. Depending on the reaction conditions, monomer, and catalytic system, one mechanism may dominate over the other, while in some cases both mechanisms may occur simultaneously [12, 59]. Alkyl-cleaved β-lactones are susceptible to a widely described and often unwanted side reaction, leading to acrylate-type side products. These species can also serve as initiating sites leading to polymers with unsaturated end-groups. This side reaction limits the control over molar mass and influences the dispersity. It is important to take these possible effects into account when choosing an appropriate ROP protocol [12].

Although ROP of β-PL results in materials with a T_g (glass transition temperature) around −20 °C, a T_m (melting temperature) around 80 °C [60–63], and excellent degradability [64–67], industrial applications of this polymer are limited. β-PL is highly toxic and by the International Agency for Research on Cancer "*reasonably anticipated to be a human carcinogen*." Therefore, research on ROP of β-lactones has mainly been shifted to the less harmful methyl-substituted counterpart of β-PL,

namely β-BL, as an alternative route to produce poly(3-hydroxybutyrate) (PHB) (or poly(β-BL)).

7.3.4.1 β-Butyrolactone

PHB is a biopolymer belonging to the class of poly(hydroxyalkanoates) (PHAs). PHAs have gained increasing attention in the field of bioplastics, due to their exceptional biocompatibility and biodegradability in compost, soil, and even marine environments [59]. PHB is the most common naturally available PHA. (R)-PHB (isotactic) is a highly crystalline polymer with a T_m around 175–180 °C and a T_g around −4 °C. Due to its high crystallinity, PHB homopolymers exhibit a high tensile strength, Young's modulus, and impact strength, while elongation at break is low. Moreover, PHB has a decomposition temperature close to its melting point, which makes processing very challenging.

PHAs are naturally produced by microorganisms as intracellular granules to serve as carbon and energy reserve. For more details on PHAs, the reader is referred to Chapter 6 in this book. However, the biotechnological synthesis of PHAs is currently very time consuming, complex, and expensive. In addition, PHAs made by microorganisms are strictly isotactic, exclusively exhibiting (*R*)-configurations without the possibility to vary the stereochemistry. As a consequence, the performance of these polymers is rather limited and with that, to some degree, their applicability [68–70]. These problems could be overcome by ROP of β-BL and other β-lactones. ROP does not only provide the possibility to change stereochemistry but also enables copolymerization and functionalization to tune properties to meet specific requirements [59, 71].

The ROP of β-BL has mostly been described in the presence of metal-based salts or metal complexes. Metal-based salts mainly include potassium salts of carboxylic acids (potassium acetate, benzoate, crotonate, etc.) [72–74] and potassium alkoxides (MeOK, t-BuOK, etc.) [72, 74–76]. Most of these anionic polymerization reactions (aROP) lead (partly) to acyl-cleavage and resultant crotonate side product formation. However, the introduction of macrocyclic ligands such as crown ethers (e.g. 18-crown-6) is described to promote acyl-cleavage mechanisms and lead to living polymerizations [76, 77]. Metal complexes for ciROP, in general, enable better control over the molar mass, dispersity, and stereochemistry of PHB. Typical metal complexes contain Cr [78], Sn [79, 80], Zn [81–84], Al [85], In [86–88], or rare earths (Y, La) [51, 89–94]. More recently, organocatalysts have also been studied, with particular promise shown by DBU, 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), and TBD [71, 95–97].

7.3.4.2 Acid-Substituted β-Lactones (β-Malolactonate)

Although PHAs are one of the best degradable polyesters described, an important shortcoming of PHB is its hydrophobic character that often limits its use or (bio)degradability in certain conditions. This disadvantage can be overcome by introducing hydrophilic groups on the polymer backbone. An important PHA-type polymer described in this field is poly(malic acid) (PMLA), which contains a

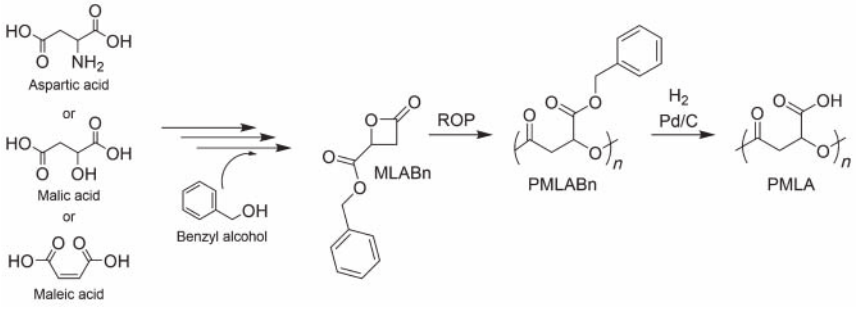


Figure 7.10 Synthesis and ROP of MLABn to PMLABn and removal of the benzyl group via catalytic hydrogenolysis to form PMLA.

carboxylic acid side group on each repeating unit (Figure 7.10). PMLA can be produced both chemically and naturally via bacterial fermentation. Due to some shortcomings of the current fermentation process (limited control over MM, low productivity, limited availability of sources, lengthy procedure, etc.) interest in the chemical ROP route via substituted lactones has risen [98]. The synthesis procedure of PMLA starts with the ROP of benzyl-β-malolactonate (MLABn) to poly(benzyl-β-malolactonate) (PMLABn). PMLA can then be obtained by removing the benzyl groups via catalytic hydrogenolysis with Pd/C to create a carboxylic acid side group (Figure 7.10). This side group leads to water solubility as well as provides a convenient handle for further modification or functionalization. Moreover, PMLA can degrade *in vitro* via hydrolysis to create malic acid, an intermediate of the Krebs cycle [99, 100]. As a consequence, this bioresorbable polymer is extensively studied in the biomedical field as a drug-carrier system.

MLABn is a biobased monomer that can be obtained from either malic acid, aspartic acid, or maleic acid, three biobased platform molecules. Different multi-step (four to six steps) synthesis methods have been described in the presence of benzyl alcohol (BnOH) with yields ranging between 3% and 11%, of which synthesis from aspartic acid is most efficient [98, 101, 102]. For more details and a clear overview of all synthesis options the reader is referred to the review by Jaffredo and Guillaume [98]. Enantiopure MLABn can be obtained starting from enantiomerically pure aspartic acid [103, 104]. Substituting benzyl alcohol by other alcohols provides access to various other β-malolactonates and thus various polyesters with diverging properties [105, 106].

7.3.4.3 Alkoxy-Substituted β-Lactones

The ROP of 4-alkoxy-methylene-β-propiolactones (BPLORs) (Figure 7.11) was first described in 2017 by Carpentier and coworkers [107]. The lactones were synthesized in high yields by carbonylation of their corresponding racemic epoxides in the presence of CO [58]. These racemic alkoxy-substituted (with R = allyl (All), methyl (Me), benzyl (Bn), or *tert*-butyl-dimethyl-silane (TBDMS)) β-lactones were enantio-selectively polymerized in the presence of Y-based catalyst complexes

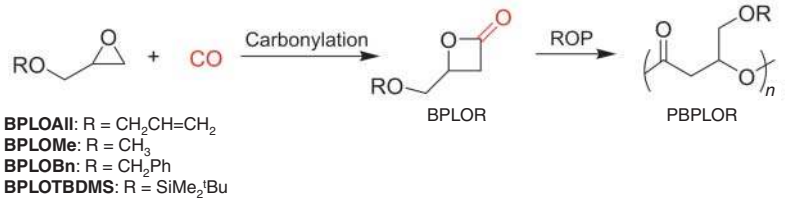


Figure 7.11 Synthesis and ROP of BPLOR with R being an allyl, methyl, or benzyl group.

resulting in either pure syndiotactic or isotactic chains depending on the ligands of the catalyst [107, 108].

The same research group recently demonstrated different ring-opening copolymerizations (ROCOPs) of these monomers in different combinations of functional groups and chirality resulting in copolymers with high degrees of alternation in both functional groups and tacticities [109]. Yet another study described the successful ROP of these substituted β-lactones aided by organocatalysts BEMP, DBU, and TBD [71]. These types of functionalized β-lactones can be interesting in the context of potential post-polymerization functionalization (Section 7.3.3.2) or biodegradation.

7.3.4.4 Alkene-Substituted β-Lactones

Alkene-substituted β-lactones are interesting monomers due to the possibility of creating polyesters with unsaturated pendant groups for post-polymerization functionalization. Two important monomers described in this context are β-6-heptenolactone (BHL) (Figure 7.13) and α-methylene-β-butyrolactone (MBL) (Figure 7.12).

The homopolymerization of MBL (synthesized from CO_2 and 2-butyne) (Figure 7.12) was recently described in the presence of Al salen complexes [110]. Later, the same research group synthesized different block copolymers with LD, ε-CL, and ω-pentadecalactone (ω-PDL) and random copolymers with β-BL aided by Al or Y complexes. Hydrolysis tests in the presence of a Lewis base showed that PMBL has significantly improved degradability compared to PHB. Tuning the amount of MBL units in random copolymers with β-BL enabled control over the polymer degradability. In addition, the unsaturation both enabled intra- and inter-cross-linking reactions between copolymers with MBL as well as post-polymerization functionalization through thiol-ene click reactions [111].

The ROP of BHL was first described in 2009 aided by a Y-based catalyst [51]. Both homopolymers of BHL and copolymers with β-BL (up to 50 mol% BHL) were synthesized with high MMs (M_n up to 58 kg/mol) and low polydispersities.

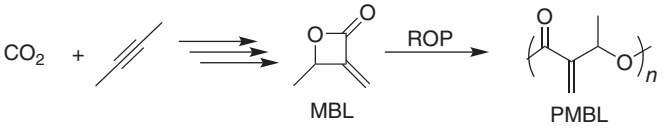


Figure 7.12 Synthesis of MBL from CO_2 and its ROP to produce PMBL.

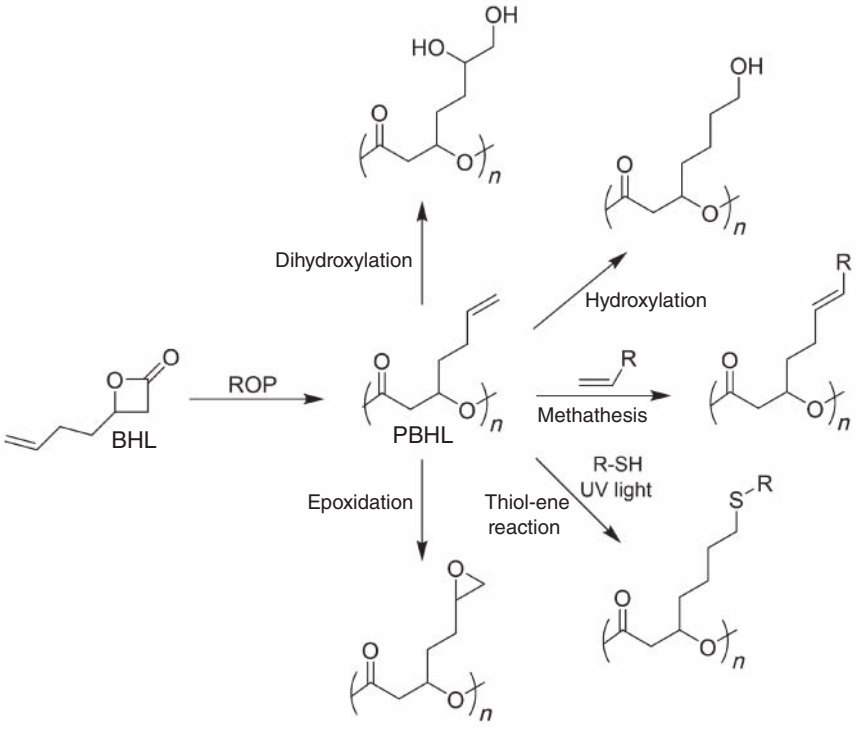


Figure 7.13 ROP of BHL and possible post-polymerization functionalizations.

In addition, the authors performed post-polymerization functionalization of the copolymers, whereby three possibilities were tested: dihydroxylation, hydroxylation via hydroboration/oxidation, and epoxidation (Figure 7.13) [51, 52]. More recent research describes BHL homopolymerization and copolymerization with LD, followed by post-polymerization cross-metathesis functionalization with alkenes bearing a wide range of functional groups (Figure 7.13) [53]. Yet another study reports the synthesis of block copolymers of ethylene oxide with BHL after which the alkene pending groups were modified using thiol-ene reactions under UV light (Figure 7.13) [112].

7.3.5 Five-Membered Lactones

7.3.5.1 γ-Butyrolactone

Carothers et al. [3] stated in 1932 that five-membered lactones do not show any tendency to form chain structures compared to their six-membered counterparts. As such, these ring structures, of which γ-BL (Figure 7.14) is the simplest, were long thought to be impossible to polymerize. This phenomenon was later explained as a thermodynamic problem resulting from the limited ring strain and high stability of five-membered lactones, leading to a positive Gibbs free energy of polymerization under normal conditions (e.g. see very low T_c in Figure 7.6) [113, 114].

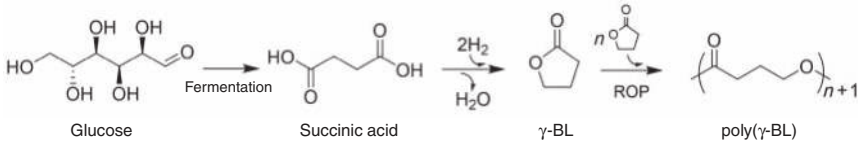


Figure 7.14 Synthesis of γ-BL from glucose via the platform molecule succinic acid and the ROP of γ-BL toward poly(γ-BL).

Despite its theoretically implausible ROP, researchers have devoted substantial effort to γ-BL due to the promising properties of this polyester (poly(γ-butyrolactone) [poly(γ-BL)]), better known as poly(4-hydroxybutyrate) (see also Chapter 6 about microbial PHA). First, γ-BL can easily be synthesized from succinic acid (Figure 7.14), a key bio-derived platform molecule [115]. Second, this polymer exhibits desirable properties: poly(γ-BL) is not only strong, but also flexible, a property which is often lacking in typically brittle bioplastics such as PHB, PGA, or PLA. Furthermore, poly(γ-BL) degrades faster *in vivo* than PLA or PCL, showing its (potential) applicability in the medical field [116–118].

Despite the thermodynamic limitations, the first successful homopolymerization of γ-BL was described in 1966 at extreme reaction conditions (20 000 atm, 160 °C, 4 hours), leading to a polymer with a low MM ranging from 1.20 to 3.35 kg/mol [119]. In its wake, various attempts have been made to improve the ROP of γ-BL under very high pressures, but the reported molar masses remained rather low using either lipase or acid catalysts [120–126]. However, more recently, the ROP of γ-BL under ambient pressure has been described. The application of temperatures below zero (−40 °C), high monomer concentrations (10 M), and the presence of a suitable La- or Y-based catalyst, resulted in high monomer conversions up to 90% and molar masses up to 30 kg/mol, creating both linear and cyclic polymer chains. By working at very low temperatures (i.e. below T_c) and high monomer concentrations, entropic barriers were overcome. In addition, controlling the reaction conditions (solvent, concentration) so that polymer chains precipitated upon formation further drove the equilibrium of the reaction toward polymerization. Moreover, the polymer structures are described to be easily recyclable to their monomers after catalyst removal without formation of by-products by simply heating the materials at 200–300 °C. [127, 128] Following this breakthrough, other successful catalytic systems have been discovered for the ROP of γ-BL at low temperatures, such as organocatalysts. Strong bases (e.g. phosphazenes) exhibited interesting results [129, 130]. However, these catalytic systems afforded both linear and cyclic polymer chains. The addition of (thio)urea to the phosphazene bases led to a selective formation of linear polymer chains of high MM, whereas a combination of urea and alkoxides proved to be successful as well [131–134]. Copolymerization of γ-BL with high ring strain monomers, such as β-PL, β-BL, G, LD, δ-VL, and ε-CL have been described as well [135–144]. The use of a high ring-strain comonomer enables ROP at temperatures above the T_c of γ-BL. In addition, copolymerization with γ-BL can potentially facilitate the recycling or degradation of other polyesters [134]. For a complete overview of the literature on

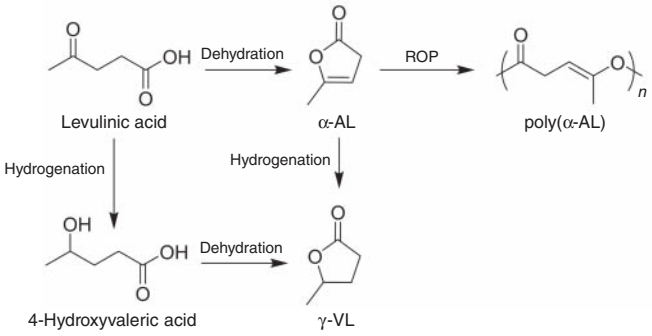


Figure 7.15 Synthesis of α-AL and γ-VL from levulinic acid and ROP of α-AL to poly(α-AL).

copolymerization of γ-BL the reader is referred to the recent reviews by Song et al. [145] and Liu et al. [134].

Due to the rather recent breakthroughs in ROP of five-membered lactones, the amount of γ-BL analogs used as monomers in ROP is limited. Only the ones interesting in the context of (bio)degradation will be further elaborated.

7.3.5.2 α-Angelicalactone

α-Angelicalactone (α-AL) is an unsaturated γ-BL analog with a methyl group at the γ-position relative to the ester carbonyl (Figure 7.15). α-AL has received increasing attention lately, due to its easy synthesis from levulinic acid through intramolecular condensation followed by dehydration. Both levulinic acid, which can be produced from lignocellulosic biomass and sugars, and α-AL are considered important biobased platform molecules that can be converted to a broad range of industrially important chemicals [146].

In 2011, the successful ROP of α-AL has been described in the presence of $Sn(Oct)_2$ at 130 °C for 30 hours in toluene [147]. The polymers, of up to 29 kg/mol, contain unsaturations in their backbone, providing a handle for further chemical modification. In addition, these double bonds are sensitive to light or heat and can generate radicals to promote facile degradation. A weight loss of 34.8% was described after exposing the polymers to daylight for 49 days, whereas placing them in an aqueous acidic or basic solution for the same time resulted in a weight loss of 63.3% and 52.0%, respectively. The rather simple ROP of α-AL compared to γ-BL was tentatively explained by a higher strain energy present in α-AL due to smaller bond angles for C—O—(C=O) and O—(C=O)—C resulting from the unsaturated bond [147–149].

The homopolymerization of γ-valerolactone (γ-VL), which can easily be made by hydrogenation of α-AL or by dehydration of 4-hydroxyvaleric acid (Figure 7.15), has not been described yet. Although copolymerization of this monomer with ε-CL or β-BL has been studied, molar masses and extent of incorporation remain rather low [150–152].

7.3.5.3 α-Methylene-γ-Butyrolactone

α-Methylene-γ-butyrolactone (MGBL) or tulipalin A is a γ-BL derivative with an unsaturated methylene group at the α-position relative to the carbonyl

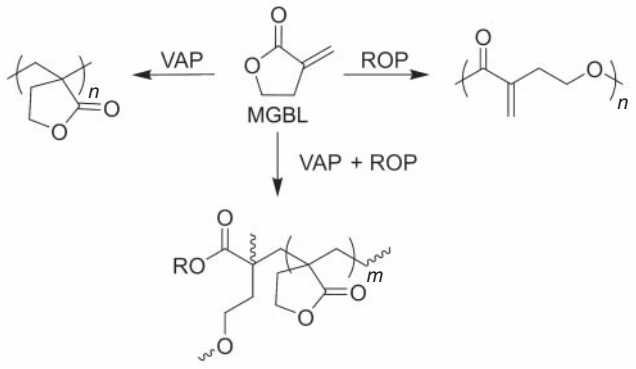


Figure 7.16 Polymerization of MGBL via vinyl-addition polymerization (VAP), ring-opening polymerization (ROP), or a combination of both. Source: Adapted from ref. Liu et al. [134].

group (Figure 7.16). This lactone is naturally present in tulips or can be chemically synthesized from biomass [153, 154]. MGBL, together with its methyl-substituted counterparts β-methyl-α-methylene-γ-butyrolactone and γ-methyl-α-methylene-γ-butyrolactone, which are derived from the biobased platform molecules itaconic acid and levulinic acid, respectively, is mainly studied with respect to its vinyl-addition polymerization (VAP) in absence of ring opening [155–157]. The ROP of MGBL is thus challenging for two reasons: (i) the high stability and low ring strain of the γ-BL ring suppresses ring opening ($\Delta H^0_p = -5.9$ kJ/mol, $\Delta S^0_p = -40.1$ J/(mol K), $T_c = -126\,^\circ$C (1 M)) and (ii) the highly reactive unsaturated bond tends to polymerize via vinyl addition.

One way to overcome these problems is via copolymerization of MGBL with a high ring-strain lactone, such as ε-CL [158–160]. However, recently the exclusive homopolymerization of MGBL was described in the presence of a $La[N(SiMe_3)_2]_3$ catalyst in combination with an alcohol initiator at low temperatures (−60 °C) and high monomer concentration (5 M) [161]. Linear polymer chains were obtained with M_n up to 21.0 kg/mol and low T_g (−46 to −35 °C) and T_m (39–44 °C) and could be depolymerized back to MGBL through chemolysis [134, 161]. Decreasing the amount of alcohol initiator, increasing the temperature, or decreasing the monomer concentration led to a combination of vinyl addition and ROP and in some cases to a crosslinked polymer network (Figure 7.16). This was explained by a calculation of $T_c = -51\,^\circ$C at a monomer concentration of 5 M. More recent research describes this polymerization aided by a cyclic trimetric phosphazene superbase catalyst. Both catalyst systems described here were also applied in copolymerization of MGBL with ε-CL or δ-VL, where decreasing temperature resulted in higher incorporation of the MGBL, lower melting points, and lower crystallinities [159, 160, 162]. The exomethylene groups on the polymer chains provide the possibility of post-polymerization functionalization (e.g. via thiol-ene-based click chemistry [160, 161]) of the polyester chains, among others to tune degradability properties.

Other α-substituted-γ-butyrolactones, such as α-bromo-γ-BL and α-acetyl-γ-BL, are interesting monomers in the context of degradability owing to their

functionalities enabling potential post-polymerization modification, without hindering ring opening. α-Bromo-γ-BL has been described in the context of copolymerizations with ε-CL, trimethylene carbonates, and L-LD ((L,L)-lactide) [163–165]. Olsén et al. [164] performed the copolymerization of α-bromo-γ-BL with ε-CL and L-LD in the presence of $Sn(Oct)_2$ at 110 °C in bulk for 30 hours. Up to 28% of α-bromo-γ-BL for ε-CL and 35% for L-LD were built-in in the polymer chains, obtaining M_n values between 17.0 and 54.8 kg/mol. The same group synthesized block copolymers with trimethylene carbonates, ε-CL, and α-bromo-γ-BL using DPP as a catalyst [163]. Both studies describe the post-polymerization modifications of the Br side group with various acrylate monomers, indicating the grafting capabilities of this functionality.

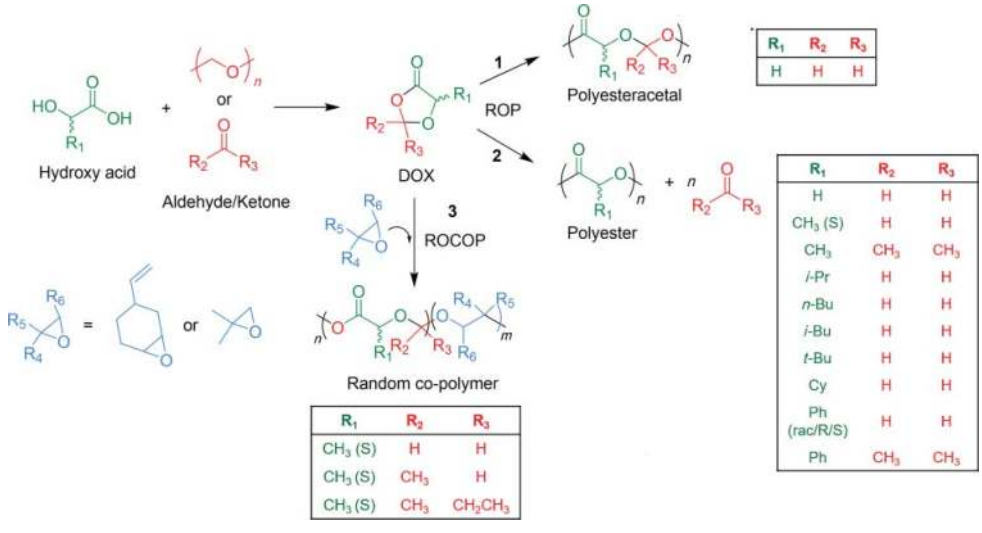
7.3.5.4 Ether γ-Lactones

Another group of five-membered lactones, more recently investigated in ROP, are the ether γ-lactones. More specifically, research has focused on the polymerization of various 1,3-dioxolane-4-one (DOX) monomers. DOXs are five-rings with both an ester and ether functional group as depicted in Figure 7.17 and can easily be synthesized by, among others, condensation of different, (often) renewable α-hydroxy acids and an aldehyde or ketone [166].

ROP of DOX monomers is an interesting alternative route to produce a wide range of divergent polyesters (Figure 7.17), being driven by the release of formaldehyde or acetone. Chain structures that are rather hard to obtain through classical cyclic diester polymerization, due to challenging monomer synthesis, can occasionally be more easily obtained via ROP of the corresponding DOX.

However, only one study describes the polymerization of the most simple ether γ-lactone, DOX ($R_1 = R_2 = R_3 = H$), and its copolymerization with LD, maintaining the acetal (O–C–O) functionality in the final polymer structure to generate polyesteracetals (up to 36 mol% DOX) (Figure 7.17 (**1**)) [167]. Incorporation of acetal groups resulted in an increase in T_g in the range of 4–19 mol% and decreased T_m of PLA. In addition, facile degradation of the copolymers was observed under acidic, neutral, and slightly basic conditions. At pH 7 (distilled water) the copolymer (4 mol% DOX) degraded with nearly 2% mass loss and more than 15% loss in molar mass (M_n) over 45 days, while no degradation was observed in PLA. Compared to separate ether functions, actals and ketals are even more labile and hydrolytically sensitive functionalities, enabling very fast degradation.

A more recent study describes the cationic ROCOP of different alkyl-substituted DOXs with two different oxiranes (Figure 7.17) using strong Lewis acid catalysts, such as $B(C_6F_5)_3$ in DCM at −78 °C. Although molar masses were mediocre (up to 18.8 kg/mol) polyesteracetal structures were obtained in which the DOX groups (9–25 mol%) were always interrupted by at least one comonomer group. The copolymers were easily hydrolyzed under acidic conditions (0.5 M HCl in 1,2-dimethoxyethane, 1 wt% polymer) at room temperature, resulting in more than 90% losses in molar mass after three hours. It was noticed that the acid-labile acetal functions disappeared most quickly from the nuclear magnetic resonance (NMR) spectra during hydrolysis [168].



R_1	R_2	R_3
H	H	H

R_1	R_2	R_3
H	H	H
CH_3 (S)	H	H
CH_3	CH_3	CH_3
i-Pr	H	H
n-Bu	H	H
i-Bu	H	H
t-Bu	H	H
Cy	H	H
Ph (rac/R/S)	H	H
Ph	CH_3	CH_3

R_1	R_2	R_3
CH_3 (S)	H	H
CH_3 (S)	CH_3	H
CH_3 (S)	CH_3	CH_2CH_3

Figure 7.17 Synthesis and ROP of 1,3-dioxolan-4-ones (DOXs) toward (**1**) polyesteracetals, (**2**) polyesters, or (**3**) substituted polyesteracetals via ROCOP with oxiranes.

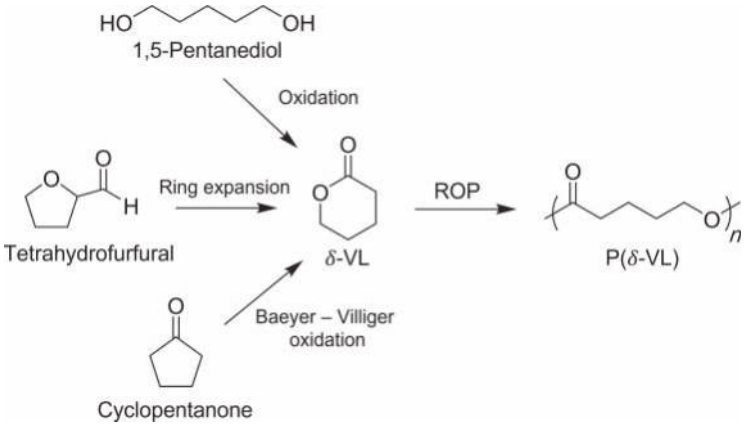


Figure 7.18 Synthesis methods and ROP of δ-VL.

7.3.6 Six-Membered Lactones

7.3.6.1 δ-Valerolactone

The simplest, unsubstituted six-membered monolactone is δ-VL. δ-VL can be synthesized in different ways such as via oxidation of 1,5-pentanediol, through Baeyer–Villiger oxidation of cyclopentanone or by ring expansion of tetrahydrofurfural (Figure 7.18) [169–171].

The first polymerization of δ-VL was described by Carothers et al. in 1932 after 29 days at room temperature [3]. Since then a tremendous amount of research has been devoted to the polymerization and copolymerization of δ-VL with the usage of a broad variety of catalysts (mainly metal-based or organocatalysts) and reaction conditions, which will not be further elaborated in detail. Poly(δ-valerolactone) (poly(δ-VL)) (Figure 7.18) is a semi-crystalline polymer with a T_g of −60 °C and a T_m around 58 °C. It is a rather strong material with a high Young's modulus of 570 MPa and a tensile strength of 12.5 MPa, but it is less flexible compared to poly(γ-BL) with an elongation at break of 150–200% [117, 172–174]. δ-Lactones in general exhibit a low-to-moderate conversion at conventional ROP conditions, and this conversion is strongly dependent on the presence and type of substituents on the six-membered ring [42].

Polymerization of analogs of δ-VL has received limited attention, certainly when compared to ε-CL or G analogs**.** The following sections will discuss a selection of δ-VL derivatives described in ROP, interesting in the context of (potentially) improved degradability.

7.3.6.2 Unsaturated δ-Lactones

As discussed above for four- and five-membered lactones, creating unsaturated (pending) structures on lactones or polyester backbones can enable functionalization of the lactone (before ROP) or polyester (post-polymerization modification).

5,6-dihydro-2H-pyran-2-one (DHP) is an α,β-unsaturated δ-VL (Figure 7.19a) that enables the generation of polymerizable, functional δ-lactones by a one-step Michael

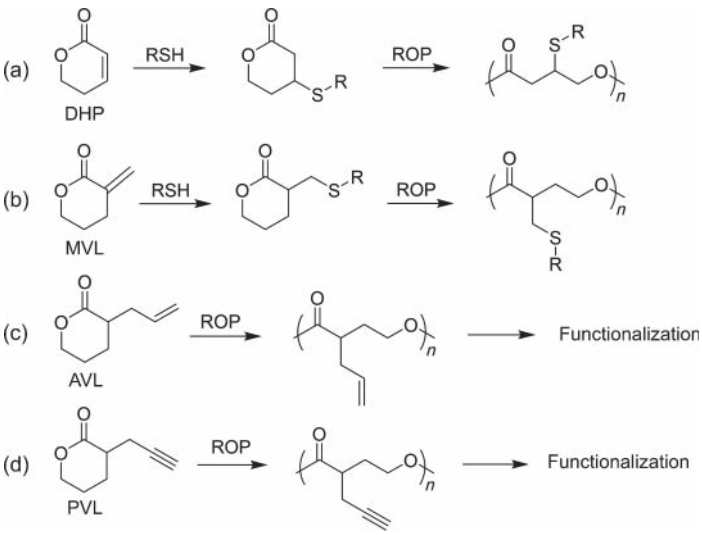


Figure 7.19 ROP and functionalization of unsaturated δ-lactones: (a) 5,6-dihydro-2H-pyran-2-one, (b) α-methylene-δ-valerolactone, (c) α-allyl-δ-valerolactone, and (d) α-propargyl-δ-valerolactone.

addition of thiols bearing various functionalities. ROP of these functionalized lactones has been described both in the presence of TBD and aided by methyllithium (aROP) [175, 176].

α-Methylene-δ-valerolactone (MVL), which can be synthesized from δ-VL, is another unsaturated δ-lactone in which the unsaturation is present as a pending methylene group at the α-position relative to the carbonyl group (Figure 7.19b). ROP of MVL was achieved with $Sn(Oct)_2$, TBD, DPP, or NHC catalysts. Functionalization, mainly performed by addition of thiols, has been described before executing ROP [177–181].

Finally, ROP of α-allyl-δ-valerolactone (AVL) (Figure 7.19c) and α-propargyl-δ-valerolactone (PVL) (Figure 7.19d) have been successfully executed as well. Various polymerizations and copolymerization have been described in which functionalization of the polyester chains always happened after polymer synthesis [182–188].

7.3.6.3 Ester-Substituted δ-Lactones

4-Carboalkoxyvalerolactone

Very recently, the ROP of ester-substituted δ-VLs has been published in which the ester function is located at the γ-position relative to the carbonyl group of the lactone. These 4-carboalkoxyvalerolactones (CAVLs) can be synthesized in three steps starting from malic acid (Figure 7.20). Malic acid is a biobased platform molecule and an intermediate in the Krebs cycle, widely available through microbial fermentation of biomass. In the first step, malic acid is treated with sulfuric acid (H_2SO_4) to create coumalic acid, which is subsequently esterified in the presence of an alcohol (methanol, ethanol, isopropanol, *n*-butanol, or *tert*-butanol) and hydrogenated over

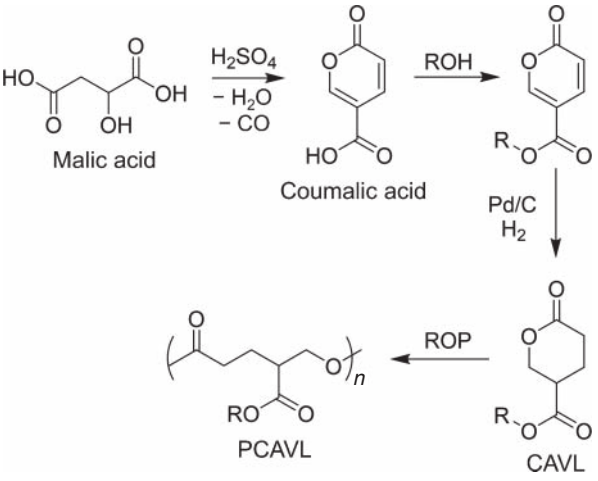


Figure 7.20 Three-step synthesis and ROP of CAVL to produce PCAVL. Source: Adapted from Fahnhorst and Hoye [189].

Pd/C in the presence of hydrogen gas (H_2) to create carboalkoxy-substituted δ-VLs (37–59% yields) [189–191].

These monomers could undergo bulk ROP in the presence of DPP at room temperature to produce linear polyesters with M_n values ranging between 8.0 and 10.1 kg/mol. Furthermore, bulk ROP at increased temperature (70 °C) allowed for the synthesis of high MM (M_n = c. 100 kg/mol) polymers containing small amounts of branched chain structures. Despite the monomers typically being racemic mixtures, the poly(carboalkoxy valerolactones) (PCAVLs) are semicrystalline, in which T_g, T_m, crystallinity, mechanical properties, and hydrolytic degradation rates vary with the type of alkoxy groups on the pending esters. For more details, the reader is referred to the research by Fahnhorst et al. [189–191].

Carbohydrate δ-Valerolactone

In 2009 Williams and coworkers [192] successfully polymerized a δ-VL monomer (acetic acid 5-acetoxy-6-oxotetrahydropyran-2-yl methyl ester [AOME]), synthesized from the carbohydrate derived molecule D-gluconolactone in two high yield steps (Figure 7.21).

In the first step, D-gluconolactone is reacted with acetic anhydride in the presence of a base and converted quantitatively to compound **2**. Subsequently, hydrogenolysis at 50 bar H_2 aided by Pd/C yielded AOME in 95% yield. The hydrogenolysis proceeded to selectively afford the syn-enantiomer (Figure 7.21). ROP was achieved in solution in the presence of $Sn(OBu)_2$ at 80 °C resulting in cyclic polyesters (PAOME) with M_n values of 1.8–7.3 kg/mol. Although amorphous polymers with a T_g of 18 °C were obtained, the materials were thermally stable showing thermal degradation at 250 °C [192]. Copolymerizations of AOME with LD [193, 194] or ε-CL [195] provided for high MM materials. Polymerization with LD resulted in random copolymers (25 mol% AOME) in which hydrolysis was observed to be four times faster than homopolymers of LD.

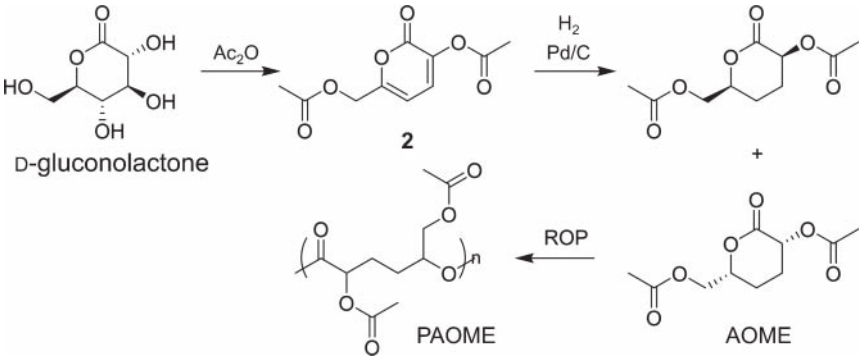


Figure 7.21 Two-step synthesis and ROP of carbohydrate-derived AOME.

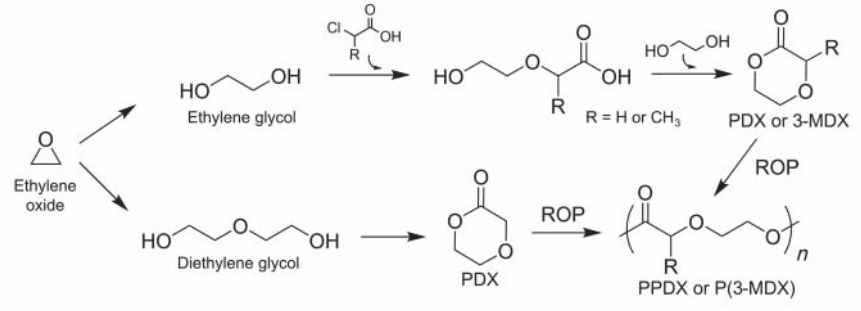


Figure 7.22 Synthesis and polymerization of p-dioxanone from ethylene glycol or diethylene glycol.

7.3.6.4 Ether δ-Lactones

Ether-δ-lactones are δ-lactone monomers containing an additional ether oxygen in their ring structure. The most well-known ether-δ-lactone in the field of ROP is *p*-dioxanone or 1,4-dioxane-2-one (PDX). PDX can be synthesized from ethylene glycol or diethylene glycol, which can both be obtained from petroleum-based feedstock as well as from biomass (Figure 7.22, R = H).

The addition of an ether functional group in a lactone ring changes the reaction properties of ROP as well as the final polymer features (Table 7.1). Poly(*p*-dioxanone) (PPDX) is a biodegradable polymer with a higher T_g and T_m than poly(δ-VL). Furthermore, it is slightly stronger and due to the oxygen atoms in the backbone, PPDX is more flexible. PPDX is most often used in degradable sutures (e.g. PDS® by Ethicon) and to a lesser extent in other applications in the medical field [198, 199]. The ring strain of PDX is comparable to the one of δ-lactones. However, the entropic change during ROP is more pronounced for PDX than for poly(δ-VL), which could be explained by increased flexibility due to the presence of the ether group in the lactone ring.

Only a few dioxanone analogs have been described in literature with regard to ROP. D,L-3-methyl-1,4-dioxanone (3-MDX) (Figure 7.22, R = CH_3), a PDX containing a racemic methyl group at the α-position relative to the carbonyl functional

Table 7.1 Polymerization thermodynamic features and polymer properties of PDX and analogs.

Monomer		ROP thermodynamics			Polymer properties				
	$[M]_0$ (M)	ΔH^0_p (kJ/mol)	ΔS^0_p (J (K/mol))	T_c (°C)	T_g (°C)	T_m (°C)	Young's modulus (MPa)	Tensile strength (MPa)	Elongation at break (%)
 PDX	Bulk (~12 M)	−15.7	−28.9	271	−30 to −1	110	620	50	500–600
	Solution (1 M)	−15.7	−49.7	43					
 3-MDX	Bulk (~10 M)	−9.9	−20.1	216	−24	Amorphous	—	—	—
	Solution (1 M)	−9.9	−41	−32					
 2-MDX	Bulk (~10 M)	−10.9	−29.6	95	−32 to −25	Amorphous	—	—	—
	Solution (1 M)	−10.9	−41	−57					

Source: Data obtained from Refs. [42, 196, 197].

group (Table 7.1), was synthesized and polymerized for the first time in 2001 [196, 200]. The synthesis method is based on the synthesis of PDX from ethylene glycol but in the presence of D,L-chloropropionic acid instead of chloroacetic acid (Figure 7.22). 3-MDX has a reduced ring strain compared to PDX. This can be explained by the emergence of a more preferable angle at the ether bond [42]. The random copolymers [201] and block-copolymers [202] of 3-MDX with PDX have been studied, as well as the block copolymerization of poly(PDX-*co*-3-MDX) with ε-CL [203]. Another PDX analog, the cyclic esteracetal 2-methyl-1,3-dioxane-4-one (2-MDX) (Table 7.1), was synthesized via Baeyer–Villiger oxidation of the commercial product 2-methyltetrahydrofuran-3-one [197]. ROP of 2-MDX was performed in the presence of diethylzinc ($ZnEt_2$) as a catalyst and benzyl alcohol as initiator. While only low $ZnEt_2$ loadings led to poly(2-MDX) of up to 30 kg/mol, high catalyst loadings led to a loss of acetaldehyde and the formation of poly(β-PL). Degradation of poly(2-MDX) at room temperature proceeded significantly faster than degradation of poly(β-PL) due to the presence of the labile acetal function in the polymer backbone. The cationic polymerization of 2-MDX has also been described in the presence of DPP [204].

7.3.6.5 Dilactones

Dilactones are cyclic molecules containing two lactone functional groups instead of one. This additional functional group affects both polymerization characteristics and the properties of the resulting polymers. Their chains contain shorter repeated ester units (less C-atoms) compared to polymers obtained from monolactones, often making the materials less hydrophobic and less flexible, while increasing the T_g.

The most important six-membered dilactones are without any doubt glycolide (G) (Figure 7.23, R = H) and LD (Figure 7.23, R = CH_3). Polyglycolide or poly(glycolic acid) (PGA) and poly(lactide) or poly(lactic acid) (PLA) can either be synthesized by condensation polymerization (polycondensation) of the corresponding α-hydroxy acids glycolic acid (GA) and lactic acid (LA) or via ROP of G and LD, respectively (Figure 7.23). However, as mentioned previously, due to the nature of polycondensation, reaching high MM is challenging [205–207]. While measures exist to remove water from the equilibrium (e.g. azeotropic polycondensation [208, 209] and solid-state polycondensation [210]) or increase molar masses (e.g. chain extension [211, 212]), these approaches will not be further discussed here. On the other hand, ROP of G and LD circumvents the challenge with equilibrium in polycondensation and is accordingly the preferred route in industry to obtain high MM polyesters.

Glycolide and Lactide

The most commonly described and industrially applied method to synthesize G and LD is a two-step process (Figure 7.23). The first step consists of a condensation polymerization of the corresponding α-hydroxy acid to produce a low MM pre-polymer. Subsequently, this pre-polymer is broken down in the presence of a catalyst (e.g. ZnO, $Sn(Oct)_2$, and SnO) to form dilactones via a backbiting depolymerization reaction. This reaction is typically performed at high temperatures and under reduced

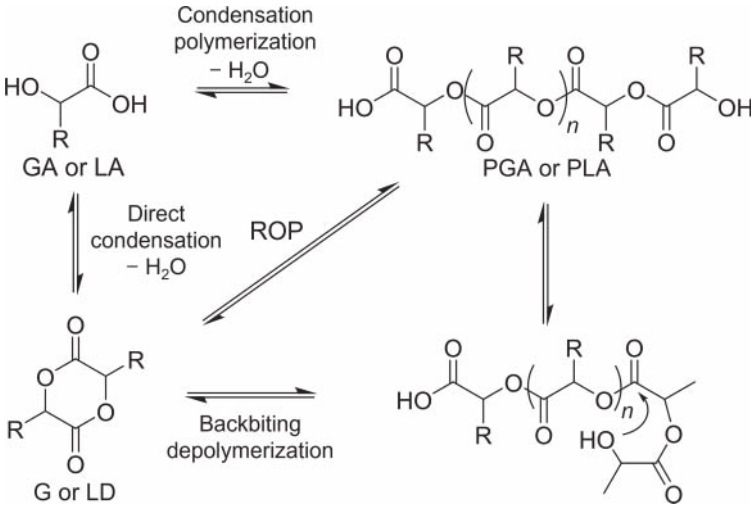


Figure 7.23 Condensation polymerization of GA (R = H) or LA (R = CH_3) to PGA or PLA, backbiting depolymerization of PGA or PLA to create G or LD and ROP of G or LD toward PGA or PLA.

pressure to constantly remove the dilactones and drive equilibrium toward depolymerization [213–215]. Although widely described and applied, this two-step process is time- and energy-intensive, whereby often only mediocre dilactone yields are obtained with, in the case of LD, loss of control over the stereochemistry [213, 216]. Another widely described method to synthesize G and LD is through cyclization of the salts of halogen-derived hydroxycarboxylic acids [217]. More recently different one-step synthesis methods have been developed directly starting from GA and LA or their corresponding esters [218, 219]. For a more detailed overview of the most prominent synthesis methods the reader is referred to some interesting reviews [217, 220].

Compared to six-membered monolactones, G and LD are thermodynamically much easier to polymerize. The reason for this can be found in the higher ring strain of dilactones compared to monolactones resulting from the presence of two ester groups (instead of one) with a planar conformation [221, 222]. In addition, the entropy change for ROP is much lower for δ-VL compared to LD (see Figure 7.6), facilitating PLA synthesis.

Poly(Glycolic Acid)

GA, which is often the main starting compound to produce G and PGA (Figure 7.23), is industrially obtained, among others, by hydrolysis of monochloroacetic acid with sodium hydroxide or by treating formaldehyde with carbon monoxide and water (main method) [56]. GA is widely used in the food industry as a preservative and flavor agent, in the cosmetic and pharmaceutical industry as a skin care product, in the textile industry as a tanning and dyeing compound, etc. [223]. Nevertheless, GA is a naturally occurring compound that can be biochemically obtained as well through

enzymatic processes [223]. Due to its biological origin, GA can be assimilated by living organisms and be eliminated via the Krebs cycle as water and carbon dioxide [222]. The good availability and biocompatibility of GA thus make it an attractive monomer for biodegradable (co-)polymers.

PGA is the structurally simplest aliphatic polyester. It is a semicrystalline, biodegradable, and biocompatible thermoplastic material first described and patented by DuPont in 1954 [4]. PGA has a T_g value of 35–40 °C, a T_m around 225–230 °C, and a high degree of crystallinity of 45–55% [224]. Compared to most other degradable polyesters, PGA is a very strong material with high tensile strength (115 MPa) and Young's modulus (7 GPa) resulting from its high crystallinity [225]. In 1962 the American company Cyanamid Co. developed PGA as the first synthetic adsorbable suture under the tradename Dexon®, which has been commercially available since the early 1970s [226–228]. This invention has led to the evaluation of PGA in other biomedical applications, such as in implants, orthopedics, drug-delivery systems, and tissue engineering [229, 230]. Nevertheless, PGA generally degrades quite fast *in vitro* and high levels of GA in the body can result in undesired inflammatory responses. Therefore, copolymers of LD and G, poly(lactic acid-*co*-glycolic acid) (PLGA), have been widely investigated in the context of biomedical applications and have been used in sutures (Vicryl®, Panacryl®, Polysorb®, Purasorb®, etc.), tissue engineering and drug delivery (Lupron®, Zoladex®, etc.) [225, 230, 231]. Changing compositions of G and LD allows tailoring of properties toward desired mechanical features and degradation rates for specific applications.

Poly(Lactic Acid)

PLA is a biodegradable, biorenewable, and biocompatible aliphatic thermoplastic polyester. LA has various natural sources; it is produced from pyruvate in the presence of the enzyme lactate dehydrogenase in metabolic processes in various living organisms.

Due to the presence of a methyl group at the α position of the hydroxy acid, LA consists of two different stereoisomers: L-lactic acid (L-LA) and D-lactic acid (D-LA) (Figure 7.24). Today, LA is industrially synthesized by microbial fermentation of carbohydrates (from corn, sugar beet, sugar cane, etc.), in which micro-organisms mainly produce the L-form [206, 232, 233]. LA can also be synthesized chemically from acetaldehyde and hydrogen cyanide to form lactonitrile, which is further hydrolyzed to LA resulting in a 50 : 50 mixture of L- and D-LA [56]. LA and its salts or esters are used in the food industry as flavoring agents, emulsifiers, or to inhibit bacterial spoilage. In addition, similar to GA, LA can be used as a tanning agent in the textile industry or is widely applied in pharmaceuticals or cosmetics [233].

PLA is top of the league in today's growing synthetic bioplastics market. In 2020, 2.11 million tons of bioplastics were produced globally, of which 13.9% was PLA [234]. PLA owes its popularity to the wide availability and promising cost structure of LA, as well as its excellent rigidity and tensile strength, comparable with commodity plastics such as poly(ethylene terephthalate) (PET) and polystyrene (PS) [235, 236].

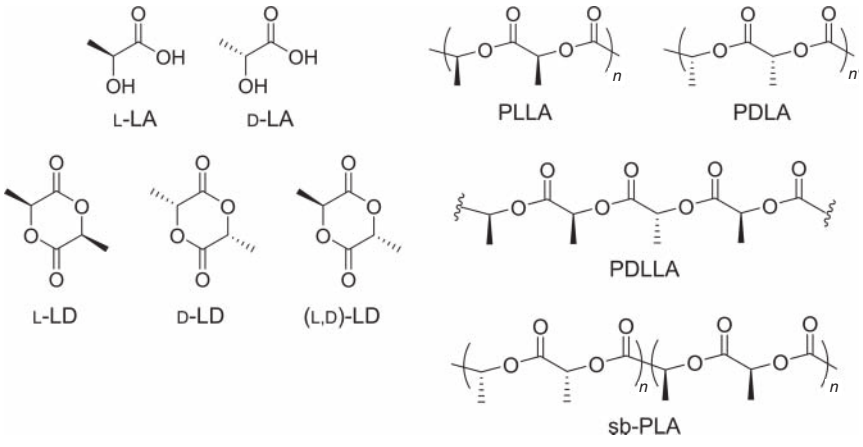


Figure 7.24 Stereochemistry of lactic acid (LA), lactide (LD), and PLA.

PLA is currently used primarily in rigid and flexible packaging, textiles, consumer goods, and medical applications (sutures, implants, drug-delivery systems, etc.).

Due to the stereochemistry of LA, LD and PLA can be produced in different isomeric forms. In contrast with G, LD consists of three stereoisomers: (L,L)-LD (L-LD), (D,D)-LD (D-LD), and (D,L)-LD or meso-LD (Figure 7.24). The properties of PLA are strongly dependent on the stereochemical configuration of the chains. The amount and sequence of L and D chiral centers will have an influence on mechanical and thermal properties as well as crystallinity and degradation rate. PLA with pure L (PLLA) or pure D (PDLA) rotating chiral centers, also called isotactic PLA (Figure 7.24), results in materials with a high crystallinity due to the possibility of the chains to easily stack into ordered structures. The high crystallinity of isotactic PLA results in excellent mechanical properties and a high T_m value (Table 7.2). When optical purity decreases by addition of for example randomly distributed D units in PLLA (atactic PLA, PDLLA [poly((D,L)-lactic acid)], (Figure 7.24)), the crystallinity, T_m and T_g values will slowly drop until the polymer becomes completely amorphous with addition of 12–15% D units. Atactic, amorphous PLA has no melting point. In addition, amorphous PLA is less strong than the semi-crystalline counterparts, showing a reduced tensile strength and Young's modulus [215, 237]. Another interesting feature of PLA lies in the possibility to create stereocomplexes. Mixing of PLLA and PDLA chains or block copolymers of PLLA and PDLA (stereoblock PLA [sb-PLA], (Figure 7.24)) can result in packing of L-based chains with D-based chains to form different crystal structures, called stereocomplex crystals. Stereocomplex PLA exhibits even better thermal stability and mechanical strength than isotactic PLA resulting in materials with a very high T_m (Table 7.2).

Although PLA is often proposed as the bioplastic with the highest potential to drive the biobased plastics industry, it exhibits some drawbacks which put a limit on the sustainability and applicability of this polyester. Although PLA is strong, it also is a brittle material, exhibiting a low-impact strength and elongation at break

Table 7.2 Thermal and mechanical properties of PLA materials with different stereochemistry.

Polymer	T_g (°C)	T_m (°C)	Tensile strength (GPa)	Young's modulus (GPa)	Elongation at break (%)
PGA	35–40	225–230	0.08–0.98	3.9–14	30–40
PLLA/PDLA	50–65	170–190	0.12–2.3	6.9–9.8	12–26
PDLLA	50–60	–	0.04–0.05	1.5–1.9	5–10
Sc-PLA	65–72 [224]	220–240	0.88	8.6	30

Source: Data based on Tsuji [224] and Hirata and Kimura [237].

(Table 7.2). In addition, this bioplastic has a poor melt strength and low melt viscosity and elasticity which limits its processability in strong elongational-flow-dominated processes, such as film blowing, blow molding, and foaming [238–241]. Although PLA is described as biodegradable, its degradability is rather limited and only occurs at a sufficient rate under industrial composting conditions. Although its degradability is described as limited, for certain applications PLA is too hydrolytically unstable. Besides copolymerization, polymer blending, or the preparation of polymer composites, functionalization of PLA can provide solutions for some of these deficiencies. For an overview of some interesting functionalized G and LD monomers used in ROP the reader is referred to some excellent reviews [49, 242, 243].

7.3.7 Seven-Membered Lactones

In general, seven-membered rings have a higher ring strain compared to their five- and six-membered counterparts, which results in high equilibrium conversions during ROP. They are less commonly found in nature and are thus mainly obtained from fossil-based sources, although more sustainable routes are emerging [244].

7.3.7.1 ε-Caprolactone

The simplest seven-membered lactone, ε-CL is used to make the well-established biodegradable polymer, PCL. The main synthetic route makes use of petroleum-derived cyclohexanone (Figure 7.25). This industrial process (i.e. Baeyer–Villiger oxidation of cyclohexanone) uses peracetic acid and is far from being "green," entailing ecological and toxicological concerns [245, 246]. Hence, efforts are ongoing to find a competitive biobased route. Novel strategies suggest a synthesis starting from the biobased platform chemical 5-hydroxymethylfufural, in which ε-CL is obtained from the intermediary product 1,6-hexanediol and in some cases 6-hydroxyhexanoic acid (Figure 7.25) [246, 247].

A myriad of catalysts can be used for the ROP of ε-CL, which can proceed accordingly via anionic, (monomer-activated) cationic, enzymatic, or coordination–insertion ROP. For an extensive review on the matter of catalysts and reaction conditions, the reader is referred to the work of Labet and Thielemans [245].

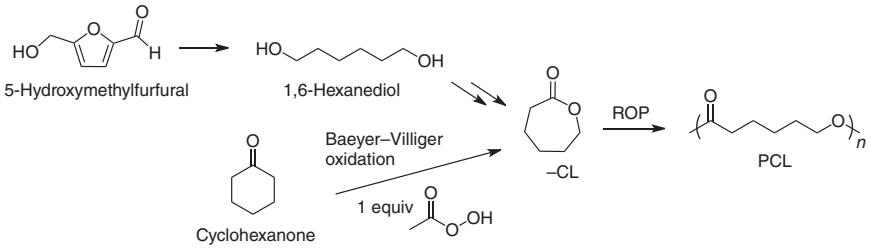


Figure 7.25 ROP and synthesis routes toward ε-CL via the biobased platform chemical 5-hydroxymethylfurfural and industrial process from cyclohexanone via Baeyer–Villiger oxidation.

The first mention of PCL dates back to the ROP reported by Carothers in the 1930s. PCL is semicrystalline, with a crystallinity content ranging from 33% for higher MMs to 70% for lower MMs [248]. It has a low T_g (–65 to –60 °C) and a low melting range of 56–65 °C and shows elastic behavior at room temperature [245, 248, 249]. Mechanical properties also depend strongly on MMs; tensile strength ranges from 4 to 785 MPa, elongation at break from 20% to 1000% with a Young's modulus of 0.21–0.44 GPa [245]. The low T_m facilitates thermal processing, for example in 3D printing (e.g. Facilan™ filament), compression molding, and heat-deformable prosthetics (X-lite™) [250]. After warming it in hot water it is used as a modeling compound for crafting purposes (e.g. Shapelock™ and Friendly Plastic™). Because of its ease of miscibility with many other polymers, PCL is also a popular plastic used for polymer blends with (non)-degradable plastics [251]. PCL is sold under the tradename Capa™ and Capromer™ for applications ranging from compostable food packaging to polyols as precursor components for the development of polyurethane elastomers.

PCL is both biocompatible and biodegradable, although the time scale of degradation largely depends on the environment. In humans, the degradation of PCL is very slow (two to four years), because of the shortfall of appropriate enzymes and inherent hydrophobicity [245, 249, 252, 253]. Its applications in the biomedical field were therefore limited to drug-delivery systems and sutures that require longer active periods (e.g. Capronor™ capsules). With the advent of tissue engineering, PCL regained traction because its material properties enable facile shaping into a multitude of scaffolds. Sutures made from copolymers of ε-CL with G (Monocryl™, Monocryl Plus™, and Suruglyde™) and LD (Neurolac™) are widely available. A review by Woodruff and Hutmacher describes in detail the applications in the biomedical field [249].

Nevertheless, PCL is biodegradable by a large population of fungi and bacteria [254]. These include both anaerobic and aerobic bacterial species from diverse habitats such as a heat-resistant strain of *Aspergillus* sp. capable of degrading PCL to completion after six days at 50 °C [251, 254]. In the presence of suitable bacteria and enzymes, the degradation time is significantly reduced to an average of several months. Enzymes that assist the degradation of PCL include esterases, lipases, and cutinases. The latter is believed to be effective because the polyester bears sufficient structural resemblance to cutin, a natural waxy polymer found in plant cuticles

[251, 255, 256]. The greater abundance and population of species capable of degrading this plastic could indicate that PCL is more prone to degradation in nature than other biodegradable plastics such as PLA [251]. Toxicological tests showed that the degradation product ε-caproic acid is less harmful to living organisms than the degradation product of PLA, LA [257]. The major drawbacks of PCL that limit its degradability and applications are its high crystallinity, hydrophobic nature, and lack of functionality [54, 252, 253].

7.3.7.2 Substituted and Functionalized ε-Caprolactone

As is the case with other lactones, properties influencing the degradability can be fine-tuned by substituting the ε-CL monomer structure with alkyl- and/or functional groups.

Alkyl Substitutions

Whereas PCL is generally semicrystalline, the addition of alkyl-groups disrupts crystallite formations by hindering stacking of the backbone, rendering the polyesters fully amorphous with low T_gs [258]. Alkyl-substituted PCLs bring added value as soft segments in block copolymers with more crystalline polyesters (e.g. PLA or PCL) and widen the scope of their applications to where ductility and elasticity are required, i.e. as thermoplastic (bio)elastomers [259, 260].

Alkyl substituents also reduce the propagation rate of polymerization relative to that of ε-CL, the extent of which depends on the nature and position of the substituent and the ROP mechanism. The addition of alkyl groups also introduces chirality into the monomers, which can result in different selectivity and propagation rates when using enantioselective catalysts [261–264]. Similarly, the rate of enzymatic hydrolysis is also influenced by the length of the alkyl pendant groups, albeit to a lesser extent than the rate of polymerization [265]. The choice of the length of the alkyl chain is always a trade-off, as it increases hydrophobicity but also the amorphous content of the resulting polymer [244].

A promising alkyl-substituted analog to ε-CL is menthide (Figure 7.28), due to its biorenewable nature. It can be synthesized via Baeyer–Villiger oxidation of (−)-menthone, a ketone derivative of (−)-menthol, a plant extract used in large quantities for a multitude of purposes across different industries [266]. The ring strain (i.e. ΔH_p) of menthide is comparable to that of ε-CL. The ΔS_p value, on the other hand, is significantly lower as, in accordance with the Thorpe–Ingold effects, the ring is more stable due to its bulky side-groups. Unsurprisingly, the polymerization rate is significantly lower than that of ε-CL because of the steric hindrance of the ester group by the isopropyl substituent. Nonetheless, ROP yields amorphous poly(menthide) with a low T_g (–25 °C) and a M_n up to 90 kg/mol [266, 267].

The steric hindrance of the alkyl groups at the ε-position can inhibit or slow down transesterification reactions. These side reactions are usually undesirable as they lead to random copolymers with large dispersities and lower MM for one-pot syntheses. Wilson et al. proved this by copolymerizing menthide with higher-membered lactones (≥ 8), which have a slower polymerization rate, and used this for controlled one-pot synthesis of the copolymers [267].

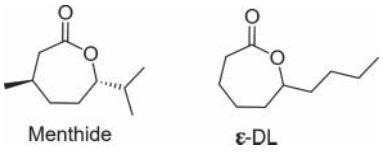


Figure 7.26 Chemical structures of menthide (right) and ε-decalactone (left).

Another biobased seven-membered lactone is ε-decalactone (ε-DL), which is derived from natural castor oil (Figure 7.26) [260]. The T_c of poly(ε-decalactone) is sufficiently high for the ROP to take place at elevated temperatures to obtain high conversion (96% at 150 °C), despite the long alkyl chain at the ε-position slowing down the polymerization [268]. The fully amorphous polymer has a T_g of −58 °C [260].

The physical crosslinking via multiphase separation of crystalline (PLLA) segments and soft segments (poly(menthide) or poly(ε-decalactone)) gives the block copolymers improved and tunable mechanical properties. These thermoplastic bioelastomers showed excellent elongations at break of 530–960% and 723–1060%, respectively [260, 268, 269].

Pendant Functional Groups

As described previously for other lactones, attaching functional groups to the backbone of the polyesters can be a powerful way to influence degradability. A crucial drawback of PCL in this regard is its hydrophobicity, which can be countered by incorporating polar functionalities such as hydroxyl groups. As mentioned before, suitable protective groups are necessary for the ROP of lactones. A prominent example in the category of protected lactones is 1,4,8-trioxaspiro[4.6]-9-undecanone (TOSUO), which is readily homo- and copolymerized (Figure 7.27).

The ketal group protects the ketone functionality and is formed by reaction with a diol. Deprotection forms the ketone group in the backbone, which can then be reduced to a hydroxyl group. Alternatively, this poly(ketone-ester) can be obtained more directly by the ROP of oxepane-1,5-dione (Figure 7.27), provided

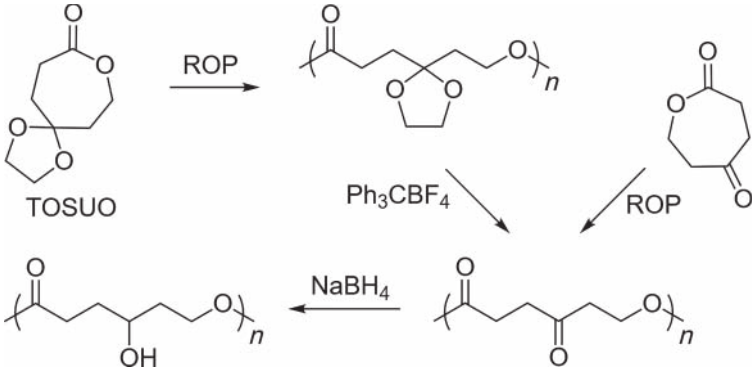


Figure 7.27 Route to poly(4-hydroxy-ε-caprolactone) from the reduction of poly(ketone ester) which is obtained from ROP of TOSUO and subsequent deprotection vs. direct ROP of oxepane-1,5-dione.

a catalyst incapable of undergoing side reactions with the ketone groups is used, such as tin-based alkoxides [48]. The cyclic ketal groups themselves can also bring added value as they decrease the crystallinity, render the polymer more flexible, and can reduce the T_m to room temperature or body temperature depending on the anticipated application of the soft material (e.g. in biocompatible physical-sensing platforms). Values for elongations of up to 1500% were observed for poly(CL-*co*-TOSUO) [270].

Obtaining PCL with amino pendant groups can be accomplished by polymerization of γ-(carbamic acid benzyl ester)-ε-CL followed by deprotection [271]. The poly(ketone ester) can also be derivatized to create an amine by reacting it with 2-hydroxyethyl hydrazine [50], or it can be used to create a graft copolymer by reacting it with an aminooxy-terminated poly(ethylene oxide) [272].

As previously mentioned, halide pendant groups offer interesting post-polymerization modification options. Yao et al., for instance, substituted the chloro-groups from ROP of α-Cl-ε-CL with azido functions to subsequently graft biocompatible rosin ester moieties onto the polyester. The resulting polymer was capable of fast microbial degradation, despite decreased hydrophilicity and higher T_g [273]. Other halogen-functionalized PCL homo- and copolymers are reported in literature, including that of α-fluoro-ε-CL [274], α-iodo-ε-CL [275], α-bromo-ε-CL [276], γ-(2-bromo-2-methylpropionate)-ε-CL, and γ-bromo-ε-CL [48, 277, 278]. The reader is referred to the reviews by Jérôme and Lecomte for further information on the matter [28, 48]. Elimination of halogen atoms attached to larger pendant groups or directly attached to the PCL backbone has also been reported. This dehydrohalogenation results in either pendant groups with allyl functions or PCL with the unsaturated function in the polymer backbone which can be further functionalized [55, 278].

7-Allyl-1-oxa-cycloheptan-2-one (Figure 7.28a) is an example of ε-CL substituted with a pendant allyl group forming poly(6-allyl ε-caprolactone) upon ROP, which could be quantitatively transformed via bromination, epoxidation, and silylation [279]. Similarly, acrylate-functionalized ε-CL, e.g. γ-acrylic-ε-CL, can also undergo ROP and can then be derivatized via Michael addition of various thiols without the necessity of an organometallic catalyst. However, some loss to cross-linking and backbiting reactions is inevitable [28]. Alkyne-substituted ε-CL such as α-propargyl-ε-CL (Figure 7.28b) can also undergo ROP and subsequently a click reaction with azide-capped compounds for post-polymerization modification [280, 281].

Recently, Wu et al. reported the ROP of ε-CL substituted with a phenylseleno group at the α-position (Figure 7.28c). Through an oxidative elimination, the pendant group is replaced by a double bond in the backbone structure, similar to the Cl-elimination reaction seen in Figure 7.7, but with the added benefit that the phenylseleno groups can be recovered (up to 90%) and reused. The authors found that both the poly(α-phenylseleno-ε-caprolactone) and unsaturated polyester, resulting from its oxidation, hydrolyze more slowly than PCL in acidic conditions. However, derivatization to a suitable functional group could increase the degradability [54]. Interestingly, this route led to a trans-(E) configuration at

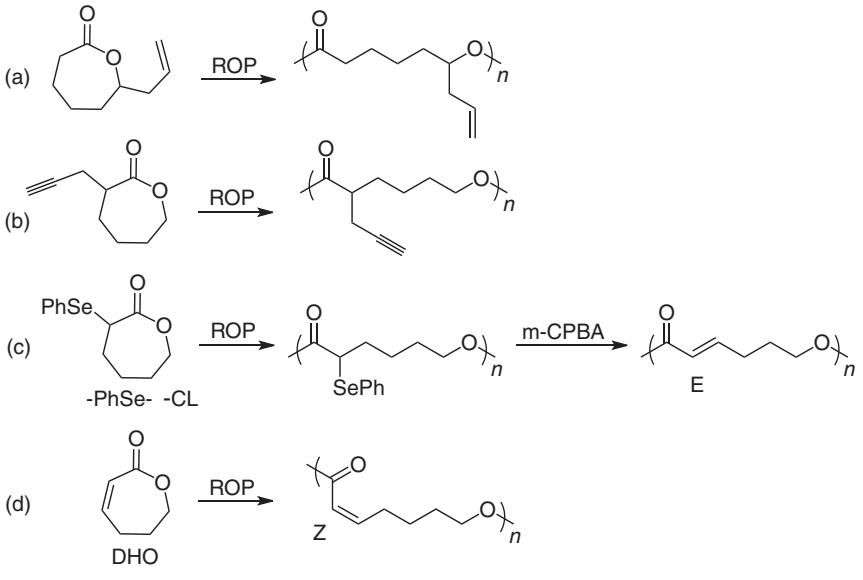


Figure 7.28 Selection of ROP reactions to obtain PCL-derived unsaturated polymers: (a) 7-allyl-1-oxa-cycloheptan-2-one, (b) α-propargyl-ε-caprolactone, (c) α-phenylseleno-ε-caprolactone, (d) 6,7-dihydro-2-(5H)-oxepinone.

the double bond, whereas the direct ROP of 6,7-dihydro-2-(5*H*)-oxepinone (DHO) (Figure 7.28d) results in a cis-(Z) configuration. Because of the trans-configuration, the polymer becomes stiffer and the T_g is higher (−28 °C) compared to that of the polymer of DHO (−50 °C) [54, 282].

7.3.7.3 Ether-ε-Lactones

Ether groups can be incorporated into the polymer backbone to effectively increase the hydrophilicity of PCL. Research on polymerizations of ether-ε-caprolactones has focused on 1,5-dioxepan-2-one (DXO), which can be synthesized from 4-oxotetrahydropyran via Baeyer–Villiger oxidation (Figure 7.29) [283].

ROP proceeds readily using numerous catalysts of metallic, organic, and enzymatic nature to yield high MM poly(1,5-dioxepan-2-one) (PDXO). PDXO is an amorphous, hydrophilic poly(ether ester) with a low T_g of −39 °C, which readily hydrolyzes [284].

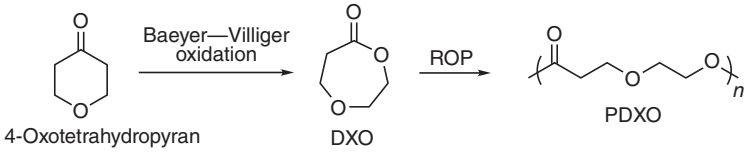


Figure 7.29 Synthesis of DXO from 4-oxotetrahydropyran and ROP forming the poly(ether ester) PDXO.

These properties greatly limit the applications of PDXO as homopolymers but make it attractive for uses in copolymers, which widens the scope of the resulting plastic to biomedical applications. These copolymers combine the flexibility and hydrophilicity of PDXO with the stiffness of, among others, PLLA and PCL [285–287].

The hydrophilicity, as measured by the contact angle, is improved by increasing the ratio of DXO to the more hydrophobic block comonomer. Similarly, PDXO blocks are more readily hydrolyzed compared to the more hydrophobic PCL and PLLA blocks [285, 288, 289]. After 23 weeks in a buffer solution at 37 °C, 70% of the DXO monomers and 10–20% of the L-LA units were hydrolyzed [289]. Despite the instant hydrolysis, the block copolymers of DXO and L-LA could retain good tensile properties (elongation of 600–800% and stress at break of 8–20 MPa) for several months [285].

7.4 Relations Between ROP Polymers and Degradability

The biodegradability of a polymer does not necessarily coincide with that of the (biobased) feedstock used to synthesize the monomer or polymer. The degree to which a polymer can (bio)degrade depends on the chemical composition of its chains and their behavior at macromolecular level, determining the possibility for water and/or enzymes to break down the chains and for micro-organisms to assimilate and convert the resulting oligomers and/or monomers to water, carbon dioxide or methane, and biomass. More details on the mechanisms of (bio)degradation can be found in Chapter 2 of this book.

In general, due to their main chain ester linkages, (aliphatic) polyesters are inherently susceptible to (bio)degradation. Nevertheless, the rate and ease of (bio)degradation do not exclusively depend on the presence of ester bonds. Characteristics such as crystallinity, molar mass, and hydrophilicity also affect a polyester's sensitivity to degradation [290]. Hence, substitution and functionalization of lactones and polyesters aid in changing these characteristics, and thus, substantially influence (bio)degradability. In this section, we will briefly discuss a few interesting examples of such relations in order of ring size, focusing on hydrolysis and not complete biodegradation.

The group of Lu [111] performed hydrolysis tests in alkaline solutions on homopolymers of α-methylene-β-butyrolactone (MBL) compared to poly(β-BL) and random copolymers of (β-BL) and MBL (see also Section 7.3.4.4). The polymers were dissolved in toluene or tetrahydrofuran in the presence of an amine (triethylamine or diisopropylethylamine) and were either heated (80 °C) or kept at room temperature while stirring. The presence of the vinylidene pendant groups in the polymer backbone resulted in faster hydrolysis rates compared to poly(β-BL), even at room temperature. Significant changes in MM were observed for PMBL (homopolymer of MBL) (88% loss) compared to poly(β-BL) (10% loss) at 80 °C after 12 hours. Increases in dispersity were linked to the chain scission mechanism of degradation taking place. Adjusting the amount of MBL units in the copolymers

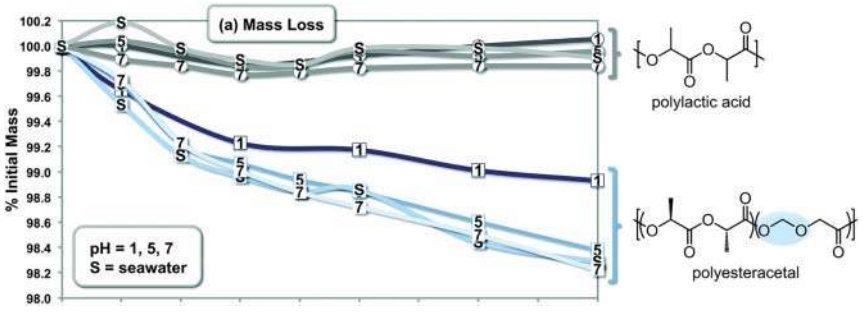


Figure 7.30 Whereas poly(DL-lactide) (PDLLA) is not affected, the polyesteracetal (4% DOX) shows considerable molar mass loss upon exposure to aqueous environments of pH 1, pH 5, pH 7 (distilled water), and seawater, over 45 days. Source: Reproduced from Martin et al. [167] with permission from the Royal Society of Chemistry.

(9–46% of MBL) could enable tuning of the degradability of the final polymer chains.

Miller and coworkers [167] described an improved hydrolytic degradability of PLA by copolymerization of (L,L)-LD with 1,3-dioxolan-4-one (DOX) to create polyesteracetals (also see Section 7.3.5.2). The acetal functional group in the main chain results in a more hydrophilic backbone with weaker linkages. Hydrolysis tests were performed on thin films (0.25 mm thickness) immersed and stirred in aqueous acidic solutions of pH 1, 5, and 7 (distilled water) and seawater (Atlantic Ocean, pH = 7.5) at room temperature for 45 days.

The mass of the films as well as the molar mass (gel permeation chromatography) were monitored over time after rinsing and drying of the films (Figure 7.30, only showing mass loss). A polyesteracetal copolymer with 4% DOX was compared to a commercial, rather amorphous Ingeo™ PLA (Natureworks), approximated as PDLLA. Figure 7.30 shows that the polyesteracetal copolymer lost more than 1% of its mass (and up to 35% of its molar mass) over 45 days, while PDLLA did not show noticeable degradation under all applied conditions. In neutral conditions (distilled water, pH 7) the polyesteracetal copolymer degraded most rapidly by mass, while molar mass loss was most pronounced under acidic conditions. Although the mechanism of degradation was not studied in this work, the authors presumed the hydrolytic cleavage to occur at the less sterically hindered acetal groups or glycolic ester groups instead of at the lactic ester groups, with formaldehyde being the final by-product [167].

As mentioned in Section 7.3.6.3, Williams and coworkers [192] performed ROCOP of (L,L)-lactide (monomer of PLLA) with a new carbohydrate-based six-membered lactone containing two methyl ester side groups (AOME), resulting in random copolymers with 1 (RP1), 6 (RP2), 11 (RP3), and 25 wt% (RP4) AOME. Incorporation of AOME led to copolymers with a lower degree of crystallinity and a lower T_g. While RP2 and RP3 showed splitting of the melting peak due to microphase separation of both crystalline regions, RP4 was completely amorphous. Degradation tests were performed on spin-coated films of the copolymers. Static

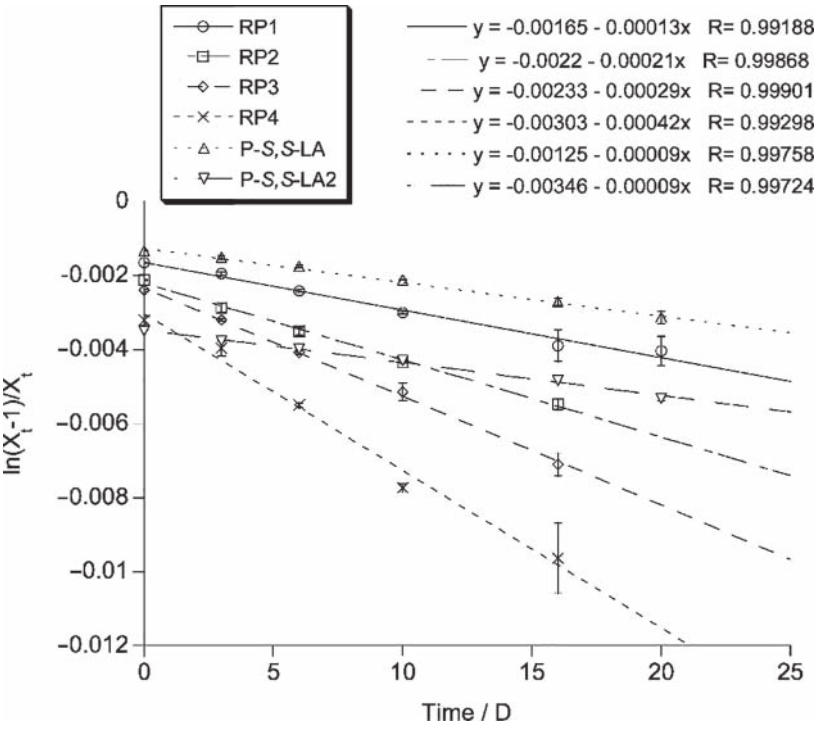


Figure 7.31 Plots of $\ln((X_t - 1)/X_t)$ vs. time for the copolymers (RP1 (88 kg/mol), RP2 (68 kg/mol), RP3 (61 kg/mol), RP4 (44 kg/mol), P((L,L)-LD) (P–S,S–LA 108 kg/mol. P–S,S–LA2 41 kg/mol). Each degradation experiment was conducted three times, and the errors for each measurement are included. Source: Reprinted with permission from Tang et al. [193]. 2010 American Chemical Society.

water contact angle measurements on the films showed a decrease in contact angle (RP4: 7° lower than P–S,S–LA (= PLLA)) with more incorporation of AOME, proving the higher hydrophilicity of AOME compared to LD.

Degradation experiments were performed in $CHCl_3$ (2 mg polymer/ml) (to dissolve the polymers) and phosphate-buffered saline (pH 7.4) at 25 °C. Figure 7.31 shows the loss in molar mass (M_n) over time with X_t being the degree of polymerization ($X_t = M_{n,t}/M_0$ with $M_{n,t}$ the number average MM at time t and M_0 the MM of the monomer). While PLLA showed a constant rate of degradation independent of initial MM, copolymers of AOME and (L,L)-LD exhibited a higher rate of degradation, while the rate increased with higher AOME contents. This higher rate of degradation was attributed to the greater hydrophilicity of the copolymers compared to PLLA.

Li et al. [291] studied the hydrolysis of copolymers of LA and GA (ratio 1 : 1, not made via ROP), PLGA, in phosphate-buffered solutions with pH 7.4. The crucial difference lies in the sequencing of the monomer units. They compared the degradation of PLGA with alternating sequences (named polyLG with MMs of 16 and 26 kDa) to that of L-PLGA (copolymer of L-LA and GA) and PLGA (copolymer of racemic LA and GA) with random sequencing (named R-SAP and R-ROP with MMs of 31

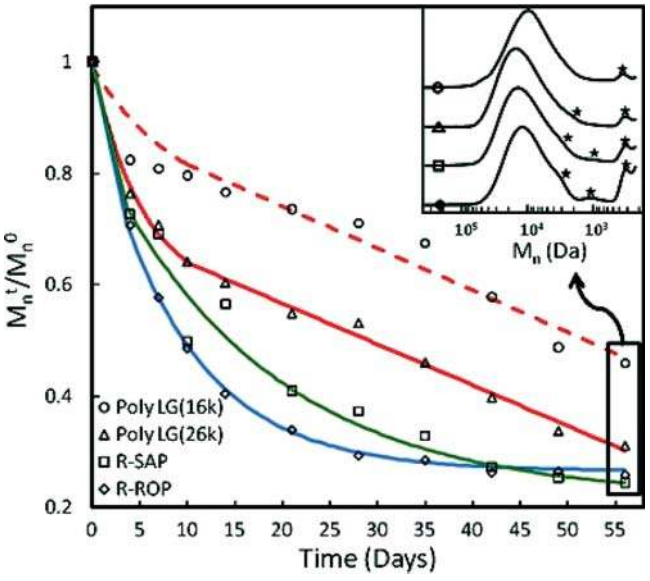


Figure 7.32 Hydrolysis profiles of PLGA copolymers with alternating (○ 16 kDa, △ 26 kDa) and random sequencing (□ L-PLGA (R-SAP), ◇PLGA (R-ROP)) normalized relative to their original M_n. Source: Reprinted with permission from Li et al. [291]. Copyright 2011 American Chemical Society.

and 32 kDa, respectively). Figure 7.32 shows the degradation profiles with marked differences. The typical randomly sequenced PLGA follows an exponential decaying trendline with a fast initial degradation followed by a stagnant degradation phase and can be problematic for the biomedical field where this polymer is often applied. The random sequencing results statistically in short block-type sequences, some of which will contain purely PGA units prone to fast hydrolysis, while other segments comprise exclusively PLA, which are less susceptible and persist longer. In contrast, the profile of the alternating copolymer shows much better control over degradation by circumventing the formation of such blocks. After an initial rapid decline in MM (by 20% and 35%), the degradation rate slows down and follows a linear trendline, which is beneficial to for instance avoid the formation of small slow degrading remnants in the body.

Hakkarainen et al. [288] investigated the hydrolysis behavior of homo- and block copolymers of ε-CL and the ether lactone analog thereof, DXO, in water at 37 °C and analyzed the degradation products via mass spectrometry (MS). They observed larger oligomers resulting from the hydrolysis of PDXO homopolymer than from PCL (up to heptadecamers of DXO versus only hexamers of ε-CL), proving that the polyester ether has a higher degree of hydrophilicity. As a result, the PDXO is preferentially hydrolyzed, which was confirmed by the degradation of copolymers. MS spectra of copolymer degradation products strongly resembled those of PDXO, while DXO signals in the NMR spectra of copolymer remnants decreased.

As can be seen from the examples shown above, functionalization and/or ROCOP of lactones (or polyesters) can provide better or more controlled degradability when hydrophilicity is increased and/or crystallinity is reduced. Nevertheless, degradability studies are performed under strongly varying conditions, making comparing different materials over different studies ambiguous at best. Hence, the development of standard methods for (bio)degradation studies of polyester, or polymers in general, could provide for higher levels of insights in degradation–structure relations of plastics. The examples highlighted above show degradation studies that were performed through hydrolysis and often in the dissolved state, a method that is regularly favored in polymer synthesis due to the ease of application. While comparisons in such conditions are surely valuable, it is not sure how these relations survive in biological and often dry real-world degradation environments. Nevertheless, other degradation assessments are also applied and thus of great importance. These will often show different results due to the different conditions. Other relevant methods in this field include hydrolysis in presence of electrolytes and/or enzymes and microorganisms, photodegradation with UV-light (especially relevant for polymers with unsaturated backbones), and composting. Further detail is found in Chapter 2 of this book.

7.5 Conclusion

ROP is, compared to some important industrial polymerization procedures (e.g. polyolefins), an interesting strategy to incorporate multiple types of heteroatoms in polymer backbones. ROP of lactone monomers enables the synthesis of aliphatic polyesters in which the ester units are inherently susceptible to (bio)degradation in certain conditions. Even though condensation polymerization of diacids with di-alcohols or of hydroxy acids also results in polyesters, ROP often has some pronounced benefits over polycondensation. In a lot of cases, ROP reactions need less stringent reaction conditions. Moreover, higher molar masses and lower polydispersities are often obtained due to the absence of equilibrium shifting side-products formed during polycondensation. On the other hand, ROP reactions are not always straightforward and can be challenging due to the sensitivity of the process to various parameters. Furthermore, certain polymer structures can only be obtained via polycondensation (di-acids with di-alcohols) and not via ROP.

This chapter presents an overview of the most prominent biodegradable ROP-based polyesters classified by ring size (four to seven membered rings) of their lactone monomers. These polyesters and some of their thermal and mechanical properties are summarized in Table 7.3. PGA, PLLA, and (R)-PHB (containing 1–2 CH_2 groups between the ester units) are strong, but brittle materials exhibiting high tensile strengths and Young's moduli, but low elongations at break. In addition, these materials have high T_ms and relatively high T_gs. However, aliphatic polyesters with chains consisting of longer C-containing units in their backbone (containing >3 CH_2 groups between ester units), such as poly(γ-BL), poly(δ-VL), and PCL, exhibit more elastomeric behaviors, showing low T_ms, negative T_gs, and high elongations at break.

Table 7.3 Most prominent ROP-based polyesters (isotactic homopolymers) and some of their thermal and mechanical properties.

Polymer	Acronym	T_g (°C)	T_m (°C)	Tensile strength (MPa)	Young's modulus (MPa)	Elongation at break (%)	References
Poly(glycolic acid)	PGA	35–40	225–230	80–98	3900–3914 000	30–40	[224, 237]
Poly(L-lactic acid)	PLLA	50–65	170–190	120–2300	6900–9800	12–26	[224, 237]
Poly(β-butyrolactone)	(R)-PHB	−4 to 1	175–180	40	3500–4000	3.0–8.0	[68–70]
Poly(γ-butyrolactone)	Poly(γ-BL)	−51 to −48	53–60	50	70	1000	[116, 117]
Poly(δ-valerolactone)	Poly(δ-VL)	−67 to −60	57–60	12.5	570	150–200	[117, 172–174]
Poly(ε-caprolactone)	PCL	−65 to −60	56–65	4–785	210–440	20–1000	[245]

Although potentially very promising, ROP-based polyesters still have a very limited presence in industry. PLA is by far the most abundant type accounting for 13.9% (≈ 293 kt) of the bioplastics market (2019) [234]. Due to its excellent strength and rigidity, PLA has similarities with commodity petroleum-based plastics such as PET and polystyrene (PS), and is mainly used in both rigid and flexible packaging, consumer goods, textiles, and medical applications. [235, 236] However, the brittle character (mainly isotactic PLA) and rather low T_g still limit its replacement potential in a broad range of other applications. Although currently microbially synthesized, PHAs (including PHB) are the second most important plastics in this group accounting for 1.2% of the bioplastics market (2020), which is expected to rise to 11.5% by 2025 [234]. Due to their good barrier properties, high strength, and good heat resistance, PHAs are interesting potential substitutes (see Chapter 6 However, current microbial production processes are still very expensive and of limited scale, and an ROP process could be envisioned if a more efficient route to the corresponding monomeric lactone could be developed [292]. PCL and PGA are also industrially available at the moment, but only to a very limited extent, and are predominantly used in medical applications.

Even though these commodity bioplastics are defined as biodegradable, their degradation capacity is often limited by the conditions at which degradation takes place. While most of these aliphatic polyesters are readily degradable under industrial composting conditions, degradation in natural environments at lower temperatures and/or lower microbial activity (soil, rivers, oceans, etc.) is often limited. Introducing additional functional groups, either pendant or within the polymer backbone, can significantly improve the hydrophilicity of a plastic and with that often also its degradation capacity. Functionalities can be introduced by either direct ROP of functionalized lactone monomers or via grafting on the polymer backbone post-polymerization. Various techniques and examples of functionalization have been described in this chapter. Functionalization of polyesters constitutes a powerful method to increase degradation rates by tuning properties such as hydrophilicity. Nevertheless, it remains a challenging undertaking for numerous reasons. For instance, the use of protective groups is often unavoidable, which requires extra reaction steps and optimization efforts. Moreover, substituted groups on lactones often hinder opening of the rings, impeding polymerization. Grafting also requires specific functionalities, such as halogens or unsaturated bonds, which are not always readily obtained, while the grafting reaction itself also demands optimization. However, examples in literature have been described in which smart and efficient chemistry and catalysis can help overcome these difficulties, making the synthesis processes less costly and time consuming. Examples of this include the use of very reactive organocatalysts, ROP of ether-lactones containing functional groups in the ring structure itself that do not interact with ROP catalysts, changing reaction conditions in a smart way (low temperatures, high concentrations, etc.), etc.

Multi-step syntheses, challenging purifications, and price-intensive processes limit the scalability of functionalized polyesters. As a consequence, a gap is frequently noticed between research on polymer chemistry and analysis of the material properties (thermal, mechanical, rheological, degradation, etc.). The gap is often a matter of scale as new polymers made in sub-10 g amounts are hard to assess mechanically for instance. Novel synthesized polyesters are also quickly described as "biodegradable" simply due to the structural resemblance to classic polyesters such as PLA and PCL, without properly analyzing their degradation potential. However, small changes in structure can greatly influence degradability. Furthermore, there is a lack of consensus on how to analyze degradability in different environments. The great variety in how degradation is assessed makes it near-impossible to compare results among different polymers, resulting in a lack of generally accepted polymer chemistry–degradability relationships.

Finally, it is important to mention that degradation should be mainly prioritized in applications in which the degradability itself has an additional value (e.g. medical applications) or in applications in which the plastic comes in close contact with the environment and leakages are hard to avoid (e.g. agriculture and fishing) [293]. Although degradation is important in these contexts, a trade-off between the plastic's degradability and performance should always be taken into account.

7.6 Outlook and Recommendations

Although ROP can be a very challenging polymerization method, certainly when applied in the context of functionalized polymers, it exhibits important advantages which can make it an industrially viable process once optimized.

A first important outlook in polyester research via ROP should be to close the gap between lab-scale polymer chemistry and material analysis. Focus should be laid on smart and efficient chemistry and catalysis to decrease synthesis times and costs, and improve scalability. It is suggested that new polymers are aimed at a scale of at least 100 g, which allows some mechanical and rheology tests, but also enables shaping for degradation experiments of solid objects. Additionally, a closer collaboration between scientists focusing on monomer synthesis, polymer chemistry, and material science (engineering, mechanical properties, and plastics processing) is recommended to improve overall efficiency and quickly spot industrially viable polymers.

Besides improving scalability, it is important to get better insights into the exact relationships between the chemical structures of polymers and their (bio)degradation behavior under specific conditions. An important step that should be taken in this context is the development of universal and straightforward degradation testing procedures, mimicking (bio)degradation in various conditions (e.g. hydrolysis and composting).

List of Relevant Abbreviations

Abbreviation	Full description
α-AL	α-Angelicalactone
ACE	Activated chain-end
α-Cl-ε-CL	α-chloro-ε-caprolactone
AM	Activated monomer
aROP	Anionic ring-opening polymerization
β-BL	β-butyrolactone
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
β-PL	β-propiolactone
ciROP	Coordination–insertion-based ring-opening polymerization
cROP	Cationic ring-opening polymerization
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
ΔG_p	Gibbs free energy of polymerization
ΔG_p^0	Standard Gibbs free energy of polymerization
ΔH_p	Enthalpy of polymerization
D-LA	D-lactic acid
D-LD	(D,D)-lactide
DMAP	4-dimethylaminopyridine
DOX	1,3-dioxolane-4-one
DPP	Diphenyl phosphate
ΔS_p	Entropy of polymerization
δ-VL	δ-valerolactone
DXO	1,5-dioxepan-2-one
ε-CL	ε-caprolactone
eROP	Enzymatic ring-opening polymerization
G	Glycolide
GA	Glycolic acid
γ-BL	γ-butyrolactone
γ-VL	γ-valerolactone
LA	Lactic acid
LD	Lactide
L-LA	L-lactic acid
L-LD	(L,L)-lactide

Abbreviation	Full description
$[M]$	Monomer concentration
$[M]_0$	Initial monomer concentration
$[M]_{eq}$	Equilibrium monomer concentration
Meso-LD = (D,L)-LD	(D,L)-lactide
MM	Molar mass
M_n	Number-average molar mass
M_w	Weight-average molar mass
NHC	N-heterocyclic carbene
PCL	Poly(ε-caprolactone)
PDLA	Poly(D-lactic acid)
PDLLA	Poly((D,L)-lactic acid)
PDX	*p*-dioxanone or 1,4-dioxane-2-one
PGA	Poly(glycolic acid)
PHA	Poly(hydroxyalkanoate)
PHB	Poly(3-hydroxybutyrate)
PLA	Poly(lactic acid)
PLGA	Poly(lactic acid-*co*-glycolic acid)
PLLA	Poly(L-lactic acid)
Poly(β-BL)	Poly(β-butyrolactone)
Poly(β-PL)	Poly(β-propiolactone)
Poly(γ-BL)	Poly(γ-butyrolactone)
Poly(δ-VL)	Poly(δ-valerolactone)
PPY	4-pyrrolidinopyridine
ROCOP	Ring-opening copolymerization
ROP	Ring-opening polymerization
(*R*)-PHB	Poly((*R*)-3-hydroxybutyrate)
$Sn(Oct)_2$	Sn(II) 2-ethylhexanoate
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
T_c	Critical temperature
T_g	Glass transition temperature
T_m	Melting temperature

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