1
Polyesters

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1.1
Historical Background

1.1.1
Biomedical Applications

Biomaterials are defined as any materials intended to interface with biological systems to analyze, treat, or replace any tissue, organ, or function of the body [1]. The current trend in biomaterial development is shifted toward the use of biodegradable materials that have definite advantages in the fields of tissue engineering [2] and drug delivery [3]. The general principle is to use a material that achieves a specific therapeutic task and is subsequently, over time, degraded and removed harmlessly from the body. As an increasingly relevant part of the medical device and controlled release industry, biodegradable polymers are used to fabricate temporary scaffolds for tissue regeneration, medical sutures, and nano- or microscale drug delivery vehicles [4–6].

The important properties that are required for biodegradable biomaterials can be summarized as follows:

- Nontoxic and endotoxin-free, aiming to minimalize unwanted foreign body responses upon implantation.
- Degradation time should be matched to the regeneration or required therapy time.
- Mechanical properties must be suited to the required task.
- Degradation products should be nontoxic and readily cleared from the body.
- Material must be easily processed to allow tailoring for the required task.

Although natural polymers such as collagen have been used in medical applications throughout history, synthetic polymers are valuable also, as they allow us to tailor properties such as mechanical strength and erosion behavior. Naturally

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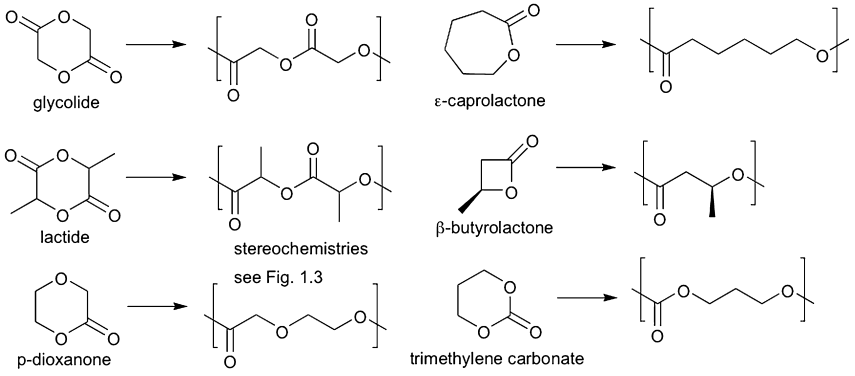
occurring biopolymers are typically degraded by enzymatic means at a rate that may be difficult to predict clinically. Furthermore, natural polymers may have unwanted side effects arising from inherent biological activity. This has led to the widespread use of biodegradable synthetic polymers in therapeutic applications. Of this class, biodegradable aliphatic polyesters, which are degraded hydrolytically, are by far the most employed.

1.1.2 Poly(Hydroxycarboxylic Acids)

All polyesters are, in principle, hydrolytically degradable. However, only (co)polyesters with short aliphatic chains between ester bonds typically degrade over the time frame required for biomedical applications. The major group of this material are the poly(hydroxycarboxylic acids), which are prepared via ring-opening polymerization of lactones or cyclic diesters. Indeed, the first biodegradable polyester used as a medical suture in the 1960s was based on the polyglycolide. Scheme 1.1 shows the most common monomers and the polymers they produce. These can be summarized as diglycolide, stereogenic dilactides, lactones such as ε-caprolactone and stereogenic β-butyrolactone, the cyclic trimethylene carbonate, and *p*-dioxanone. As the polymerization methods of these monomers are broadly applicable to each, copolymers such as poly(lactide-*co*-glycolide) are readily produced.

Another source of poly(hydroxycarboxylic acids) is from bacteria, which store polyesters as their energy source [7]. These polymers are known as polyhydroxyalkanoates (PHAs) in the literature. The most common polymer derived from bacteria is poly(3-hydroxybutyrate), which has the same structure as the polymer which can be obtained from optically active β-butyrolactone [8]. Poly(3-hydroxybutyrate) formed in this way is strictly stereoregular, showing the (*R*) configuration. Biotechnologically produced polymers are discussed in more details in Chapter 2 of this handbook.



Scheme 1.1 Common cyclic monomers for the preparation of polyester derivatives.

1.2
Preparative Methods

1.2.1
Poly(Hydroxycarboxylic Acid) Syntheses

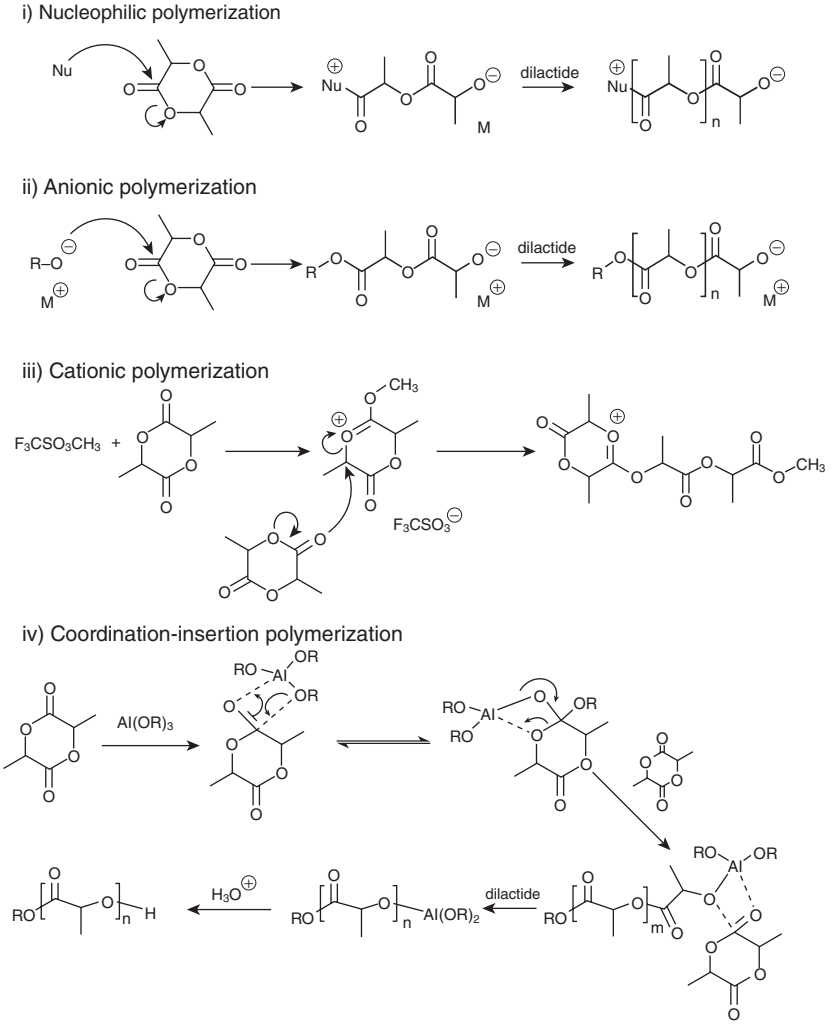
Polyesters can be synthesized via the direct condensation of alcohols and acids. This may take the form of condensing dialcohols and diacids, for example, AA + BB systems, or the direct condensation of hydroxycaboxylic acid monomers, for example, AB systems. Various catalysts and coupling reagents may be used but typically the polyesters formed in this manner have low and uncontrolled molecular weight and are not suitable for biomedical applications. The majority of cases where a high degree of polymerization was obtained came via ring-opening polymerizations of cyclic monomers of the type shown in Scheme 1.1 [9]. The cyclic dilactones are prepared from the corresponding hydroxycarboxylic acid by elimination of water in the presence of antimony catalysts such as Sb_2O_3 [10]. These dimers have to be purified rigorously if high degrees of polymerization are sought, as impurities such as water and residual hydroxycarboxylic acids can hinder polymerization. Enantiomerically pure lactic acids are typically produced by fermentation.

Ring-opening polymerizations may be initiated by nucleophiles, anionically, cationically, or in the presence of coordinative catalysts. Representative mechanisms are shown in Scheme 1.2. However, precise mechanisms may vary from case to case and are an ongoing important area of study [11, 12]. As a testament to the popularity of the ring-opening polymerization approach, over 100 catalysts were identified for the preparation of polylactide [13].

The typical complex used for the industrial preparation of polyglycolide derivatives is tin(II)-bis-(2-ethylhexanoate), also termed tin(II)octanoate. It is commercially available, easy to handle, and soluble in common organic solvents and in melt monomers. High molecular weight polymers up to 10^6 Da and with narrow polydispersities are obtained in a few hours in bulk at 140–220 °C. Approximately 0.02–0.05 wt% of catalyst is required. Care must be taken when polymerizing dilactides, if stereochemistry is to be preserved. This means that milder conditions are to be selected relative to the homopolymerization of diglycolide.

For the copolymerization of dilactide and diglycolide catalyzed with tin(II) octoate, different reactivities are observed. A chain with a growing glycolide end will add a further diglycolide with a preference of 3:1. With a terminal lactide unit, the preference for diglycolide is 5:1. Due to this, glycolide blocks tend to form, separated by single dilactides. One possibility to improve the homogeneity of the composition of the obtained polyesters is the online control of the monomer ratio by addition of further monomer. However, this method is technically complicated.

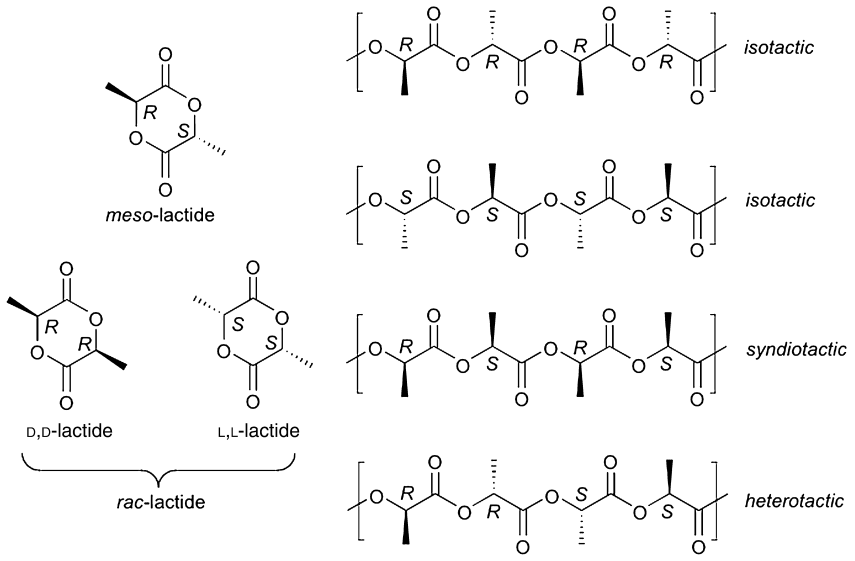
The mechanism is a nonionic coordinated insertion mechanism, which is less prone to the side reactions commonly found in ionic polymerizations, such as transesterification or racemization [14, 15]. It has been found that the addition of alcohols to the reaction mixture increases the efficiency of the tin catalyst albeit



Scheme 1.2 Overview of various mechanisms relevant to polylactide synthesis.

by a disputed mechanism [16]. Although tin(II)octoate has been accepted as a food additive by the U.S. FDA, there are still concerns of using tin catalysts in biomedical applications.

Aluminum alkoxides have been investigated as replacement catalysts. The most commonly used is aluminum isopropoxide, which has been largely used for mechanistic studies [17]. However, these are significantly less active than tin catalysts requiring prolonged reaction times (several hours to days) and affording polymers with molecular weights generally below 10^5 Da. There are also suspected links between aluminum ions and Alzheimer's disease. Zinc complexes, especially



Scheme 1.3 Stereochemical possibilities observed with polylactide synthesis.

zinc(II)lactate, are a plausible replacement with low toxicity and activities of the same order as aluminum complexes [18]. Zinc powder may also be used but then the active species has been identified as zinc(II)lactate in the preparations of polylactide [19]. Iron salts and particularly iron(II)lactate show comparable activity, but prolonged reaction times mean that some racemization occurs in the synthesis of high molecular weight (50,000 Da) poly(L-lactide) [20].

As can be seen in Scheme 1.3, polylactides can exist in isotactic, syndiotactic, and heterotactic blocks. The configuration has obvious consequences for the material properties of the final polymer. While the ring-opening polymerization of L,L-dilactide or D,D-dilactide leads to isotactic polymers, the polymers of the *rac*-dilactide should consist mainly of isotactic diads. This is due to the fact that *rac*-dilactide is commonly used as a mixture of D,D- and L,L-dilactide with very little *meso*-dilactide content. The formation of syndiotactic diads is expected in the case of *meso*-dilactide polymerization, but the longer range sequence structure of such polymers is typically atactic. Due to the expense of producing stereopure dilactides, a kinetic resolution procedure was developed whereby chiral SALEN (salicylimine) ligands in combination with aluminum isopropoxide catalyst produced isotactic polylactides from *rac*-dilactide. Optical purities were high at 50% conversion; kinetics show that the catalyst system has a 28:1 preference toward one isomer. By choosing the appropriate SALEN ligand enantiomer, selective polymerization of either L,L- or D,D-dilactide could be achieved [21]. Similar approaches using SALEN ligands have been employed to produce syndiotactic and heterotactic polylactides [22].

Tin(II)octoate is also the most common catalyst used for the polymerization of cyclic lactone monomers such as ε-caprolactone; although the mechanism of

polymerization may differ [23]. In addition, rare-earth metal complexes have been shown to work as effective catalysts leading to high molecular weight polylactones with low polydispersity [24, 25]. An efficient cationic ring-opening polymerization of lactones has been developed using scandium trifluoromethanesulfonate as catalyst. Poly(ε-caprolactone) with narrow polydispersity and a molecular weight in the order of 10^4 Da was produced in quantitative yield after 33 h at room temperature in toluene. Only 0.16 mol% of catalyst was required. Similar results were obtained for poly(δ-valerolactone). Notably, the reaction was relatively tolerant to the presence of moisture and other contaminants [26].

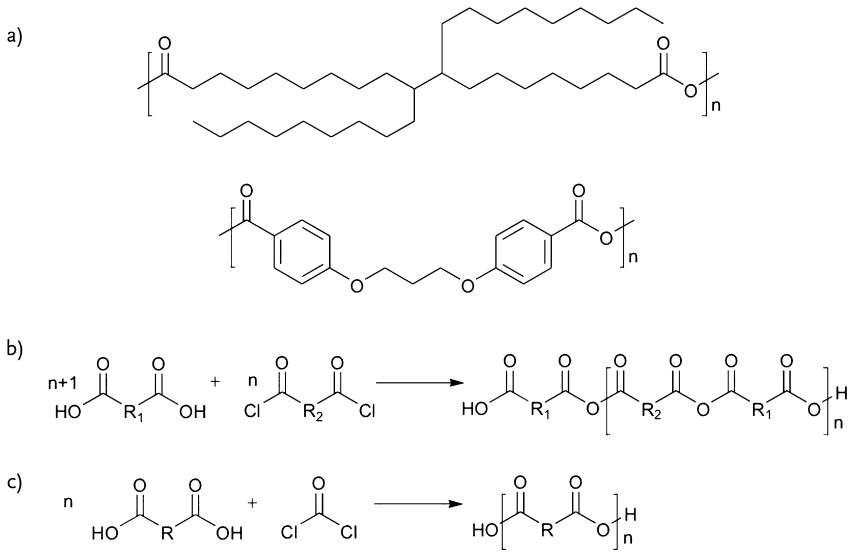
1.2.2 Metal-Free Synthetic Processes

The use of low molecular weight organic molecules to catalyze ring-opening polymerization is a rapidly expanding field [27]. Organocatalytic routes toward polyesters typically involve a nucleophilic polymerization mechanism; problems with side reactions are minimal and products with high molecular weights and very narrow polydispersities can be formed. In addition, organocatalysts may be significantly more abundant and less toxic than metal containing catalysts. These factors point toward future large-scale synthesis applications. Many examples are based around traditional acyl substitution catalysts such as phosphines [28], and pyridine-derivatived nucleophiles [29]. In more recent developments, *N*-heterocyclic carbenes have shown great promise, allowing the synthesis of polylactides with molecular weights up to 10^4 Da [30]. Supramolecular catalysts are known, which can stabilize transition-states in a noncovalent fashion and thus can exert a great effect on reaction rate and mechanism. To this end, thiourea-containing supramolecular catalysts have shown excellent promise [31].

The enzyme-catalyzed synthesis of polyesters is another technique that is being developed as a very ecologically friendly process with several benefits over conventional chemical polymerization [32]. Enzymatic reactions are often extremely regio- and stereospecific, so unwanted side reactions can be largely eliminated. Lipase-catalyzed ring-opening polymerization has been applied to many substrates including a wide range of lactones and lactides. As an example, poly(D,L-lactide) with molecular weights up to 10^5 Da could be synthesized in bulk, but recovery yields were relatively low [33]. Among the problems associated with enzymatic polymerization are the high cost of enzymes, long reaction times, and relatively low molecular weight products. These challenges are to be met before enzymes can be used for industrial scale synthesis.

1.2.3 Polyanhydrides

Polyanhydrides are an important class of biodegradable polymers which are closely related to the polyesters [34, 35]. Monomers used are commonly hydrophobic long chain fatty-acid-derived diacids or aromatic group containing diacids such as shown in Scheme 1.4a. Polyanhydrides are treated in detail in Chapter 3. They are



Scheme 1.4 Typical polyanhydrides and synthetic methods.

mentioned here for comparative reasons, as they typically degrade in an alternative manner to poly(hydroxycarboxlic acids) due to their hydrophobic nature (Section 1.4).

Aliphatic diacids can be polycondensated to polyanhydrides by reaction with acetic acid anhydride. The reaction proceeds in two steps. First of all, oligomeric polyanhydrides with terminal acetate groups are received, further reacting to high molecular weight products at elevated temperatures and under vacuum. Using catalysts like cadmium acetate in the second step, average molecular weights of 10^5 Da are reached. Under comparable conditions, glutaric acid and succinic acid form cyclic monomers in contrast to sebacic acid. The reaction of dicarboxylic acids and diacidchlorides results in poor molecular weight products (Scheme 1.4b). A method to gain high molecular weight products even at low temperatures is the use of phosgene as condensation agent (Scheme 1.4c). Formed hydrochloric acid in the reaction is sequestered and removed from the growing polymer by use of insoluble proton scavengers.

1.3 Physical Properties

1.3.1 Crystallinity and Thermal Transition Temperatures

As shown in Table 1.1, high molecular weight polyglycolides, polylactides, and copolymers thereof are typically strong, stiff materials with high modulus (E) and

Table 1.1 Material properties of various poly(lactide-*co*-glycolides) [5].

Comonomer proportion (mol%)			Polymer properties				
Diglycolide	**L,L-dilactide**	***rac*-Dilactide**	T_g (°C)	T_m (°C)	*E* (GPa)	σ_B (MPa)	ε_B (%)
0	100	0	57	174	3.6	58	2.1
0	84	16	55	124			
0	75	25	60	–	3.4	46	1.6
0	50	50	60	–	3.3	46	3.2
0	25	75	59	–	2.8	41	2.9
0	0	100	59	–	3.2	48	8.7
100	0	0	36	228	7.0		15.0
90	10	0	37	200			
75	25	0	44	–			
50	50	0	44	–			
25	75	0	52	–			
75	0	25	43	–			
25	0	75	54	–			

tensile strength (σ_B). These properties are of similar magnitude to those found within human hard tissues (bones, ligaments, tendons) [36], and are useful for the biomaterial applications mentioned in Section 1.1.1.

Polyglycolide is of high crystallinity, 40–55%, and has a relatively high melting point of 228 °C. The glass transition temperature is 36 °C. Polyglycolide is insoluble in most organic solvents with the exception of highly fluorinated solvents, which must be taken into account when processing materials. Upon copolymerization with dilactides, amorphous materials are produced if the diglycolide content is less than 25%. The glass transition temperature rises from 36 °C to 54 °C as the amount of dilactide monomers are incorporated into the polymer. Poly(L-lactide) has slightly lower crystallinity of 37%; T_g = 57 °C and T_m = 174 °C. Incorporation of *rac*-dilactide as a comonomer gradually decreases the crystallinity and at 25% *rac*-dilactide content amorphous polymers result. Poly(D,L-lactide) with a glass transition temperature of 65 °C is completely amorphous. The bacterially produced poly(3-hydroxybutyrate) is highly crystalline at 60–80% and has T_g = 10 °C and T_m of 179 °C. The modulus is 3.5 GPa. As shown in Table 1.2, incorporation of 3-hydroxyvaleric acid as comonomer leads to a softer and more elastomeric material [37].

Materials comprised of the other major groups of poly(hydroxycarboxylic acid) are considerably softer and more elastic. The polyetherester polydioxanone has a melting point of 115 °C and a glass transition temperature in the range of –10–0 °C. The crystallinity is approximately 55%. Polydioxanone has a lower modulus (1.5 GPa) than the polylactide materials, and loses mechanical strength at a higher rate during hydrolytic degradation. Poly(ε-caprolactone) is a semicrystalline

Table 1.2 Physical properties of various poly([3-hydroxybutyrate]-*co*-[3-hydroxyvalerate])s [5].

Amount of 3-hydroxyvaleric acid (mol%)	T_g (°C)	T_m (°C)	E (GPa)	ε_B (%)
0	10	179	3.5	6
9	6	162	1.9	
20	–1	145	1.2	
25	–6	137	0.7	

polymer with a melting point in the range of 59–64 °C. The glass transition temperature is –60 °C. Poly(ε-caprolactone) has a relatively very low modulus (0.4 GPa) but an extremely high elongation at breakage of over 700%. Poly(trimethylene carbonate) is an elastomeric polyester with high flexibility but limited mechanical strength, and is the most commonly employed in copolymers to increase elasticity [38].

1.3.2 Improving Elasticity by Preparing Multiblock Copolymers

While the degradation rate and the degradation behavior of the polymers described previously are adjustable, the mechanical properties of these materials are only of restricted variability. The homopolymers of the α-hydroxycarboxylic acids are highly crystalline, brittle materials. The elongations at break are relatively low compared to polymers such as polyethylene terephthalate (ε_R = 100%) and polypropylene (ε_R = 400%) [37]. The mechanical properties are sufficient for the production of fibers [39]. However, in addition to the described polymer systems, elastic, tough materials are desirable. A concept to realize this requirement is the preparation of phase-segregated block copolymers. One segment should be crystallizable and act as crosslinking unit to give the material the desired strength. The second segment should be amorphous, with a low glass transition temperature that is responsible for the elasticity. This principle is shown in Figure 1.1.

One method to generate high molecular weight multiblock copolymers is to the co-condensation of two bifunctional linear prepolymers, known as telechelic polymers [40]. A group of copolyesterurethanes can be used as a case in point [41]. Poly([3-*R*-hydroxybutyrate]-*co*-[3-*R*-hydroxyvalerate])-diol is used as crystallizable segment. It is prepared by transesterification of high molecular weight bacterially produced polyester with a low molecular weight diol. The number average molecular weight, $M_{n,}$ of this telechelic polymer ranges from 2100 to 2500 g mol^{-1}. The soft segments are telechelic copolyester diols (M_n = 500–3000 g mol^{-1}), prepared by ring-opening polymerization of lactones with a low molecular weight diol. A low molecular weight diisoyanate was used to link the polymer blocks through urethane linkages. In this way, the final polymers may be considered as poly(ester urethane)s. With the correct conditions, products with an average molecular

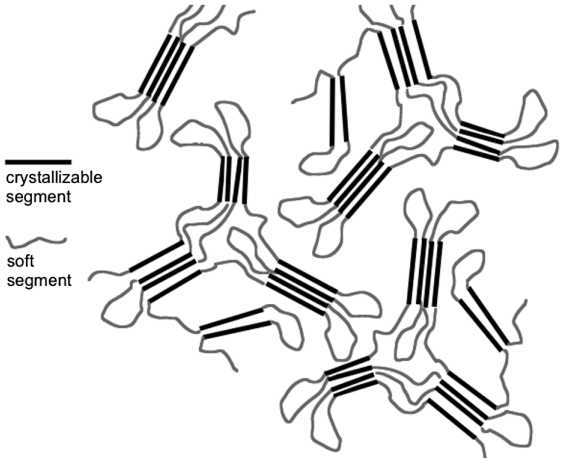


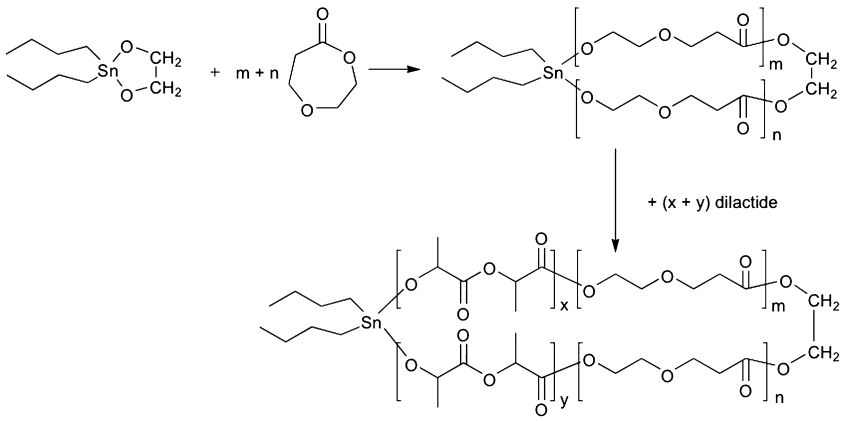
Figure 1.1 Schematic diagram of the morphology of multiblock copolymers.

Table 1.3 Influence of the weight content of hard segments in multiblock copolymers on material properties [41].

Hard segment content (wt%)	E (MPa)	ε_R (%)	T_g (°C)	T_m (°C)
31	60	1250	–24	132
46	186	1130	–18	134
61	400	270	–10	136

weight of more than 10^5 Da were obtained. As can be seen in Table 1.3, lowering the weight percentage of hard segments lowers the material modulus and increases the elongation at break. These polymers have low glass transition temperatures, which prevents them from forming brittle materials at body temperature.

Routes to prepare polyester-based block copolymers have been widely studied [42]. The most direct route is via sequential addition of monomers to systems polymerizing under living conditions. However, this is not broadly applicable to polyester synthesis as the monomers must have comparable reactivities under one set of conditions. This approach is more effective for the copolymerization of similarly functionalized lactones, although the resultant blocks generally have similar physical properties, so phase segregation is not realized [43]. The large difference in reactivity ratio between dilactides and lactones makes it difficult to synthesize such block copolymers. However, an elegant approach using a cyclic tin oxide catalyst has been developed to produce ABA-type triblocks [44, 45]. The ring-expansion mechanism is outlined in Scheme 1.5. This process forms telechelic polymers that can be crosslinked directly with diisocyanates or activated diesters.



Scheme 1.5 Ring-expansion mechanism for the preparation of ABA triblock polyesters.

1.3.3
Covalently Crosslinked Polyesters

A further method to produce elastomeric polyester-based materials is the preparation of crosslinked amorphous polyesters. In this case, crystalline regions are absent but mechanical strength is given by the inherent rigidity of the network. Such materials are often described as "cured" polymers [46]. Due to the absence of crystalline regions, erosion occurs more homogeneously, and properties can be tailored by composition. Such elastomers were prepared by the photopolymerization of methacrylate functionalized star-shaped poly([ε-caprolactone]-*co*-[*rac*-lactide]) (see Section 1.5.2). Networks suitable for implant materials were obtained, with physical properties adjustable by selecting the molecular weight of the precured polymers [47]. Poly(diol citrates) were synthesized by reacting citric acid with various diols to form a covalent crosslinked network via polycondensation [48]. The physical properties and degradation characteristics could be controlled by choosing different diols and by controlling the crosslink density of the polyester network. Biocompatible materials with elongations at break as high as 500% could be obtained. Other common crosslinkers used for curing polymers are multifunctional isocyanates and acid chlorides.

1.3.4
Networks with Shape-Memory Capability

Polymer networks can be designed in a way that they become capable of a shape-memory effect [49]. Such materials possess the ability to memorize a permanent shape, which can substantially differ from their temporary shape. The transition from the temporary to the permanent shape could be initiated by an external stimulus such as a temperature increase above a characteristic switching

temperature of the polymer (thermally induced shape-memory effect). Exemplary shape-memory biodegradable polyesters have been prepared as networks of star-shaped polymers crosslinked by diisocyanates [50], or as photocrosslinkable macrodimethacrylates [51]. Biodegradable shape-memory polymers will be covered in more detail in Chapter 8.

1.4 Degradation Mechanisms

In general, two different mechanisms for the biodegradation of polyesters are discussed in literature: bulk degradation and surface erosion [52]. In the bulk degradation process, water diffuses into the polymer matrix faster than the polymer is degraded. The hydrolyzable bonds in the whole polymer matrix are cleaved homogeneously. Therefore, the average molecular weight of the polymer decreases homogeneously. In the case of surface erosion, the diffusion rate of water into the polymer matrix is slower than the degradation rate of the macromolecules. The degradation only takes place in the thin surface layer while the molecular weight of the polymer in the bulk remains unchanged. Surface erosion is a heterogeneous process, with a rate strongly dependent on the shape of the test sample (e.g., size of the surface) [53].

The majority of polyester materials undergo bulk hydrolysis, as will be explained in the following section. Polyanhydride materials differ from the common polyesters by the fact that they undergo linear mass loss by surface erosion mechanisms [54]. The hydrophobic chains preclude water penetration into the bulk of the material, thus negating bulk erosion mechanisms.

1.4.1 Determining Erosion Kinetics

Erosion rates can be determined *in vitro* and *in vivo* [55]. For *in vitro* experiments, the polymers are exposed to an aqueous solution, in which ionic strength, pH-value, and temperature can be varied. The degradation products of the polymer can be isolated from the aqueous solution and characterized. The addition of enzymes is also possible. Furthermore, the polymers can be exposed to cell- and tissue cultures. By suitable selection and systematic variation of the *in vitro* test conditions, the influence of single parameters on the degradation behavior of the polymer can be determined. Accelerated degradation tests at elevated temperature (usually 70 °C) serve as preliminary experiments for planning the 37 °C experiments and to give reference to the extended degradation behavior of the materials. Another method to accelerate hydrolysis tests is the elevation of the pH-value of the degradation medium to the alkaline region (as a rule 0.01 or 0.1 M NaOH solution). The reaction of cell- and tissue cultures in contact with the material gives information on the compatibility of the partially degraded polymer samples and their degradation products.

In vivo experiments are performed with different species such as dogs, monkeys, rats, mice, and sheep [56]. To investigate the degradation behavior, the implants are typically placed subcutaneously or intramuscularly. The tissue compatibility of the polymer can be determined by histological investigations. There are several characteristics to follow in implant material degradation, for example, height, weight, and mechanical properties of the test device. An additional method for *in vivo* tests is marking of the implant with ^{14}C or by fluorescent chromophores. In this case, it can be observed where the fragments of the degraded polymer and the degradation products in the test animal remain. Furthermore, the change in thermal properties, crystallinity, and the surface properties (wettability, roughness), depending on the degradation- and implantation time duration, can be determined.

1.4.2
Factors Affecting Erosion Kinetics

Poly(hydroxycarboxylic acid)s degrade via the bulk process [57]. The degradation process can be divided into three parts. In the first step, water is absorbed and the polymer swells. Several ester bonds are cleaved already, but there is no mass loss. In the second step, the average weight is significantly reduced. As ester bonds are cleaved, carboxylic groups are formed, which autocatalyze the hydrolysis. During this period, the polymer loses mechanical strength. The third step is characterized by mass loss of the test sample and an increase in degradation rate. The degradation of an implanted material is completed when oligomeric and low-molecular-weight fragments are dissolved in the surrounding medium. The dissolved polymer fragments are then hydrolyzed to the free hydroxycarboxylic acids. Degradation products, many of which occur naturally within the metabolic cycle (e.g., lactic acid), are typically removed from the body without toxic effect. To some extents, smaller crystalline segments may remain, which are eliminated from the body by phagocytosis [58].

The degradation times of several poly(hydroxycarboxylic acids) are summarized in Table 1.4. The differences in degradation rates may be rationalized mainly by the ability of water to permeate the polymers (crystallinity and hydrophobicity), and in the case of polylactides the presence of an α-methyl group which hinders hydrolysis on steric grounds. Copolymers, due to the greater prevalence of amorphous regions, are generally degraded faster than homopolymers [59].

The higher degradation rate of poly(*rac*-lactide) compared to poly(L-lactide) is due to the higher crystallinity of the isotactic poly(L-lactide). Polyglycolide, being less hindered at the scission site, is degraded relatively quickly. The degradation rate of poly(lactide-*co*-glycolide) can be finely tuned by varying the monomer content. Polydioxanone and poly(ε-caprolactone) are also less sterically hindered but increased hydrophobicity hinders erosion. Poly(ε-caprolactone), with a pentylene ($–C_5H_{10}–$) chain, erodes an order of magnitude slower than polyglycolide.

Due to the high crystallinity, poly(3-*R*-hydroxybutyrate) is relatively slowly degraded. In this case, a certain amount of surface erosion takes place first. With

Table 1.4 Comparative degradation times of different polyesters in physiological conditions [5].

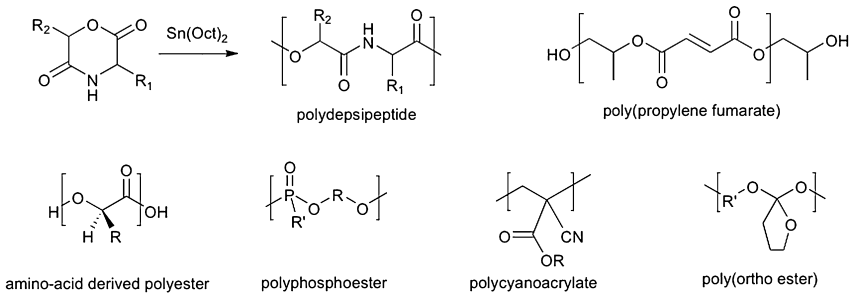
Polymer	Degradation time (months)
Poly(L-lactide)	18–24
Poly(*rac*-lactide)	12–16
Polyglycolide	2–4
Poly(3-hydroxybutyrate)	≫36
Polydioxanone	6–12
Poly(ε-caprolactone)	>24
Poly([L-lactide]-*co*-glycolide) 50:50	2
Poly([*rac*-lactide]-*co*-glycolide) 85:15	5
Poly([*rac*-lactide]-*co*-[ε-caprolactone]) 90:10	2

proceeding degradation, a loss of weight and increasing porosity lead to a bulk degradation. Poly([3-*R*-hydroxybutyrate]-*co*-[3-*R*-hydroxyvalerate]) is hydrolyzed more rapidly due to lowered crystallinity. The degradation of the poly(3-*R*-hydroxybutyrate) can be accelerated by microorganisms and enzymes [60]. Bacterially produced poly(3-*R*-hydroxybutyrate) is degraded faster than synthetic poly(3-*R,S*-hydroxybutyrate), while poly(3-*S*-hydroxybutyrate) is not hydrolyzed at all [61]. Enzymatic digestion proceeds at the surface of the sample as proved by scanning electron microscopy. The enzyme, because of high molecular weight, is too large to diffuse into the bulk of the material. Another important factor to take into account when considering the processing of these polymers is that above 200 °C thermal degradation can occur [62].

1.5 Beyond Classical Poly(Hydroxycarboxylic Acids)

1.5.1 Alternate Systems

In addition to the broadly studied groups described previously, there are some notable examples to include when discussing biodegradable polyesters. Scheme 1.6 shows a selection of such alternate polyester structures. Various amino acids were converted to the corresponding α-hydroxycarboxylic acid and then polymerized to give stereogenic α-substituted polyglycolide analogs [63, 64]. This approach could give access to polymers with more tailored properties and sophisticated material properties. Polydepsipeptides are an interesting class of poly(ester amide) which are copolymers of α-hydroxycarboxylic acids and α-amino acids [65]. They are synthesized from morpholine diones (analogs of diglycolide, in which one lactone is replaced by a lactam group) by many of the same procedures outlined for polyglycolide synthesis. Polydepsipeptides degrade through the ester bonds, whereas the amide linkages remain intact under physiological conditions [66].



Scheme 1.6 Alternative polyesters and closely related polymers.

There is the possibility to select the amino acid component to incorporate functional groups into the chain in a facile manner [67].

Poly(propylene fumarates) are a bulk eroding class of polyester which are synthesized typically via transesterification [68, 69]. Although molecular weights are generally low, the unsaturated polymer backbone can be photochemically crosslinked to provide polymer networks with desired properties for implant materials. The general concept of crosslinking by photopolymerization has been extended to the other polyester classes, typically by methacrylate functional groups, which have been appended to polymeric precursors [70]. Supramolecular polyesters have been developed by attaching self-recognizing binding units on either end of telechelic polylactones [71]. These polymers are shown to self-assemble via noncovalent means into long strands composed of multiple individual blocks. Such systems show a high level of sensitivity to environmental conditions, and as such may be considered as "smart" polyester systems.

Although not strictly polyesters, some interesting analogs remain. Poly(ortho esters) are materials which are studied mainly as drug delivery vehicles [72]. Like polyanhydrides, they have very labile bonds but are hydrophobic in nature. Water is precluded from the bulk polymer, hence retarding degradation. As such, polyorthoesters have fairly linear surface erosion behavior, ideal for controlled drug release. Polyphosphoesters are hydrolytically degraded polymers that have an extra degree of versatility due to the pentavalent nature of the phosphorous atom [73]. They are highly hydrophilic and show good biocompatibility. Copolymers with other esters such as lactides have been prepared and studied for the range of applications from tissue engineering to drug delivery. Poly(alkyl cyanoacrylates) are rapidly degrading polymers which have widespread medical applications [74]. Although they only contain ester units in the side chains, they are degraded not only at the carbonyl position but at the carbon–carbon sigma bond of the polymer backbone chain. This behavior separates this class of material markedly from the polyesters.

1.5.2 Complex Architectures

While the properties of linear polyesters have been widely studied, branched polyesters are becoming the subject of increasing study. The search for more complex

architectures is stimulated mainly by the desire to lower crystallinity, increase the amount of endgroups for further functionalization, or to further control degradation behavior.

Star-shaped poly(caprolactones) with molecular weights in the 10^4 Da range were prepared starting with triol or tetraol multifunctional initiators [75]. These multivalent products were further reacted with glycolide derivatives to give a star-shaped block copolymer of poly([ε-caprolactone]-block-[lactide-*alt*-glycolide]). This globular architecture has a soft segment on the interior with a more crystalline outer sphere. Hyperbranched polyesters of $M_n \approx 10^4$ Da were prepared by copolymerizing polylactide with an alcohol-containing lactone as a latent AB_2 monomer [76]. This dramatically changed the material properties of the polymer with reduced crystallinity and lowered glass transition temperature due to the branching. Poly(ether ester) dendrimers were synthesized from lactic acid and glycerol [77]. These structures have perfect branching radiating from a single point, and make an interesting class of polyvalent biocompatible material.

Polysaccharides have been used as a multivalent scaffold, from which to graft polyesters. Polylactide grafted onto pullulan showed a relatively increased degradation rate which was attributed to the branching effect and the increased hydrophilicity of the pullulan core [78]. Comb polymers were prepared by grafting multiple polylactides to a linear polymethacrylate chain [79]. Highly crystalline regions were observed at the interdigitating comb regions, leading to novel material properties. Interesting and complex structures were formed from polylactides attached to ligands which are able to aggregate into defined supramolecular complexes with Cu(I) ions [80]. Size defined nanoparticles resulted.

1.5.3 Nanofabrication

The previous analyses of polyester materials were given largely in the context of mechanical properties required for tissue engineering or medical implant applications. Polyesters with nanoscale dimensions, however, are widely studied as nanovehicular delivery agents for drugs and biodiagnostic molecules [81, 82]. For the "top-down" approach, submicron polyester spheres can be prepared by a range of molding and lithography techniques [83]. In addition, electrospinning techniques are emerging as a powerful tool for the preparation of nanoscale fibers [84]. Biodegradable polyesters may be formulated with inorganic nanomaterials to provide nanobiocomposites which have relatively controllable physical properties [85]. Polyester/clay biocomposites have been the subject of considerable study.

"Bottom-up" approaches allow the preparation of nanoscale materials without the need for further processing. Various nanospheres of polylactides and polylactones were prepared in the size range of 80–200 nm using a miniemulsion technique. Endocytic, cellular uptake of fluorescently labeled particles was observed, with kinetics revealing that polyesters are endocytozed much faster than polystyrene particles [86]. Polylactide nanoparticles presenting mannose residues at their surface were prepared with dimensions of 200–300 nm by a nanoprecipitation

technique [87]. Biochemical assays were used to quantify their recognition of lectin proteins. Such nanoparticles are designed to be specifically recognized by mannose receptors, which are highly expressed in cells of the immune system. Future applications as vaccine delivery agents are anticipated. Thiol-capped polylactides were used to coat photoluminescent quantum dots, which are designed as drug delivery nanovehicles with both diagnostic imaging properties and controlled drug release properties [88]. Another route to nanoscale particles is via micelle formation of amphiphilic block copolymers [89]. Polyethylene glycol-block-lactides were shown to form polymeric micelles, into which paclitaxel as a model drug was encapsulated. Biodistribution and drug release behaviors were studied.

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