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Chemical syntheses of biodegradable polymers

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Abstract

Commercially available synthetic biodegradable polymers had been limited to aliphatic polyesters until polyesters containing aromatic moieties recently appeared on the market. Currently, several different types of biodegradable polymers have been developed and are being evaluated for practical uses. The present article reviews recent advances in chemical syntheses of biodegradable polymers from the standpoint of molecular design. Thus, synthetic biodegradable polymers are herein classified into three groups: (1) polyesters, (2) polymers containing both ester and other heteroatom-containing linkages in the main chains, and (3) polymers with heteroatom-containing linkages other than ester linkages in the main chains. Progress in the synthesis of the representative polymers in each category is described with emphasis on controlled synthesis, and their biodegradability is discussed in relation to the molecular structure. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Polyester; Poly(ester amide); Poly(ester carbonate); Poly(ester ether); Polycondensation; Ring-opening polymerization; Biodegradation; Enzymatic degradation

Contents

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1. Introduction

At the beginning of the 21st century, about six billion people live on the earth, and it is anticipated that the population will surpass ten billion in the middle of this century. Because of this explosive increase in population, we are confronting several serious problems such as deficiencies in food, resources and energy, and global environmental pollution. Sciences and technologies in the last century have made astonishing progress, particularly after the World War II, and made our daily life more comfortable and convenient. As for polymeric materials, a variety of synthetic polymers have been developed and used as synthetic fibers, plastics, and synthetic rubbers in place of traditionally used natural fibers, woods, and natural rubbers. Synthetic polymers are utilized in a wide variety of fields including transportation, construction, packaging, electronic devices, medical appliances, etc. Nowadays, about 150 million tons of plastics are produced annually all over the world, and the production and consumption continue to increase. Most of these plastics are of petroleum origin, and the increase in the production of plastics, as a consequence, results in the increase of oil consumption. More importantly and worrying, higher durability of synthetic polymeric materials compared to the traditionally used naturally occurring polymeric materials ironically causes serious environmental pollution due to wasted and undegraded polymers.

One of the strategies to solve these difficult problems on fossil resources and global environment is thorough recycling of wasted polymeric materials. In fact, plastic recycling has become increasingly popular all over the world, and effective methods for chemical recycling as well as material recycling have been developed and put into effect. Plastic recycling should be promoted more intensively, but the serious plastic pollution could not be solved by means of plastic recycling alone. It is not always possible to recover all the used plastics. In such cases it would be indispensable to use biodegradable polymers. In addition, it is to be noted here that recycling processes of wasted plastics, whether it is material recycling or chemical recycling, consume a considerable amount of thermal energy, and that we cannot recycle plastics forever, that is, wasted plastics are eventually destined to be burnt or buried in land. Taking these into consideration, we can easily understand the necessity of biodegradable polymers that are recycled by microorganisms without consumption of thermal energy.

Biodegradable polymers are defined as polymers that are degraded and catabolized, eventually to carbon dioxide and water, by microorganisms (bacteria, fungi, etc.) under natural environment. Needless

to say, these polymers, when they are degraded, should not generate any substances that are harmful to the natural environment. Biodegradable polymers are classified into three major categories: (1) polyesters produced by microorganisms, (2) natural polysaccharides and other biopolymers, (3) synthetic polymers, particularly aliphatic polyesters. The advantages and disadvantages of biodegradable polymers of these three different categories have been discussed so far, and therefore they are not repeated in the present article. Briefly speaking, polyesters of microorganism origin are derived from renewable bioorganic resources such as starch and fats, and are completely biodegraded in soil, rivers, and sea. Furthermore, many different types of poly(hydroxyalkanoate)s can be produced by the proper choice of carbon sources. However, their production in an industrial scale is not so efficient, preventing cost reduction and hence the extensive use of biodegradable polyesters of this type.

Biodegradable polymers based on natural polysaccharides, particularly starch, can be produced at low cost and in a large scale. As polysaccharides themselves do not have plasticity, they are often used after chemical modifications and/or as a blend with a biodegradable synthetic polymer. However, the effective combinations of such natural and synthetic polymers are rather limited. In view of a wide variety of currently used plastics, it is necessary to develop various kinds of biodegradable polymers having properties and functions most suitable for individual purposes. In this sense, synthetic biodegradable polymers have a great advantage, since recent advances in polymer science and technology have made it possible to design and synthesize at will a great variety of polymers with desirable properties. Furthermore, they are adaptable for mass production.

As to synthetic biodegradable polymers, aliphatic polyesters are the representatives. Nowadays, aliphatic polyesters such as poly(ϵ-caprolactone), poly(L-lactide), poly(butylene succinate) are commercially produced, and their output continues to increase. Besides these aliphatic polyesters, various types of synthetic biodegradable polymers have been designed and tested for practical applications. They are, for example, polyesters containing aromatic rings or cyclic ether moieties, poly(ester amide)s, poly(ester carbonate)s, poly(ester urethane)s, etc. Most of them are still in a premature stage, except polyesters containing terephthalate moieties. High molecular weight vinyl polymers are generally resistant to biodegradation, although it is well known that some polymers such as poly(vinyl alcohol) is biodegradable. Some attempts, e.g. introduction of ester moieties into vinyl polymer chains, have been proposed to make vinyl polymers biodegradable. However, there has not yet been developed any effective and practical method that bestows sufficient biodegradability to vinyl polymers without sacrificing their intrinsic mechanical and thermal properties.

In this review article, we deal with recent development in the chemical syntheses of biodegradable polyesters in Section 2, particularly focusing on molecular design and structure-biodegradability relationships. In Section 3, we survey the above-mentioned potentially biodegradable, synthetic polymers having not only ester linkages but also other heteroatom-containing linkages in their main chains. In Section 4 we refer to synthetic polymers with heteroatom-containing linkages other than ester linkages in the main chains. So far many excellent articles and books have reviewed biodegradable polymers from different points of views [1–9]. To minimize overlapping with these previous articles, the references cited herein are, as a principle, limited to those appeared in these few years.

2. Syntheses of biodegradable polyesters

Polyesters are synthesized by polycondensation of combinations of diols and dicarboxylic acids or by

self-polycondensation of hydroxyacids, or by ring-opening polymerization of lactones and lactides. In fact, commercially available biodegradable polyesters are produced by these methods. Polycondensation can be applicable for a variety of combinations of diols and diacids, but it requires, in general, higher temperature and longer reaction time to obtain high molecular weight polymers. In addition, polymers obtained do not have controlled chain lengths. In contrast, ring-opening polymerization has a restriction on monomers, but it can be carried out under milder reaction conditions to produces high molecular weight polymers in shorter time. Furthermore, recent progress in catalysts and initiators for living polymerization has enabled us to produce polyesters of controlled chain lengths.

Recently, use of enzymes as a catalyst in organic syntheses is a new trend. In general, enzymatic reactions can be carried out under moderate conditions. More importantly, enzymes can easily realize high regiospecificity as well as high stereospecificity that conventional catalysts can never achieve. For polymer synthesis, in vitro enzyme-catalyzed polymerization has been developed as an effective method to synthesize environmentally benign polymers. A variety of polyesters have been prepared by polycondensation of various combinations of diols and dicarboxylic acids as well as ring-opening polymerization of lactones of various ring-sizes using enzyme as a catalyst [10–14].

This section reviews recent development in the synthesis of biodegradable polyesters, with reference to some selected papers that appeared in these few years. For the sake of convenience, this section is divided into two sections, first, polyester synthesis by polycondensation, and secondly, polyester synthesis by ring-opening polymerization.

2.1. Polyesters by polycondensation

2.1.1. Aliphatic polyesters

Synthesis of aliphatic polyesters by polycondensation of diols with dicarboxylic acids traces back to Carothers' work in the 1930s. However, the low melting points inherent to aliphatic polyesters, together with the difficulty in obtaining high molecular weight polymers, had prevented a wide usage of aliphatic polyesters as polymeric materials for a long time. However, as the environmental pollution on the earth has increasingly widely spread, aliphatic polyesters are spotlighted because of their characteristic biodegradability. Nowadays, effective techniques have been developed to produce high molecular weight polyesters applicable for practical purposes, and aliphatic polyesters such poly(butylene succinate) and poly(butylene succinate-*co*-butylene adipate) have been commercialized as biodegradable polymeric materials. In addition, the direct polycondensation procedure has also been established to produce high molecular weight poly(lactic acid) in an industrial scale.

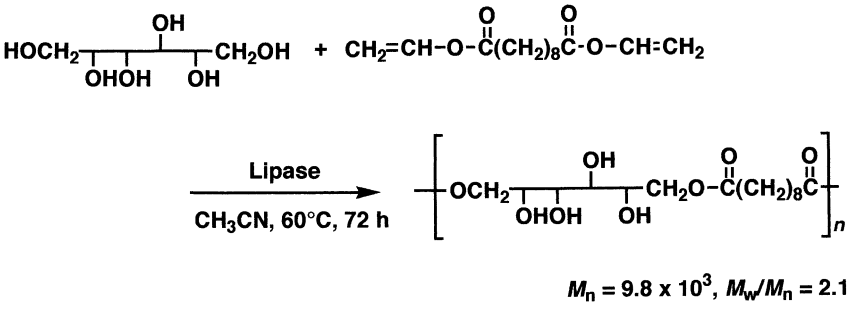
Although poly(L-lactic acid) has usually been prepared by ring-opening polymerization of L-lactide, polycondensation of L-lactic acid also gives poly(L-lactic acid) with a significantly high molecular weight [15,16]. Recently Kimura et al. [17] reported a new synthetic route to high molecular weight poly(L-lactic acid) by melt/solid polycondensation of L-lactic acid. Thus, a polycondensate with a molecular weight of 2×10^4 was first prepared by ordinary melt polycondensation using a tin(II) chloride hydrate/*p*-toluenesulfonic acid binary system, crystallized by heat-treatment around 105°C, and heated at 150°C for 10–30 h for further polycondensation. A high quality poly(L-lactic acid) was obtained in high yield in a relatively short reaction time and its molecular weight exceeded 5×10^5 which is comparable with that of the poly(L-lactic acid) obtained by the ring-opening polymerization of L-lactide. In solid-state, the polymerization reaction can be favored over the depolymerization or other side reactions. Particularly, in the process of crystallization of the resultant polymer, both monomer and

catalyst can be segregated and concentrated in the noncrystalline part to allow the polymer formation to reach 100% [18].

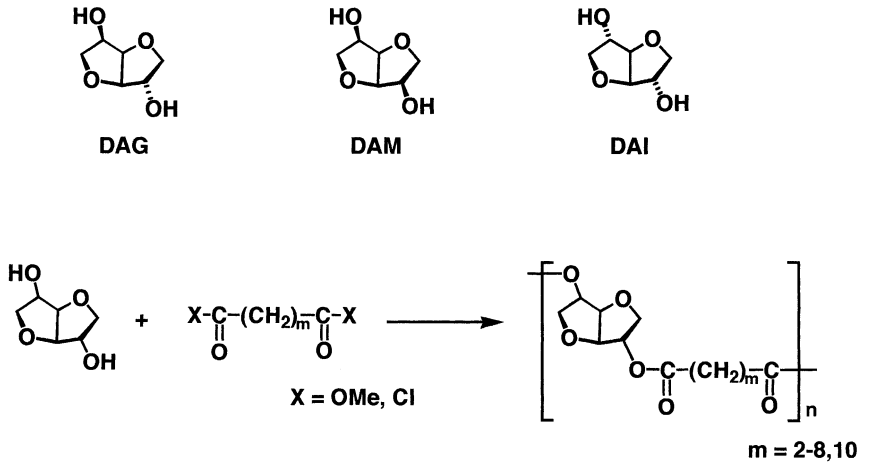
Use of enzyme in polyester synthesis is noteworthy from the standpoint of 'Green Chemistry', in addition to the characteristics of the enzyme-catalyzed reactions mentioned above. Kobayashi et al. [19] reported that divinyl dicarboxylates are effective monomers for the enzyme-catalyzed polycondensation. For instance, a sugar-based polyester was successfully synthesized by a regioselective polymerization of hexa-functional sorbitol and divinyl sebacate using lipase derived from *Candida antarctica* as a catalyst (Scheme 1). This is the first example using a sugar alcohol as monomer of the enzyme-catalyzed polymerization. The polymerization proceeded in acetonitrile, acetone, *tert*-amyl alcohol, and 1,4-dioxane. The yield increased as a function of the temperature, and the polymerization at 80°C gave the polymer with the molecular weight of higher than ten thousands. According to the ^{13}C NMR analysis, the polymer consisted exclusively of the acylated unit of sorbitol at 1 and 6 positions, verifying that the regioselectivity was perfectly controlled through the enzyme catalysis.

Effective utilization of renewable natural resources as precursors for the production of polymeric materials, organic chemicals, and fuel has been increasingly important, since oil resources are very likely to run out in a near future. Among the versatile utilization of renewable natural resources, synthesis of environmentally compatible polymers based on biomass resources, particularly plant-based resources including wood, agricultural crops and residues, grasses, and components from these sources is an attractive and challenging target of investigation. For example, 1,4:3,6-dianhydro-D-glucitol (DAG) that is easily derived from D-glucose has been used as a diol component in the synthesis of polyesters, polyurethanes, and polycarbonates [20]. Okada et al. [21–23] synthesized a series of polyesters from DAG, 1,4:3,6-dianhydro-D-mannitol (DAM) or 1,4:3,6-dianhydro-L-iditol (DAI), and aliphatic dicarboxylic acids of the methylene chain length ranging from 2 to 10 (Scheme 2). Enzymatic degradability of these polyesters as estimated by water-soluble total organic carbon (TOC) measurement is dependent on the methylene chain length (m) of the dicarboxylic acid component for most of the seven different enzymes examined. The most remarkable substrate specificity was observed for *Rhizopus delemar* lipase which degraded polyester derived from DAG and suberic acid ($m = 6$) most readily. In contrast, degradation by *Porcine pancreas* lipase was nearly independent of the structure of the polyesters.

Enzymatic degradability of the polyesters based on the three stereoisomeric 1,4:3,6-dianhydrohexitols and sebacic acid was found to decrease in the order of DAG > DAM > DAI. Structural analysis of water-soluble degradation products formed during the enzymatic hydrolysis of the polyester derived



Scheme 1. Synthesis of a sugar-based polyester by enzyme-catalyzed polycondensation.



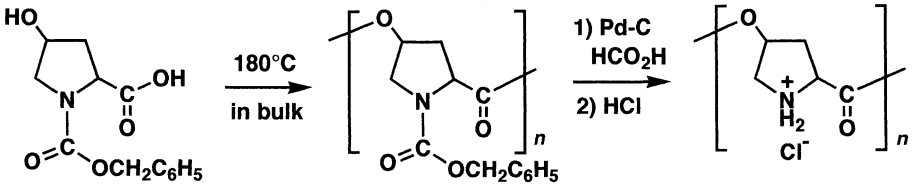
Scheme 2. Polyesters containing stereoisomeric 1,4:3,6-dianhydrohexitol units.

from DAG and sebacic acid showed that the preferential ester cleavage occurred at the O(5) position of 1,4:3,6-dianhydro-D-glucitol moiety in the polymer chain by *Porcine pancreas* lipase, *Rhizopus delemar* lipase and *Pseudomonas* sp. lipase.

One of the important criteria for the use of synthetic polymers in biomedical applications seems to be that polymers should be not only biodegradable but also have functional groups to which drugs or biologically active compounds can be attached covalently or noncovalently. Park et al. [24] synthesized poly(*trans*-4-hydroxy-L-proline ester) (PHP ester) from *N*-benzyloxycarbonyl-4-hydroxy-L-proline by polycondensation, followed by the removal of the protecting group by catalytic transfer hydrogenation (Scheme 3). PHP ester is likely to be nontoxic, because this polymer degrades very fast and completely to hydroxyproline, a constituent of collagen, gelatin, and other proteins. Although PHP ester degrades very quickly when it is alone in solution, it is more stable when complexed with DNA. PHP ester complexed with DNA transfects mammalian cells, showing the possibility of using the polymer as a gene delivery carrier.

Biodegradation of aliphatic polyesters has been extensively studied so far, and principal factors influencing the biodegradability have been proposed [25–29]. As to the primary structure, chemical bonds, hydrophilic/hydrophobic balance, bulkiness of substituents, cross-linking, and chain length are important factors dominating biodegradability. Higher-order structures including conformation, crystal structure, crystallinity, morphology, orientation, etc. also affect the biodegradability of polyesters.

For example, Cho et al. [28] investigated the effect of crystallinity on the hydrolytic degradation



Scheme 3. Synthesis of poly(*trans*-4-hydroxy-L-proline).

behavior of poly(butylene succinate) (PBS) in an alkaline solution. They found that even with a similar degree of crystallinity, the hydrolytic degradation rate of an isothermally crystallized sample at 60°C was higher than that of a melt-quenched sample. The internal structure of spherulite in an isothermally crystallized sample consisted of coarse and loosely packed fibrils, whereas a melt-quenched sample contained finer and tightly packed fibrils. This result, therefore, suggests that the internal structure of the spherulite of PBS samples plays an important role in the hydrolytic degradation.

Despite their good properties, the infiltration of poly(butylene succinate) and the related biodegradable polyesters into daily life seems to be rather slow chiefly due to their relatively high cost. To circumvent this difficulty, Ratto et al. [30] investigated the addition of low cost biodegradable starch to poly(butylene succinate-*co*-butylene adipate) (PBSA) as a route to producing biodegradable composites with improved cost competitiveness, while maintaining good mechanical properties and processability. The PBSA/starch films were prepared with starch contents of 5–30% by weight and processed by blown film extrusion. Increasing the starch content led to an increase in modulus and decrease in tensile strength, elongation to break and toughness. The rate of biodegradation in soil as measured by respirometry increased significantly as the starch content was increased to 20% and then leveled off. Scanning electron microscopy revealed that the starch granules embedded in the continuous-phase PBSA promotes the biodegradation of PBSA. SEC measurements indicated a molecular weight decrease for the PBSA after the soil burial and confirmed that biodegradation was enhanced by the presence of starch.

2.1.2. Polyesters containing aromatic moieties

One of the effective approaches to improve the thermal and mechanical properties of aliphatic polyesters is incorporation of aromatic ester moieties in the polyester chain [31–35]. Lee et al. [32] synthesized a series of aliphatic/aromatic copolyesters by polycondensation of succinic acid, dimethyl terephthalate and 1,4-butandiol, and evaluated their material characteristics and biodegradability. The tensile strength is relatively unaffected, while the elongation at break increases remarkably with increasing butylene terephthalate content. In particular, the sample with 40 mol% butylene terephthalate content shows 550% elongation at break. At high butylene terephthalate content where the crystallinity of the copolyesters is suppressed, the tangent modulus of the copolyesters is relatively low. However, the butylene terephthalate segments contribute largely to increase the elongation at break, leading to good tensile strength of the copolyesters.

As expected, the rate of biodegradation decreases with increasing butylene terephthalate content in the copolyesters. Although it is well known that the degree of crystallinity is an important factor in determining microbial degradability, the effect of the degree of crystallinity on the biodegradation rate was not observed, probably because the influence of the chemical structure on biological resistance overrides the biodegradability of the copolyesters. In soil burial tests, the mechanical properties of the copolyester films decreased rapidly, and the films with a butylene terephthalate content of less than 20 mol% could not be recovered after four weeks.

Maeda et al. [33] synthesized random copolyesters by transesterification of poly(ethylene terephthalate) (PET) and poly(succinic anhydride-*co*-ethylene oxide) using titanium tetrabutoxide as a catalyst. The tensile strength and elongation at break of the copolymer films increased compared to the chain-extended poly(ethylene succinate) films due to the introduction of phthalate units. The enzymatic hydrolyzability of the copolymers by a lipase from *Rhizopus arrhizus* and biodegradability by activated sludge decreased with an increase in PET content. When the length of succinate unit in the copolymer was below 2, the hydrolyzability of the copolymers decreased considerably.

Recently, Kint et al. [34] reviewed the potential biodegradability of poly(ethylene terephthalate). They propose the following three factors for increasing the hydrolytic biodegradability of PET, i.e. the presence of hydrolyzable linkages along the polymer chains, balancing between amorphous and crystalline morphology, and lowering the glass temperature. In addition, they state that transesterification caused by reactive blending appears to be the most efficient method for incorporating suitable hydrolyzable and hydophilic segments in the polymer backbone. However, the high temperature required for this reaction to take place in high melting PET restricts the choice of the degradable aliphatic polymer. Kint et al. point out that the impact of the modification on the overall behavior of PET, specifically on the thermal and mechanical properties, should be controlled, a point that has not been duly considered in most of the work carried out so far.

Aliphatic polyesters with aromatic side groups should have properties and biodegradability different from those with aromatic groups in the main chain. Jin et al. [35] investigated mechanical and thermal properties of poly(ethylene adipate) and poly(butylene succinate) when phenyl side branches were introduced by copolymerizing styrene glycol with the respective diacids and diols (Chart 1). Elongation at break and tear strength of both polyesters declined as the styrene glycol content increased, which could be partly ascribed to the decrease in molecular weight and to the decrease in crystallinity as well. However, tensile modulus was relatively unaffected, possibly due to the increase in T_g.

In sharp contrast to polyesters containing aromatic diacids or diols in the backbone chain of aliphatic polyesters, the copolyesters with pendant phenyl groups based on poly(butylene succinate) and poly(ethylene adipate) were biodegraded in an activated sludge more easily as the styrene glycol content increased. Presumably, the decreasing crystallinity and molecular weight played a more important role in the enhancement of the biodegradability compared to the change in the hydrophobicity.

Furan derivatives can be prepared from renewable plant resources and therefore they are available widely and continuously. Furfural, a versatile member of a furan family, which is obtained from polymeric pentoses by acid-catalyzed hydrolysis followed by acid-catalyzed dehydration, can be chemically transformed in various ways to give monomers for polymer synthesis as well as useful

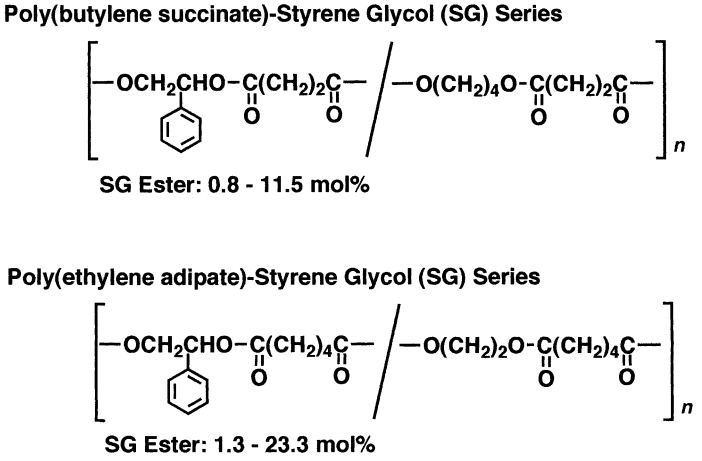
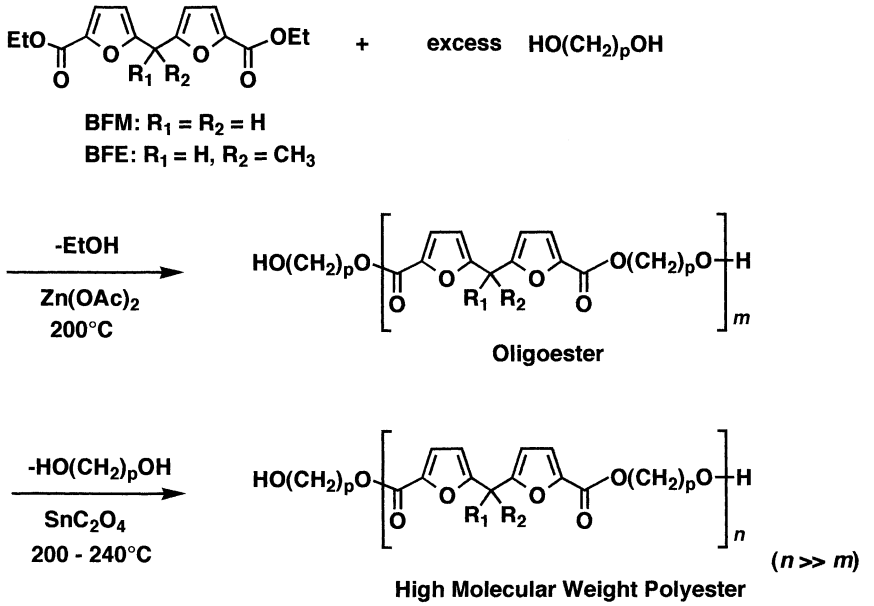


Chart 1. Polyesters with pendant phenyl groups.

intermediates for organic syntheses [36–40]. A two-step transesterification procedure was applied to combinations of difuranic diesters such as bis(5-(ethoxycarbonyl)-2-furyl)methane (BFM) and 1,1-bis(5-ethythoxycabonyl)-2-furyl)ethane (BFE), and both aliphatic and furanic diols [40] (Scheme 4). The best results related to the first phase of the synthesis were obtained using $Zn(OAc)_2$, $Pb(OAc)_2$ or $Ti(OBu)_4$ at 200°C with a large excess of diol. The second phase, which led to the actual polymer at 200–240°C, required the catalytic action of SnC_2O_4, Sb_2O_4, Sb_2O_3 and $Ti(OBu)_4$. Specific problems, related to some fragile moieties, limited the success of these polymerizations to a number of combinations that gave polyesters bearing regular structures and molecular weights of up to 3.7×10^4.

A series of polyesters were synthesized by the bulk polycondensations of the respective combinations of the two difuranic diesters (BFM and BFE), with 1,4:3.6-dianhydro-8-glucitol (DAG), 1,4:3.6-dianhydro-D-mannitol, four aliphatic diols, and three oligo(ethylene glycol)s [41,42]. The polycondensations were carried out at 220–230°C in the presence of titanium isopropoxide as a catalyst to give polyesters having number-average molecular weights of up to 2.4×10^4. Various copolyesters were also synthesized in a similar manner from DAG as the diol component, and BFE and seven dimethyl dialkanoates with methylene chain lengths of 4, 5, 6, 7, 8, 10, and 12 as the dicarboxylic acid components. Most of these homo- and copolyesters were amorphous, and they were soluble in organic solvents including chloroform, dichloromethane, pyridine, trifluoroacetic acid, and *m*-cresol.

Biodegradability of these homo- and copolyesters was assessed by enzymatic degradation using four different enzymes in a phosphate buffer solution at 37°C, and by soil burial degradation tests in composted soil at 27°C [42]. The biodegradability of the copolyesters decreased with the increase in the BFE content. The copolyesters containing sebacic acid units showed higher biodegradability. Soil burial degradation in the soil that was treated with antibiotics, together with electron microscopic



Scheme 4. Synthesis of furan-containing polyesters by two-step polycondensation.

observation, indicated that actinomycetes were mainly responsible for the degradation of the copolyesters containing BFE units in the soil burial test.

2.2. Polyesters by ring-opening polymerization

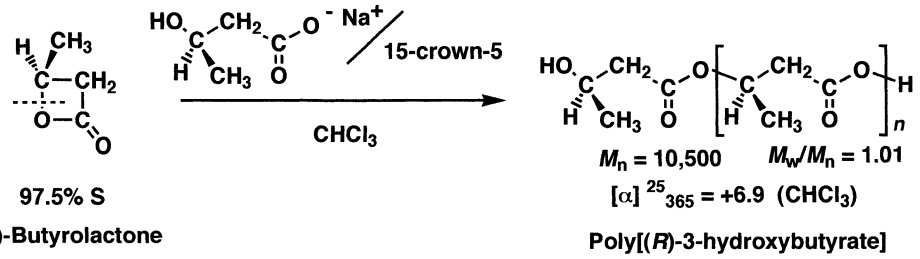
Ring-opening polymerization of lactones is an effective method for synthesizing biodegradable polyesters. Poly(ϵ-caprolactone) and poly(L-lactide) are the representative examples. Ring-opening polymerization of lactones has some advantages over polycondensation of diacids (or their derivatives) with diols. The former does not require equimolar balance of functional groups that is essential for the synthesis of high molecular weight polymer by the latter. In addition, ring-opening polymerization occurs under milder reaction conditions, and it sometimes proceeds in a 'living' manner, that is, without side reactions to give polyesters of controlled molecular weight. So far, numerous papers and patents have been published on the synthesis and properties of polyesters by ring-opening polymerization of lactones. In this section, however, we limit the description to recent publications closely related to the syntheses and biodegradability of polyesters in order to avoid discursiveness. For convenience's sake, polyesters from lactones and those from lactides are separately dealt with in this section.

2.2.1. Polyesters from lactones

2.2.1.1. Catalysts. One of the most frequently used catalysts for the polymerization of lactones and lactides is tin(II) 2-ethylhexanoate ($Sn(Oct)_2$). However, the mechanism of lactone polymerization with $Sn(Oct)_2$ has been a subject of controversy [43]. In a series of studies concerning the mechanism of lactones and lactides by $Sn(Oct)_2$, Penczek et al. [44] recently investigated the kinetics of the polymerization of ϵ-caprolactone and L,L-lactide in the presence of 2,6-di-*tert*-butylpyridine or 1,8-bis(dimethylamino)naphthalene, which are known as a 'proton trap' or 'proton sponge'. Polymerizations involving cationic or 'cationic-like' species should be trapped by the hindered amines. Actually, the polymerization were not stopped nor retarded, and they concluded that 'protons' or extended hydrogen bonds in any form are not actively involved into polyester chain growth in the presence of $Sn(Oct)_2$.

In contrast to unsubstituted four-membered β-propiolactone, β-butyrolactone is not polymerized by common anionic initiators such as metal alkoxides and alkali metal carboxylate salts. However, these initiators, when activated by addition of a macrocyclic ligand such as crown ether, can initiate polymerization of β-butyrolactone with the inversion of configuration from (*S*)-monomer to yield poly[(*R*)-3-hydroxybutyrate] (PHB). The structure of the polymer is similar to that of microbial PHB except for the presence of crotonate end groups. The polymerization of β-butyrolactone via electron transfer from the catalyst consisting of alkali metal supramolecular complexes, e.g. K^+/18-crown-6, yields polymers with similar architecture bearing acetoxy end groups [45].

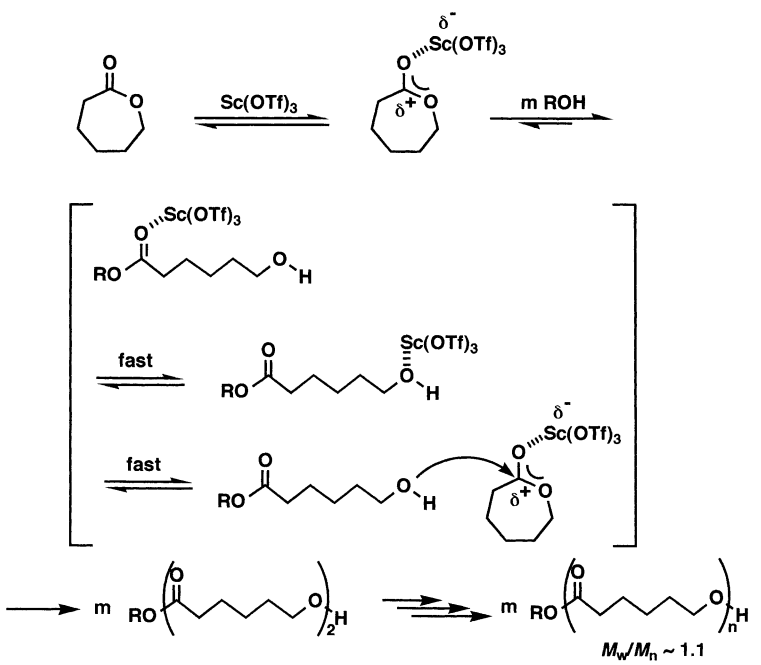
Jedlinski et al. [46] found that the sodium salt of (*R*)-3-hydroxybutyric acid activated by a crown ether produced poly[(*R*)-3-hydroxybutyrate] bearing only hydroxyl and caboxyl terminal groups from (*S*)-β-butyrolactone (Scheme 5). The hydroxybutyrate anion of the initiator attacks the chiral carbon atom of the monomer (alkyl–oxygen bond scission) with inversion of configuration at the chiral atom. The polymer chain growth proceeds entirely via carboxylate anions, and polymers formed bear hydroxyl and carboxyl end groups. Polymers of desired molecular weights of up to 2×10^4 were synthesized, and moreover, the molecular weight distribution was relatively narrow ($M_w/M_n \sim 1.10$). The polymers were entirely isotactic and crystalline.



Scheme 5. Synthesis of poly[(*R*)-3-hydroxybutyrate] by ring-opening polymerization of (*S*)-β-butyrolactone.

Living ring-opening polymerization of lactones has been reported mostly in an anionic or coordinated anionic fashion [47–49], whereas there have been rarely found successful cationic examples in the literature [50,51]. Okada et al. [52] reported a practical catalytic approach for cationic living ring-opening polymerization of lactones using scandium trifluoromethanesulfonate, $Sc(OTf)_3$, as a catalyst, in which one reactive $Sc(OTf)_3$ molecule catalytically produced a large number of polymer molecules and also in which contamination of protic compounds such as water and alcohol did not suppress the catalytic activity of $Sc(OTf)_3$ for cationic polymerization. The plausible mechanism is shown as an activated monomer mechanism in (Scheme 6).

They obtained poly(ϵ-caprolactone) with $M_n = 2.6 \times 10^4$ and $M_w/M_n = 1.1_5$ in 99% yield by the polymerization in toluene at 25°C for 33 h with 0.16 mol% $Sc(OTf)_3$. Similar results were obtained for the polymerization of δ-valerolactone. A noteworthy point is that polymerization of lactones proceeded



Scheme 6. Possible mechanism of cationic living polymerization of ϵ-caprolactone catalyzed by $Sc(OTf)_3$). Reprinted with permission from Macromolecules 2000;33:1497. ©2000 American Chemical Society [52].

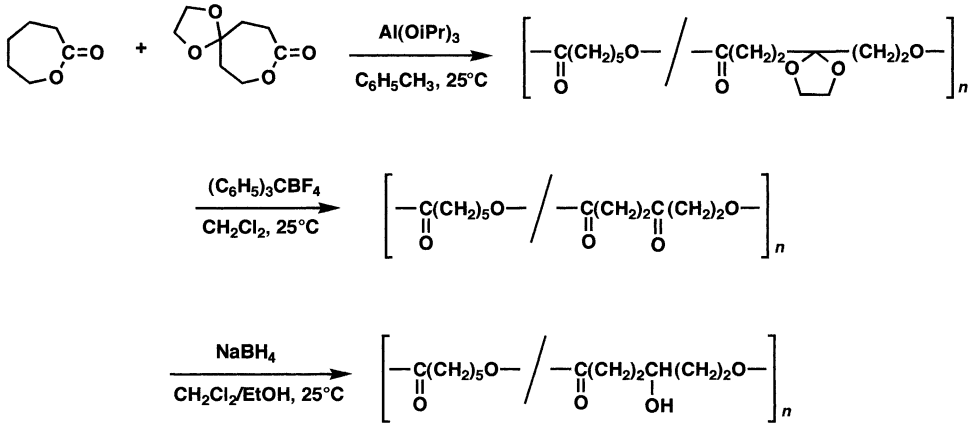
in the presence of 20 equiv. of benzyl alcohol or water to $Sc(OTf)_3$ to yield polyesters of narrow molecular weight distributions ($M_w/M_n = 1.1_0 - 1.1_5$). The characteristics of this systems are: (i) commercially available $Sc(OTf)_3$ acts as an excellent catalyst for cationic polymerization of lactones under mild conditions, and it is reactive in the presence of protic compounds and easy to handle under air; (ii) one reactive $Sc(OTf)_3$ molecule catalytically produces a large number of polymer molecules with a narrow molecular weight distribution; (iii) analytically pure polyester is readily obtained in nearly quantitative yields from an organic layer washed with water to remove the water-soluble catalyst after the monomer was completely consumed, and no further purification was required.

2.2.1.2. Functionalized polyesters. Compared to conventional uses such as multilayered films for agricultural purposes, more precise control of biodegradation is required for biomedical applications including surgery and medicines. One of the approaches to design sophisticated polyesters with controlled biodegrdation rate is to use functional polymers, which permit subsequent chemical modification to allow desirable properties including hydrophilicity, biodegradation rate, bioadhesion, etc.

For example, Jérôme et al. [53] synthesized multihydroxy functional polyester by the copolymerization of ϵ-caprolactone with 5-ethylenedioxy-ϵ-caprolactone, followed by deprotection and reduction of the generated ketone functionality (Scheme 7). The hydrophilic copolyester can be used for applications that utilize the hydroxyl groups including the preparation of amphiphilic block copolymers and nanoparticles.

Oligo(ϵ-caprolactone)s functionalized with acid groups were prepared by reacting hydroxyl terminated oligo(ϵ-caprolactone)s with succinic anhydride, maleic anhydride, or glutaric anhydride [54]. The reactivity of these acid terminated oligo(ϵ-caprolactone)s was enhanced by conversion of the acid functionality to an acid chloride functionality using thionyl chloride or an anhydride functionality using acetic anhydride. These activated oligo(ϵ-caprolactone)s can be used for coupling reactions with compounds containing alcohol- or amino functionalities.

Hedrick et al. [55] synthesized and polymerized new lactones containing protected functional groups (hydroxy-, bis(hydroxyl)-, amino-, and carboxyl-substituted). Polymerization of these monomers was accomplished either in bulk at 110°C initiated from benzyl 2,2′-bis(hydroxymethyl)propionate in the

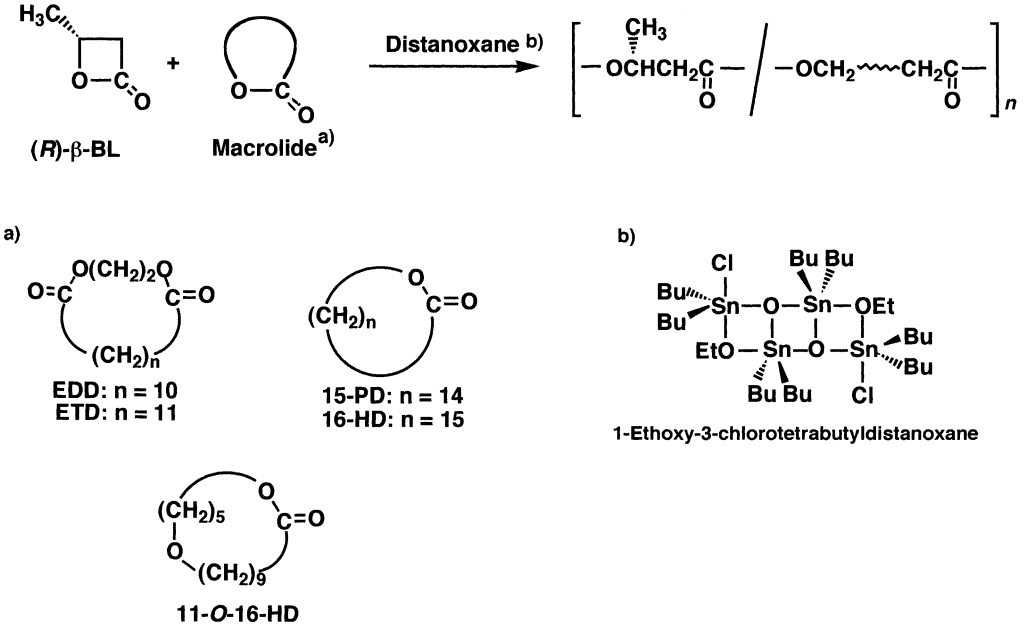


Scheme 7. Synthesis of polyester with pendant hydroxyl groups.

presence of $Sn(Oct)_2$ or in toluene at 0°C initiated from $Al(OiPr)_3$, yielding polymers close to their targeted molecular weights ($M_n = 5 \times 10^3$–15×10^3) with modestly narrow polydispersities ($M_w/M_n =$ 1.20–1.35). Removal of the protecting groups on the polymers gave polyesters having the corresponding functional groups.

2.2.1.3. Copolymers. Copolymerizations including block- and graft-copolymerizations are frequently employed to modify the properties of hompopolymers. Up to the present, various types of copolyesters have been prepared for improving the properties of aliphatic biodegradable polyesters. The poly(hydroxyalkanoate)s (PHAs) produced by a fermentation process are limited to copolyesters such as poly[(*R*)-3-hydroxybutanoate-*co*-(*R*)-3-hydroxyalkanoate]s and poly[(*R*)-3-hydroxubutanoate-*co*-4-hydroxybutanoate]. Hori et al. [56] prepared a new series of biodegradable PHAs, which are difficult to obtain by a fermentation method. For example, they obtained a series of poly[(*R*)-3-hydroxybutyrate-*co*-macrolide]s by the ring-opening polymerization of (*R*)-β-butyrolactone with ethylene dodecanedioate (EDD), ethylene tridecanedioate (ETD), 15-pentadecanolide (15-PD), 16-hexadecanolide (16-HD), or 11-*oxa*-16-hexadecanolide (11-*O*-16-HD) in the presence of the distannoxane catalyst in excellent yield (Scheme 8). All polyesters had high molecular weight ($M_n > 1 \times 10^5$). The tensile strength and elongation to break measurements showed that the incorporation of only 10 mol% amounts of 15-PD and 16-HD units increased the elongation to break of the copolymers remarkably (749 and 466%, respectively). In contrast, EDD, ETD, and 11-*O*-16HD did not increase the elongation to break so much.

Unlike the optically active poly[(*R*)-3-hydroxybutyrate], racemic poly[(*R,S*)-3-hydroxybutyrate] is elastomeric. For the application as biodegradable elastomer, cross-linking is necessary for decreasing their creep behavior. The cross-linking of aliphatic polyesters cannot be achieved by the ordinary



Scheme 8. Synthesis of copolyesters by ring-opening polymerization of (*R*)-β-butyrolactone with macrolides.

methods because they are likely to be decomposed rather than cross-linked. An alternative method is physical crosslinking arising from microphase separation of block copolymers.

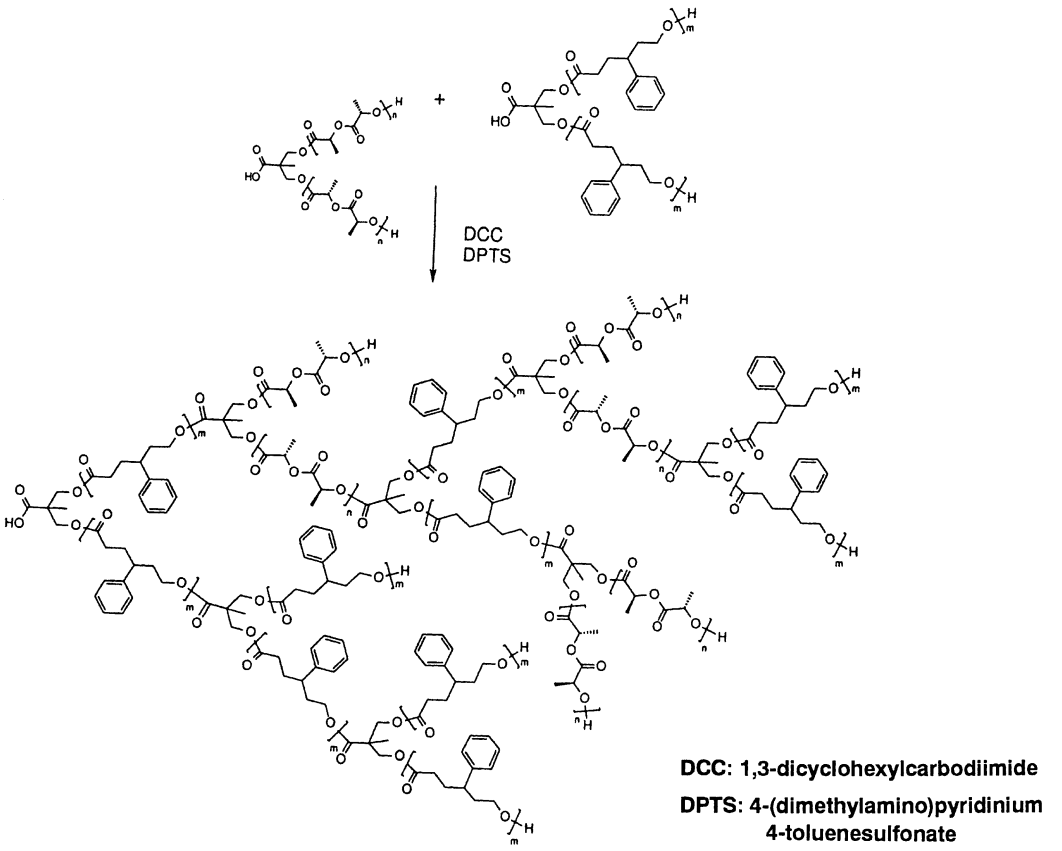
To avoid scrambling during polymerization in block polymer synthesis [57], Kimura et al. [58] first prepared a telechelic poly[(*R*,*S*)-3-hydroxybutyrate] by the ring-opening polymerization of (*R*,*S*)-β-butyrolactone in the presence of 1,4-butandiol with distannoxane as the catalyst. It was subjected to block copolymerization with L-lactide using tin(II) octoate as the catalyst to obtain A–B–A type triblock copolyester comprising poly(L-lactide) (A) and poly[(*R*,*S*)-3-hydroxybutyrate) (B). The DSC measurements indicated that microphase separation occurs if the segment crystallization was induced. In addition, the mechanical properties of the elastomeric triblock copolymers were improved by the introduction of poly(L-lactide) as the hard segment. These results suggest that the triblock copolymer has high potential for use as a biodegradable thermoplastic elastomer.

Dendrimers and hyperbranched macromolecules are attracting, both scientifically and industrially, a great deal of expectation that some novel properties may arise from their unique molecular architecture [59–64]. Dedrick et al. [65] proposed new approaches to biodegradable dendritic aliphatic block copolymers using a series of new substituted ϵ-caprolactones containing methyl, ethyl, phenyl, and dimethyl groups. These monomers were used as a comonomer for preventing crystallization and imparting desirable mechanical properties to the dendritic polyesters ranging from thermoplastic elastomer to rubber toughened systems. The hyperbranched polymers were obtained by the cocondensation of different intrinsically branched AB_x macromonomers (Scheme 9). The macromonomers were prepared by ring-opening polymerization of either ϵ-caprolactone, L-lactide, or various substituted lactones using the benzyl ester of 2,2′-bis(hydroxymethyl)propionic acid as initiator. Catalytic hydrogenation of the benzyl ester generated the requisite acid function.

The second route to block copolymers with controlled branching utilizes a new type of molecular architecture, denoted as dendrimer-like star polymers. These block copolymers are described by a radial geometry where the different layers or generations consist of high molecular weight polymer emanating from a central core. With this architecture, more control in the placement of the different blocks is afforded over the hyperbranched analogue. Irrespective of the molecular architecture, microphase morphologies were observed when poly(L-lactide) was employed as one of the blocks.

Among naturally occurring polysaccharides, starch is a potentially useful raw material for biodegradable plastics because of its natural abundance and low cost. However, starch-based plastics have some drawbacks, including poor long-term stability caused by the water absorption, poor mechanical properties, and processability. One of the effective ways to improve some of these properties is grafting of synthetic polymers onto starch. Park et al. [66] synthesized starch-*graft*-polycaprolactone (PCL) by the ring- opening graft polymerization of ϵ-caprolactone (CL) onto starch backbone. The graft reactions were conducted in the presence of water to obtain starch-*graft*-PCL copolymers, although the grafted PCL lengths were very short. The initial increase in water content under the fixed starch/CL feed ratio only increased in the number of PCL grafts, and the additional increase in water content lengthened the PCL grafts to some extent. On the other hand, the change of CL content in the feed at the fixed starch/water ratio brought about the maximum in graft length. Presumably, these phenomena are attributed to the change of hydrophilicity of the graft copolymers formed in the reaction medium affecting the reactivity of the grafting reactions.

Dubois et al. [67] developed a three-step procedure for controlled synthesis of PCL-grafted dextran of a wide range of copolymer compositions. It consists of the reversible protection of the hydroxyl groups of the polysaccharide backbone by silylation, followed by the ring-opening polymerization of CL



Scheme 9. Copolymerization of intrinsically branched AB_2 macromonomers using dicyclohexylcarbodiimide (DCC) and 4-(dimethyleamino)pyridinium 4-toluene-sulfonate (DPTS). Reprinted with permission from Macromolecules 1999;32:4917. ©1999 American Chemical Society [65].

initiated by the free remaining hydroxyl groups of the partially silylated dextran in the presence of aluminum and tin-based catalysts. The last step relies upon the removal of silylating groups under mild acidic conditions yielding the desired amphiphilic graft copolymers. According to the ^{1}H NMR spectroscopy, the graft copolymer can adopt a core-shell cylindrical-shaped conformation, particularly at high weight fraction of hydrophobic polyester branches and/or high degree of polymerization of PCL. Preliminary dynamic surface tension experiments have shown the potential of these amphiphilic graft copolymers as surfactants.

2.2.1.4. Biodegradation. Biodegradation of aliphatic polyesters derived from lactones has been investigated from various aspects. Here we discuss biodegradation of aliphatic polyesters focusing on the stereochemical aspect. Jaimes et al. [68] studied the enzymatic degradability of poly[(*R*,*S*)-3-hydroxybutyrate] (P[(*R*,*S*)-3HB]) with different isotactic diad fractions (from 0.41 to 0.72) and copolymers, poly(β-butyrolactone-*co*-ϵ-caprolactone) [P(BL-*co*-CL)] and poly(β-butyrolactone-*co*-δ-valerolactone) [P(BL-*co*-VL)] under aerobic and anaerobic conditions in water. The degradation rate measured for bacterial P[(*R*)-3HB] (100%R) was the highest and the degree of aerobic biodegradation reached after 36

days was around 94%. A 40–50% biodegradation was obtained for synthetic P[(*R*,*S*)-3HB] which were highly isotactic and predominantly syndiotactic, respectively. The non-crystalline and atactic P[(*R*,*S*)-3HB] synthesized from tetraisobutyldialuminoxane (TBAIO) catalyst had a high degree of biodegradation of around 88%. This result may suggest that not only the (*R*)-3HB units are hydrolyzed but also the (*S*)-3HB units. All the copolymers synthesized from TIBAO catalyst exhibit a high degree of biodegradation of around 85% except for copolymers containing a very high portion of unsubstituted units, CL or VL. The anaerobic biodegradation of P(3HB) and copolymers P(BL-*co*-CL) is much lower than the aerobic biodegradation, as are the initial rates, even for bacterial P[(*R*)-3HB].

Although earlier investigations have provided valuable information about the initial rate of cleavage, the products of degradation of *all*-(*R*)-oligo(3-hydroxybutyrate)s by PHB depolymerase from *Alcaligenes faecalis*, and the enzyme's substrate specificity, its stereoselectivity has hitherto not been reported. Seebach et al. [69] investigated the degradation rates and cleavage pattern of oligo(3-hydroxybutyrate)s containing up to eight HB units with given sequences of (*R*) and (*S*) configurations along the chains using *Alcaligenes faecalis* T_1. They used a highly sensitive titristat/HPLC method [70] for monitoring the degradation. Analysis of the measurements allowed them to propose detailed structural features at the binding site of the depolymerase: (1) The enzyme is an endo esterase; (2) It recognizes the orientation of the chain relative to its active site; (3) The binding site contains four subsites, three of which have to be occupied by HB units for cleavage to occur at all (rate $\nu_{max}\beta$) and all four for cleavage to take place at the maximum rate ($\nu_{max}\alpha$); (4) The central two subsites, between which cleavage occurs, must be occupied by (*R*)-HB units, whereas the terminal subunits may also be occupied by (*S*)-HB units (Fig. 1). The degradation of oligo(3-hydroxybutyrate)s can then be explained as a combination of all possible cleavages with $\nu_{max}\alpha$ or with $\nu_{max}\beta$. The model that they proposed is in accordance with previous degradation studies of PHB with different tacticities [71], although it does not take into account the effects of crystallinity on the rate of degradation.

Lenz et al. [72] obtained copolyesters from the copolymerization of (*R*,*S*)-β-butyrolactone and γ-butyrolactone catalyzed by isobutylaluminoxane. Copolymer with γ-butyrolactone contents up to 33% were prepared and compared their structure and properties with copolymers having the same types of repeating units produced by *Alcaligenes eutrophus*. The copolymers had a sequence distribution of 3-hydroxybutyrate (3HB) and 4-hydroxybuyrate (4HB) units, which were non-random in that very few, if any, sequences of more than two successive 4HB units were present. DSC showed that both the glass transition temperatures and melting temperatures decreased in a regular manner with increasing contents of 4HB units.

The enzymatic degradation of the copolymers by an extracellular hydrolase showed that the presence of the 4HB units accelerated the biodegradation of the polymers as was previously observed for the bacterial copolymers containing these two units. However, the effect of 4HB units on the rates of degradation of the two types of copolymers is very different because the synthetic copolymers contain both (*R*)- and (*S*)-3HB units. This is particularly important because hydrolase enzymes, which degrade bacterial P3HB, are specific for (*R*)-3HB units. These enzymes do not hydrolyze (*S*)-3HB units, so the degradation rates of the present copolymers are expected to be considerably different from those of bacterial copolymers containing equivalent amount of 3HB and 4HB. However no data is available for a direct comparison of these rates using identical enzymatic degradation systems.

Blends of atactic poly[(*R*,*S*)-3-hydroxybutyrate] (a-P(3HB)) with poly(ϵ-caprolactone) (PCL), and with poly(L-lactic acid) (PLLA) were obtained in the form of compression-molded films [73]. The phase

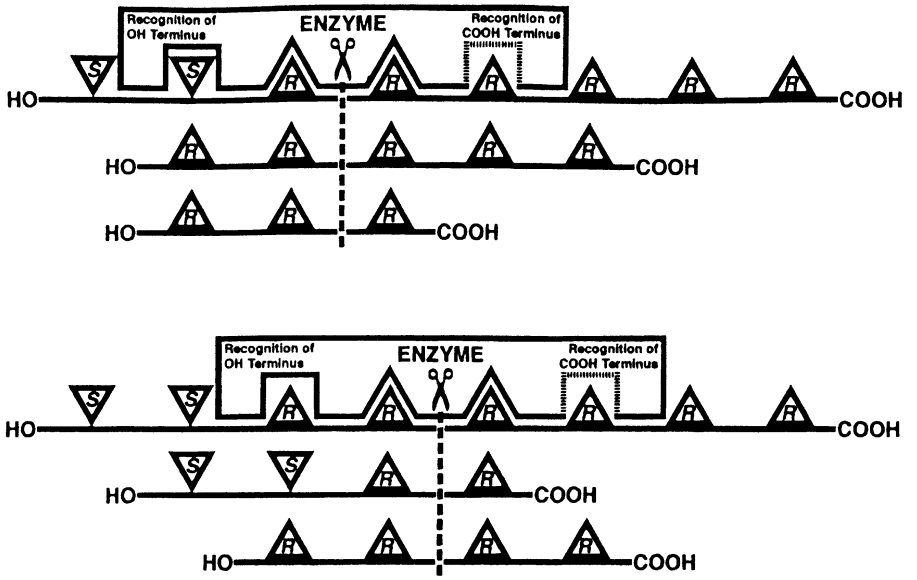


Fig. 1. Two different degradation pathways for the cleavage of the octamer by PHB depolymerase from *A. faecalis* T1. Reprinted with permission from Macromolecules 1999;32:1777. ©1999 American Chemical Society [69].

behavior of the blends was different: a-P(3HB) and PCL were totally immiscible, whereas a-P(3HB)/PLLA blends were miscible over the whole composition range. Biodegradation experiments were carried out on the blends and on the plain polymers in a buffered solution of P(3HB)-depolymerase A from *Pseudomonas lemoignei* (Tris–HCl, pH 8, $T = 37°C$). None of the pure blend components (a-P(3HB), PCL, PLLA) showed any weight loss upon enzyme exposure. Conversely, both a-P(3HB)/PCL and a-P(3HB)/PLLA blends biodegraded. In both blends only the a-P(3HB) component underwent enzymatic hydrolysis. These results support the hypothesis that the crystalline polyester blended with a-P(3HB) promotes a-P(3HB) enzymatic hydrolysis by providing stable binding sites to the enzyme.

Recently, Inoue at al. [74] investigated the phase structure and biodegradability of a blend of chemosynthetic a-P(3HB) and poly(methyl methacrylate) (PMMA). The thermal analysis indicated that amorphous a-P(3HB)/PMMA blends with 20 and 40 wt% PMMA showed sophisticated phase behavior and were partially miscible. The depolymerase of natural poly[(*R*)-3-hydroxybutyrate], P[(*R*)-3HB], purified from *Alcaligenes faecalis* TY1 did not degrade chemosynthesized a-P(3HB) at all in the pure state, but it degraded a-P(3HB) in some a-P(3HB)/PMMA blends. This means that blending with amorphous non-biodegradable PMMA can provide the stable binding site for the enzyme adsorption and enhance the biodegradation of a-P(3HB) in the blend in the presence of P((R)-3HB) depolymerase, offering a conclusive evidence for the enzymatic biodegradation of a-P(3HB) chains even without a crystalline phase.

Inoue et al. [74] proposed four necessary conditions for the enzymatic hydrolysis of a-P(3HB) in a blend system: (1) There are stable binding sites, provided by either a crystalline phase or a glassy amorphous phase, on the film surface; (2) The stable binding sites must meet a certain hydrophilic/hydrophobic balance to allow enzyme binding; (3) The hydrolyzable a-P(3HB) chains possess a certain degree of mobility; (4) The stable binding sites and the mobile a-P(3HB) chains to be hydrolyzed are

close enough to permit the catalytic domain of the depolymerase to be in contact with the a-P(3HB) chains when the binding domain is bound on the stable binding site. Condition (4) is met in the above system by the partial miscibility of a-P(3HB) and PMM.

2.2.2. Polyesters from lactides

Polylactides are widely used for medical purposes such as sutures, fracture fixation, oral implant, and drug delivery microspheres. Polylactides including polyglycolide are hydrolyzed at a relatively high rate even at room temperature and neutral pH without any help of enzymes if moisture is present. High molecular weight polylactides are not hydrolyzed by enzymes, but when their molecular weights become lower than about ten thousands, polylactides are reported to undergo enzymatic hydrolysis. Polylactides, especially polyglycolide, are hydrolyzed in our body to the respective monomers and oligomers that are soluble in aqueous media, and hence they are often called bioabsorbable polymers rather than biodegradable polymers. In this article, however, polylactides are also included in the category of biodegradable polymers for convenience's sake. The synthesis, properties, and applications of polylactides have been dealt with in numerous papers and review articles. Since it is beyond the scope of this review article to cover the entire fields of polylactides, those who want to know the recent advances in more detail should refer to review articles [75–77].

2.2.2.1. Catalysts. A variety of initiators and catalysts have been employed in the ring-opening polymerization of lactides. Among them, stannous octoate $Sn(Oct)_2$ has been frequently used as one of the effective catalysts that produce high molecular weight polymers in high yields. However, like many other catalysts, the cytotoxicity and difficulties in removal of the catalyst from the resulting polymer have limited its use in many cases. Another disadvantage of this catalyst is occurrence of transesterifications including back-biting reaction. Jérôme et al. [78] reported that the addition of an equimolar amount of triphenylphosphine PPh_3 to $Sn(Oct)_2$ improves this situation. Indeed, PPh_3 has a twofold beneficial effect: It increases the polymerization rate and delays the occurrence of the undesirable backbiting reactions, at least when the molar ratio of monomer to $Sn(Oct)_2$ is larger than 5×10^3. Therefore, the balance between propagation and depolymerization rate is improved, and the polymerization is fast enough for being conducted in an extruder according to a continuous single-stage process. However, the role of PPh_3 and the favorable effect on the bulk polymerization of lactides still remain to be clarified.

Continuous efforts have been devoted to the development of new catalysts for ring-opening polymerization of lactides. In particular, the biomedical applications of polylactides necessarily require low levels of impurities, and therefore, there is a great impetus for the development of highly active catalysts that contain low toxicity metals. A number of iron compounds are present in living organisms and in nature, and they are regarded as less harmful than most other metal compounds. Kricheldorf et al. [79] used iron lactate in the L-lactide polymerization. Under optimal conditions, they obtained polymers having the molecular weight of around 5×10^4 in yields above 90%. However, some degree of racemization occurred.

Stolt et al. [80] also investigated the polymerization of L-lactide using monocarboxylic iron derivatives. Iron acetate, iron trifluoroacetate, and iron isobutyrate complexes were efficient catalysts yielding a high molecular weight poly(L-lactide) in high yield. Under optimum conditions a poly(L-lactide) with M_w of ca. 1.5×10^5 was obtained. However, high polymerization temperatures (170–210°C) are required with these iron catalysts, and the occurrence of some racemization of the product is unavoidable.

Tolman et al. [81] prepared $Fe_5(\mu_5\text{-}O)(OEt)_{13}$ from commercially available ferric ethoxide by extraction with THF, evaporation of the solvent, and finally recrystallization of the residue from hexamethyldisiloxane (Fig. 2). The ferric alkoxide is highly active for the polymerization of lactides; for example, under the conditions of $[LA]_o/[Fe]_o = 450{:}1$ in toluene at 70°C, the conversion reached 97% in 21 min, and the polymer with a narrow molecular weight distribution ($M_w/M_n = 1.17$) was obtained. In addition, racemization did not occur under the reaction conditions. They also prepared $Fe_2(OCMe_2Ph)_6$, which was also effective for the polymerization of lactides, although the M_w/M_n values for the product polymers were slightly higher. It is noteworthy that the polymerization catalyst behavior of these ferric alkoxides supersedes those of other reported iron complexes with respect to rate, molecular weight distribution control, and racemization.

Wang et al. [82] reported that lithium chloride is an effective and biocompatible catalyst for the ring-opening polymerization of lactide in the presence of hydroxyl-containing compounds such as ethylene glycol and methyl α-D-glucopyranoside used as multifunctional initiators. The polymerization at 128°C in bulk with 1% (w/w) of LiCl yielded polylactide with the molecular weight of several thousands but racemization occurred to some extent. The mechanism of the LiCl-catalyzed polymerization has not been well understood yet. Possibly, the ring-opening is initiated through the reversible formation of ROLi.

Lantanide alkoxides are effective to initiate polymerization of lactides. However, Spassky et al. [83] obtained the evidence of substantial transesterification in the case of a polymerization initiated by lantanum alkoxide and bimetallilc aluminum–yttrium alkoxide. In the case of Y and Sm alkoxide initiators, the MWD remained narrow up to high conversions for reasonable polymerization times. The presence of odd-numbered oligomers in MALDI-TOF MS spectra implies that transesterification

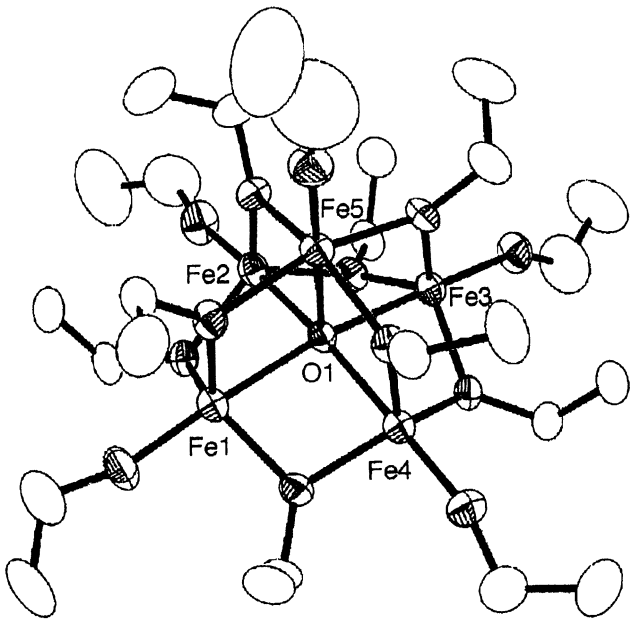


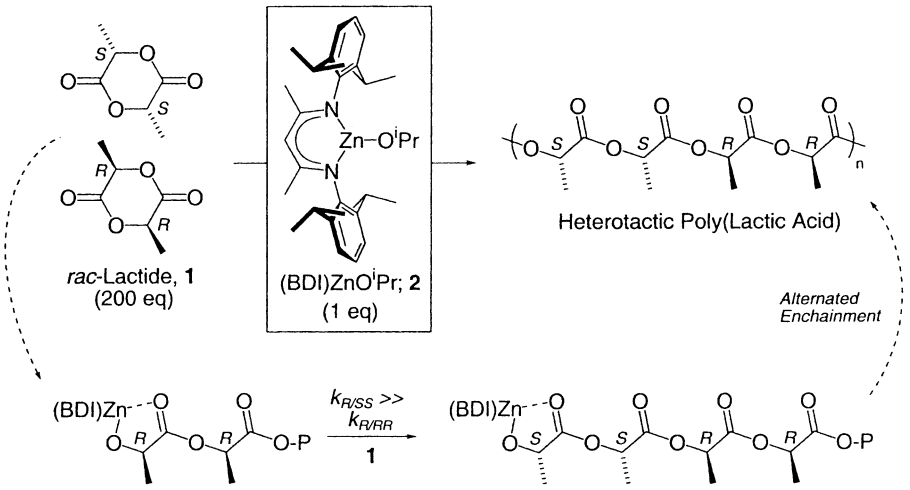
Fig. 2. Representation of the X-ray crystal structure of $Fe_5(\mu_5\text{-}O)(OEt)_{13}$ as 50% ellipsoids. Hydrogen atoms are omitted for clarity. Reprinted with permission from J Am Chem Soc 2001;123:339. ©2001 American Chemical Society [81].

reactions occur from the beginning of the polymerization. Linear and cyclic oligomers were detected in some cases indicating the simultaneous occurrence of inter- and intramolecular exchange reactions. The microsturucture analysis of the polymers by ^{13}C NMR spectroscopy indicated a preference for a syndiotactic addition during the polymerization of D,L-lactide.

Single-site catalysts are molecular compounds having the general formula L_nMR, where L_n is a ligand set that remains attached to and thus modifies the reactivity of the active metal center (M) during the reaction, and R is a group that can initiate polymerization. Through ligand design, homogeneous catalysts are available that can control polymer molecular weights, molecular weight distributions, stereochemistry, comonomer incorporation in ways that cannot be achieved with conventional heterogeneous catalysts. Coates et al. [84] used a single-site β-diiminate zinc complex [(BDI)ZnOiPr] for the polymerization of *rac*-lactide. The zinc complex was prepared by the reaction of $Zn[N(TMS)_2]_2$ with the 2,6-diisopropyl phenyl-substituted β-diimine ligand [(BDI)H], followed by the reaction with 2-propanol (Scheme 10). [(BDI)ZnOiPr] is highly active for the polymerization of *rac*-lactide, e.g. the reaction reached 95% conversion at 0°C after 2 h to give a polymer with a M_n of 3.88×10^4 and a M_w/M_n of 1.09. The polymer obtained was highly heterotactic, the probability of a racemic enchainment in the polymer (P_r) being 0.94. Despite the stereoregularity of the polymer, it was an amorphous material with a T_g of 49°C. Mass spectrometry experiments revealed that the isopropoxide group initiates polymerization, while the β-diiminate ligand remains chelated to the zinc center.

Coates at al. [85] polymerized racemic lactide with a racemic aluminum alkoxide catalyst derived from $SalBinapH_2$ and aluminum isopropoxide to obtain an isotactic stereoblock poly(lactic acid), where each enantiomerically pure block contained an average of 11 lactide monomer units. The kinetic selectivity of the catalyst was as high as 0.98. The melting point of this polymer, 179°C, was higher than that of the enantiomerically pure polymer, consistent with the cocrystallization of the enantiomeric blocks of the polymer.

Besides residual catalysts, unreacted monomer and residual solvents may pose risk for a material in contact with biological fluids and tissue. In this respect, the use of supercritical carbon dioxide (SC-CO_2)



Scheme 10. Formation of heterotactic poly(lactic acid). Reprinted with permission from J Am Chem Soc 1999;121:11583. ©1999 American Chemical Society [84].

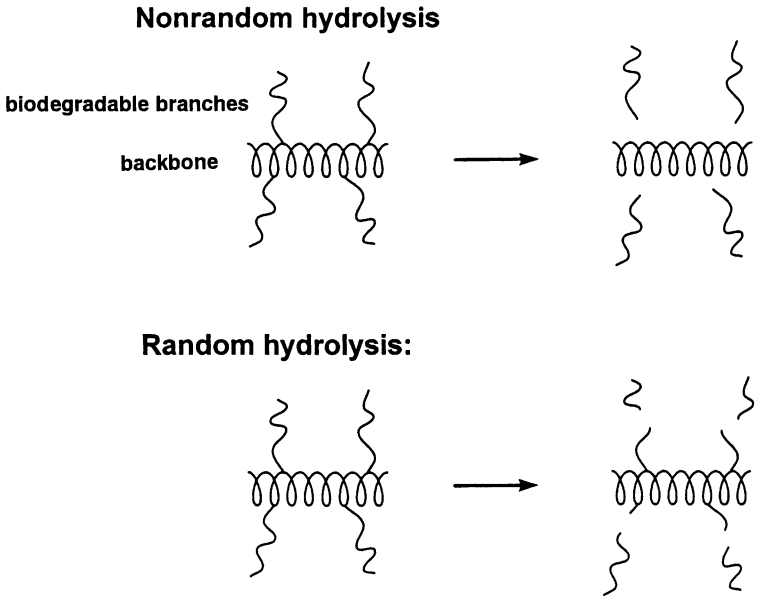
as a solvent for polymerization is attractive because SC-CO_2 is nontoxic and could easily be separated from the polymer by depressurization [86,87]. Polymers could therefore be synthesized in solution but remain free of residual organic solvents to yield a high-purity polymer suitable for biomedical applications. An additional advantage of using SC-CO_2 as the continuous phase is the ability of SC-CO_2 to plasticize the forming polymer phase [88,89], that enhances diffusion of the monomer into and through the polymer phase to the site of reaction.

Hile et al. [90] synthesized poly(D,L-lactide-*co*-glycolide) with an emulsion copolymerization in SC-CO_2. They used poly(1,1-dihydroperfluorooctyl acrylate) as a surfactant, which stabilized the growing chain, resulting in improved monomer conversion (99% for glycolide and 65% for lactide at 70°C after 72 h) and weight average molecular weight (2.5×10^3–3.0×10^4) compared to the polymer synthesized in the absence of the surfactant. With emulsion copolymerization in a benign solvent, these studies demonstrate the ability to generate high-purity copolymers of D,L-lactide and glycolide for biomedical applications such as resorbable sutures, drug delivery vehicles, or scaffolds for tissue engineering. Polymerization of ϵ-caprolactone in SC-CO_2 was also reported recently [91].

2.2.2.2. Copolymers. Parenteral delivery systems for proteins and peptides based on aliphatic polyesters are currently the subject of intensive research efforts. Linear polyesters of lactic acid and glycolic acid present significant problems with respect to the modulation of release properties of higher molecular weight substances, such as proteins. Kissel et al. [92,93] modified the molecular architecture of poly(-lactic acid) (PLA) and its copolymers with glycolic acid (PLG) by the introduction of a hydrophilic charge-containing backbone, e.g. dextran sulfate sodium salts (DSS) or diethylaminoethyl dextran hydrochloride (DEAED). The degradation of the graft PLG was significantly accelerated by the nonlinear structure containing many short biodegradable branches attached to a hydrophobic backbone substance. In the case of DEAED as backbone, the predominant chain scission of the graft polyester occurred in a random hydrolytic ester cleavage, similar to PLG. By contrast, a nonrandom chain scission in the vicinity of the branching points of the backbone was found for DSS–PLG (Scheme 11). The erosion of the graft PLG proceeded more rapidly in the center of the devices than at the surface. In contrast to linear PLG, the release of FITC-dextran and bovine serum albumin (BSA) from the microspheres prepared from the graft PLG was continuous. These results suggest that graft PLGs offer additional possibilities for adjusting the release of proteins and peptides from biodegradable parenteral delivery systems.

Furch et al. [94] synthesized graft copolymers composed of poly(methyl acrylate) as a backbone and PLG side chains by radical copolymerization of methyl acrylate and PLG chains with a methacrylic residue. Thermal analysis indicated that the copolymers have a biphasic morphology. Ouchi et al. [95,96] synthesized graft copolymers composed of PLA and polysaccharides such as pullulan and amylose through the trimethylsilyl protection method. The biodegradability of polymers obtained was controlled by introduction of hydrophilic units and/or branched structure into PLA.

2.2.2.3. Degradation. As described above, polylactides undergo nonenzymatic hydrolysis in the presence of water. Tsuji et al. [97] investigated the effects of crystallinity x_c on the hydrolysis of high molecular weight poly(L-lactide) (PLLA) films in a phosphate-buffered solution at 37°C. The hydrolysis of PLLA film in a buffered-solution proceeded homogeneously along the film cross section, mainly via the bulk-erosion mechanism. The rate of molecular weight reduction was higher as the initial x_c of the PLLA films increased when hydrolysis was carried out up to 24 months. Melting and glass transition temperatures



Scheme 11. Schematic diagram of the hydrolytic mechanisms of the graft poly(L-lactide-*co*-glycolide)s. Reprinted with permission from Polymer 1998;39:3087. ©1998 Elsevier Science Ltd [92].

of the PLLA films increased in the first 12 months of hydrolysis, while they decreased in another 24 months, irrespective of the initial x_c. The x_c value of the PLLA films increased monotonously by hydrolysis. The lamella disorientation in PLLA spherulites after hydrolysis implied that the hydrolysis of PLLA chains occurred predominantly in the amorphous region between the crystalline regions in the spherulites.

De Jong et al. [98] studied the hydrolytic degradation of monodisperse lactic acid oligomers at 37°C. The amount of lactic acid oligomer decreased according to pseudo-first-order kinetics and was dependent on the dielectric constant of the medium and the pH. The hydroxyl end group was found to play a crucial role in the hydrolytic degradation, because the protection of the hydroxyl group substantially retarded the degradation. At acidic pH, hydrolysis proceeded by chain-end scission whereas in alkaline medium, lactide was formed via an intramolecular cyclization reaction.

Albertsson et al. [99] hydrolyzed the tri-block copolymer poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) of different composition in buffered salt solution at 37°C and pH 7.4. The degradation started immediately after the sample was immersed into the aqueous buffer solution. The rate of degradation was influenced only by the original molecular weight, and the copolymer composition did not show any significant effect. The heat of fusion and T_g increased with degradation time due to an increased amount of L-lactide in the remaining polymer films. The GC-MS analysis showed that up to 70% of the theoretical amount of 3-(2-hydroxyethoxy)-propanoic acid and 10–20% of lactic acid was released after 23 weeks of degradation.

The parameters influencing the degradation behavior of D,L-PLGA have been the subjects of numerous publications. The effective influencing factors are the copolymer composition, the molecular weight and molecular weight distribution, and the sequence structure of the copolymer [100–102]. The control of the structure of such copolymers would allow the proper selection of the rates of both the drug release and the biodegradation of microspheres or nanospheres. As an approach to increase the uniformity of the

copolymers, Dong et al. [103] synthesized alternating copolymer of D,L-lactic acid and glycolic acid by the polymerization of D,L-3-methylglycolide. However, no description was given on the biodegradability of the alternating copolymers.

The enzymatic degradation of PLA has been investigated by a number of researchers. For example, Reeve et al. [104] observed that proteinase K preferentially degraded L-lactyl units as opposed to D-lactyl ones, PLA_0 being undegraded, where the abbreviation PLA_x refers to PLA with x reflecting the percentage of L-lactyl units. MacDonald et al. [105] observed that amorphous films of PLA_x derived from L-/D-lactides with x ranging from 80 to 95 exhibited almost identical weight loss rates, in contrast to the results of Reeve et al. On the other hand, PLA_x derived from L-/*meso*-lactides showed lower weight loss rates than those of the L-/D-lactides series. Cai et al. [106] found that the degradation rate of PLA_{96} decreased with increase in crystallinity. A threshold was observed when the heat of fusion was less than 20 J/g. McCarthy et al. [107] showed that below a certain crystallinity (about 26%), PLA_{100} exhibits actually the same enzymatic degradability because the great majority of material is amorphous and accessible for enzymatic attack. Above that crystallinity the degradation rate decreases with increase of crystallinity.

Another influential factor is the water uptake ratio or hydrophilicity of the polymers. PLA_{50} degraded only slightly less rapidly than PLA_{100}. This finding could be assigned to the much higher water uptake ratio of the former. It is likely that the large amounts of absorbed water led to the swelling of PLA_{50} samples and facilitated the enzymatic attack. Since the effect of stereochemistry is more important than that of water uptake, the overall degradation rate of PLA_{100} is slightly higher than that of PLA_{50}.

Albertsson et al. [108] reported that the presence of low molecular weight lactic acid and derivatives in films enhanced the degradability of polylactide in a biotic medium. Lactic acid and lactoyl lactic acid were rapidly assimilated from the films aged in a biotic medium, new degradation products (e.g. ethyl ester of lactoyllactic acid, acetic acid, and propanoic acid) were formed during aging in a biotic medium. Acetic acid and propanoic acid were formed as intermediate degradation products during the initial stages, but they were no longer detected after prolonged aging. The concentration of the ethyl ester of lactoyl lactic acid increased with aging time.

2.2.2.4. Hydrogels. The use of biodegradable hydrogels in medicine has become promising because recent advancements in biotechnology have led to a great variety of pharmacologically active peptides and proteins that may be difficult to release adequately from existing nonbiodegradable biomaterials. In addition, due to their good tissue biocompatibility and the possibility of tailoring the permeability of the hydrogels to specific drugs, biodegradable hydrogels appear to be a viable alternative to existing drug carriers. Zhang et al. [109] synthesized a new class of biodegradable hydrogels consisting of hydrophobic poly(D,L-lactic acid) (PDLLA) and hydrophilic dextran segments. Acrylate groups were introduced to the both chain ends of PLLA and to the pendant hydroxyl groups of dextran, followed by a crosslinking reaction of these two components by photopolymerization. The swelling ratio decreased as the PDLLA composition increased. The hydrophilicity/hydrophobicity of the polymer segments, the hydrolysis of the ester groups, and its dependence on pH all affected the swelling properties of the dextran/PDLLA hydrogels. These bicomponent network hydrogels had a wide range of hydrophilicity to hydrophobicity that was difficult to achieve in totally hydrophilic hydrogels.

Recently, Jeong et al. [110,111] reported biodegradable, in situ gelling poly(ethylene glycol-*b*-(D,L-lactic acid-*co*-glycolic acid)-*b*-ethylene glycol) triblock copolymers and poly((D,L-lactic acid-*co*-glycolic acid)-*g*-ethylene glycol) copolymers with hydrophobic PLGA backbones. In vivo studies in rats

demonstrated that the copolymer gels were still present after one month. Certain drug formulations need a 1–2 week delivery system. To prepare a short-term delivery system, Jeong et al. [112] designed poly(ethylene glycol) grafted with poly(lactic acid-*co*-glycolic acid) (PEG-*g*-PLGA). The aqueous solutions of the graft copolymer flow freely at room temperature but form gels at higher temperature (Fig. 3). The critical gel concentration, above which a gel phase appears, was 16 wt%, and the sol-to-gel transition temperature was slightly affected by the concentration between 16 and 25 wt%. At sol-to-gel transition, viscosity and modulus increased abruptly, and ^{13}C NMR showed that molecular motion of hydrophilic poly(ethylene glycol) backbone decreased, while that of hydrophobic poly(lactic acid-*co*-glycolic acid) side chains increased. The hydrogel of the graft copolymer with hydrophilic backbones was transparent during degradation and remained a gel for 1 week, suggesting a promising material for short-term drug delivery.

Seppälä et al. [113] prepared mechanically strong biodegradable crosslinked polymers from triethoxysilane-terminated polylactide oligomers. Thus, crosslinked polymers were produced from D,L-lactide oligomers, which were functionalized with (3-isocyanatopropyl)triethoxysilane and crosslinked by acid catalysis in the presence of water without the use of solvent. The formation of a strong polymer network was found to require a curing temperature of at least 90°C. The best mechanical properties were achieved with the polylactide oligomer obtained with 5% pentaerythritol as the initiator. The polymer had compressive yield strength of 81 MPa, modulus of 2260 MPa, and 4.4% strain at yield point.

2.2.2.5. Microspheres. Biodegradable polyesters have increasing importance also as materials for the preparation of microspheres. The knowledge of their degradation process is important to prepare microparticulate delivery systems with suitable drug release rates. Giunchedi et al. [114] studied the degradation of empty and diazepam-loaded microspheres using two poly(D,L-lactide)s (PDLLA) of different molecular weight and a poly(D,L-lactide-*co*-glycolide) (50:50) (PLGA). They showed that the preparation methods play an important role in determining the degradation behavior of microspheres; the unloaded spray-dried particles were characterized by a higher monomer release rate than

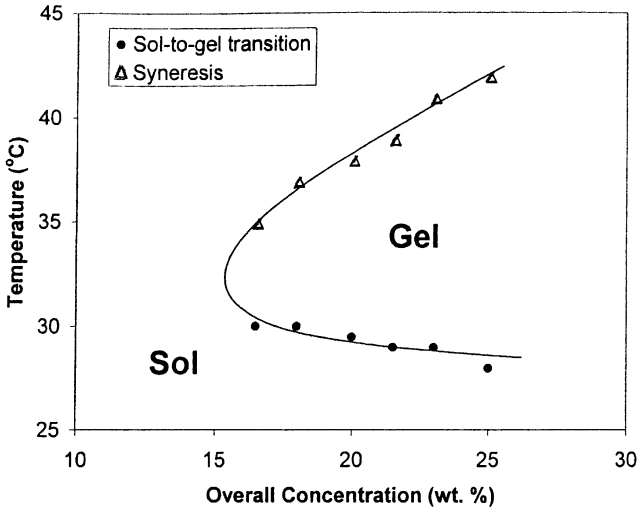


Fig. 3. Phase diagram of PEG-g-PLGA aqueous solution. Filled circles and open triangles indicate sol-to-gel transition and syneresis. Reprinted with permission from Macromolecules 2000;33:8317. ©2000 American Chemical Society [112].

the microspheres obtained by solvent evaporation. PLGA spheres degraded faster than PDLLA microparticles, according to the higher hydrophilicity of the copolymer; the two monomers were released at a different rate in the case of PLGA (faster for GA, slower for LA); the presence of diazepam increased the polymer degradation rate compared to empty particles.

Li et al. [115] prepared poly(D,L-lactide) (PLA), poly(D,L-lactide-*b*-poly(ethylene glycol)-*b*-D,L-lactide) (PELA) microspheres, and PELA microspheres containing the outer membrane protein (OMP) of *Leptospoira interrogans* with the size of 1.5–2 μm by a solvent evaporation process. In vitro degradation and release tests of these microspheres in pH 7.4 buffer solution indicated a bulk erosion process rather than surface erosion for PELA microspheres. The OMP-loaded PELA microspheres presented triphasic release profile, and a close correlation was observed between the polymer degradation and the coefficient, and the water-swollen structure of microspheres matrix commonly contributed to the OMP release from PELA microspheres.

Successful delivery of hydrophilic macromolecular drugs from microspheres or implants strongly depends on the properties of the polymers used for encapsulation, affecting water uptake, thermomechanical properties, rates of biodegradation, and erosion. Matsumoto et al. [116] prepared the multi-reservoir type microspheres of cisplatin on the basis of the phase separation of poly(D,L-lactic acid) (PLA) and poly(D,L-lactic-*co*-glycolic acid)(PLGA). The PLGA–PLA biphasal polymeric solution dispersing the drug powder was emulsified, and then solidified by the solvent evaporation method. The obtained microspheres had the unique polymer alloy structure and the drug was distributed in the internal phase (PLGA-rich phase). The encapsulation efficiency was almost 100% at 10% loading. The in vitro dissolution study revealed that the release of cisplatin lasted 45 days without initial burst.

As described above, phase separation of poly(lactide) (PLA) and poly(lactide-*co*-glycolide), often called ‘coacervation’ in the pharmaceutical fields, is one of the classical methods for peptide drug microencapsulation in biodegradable polyesters. Although numerous studies have used this technique, the underlying physicochemical mechanisms of polyester coacervation under conditions of microshpere production have not been well described yet. Thomasin et al. [117] reviewed the scientific and patent literature on PLA/PLGA coacervation and discuss the underlying physicochemical principles of polyester coacervation and presented thermodynamic models. They attempted to clarify the necessary characteristics of polymers, solvents and coacervating and hardening agents for successful phase separation and microsphere formation.

Yang et al. [118] modified poly(lactic acid) (PLA) and its random copolymers with glycolide (PLG) by grafting onto hydrophilic poly(vinyl alcohol) (PVA) to increase both hydrophilicity and to manipulate the polymer structure. They investigated the release of hydrophilic dextran from the microspheres prepared from the graft polymers as a function of polymer structure. A reduction of the PLG chain lengths increased erosion controlled release rates, while an increase of the molecular weight of the core PVA resulted in a diffusion-controlled release mechanism. Release profiles could be adjusted over a broad range from 2 weeks to 3 months. In combination with the possibility of avoiding accumulation of acidic breakdown products in the delivery device, PVA-*g*-PLG is of particular interest for parenteral delivery system containing proteins, peptides or oligonucleotides.

Kissel et al. [119] prepared drug-loaded nanoparticles of poly(ϵ-caprolactone) (PCL), poly(L-lactide) (PLLA), and their copolymers (PCLLA) by the precipitation method. The nanoparticles had a spherical shape, and the size of PCLLA nanoparticles (~85 nm) was smaller than that of the PCL and PLLA nanoparticles. In vitro drug release experiments showed that the drug release from PCLLA nanoparticles

was slower than that from PCL and PLLA nanoparticles, and the release profile of PCLLA (6:4) nanoparticles appeared to follow zero order kinetics.

3. Synthesis of biodegradable polymers with both ester and other heteroatom-containing linkages

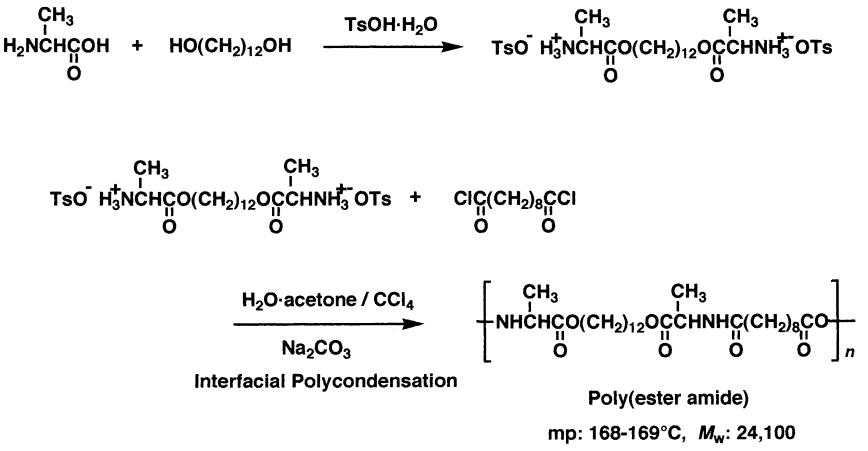
In Section 2 we have dealt with recent advances in the synthesis of biodegradable polyesters. Although commercially available, synthetic biodegradable polymers are confined to polyesters at present, basic researches have been actively carried out to develop other types of biodegradable polymers in order to meet various requirements for specific applications. Most of them contain ester linkages as a key site for biodegradation, together with other heteroatom-containing linkages such as amide, carbonate, and ether linkages. In this section, we shed light on some potentially biodegradable polymers with both ester and other heteroatom-containing linkages in the backbone structure.

3.1. Poly(ester amide)s

Aliphatic polyamides are not readily biodegraded, although there are a few reports demonstrating their biodegradability as will be described in Section 4. Compared to aliphatic polyesters, aliphatic polyamides possess higher thermal stability, higher modulus, and higher tensile strength. Therefore, it is reasonable to combine the favorable properties of these two classes of polymers to produce new polymeric materials possessing not only good biodegradability but also good materials and processing properties. In fact, a variety of poly(ester amide)s containing both ester and amide bonds along the main chain have been prepared by polycondensation of ester-containing diamines with dicarboxylic acids or their derivatives, or by ring-opening polymerization of depsipeptides, and their biodegradability has been evaluated. Most of the poly(ester amide)s designed as potentially biodegradable polymers have α-amino acid moieties so as to be biocompatibe as well as biodegradable. The presence of hydrolytically readily cleavable ester bonds in the backbones and the lowering of the crystallinity thereby make poly(ester amide)s promising materials for their use in medical fields.

3.1.1. Poly(ester amide)s by polycondensation

A number of papers concerning syntheses of poly(ester amide)s have been reported in the literature, and some of them have dealt with their biodegradation [120–130]. Puiggali et al. [122,123] synthesized a series of aliphatic poly(ester amide)s from various combinations of diols, amino acids and dicarboxylic acids. The synthesis consists of two steps (Scheme 12). Thus, diol was first esterified with two moles of α-amino acid in the presence of *p*-toluenesulfonic acid. Subsequently the resulting diamine salt was allowed to react with the appropriate dichloride by the interfacial polycondensation method to give highly crystalline poly(ester amide)s with the number average molecular weight of several thousands. The decomposition temperatures of the poly(ester amide)s are always higher than the corresponding melting temperatures, and therefore the polymers can be processed from the melt. Transamidation–transesterification reactions do not take place during the melting process. Degradation studies using different enzymes (pronase, trypsin, chymotrypsin, and papain) indicated that papain was the most efficient of these and that the poly(ester amide)s that degrade with slower rates are those containing the higher density of hydrogen bonds or the higher proportion of methylene groups.



Scheme 12. Synthesis of poly(ester amide)s containing L-alanine units.

Puiggali et al. [124] also studied the hydrolytic degradation of two poly(ester amide)s derived from sebacic acid, 1,12-dodecandiol, and alanine in both the chiral L-configuration and the racemic L,D-mixture. These poly(ester amide)s degraded slowly in a pH 7.4 buffered solution at 37°C mainly through the ester linkages. The enzymatic degradation of the poly(ester amide)s with papain was stereospecific and appreciable differences in the degradation rate were found between the stereoregular and the racemic polymers, indicating that papain fundamentally degrades the linkages where the natural L-amino acid is involved.

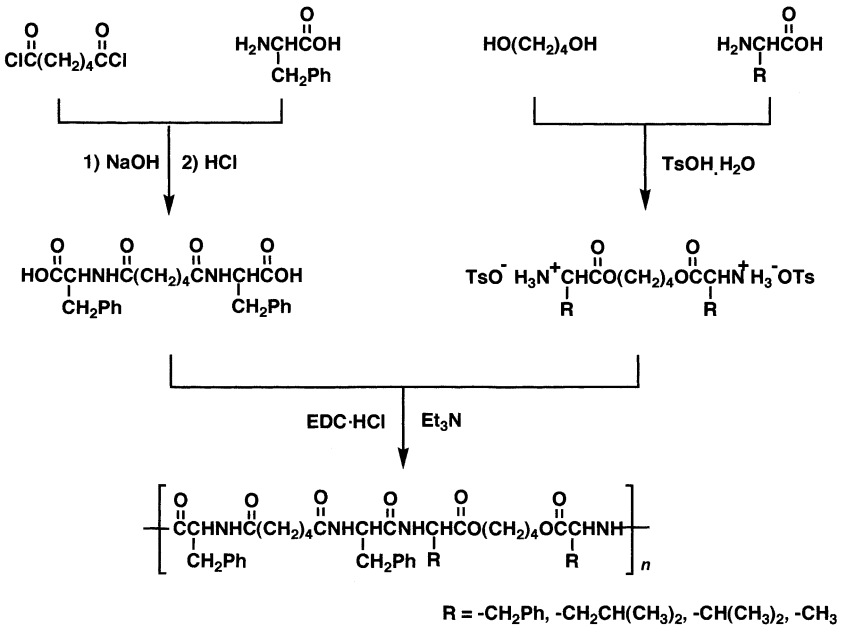
Katsarava et al. [125] prepared poly(ester amide)s by solution polycondensation of di-*p*-toluenesulfonic acid salts of bis(α-amino acid) α,ω-alkylene diesters and di-*p*-nitrophenyl esters of diacids in chloroform or *N*-methyl-2-pyrrolidone in the presence of triethylamine as an acceptor for *p*-toluenesulfonic acid at room temperature. High molecular weight poly(ester amide)s ($M_w = 2.4 \times 10^4$–16.7×10^4) with relatively narrow polydispersity ($M_w/M_n = 1.20$–1.81) were obtained under the optimal reaction conditions. They were mostly amorphous with T_g from 11 to 59°C, showing excellent film forming properties. Among all the poly(ester amide)s that they synthesized, those based on L-phenylalanine showed the highest tendency toward the α-chymotrypsin-catalyzed hydrolysis, while the hydrolysis of the D,L-isomer occurred at a lower rate than the L-isomer. The high hydrophobicity of the benzyl side groups in the phenylalanine-based poly(ester amide)s was suggested to be responsible for the facile enzymatic hydrolysis. They also found that an increase in methylene chain length of diols and dicarboxylic acids increased the sensitivity of poly(ester amide)s toward the α-chymotrypsin-catalyzed hydrolysis. In addition to the hydrophobicity factor, the change in chain mobility due to different methylene chain length should be one of the important factors that contribute to the different rate of enzyme-catalyzed hydrolysis of poly(ester amide)s.

In contrast, the L-valine-based poly(ester amide)s with a shorter and less hydrophobic side group, and the L-isoleusine-based poly(ester amide)s with a sterically more hindered side group, showed nondetectable hydrolytic degradation activity toward α-chymotrypsin-catalyzed hydrolysis. Katsarava et al. concluded that the general tendency of the poly(ester amide)s toward the α-chymotrypsin-catalyzed hydrolysis is consistent with Hansch's constants [126] used to characterize the hydrophobicity of the side substituent of α-amino acids and the effectiveness of the interaction of the side groups with

the enzyme's hydrophobic pocket. The higher the overall hydrophobicity of the polymer backbone, the more sensitive the polymer toward the enzyme-catalyzed hydrolysis.

Nagata [127] prepared poly(ester amide)s with various L-alanine contents by interfacial polycondensation of the mixtures of 1,6-hexanediol diesters of L- and D-alanine with sebacoyl chloride. Proteolytic enzymes (proteinase-K, papain, and α-chymotrypsin) degraded poly(ester amide) (100% L-alanine) much faster than lipase enzymes (*Rhizopus delema*, *Pseudomonus cepacia* and *Candida rugosa*). Above all, proteinase-K was most effective and the weight loss was about 78% after 8 h of incubation. It was found that the degradation with the proteolytic enzymes is not caused by hydrolysis of the semi-peptide linkage but of the ester linkage. Proteinase-K and papain degraded the poly(ester amide) with 100% L-alanine content as opposed to that with 100% D-alanine content. The highest rate of degradation was observed for the poly(ester amide) with 90% L-alanine content.

Kise et al. [128] synthesized poly(ester amide)s containing dipeptide linkages (Phe–Phe, Phe–Leu, Phe–Val, and Phe–Ala) from monomers having amino acid residues at the both ends by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride as the coupling agent (Scheme 13). Polycondensation of dicarboxylic acid and diamine, either of which have dipeptide groups, would give dipeptide-containing polymers. However, the disadvantage of this method is the difficulty of the synthesis of dipeptide-containing monomers. Many reactions for protection and activation of amino- or carboxyl groups would be required. In contrast, the polycondensation of an acid component and an amine component, each of which has an amino-acid residue, has advantages of easy synthesis of the monomers and of the possibility of wide selection of amino acids to form dipeptide groups. In addition, another advantage of this method is that the technique of amino acid coupling using carbodiimide has been established in peptide chemistry. All these polyamides ($M_n = 5600–7700$) were hydrolyzed by enzymes



Scheme 13. Synthesis of poly(ester amide)s containing dipeptide linkages.

such as α-chymotrypsin, subtilisin Carlsberg, and lipase. Introduction of Phe–Ala linkages in polymer chains was the most effective for accelerating degradation.

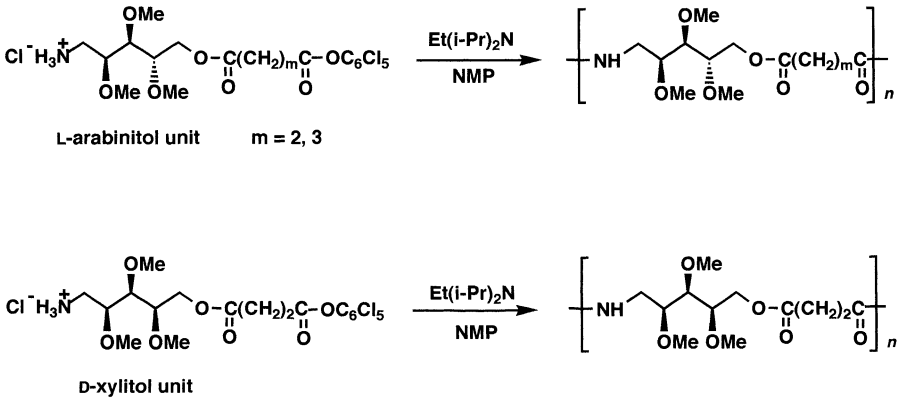
The use of plant-based renewable resources for polymer synthesis has attracted increasingly much attention. Kricheldorf et al. [129] prepared poly(ester amide)s composed of hydrophobic α-amino acids and dianhydrohexitols (1,4:3,6-dianhydro-D-glucitol and 1,4:3,6-dianhydro-D-mannitol) by a two step method as described above. The resulting poly(ester amide)s had glass-transition temperatures in the range of 60–120°C. The tendency of the poly(ester amide)s to undergo α-chymoptrypsin-catalyzed hydrolysis decreased with the longer methylene chain of the diacids, i.e. with increasing hydrophobicity of the diacid residues in the polymer backbone. Virtually no enzymatic hydrolysis occurred in the case of poly(ester amide) derived from 1,4:3,6-dianhydro-D-glucitol, phenylalanine, and dodecanedioic acid. Kricheldorf et al. explained this finding by competitive interaction of hydrophobic acyl residue with the hydrophobic sites of the enzyme leading to non-productive binding and decreasing overall hydrolysis rate.

Okada et al. [130] also synthesized similar poly(ester amide)s containing 1,4:3,6-dianhydro-D-glucitol and α-amino acids (L-alanine, glycine, and glycylglycine), and examined their biodegradability by soil burial degradation tests, BOD measurements in an activated sludge, and enzymatic degradation tests using *Porcine pancreas* lipase and papain. The poly(ester amide)s were, in general, degraded more slowly than the corresponding polyesters having the same aliphatic dicarboxylic acid units, both in composted soil and in an activated sludge. In the enzymatic degradation, some poly(ester amide)s containing dicarboxylic acid components with shorter methylene chain lengths were degraded more readily than the corresponding polyesters with *Porcine pancreas* lipase, whereas most of the poly(ester amide)s were degraded more rapidly than the corresponding polyesters with papain.

Galbis Pérez et al. [131] synthesized three stereoregular poly(ester amide)s by polycondensation reactions of 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)-succinyl]-L-arabinitol, 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)glutaryl]-L-arabinitol, and 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)succinyl]-D-xylitol hydrochlorides (Scheme 14). The degradation in buffered solution at pH 7.4 occurred by hydrolysis of the ester linkages and was characterized by rapid rates of hydrolysis. The rate of degradation increased with the increase of hydrophilicity. The poly(ester amide)s from succinic anhydride degraded to a final monomeric product in which a succinimide ring was formed.

The hydrolytic and enzymatic degradation of a series of crystalline copoly(ester amide)s derived from L-tartaric and succinic acids, 1,6-hexadiamine, and 1,6-hexanediol with various ester/amide group ratios was investigated at 37°C in a buffered solution at pH 7.4 [132]. Degradation proceeded with a notable increment in crystallinity and entailing slight but significant changes in the T_g and T_m. Copoly(ester amide)s degraded faster than the parent poly(hexamethylene-di-*O*-methyl-L-tartaramide) and the rate of degradation increased with the content in ester groups. The degradation was accompanied by formation of cyclic succinimide units, indicating a scission mechanism based on the occurrence of intramolecular imidation reactions. The enzymatic degradation of these copoly(ester amide)s with papain was examined for a preliminary evaluation of their potential biodegradability.

Poly(hexamethylene 2,3-di-*O*-methyl-L-tartaramide)s, either pure or containing minor amounts of succinate ester groups (<10%), were exposed to humidity or incubated in buffered water at pH 7.4 and 37°C [132]. Both moisture uptake and hydrolysis induced a noticeable decay in the tensile properties of polymers. These effects were greatly enhanced by the presence of ester



Scheme 14. Synthesis of poly(ester amide)s containing L-arabinitol or D-xylitol units.

groups, whereas no large differences were noticed for changes in the enantiomeric composition. Variations in the glass transition temperatures and melting points appeared to be slight, whereas crystallinity clearly increased with incubation time. The later effect was most apparent in poly(ester amide)s with a nearly racemic composition, in which a crystal-to-crystal transition was observed to take place upon degradation.

Goodman et al. [133] prepared several 6-iminohexanoyl/12-oxydodecanoyl random copolymers containing from 19 to 46 wt% (29–60 mol%) of 6-aminohexanoyl units, and incubated their films at pH 7.4 in vitro for 336 h at 37°C with solutions of protease, collagenase, α-chymotrypsin, and pancreatin. The first three mentioned enzymes were without visible effect on any of the polymer films, and there was no significant evidence of the formation of 6-aminohexanoic acid as a product of amide-bond cleavage. By contrast, incubation with pancreatin caused the topochemical surface erosion of each copolyesteramide (but not of nylon 6), with the depletion of ester group content in the surface layer and the development of an amide-richer characteristic striated surface morphology. Random incorporation of amide groups into polyesters, in the form of oligoamide sequences, is suggested as a means of protecting the ester component against esterolytic attack.

Kawasaki et al. [134] synthesized copoly(ester amide)s with molecular weights of several thousands by reacting L-lactic acid with ϵ-caprolactam in the presence of water and metal (Fe, Sn, or Zn) powder. As a possible reaction pathway, they proposed that ϵ-caprolactam reacts with water to give ϵ-aminocaproic acid, which in turn copolymerizes with L-lactic acid. The reaction products are soluble in methanol, in which poly(lactic acid) and poly(ϵ-caprolactam) are insoluble, suggesting the formation of copolymer. The copolymer (mole ratio LLA/CLM = 45/55, $M_n = 8.4 \times 10^3$) was degraded up to 50% after 33 days in contact with an activated sludge.

3.1.2. Poly(ester amide)s by ring-opening polymerization

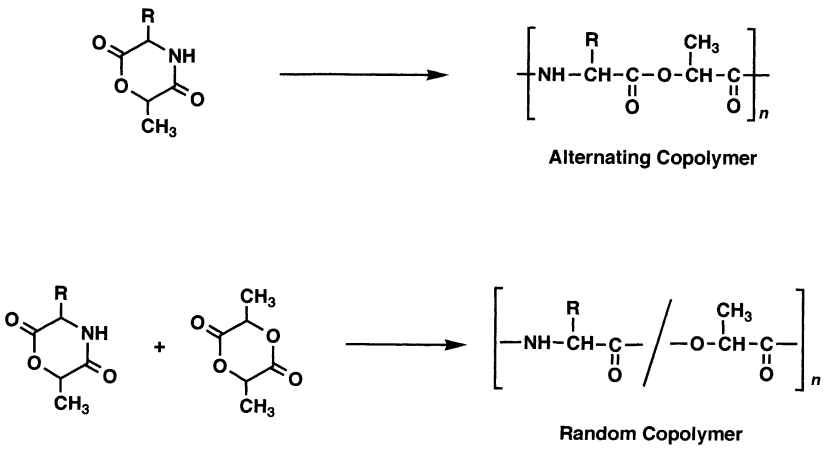
Ring-opening polymerization of cyclic depsipeptides (morpholine-2,5-dione derivatives) provides a convenient method to prepare a wide range of biodegradable poly(ester amide)s, because various α-amino acid residues can be incorporated into morpholine-2,5-dione derivatives and these monomers can be copolymerized with other lactones [135]. Alternating copolymers, poly(α-amino acid-*alt*-D,L-lactic acid)s, are obtained by ring-opening polymerization of the corresponding 2,5-morpholinedione

derivatives, whereas random copolymers are also synthesized by their copolymerization with D,L-lactide (Scheme 15).

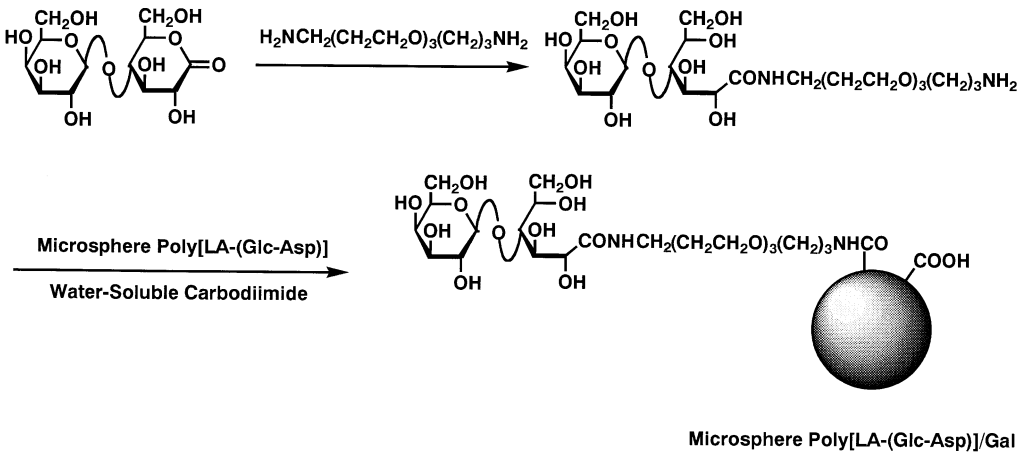
As in the synthesis of polyesters, enzyme-catalyzed polymerization can be applied to the polymerization of depsipeptides. Höcker et al. [136–138] carried out enzyme-catalyzed ring-opening polymerization of several morpholine-2,5-dione derivatives, such as 3(*S*)- and 3(*R*)-isopropylmorpholine-2,5-diones, 3(*R*,*S*)-isopropylmorpholine-2,5-dione, 3(*S*)-isobutyl-morpholine-2,5-dione, 3(*S*)-sec-butylmorpholine-2,5-dione, 6(*S*)-methylmorpholine-2,5-dione, and 6(*R*,*S*)-methylmorpholine-2,5-dione by using *Porcine pancreas* lipase as a catalyst at 100–130°C in bulk. These monomers gave poly(ester amide)s with M_n ranging from 6.9×10^3 to 1.5×10^4. In the absence of the enzyme, all these monomers were recovered, indicating that the polymerization proceeds through enzymatic catalysis.

Interestingly, the configuration of the amino acid moieties in the monomers did not affect the enzyme-catalyzed polymerization of morpholine-2,5-dione. In contrast, the configuration of the lactic acid residues in the monomer strongly affected the polymerization behavior. The reason may be that the enzyme-catalyzed polymerization takes place at the ester group of the morpholine-2,5-dione derivatives and that the steric effect of the methyl group of the lactic acid residue decreases the activity of the monomers. Infrared spectral data together with the measurement of specific rotation indicated that both the amino acid and the lactic acid residues were racemized during *Porcine pancreas* lipase catalyzed ring-opening polymerization of morpholine-2,5-dione derivatives.

Introduction of functional groups in polylactide has been attempted by means of copolymerization of lactide with depsipeptides in order to modify its properties [139–144]. Ouchi et al. [145] prepared poly(L-lactic acid) based microspheres having chemically reactive groups on their surfaces from the respective biodegradable L-lactic acid (LA)-depsipeptide copolymers, poly[LA-(Glc-Asp)] and poly[LA-(Glc-Lys)], having low contents of depsipeptide units by an oil-in-water emulsion and solvent evaporation method (Scheme 16). The average diameters of the dried microspheres obtained were estimated to be 390–450 nm by scanning electron microscopy. As an example of the chemical modification of the microspheres, the immobilization of galactose residues onto the surface of the microspheres with carboxyl groups was achieved by the reaction with galactose–tetraethylene glycol amine



Scheme 15. Synthesis of poly(α-amino acid-*alt*-D,L-lactic acid)s by ring-opening polymerization of the corresponding 2,5-moropholinedione derivatives.

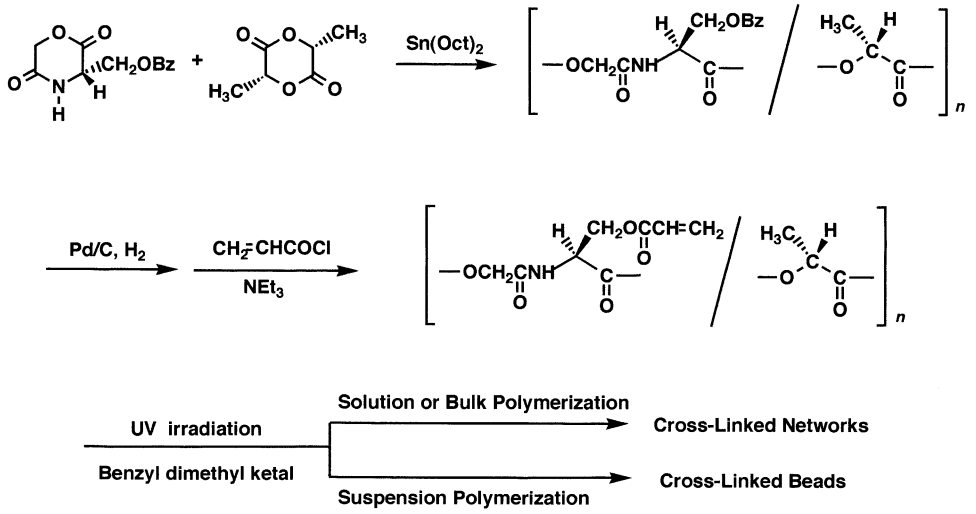


Scheme 16. Immobilization of galactose residues onto the surface of the microspheres with carboxylic groups. Reprinted with permission from Macromol Chem Phys 1999;200:436. ©1999 Wiley-VCH [145] (original has been modified slightly for simplification).

conjugate and demonstrated by APA lectin mediated aggregation of the microspheres. In addition, the entrapment of 1-naphthalenesulfonic acid as a hydrophilic model drug into these microspheres and its release behavior were investigated. The release from the microspheres with amino side groups was slower than that from the microspheres with carboxyl side groups or without functional side groups. This behavior is explained by the electrostatic interaction between the lysine groups in the microspheres and the model drug.

Hydrogels have been a recent focus for the encapsulation of cells in tissue engineering. Hubell and coworkers [146] synthesized acrylates based on lactic acid polymers and photopolymerized the acrylate functionalities in the presence of cells to encapsulate the cells in the resulting gel without damaging them. Elisseeff et al. [147] reported the UV polymerization of lactic acid/aspartic acid polymers by the methacrylate grafting method. Photopolymerization with these polymers produces minimal heat and requires small quantities of photoinitiator, resulting in a biocompatible gel system that may be polymerized in vivo.

John et al. [148] prepared serine/glycolic acid-based biodegradable poly(ester amide)s by ring-opening polymerization of 3-(*O*-benzyl)-L-serinylmorpholine-2,5-dione, and its copolymerization with L-lactide or ϵ-caprolactone using satannous octanoate as an initiator. The polymers were deprotected by catalytic hydrogenation using palladium carbon as the catalyst and functionalized through the side chain hydroxyl group of serine residues by reacting with acryloyl chloride. By UV photopolymerization of the acrylated poly(L-lactic acid-*co*-glycolic acid-*co*-L-serine)[PLA-(Glc-Ser)], they obtained glassy and transparent polymer networks, and the gel content was approximately 90% [149,150] (Scheme 17). The networks showed relatively low swelling in water, due to their cross-linked nature, but were easily swollen in chloroform and in dimethyl sulfoxide. The acrylate polymers on copolymerization with 2-hydroxyethyl methacrylate resulted in cross-linked networks, which were swollen in water and in dimethyl sulfoxide showing potential of the polymer in hydrogel applications. The modified PLA(Glc-Ser) beads were also prepared by UV-initiated suspension polymerization. These materials could be



Scheme 17. Synthesis of network polymers based on serine/glycolic acid-containing poly(ester amide).

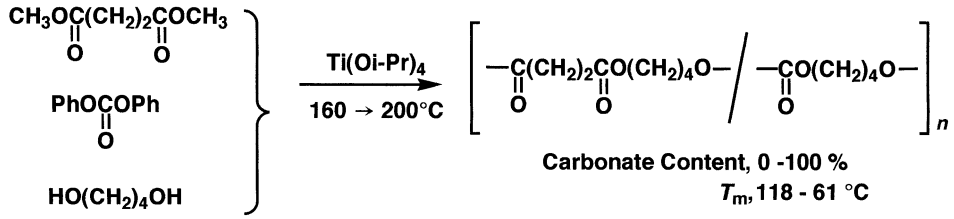
used as polymer scaffolds in tissue engineering, cell encapsulation, and injectable drug delivery, which have ligand-immobilizable and biodegradable characteristics.

3.2. Poly(ester carbonate)s

Aliphatic polycarbonates are in general prepared by ring-opening polymerization of cyclic carbonates such as ethylene carbonate, trimethylene carbonate and 2,2,-dimethyltrimethylene carbonates. These aliphatic polycarbonates are not only readily hydrolyzed but also some of them are biodegraded. Therefore, it is quite reasonable to design new biodegradable polymers containing both ester and carbonate linkages in order to modify the properties of aliphatic polyesters. Poly(ester carbonate)s can be prepared by polycondensation or by ring-opening polymerization. Biodegradation of poly(ester carbonate)s has been reported in a very limited number of papers [151–155].

Masuda et al. [154] prepared poly(ester-carbonate) with number average molecular weights of about 3×10^4 by titanium isopropoxide-catalyzed polycondensation of dimethyl succinate, diphenyl carbonate, and 1,4-butandiol (Scheme 18). Introduction of carbonate linkages into the polyester backbone improved the elongation and elasticity to some extent, with slight decrease in the yield strength and fracture strength. Enzymatic degradation using *Rhizopus delemar* lipase together with soil burial degradation showed that the biodegradability was enhanced with the decrease in crystallinity in the region of the carbonate content less than 30–40%.

Yasuda and his colleagues [155] synthesized optically active copolymers by ring-opening copolymerization of (*R*)-1-methyltrimethylene carbonate [(*R*)-1-MTC], (*S*)-1-methyltrimethylene carbonate, (*R*,*R*)-1,3-dimethyltrimethylene carbonate [(*R*,*R*)-1,3-DTC] and 1,3-dimethyltrimethylene carbonate with ϵ-caprolactone (CL), respectively, using $Sm(C_5Me_5)_2(THF)_2$, $SmMe(C_5Me_5)_2(THF)$ or $AlEt_3$–H_2O as the initiators (Scheme 19). The copolymers had high molecular weights with rather narrow molecular weight distribution and formed thermoplastic films when (*R*)-1-MTC or (*R*,*R*)-1,3-DTC content was less than 50 mol%.

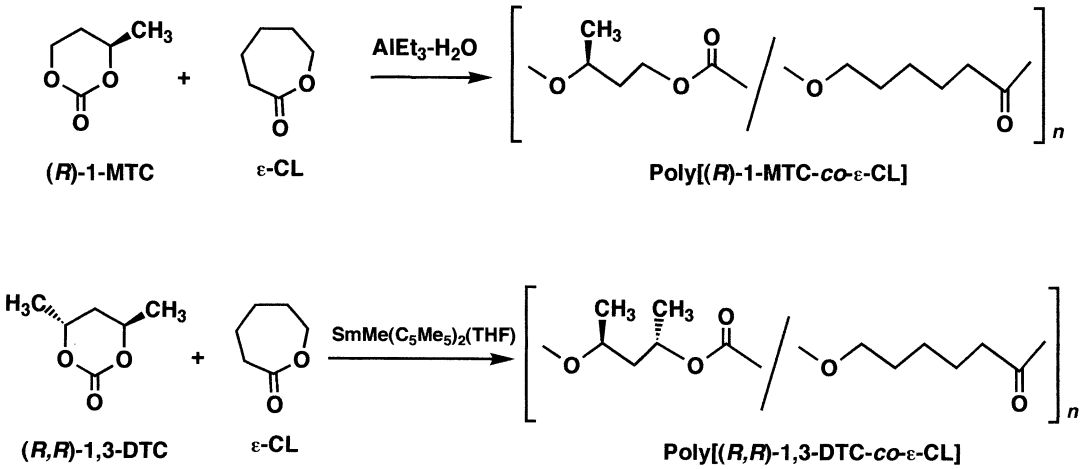


Scheme 18. Synthesis of poly(ester carbonate) by polycondensation.

Biodegradation tests using lipoprotein lipase and activated sludge indicated that the copolymers, poly[(*R*)-1-MTC-*co*-CL], with 1-MTC/CL ratios of 18/82 and 6/94 were rapidly biodegraded, while the copolymers containing more than 30 mol% (*R*)-1-MTC unit showed extremely low degradability. The fast degradation of the former is most likely to originate from the reduction of crystallinity as indicated by the heat of fusion [e.g. $-\Delta H_f$ of poly(CL) = 118 J/g; $-\Delta H_f$ of poly[(*R*)-1-MTC-*co*-CL](18/82) = 24.3 J/g]. The good degradability of 1-MTC/CL copolymers was realized by adding a small amount of *rac*-carbonate and does not require the use of expensive optically active carbonates. The ϵ-caprolactone copolymers containing small amounts of 1,3-DTC units also show high enzymatic degradation and high decomposition by activated sludge.

3.3. Poly(ester ether)s

It is well known that poly(ethylene glycol) undergoes biodegradation. Therefore, poly(ester ether)s containing both ester and ether linkages in their main chain are likely to be biodegradable polymers with thermal and mechanical properties different from those of polyesters. Poly(ester ether)s are chiefly prepared by ring-opening polymerization of cyclic ester–ether or by ring-opening copolymerization of cyclic acid anhydride with cyclic ether. Ring-opening polymerization of cyclic ester–ethers such as 1,4-dioxane-2-one, 1,5-dioxepan-2-one, and 4-methyl-1,5-dioxepan-2-one gives alternating poly(ester



Scheme 19. Synthesis of poly(ester carbonate)s by ring-opening copolymerization of ϵ-caprolactone with trimethylene carbonates.

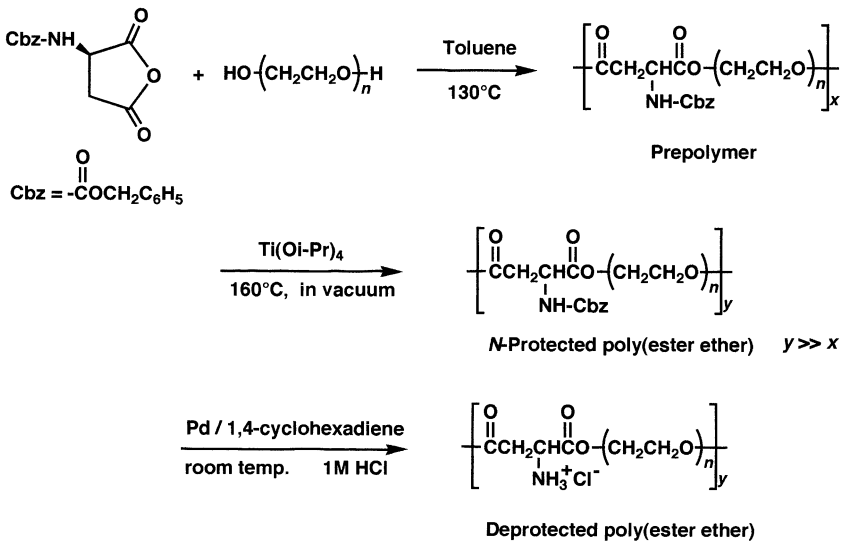
ether)s. Block copolymers of polyester and polyether are prepared by two-step ring-opening living polymerization of cyclic ether and lactone, or by ring-opening polymerization of lactone initiated with polyether, or by polycondensation of telechelic polyester with telechelic polyether [156].

Chu et al. [157,158] synthesized poly(L-aspartic acid-*co*-poly(ethylene glycol)) having pendant amine functional groups by the melt polycondensation of prepolymer prepared from *N*-(benzyloxycarbonyl)-L-aspartic acid anhydride and poly(ethylene glycol) (PEG) using titanium isopropoxide as a catalyst (Scheme 20). The optimum conditions for the preparation of prepolymer were obtained by using a 0.12 mol% of *p*-toluenesulfonic acid with PEG 200 for 48 h. The weight average-molecular weight of the prepolymer increased from 1290 to 31,700 upon melt polycondensation for 6 h at 130°C. The hydrolytic degradation of these amine-containing poly(ether ester)s was pH dependent and characterized by a rapid loss of molecular weight during an earlier period of hydrolysis, particularly at an alkaline pH. A simple hydrolysis of backbone ester bonds was believed to be the mode of degradation.

Yamamoto et al. [159] synthesized block copoly(ester ether)s based on poly[succinic anhydride (SA)-*co*-ethylene oxide (EO)] and poly(ethylene glycol) (PEG) or poly(propylene glycol) (PPG). Enzymatic degradability of the block copoly(ester ether)s and PEG was significantly lower than that of the chain-extended poly(SA-*co*-EO) used as a prepolymer. In the biodegradation tests with standard activated sludge, the block copoly(ester ether)s were degraded by microorganisms in the activated sludge. The relationship between polymer composition and the biodegradation rate by activated sludge shows a trend similar to that of enzymatic hydrolysis.

3.4. Poly(ester urethane)s and poly(ester urea)s

Although a considerable attention has recently been paid to poly(ester urethane)s in relation with biodegradation, only a few publications have dealt with their biodegradability. Katsarava et al. [160] synthesized biodegradable regular poly(ester urethane)s by polycondensation of di-*p*-toluenesulfonic acid salts of bis(L-phenylalanine) α,ω-alkylene diesters with di-*p*-nitrophenyl trimethylenedicarbonate



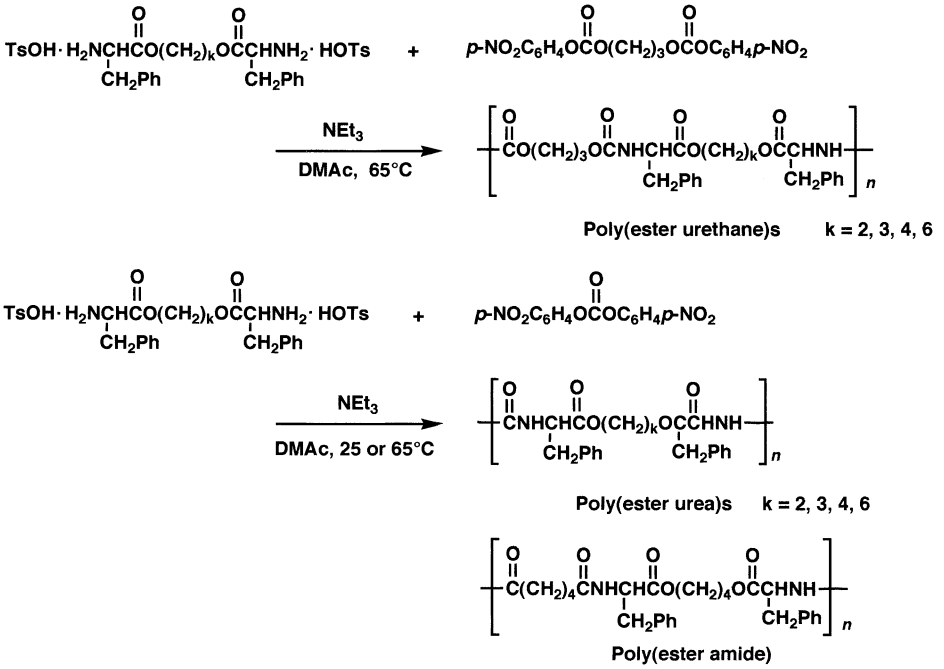
Scheme 20. Synthesis of poly(ester ether) from L-aspartic acid anhydride and poly(ethylene glycol).

in *N*,*N*-dimethylacetamide at 65°C in the presence of triethylamine as an acid acceptor. They also synthesized poly(ester urea)s by polycondensation of the *p*-tolunesulfonic acid salts with di-*p*-nitrophenyl carbonate under the same conditions (Scheme 21).

The in vitro hydrolysis study of these polymers showed that the poly(ester urethane) was more disposed to the nonspecific hydrolysis than the corresponding poly(ester amide) and that the nonspecific hydrolysis rate of the poly(ester urethane)s increased with increasing hydrophilicity, i.e. with shortening the polymethylene chain in the diol residue. On the contrary, the enzymatic hydrolysis rate of poly(ester amide) by α-chymotrypsin was higher than the corresponding poly(ester urethane), which could be explained by higher hydrophobicity of the former and, correspondingly, by the higher affinity of α-chymotrypsin to the poly(ester amide) surface.

The nonspecific hydrolysis rate of the poly(ester urea)s was as low as that of the corresponding poly(ester amide) based on the diamino–diester and adipic acid. In contrast to the poly(ester amide)s and the poly(ester urethane)s, no noticeable enzymatic hydrolysis of the poly(ester urea)s was observed under the conditions used. The lower tendency of poly(ester urea)s to enzymatic hydrolysis might be connected with the low mobility of the poly(ester urea) chains arising from strong intermolecular interactions via hydrogen bonds. Thus, among the three classes of heterochain polymers prepared from the diamino–diesters, poly(ester urethane)s are most inclined to nonspecific hydrolysis. As to the tendency of the enzymatic hydrolysis (α-chymotrypsin) these polymers form the following order: poly(ester amide) > poly(ester urethane) ≫ poly(ester urea).

Seppälä et al. [161] synthesized thermoplastic poly(ester urethane)s by a condensation copolymerization of lactic acid and ϵ-caprolactone (CL) using stannous octoate as catalyst, followed by chain extension through urethane linking. All poly(ester urethane)s were amorphous, and the glass transition



Scheme 21. Synthesis of poly(ester urethane)s and poly(ester urea)s containing L-phenylalanine.

temperature decreased with an increase in the CL content from 53 to −45°C. The poly(L-lactic acid-*co*-ϵ-caprolactone-urethane)s varied from rigid plastic to soft elastomers and varied widely in their mechanical properties with monomer composition. Small amounts of CL units increased the maximum strain, and at higher CL content the poly(ester urethane)s exhibited significant elongation. In hydrolytic degradation experiments in a phosphate buffer solution (pH 7.4) at 37°C, poly(ester urethane)s with high L-lactic acid content underwent weight loss at an earlier stage than polymers with low L-lactic acid content.

David et al. [162] synthesized poly(ester urethane)s by the chain extension reactions of poly(butylene adipate) (PBA) and poly(ethylene succinate) (PES) with a M_n of 2×10^3. Trimethylhexamethylene diisocyanate (TMDI), TMDI/2-methyl-1,5-pentanediamine (MPDA)/TMDI and 4,4′-methylenediphenyl diisocyanate (MDI) were used to build diurethane units into the polymer with a final M_n of the order of 3×10^4. Oxygen consumption was measured during incubation of a pure strain of gram-positive non-sporulating bacteria isolated from industrial compost for household refuses, in the presence of powder and films. PES degraded much more slowly than PBA, most probably due to the rigidity of the amorphous phase of the former. The last parameter is reflected by the T_g values. However, both polymers attained a degree of mineralization higher than 90%. In PES, the fragments assimilated by microorganisms were larger than the monomeric units, succinic acid and ethylene glycol. Indeed the latter compound, which was very slowly assimilated, did not accumulate in the culture medium. The junction units used to extend PBA and PEG (TMDI or MDI) were quantitatively recovered in the culture medium. If the more rigid and stronger H-bonding TMDI–MPDA–TMDI is used, no degradation could be observed in the time-scale used in the experiments (of the order to 600 or 1200 h). The rate of assimilation of the PBA segments used in the work ($M_n = 2000$) was shown to be related to their flexibility, which does not bear any direct relation to T_g or the crystallinity but to the chemical structure and specific interactions between the junction units.

Kim et al. [163] investigated biodegradability of various poly(ester–urethane)s by hydrolytic degradation in sodium hydroxide solution, enzymatic degradation by lipase, and composting. Hydrolytic and enzymatic degradation decreased with the increase of the diol carbon chains in polyol, and increased by substituting aromatic diisocyanate with aliphatic diisocyanate. Poly(ester urethane)s were biodegraded under composting conditions to a certain extent depending on their chemical structures. As the hard segment content was increased, biodegradation rate decreased. Polyurethane composed of aliphatic diisocyanate showed higher biodegradation rate than polyurethane composed of aromatic diisocyanate, indicating that the presence and content of hard segment in polyurethane effect the biodegradability under composting conditions. As the diol carbon chain increased, biodegradation rate under composting conditions increased. When the polyol used is poly(hexamethylene adipate)diol or poly(ϵ-caprolactone)diol, polyurethane showed maximum biodegradation rate under composting conditions. Surface hydrophobicity, which is related to good adhesion of bacteria on the polymer surface, is considered to be a factor on biodegradation rate under composting conditions.

Poly[(ester)urea–urethane]s with ^{14}C-labeled toluene diisocyanate or ^{14}C-labeled chain extender ethylene diamine were incubated with cholesterol esterase in a phosphate buffer solution at 37°C [164]. A number of biodegradation products were isolated from this simulated physiologic system. The two different radiolabels were used to assist in the identification of degradation products from hard- and soft-segment domains. Approximately 20 degradation products were isolated, but toluene diamine (TDA) was not identified by tandem mass spectrometry. The absence of free TDA suggests that

there could be a stabilization of urethane and urea linkages within the toluene diisocyanate (TDI) segments of the polyurethanes.

4. Syntheses of biodegradable polymers with heteroatom-containing linkages other than ester linkages in the main chains

In the previous two sections, we have reviewed recent progress in the synthesis of biodegradable polymers that contain ester linkages in the backbone chains. Polymers with both ester and other heteroatom-containing linkages in their backbones often undergo enzymatic degradation preferentially at ester linkages, but in some cases, bond cleavage takes place also at other heteroatom-containing linkages. To enlarge the scope of biodegradable polymers, it would be desirable to develop different types of biodegradable polymers without ester linkages along the main chain. In fact, some polymers without ester linkages are biodegradable. This section deals with basic researches along this line.

4.1. Polyamides

Aliphatic polyamides are generally resistant to microbial and enzymatic attacks, although some examples of degradation have been reported in the literature [165,166]. Obviously, highly ordered structures due to strong intermolecular interactions caused by hydrogen bondings are responsible for their low biodegradability. Loose packing, improved chain flexibility, and hydrophobicity bestowed by introduction of substituents such as benzyl and alkyl groups may enhance the susceptibility of the amide linkages of synthetic polyamides to enzymatic hydrolysis. Chemical modification and even physical processing are effective for the increase of their biodegradability. Beside the introduction of ester linkages into polyamide backbones as described in the foregoing section, the incorporation of α-amino acid residues along the aliphatic polyamide chain seems to be an effective strategy for enhancing the biodegradability of aliphatic polyamides.

Palumbo et al. [167] prepared aliphatic polyamides from sebacic acid and tetradecanedioic acid and amide–diamines containing one or two preformed amide linkages susceptible to enzymatic cleavage in their molecules (Chart 2). L-Phenylalanine, either by itself or together with L-valine, was used to generate amide bonds that are cleavable by chymotrypsin. Improved chain flexibility and hydrophobicity were given to the polyamides using a triethyleneoxy-based amide–diamine. Varying the chemical structure of the amide–diamine monomers could properly regulate the crystallinity, melting temperature, and solubility of the polyamides, as well as their hydrophobic/hydrophilic character. The polymers tested were capable of supporting fibroblast adherence and proliferation, and proved to be non-cytotoxic. However, no description was given as to the biodegradability of the polymers.

Russo et al. [168] prepared a series of copolyamides by hydrolytic polymerization of ϵ-caprolactam (CLm) in the presence of various amounts of L-phenylalanine (Phe) aiming at improving the low environmental degradability and biodegradability of nylon 6. The environmental degradability was ascertained by testing the resistance of CLm–Phe copolymers to both alkaline hydrolysis and composting conditions. The degradation rate and the extent of hydrolysis of the copolyamides were evaluated by using the mass loss, thermogravimetric analysis, and viscosity measurements. On the basis of the evaluation, Russo et al. stated that the copolyamides could be suitable film-forming materials for

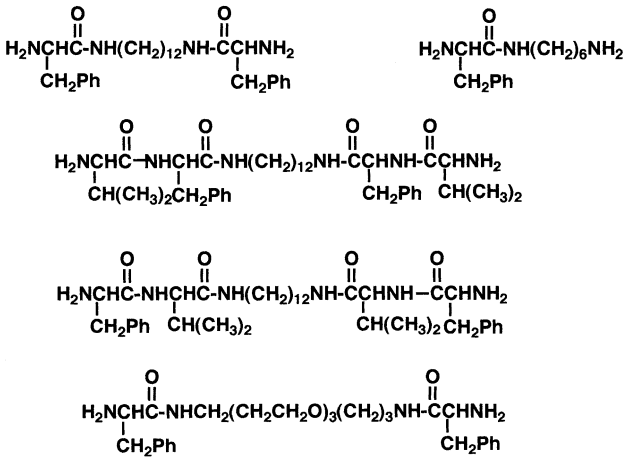


Chart 2. Structures of the amide–diamines used in the synthesis of polyamides based on α-amino acids.

environmentally degradable applications in various fields, such as agricultural coverage and food packaging, when time-limited performance are requested.

Polyamides derived from carbohydrates are the object of current attention, for its potential as biodegradable and biocompatible materials [169–174]. Muñoz-Guerra and coworkers [175] synthesized polyamides by polycondensation in solution from mixtures of 2,3-di-*O*-methyl-D- and L-tartaric acids and hexamethylene diamine using the active ester method (Chart 3). The diacid was activated as bis(pentachlorophenyl) ester and the diamine as its *N*,*N*′-bis(trimethylsilyl)derivative. They obtained optically pure enantiomorphs (100% D and 100% L) as well as a series of copolymers with D:L ratio varying from 1:9 to 1:1. Degradation in water under physiological conditions (pH 7.4 and 37°C) took place slowly and also increased with the increase in the D:L ratio of the copolymers. Weight loss between 10 and 30% and decays in the molecular weight down to nearly 50% were observed after 2 months of incubation. Degradation by *Aspergillius niger* was tested on cast films in the presence of Sabouraud's dextrose broth medium. Extensive surface growing and a considerable pervading of the bulk materials by the fungi was observed for the copolyamides with the D:L ratios of 1:4 and 1:1. On the contrary, the microorganism appeared to be completely inactive in culture of either of the two optically pure polymers. These results indicated that the dominant factor determining the biodegradability of polytartaramides is water affinity rather than the configurational nature of the polyamide. Thus, the sensitivity of the material to fungal attack seems to be determined by the accessibility of the amorphous phase to water. The mechanism may be envisioned as the one taking place by growth and penetration of hyphae in water-enriched zones with concomitant chemical degradation of the polymer.

4.2. Polypeptides

Since α-amino acids are naturally occurring compounds, synthetic poly(α-amino acid)s derived therefrom are expected to be biodegradable, biocompatible, and nontoxic. In addition, α-amino acids are themselves biologically active, so that it is a great advantage to use α-amino acids for synthesizing biologically active, biodegradable polymers. In fact, poly(α-amino acid)s and their copolymers have potential for biodegradable medical applications such as temporary artificial skin substrates and polymer

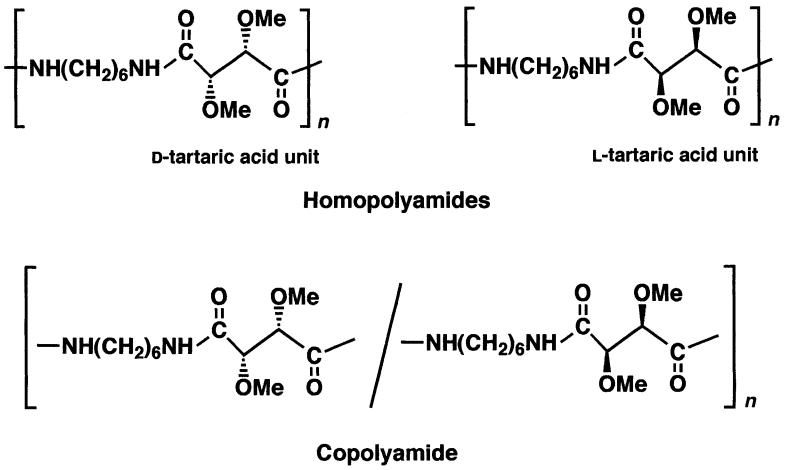


Chart 3. Structures of homo- and copolyamides based on D- and L-tartaric acids.

carriers for protein conjugates and drug delivery systems. It is well known that poly(α-amino acid)s are most conveniently synthesized by ring-opening polymerization of α-amino acid *N*-carboxyanhydrides (NCAs). Under proper selection of reaction conditions, ring-opening polymerization of NCAs gives poly(α-amino acid)s of a controlled chain length [176–178].

Hayashi et al. [179] prepared random copolypeptides consisting of *N*-(2-hydroxyethyl)-D-glutamine and *N*-(2-hydroxyethyl)-L-glutamine by copolymerization of γ-methyl-D-glutamate NCA and its L-counterpart, followed by aminolysis with 2-amino-1-ethanol. Hydrolysis of these copolymers by bromelain in a pseudo-extracellular fluid at pH 7.4 showed that D,L-copolypeptides underwent random chain scission, following the Michaelis–Menten rate law. Furthermore, the rate of degradation was controlled not only by the copolymer composition but also by the sequence distributions of comonomer units in the copolymer chains. These findings seem to provide helpful information to the molecular design of the biodegradable polymers applicable for biomedical purposes.

Commonly used water-absorbent polymeric materials such as poly(acrylic acid) are not biodegradable, and hence they are likely to cause an environmental pollution if they are left as they are in nature. Since poly(α-amino acid)s are biodegradable, modified poly(α-amino acid)s with carboxyl or amino groups seem to be promising as biodegradable water-absorbent polymeric materials. In fact, microbial poly(γ-glutamic acid) and microbial poly(ε-lysine) were converted on γ-irradiation to biodegradable transparent hydrogels with a high water sorption ability. Kunioka et al. [180] obtained hydrogels by γ-irradiation of poly(aspartic acid) prepared by thermal polycondensation of L-aspartic acid with 85% *o*-phosphoric acid as a catalyst, followed by hydrolysis (Scheme 22). Hydrogels were formed by γ-irradiation when poly(aspartic acid) with a high molecular weight ($M_w = 9.5 \times 10^4$) was used, whereas hydrogel was not obtained for poly(aspartic acid) with a low molecular weight ($M_w = 1.5 \times 10^4$). The maximum swelling of the hydrogel by deionized water was 3400 g-water/g-dry hydrogel, whereas the swelling of the hydrogel using artificial urine was 27.4 g-water/g-dry hydrogel. Biodegradation test of the hydrogels using the activated sludge (Japanese Industrial Standard JIS K6950) indicated that the hydrogels showed about 50% biodegradation for 28 days.

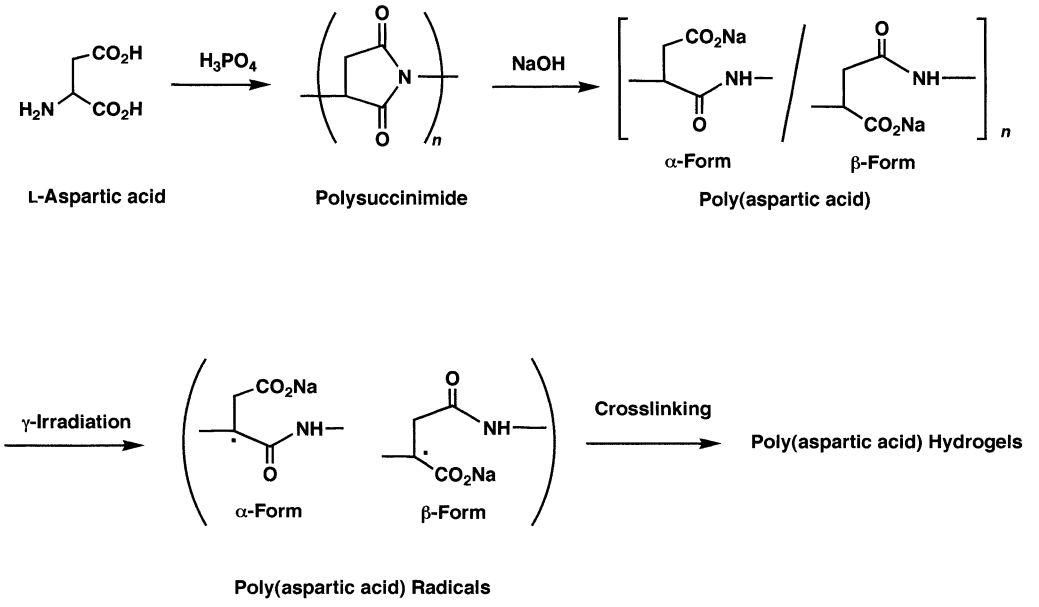
Poly(α,β-(3-hydroxypropyl)-D,L-aspartamide) (PHPA) was synthesized by the ring-opening reaction of polysuccinimide and 3-hydroxypropylamine [181]. Examination of the acute toxicity of PHPA

revealed no death in ICR mice up to the dose treated of 1.3 kg/kg, and hematological parameters showed no significant difference between treated and control animals. The potential use of PHPA as a drug carrier was also investigated. In a typical case, a contraceptive drug, norethindrone (NET), was bonded to PHPA, and the drug sustained release as long as 120 days at in vitro test.

A triblock copolymer based on poly(γ-benzyl-L-glutamate) (PBLG) as the hydrophobic part and poly(ethylene oxide) (PEO) as the hydrophilic part was synthesized, and PBLG/PEO/PBLG block copolymer (GEG) nanoparticles were prepared using the dialysis technique [182]. The particle size and drug loading contents of GEG nanoparticles were significantly changed with the initial solvent used. From transmission electron microscope observations, the GEG polymeric micelle was a nice spherical shape and the sizes ranged from approximately 20–60 nm in diameter. Results from assessing the drug-loading contents against the initial solvent showed that the use of tetrahydrofuran or 1,4-dioxane as the initial solvent resulted in higher drug-loading contents than other solvents. In the drug-release studies, the higher the molecular weight of the polymer and drug-loading contents, the slower the drug release. Also, the initial solvent significantly affected not only the drug-loading contents but also the drug-release kinetics.

4.3. Polyurethanes

Modified segmented polyurethanes were examined for biostability and biocompatibility using an in vivo cage implant system [183]. By 10 weeks, biodegradation in the case of unmodified poly(ether–urethane)s was extensive as compared to polydimethylsiloxane (PDMS) end-capped poly(ether–urethane), because the PDMS endcaps of the latter provided a shield against the oxygen radicals secreted by macrophages and foreign body giant cells, and lowered the rate of biodegradation. In the case of poly(carbonate–



Scheme 22. Synthesis of biodegradable hydrogels by γ-irradiation of poly(aspartic acid)s synthesized by thermal polycondensation.

urethane)s, the oxidative stability of the carbonate linkage lowered the rate of biodegradation significantly as compared to the poly(ether–urethane)s. The minor amount of biodegradation seen in poly(carbonate–urethane)s after 10 weeks was attributed to hydrolysis of the carbonate linkage.

It is generally accepted that biodegradation of poly(ether urethane urea)(PEUU) involves oxidation of the polyether segments on the surface where leukocytes are adhered. Schubert et al. [184,185] investigated the influence of dissolved oxygen and suggested that PEUU degrades by an auto-oxidation mechanism sustained by oxygen. By successfully modeling the depth of the surface degraded layer with a diffusion-reaction model, they demonstrated that PEUU biodegradation is controlled by diffusion of oxygen into the polymer. The same authors examined the effect of deformation state on degradation of a PEUU without added stabilizers in an oxidative environment that simulates the in vivo biodegradation of the polymer. Macroscopic damage was confined to a thin peeling surface layer if the stress was uniaxial. In comparison, biaxially stressed PEUU ruptured.

Polyester-based poly(urethane–urea)s are reported to be susceptible to enzymatic hydrolysis. Furthermore, the degree of hard segment microdomain formation in polyurethane materials, as well as its structure, influences the ability of enzymes to degrade the polymers. Santerre et al. [186] prepared a series of segmented poly(ether–urethane–urea)s with the same reagents but having different hard segment content and investigated their enzymatic hydrolysis. Both DSC and X-ray photo-electron spectroscopy data indicated that the three materials differed significantly in the extent of hard segment domain formation and that the polymer containing the highest number of hydrolytically labile urea and urethane bonds exhibited the least degradation. The ability of a polyurethane material to form hard segment microdomains may contribute to the formation of a protective structure for the hydrolyzable hard segment linkages located within the microdomains.

4.4. Polyethers

Microbial hydrolytic degradation of polyethers, particularly poly(ethylene oxide)(PEO), has been studied by some groups. For example, Kawai [187] proposed that the microbial degradation of PEO occurred as a combination of oxidation and hydrolysis. Thus, the terminal hydroxyl groups are first oxidized and then the ether bonds are cleaved. The metabolic pathways for PEG was confirmed by metabolic products and metabolizing enzymes. Otal et al. [188] found that the partial wet air oxidation converted the original PEO ($M_n = 1 \times 10^4$) into lower molecular weight compounds and that subsequent treatment with wastewater achieved more than 90% TOC removal after a four day residence time compared with 60–70% TOC removal with no pretreatment.

Fungi that cause brown rot of wood are essential biomass recycleres and also the principal agents of decay in wooden structures, but the exracellular mechanisms by which they degrade lignocellulose remain unknown. To test the hypothesis that brown-rot fungi use extracellular free radical oxidants as biodegradative tools, Kerem et al. [189] examined the ability of *Gloeophyllum trabeum* to depolymerize poly(ethylene oxide) (PEO) that cannot penetrate cell membranes. Analyses of degraded PEOs by SEC showed that the fungus cleaved PEO rapidly by an endo route. ^{13}C NMR analyses of unlabeled and perdeuterated PEOs recovered from *G. trabeum* cultures showed that a major route for depolymerization was oxidative C–C bond cleavage, a reaction diagnostic for hydrogen abstraction from a PEO methylene group by a radical oxidant. Fenton reagent ($Fe(II)/H_2O_2$) oxidized PEO by the same route in vitro and therefore might account for PEO biodegradation if it is produced by the fungus, but the data do no rule out involvement of less reactive radicals. The reactivity and extrahyphal location of this PEO-degrading

system suggest that its natural function is to participate in the brown rot of wood and that it may enable brown-rot fungi to degrade recalcitrant organopollutants.

5. Concluding remarks

In the foregoing sections, we have seen recent advances in the syntheses of biodegradable polymers from the viewpoint of molecular design. Needless to say, synthetic researches on biodegradable polymers would never bring truly fruitful results without due consideration of fundamental biological studies on the kinds and distributions of microorganisms that can degrade plastics, their degradation mechanisms, and safety of degradation products. Up to the present, a variety of synthetic polymers have been designed and synthesized as potentially biodegradable polymeric materials. However, there is still a long way for us to reach the final goal for ideal biodegradable polymers, that is, polymers that display high performance while they are being used and that readily biodegrade when their roles came to the end. In view of the depletion of the fossil resources in a near future, it is to be stressed here that raw materials from renewable resources should be employed for synthesizing biodegradable polymers. Effective synthesis and utilization of biodegradable polymers from renewable resources could positively contribute not only to the preservation of the global environment but also to the reduction of the consumption of fossil energy resources and the construction of sustainable material systems. To realize more common and wide use of biodegradable polymers throughout the world, further efforts should be devoted toward the development of new technologies capable of producing more useful biodegradable polymers at a lower cost. In addition, the critical prerequisite would be the consumer's awareness that one can actively contribute to the preservation of the global environment by using biodegradable polymers.

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