5
Biodegradable Polymers Composed of Naturally Occurring α-Amino Acids

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5.1
Introduction

The synthesis and study of biodegradable polymers is at the forefront of modern polymer chemistry because of the technological challenge and commercial potential. For many medical, agricultural, and environmental purposes, it is important to have biodegradable polymers that degrade under the action of physiological environment or in soil. Biodegradable polymers have become increasingly important for the development of surgical and pharmaceutical devices like wound closure devices, vascular grafts, nerve guidance tubes, absorbable bone plates, orthopedic pins and screws, body-wall/hernia repair, sustained/controlled drug delivery systems, to name a few. Different materials with tailored properties are required for each of these applications. Therefore, biodegradable polymers with a variety of hydrophilicity/hydrophobicity, permeability, morphology, degradation rates, chemical, and mechanical properties are needed.

The limitation for many synthetic biodegradable polymers as biomedical materials is the potential toxicity of the degradation products. Therefore, research was focused toward the materials entirely composed of naturally occurring and nontoxic ("physiological") building blocks. Such polymers release metabolic components upon biodegradation, which are digested by cells and reveal certain nutritious values, in parallel with high biocompatibility.

In the light of this, heterochain polymers composed of α-hydroxy acids (α-HAs) and α-amino acids (α-AAs) are considered as promising representatives of synthetic resorbable biomaterials, especially the latter because after biodegradation the release products are essential α-AAs and their derivatives.

Well-characterized aliphatic polyesters (PEs), for example, PGA, PLA, PLGA, PDLLA [1], are far from perfect: the synthesis of PEs requires dry conditions, which is rather complex and costly. The shelf-life of the PEs is rather short. Also, aliphatic PEs reveal useful material properties only at high molecular weights (100,000 Da and higher) due to weak intermolecular forces. They show low hydrophilicity and hence do not actively interact with the surrounding tissues in a desirable manner after implantation that diminishes the biocompatibility [2].

Handbook of Biodegradable Polymers: Synthesis, Characterization and Applications, First Edition. Edited by Andreas Lendlein, Adam Sisson.

On the other hand, α-AA-based polymers have strong hydrogen bonds due to amide linkages that increase both intermolecular forces (that means desirable material properties at much lower molecular weights) and hydrophilicity, and hence biocompatibility [3].

The earliest representatives of α-AAs based synthetic polymers were poly(α-amino acids) (PAAs). The most common method for the synthesis of high-molecular-weight PAAs is ring-opening polymerization of N-carboxyanhydrides. In spite of expectations, PAAs that belong to the class of polyamides (Nylons-2) and contain only amide bonds in the backbones turned out to be less suitable as biodegradable materials for biomedical engineering use for many reasons, such as difficult and costly manufacturing processes because of unstable N-carboxyanhydrides, insolubility in common organic solvents, thermal degradation on melting, and poor processability. The rates of degradation under physiological conditions are often too slow to be useful as biodegradable biomaterials. These limitations of PAAs could be somewhat reduced by the synthesis of copolymers containing two or more α-AAs. However, this originates immunogenicity, and the biodegradation rate was still low due to the polyamide (PA) nature of the polymers [3].

Therefore, the research efforts were redirected to the synthesis of α-AAs-based polymers that contain easily cleavable (degradable) chemical bonds in the backbones with molecular architecture that diminishes (or at all excludes) immunogenicity.

How could macrochains using α-AAs as building blocks be constructed? Let us consider the structure of α-AAs as a vector directed from N-terminus to C-terminus (Figure 5.1).

Linear macrochains on the basis of α-AAs can be constructed using both α-functional groups (H_2N and COOH), or one α-(H_2N or COOH) and one lateral functional group F (which could be NH_2, COOH, or OH). Hence, the orientation of α-AAs in macrochains can be diverse (Figure 5.2).

This multifunctionality along with a high number of naturally occurring α-AAs opens unlimited synthetic possibilities for constructing various macrochains.

Among the various possible orientations of α-AAs in the polymeric backbones, the directional, "head-to-tail" orientation is conventional observed in biopolymers, proteins, and polypeptides. This orientation determines their primary and secondary structures that, in turn, determine their biochemical properties including immunogenicity. The same is true for synthetic poly-α-AAs [3]. All the said polymers belong to the class of polypeptides, in fact AB type polyamides.

More promising for biomedical applications are synthetic polymers in which the α-AAs have nonconventional orientations – adirectional ("head-to-head" and

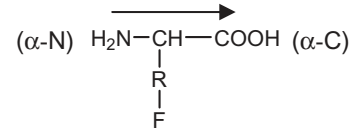


Figure 5.1 The general structure of α-AAs.

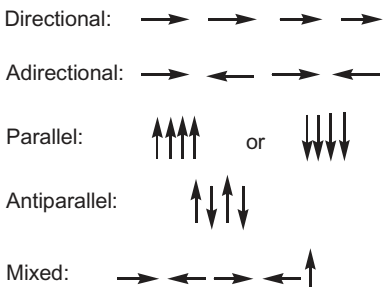


Figure 5.2 The possible orientations of α-AAs in the polymeric backbones.

"tail-to-tail"), parallel, antiparallel, or mixed (Figure 5.2). These could be polymers of other classes – polyurethanes and polyureas along with the said polyamides. To render the polymers easily cleavable (in most cases hydrolysable), the labile chemical bonds have to be incorporated into the polymeric backbones to provide desirable rates of biodegradation. Preference should be given to ester bonds taking into account both biodegradation rates and the stability (shelf life). The new polymers comprising different types of heterolinks such as ester, urethane, urea, along with peptide (amide) bonds, with the nonconventional orientation of α-AAs are expected to diminish the immunogenicity of the polymers by "confusing nature" due to "unrecognizable" structures of macromolecules.

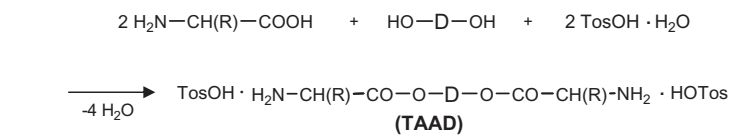
5.2
Amino Acid-Based Biodegradable Polymers (AABBPs)

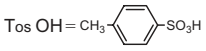
5.2.1
Monomers for Synthesizing AABBPs

In this chapter, three classes of AABBPs containing ester bonds as biodegradable sites are considered. These are AA-BB polycondensation polymers with nonconventional "head-to-head" and "tail-to-tail" orientation of α-AAs in the polymeric backbones – poly(ester amide)s (PEAs), poly(ester urethane)s (PEURs), and poly(ester urea)s (PEUs). The PEAs are composed of three building blocks: (i) α-AAs, (ii) fatty diols, and (iii) dicarboxylic acids. They allow manipulation of polymer properties in a wide range. PEURs and PEUs are also composed of three types of building blocks – two blocks are (i) α-AAs and (ii) diols; however, the third block is (iii) carbonic acid.

5.2.1.1 Key Bis-Nucleophilic Monomers

Key monomers for synthesizing all three classes of AABBPs are bis-nucleophiles that represent dimerized α-AAs-bis-(α-amino acyl)-alkylene diester (tosic acid salt of amino acid/alkylene diester, TAAD). These compounds are stable in the salt form, commonly as di-*p*-toluenesulfonic acid (TosOH) salts. They are generally

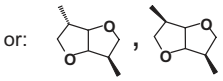




R is the lateral substituent of hydrophobic amino acids like: L-alanine ($R=CH_3$), L-valine ($R=CH(CH_3)_2$), L-leucine ($R=CH_2CH(CH_3)_2$), L-isoleucine ($R= CH(CH_3)CH_2CH_3$), L phenylalanine ($R=CH_2C_6H_5$), L and DL-methionine ($R=(CH_2)_2SCH_3$), L-arginine ($R=(CH_2)_2NHC(=NH)NH_2$).

D is divalent alkyl radical like $(CH_2)x$ with x = 2, 3, 4, 6, 8, 12;

$(CH_2)_2-O-(CH_2)_2$, $(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2$, $(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2$



Scheme 5.1 Synthesis of TAADs.

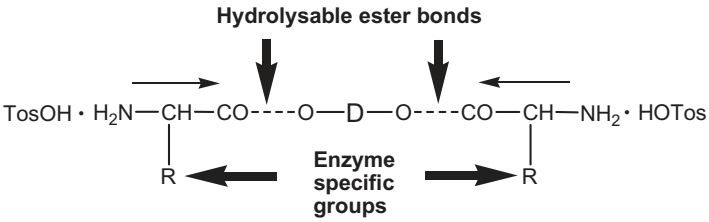


Figure 5.3 Structural peculiarities of TAADs.

prepared by direct condensation of α-AAs (2 mol) with fatty diols (1 mol) in refluxed benzene or toluene in the presence of TosOH monohydrate (2 mol), Scheme 5.1.

The presence of TosOH•H_2O (2 mol) serves as both the reaction catalyst and amino group protector, preventing undesirable side reactions including amine interaction with inherent ester groups of TAAD.

This strategy allows us to generate diamine monomer with two inherent biodegradable (hydrolysable) ester bonds, along with enzyme specific groups, Figure 5.3, and the nonconventional "head-to-head" orientation of α-AAs put at a monomer stage.

The first synthesis of TAAD according to this very simple procedure was reported by Huang and coworkers [4], on the basis of L-phenylalnine and 1,2-ethanediol. Later, TAADs were obtained from other hydrophibic α-amino acids: glycine [5–9], alanine [10–13], valine [14], leucine [6, 14–21], isoleucine, norleucine, methionine [14], phenylalanine [6, 7, 14–31], and arginine [32–35]. Accordingly, arginine-based TAADs are tetra-(TosOH) salts.

Various aliphatic α,ω-alkylene diols [8–17, 21, 24, 27–35], dianhydrohexitols [25, 26], and di-, tri, and tetraethylene glycols [35, 36] were used by different authors for synthesizing TAADs.

The obtained di- or tetra-TAADs are stable compounds. The most of these monomers were purified by recrystallizing from water or organic solvents. The yields of pure, polycondensation grade products ranged within 60–90%.

5.2.1.2 **Bis-Electrophiles**

For successful synthesis of AABBPs with tailored architecture, the selection of suitable bis-electrophilic monomer(s) is also important – counterpartners of TAADs. The syntheses of various bis-electrophiles are discussed below as detailed as possible within the bounds of this chapter.

Dicarboxylic acids HO–CO-A-CO–OH can be incorporated into the PEA backbones by means of either dichlorides Cl–CO-A-CO–Cl (dicarboxylic acid dichloride, DDC) or active diesters R_1-CO-A-CO-R_1 (dicarboxylic acid active diester, DAD) as bis-electrophilic monomers (for A and R_1, see Scheme 5.2).

Many DDCs are commercial products. DADs are obtained using three synthetic methods: (i) by interaction of DDCs with various hydroxyl compounds HOR_1 (activating agents), Scheme 5.2 [14, 15, 20, 24, 25], or by direct interaction of dicarboxylic acids (ii) with HOR_1 in the presence of various condensing (coupling) agents, Figure 5.4 [15, 21, 37], or (iii) with various *trans*-esterifying agents that are derivatives of HOR_1, Scheme 5.3 [37].

All three methods give DADs in a good yield ranged from 60% to 90%.

Monomers for synthesizing PEURs. The third building block of PEURs – carbonic acid – can be incorporated into the polymeric backbones by means of either bis-chloroformates Cl–CO–O-D_1-O–CO–Cl (diol bis-chloroformate, BCF) or active bis-carbonates R_1-CO–O-D_1-O–CO-R_1 (DBCs) as bis-electrophilic monomers (D_1 can be the same as D in Scheme 5.1).

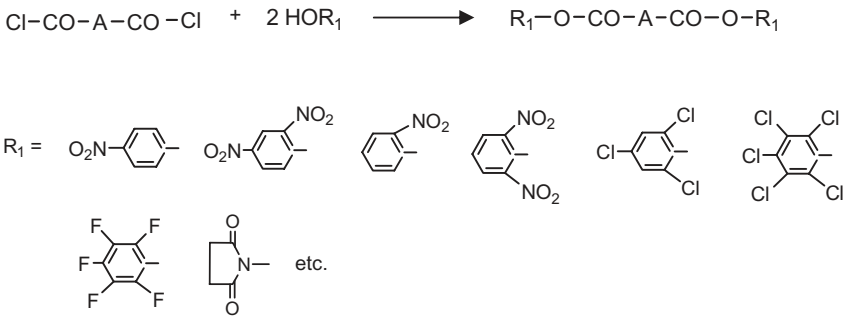
Diol bis-carbonates (DBCs) can be obtained using two synthetic methods: (i) by interaction of BCFs with hydroxyl compounds HOR_1, Scheme 5.4 [38], or (ii) by interaction of diols with mono-chloroformates of hydroxyl compounds Cl–CO–O-R_1, Scheme 5.5 [39].

The building block for PEUs, carbonic acid, can be incorporated into the polymeric backbones by means of polycondensation using either phosgene (derivatives), or active carbonates (AC) obtained according to Scheme 5.6 or related compounds [40].

5.2.2 AABBPs' Synthesis Methods

PEAs. The synthesis of PEAs on the basis of TAADs can be carried out at a low temperature via interfacial polycondensation (IP) and solution polycondensation (SP). The IP and SP reactions proceed according to Figure 5.5 in the presence of acid acceptor (HCl and/or TosOH).

The selection of the polycondensation method depends on the nature of bis-electrophilic monomer. The IP is suitable method when DDCs are used.



Scheme 5.2 Synthesis of DADs by interacting DDC with HOR1, method (i).

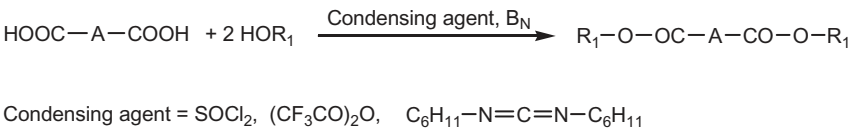
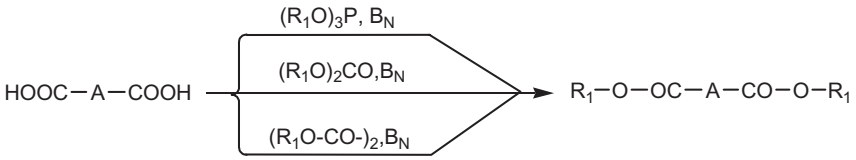
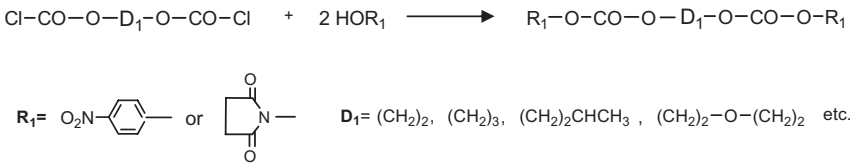


Figure 5.4 Synthesis of DADs from free dicarboxylic acids using condensing agents, method (ii).

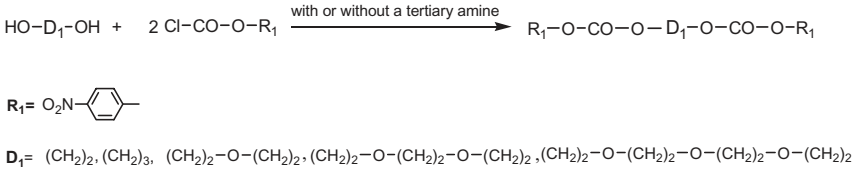
However, this method results into high-molecular-weight PEAs only with the hydrophobic diacids like sebacic acid with $y = 8$, or higher (Scheme 5.2) or aromatic DDCs, such as terephthaloyl chloride [8–13]. It has to be noted that DDCs are less suitable monomers for SP with aliphatic diamines since these electrophiles enter into numerous undesirable side reactions with tertiary amines [41] that are



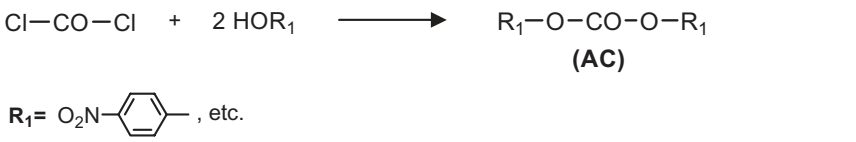
Scheme 5.3 Synthesis of DADs from free dicarboxylic acids using *trans*-esterifying agents, method (iii).



Scheme 5.4 Synthesis of DBCs by interacting BCFs with activating agents HOR1, method (i).



Scheme 5.5 Synthesis of DBCs by interacting diols with *p*-nitrophenyl-chloroformate, method (ii).



Scheme 5.6 Synthesis of active carbonates (AC).

used as acceptors of liberated hydrogen chloride; for TAADs, tertiary amines are used to remove TosOH from amino groups as well. These side reactions cause the limitation of the chain growth resulting in the formation of low-molecular-weight polymers with poor material properties.

For hydrolytically less stable DDCs, or DDCs that are unavailable at polycondensation purity (like short-chain succinic ($y = 2$), adipic ($y = 4$), fumaric, and

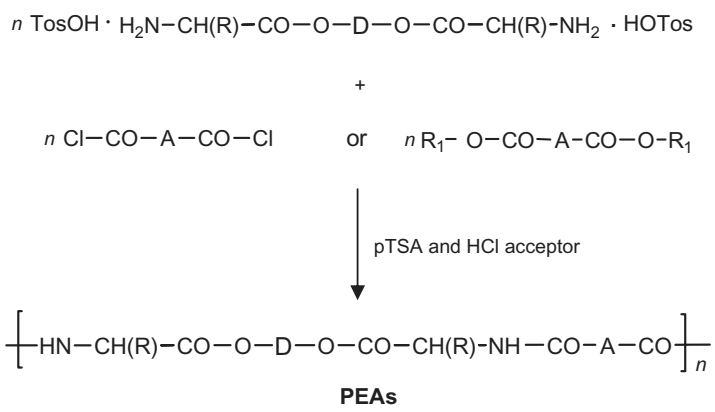


Figure 5.5 Synthesis of PEAs by IP and SP (AP).

epoxy-succinic acids, as well as bis-(succinic acid)-α,ω-alkylene diesters and *O,O′*-diacyl-bis-glycolic acids, see Scheme 5.2), the preference should be given to SP using DADs as bis-electrophilic monomers. The SP via active diesters of various classes – DADs, DBCs, and ACs – is called "active polycondensation" (AP) [42] to distinguish it from traditional polycondensation methods. Hereafter we use the term AP for polycondensation with participating active diester of diacid. The AP with DADs is normally carried out in polar aprotic solvents DMA, DMSO, etc., or in common organic solvents like chloroform, THF, etc., at 20–80 °C using mostly triethylamine (TEA) as TosOH acceptor [14–16, 20–22, 24, 25, 27, 28, 32, 33, 42–47]. It was shown that DADs are stable against both amide-type solvents and tertiary amines [48] under the conditions of AP that minimizes undesirable side reactions and results in the formation of high-molecular-weight polymers.

It has to be noted that PEAs composed of the same three building blocks – α-AA (glycine), fatty diols, and dicarboxylic acids – were synthesized recently [5] using the third method – thermal polycondensation (TP) in melt, in the presence of titanium butoxyde as a catalyst at 160–220 °C.

The advantage of TP is the possibility to process polymers from melt directly after the polycondensation, that is, without the separation and purification of the resulting polymers. However, the method is less suitable for thermally sensitive and unstable monomers including optically active ones since high reaction temperature can cause racemization and destruction. The use of metalorganic catalyst is one of the drawbacks as well.

The AABBPs type PEURs can be synthesized on the basis of TAADs under the conditions of either IP or AP similar to Figure 5.5 using as bis-electrophilic monomers BCFs instead of DDCs, and DBCs instead of DADs.

Like for the PEA, the PEUR synthesis by IP is less suitable with short-chain DBC due to their hydrolytic instability that results in low-molecular-weight polymers. Kohn *et al.* [49–51] suggest that more appropriate monomers for polyurethane synthesis via IP are DBCs that are hydrolytically more stable. The results

are high-molecular-weight lysine based poly(ether urethane)s even on the basis of water-soluble monomers – bis-succinimidyl carbonates of PEGs (PEG-based DBCs). The same approach seems promising for the synthesis of PEURs on the basis of TAADs.

DBCs were very effective as bis-electrophiles in AP as well. They resulted in the high-molecular-weight PEURs [16, 52] having excellent film-forming properties. The conditions of AP with DBCs are the same as for DADs above.

The PEUs on the basis of TAADs can also be synthesized via IP or AP similar to Figure 5.5 using phosgenes (mono, di, or tri) as bis-electrophilic monomers instead of DDCs [53], and ACs instead of DADs [52]. In contrast to PEAs and PEURs above, IP unambiguously led to high-molecular-weight PEUs.

5.2.3
AABBPs: Synthesis, Structure, and Transformations

5.2.3.1 Poly(ester amide)s

Regular PEAs. We consider as "nonfunctional" those PEAs that have no functional groups except two terminal reactive groups – normally one nucleohpile and one electrophile, Figure 5.6.

According to the polycondensation theory of Kricheldorf [54, 55], a substantial portion of macromolecules obtained via AP have no terminal functional groups, since they form macrocycles.

The first "nonfunctional" regular PEAs representing AABBPs [6, 7, 14, 17, 18, 24–26] was synthesized via AP of TAADs with active diesters of α,ω-alkylenedicarboxylic acids [A = $(CH_2)y$], according to Figure 5.5 above.

Polysuccinates. Recently [44] a new class of nonfunctional AABBPs – PEAs based on succinic acid (rather alkylene disuccinates) with higher density of cleavable ester bonds – were synthesized by AP of TAADs with active di-*p*-nitrophenyl esters of bis-(succinic acid)-α,ω-alkylene diesters (Scheme 5.2). Their general structure is given in Figure 5.7.

Polysuccinates have two additional ester bonds (in total four ester bonds) as compared with regular PEAs above, having in total two ester bonds per repeating

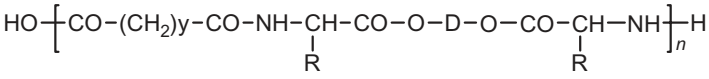


Figure 5.6 Regular PEAs composed of α-AAs, diols and α,ω-alkylenedicarboxylic acids.

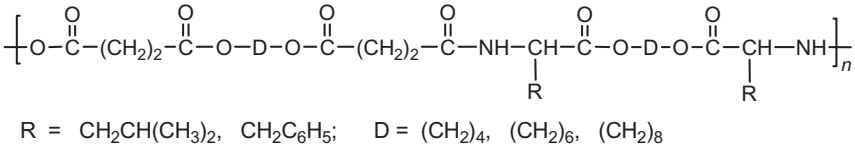
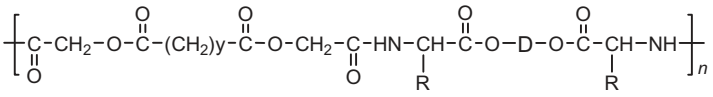
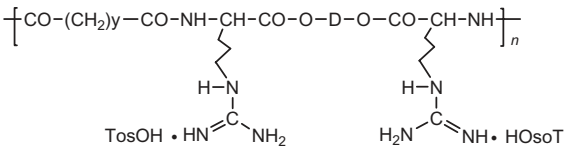


Figure 5.7 PEAs on the basis of bis-(succinic acid)-α, ω-alkylene diesters.



R = $CH_2CH(CH_3)_2$, $CH_2C_6H_5$; D = $(CH_2)_8$, $(CH_2)_{12}$; y = 4, 8.

Figure 5.8 AA-BB PDPs composed of glycolic acid, α-AAs, and dicarboxylic acids.



y = 2, 4, 8; D = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_6$

Figure 5.9 Arginine-based cationic ABBPs-PEAs.

unit, and showed increased biodegradation rates. Additionally, the enhanced hydrolysis of polysuccinates is linked with intramolecular catalysis (see Ref. [56] and references cited therein).

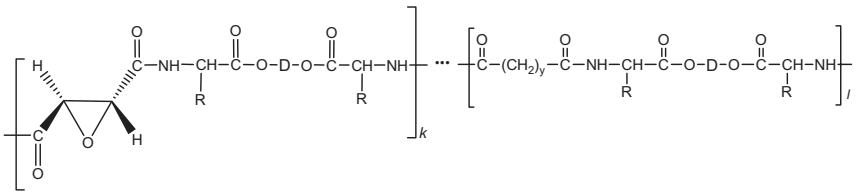
Poly(depsipeptide)s (PDPs). Very recently [21, 43] a new class of nonfunctional AABBPs–AA-BB-type PDPs–were obtained by AP of TAADs with active di-*p*-nitrophenyl esters of *O,O′*-diacyl-bis-glycolic acids (Scheme 5.2) and have the general structure given in Figure 5.8.

PDPs also have two additional and highly polarized (close by nature to the ester bonds in poly(glycolic acid)) ester bonds (in total four ester bonds) as compared with regular PEAs above, containing two ester bonds per elemental links, and hence showed increased biodegradation rates.

Functional PEAs. Polyacids. Katsarava and Chu [15, 16] synthesized functional *co*-PEAs containing a variable amount of lateral carboxyl groups, applying di-TosOH salt of L-lysine benzyl ester as a comonomer. The goal *co*-PEAs were obtained by selective catalytic hydrogenolysis (debenzylation) of benzyl ester prepolymer using Pd catalyst. Free lateral COOH groups can be used for numerous chemical transformations and *co*-PEAs are suitable drug carriers that will be discussed below. It has to be noted that lysine has parallel orientation (Figure 5.2), whereas other amino acids' orientation is adirectional, that is, in whole α-AAs' orientation in this types of polymers is mixed.

Polycations. Arginine-based TAADs are tetra-*TosOH* salts that act as bifunctional nucleophilic monomer (via two α-amino groups). This allows to synthesize the linear and soluble polycationic PEAs (Figure 5.9) by AP of L-arginine-based TAADs with di-*p*-nitrophenyl esters of α,ω-alkylenedicarboxylic acids [33–35].

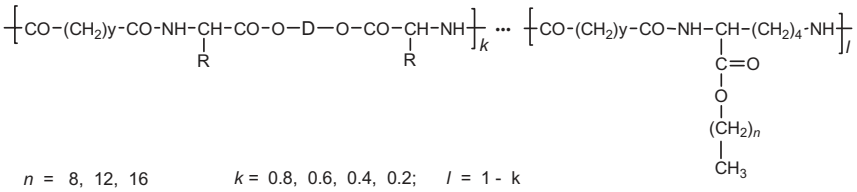
The arginine-based PEA composed of succinic acid and 1,3-propanediol (the less hydrophobic one among the PEAs obtained) was water soluble at room temperature. Very recently Memanishvili *et al*. [35] obtained arginine-based poly(ether ester amide)s, PEEAs, and poly(ether ester urethane)s, PEEURs, and poly(ether ester



k = 1.0, 0.8, 0.6; *l* = 1 - k

R = $CH_2CH(CH_3)_2$, $CH_2C_6H_5$; D = $(CH_2)_4$, $(CH_2)_6$, $(CH_2)_8$; y = 4, 8.

Figure 5.10 Epoxy-PEAs on the basis of *trans*-epoxy-succinic acid.



n = 8, 12, 16 *k* = 0.8, 0.6, 0.4, 0.2; *l* = 1 - k

R = $CH_2CH(CH_3)_2$, $CH_2C_6H_5$; D = $(CH_2)_6$; y = 4, 8.

Figure 5.11 Brush-like PEAs containing long-chain *n*-alkyl substituents.

urea)s, PEEUs, having polyethylene glycol like polymeric backbones and showing enhanced water solubility as compared with the said arginine-based PEAs.

Biodegradable cationic PEAs were also obtained [57] by covalent conjugation to PEA-polyacids with arginine methyl ester and agmatine.

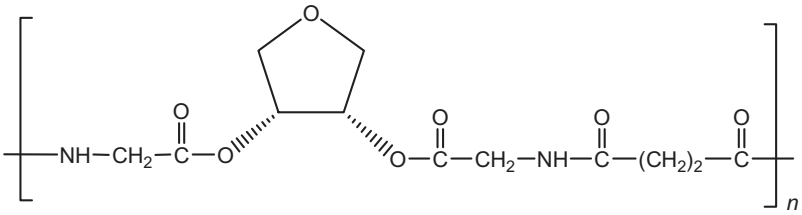
Unsaturated PEAs. One of the most convenient and universal ways to render biodegradable polymers functional is the incorporation of unsaturated double bonds in the polymeric backbones [58]. Unsaturated PEAs (UPEAs) containing a variable amount of double bonds in the backbones were obtained by Katsarava, Chu, and coworkers [19, 27–30, 45] using TAADs on the basis of 1,4-butendiol, or DAD based on fumaric acid as monomers/comonomers in combination with saturated TAADs and DADs.

The unsaturated double bonds can be subjected to various chemical and photochemical transformations.

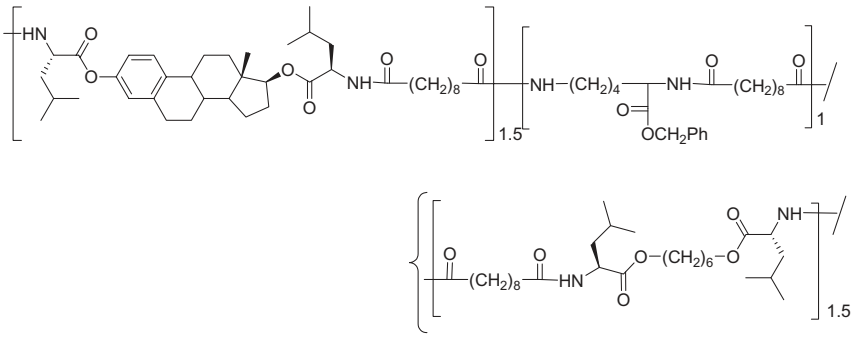
Epoxy-PEAs. Very recently Katsarava, Tugushi, and coworkers [20, 46] have synthesized a new class of functional biodegradable polymers – epoxy-PEAs – using active di-*p*-nitrophenyl ester of *trans*-epoxy-succinic acid as a monomer, or comonomer in combination with DADs containing α,ω-alkylenedicarboxylic acids in AP with TAADs. They have the structure given in Figure 5.10.

The epoxy groups of PEAs can be subjected to various chemical transformations under mild conditions, as well as thermal or chemical curing.

Brush-like PEAs. PEAs with a brush-like architecture containing long-chain alkyl substituents were obtained by Katsarava and coworkers [59] using L-lysine *n*-alkyl esters as comonomer in a mixture with TAADs in AP with DADs. They have the structure shown in Figure 5.11.



Scheme 5.7 Water-soluble PEAs on the basis of 1,4-anhydroerythritol, glycine, and succinic acid.



Scheme 5.8 Biodegradable polymeric drug composed of 17β-estradiol, 1,6-hexanediol, L-leucine, L-lysine benzyl ester, and sebacic acid.

These PEAs are suitable for constructing devices with sustained/controlled release in which a drug is attached to the macromolecules via hydrophobic forces.

Hydroxyl-containing and water-soluble PEAs. PEAs containing free OH groups were obtained by Gomurashvili *et al.* [60] by AP of TAADs composed of unsubstituted α-AA glycine and glycerol with di-*p*-nitrophenyl esters of succinic, glutaric, adipic, and diglycolic acids. Depending on the synthetic strategy used, three types of hydroxyl-containing polymers were synthesized: PEAs with pending primary hydroxyls, with pending secondary hydroxyls, or a copolymer containing both primary and secondary glycerol hydroxyls (not shown here). PEAs composed of short aliphatic diacids such as succinic, glutaric, and diglycolic acids are water soluble.

Water-soluble PEAs, having the structure given in Scheme 5.7, were also obtained by AP of TAAD composed of 1,4-anhydroerythritol and glycine with di-*p*-nitrophenyl succinate [60].

Polymeric drugs. The strategy of the synthesis of AABBPs allows constructing biodegradable polymeric drugs. For example, therapeutic copolymers composed of sebacic acid, L-leucine, 1,6-hexanediol, 17β-estradiol, and L-lysine benzyl ester (M_w up to 82,000 Da) was obtained by Gomurashvili *et al.* [61] via AP of di-*p*-nitrophenyl sebacate with three comonomers – two TAADs composed of L-leucine/1,6-hexanediol and L-leucine/17β-estradiol, and di-*p*-toluensulfonic acid salt of L-lysine benzyl ester, Scheme 5.8.

5.2.3.2 Poly(ester urethane)s

Regular PEURs. This class of AABBPs was synthesized for the first time by Katsarava and coworkers [52] by AP of TAADs with DBCs as discussed above.

These polymers, like the regular PEAs above, have only two terminal functional groups and are considered nonfunctional.

Functional PEURs. PEURs containing a variable amount of lateral carboxyl (COOH) groups were obtained by Katsarava and Chu [16] similar to PEAs discussed above. The only difference consists in the use of DBCs instead of DADs in AP with α-AAs-based comonomers for synthesizing benzyl ester prepolymer.

5.2.3.3 Poly(ester urea)s

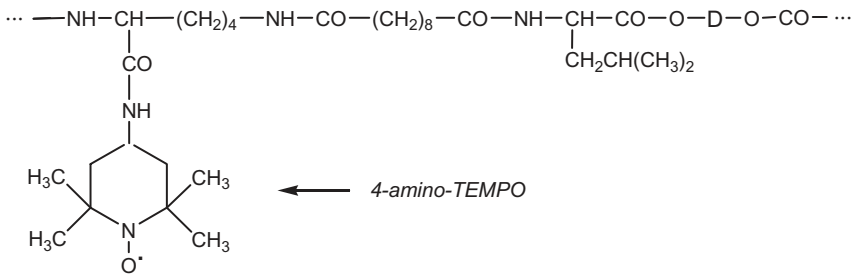
Historically PEUs were the first examples of AABBPs synthesized by Huang and coworkers [4] by interaction of bis-(L-phenylalanine)-1,2-ethylene diester as free base (separated from corresponding di-*TosOH* salt) with aromatic diisocyanates. As a result, low-molecular-weight powdery PEUs were obtained. The main cause of low-molecular-weight polymers presumably is a high tendency of alkyl esters of α-AAs to enter into various undesirable self-condensation reactions [62] with the formation of diketopiperazines and other cyclic and linear unidentified products. This leads to imbalance of stoichiometry and contributes to the limitation of chain growth. In spite of this, Huang's study initiated a rational synthesis of a large variety of key monomers – TAADs – and showed the suitability of the incorporation of enzyme-specific α-AAs and ester bonds into macro-chains for constructing biodegradable biomaterials.

The synthesis of PEUs by AP of TAADs with ACs in DMA solution was carried out by Katsarava and coworkers [52]. However, recently Katsarava *et al*. [53] have found that high-molecular-weight PEUs having excellent material properties could be synthesized via IP of TAAD with phosgene or triphosgene using a two-phase system chloroform/water+Na_2CO_3 similar to Figure 5.5. These results are quite contrary to the synthesis of PEAs and PEURs above where the synthesis of high-molecular-weight polymers on the basis of short-chain DDCs or BCFs is problematic. This is because in the synthesis of PEAs and PEURs, the hydrolysis of bis-electrophiles – DDCs and BCFs – generates mono-functional impurities that cause the termination of the chain growth, whereas in case of phosgene no mono-functional compound is formed since it hydrolyses with the liberation of CO_2 and HCl.

5.2.3.4 Transformation of AABBPs

All the AABBPs containing lateral functional groups can be subjected to various chemical transformations that modify their properties, for chemical attachment of drugs, bioactive substances, etc.

Free COOH groups in polyacids containing L-lysine residues can be used for chemical modification with condensing agents. For example, 4-amino-2,2,6,6-tetramethyl-piperidinyloxy free radical (4-amino-TEMPO) was covalently attached to functional *co*-PEA (Scheme 5.9) using carbonyldiimidazole (Im_2CO) as a condensing agent [15–17, 61].



Scheme 5.9 Functional *co*-PEA containing covalently attached 4-amino-TEMPO.

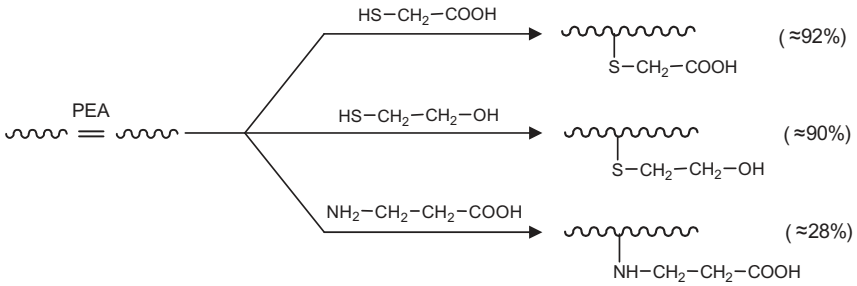


Figure 5.12 Chemical transformations of fumaric acid based UPEA.

The covalent attachment of mono-ethanolamine to these polymers increases their hydrophilicity and water solubility (depending on mole portion of lysine residue in the polymers backbones). The obtained polyols can be used for further transformations, for example, to obtain chemically and photochemically active polymers by attaching unsaturated acids like acrylic, methacrylic, etc. [63, 64].

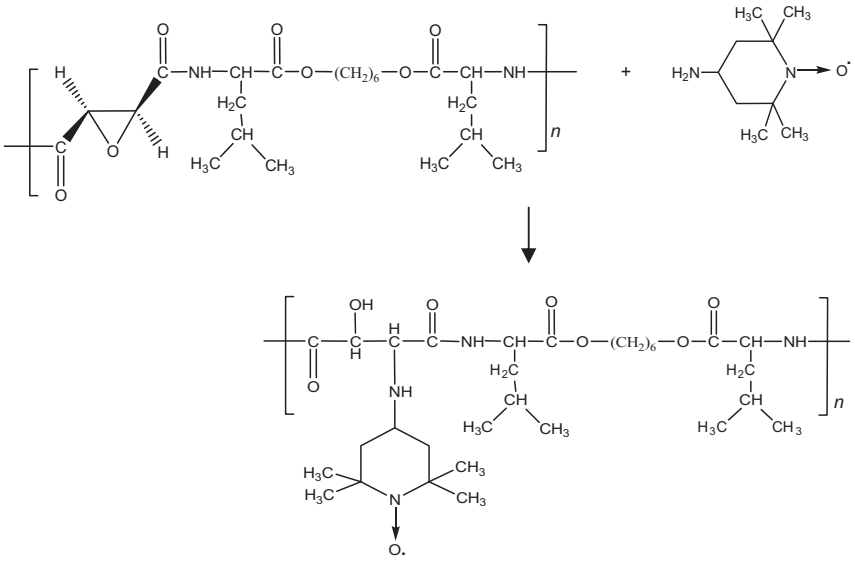
UPEAs, containing active double bonds of fumaric acid's residue can be functionalized by their interaction under mild conditions with thiol- and amino-compounds [19] as is shown in Figure 5.12.

As one can conclude, the thio-compounds are far more active in these transformations.

The epoxy-PEAs given in Figure 5.10 contain activated (by two adjacent electron-withdrawing carbonyl groups) oxirane cycles and interact under mild conditions (DMA, 20–60 °C) with various compounds of both nucleophilic and electrophilic nature [20].

Due to the high activity of epoxy-PEAs, they can be considered as "ready for use" carriers – in contrast to polyacids above, because they interact with 4-amino-TEMPO in DMA solution at 60 °C without using condensing agent, as shown in Scheme 5.10.

Both UPEAs and epoxy-PEAs are also subjected to chemical, thermal and photochemical curing that allows one to regulate their properties, for example, to increase mechanical characteristics and decrease biodegradation rate.



Scheme 5.10 Covalent attachment of 4-amino-TEMPO to epoxy-PEA.

5.2.4 Properties of AABBPs

5.2.4.1 MWs, Thermal, Mechanical Properties, and Solubility

All the AABBPs obtained via AP [14] have high molecular weights (M_w = 24,000–180,000 Da, GPC) and narrow polydispersity (1.20–1.81).

DSC study of AABBPs showed that these polymers have a wide range of glass transition temperature (T_g from 5 °C to 102 °C), some of them (PEAs and PEUs) are semicrystalline with T_m = 103–153 °C [14, 53]. It was shown that T_g of the polymers can be increased by incorporating rigid fragments into macrochains such are dianhydrohexitols [25, 26] or aromatic diacid-1,3-bis(4-carboxyphenoxy)propane [61].

The chemical structure affects the mechanical properties of AABBPs, which varies in a wide range: tensile strength from 15–20 (PEURs and some PEAs) to 80–100 MPa (PEUs and some PEAs), elongation at break from 8–100 (PEUs and some PEAs) to 800–1000% (PEURs and some PEAs), Young's modulus up to 2–6 GPa (PEUs and some PEAs).

The AABBPs are soluble in common organic solvents such as DMF, THF, methylene chloride, chloroform, some of them in dioxane, acetone, and ethanol. The low melting temperatures and solubility of AABBPs in common solvents substantially facilitate their processing into different shapes.

5.2.4.2 Biodegradation of AABBPs

Katsarava, Chu *et al.* studied *in vitro* biodegradation of AABBPs under the conditions close to physiological (t = 37 °C and pH 7.4) using both potentiometric

titration (PT) [14, 24, 52, 65] and weight loss (WL) [66]. Among the synthesized AABBPs, the PEAs are the most studied polymers for both *in vitro* and *in vivo* biodegradation.

Titration is a facile and fast method to assess the tendency of polymers to hydrolytic degradation, especially for the polymers with labile ester linkages that provide rather high rates of chain scission. During ester hydrolysis generated COOH groups will be neutralized automatically by an alkaline solution, which consumption profile represents the kinetic curve of biodegradation.

This method has an advantage over WL because gravimetric measurements at early stage of biodegradation (the first 1–3 h, the time normally used for short-term assessment) are complicated due to the water absorption, particularly for those polymers having high water affinity [66].

A systematic *in vitro* biodegradation study of regular PEAs using PT method was carried out in the presence of hydrolases: trypsin, α-chymotrypsin, and lipase [65]. The spontaneous immobilization (absorption) of key enzymes from buffer solutions onto the PEA film surfaces was observed. The surface-immobilized enzymes extend the erosion of polymer and also catalyze the hydrolysis of both low- (ATEE) and high-molecular-weight (protein) external substrates. It is found that the enzyme surface absorption is reversible by nature. A kinetic method for a quantitative determination of the enzyme desorbed from the film surface was developed. The enzymes could also be impregnated into the PEAs to make them "self-destructive" at a target rate. A comparison of the PEAs and polylactide (PDLLA) *in vitro* biodegradation data showed that PEAs exhibited a higher tendency toward enzyme-catalyzed biodegradation than PDLLA.

For complete understanding of the PEA biodegradation phenomena, it would require the data from WL method, particularly in the late stage for slowly degrading biomaterials.

A systematic *in vitro* WL study of PEAs was carried out in the presence of hydrolases such as α-chymotrypsin, lipase, and a complex of proteases of Papaya [65]. The last enzyme was used for modeling the catalytic action of nonspecific proteases. It was found that the PEAs, in the presence of enzyme solutions, were biodegraded by surface erosion mechanism (close to the zero order kinetics) without compromising bulk properties: no change of polymer molecular weight and polydispersity was observed. The WL method also confirmed the catalytic action of the spontaneously immobilized enzymes and the effectiveness of impregnated enzymes, making polymers "self-destructive" at a target rate. The erosion rates of the PEAs were studied in the enzyme-catalyzed three cases: enzyme in solution, surface immobilized enzyme, and impregnated enzyme. The results ranged from 10^{-3} to 10^{-1} mg/cm^2/h, and are comparable with the erosion rates of polyanhydrides [67], the fastest biodegradable polymers. The WL also demonstrated that PEAs exhibited a higher tendency toward enzyme-catalyzed biodegradation than PDLLA.

The analysis of biodegradation products showed that the hydrolases mediated biodegradation of PEAs takes place preferentially by cleaving the ester bonds in the polymeric backbones. *N,N′*-adipoyl-bis-L-phenylalanine was separated as one of the main products of biodegradation of PEAs composed of adipic acid, phenylalanine, and 1,4-butanediol (PEA **4F4**) [66].

Based on the ^{1}H NMR study, Puiggali *et al.* [10] also concluded that the hydrolytic degradation of PEA composed of sebacic acid, L-alanine, and 1,2-dodecanediol (PEA **8A12** obtained by IP) takes place in the ester bonds and amide groups remain unchanged.

Nagata [13] also studied the enzymatic degradation of PEAs stereopolymers derived from L- and D-alanine, using proteolytic enzymes (proteinase-K, papain, and α-chymotrypsin), and lipase, and also confirmed that the degradation of PEAs with this group of hydrolases proceeds via the hydrolysis of the ester linkages and amide groups remain unchanged. The *in vitro* biodegradation mechanism of PEAs predominately via ester bonds hydrolysis was also suggested by Saotome *et al.* [6].

It has to be noted that the biodegradation rate as well as mechanical and physical–chemical properties of AABBPs can be manipulated in the widest range not only by changing their stereochemical composition (i.e., using L- and D-isomers of one α-AA [10, 13]) but also by preparing copolymers with two or more α-AAs [7, 19, 66], two or more dicarboxylic acids [19, 28]. An alternative way to tailor the properties of AABBPs lies in blending the polymers [18]. The blending of AABBPs of various classes looks possible as well because high affinity of macromolecules can guarantee their compatibility.

A preliminary *in vivo* biodegradation study of selected PEA (**4F4**) films in rats, with and without impregnated lipase [66], showed that PEAs impregnated with lipase were completely absorbed within 1–2 months, or within 3–6 months for the lipase-free samples. These findings prompt to suggest that new PEAs may have a great potential for designing drug-sustained/controlled release devices as well as implantable surgical devices.

5.2.4.3 Biocompatibility of AABBPs

Among AABBPs, only few PEAs were studied for biocompatibility. For example, the PEA composed of adipic acid, L-phenylalanine, and 1,4-butanediol (PEA **4F4**) supported the growth of human osteosarcoma and fibroblasts cells and showed the material to be biocompatible (Y. Shved and R. Katsarava, unpublished results). Aqueous solutions of model biodegradation products – *N,N′*-adipoyl-bis-L-phenylalanine and 1,4-butanediol – at 1:1 mol ratio were subcutaneously injected to rats. No acute or chronic toxicity was observed [68]. LD_{50} could not be determined since it was higher than 1500-fold excess (6 g/kg) of an average therapeutic dose, confirming high biocompatibility of the PEA and its biodegradation products.

Elastomeric functional *co*-PEA on the basis of sebacic acid (1.00 mol), TAAD composed of L-leucine and 1,6-hexanediol (0.75 mol), and L-lysine (0.25 mol) [*co*-PEA **8(L6)$_{0.75}$K$_{0.25}$**] [15, 16] showed excellent blood and tissue compatibility in both *in vitro* [69] and *in vivo* (pigs) [70] tests. The same *co*-PEA selectively supported the *in vitro* growth of epithelial cells [69]. The *in vivo* biocompatibility was tested in porcine coronary arteries, comparing the polymer-coated stents with bare metal stents in 10 pigs [70]. All animals survived till sacrificed 28 days later. Prior to sacrifice, angiography revealed identical diameter stenosis in both groups. Histology confirmed similar injury scores, inflammatory reaction, and area stenosis.

These results support the notion that polymer has a high potential for cardiovascular applications [71].

Recently Yamanouchi *et al.* [34] reported that the arginine-based PEAs showed good cell compatibility over a wide range of dosages and had minimal adverse effects on the cell morphology, viability, and apoptosis. Very recently, Memanishvili *et al.* [35] showed that arginine-based PEEAs, PEEURs, and PEEUs, having PEG-type polymeric backbones, possess higher cell compatibility than the said arginine-based PEAs.

The above-mentioned biological studies of several biodegradable AABBPs indicate that this family of biodegradable polymers is biocompatible. However, these studies are rather sporadic and comprise mostly the assessment of biocompatibility. So far there is no systematic study of biocompatibility and/or tissue regeneration potential. In particular, there is no relevant data about tissue regeneration mechanisms and the influence of factors like chemical composition and biodegradation rate that determines discharging of degradation products into surrounding environment that can activate macrophages to produce cell growth factors, mediators, and so forth, for accelerated wound healing [72, 73]. Therefore, for wide practical applications of this very promising family of biodegradable polymers, it is indispensable to carry out a comprehensive study of the interaction of AABBPs of various chemical compositions with living organism to assess their biocompatibility (including immune response), and tissue regeneration capability.

5.2.5
Some Applications of AABBPs

Selected representatives of PEAs were used for constructing biodegradable hydrogels, nanoformulations, drug-eluting devises and coatings, and so forth.

Chu and Guo used the UPEAs for obtaining hybrid hydrogels through photochemical conjugation with either PEG diacrylate [30] or polysaccharides containing unsaturated double bonds (e.g., methacryloyl dextrane) [29]. The biodegradable hybrid hydrogels are promising for many biomedical and pharmaceutical applications, such as drug delivery systems and tissue engineering and so forth.

Legashvili *et al.* [31] used brush-like *co*-PEAs (Figure 5.11) to obtain molecular complexes with PEGs that are promising as nanocarriers of drugs.

Yamanouchi *et al.* [34] evaluated complexation of a novel family of synthetic biodegradable L-arginine-based PEAs (Figure 5.9) with DNA, for their capability to transfect rat vascular smooth muscle cells, a major cell type participating in vascular diseases. Arg-PEAs showed high binding capacity toward plasmid DNA. The binding activity was inversely correlated to the number of methylene groups in the diol segment of Arg-PEAs. All Arg-PEAs transfected smooth muscle cells with an efficiency that was comparable to the commercial transfection reagent Superfect. However, unlike Superfect, Arg-PEAs, after a wide range of dosages, had minimal adverse effects on cell morphology, viability, and apoptosis. The authors demonstrated that Arg-PEAs were able to deliver DNA into nearly 100% of cells under optimal polymer-to-DNA weight ratios, and the high level of delivery

was achieved through an active endocytosis mechanism. A large portion of DNA delivered, however, was trapped in acidic endocytotic compartments, and subsequently was not expressed. These results suggest that with further modification to enhance their endosome escape, Arg-PEAs can be attractive candidates for nonviral gene carriers owning to their high cellular uptake nature and reliable cellular biocompatibility.

Katsarava *et al*. [18] used PEA and their blends for constructing various medical biocomposites. One of them, registered as "PhagoBioDerm" in Republic of Georgia and is produced as elastic films, represents novel wound-dressing device (artificial skin). Product consists of lytic bacteriophages, antibiotics, pain killer, and proteolytic enzymes. PhagoBioDerm showed an excellent therapeutic effect in the management of infected wounds and ulcers (of both trophic and diabetic origin) [74] and in the complex treatment of infected local radiation injuries caused by the exposure to ^{90}Sr [75].

Recently, Katsarava *et al*. [76] have developed bactericidal wound dressing that represents an alcohol solution of biodegradable *co*-PEA containing silver sulfadiazine and other antimicrobials. The preparation sprayed onto the wound forms a thin, elastic, and transparent film that accelerates healing of superficial wounds, ulcers, and burns.

The functional biodegradable *co*-PEAs $\mathbf{8(L6)_{0,75}K_{0,25}}$ with covalently attached 4-aminoTEMPO (Scheme 5.9) revealed high elastic properties and excellent adhesion to stainless steel, and is being used as vascular stent coating. Currently the polymer-coated stents are under clinical trials[1)]. The results of this study suggest that the polymer is biocompatible and should not elicit an inflammatory reaction. Therefore, MediVas LLC (San Diego, CA) uses the biodegradable *co*-PEAs as bioactive wound dressings [77], wound care polymer compositions [78], vaccine delivery compositions [79], polymer particle delivery compositions [80], delivery of ophthalmologic agents to the exterior or interior of the eye [81], therapeutic polymers [82], and so forth.

5.2.6
AABBPs versus Biodegradable Polyesters

Here in brief are listed some advantageous properties of AABBPs over aliphatic PEs like polyglycolic and poly(lactic acids), their copolymers, poly(caprolactone), and so forth:

- polycondensation synthesis without using any toxic catalyst;
- higher hydrophilicity and, hence, better compatibility with tissues;
- longer shelf-life;
- a wide range of desirable mechanical properties at lower molecular weights;

1) Medivas' polymer technology was licensed to DSM Biomedical, http://www.dsm.com/en_US/html/dbm/homepage.htm.

- a variable hydrophobicity/hydrophilicity balance suitable for constructing drug-sustained/controlled release devices;
- an erosive mechanism and *in vitro* biodegradation rates ranged from 10^{-3} to 10^{-1} mg/(cm^2 h) that can be regulated by impregnating enzymes;
- fusibility (<150 °C) and solubility in common organic solvents (ethanol, THF, chloroform, methylene chloride, etc.) and ease of processing into different forms and shapes; and
- excellent adhesion to plastic, metallic, and glass surfaces that is important for their use as coatings.

5.3 Conclusion and Perspectives

The concise review highlights how dimerized and polyfunctional forms of naturally occurring α-AAs are suitable building blocks for constructing new bioanalogous macromolecular systems with non-natural orientation of α-AAs' residues in the polymeric backbones. This nonconventional architecture of polymer chain is expected to provide low immunogenicity of α-AAs-based polymeric biomaterials by "confusing nature." For practical biomedical applications as biodegradable biomaterials, the most promising are polymers containing hydrolysable ester bonds in the backbones called as amino acid based biodegradable polymers (AABBPs). There are various classes of high-molecular-weight AABBPs: PEAs, PEURs, and PEUs obtained with α-AAs and other nontoxic building blocks such as fatty diols, dicarboxylic acids, α-Has, and carbonic acid. The selection of appropriate building blocks under optimal polycondensation methods allows the synthesis of AABBPs with tailored material properties. Listed AABBPs contain H-bond-forming chemical units that enhance their mechanical characteristics, hydrophilicity, and biocompatibility. The AABBPs exhibit some obvious advantages over existing and commercially successful aliphatic PEs: polyglycolic and poly(lactic acids), their copolymers, poly(caprolactone), and so forth.

The most extensively studied AABBPs to date are PEAs because of ample availability, low cost of starting monomers, and desirable material properties that can be tailored in a wide range. PEAs have been successfully tested, for example, as medicated wound dressing, also, in animals and humans for cardiovascular applications. *Ex vivo* cell-based assays have strongly supported recent human trial data indicating that PEAs are blood and tissue compatible, with advantageous properties for implantation into tissue. Tremendous value that PEAs have in the health science and industry is the mechanism by which they degrade, and drug release profile. PEAs' biodegradation and mechanism of drug release is believed to proceed by surface erosion and primarily follows zero-order kinetics. These unique material properties have shown PEAs' multiuse potential as a new family of biodegradable biomaterials as drug delivery platforms or as components of resorbable surgical implants.

Other AABBPs – PEURs and PEUs – also have potential for numerous biomedical applications. However, for wider applications of these polymers, as well as for expanding scopes of PEAs' applications, it is important to carry out a comprehensive study on the whole family of AABBPs, to determine how they interact with living organism, to assess their biocompatibility (including immune response), and tissue regeneration capability. This study has to answer the question "are high biocompatibility, toxicological safety, and accelerated tissue regeneration inherent characteristics of AABBPs?"

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6
Biodegradable Polyurethanes and Poly(ester amide)s

Alfonso Rodríguez-Galán, Lourdes Franco, and Jordi Puiggalí

Abbreviations

BDI	1,4-buthylenediisocyanate
BDO	1,4-butanediol
DSC	differential scanning calorimetry
DMSO	dimethyl sulfoxide
DMPA	dimethylol propionic acid
DUD	diurethanediol
DMTA	dynamic mechanical thermal analysis
EM	electron microscopy
ED	ethylene diamine
H12MDI	dicyclohexylmethane diisocyanate
HS	hard segment
HDI	1,6-hexamethylene diisocyanate
IR	infrared spectroscopy
IPDI	isophorone diisocyanate
LDI	lysin methyl ester diisocyanate
MDI	diphenylmethane diisocyanate
NMR	nuclear magnetic resonance
PCL	polycaprolactone
PCUs	polycarbonate-based polyurethanes
PDA	propanediamine
PDMO	poly(decamethylene glycol)
PEAs	poly(ester amide)s
PEEA	poly(ether ester amide)
PEO	poly(ethylene glycol)
PEUs	polyester-based polyurethanes
PHMO	poly(hexamethylene glycol)
POMO	poly(octamethylene glycol)
PTMO	polytetramethylene oxide glycol
PURs	polyurethanes
SAXS	small-angle X-ray scattering

Handbook of Biodegradable Polymers: Synthesis, Characterization and Applications, First Edition. Edited by Andreas Lendlein, Adam Sisson.

TMDI trimethylhexamethylene diisocyanate
WAXD wide-angle X-ray diffraction

6.1 Chemistry and Properties of Biodegradable Polyurethanes

Polyurethanes (PURs) were first used for industrial applications in the 1940s, but the development of biocompatible polymers did not start until the 1960s. PURs have since then remained one of the most popular groups of biomaterials employed in medical devices. Toughness, durability, biocompatibility, and biostability are some of the characteristics that make PURs interesting for a wide variety of long-term implantable devices. However, the number of applications requiring biodegradability instead of biostability is on the rise, and consequently also the demand for new PURs with a controlled degradation rate.

Biodegradable PURs employed as thermoplastics are basically synthesized using a diisocyanate, a diol, and a chain-extension agent as main raw components [1, 2] (Tables 6.1–6.3, Figure 6.1). Although both aromatic and aliphatic diisocyanates have an applied interest, it should be pointed out that the putative carcinogenic nature of aromatic compounds [3, 4] is leading to an increasing use of HDI, BDI, and LDI, whose ultimate degradation products are more likely to be nontoxic (e.g., lysine).

The diol component commonly chosen is a low-molecular-weight polymer with hydroxyl end groups and a backbone that, in the case of biodegradable PURs, may correspond to a polyether, polyester, or polycarbonate [5]. The first gave rise to the

Table 6.1 Diisocyanate raw materials.

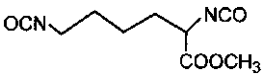
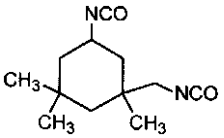
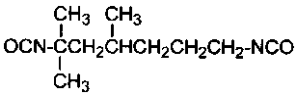
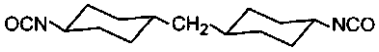
OCN–$CH_2CH_2CH_2CH_2CH_2CH_2$–NCO ***1,6-Hexamethylene diisocyanate (HDI)***	 ***Lysine methyl ester diisocyanate (LDI)***
OCN–$CH_2CH_2CH_2CH_2$–NCO ***1,4-Butylenediisocyanate (BDI)***	 ***Isophorone diisocyanate (IPDI)***
 ***trans-1,4-Cyclohexylene diisocyanate***	 ***2,2,4-Trimethylhexamethylene diisocyanate (TMDI)***
 ***Dicyclohexylmethane diisocyanate (H12MDI)***	

Table 6.2 Macrodiol raw materials.

Polyether-based PURs		Polyesther-based PURs	
Poly(ethylene glycol), PEO	$HO[(CH_2)_2O]_nH$	***Polyglycolide***	$HO[CH_2COO]_n–R–[OOCCH_2]_mOH$
Poly(tetramethylene glycol), PTMO	$HO[(CH_2)_4O]_nH$	***Poly(D,L-lactide)***	$HO[CH_2COO]_n\text{-}R\text{-}[OOCCH_2]_mOH$ $HO[CHCOO]_n\text{-}R\text{-}[OOCCH]_mOH$ (CH$_3$ on each)
Poly(hexamethylene glycol), PHMO	$HO[(CH_2)_6O]_nH$	***Poly(ε-caprolactone)***	$HO[(CH_2)_5COO]_n–R–[OOC(CH_2)_5]_mOH$
Poly(octamethylene glycol), POMO	$HO[(CH_2)_8O]_nH$		
Poly(decamethylene glycol), PDMO	$HO[(CH_2)_{10}O]_nH$	***Poly(ethylene adipate)*** m = 2 ***Poly(propylene adipate)*** m = 3 ***Poly(butylene adipate)*** m = 4	$HO[(CH_2)_mOOC(CH_2)_4COO]_nH$

Table 6.3 Chain extender raw materials.

Diols		Diamines	
Ethylene glycol	$HOCH_2CH_2OH$	***Ethylene diamine (ED)***	$H_2NCH_2CH_2NH_2$
1,4-Butanediol (BDO)	$HOCH_2CH_2CH_2CH_2OH$	***1,3-Propanediamine (1,3-PDA)***	$H_2NCH_2CH_2CH_2NH_2$
1,3-Butanediol	$HOCH_2CH_2CHCH_3$ (OH)	***1,2-Propanediamine (1,2-PDA)***	$H_2NCH_2CHCH_3$ (NH_2)
2,2-Dimethyl-propanediol	$HOCH_2C(CH_3)_2CH_2OH$	***1,4-Butanediamine***	$H_2NCH_2CH_2CH_2CH_2NH_2$
$HOCH_2$–(cyclohexane)–CH_2OH		$PhCH_2CHNH_2CO–OCH_2$–(cyclohexane)–$CH_2O–OCCHNH_2CH_2Ph$	
1,4-Cyclohexanedimethanol		***1,4-Cyclohexanedimethanol-L-phenylalanine diester***	

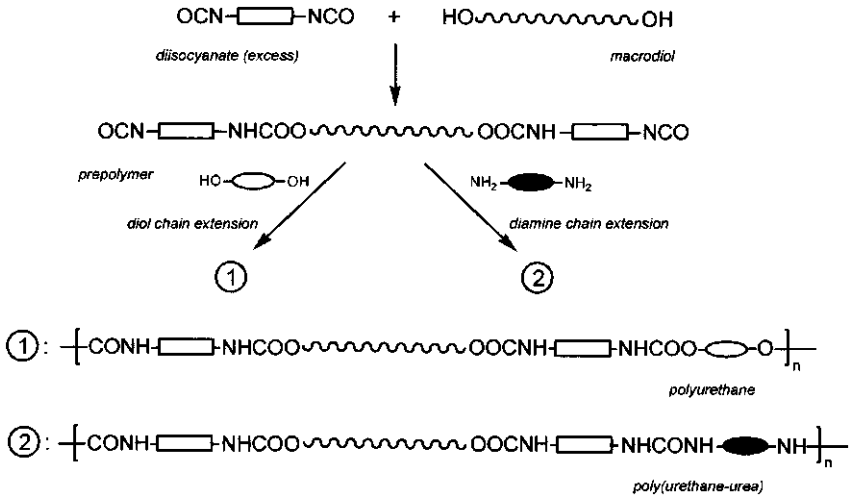
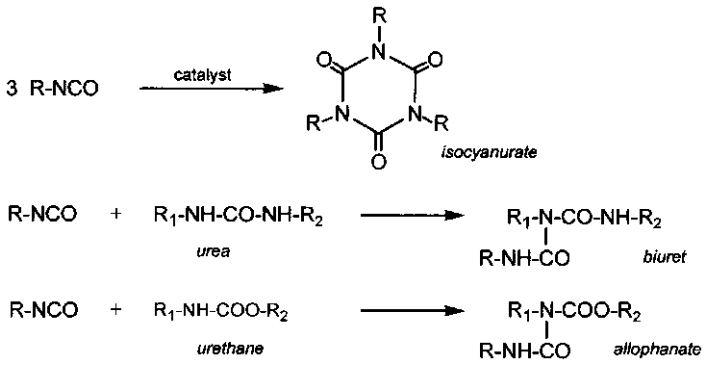


Figure 6.1 Schematic representation showing the two steps involved in the synthesis of segmented polyurethanes.

so-called polyether-based urethanes, which have been the most common so far. Nevertheless, in recent years polyester-based PURs have begun to be developed due to their increased biodegradability. Selected macrodiols are all viscous liquids with a number average molecular weight ranging between 400 and 5000 g/mol. Polyester diols can be prepared by ring-opening polymerization of a cyclic lactone [6] or condensation between a dicarboxylic acid and an excess of a diol. In some cases, the polyester diol, which is characterized by a hydrophobic character, is mixed with the more hydrophilic polyethylene glycol (PEG) before performing the reaction with the corresponding diisocyanate. This way, PURs with an increased biodegradation rate and enhanced cell attachment can be obtained. Note that these characteristics can be easily tailored by a simple change in the composition of the mixture [7].

The reaction between the diol and the diisocyanate is carried out with an excess of the latter (keeping the isocyanate/hydroxyl molar ratio usually close to 2:1) in order to obtain a reactive prepolymer with isocyanate end groups. Catalysts (typically tertiary amines, stannous octoate, or dibutyltin dilaurate) and high temperatures (60–90 °C) are required to increase the reaction rate. A thermoplastic PUR material characterized by a segmented architecture is finally obtained by reaction of the terminal isocyanate groups with a chain extender (Figure 6.1) which may be either a diol or a diamine with low molecular weight [8]. In the first case, urethane bonds are formed and the final polymer is usually thermally processable, whereas in the second case new urea bonds are formed and the resulting poly(urethane/urea) is usually only suitable for solvent casting.

Some secondary reactions, which generally result in branched or cross-linked polymers, can also occur under certain conditions [9]. The most usual are



Scheme 6.1 Characteristic secondary reactions observed in the synthesis of polyurethanes.

(Scheme 6.1) (i) trimerization of isocyanate groups leading to isocyanurates, (ii) formation of biuret linkages from urea groups, and (iii) formation of allophanate units by reaction between an isocyanate group and the NH of a urethane group. This last reaction may sometimes be of interest since mechanical properties can be improved by a small number of crosslinking bonds. A great advantage is that the allophanate formation reaction is thermally reversible, and so it is feasible to obtain thermally processable materials.

From an industrial point of view, PUR synthesis can be performed in a single step by mixing all reagents or following the above two-step methodology [8–10]. In the first case, bulk polymerization can be carried out by a single batch procedure or by a semicontinuous process using reactive extruders or injection-molding machines. The two-step procedure has two main advantages: (i) the polymer architecture can be well controlled, and (ii) polymers with a heterogeneous composition, which are obtained when nonpolar macrodiols are involved, can be avoided. This synthesis can be accomplished in bulk or in solvents (typically *N*,*N*-dimethylacetamide and *N*,*N*-dimethylformamide) [11] although the latter option is commercially less attractive.

The mechanical properties of segmented PURs are highly interesting due to the microphase separation (Figure 6.2a) of their two constitutive segments [12]: nonpolar soft segments and more polar hard segments derived from the diisocyanate and the chain extender. The soft microdomain is amorphous and often has a glass transition temperature lower than 0 °C, resulting in rubber characteristics like extensibility and softness. In contrast, hard segments can crystallize as a consequence of the strong hydrogen-bond intermolecular interactions that can be established between their urethane or urea groups. These ordered domains act as physical crosslinks providing cohesive strength to the polymer matrix and allowing the material to resist flow when stress is applied. Segmented PURs can be considered thermoplastic elastomers since physical crosslinks can be easily disrupted by heating the polymer above the melting temperature of hard segment domains or by dissolving the material in aprotic solvents like dimethylformamide.

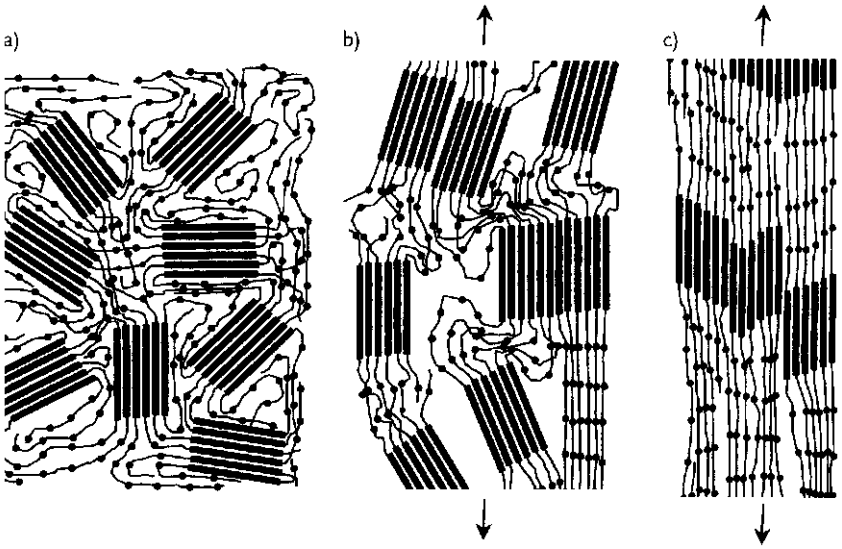
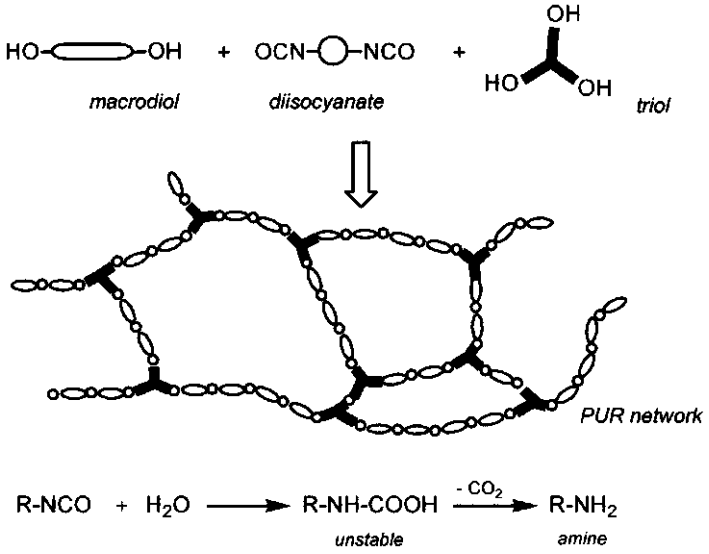


Figure 6.2 Representation of the characteristic microphase separation in a segmented polyurethane (a) and the influence of stretching into orientation and crystallization of microdomains (b, c). Moderate (b) and high extension (c) are represented. The thick strokes represent hard segments and the thin strokes soft segments.

Thermoset PURs can be prepared by inducing chemical crosslinks, either in the hard segment or the soft segment, or both. The resulting material has greater strength and durability, and worse phase separation. Crosslinking is achieved by using intermediates with a functionality higher than two (e.g., trimethylolpropane, glycerol, and 1,2,6-hexanetriol) (Scheme 6.2). These networks can have rigid or flexible characteristics, mainly depending on the density of chemical crosslinks, and may give rise to biodegradable foams useful for many applications such as scaffolds [13–15]. In fact, the reaction of water with an isocyanate group leads to the formation of carbon dioxide gas, which can be used as a blowing agent in the creation of pores.

Several factors must be considered when designing PUR materials with targeted properties [16]: (i) harder and stiffer polymers with higher tear strength and lower elongation at break can be prepared by increasing the chain extender to diol ratio and/or decreasing the molecular weight of the macrodiol unit; (ii) diamine chain extenders lead to hard segments with higher melting temperature and harder mechanical properties; (iii) aromatic diisocyanates increase chain stiffness and facilitate aggregation of the hard phase by π-electron association; and (iv) variation in the number of substitutions and spacing between and within branch chains affects the flexibility of molecular chains. The knowledge of the hard segment content is thus an easy way to predict mechanical properties of PURs: soft material (HS < 15 wt%), rubbery elastomer (15 wt% < HS< 40 wt%), tough elastomer (40% < HS < 65 wt%), and strong engineering polymer (HS > 65 wt%) [17].



Scheme 6.2 Synthesis of PURs' networks and reaction conducing to CO_2 as blowing agent.

Indeed, understanding the morphology is crucial for the design of materials with specific properties. Molecular organization of PURs has been investigated by several techniques, including differential scanning calorimetry (DSC), wide-angle X-ray diffraction (WAXD), small-angle X-ray scattering (SAXS), infrared spectroscopy (IR), electron microscopy (EM), dynamic mechanical thermal analysis (DMTA), and nuclear magnetic resonance (NMR) [18].

DSC experiments show that PURs have several thermal transitions, the interpretation of which is rather complex [19]. Glass transitions of both hard and soft amorphous microphases can be detected. The T_g value of the soft domain, which appears at the lowest temperature, may be used to evaluate the number of hard segments in this domain since T_g should increase when the degree of mixing is raised. However, a quantitative analysis is problematic due to the influence of factors like restrictions on the motion of soft segments caused by the presence of microcrystals. In addition, DSC traces can show multiple endothermic peaks which may be ascribed to morphological effects and be broadly divided into loss of long- and short-range order.

Early explanations about these multiple endotherms were based on the disruption of different kinds of hydrogen-bonding interactions [20, 21]. However, infrared thermal analysis led to discarding a clear relationship between endothermic peaks and these interactions [22]. Hydrogen bonding plays a significant role in the design of biostable or biodegradable materials as it is a determinant factor of their hydrolytic stability. Susceptibility to hydrolytic degradation is clearly enhanced when the carbonyl groups in the hydrolyzable group do not act as hydrogen-bond acceptors. The knowledge of hydrogen-bond distribution in PUR materials is thus essential to obtain materials with a specific degradation rate.

Molecular ordering crystallization may be favored by subjecting a PUR chain to stress [23]. Thus, at a moderate extension (e.g., 250%) macrodiols of the soft segment become partially aligned and crystallized. When the extension is increased, further crystallization occurs and hard segments turn into the direction of elongation and form paracrystalline layer lattice crystals (Figure 6.2).

6.2 Biodegradation Mechanisms of Polyurethanes

Susceptibility of PURs to biodegradation is an inherent feature of their chemistry [24, 25]. It was detected by the industrial manufacturing community before systematic biodegradation studies were conducted in the 1980s. In fact, degradation of PURs may initiate during fabrication due to high temperatures, the presence of liquids, and the difficulty to completely remove moisture from the reaction mixture [26].

Microorganisms can be easily grown in appropriate cellular media following well-established technologies that allow using enzymes segregated outside cells, even in industrial applications. Biodegradation is governed by organism type, polymer characteristics, and the pretreatment performed on the sample. During degradation, the polymer is first converted into its monomers, which should then be mineralized. It is clear that polymers are too large to pass through cell membranes, so they must first be depolymerized into smaller compounds which may then be absorbed and biodegraded within microbial cells [27] (Figure 6.3). Complete mineralization can thus be achieved, the end products being biomass, CO_2, and water when aerobic microorganisms are involved, plus CH_4 when anaerobic

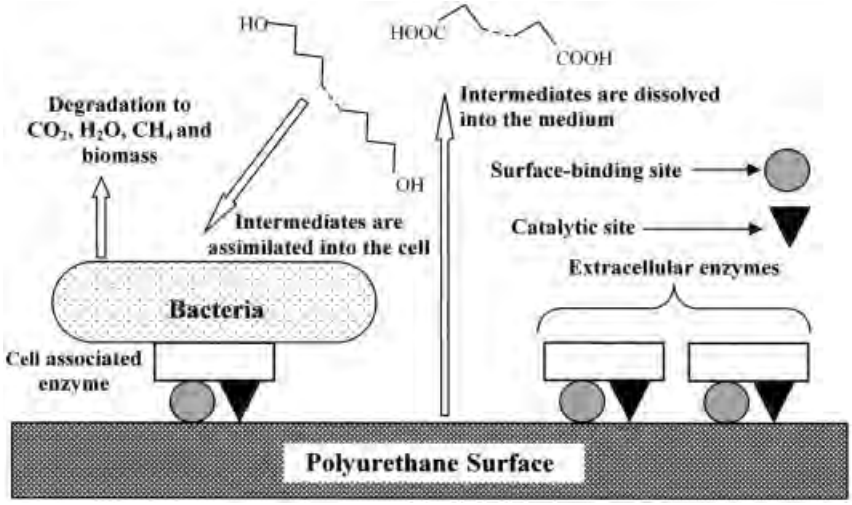


Figure 6.3 Proposed model for the degradation of PURs by the action of a cell-associated enzyme and extracellular enzymes.

conditions are used [28]. Degradation processes can be roughly classified into those involving urethane bonds and those involving the macrodiol units of both polyester and polyether types [24].

It is well known that low-molecular-weight urethanes may be easily degraded by some microorganisms, hydrolysis being catalyzed by enzymes with an estearase activity [29]. Although cleavage of urethane bonds has also been reported for polymers [30], it is not clear whether these bonds were hydrolyzed directly or after a first degradation step, resulting in lower molecular weight compounds.

Degradation of polyester-based PURs by microorganisms mainly occurs by hydrolysis of their ester bonds. It has been stated that aliphatic polyesters used in the synthesis of PURs (e.g., polyethylene adipate or poly(caprolactone)) are easily degraded by microorganisms or estereolytic enzymes like lipase [31]. It has also been reported that PURs prepared from high-molecular-weight polyesters degrade faster than those prepared from low-molecular weight polyesters [32].

Experiments show that a large variety of fungi can be highly effective in degrading PURs [32, 33]. Systematic studies on the effects of fungi are relatively scarce but point to a remarkable influence of the specific diisocyanate used in the synthesis, as well as an improvement of resistance to degradation by the presence of side chains in the polyester segment. In general, degradation by fungi requires the addition of several nutrients such as gelatin. A degradation mechanism of polyester PURs, based on extracellular estearases, has been proposed: a synergic effect is obtained by random action throughout the polymer chain of endoenzymes and successive monomer scission from the chain ends by exoenzymes [34].

Both Gram-positive and Gram-negative bacteria have been reported as PUR degraders, although few detailed works have been performed until now. Kay *et al.* [35] investigated the ability of 16 kinds of bacteria to degrade polyester PURs following their burial in soil for 28 days. In all cases, IR led to determining that the ester segments were the main site of attack because of the hydrolytic cleavage of the ester bonds. The bacterial attack usually proceeded by the binding of cells to the polymer surface with subsequent floc formation and degradation of the substrate to metabolites. Estearase and/or protease activities were identified and two kinds of enzymes were observed: (i) a cell-associated membrane bound polyurethanase and (ii) an extracellular polyurethanase [36] (Figure 6.3). The former provides cell-mediated access to the hydrophobic polymer surface, and must consequently be characterized by both a surface-binding domain and a catalytic domain. Note that enzyme molecules can easily attack water-soluble substrates, resulting in a high degradation rate. However, when the substrate is insoluble, it seems necessary to improve the contact between the enzyme and the substrate by means of a binding domain. Adherence of the bacteria enzyme to the polymer substrate must be followed by hydrolysis to soluble compounds, which will then be metabolized by the cell. This mechanism would decrease competition between degrading bacteria and other cells, as well as allowing adequate access to metabolites. The soluble extracellular enzymes should stick on the polymer surface and also hydrolyze the polymer into smaller units, facilitating the metabolization of soluble products and providing easy access of enzymes to the partially degraded polymer.

Studies on the dependence of the degrading activity upon enzyme concentration indicate that activity increased to a saturation value that remained constant when an excess of the enzyme was present [29]. This observation contrasts with the decrease in activity reported for depolymerases with a similar two-domain structure (e.g., polyhydroxyalkanoate depolymerase) [37]. It has been suggested that both domains of polyurethanases are either located in three-dimensionally close positions or separated by a flexible linker. In the former case, the catalytic domain can access the polymer substrate even if the surface is saturated with the maximum number of enzymes molecules per unit surface. It might be possible to obtain new solid polyester degrading enzymes by adding new binding domains to estearases, which are ineffective in solid substrate degradation.

Unlike polyester derivatives, polyether-based PURs are quite resistant to degradation by microorganisms [32]. *Sthaphylococcus epidermidis* was reported to degrade some kinds of polyether derivatives although the degradation rate was very slow. This feature was interpreted according to a degradation mechanism involving an exo-type depolymerization that differed from the endo-type depolymerization typical of polyester-based PURs [38]. Despite this, polyether urethane materials are known to be susceptible to a degradative phenomenon involving crack formation and propagation, which is considered environmental stress cracking [39]. This seems to be the result of a residual polymer surface stress introduced during fabrication and not sufficiently reduced by subsequent annealing.

6.3 Applications of Biodegradable Polyurethanes

Nowadays PURs play a dominant role in the design of medical devices with excellent performance in life-saving areas. PURs are highly interesting for internal (*in vivo*) uses, particularly for short-term applications like catheters or long-term applications like implants. External (*in vitro*) uses like controlled drug delivery systems must also be considered. Biodegradable properties are only required for some of their biomedical applications.

6.3.1 Scaffolds

Degradation characteristics are of special interest for design of scaffolds for *in vivo* tissue engineering. The advantages of these devices lie in that they do not have to be removed surgically once they are no longer needed, and that problems such as stress shielding may be avoided by adapting the degradation rate to the specific application. Scaffolds can be prepared by a wide range of well-established techniques such as salt leaching/freeze drying, thermally induced phase separation, and even electrospinning. Features like suitable mechanical properties, overall porosity, pore size, and interconnectivity are basic to develop materials for scaffold applications. Thus, literature data indicate that a correct cell in-growth requires a

pore size of about 150–350 μm, and that minimum interconnecting openings should be larger than 10–12 μm in order to facilitate the transport of nutrients and cellular waste products, as well cell diffusion in the scaffold [40]. In general, the design of degradable devices for reconstruction must meet several biological and mechanical criteria, such as (i) high initial strength to prevent mechanical failure of the implant prior to tissue in-growth; (ii) a moderate degradation rate to induce in-growth of organized tissue since rapid degradation may cause failure of host tissue, whereas stress yielding may occur if the degradation rate is too slow, and (iii) good blood compatibility. It is worth noting that in segmented PURs, surface composition varies due to the mobility of soft segments and the trend to minimize interfacial free energy. Thus, the interface should be enriched of polar hard segments when the environment is polar (e.g., blood or water) and of nonpolar soft segments when the environment is nonpolar (e.g., air or vacuum). This is important because the host response is strongly influenced by the surface composition of the material [41].

6.3.1.1 Cardiovascular Applications

Soft-tissue engineering requires elastic scaffolds as these can be adapted to mechanical conditions during tissue development. Thus, scaffolds for cardiovascular tissue engineering should have high elongation at break and high tensile strength. These properties can be achieved using, for example, segmented PURs derived from macrodiols such as PCL and PCL-*b*-PEO-*b*-PCL, a diisocyanate like BDI or LDI and a chain extender like 1,4-butanediamine (putrescine) [42]. The last compound, which forms during polymer degradation, is essential for cell growth and differentiation. *In vivo* studies have revealed the promising applications of PUR scaffolds [43].

6.3.1.2 Musculoskeletal Applications

Common uses of PURs in musculoskeletal tissue regeneration include (i) anterior cruciate ligament reconstruction. PURs prepared from MDI, 1,3-PDA, and a poly(caprolactone) diol of a M_n molecular weight of 530 have been found suitable since they exhibit high tensile strength, a high modulus, and retention of mechanical properties when degraded adequately to the time required for the application [16, 44]. (ii) Meniscal and fibrocartilage reconstruction. In this case, high shear stresses to which prostheses are exposed, and consequently problems associated with stress hysteresis, must be born in mind. Some examples of PUR materials are those prepared from 1,4-*trans*-cyclohexane diisocyanate, a poly(caprolactone) macrodiol and a mixture of ciclohexanedimethanol and glycerol, which act as chain extenders [45]. (iii) Bone-tissue engineering. Scaffolds are prepared with an aliphatic diisocyanate (BDI or LDI), a polyethylene oxide macrodiol, and a diurea diol chain extender synthesized by coupling two equivalents of tyrosine or tyramine with one equivalent of BDI. The aromatic rings of tyrosine or tyramine units increase the rigidity of the hard segment; furthermore, these units favor *in vitro* attachment and proliferation of viable human osteoblast-like cells [46].

6.3.1.3 Neurological Applications

Once the nervous system is impaired, recovery is difficult and malfunctions in other parts of the body may occur. In order to increase the prospects of axonal regeneration and functional recovery, research has focused on the design of "nerve guidance channels" or "nerve conduits," which can be made using a biodegradable and porous channel wall. A biodegradable PUR based on hexamethylene diisocyanate, poly(ε-caprolactone), and dianhydro-D-sorbitol has been used to prepare tubular scaffolds by extrusion of the polymer solution in dimethyl formamide into a water-coagulation bath [47]. The implants had an uniaxially oriented pore structure with a pore size ranging between 2 (the pore wall) and $75 \times 700\,\mu m$ (elongated pores in the implant lumen), whereas the skin of tubular implants remained nonporous. *In vivo* results suggest that these scaffolds support peripheral nerve regeneration.

6.3.2 Drug Delivery Systems

Smooth delivery of a consistent dosage over time can be achieved by combining an active ingredient with a carefully developed and selected polymer. Oral and transdermal patches are the preferred routes of delivery for both the pharmaceutical industry and patients. However, the possibilities of nanotechnology should also be considered as smaller doses can be used and higher levels of bioavailability are reached. Furthermore, nanoparticles have proved capable of crossing blood barriers easily.

PURs are receiving attention as new polymer matrices for drug delivery since they allow direct link between drugs and polymers and encapsulation into micro- or nanoparticles, as shown in the following representative examples:

- Sivak *et al.* [48] developed a biodegradable and biocompatible PUR drug delivery system based on lysine diisocyanate and glycerol for controlled release of 7-*tert*-butyldimethylsilyl-10-hydroxy-camptothecin. This special type of anticancer agent was covalently bonded to the polymer matrix to improve its efficiency. Ghosh *et al.* reported the synthesis and release characteristics of a novel PEG-based PUR bearing covalently bonded ibuprofen, an anti-inflammatory drug. Ibuprofen was first reacted with butane diol diglycidyl ether, and the PUR was then obtained by reaction with 2,4-toluidene diisocyanate [49]. Antibacterial agents have also been incorporated into PURs in an effort to address bacterial infection associated with the use of medical devices. Thus, Woot *et al.* [50] synthesized a novel biodegradable polymer using 1,6-hexane diisocyanate, poly(caprolactone) diol and a fluoroquinolone antibiotic, that is, ciprofloxacin.
- Campos *et al.* reported the development of PUR-based microparticles prepared by emulsion polymerization using a poly(caprolactone) macrodiol and poly(propylene glycol)-tolylene 2,4-diisocyanate terminated or poly(propylene oxide)-based tri-isocyanated prepolymers [51]. The microparticles had a spherical shape and smooth surface.

- The encapsulation of organic liquids in PUR nanocapsules prepared by interfacial miniemulsion polycondensation of isophorone diisocyanate and propanetriol has also been reported [52]. Encapsulation efficiency was found to be dependent on the water solubility, interfacial tension against water, and compatibility with PUR of the liquids.

6.3.3
Other Biomedical Applications

Bone cements and hydrogels are other examples of biomedical applications where biodegradable PURs have a promising future. Guelcher *et al.* [53] studied biodegradable PURs as an alternative to acrylic bone cements. New PUR networks have been prepared by two-component reactive liquid molding of low-viscosity prepolymers derived from lysine polyisocyanates (lysine methyl ester diisocyanate and lysine triisocyanate) and poly(3-caprolactone-*co*-DL-lactide-*co*-glycolide) triols.

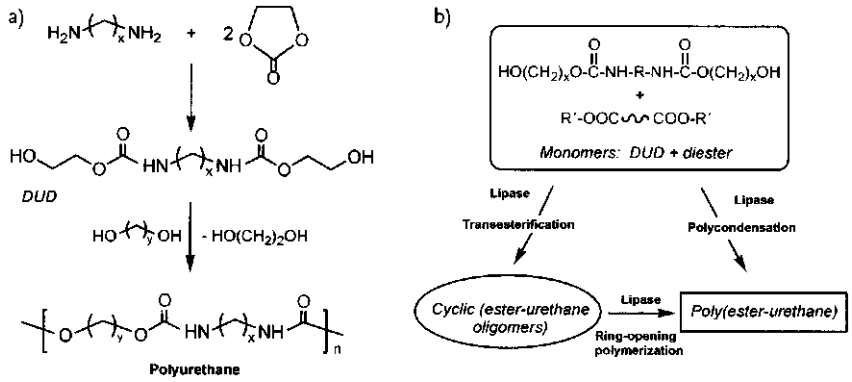
Loh *et al.* developed thermoresponsive multiblock poly(ester urethane)s synthesized from poly(ε-caprolactone), PEG, and poly(propylene glycol) using 1,6-hexamethlyene diisocyanate (HDI) as a coupling agent [54]. Bulk hydrophilicity of the obtained copolymers could be controlled either by adjusting the composition of the copolymer or by changing the temperature of the environment. These materials give rise to a hydrogel-like material without using toxic crosslinking agents. Furthermore, films of these samples are thermoresponsive since they form highly swollen hydrogel-like materials when soaked in cold water and shrink when soaked in warm water, these changes being reversible.

6.4
New Polymerization Trends to Obtain Degradable Polyurethanes

New synthetic routes are currently being studied to obtain green and sustainable PURs [55]. New polymers should avoid diisocyanate reactants, improve chemical recyclability, and enhance biodegradability while keeping high-performance properties of typical PURs.

6.4.1
Polyurethanes Obtained without Using Diisocynates

Several approaches can be considered although none has been used at an industrial level. The first representative example is the reaction between a cyclic carbonate and an amine rendering the urethane bond. In particular, the polyaddition reaction between L-lysine and a bifunctional five-membered cyclic carbonate in the presence of a strong base was described by Kihara *et al.* [56]. An alternative route (Scheme 6.3a) was reported by Rokicki *et al.* [57], who obtained PURs by reaction of ethylene carbonate with 1,6-hexanediamine or 1,4-butanediamine at room temperature and without any catalyst, the authors obtained a diurethanediol



Scheme 6.3 (a) Synthesis of polyurethanes from cyclic carbonates. (b) Enzymatic synthesis of polyester-based polyurethanes by direct polymerization and cyclization with subsequent ring-opening polymerization.

(DUD) which was polycondensated with α,ω-diols containing six or more carbon atoms and rendered samples with M_n molecular weights between 1600 and 3500. The process required the presence of tin catalysts, such as $Bu_2Sn(OCH_3)_2$ or Bu_2SnO, to prevent thermal decomposition of the urethane group.

Other authors have prepared PURs with a regular sequence by ring-opening polymerization of cyclic trimethylene urethane and tetramethylene urethane at 100 °C [58]. A more recent route was developed by Schmitz *et al.* [59], who studied the copolymerization of equimolar amounts of 2,2-dimethyltrimethylene carbonate and tetramethylene urea. The obtained copolymers had microstructures that were strongly dependent on reaction conditions and the catalyst used.

6.4.2
Enzymatic Synthesis of Polyurethanes

Enzymes have remarkable characteristics compared with conventional chemist catalysts, like high catalyst activity, stereoselectivity, and lack of side reactions. Furthermore, enzymes are interesting as a renewable and naturally occurring catalyst. Because enzymatic polymerization can be considered the reverse reaction of degradation, polyester-based PEUs obtained using a biological catalyst are expected to be biodegraded by the same enzyme.

Many authors have reported the enzymatic synthesis of PEUs by enzymatic polyesterification [55]. Thus, lipase has been employed to promote the esterification reaction between a low-molecular-weight DUD and various diacids/diesters. Two strategies can be applied (Scheme 6.3b): (i) direct polycondensation of the DUD and the appropriate diester, and (ii) ring-opening polymerization of a cyclic ester–urethane oligomer which has been previously prepared by a lipase-induced transesterification reaction between a biodegradable DUD and a diester. The latter method gives higher molecular weights.

Soeda *et al.* [60] prepared polyester PURs by both enzymatic polycondensation of the DUD with the diethylester of a dicarboxylic acid and enzymatic cyclization and subsequent ring-opening polymerization of the cyclic ester–urethane monomer. Molecular weights and polymer yields increased with increasing temperature and the number of methylene groups of the dicarboxilate moiety (malonate, succinate, glutarate, and adipate). This PEU showed chemical recyclability.

McCabe and Taylor [61] proposed an enzymatic synthesis using also a DUD and a mixture of diol and dicarboxylic acid monomers. Thus, bis(hydroxyethyl)carbamate was dissolved in 1,4-butanediol (BDO) and reacted with adipic acid using lipase as catalyst under reduced pressure to render a polymer with a M_w molecular weight of 9350.

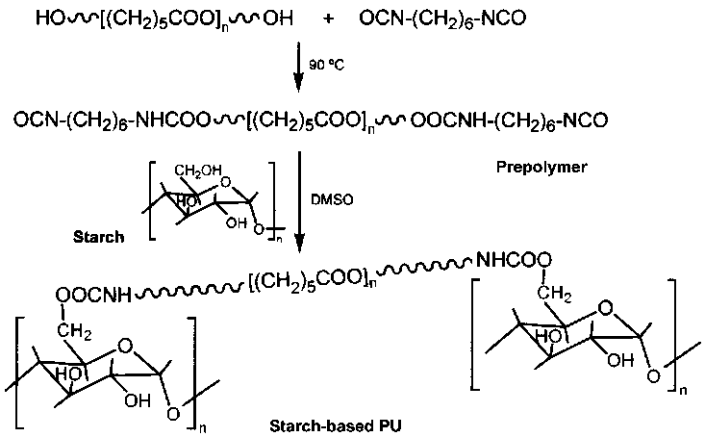
Although the carbonate bond is more resistant to hydrolysis against alkaline media than the ester linkage, polycarbonate-based PURs (PCUs) can also be degraded by enzymes. An enzymatically biodegradable PCU has been synthesized by reaction of a low-molecular-weight DUD with diethyl carbonate in the presence of *Candida antarctica* lipase [55].

6.4.3
Polyurethanes from Vegetable Oils

PURs can also be prepared with polyols derived from vegetable oils such as castor oil, soybean oil, palm oil, and rapeseed oil, which are most commonly employed for large-scale products [62]. The obtained PURs are ideal for foam applications when the hydroxyl functionality of the polyol is higher than two. It is also desirable that the molecular weight of the polyol ranges between 3000 and 6000. PURs from vegetable oils have some advantages derived from their good oxidative thermal stability. For example, soybean oil-based polyisocyanurate foams have been reported to exhibit better thermal stability, lower flammability, greater rigidity (modulus), and higher compression strength than those based on propylene oxide polyols of the same molecular weight and functionality. Furthermore, these PURs are assumed to be biodegradable since this is a characteristic of vegetable oils. Shogren *et al.* [63] studied the degradation of polymers prepared from soybean oil, triolein, and linsed oil by respirometry. Rapid degradation of a small fraction of PURs and a trend toward less degradation as the polyol functionality increased (linsed < soy < triolein) were observed, although differences were small. However, it is also clear that the hydrophobic character of fatty acid chains may reduce susceptibility to hydrolysis.

6.4.4
Polyurethanes from Sugars

Polysaccharides (e.g., starch, cellulose, chitin, or chitosan) are naturally occurring polymers obtained from renewable sources which tend to degrade in biologically active environments like soil, sewage, and marine locations where bacteria are active. Much effort has been made to develop PURs based on the above biopolymers as an increase in biodegradability is expected to be achieved.



Scheme 6.4 Synthesis of starch-based polyurethanes.

Starch, which is the second largest biomass on earth, and synthetic plastics do not mix easily. This problem can be overcome by chemically linking the synthetic and the natural polymer. Barikani and Mohammadia [64] used the hydroxyl functionality of the biopolymer and grafted a prepolymer derived from HDI and a PCL macrodiol onto starch (Scheme 6.4). SEM micrographs confirmed that the starch granules were completely coated by PUR.

It was found that larger amounts of prepolymer led to an increase in hydrophobicity and a decrease in glass transition temperature.

Current research is aimed at combining natural products containing cellulose with different materials like plastics to obtain new materials that can be tailored according to final use requirements. Since 1998, new biocomposite wood-replacement panels made from wheat straw and a PUR resin have been commercialized by Dow Polyurethanes [65]. The resulting biocomposite material can be used for kitchen counters, shelving, ready-to-assemble furniture, cabinets, door cores, and floor underlays.

Chitin, which is widely distributed in nature mainly as the skeletal material of crustaceans, is structurally similar to cellulose as it has an acetamide group in place of a hydroxyl group. Chitin-based PUR elastomers with potential as biomedical implants and tunable mechanical properties have been synthesized by step-growth polymerization techniques using PCL and MDI [66]. The prepolymer was extended with different mass ratios of chitin and BDO. The mechanical properties of these polymers were improved by increasing chitin content, which furthermore lowered the cytotoxicity of samples.

Chitosan, commercially produced by deacetylation of chitin, has several applications in the biomedical field (e.g., in bandages and other hemostatic agents). A number of graft and block PUR derivatives have been investigated: (i) PUR prepolymers prepared from PEG and isophorone diisocyanate have been successfully grafted onto chitosan [67]; (ii) Xu *et al.* described a novel blood-compatible water-

borne PUR using chitosan as the chain extender. The prepolymer was obtained from poly(tetramethylene oxide glycol) (PTMO), isophorone diisocyanate (IPDI), and 2,2'-dimethylol propionic acid (DMPA) [68]. The authors concluded that the addition of chitosan lends a remarkable anticoagulative character to the final polymer.

6.5 Aliphatic Poly(ester amide)s: A Family of Biodegradable Thermoplastics with Interest as New Biomaterials

Poly(ester amide)s (PEAs) have been regarded as a new promising family of biodegradable polymers since the 1990s, although the first syntheses were reported in 1979 when a polyamide (i.e., nylon 6) and a polyester (i.e., poly(caprolactone)) were subjected to amide–ester interchange reactions induced by temperature [69]. PEAs can combine a degradable character due to the existence of hydrolyzable ester groups (–COO–) with relatively good thermal and mechanical properties afforded by strong intermolecular hydrogen-bonding interactions established between their amide groups (–NHCO–). Initially, the main interest was the technical potential of PEAs due to their good fiber-forming properties and ease of processability. Indeed, the degradable characteristics and low cost of raw materials made the commercialization of a random polymer derived from 1,4-butanediol, adipic acid, and ε-caprolactam as a commodity material feasible (BAK 1095) [70]. PEAs are currently being intensively investigated as a new class of promising materials for biomedical applications such as those mentioned above for PURs.

PEAs can be synthesized by different chemical methods which allow polymers with segmented, random, and regular distributions to be obtained.

Segmented PEAs are basically similar to those described for PURs, that is, they may have a microphase separated structure with amide-rich hard domains acting as physical crosslinkers and ester-rich soft domains, which confer flexibility and extensibility upon the polymer. Bera *et al.* [71] reported the synthesis of segmented PEAs by reaction of an alternating ester–amide oligomer with an oligoester prepared from 1,2-ethanediol and dimethyl adipate. The ester–amide compound was obtained by reaction of adipic acid with a bisamide-diol derived from 1,6-diaminohexane and γ-butyrolactone. By decreasing the oligoester soft block content from 80 to 20 mol%, the modulus increased from 70 to 600 MPa and the yield stress increased from 70 to 600 MPa. *In vivo* assays have revealed both nontoxicity and biodegradability characteristics. Direct polycondensation of bisamide-diols with aliphatic diols and dimethyl adipate has also been extensively studied (Figure 6.4a). Stapert *et al.* [72] prepared PEAs by reaction of dimethyl adipate, 1,4-butanediol, and a bisamide-diol derived from 1,4-diaminobutane and ε-caprolactone. The mechanical properties of final samples were easily tuned by changing the molar ratio of the two diols. Thus, the elastic modulus varied from 70 to 524 MPa when the hard segment content was increased from 10% to 85%. *In vitro* and *in vivo* assays performed with such polymers indicated good

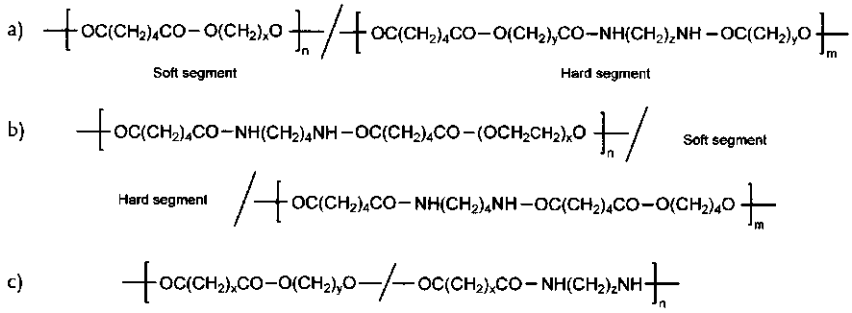


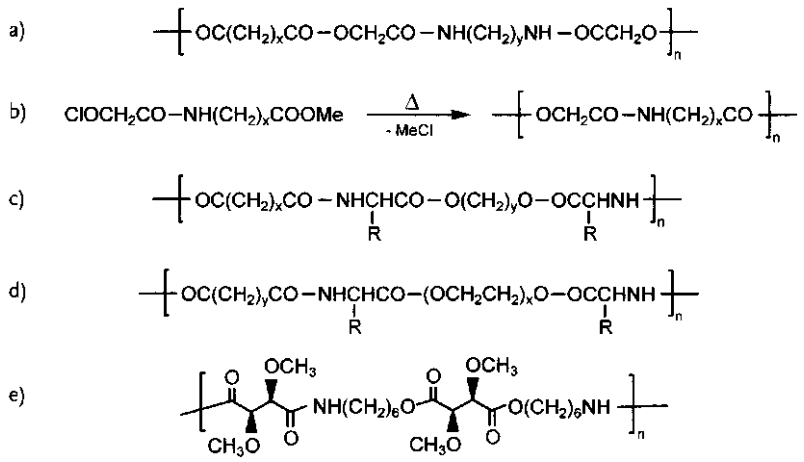
Figure 6.4 Representative segmented and random poly(ester amide)s.

biocompatibility and a relatively slow degradation rate. Additionally, it has been demonstrated that closed-cell foams of these materials can be obtained using CO_2 as a blowing agent [73]. Poly(ether ester amide) (PEEA) copolymers based on PEG, 1,4-butanediol, and dimethyl-7,12-diaza-6,13-dione-1,18-octadecanedioate [74] (Figure 6.4b) have also been evaluated as scaffold materials for tissue engineering and have proved to sustain adhesion and growth of endothelial cells.

Random PEAs can be easily obtained by a two-step procedure firstly described by Castaldo *et al.* [75] (Figure 6.4c). In this work, an oligoester mixture was prepared by reaction of a diol (1,6-hexanediol, 1,10-decanediol, or 1,12-dodecanediol) with an excess of sebacoyl dichloride. Oligoesters and the excess of dichloride were then reacted with a stoichiometric amount of the appropriate diamine (1,6-hexanediamine, 1,10-decanediamine, 1,12-dodecanediamine). Thermal properties turned out to be strongly dependent on the final amide ratio, as also found for polymers based on adipic acid, 1,6-hexanediamine, and 1,4-butanediol. PEAs related to nylons 6 or 66 and poly(caprolactone) have also been studied and their enzymatic degradation has been demonstrated [76, 77].

PEAs with a regular microstructure can be obtained by using different kinds of monomers. Thus, polymers differing in the arrangement of amide and ester groups within their molecular chain can be derived. Obviously, the amide/methylene ratio may also be easily varied depending on the methylene content of the involved monomers. These materials are generally crystalline and render oriented fiber X-ray diffraction patterns as well as single-crystal electron diffraction patterns. Analysis of their structure has shown a complex unit cell arrangement which reflects the packing preferences of amide and ester groups [78]. Biodegradable PEAs with a regular structure can be classified on the basis of their main representative chemical units:

- Derivatives of α-amino acids and α-hydroxy acids (polydepsipeptides). They can combine useful properties of poly(α-hydroxy acid)s and poly(α-amino acids)s and are considered as particularly attractive reabsorbable materials. Polymers can be prepared by ring-opening polymerization of morpholine-2,5-diones. However, the synthesis of these monomers is complex and polymerization usually requires severe reaction conditions resulting in unexpected by-products from side reactions. This, together with the usual low molecular



Scheme 6.5 Representative regular poly(ester amide)s.

weight of samples, hinders the use of such polymers in the biomedical field, where material purity becomes essential.

- Derivatives of α-hydroxy acids. Alternating PEAs with potential interest as bioabsorbable sutures have been obtained by solution polymerization of an acid dichloride such as succinyl dichloride with a bisamide-diol prepared from glycolic acid and diaminoalkanes containing 2–12 methylene groups (Scheme 6.5a). Their mechanical properties, degradability, and biocompatibility have been evaluated and results are highly promising [79, 80]. A different synthetic route based on the formation of metal halide salts as the driving force of a thermal polycondensation reaction has recently been proposed [81]. This method has also been successfully applied to prepare alternating copolymers of glycolic acid and ω-amino acids (Scheme 6.5b).

- Derivatives of α-amino acids. Polymers derived from naturally occurring units should be preferred for biomedical applications since degradation products are nontoxic and easily metabolized by the organism. For this reason, poly(α-amino acids) were polyamides extensively studied as an interesting alternative but were finally discarded due to inherent problems like production costs, insolubility in common organic solvents, thermal instability, and processing difficulties. In contrast, PEAs incorporating α-amino acid units have been developed and extensively studied [82, 83] (Scheme 6.5c). They can be obtained by interfacial polymerization of an acid dichloride and the *p*-toluensulfonic salt of a bis-(α-amino acid) α,ω-alkylene diester [84, 85]. Alternatively, thermal polyesterification between a diol and a bisamide diester derived from acid dichloride and α-amino acid methyl ester units has been proposed [86]. This kind of polymers has proved to be biodegradable, biocompatible, and with the mechanical, thermal, and degradation properties that may be tuned by changing the methylene/amide ratio. Moreover, the enzymatic degradation rate has been found to be easily modified by the stereochemical composition of the

polymer (i.e., the ratio between L- and D-amino acid units) [87]. Some of these polymers have been studied as matrices in the form of microspheres for drug delivery systems [88]. Similar PEAs have also been prepared by using an unsaturated dicarboxylic acid or an oligomer derived from an α-amino acid and oligoethylen glycol [89] (Scheme 6.5d).

- Carbohydrate derivatives. Carbohydrates like arabinose, xylose, and tartaric acid [90] have been reacted with amino alcohols to render new PEAs whose degradation properties were investigated [90] (Scheme 6.5e). The same procedure has been extended to succinic and glutaric acid derivatives [91, 92]. Polymers can be directional or adirectional depending on the synthesis procedure. The hydrolytic degradation rate has proved to be strongly influenced by chain microstructure since formation of amide rings can accelerate the process.

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