In: Biodegradable Polymers: Processing, Degradation… ISBN: 978-1-61209-534-9
Editor: Gary P. Felton

Chapter 4

BIODEGRADABLE POLY (ESTER AMIDE) S: SYNTHESIS AND APPLICATIONS

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ABSTRACT

Nowadays, there is an increasing demand for biodegradable polymers that can be used as specialties, for example in the biomedical field, and even as commodities. In general, combination of adequate polymer material properties, easy thermal processing, low price and biodegradability are some desirable characteristics that should be fulfilled and that require a great scientific effort. Synthesis of newly designed polymers, use of natural monomers and chemical modification of conventional polymers are suitable strategies that have been applied to meet the indicated goals.

Poly(ester amide)s (PEAs) have been developed as promising biodegradable materials since they combine a degradable character caused by the existence of hydrolizable ester groups (-COO-) in their backbone with relatively good thermal and mechanical properties afforded by the strong intermolecular hydrogen bonding interactions established between their amide groups (-NHCO-). Currently, a considerable body of literature exists about PEAs and a systematization concerning synthesis, properties and applications appears highly necessary.

PEAs can be classified according to their microstructure (e.g. random, segmented and sequential) and their components, which in addition may lead to different dispositions between their amide and ester groups. Synthesis strategies (e.g. ring opening polymerization and polycondensation) will be discussed as well as the properties of the main families (e.g. α-amino acid, α-hydroxy acid, α,ω-aminoalcohol and carbohydrate based PEAs). Special attention will be given to biomedical applications of PEAs which mainly concern to drug delivery systems and tissue engineering.

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Functionalized PEAs become also an interesting group due to their capability to link compounds with a pharmacologic activity and also to the possibility to get biodegradable elastomers that can avoid deficiencies of typical cross-linked aliphatic polyesters (e.g. rapid degradation upon implantation, or limited chemical moieties for chemical modification).

Properties of materials can be significantly modified by adding nanoparticles (e.g. layered silicates) which can provide materials with a suite of characteristics that organic chemistry and traditional polymer-blending approaches cannot supply from an economical point of view.

Keywords: Poly(ester amide)s, biodegradation, renovable sources, tissue engineering, drug delivery systems, biomedical applications.

1. INTRODUCTION

Development of biodegradable polymers is nowadays a crucial point for different industrial sectors like agriculture, automotive industry, medicine, and packaging which require the use of environmentally friendly materials and, in some specific cases, biocompatible polymers. Because the level of biodegradation may be tailored to specific needs, each industry is able to create its own ideal material.

Biodegradable polymers susceptible to be employed in packaging are receiving more attention than those designated for any other application since it is estimated that more than 40% of plastics are used in this area. Plastics based upon polyester and starch have been successfully commercialized with appropriate properties for application as a packaging wrap and even some PEAs were introduced to consumers.

The biomedical field is a constantly changing and highly specific area where it is essential the research on new biodegradable and biocompatible polymers. These must accomplish several strict requirements, must be compatible with the tissue where they will be in contact, and must be biodegraded according to their temporary function.

Biodegradable polymers can be derived from natural sources (such as starch or microbially grown polymers), or have a synthetic nature like aliphatic polyesters (e.g. poly(ε-caprolactone), polyglycolide, polylactide, poly(butylene succinate)). Developments in polymer science and technology allow to design and synthesize, in a production scale, a material to fulfill some specific properties. Thus, nature of monomers, composition and microstructure are some factors that may be changed for obtaining a great variety of synthetic materials. PEAs are new class of polymers that combine the good degradability of polyesters with the high thermal stability, high modulus and high tensile strength of polyamides. In this way, it is possible to get good material and processing properties while keeping degradability. PEAs are also highly attractive since properties can be tunned due to the great variety of monomers than can be used (e.g. α-amino acids, α,ω-aminoalcohols, carbohydrates). Thus, polymers can be obtained with variable ester/amide ratio, variable aliphatic/aromatic ratio, variable hydrophilicity (e.g. incorporating poly(ethylene oxide) blocks or changing the length of polymethylene sequences), variable stereochemistry and variable monomer distribution. Thermoplastic elastomers, and amorphous and semicrystalline materials can be obtained from segmented, random and ordered microstructures, respectively. PEAs have received attention

from the scientific community and different reviews on biodegradable polymers include interesting data about their synthesis and degradable properties [1,2].

PEAs can be synthesized by applying different polymerization methodologies which are reviewed in chapter 2. The next section is devoted to the explanation of the main families of PEAs such as unsaturated, functionalized and derivatives of renewable sources. PEAs constituted by α-amino acid units give rise to a particular group that is discussed in different subsections (i.e. those corresponding to melt, interfacial and active ester polymerization methods and also in the topic concerning to functionalized polymers). Finally, specific applications (e.g. drug delivery systems, hydrogels, nanocomposites) are introduced in chapter 4.

2. SYNTHESIS OF POLY (ESTER AMIDE) S

2.1. Ring Opening Polymerization

2.1.1. Polydepsipeptides

Copolymers of α-hydroxy acids and α-amino acids, polydepsipeptides, were initially produced by stepwise active ester coupling reactions [3,4] but nowadays the ring-opening polymerization of morpholine-2,5-dione derivatives has become the preferred methodology. This can be applied to obtain PEAs with a regular chemical structure and even random and block copolymers, which could be used as biomaterials in drug controlled release, tissue engineering and shape-memory materials.

Derivatives of the 6-membered ring of morpholine-2,5-dione have been obtained by different methods (Figure 1):

1. Cyclization of *N*-(α-haloacyl)-α-amino acids in high diluted solutions of dimethylformamide and using triethylamine, NaOH, Na_2CO_3, or $NaHCO_3$ to neutralize the acid products [5-9]. The acylation of amino acids can be performed with bromopropionyl bromide or chloroacetyl chloride under Schotten Baumann reaction conditions. The cyclization reaction goes through an intramolecular S_N reaction mechanism that can lead to some racemization when optically active monomers were employed. The reaction also competes with intermolecular reactions that conduce to linear oligomers.
2. Cyclization of *N*-(α-hydroxyacyl)-α-amino acids by intramolecular esterification. This reaction should not cause racemization and can be performed under reduced pressure and high temperature, using carbonyl diimidazole as condensing agent or using *p*-toluenesulfonic acid, methanesulfonic acid or trifluoromethanesulfonic acid as catalysts [10,11].
3. Cyclization of *O*-(α-aminoacyl)-α-hydroxycarboxylic acids [12,13]. This method can avoid racemization but similarly to peptide synthesis involves multiple steps that led to yields usually lower than 10% [7].

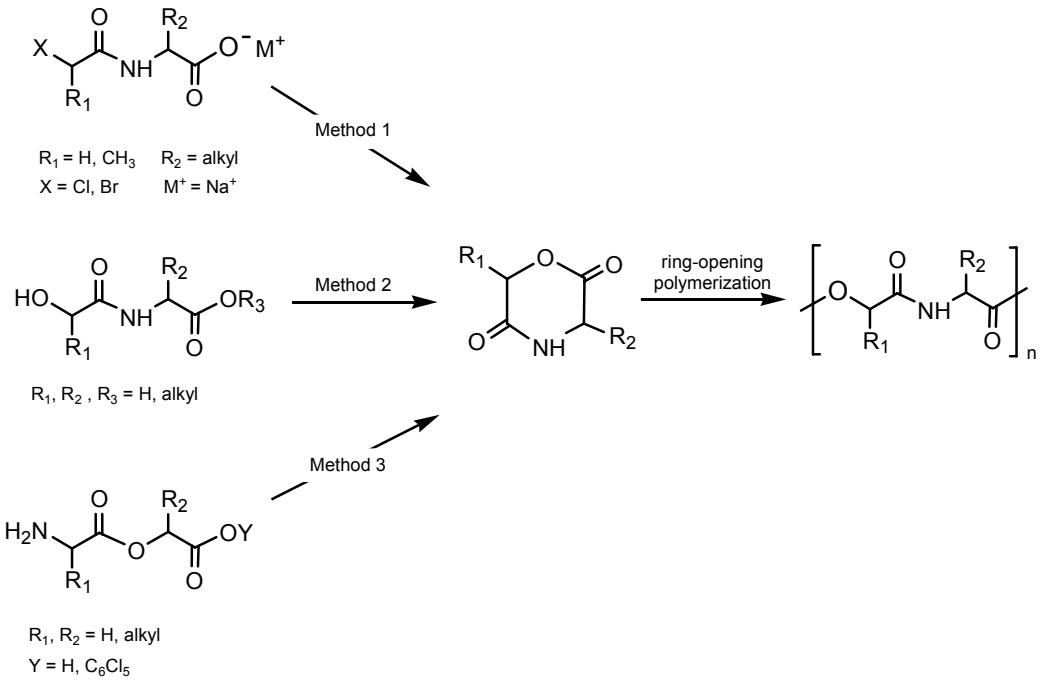


Figure 1. Synthesis of morpholine-2,5-dione derivatives.

Polymerization of morpholine-2,5-diones was firstly carried out in bulk using stannous octoate [$Sn(Oct)_2$] as a catalyst at reaction temperatures close to the melting temperature of the monomer [14]. *p*-Dioxanone [15], ε-caprolactone [16] and lactide [17] have been usually employed as comonomers for random polymerizations that have been conducted using the same catalyst.

Triblock copolymers with a middle block of poly(ethylene oxide) have been prepared by ring-opening polymerization of morpholine-2,5-diones using in this case calcium alcoholates of hydroxytelechelic polyethylene oxide as the initiator [18]. Polymerization yields were usually low and racemization was detected.

Enzymes such as lipases are a third type of efficient catalysts for reaction of morpholine-2,5-diones [19-21]. The polymerization possibly proceeds through ring-opening at the ester bond. It is significant that the configuration of the α-amino acid moiety did not affect the enzyme catalyzed polymerization, but in contrast the configuration of the hydroxy acid moiety strongly influenced the polymerization behaviour. In general, an enhanced racemization of the amino acid residues during enzymatic polymerization was observed.

2.1.2. Ring Opening Polymerization of Macrocycles

Polymerizations of five-, six-, and seven-membered rings are driven by the negative change of enthalpy since both the standard enthalpy and entropy change are expected to be negative. For the polymerization of larger rings both the standard enthalpy and entropy change are expected to be positive and consequently these polymerizations are driven by the entropy change and need a reaction temperature higher than a critical value defined as floor temperature.

Reports on ring opening polymerization of cyclic ester amides with larger rings than the 2,5-morpholinodione six-membered ring are relatively scarce. However, preparation of cyclic ester amides with 11, 13 and 14-membered rings have extensively been studied by Höcker *et al* [22-25].

Cyclic ester amides of ε-amino acids and β-hydroxy acids (11-membered rings) were obtained by ring-enlargement reactions of corresponding *N*-hydroxyacyl-lactams [26]. In particular, an alternating copoly(ester amide) constituted by ε-caprolactam and β-hydroxypropionic acid units was successfully prepared using the two commercial monomers: ε-caprolactam and acrylic acid [22]. The preferred polymerization conditions corresponded to the use of dimethylformamide as solvent, dibutyldimethoxytin as initiator and a reaction temperature close to 100 ºC. A M_n molecular weight of 16,600 g/mol was derived and a polymerization mechanism was proposed based on kinetic measurements and NMR-spectroscopic analysis.

A series of alternating semicrystalline PEAs was obtained by polycondensation of α-carboxyl-ω-hydroxyl amides in bulk at temperatures above the melting point of the monomers or in solution under mild conditions using a carbodiimide for the activation of the carboxyl group [23]. The raw materials were adipic anhydride and α-ω-aminoalcohols with a number of methylene groups ranging from 2 to 6. At a temperature of 170 ºC the melt polycondensation process was followed by a ring-closing depolymerisation and the formation of cyclic ester amides (Figure 2). These cycles were obtained in high purity and were prone to ring-opening polymerization with nucleophilic initiators. The obtained alternating PEAs had M_n molecular weigths in the 10,000-30,000 g/mol range. All polymers were semicrystalline with a melting point that varied between 105 and 148 ºC and showed the odd/even effect described for polyamides and polyurethanes.

The synthesis and ring-opening polymerization of 1-oxa-7-aza-cyclotridecane-8,13-dione, the 13-membered cyclic ester amide prepared from adipic anhydride and 1-amino-5-pentanol, was studied in detail [24]. Melt polymerizations at temperatures above 145 °C with $Bu_2Sn(OMe)_2$, $Ti(OBu)_4$, $Al(O\text{-}sec\text{-}Bu)_3$, or $Sn(octoate)_2$ as initiator were successful and had good yields. The monomer-to-initiator ratio and the conversion degree determined the number average molecular weight which could attain values of 30,000 g/mol. The resulting PEA was semicrystalline with a melting point of 108 °C. It was stated that the elementary chain growth reaction proceeded by a coordination insertion mechanism in analogy to the polymerization of lactones.

A 14-membered cyclic ester amide (1-oxa-8-aza-cyclotetradecane-9,14-dione) was synthesized from adipic anhydride and 1-amino-6-hexanol and melt polymerized at 165 ºC using $Bu_2Sn(OMe)_2$ as initiator [25]. The resulting alternated PEA had M_n molecular weights in the 20,000-30,000 g/mol range and a melting point of 140 ºC. Transfer and termination reactions could not completely be excluded when polymerization was performed in solution and consequently low molecular weights were in this case attained.

Block copolymers comprising poly(ethylene oxide) and alternating PEA segments could also be obtained from the 1-oxa-7-aza-cyclotridecane-8,13-dione and 1-oxa-8-aza-cyclotetradecane-9,14-dione rings [24,25]. The cyclic monomers were polymerized with both mono- and bis-(hydroxyl)-functional poly(ethylene oxide)s of various molecular weights (from 2 000 to 20,000 g/mol) and using $Sn(octoate)_2$ as catalyst. A-B and B-A-B block copolymers were obtained depending on the use of mono and bifunctional macroinitiators,

respectively. Lower conversion and lower initiation efficiency were attained by increasing the molecular weight of the macroinitiator. The efficiency was also lower when a monofunctional initiator was employed. Interestingly, the thermal characterization revealed phase separated systems showing the characteristic melting peaks of the respective homopolymers when the poly(ethylene oxide) block had a M_n greater than 5000 g/mol.

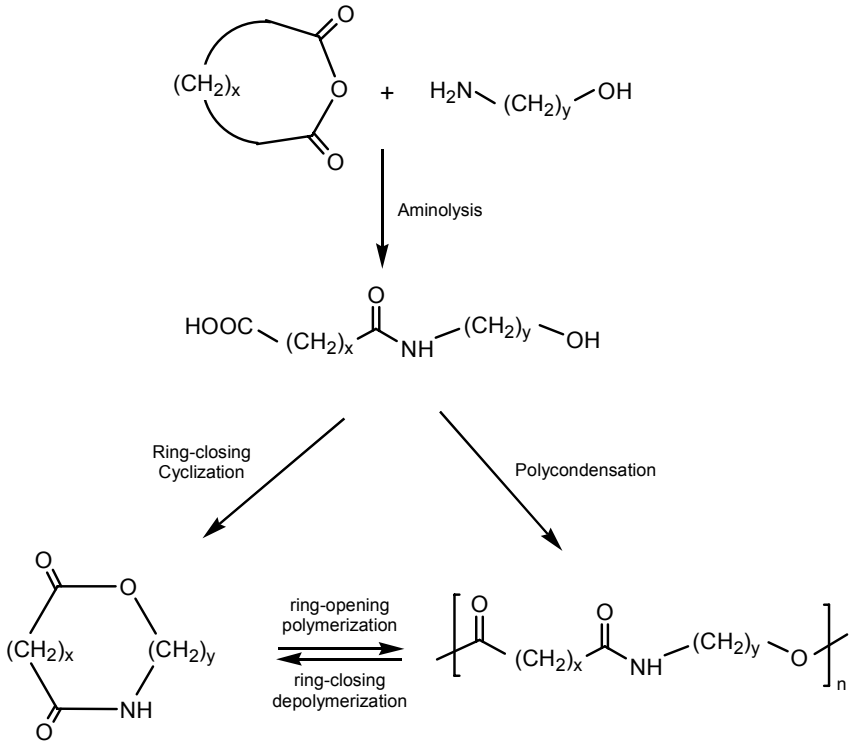


Figure 2. Synthesis of poly(ester amide)s from ring opening polymerization of macrocycles derived from α,ω-aminoalcohols and acid anhydrides.

2.1.3. Ring Opening Polymerization of Lactones and Lactams

The ring opening polymerization of mixtures of lactones and lactams (Figure 3) is one of simplest procedures to prepare random PEAs with the added advantage that polymerization can be performed under mild conditions and sometimes may proceed in a "living" manner (i.e. without side reactions and giving rise to polymers with controlled molecular weight).

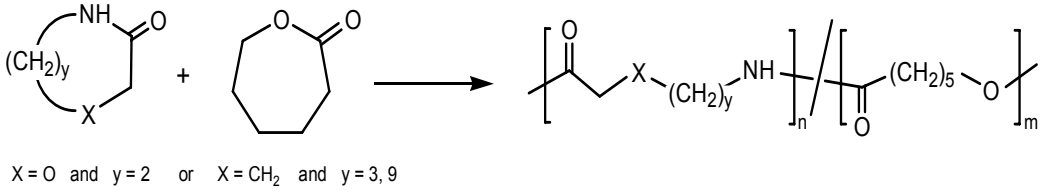


Figure 3. Synthesis of copoly(ester amide)s by ring opening polymerization of caprolactone and lactams / 3-morpholinone (X = O and y = 2).

Goodman *et al*. [27] studied the anionic copolymerization of ε-caprolactam/ε-caprolactone mixtures using *N*-sodium caprolactam as a catalyst, at both high and low initial ε-caprolactam feed ratio (i.e. 70 and 25%). They found that ε-caprolactone was the more rapidly reacting monomer and that it polymerized selectively at the 0.5% sodium caprolactam catalyst level. However, incorporation of ε-caprolactam units could be increased with a higher catalyst concentration (> 1%) and reaction time [27,28]. Copolymers could reach molecular weights of 10^4 g/mol and showed an amorphous or semicrystalline nature depending on composition and thermal history [29]. Stiffness and extensibility also varied with composition, increasing logically the brittleness with the amide content.

Nakayama *et al*. [30] also reported the synthesis of copoly(ester-amide)s derived from ε-caprolactone and ε-caprolactam. The obtained copolymers exhibited a single melting temperature between that of poly(ε-caprolactone) and nylon 6 (poly(ε-caprolactam)) as presumable for a random distribution. The ester-rich copolymers were soluble in less polar solvents such as chloroform, while the amide-rich copolymers required formic acid for good solubility. All of these PEAs were hydrolyzed by *Rhizopus arrhizus* lipase and by hog liver esterase.

Random PEAs based on ε-caprolactone and ε-caprolactam, with an ester/amide composition varying from 75/25 to 10/90, were also prepared by anionic ring opening polymerization at 100-160 ºC with sodium caprolactam as a catalyst [31]. The crystallinities of the copolymers with 40-45% amide content were significantly reduced as compared to those of nylon 6 and poly(ε-caprolactone). The tensile properties of copolymers indicated that the mechanical strength increased with increasing lactam content. Polymers were hydrolytically (pH 7.4 buffered solution, 37 ºC) and enzimatically (*F. moniliforme* medium) degradable through ester bond cleavages.

Poly[(ε-caprolactam)-*co*-(ε-caprolactone)] copolymers were also synthesized by anionic polymerization promoted by ε-caprolactam magnesium bromide in a temperature range from 120 to 180 ºC [32]. Anionic promoter had a remarkable influence on the polymer microstructure favouring a sequential distribution. Thermal degradation studies showed the formation of ε-caprolactone at the low temperature range which confirmed the blocky structure of the copolymer since this lactone could only be produced by a mechanism of unzipping depolymerization of poly(ε-caprolactone) blocks.

The use of twin-screw extruders as polymerization reactors has been considered with great interest in the polymer industry since offers some advantages. In particular, great efforts have been focused on condensation homopolymers such as polyurethanes and poly(ether imide)s, and ring-opening polymerization of polylactams, polyacetals and polylactones. Since 1990s investigations have also been conducted to the preparation of both block and random copolymers. These different microstructures could be attained depending how monomers were fed (i.e. sequentially or simultaneously) [33].

The synthesis of block copolymers of lactams and lactones by reactive extrusion were firstly reported by Kim and White [34]. Specifically, ε-caprolactam/ε-caprolactone and ω-lauryl lactam/ε-caprolactone copolymers were prepared using sodium hydride and *N*-acetyl caprolactam as anionic initiator and coinitiator, respectively. These block copolymers have potential as compatibilizing agents in polymer blends involving polyamides and polymers like polyesters and halogenated polymers which are expected to be miscible with poly(ε-caprolactone). High molecular weight (34,000 - 87,000 g/mol) copolymers with different

block lengths were obtained by sequential feeding of monomers. Furthermore, the block length could be adjusted by controlling the feed rate of each monomer during reactive extrusion.

A PEA block copolymer was also obtained by copolymerization of lauryl lactam and diisocyanate-end-capped poly(ε-caprolactone)s of different molecular weights (500-3,200 g/mol) [35]. Reaction was studied for a simultaneous and a sequential load of reactants into the internal mixer. The sequential feeding method was better because it avoided the hindrance of diisocyanate-end-capped poly(ε-caprolactone) in the polymerization of lauryl lactam to polyamide 12 and led to the formation of linear chains. Chemical reaction between polyamide 12 and diisocyanate-end-capped poly(ε-caprolactone) was verified with FTIR. DSC results showed that the melting temperature of the hard polyamide segment decreased as the molecular weight of the soft polyester segment decreased. The decrease on the molecular weight of the polyol caused also an increase in the modulus and tensile strength and a decrease on the elongation at break of the synthesized PEA. The tensile strength ranged from 32 to 55 MPa and the elongation at break from 80 to 105%.

The ring-opening copolymerization of 3-morpholinone and ε-caprolactone in bulk with stannous octoate, aluminium isopropoxide, or aluminium isobutoxide as an initiator gave rise to a series of biodegradable PEAs having ether linkages in the main chain (Figure 3) [36]. It was found that the ε-caprolactone monomer had a higher reactivity ratio than the morpholinone comonomer (1.28 versus 0.74) and that an enhancement on the morpholinone content increased the water absorption of the polymers, and both the *in vitro* degradation rate and drug (e.g. 5-fluorouracil) release rate. In comparison with traditional PEAs, these copolymers containing additional ether linkages in the backbone chain showed enhanced hydrophilicity and flexibility.

2.2. Polycondensation Methods

2.2.1. Melt Polycondensation

The melt polymerization method is advantageous for industrial production because no post-treatment is necessary after the polymerization reaction. This is performed under high vacuum and temperature to favour the elimination of condensation products, and using a trasesterification catalyst. The synthesis is usually carried out in two temperature steps since in order to favour the polycondensation process and get a high molecular weight sample, the reaction temperature is increased once a prepolymer is obtained.

A) Regular Poly(Ester Amide)S

α-Amino Acid Derivatives

Polymers derived from naturally occurring α-amino acid units have a great interest for biomedical applications since degradation products are non toxic and can be well metabolized by the organism. Poly(α-amino acids) were firstly considered but their application was discarded due to inherent problems like production costs, insolubility in common organic solvents, thermal instability and processing difficulties. New polymers that incorporate α-amino acid units were developed, being PEAs one of the most studied families. These include

the above mentioned group of polydepsipeptides and other derivatives with a more complicated and variable chemical structure that allows to fit the requirements necessary for some specific applications. PEAs constituted by α-amino acids can also be prepared by melt polycondensation of diamide-diesters, or by interfacial or active ester polycondensation of diester-diamine derivatives as will be explained in next sections.

A thermal polyesterification between a diol and a diamide-diester derived from acid chloride and α-amino acid methyl ester units has been proposed (Figure 4) [37]. In this way, the polymer constituted by sebacic acid, 1,4-butanediol and glycine units was synthesized with a high yield and moderate molecular weight. Calorimetric analysis showed that this PEA was semicrystalline (degree of crystallinity close to 40%) with a melting temperature (160 ºC) higher than that of polyesters derived from the same diol and dicarboxylic acid. The hydrogen bonding interactions between the amide groups played a fundamental role, increasing the range of temperatures at which the new materials belong to the solid state. Despite the presence of glycine units the new PEA was thermally stable, because decomposition began above 300 °C and consequently the polymer should be easily processed from the melt state. The new PEA degraded faster than the related polyester in both aqueous and proteolytic enzymatic media. However, the polyester showed higher degradability in an esterase medium.

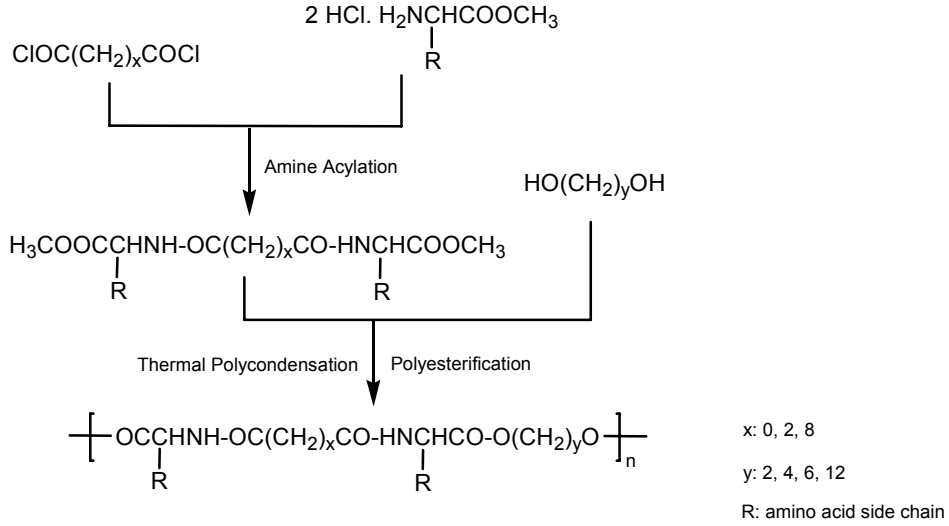


Figure 4. Synthesis of poly(ester amide)s containing α-amino acids from a thermal polycondensation of a diol and a diamide-diester.

This synthesis method was also applied to obtain polymers derived from glycine, diols like 1,2-ethanediol, 1,4-butanediol, 1,6-hexanediol, 1,12-dodecanediol and dicarboxylic acids like succinic and sebacic acid (Figure 4) [38]. Furthermore, the incorporation of stiff units (oxaloyl and terephthaloyl derivatives) was considered. The thermal polycondesation reaction occurred always with high yield and generally provided polymers with the right molecular weight to render fiber- and film-forming properties. Thermal synthesis seems to be useful for preparing polymers derived from diacid chlorides such as oxaloyl or succinoyl chlorides and diols such as 1,4-butanediol because the synthesis of these polymers by interfacial methods was highly deficient. Furthermore, intrinsic viscosities of the studied polymers were generally higher when thermal synthesis was used instead of the interfacial polymerization. PEAs with

oxaloyl or terephthaloyl moieties showed high glass-transition temperatures (i.e. 52 and 87 ºC, respectively) that contrast with the values close to 0 ºC that were found in polymers derived from flexible dicarboxylic units. The new PEAs were susceptible to the proteolytic enzymatic attack with papain as a result of the presence of glycine units.

In general, the research carried out with PEAs derived from α-amino acids pointed out that they can be seriously considered as a new class of promising biomaterials for many biomedical applications ranging from surgical implants to drug delivery devices. In addition, these PEAs may be used as new substrates in enzymology as well as for the study of the pharmacological and immunologic activities of α-amino acid derived polymers [39]. This diversity in biomedical applications requires a wide variety of mechanical, physicochemical, and biochemical properties that could be easily achieved by varying the components in the building block of the macromolecular backbone (e.g. α-amino acid, diol, and dicarboxylic acid).

B) Segmented Poly (Ester Amide) S

Segmented PEAs constituted by soft and hard segments are highly interesting due to their potential mechanical properties since they combine the rubber characteristics provided by the amorphous soft segments (e.g. extensibility and softness) with the cohesive strength provided by their crystallizable hard segments. These act as physical cross-links and allow the material to resist flow when stress is applied. Polymers can be considered as thermoplastic elastomers since cross-links can be disrupted by heating above the melting temperature of the hard segments or by using solvents.

Poly(ether ester amide) multiblock copolymers based on hydrophilic poly(ethylene glycol) oligomers (soft segment with M_w 1000 g/mol), 1,4-butanediol and diamide-diester blocks were succesfully synthesized by melt polycondensation and using $Ti(OBu)_4$ as catalyst (Figure 5) [40]. The small and symmetrical diamide-diester monomer was prepared from 1,4-diaminobutane and dimethyl adipate, and was selected because the resulting hard segment showed rapid crystallization and high crystallinity. Differential scanning calorimetry showed melting transitions for the poly(ethylene glycol) blocks and for the ester-amide blocks, suggesting a phase separated structure. By variation of the ratio between the oligomeric diol (PEG) and 1,4-butanediol, a series of polymers was obtained with a range of thermal, swelling, and degradation characteristics. Thus, the increase on the PEG content caused a decrease on the melting temperature and crystallinity of the hard amide-ester segments, an increase on the equilibrium swelling ratio, and an increase on the hydrolytical (i.e. in a phosphate buffered saline medium) degradation rate. Copolymers were considered as promising candidates for application as matrix material for controlled release systems for proteins. Investigations using the model protein lysozyme showed that the release rate increased logically with the degree of swelling of the polymers.

Segmented PEAs were also prepared by melt polycondensation of dimethyl adipate, 1,4-butanediol and a symmetrical diamide-diol with 2 or 4 methylene units between the amide groups (Figure 6) [41,42]. The diamide-diol was prepared by reaction of ε-caprolactone with the appropriate diamine. The molar ratio between hard and soft segments in the PEAs was varied by changing the monomer feed ratio (i.e. between diamide-diol and 1,4-butanediol units). All polymers had a sub-ambient glass transition temperature and two melt transitions, which corresponded with the melting of crystals comprising single ester amide sequences or

two or more ester amide sequences. The PEAs had a micro-phase separated structure with an amide-rich hard phase and an ester-rich flexible soft phase. The polymers had an elastic modulus in the range of 159–359 MPa, a stress at break in the range of 15–25 MPa combined with a high strain at break (590–810%). The thermal and mechanical properties were only influenced by the amount of crystallizable hard segment present.

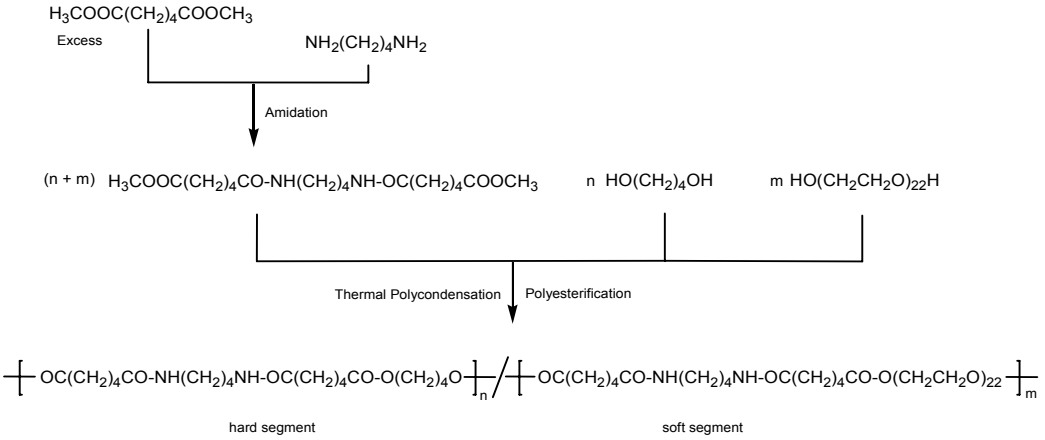


Figure 5. Synthesis of copoly(ester amide)s constituted by poly(ethylene glycol) soft segments and hard segments derived from dimethyl adipate and 1,4-diaminobutane.

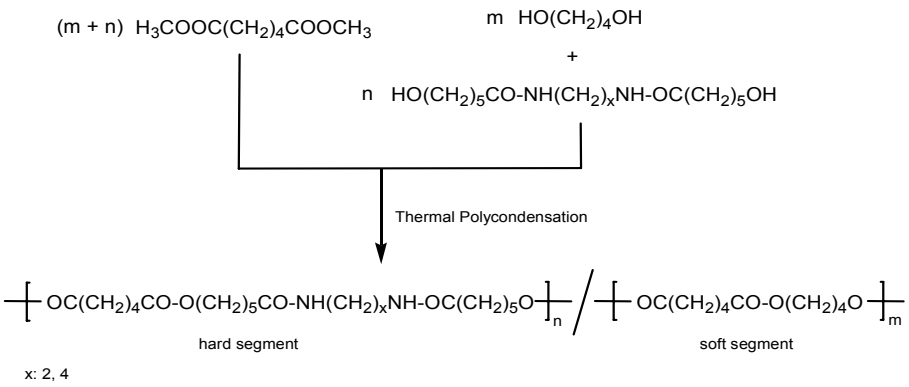


Figure 6. Synthesis of segmented copoly(ester amide)s constituted by soft polyester segments and hard segments derived from diamide-diol units.

C) Random Aliphatic Poly(Ester Amide)S Based on Diols, Dicarboxylic Acids and ω-Amino Acids/Lactams

Random copoly(ester amide)s were easily obtained by reaction of a lactam (e.g. ε-caprolactam) or an ω-amino acid (e.g. 6-aminohexanoic acid) with an equimolar mixture of a diol and a dicarboxylic acid (Figure 7) [43-45]. Reactions were performed under vacuum at high temperature (> 180 ºC) and usually adding a transesterification catalyst. The copolymer derived from ε-caprolactam/6-aminohexanoic acid, 1,4-butanediol and adipic acid having an ester/amide ratio of 40/60 was easily processed. This random PEA was suitable for a wide range of commodity applications and even commecialized (BAK copolymers). Degradation

studies were extensively performed with BAK and compared with a new PEA constituted by the same monomers with a regular distribution and an ester/amide ratio of 50/50 [46]. Both samples were hydrolitically and enzimatically (proteinase K medium) degradable, corresponding the higher degradation rate to the random copolymer. It was deduced that the lower crystallinity had a higher influence on degradability than the increase on the ester content.

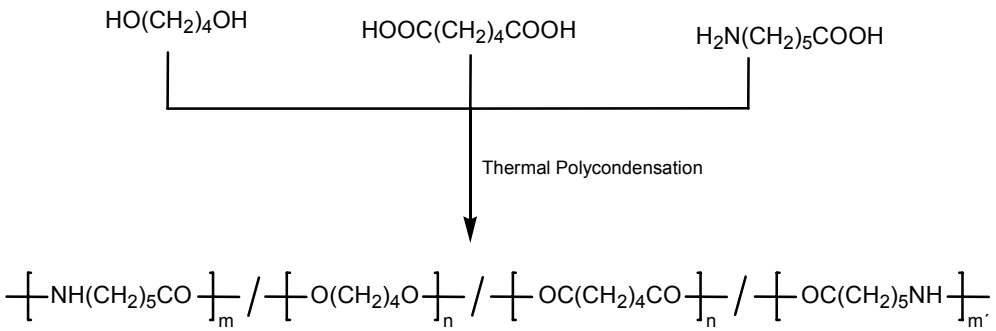


Figure 7. Synthesis of random copoly(ester amide)s based on adipic acid, 6-aminohexanoic acid (or alternatively ε-caprolactam) and 1,4-butanediol.

2.2.2. Interfacial Polymerization

Interfacial polymerization can be carried out by reaction of a diacid chloride soluble in an organic solvent with a diamine or a diol soluble in an aqueous medium. Polymerization reaction is influenced by solvent system, catalytic and surfactant additives. The choice of the organic solvent is more important since it affects other polymerization factors such as the potential partition of reactants between the two phases, diffusion of the reactants, reaction rate, solubility and swelling or permeability of the growing polymer [47]. Surface-active agents can be added to increase interfacial area and contact between reactants. Phase-transfer catalyst, generally a small symmetric quaternary ammonium cation, may favour the nucleophilic displacement reaction characteristic of the interfacial polycondensation [48].

α-Amino Acid Derivatives

Interfacial polymerization was extensively applied to obtain PEAs derived from α-amino acids (Figure 8). These units were incorporated in a diester-diamine monomer prepared by reaction of the amino acid with a diol. The diester-diamine was unstable as free base and tended to produce undesirable side reactions. Therefore, they were prepared as stable salts of *p*-toluenesulfonic acid (pTSA).

The synthesis was successfully applied to prepare a series of PEAs derived from glycine, dicarboxylic acids with a variable number of methylenes (fom 2 to 8) and 1,6-hexanediol [49] or 1,12-dodecanediol [50]. These materials were semicrystalline with a melting temperature that decreased with the increase of the methylene content in the repeat unit. The degradability of these polymers was corroborated by enzymatic incubation in a papain medium. Crystallization from the melt rendered negative spherulites whereas crystallizations from diluted solutions rendered lamellar crystals with a preferred growing direction that was

associated with the single direction where hydrogen bonds were established. Structural analysis indicated that derivatives of odd dicarboxylic acids formed superstructures constituted by six hydrogen-bonded sheets [51]. These structures were explained in terms of specific intermolecular interactions that rested on differences in the packing requirements for amide and ester groups. On the contrary, the crystalline structure of derivatives of even-numbered dicarboxylic acids was based on a periodic arrangement of only two layers of hydrogen-bonded molecular chains, whose polymethylene sequences mimicked the packing of polyethylene and the majority of polyesters [50].

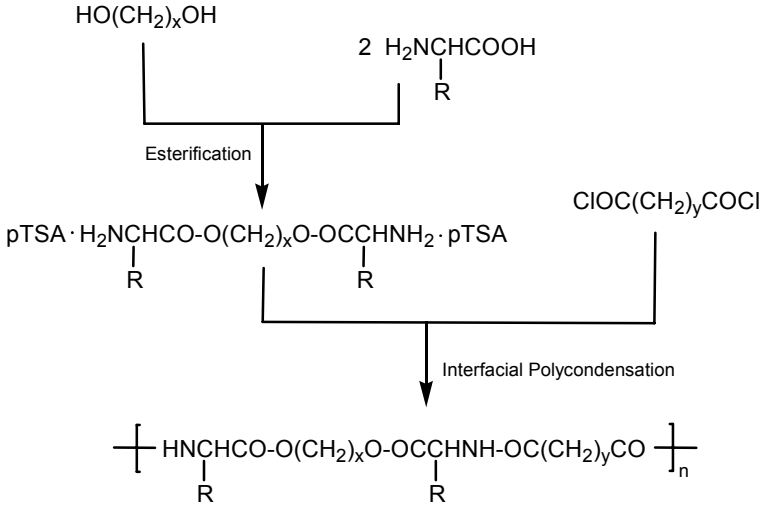


Figure 8. Synthesis by interfacial polycondensation of regular poly(ester amide)s containing α-amino acids.

A series of PEAs derived from an amino acid (glycine or 4-amino butyric acid), a diol (1,6-hexanediol or 1,4-butanediol) and sebacoyl chloride were prepared by interfacial polymerization following the indicated two step methodology [52]. Polymerizations were carried out in water/dichloromethane using Na_2CO_3 as a proton acceptor and rendered samples with moderate molecular weights but adequate for performing FTIR analysis and degradation studies. Polymers with amide and ester groups may show peculiar hydrogen bonding interactions (i.e. amide-amide and amide-ester hydrogen bonds) and different C=O ester bonds (i.e. free C=O ester and hydrogen-bonded C=O ester), which could affect both the crystallinity and the degradability [53]. Different positions of the amide and ester groups in the repeat unit caused by employing different amino acids and different diols may affect the bonding states of hydrogen bonds and C=O ester groups. In addition, amide groups or free NH groups in PEAs are thought to be an important factor determining the interactions between resulting PEAs and cultured cells [54]. FTIR analyses showed that hydrogen bonds of glycine derivatives were established between only amide groups in the adjacent chains, whereas butyric acid derivatives showed the coexistence of hydrogen bonds with different bond length. In addition, polymer surfaces had a greater hydropilicity caused by the presence of free NH groups. Enzymatic degradation using papain demonstrated a higher degradation rate for glycine derivatives which was justified through the existence of free C=O ester groups [52]. Transmission electron microscopy observations suggested that degradation of

crystalline lamellae appeared to proceed preferentially from the empty spaces caused by lamellar twisting. Attachment and cell proliferation was found greater for the PEAs derived from 4-amino butyric acid, an interesting feature that was correlated with the increased hydrophilicity of the polymer surface [52].

Interfacial polycondensation in CCl_4/water was highly efficient to prepare L-alanine derivatives, in particular PEAs from 1,12-dodecanediol, and sebacic acid [55] or 1,12-dodecanedioic acid [56]. These polymers with high methylene content were soluble in chlorinated polar organic solvents like chloroform and dichloromethane, an interesting feature that facilitates processing and increases their applicability. Molecular weights were sufficient to ensure fiber- and film-forming properties. New polymers were hydrolytically and enzimatically degradable. Moreover, cell proliferation studies demonstrated that they can be used as biocompatible substrates.

The physical and biodegradable properties of polymers may change dramatically by varying the stereochemical composition. In this way, the effect of stereochemistry on the enzymatic degradability has been reported for a few polyesters such as polylactide [57] and poly(3-hydroxybutyrate) [58]. Some works have also been performed with PEAs derived from quiral α-amino acids like alanine. Specifically, poly(ester-amide)s with L-alanine contents of 100, 90, 80, 70, 50, 30 and 0% (percentages referred to the total alanine content) were obtained by interfacial polycondensation of secacoyl chloride with the *p*-toluenesulfonic acid salt of the diester-diamine prepared from L- or D-alanine and 1,6-hexanediol [59]. Number average molecular weights ranged from 5100 to 11,100 g/mol when polymerizations were performed in water/dichloromethane and using Na_2CO_3 as a base. Polymers were degraded faster in proteolytic enzymatic media (e.g. proteinase K, papain and α-chymotrypsin) than in lipase enzymatic media (e.g. *R. delemar, P. cepacia* and *C. rugosa*). It was also found that the degradation with the proteolytic enzymes was only caused by hydrolysis of the ester linkage. The effect of the stereochemical composition on the enzymatic degradation was examined using proteinase K and papain, which degraded faster the polymers with L-alanine content of 100% than those with D-alanine content of 100%.

PEAs derived from sebacic acid, 1,12-dodecanediol, and alanine in both the quiral L configuration and the racemic L,D mixture were also synthesized by interfacial polycondensation [60]. Both PEAs were degraded at a very fast ratio by using again a proteolytic enzyme such as papain. The enzymatic degradation was stereospecific and occurred at a faster rate with the stereoregular polymer.

Other Poly(Ester Amide)S

Interfacial polymerization has also been applied to obtain random multiblock PEAs based on polyester and polyamide sequences. Specifically, copolymers related to polyester 10,6 and nylon 6,6, polyester 6,10 and nylon 6,10 or polyester 12,10 and nylon 12,10 have been described [61,62]. The synthesis involves two steps: first, an esterification between the appropriate diol and an excess of sebacoyl or adipoyl dichloride to give a mixture of oligomers having terminal -COCl reactive groups, together with a variable amount of unreacted dichloride; second, an interfacial polyamidation between the mixture obtained in the former step and the stoichiometric amount of the appropriate diamine (Figure 9). In general, polymers were prepared with high yields and adequate molecular weights to render film- and fiber-forming properties. New PEAs showed a complex melting behaviour, being observed fusion peaks characteristic of the related polyamides. This feature is significant

since these copolymers may be used at higher temperatures than parent polyesters. The hydrolytic degradation rate of the new PEAs depended on the amide molar ratio and the nature of monomers since the decrease of the ratio and the increase in hydrophilicity enhanced degradability. New PEAs were scarcely susceptible to proteolytic enzymatic degradation, a feature that contrasts with results obtained with related PEAs derived from α-amino acids.

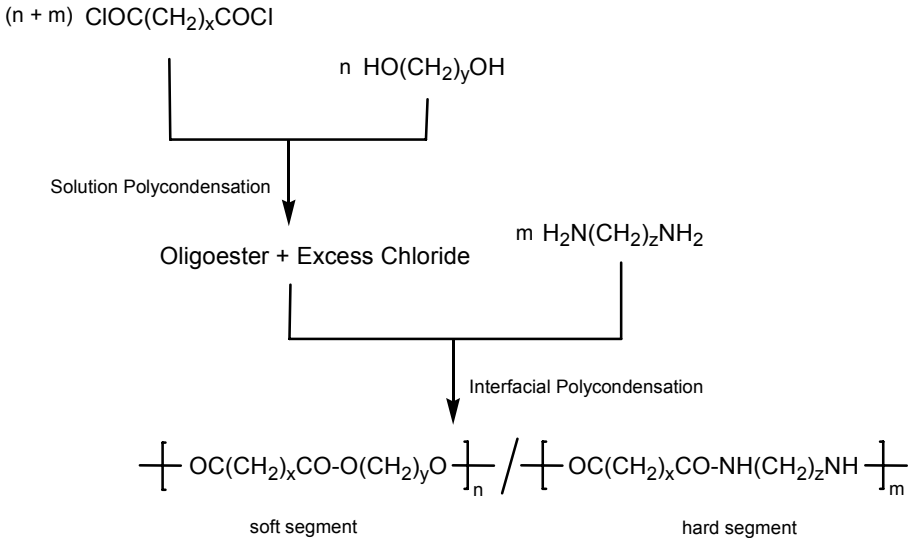


Figure 9. Synthesis by interfacial polycondensation of random poly(ester amide)s based on polyester and polyamide segments.

A similar synthetic procedure was applied to prepare multiblock PEAs containing poly(L-lactide) and cycloaliphatic amide segments. Telechelic oligomers of α,ω-hydroxyl terminated poly(L-lactide), 1,3-cyclohexylbis(methylamine), and sebacoylchloride were employed in a synthesis carried out in chloroform/*n*-hexane and using KOH as proton acceptor [63]. The poly(L-lactide) macromer was synthesized by bulk reaction of L-lactide using 1,4-butanediol as initiator and stannous 2-ethylhexanoate as a ring-opening catalyst. These new copolymers become interesting since may improve properties of poly(L-lactic acid), one of the best-known biodegradable and biocompatible polymers. Therefore, incorporation of polyamide segments into the poly(L-lactide) main chain was expected to render polymers with good material and processing properties as well as biodegradable characteristics. Furthermore, incorporation of rigid cycloaliphatic units may enhance physical properties [64,65] without affecting biocompatibility since these monomers are nontoxic.

The effect of relative content of ester and amide segments on the crystallization nature was investigated by WAXD and DSC analyses. Results indicated that polymers having lower content of poly(L-lactide) blocks showed a crystallization pattern analogous to polyamides, whereas those having higher content showed two crystalline phases which were associated to polyester and polyamide segments. Biodegradation studies using the lipase from *Candida Cylindracea* indicated a higher degradation rate for the sample with a higher content on poly(L-lactide) blocks. Analysis of degradation products suggested that the enzymatic attack mainly involved the ester linkages.

Block-copolymers of cyclohexyl sebacate and cyclohexyl sebacamide were also produced by controlling the length of the ester block and the amount of amide during a similar two-step melt/interfacial polycondensation reaction [66]. Chloride-terminated oligoesters of a predetermined length were first synthesized by melt polycondensation, using a 1,4-cyclohexane diol with a 40% of *trans* content. Block-copolymers were obtained with a variable length of their oligoester blocks and a variable amount of amide bonds introduced. The cyclohexane ring provided a way to tune the crystallinity (and hence the thermal properties) of the material since the *trans* isomer is thermodynamically easier to stack than the *cis* isomer. Films produced from these aliphatic PEAs could retain their shape above 373 K due to the physical network of amide hydrogen-bonding. Thermal properties showed that the presence of amide moieties disrupted the crystalline order of the ester units. Various melting and softening points were observed depending on the composition. Tensile properties typical of an amorphous viscoelastic material were found, but with much superior elongation to break achievable (~1700%). These materials were also hydrolyzable, noncytotoxic, and favorable for cell attachment.

2.2.3. Solution Polycondensation

The use of condensing agents or the activation of the carboxylic groups to facilitate aminolysis reactions allows performing polymerizations under milder conditions than those employed in the conventional melt condensation methods. Side reactions which lead to decomposition of the functional groups (and hence lead to chain-termination) can be avoided as well as the formation of anomalous units in the polymeric backbones. Furthermore, polymerization can take place with high rates due to the increased reactivity.

The low-temperature interfacial polycondensation method has also several drawbacks, among which numerous side reactions that lead again to chain-termination and unit-heterogeneity should be noted. Interactions between aliphatic diacid chlorides and tertiary amines are special remarkable side reactions that prevent the formation of high molecular weight polymers.

A) Activation of Carboxylic Groups

This method comes from peptide chemistry and is based on the activation of the carboxylic function by leaving groups that form new ester or amide derivatives. These called leaving groups are liberated as low molecular weight by-products after polycondensation.

α-Amino Acid Derivatives

Active polycondensation has been revealed highly effective to synthesize PEAs containing α-amino acids (Figure 10). Thus, reaction of the di-*p*-toluenesulfonic acid salts of bis-α-(L-amino acid) α,ω-alkylene diesters with active diesters of dicarboxylic acids lead to PEAs with a high yield and molecular weight (M_w ranging from 24,000 to 167,000 g/mol), and narrow polydispersity (from 1.20 to 1.81) [67,68]. *p*-Nitrophenyl esters were usually employed since could be easily obtained by the reaction of *p*-nitrophenol with either a diacid chloride in the presence of a tertiary amine or a free diacid in the presence of a condensing agent. This systematic study was performed with diester-diamine monomers derived from six hydrophobic α-amino acids (L-phenylalanine, L-leucine, L-isoleucine, L-valine, L-methionine and L-norleucine) and three α,ω-diols (1,3-propanediol, 1,4-butanediol and 1,6-

hexanediol). Polymerizations were undertaken with the adipic and sebacic acid derivatives and gave rise to mostly amorphous materials with T_gs from 11 to 59 °C. α-Chymotrypsin catalyzed *in vitro* hydrolysis of these PEA substrates with a different rate that mainly depended on the hydrophobicity of the side substituent of the α-amino acid and the effectiveness of the interaction of the side groups with the enzyme hydrophobic pocket. Furthermore, the increase on the overall hydrophobicity of the polymer backbone led to a higher sensitivity of the polymer toward the enzyme-catalyzed hydrolysis. In addition to the hydrophobicity factor, the change in chain mobility due to different length of the polymethylene segments was also a factor that contributed to the different rate of enzyme-catalyzed hydrolysis of PEAs.

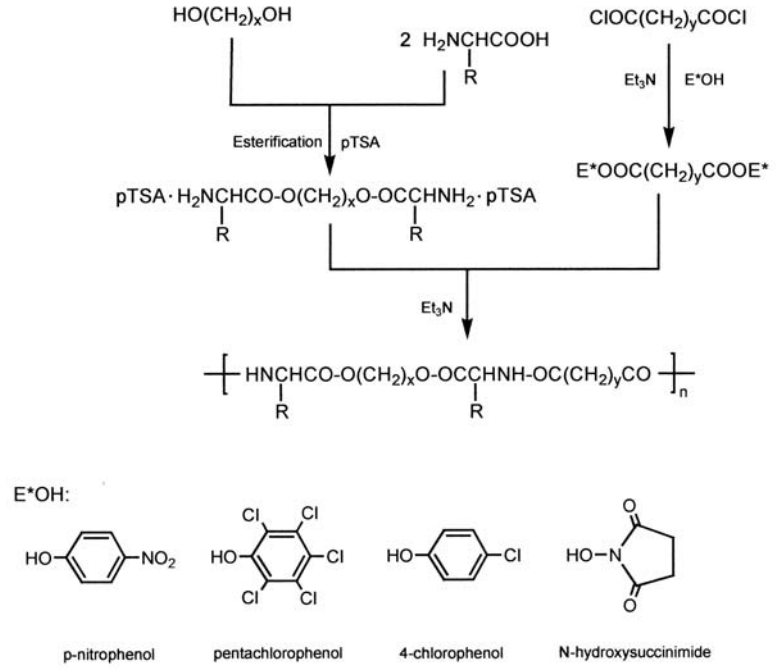


Figure 10. Synthesis by interfacial polycondensation of regular poly(ester amide)s containing α-amino acids. Main activating compounds are indicated.

PEAs containing phenylalanine units were synthesized by the polycondensation of di-*p*-nitrophenyl sebacate with diamines containing phenylalanine ester groups with different L/D ratios (Figure 11) [69]. These diamines were previously prepared by the reaction of phenylalanine with 2-aminoethanol. Polymerizations were carried out in dimethylsulfoxide and using triethylamine as a proton acceptor. M_n molecular weights and polydispersity indices ranged from 11,000 to 15,100 and from 1.65 to 1.92, respectively. The biodegradability of these polymers by proteases (e.g. α-chymotrysin and subtilisins) was strongly dependent on the L/D ratio of phenylalanine residues. Thus, degradation was largely retarded by the introduction of D-phenylalanine residues as expected for the specificity of proteases for L-amino acid residues, regardless of the type of compound (e.g. amino acid esters, amides, peptides, and proteins). It is highly interesting to note that changes in the L/D ratio affected

the degradation rate but not the chemical and physical properties of the polymers. This result is also interesting from a practical point of view since α-amino acids undergo racemization at the high temperatures that could be necessary for spinning or molding processes.

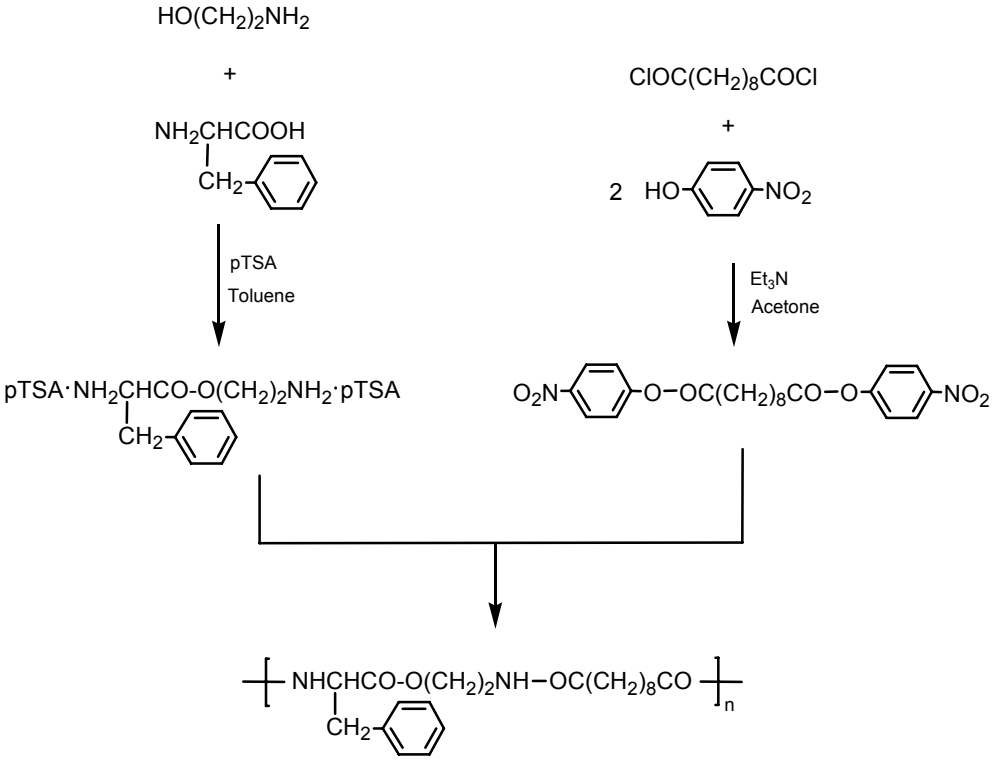


Figure 11. Synthesis by interfacial polycondensation of regular poly(ester amide)s derived from α-amino acids and α,ω-aminoalcohols.

B) Condensing Agents

Endo *et al*. [70] used 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) as a condensing agent for the preparation of PEAs from hydroxycarboxylic acids (Figure 12) previously synthesized by reaction of acid anhydrides (succinic or maleic anhydride) and β-aminoalcohols. These can be obtained by a reduction of an amino acid and are useful compounds for bio and organic chemistries since can be ligands where the heteroatoms are used to form complexes with metal.

A series of alternating PEAs was also obtained by polycondensation of α-carboxyl-ω-hydroxyamides using a carbodiimide as activating agent, dimethylformamide as a solvent and 4-dimethylaminopyridine (DMAP) as a catalyst [71]. The hydroxyamide was previously obtained from glutaric anhydride and an aminoalcohol with a number of methylene groups ranging from 2 to 6. Polymers had M_n molecular weights that varied from to 6 800 to 10,900 g/mol, were semicrystalline materials and had melting points that showed the typical odd/even effect.

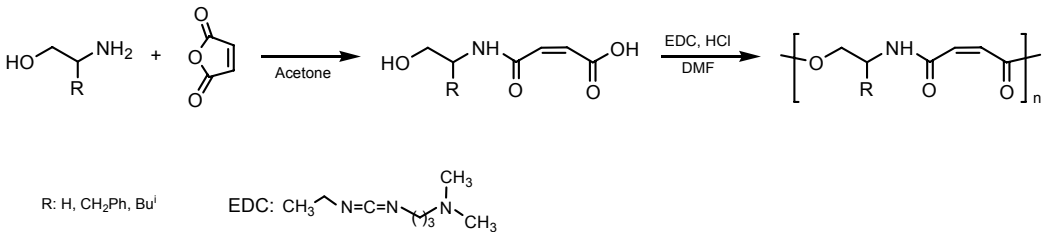


Figure 12. Synthesis of regular poly(ester amide)s derived from α,ω-aminoalcohols using EDC as a condensing agent. Succinic anhydride can be used instead of maleic anhydride to get a saturated repeat unit.

A carbodiimide condensing agent was also successfully applied to synthesize PEAs from aliphatic dicarboxylic acids with a number of methylene groups ranging from 2 to 8 and diols having amide moieties (Figure 13). These diols were derived from optically active aminoalcohols (i.e. L-phenylalaninol and L-leucinol) and dicarboxylic acids (i.e. succinic and adipic acid) [72]. Polymers with M_n ranging from 8,700 to 17,400 g/mol were obtained with satisfactory yields. The glass transition temperature logically increased by decreasing the methylene chain length of the dicarboxylic acid. An even - odd effect for the T_g was observed for the L-leucinol derivatives.

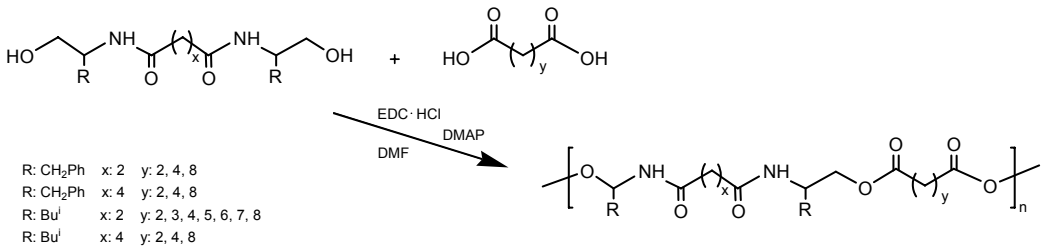


Figure 13. Synthesis of regular AABB poly(ester amide)s derived from α,ω-aminoalcohols using EDC as a condensing agent.

Direct phosphorylation polycondensation reactions have been mainly developed to synthesize polypeptides and polyamides. This method can also be applied to get amide linkages from the reaction of a diester-diamine monomer with a dicarboxylic acid. In this way Hsiao *et al*. [73] prepared new aromatic PEAs with a high polyamidation yield from 1,5-bis(3-aminobenzoyloxy)naphthalene and different aromatic dicarboxylic acids (Figure 14a). The new PEAs derived from less rigid and symmetrical diacids were amorphous and readily soluble in most polar organic solvents. Samples could be solution-casted into transparent, flexible and tough films with good mechanical properties. Incorporation of flexible ester groups and *m*-phenylene linkages to the polymer backbone enhanced the solubility and processability of aromatic polyamides, which are serious limitations for their wide application.

Palladium catalyzed carbonylation–polycondensation reactions are emerging as a new versatile synthetic tool for the preparation of high performance polymers such as polyamides and polyesters. The method appears attractive since can avoid the use of corrosive acids or their functionalized derivatives and provides a cleaner synthetic route. Chaudhari *et al*. [74] obtained PEAs by the reaction of aromatic diiodides and aminohydroxy compounds in the

presence of carbon monoxide, a catalytic amount of palladium complex and a base (Figure 14b). The carbonylation reactions were carried out under mild conditions (120 °C and 3 atm of CO pressure) and led to the successful preparation of different aromatic PEAs. The main problem of the method was the fairly low degree of polymerization that was attained.

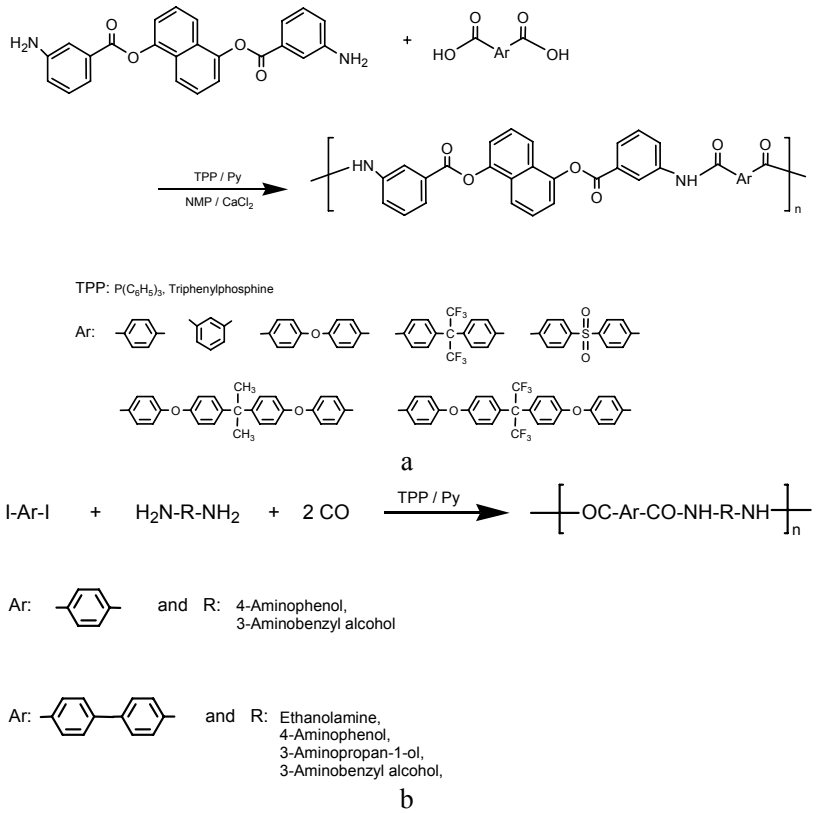


Figure 14. Synthesis of aromatic PEAs by direct phosphorilation reactions (a) and by catalyzed carbonylation-polycondensation reactions (b).

2.2.4. Polycondensation through Elimination of Metal Halide Salts

Thermal polycondensation of halogenoacetates lead to polyglycolide through the elimination of a metal halide salt which can be considered as the driving force of the polycondensation reaction [75-77]. The molecular weight was usually limited because the reaction took place in the solid state and thermal decomposition occurred at the high temperatures required for the progress of the reaction. This kind of solid-state reaction was also tested to obtain different polyesters (polylactide, poly(3-hydroxypropionate and poly(2-hydroxybutyric acid)) with, in general, worse results than polyglycolide [78].

The method was also applied to get PEAs constituted by an alternating sequence of glycolic acid and ω-amino acid units, whose synthesis was previously proposed in base of high time consuming methods since involved selective protection and deprotection of reactive groups [79]. New monomers were easily synthesized, in this case, by the reaction of chloroacetyl chloride with the appropriated ω-amino acid and by a subsequent neutralization with the selected metal hydroxide (Figure 15a).

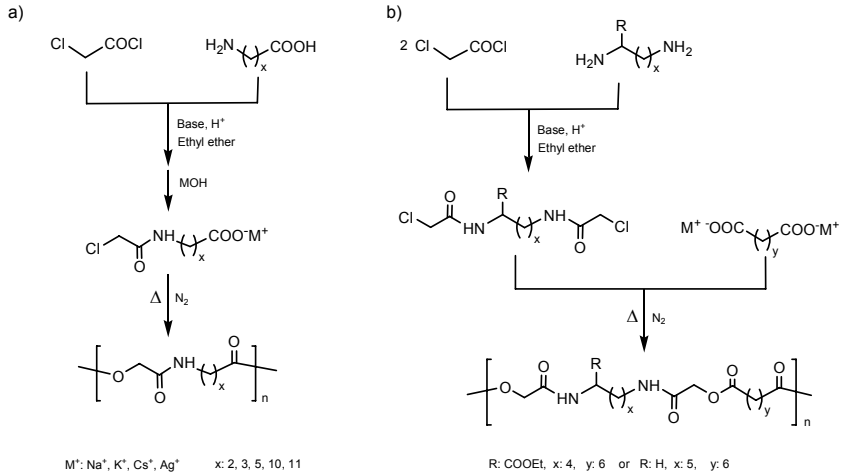


Figure 15. Synthesis of regular poly(ester amide)s by bulk polycondensation and formation of metal halide salts: Derivatives of ω-amino acids and glycolic acid (a), and diamines, dicarboxylic acids and glycolic acid (b).

Bulk polymerizations were carried out at temperatures between 110 and 170 ºC depending on the ω-amino acid and the metal cation. The inorganic salt by-product was easily removed by washing the sample with water or by reprecipitation. In the first case, porous textures of potential interest for biomedical technology were attained. Different works concerning the synthesis of β-alanine [80], 4-aminobutyric acid [80], 6-aminohexanoic acid [81,82], 11-aminoundecanoic acid [82,83] and 12-aminododecanoic acid [84] derivatives have up to now been performed. In addition, random copoly(ester amide)s were also prepared by heating co-precipitated crystals of sodium chloroacetate and sodium *N*-chloroacetyl alaninate [80].

The solid state polymerization of metal salts (sodium and silver) of *N*-chloroacetyl-β-alanine gave a mixture of polymer and a seven-membered cyclic compound (4-oxo-azepan-2,5-dione). The polymerization activation energy was lower for the silver derivative and consequently polycondensation of this salt could be performed at a lower temperature than the sodium salt (120-135 ºC respect 140-155 ºC) and furthermore gave rise to a lower ratio of the cyclic compound. The proposed synthesis rendered high molecular weight samples when amino acids had high methylene content (i.e. 6-aminohexanoic, 11-aminoundecanoic and 12-aminododecanoic acid derivatives). Polymerizations could take place in the solid phase, the liquefied phase, or both phases, depending on the number of methylene groups and the kind of salt. In fact, these two conditioning factors had an influence on the melting point of the monomer, which can be either higher or lower than the reaction temperature.

Different works concerning the study of the polymerization kinetics have also been performed, being determined the corresponding kinetic triplet (activation energy, pre-exponential factor and integral function of the degree of conversion) [82-84]. Alternating polymers crystallized from solution as lamellae with a high aspect ratio and from the melt as negative birefringent spherulites [85]. Structural studies suggested molecular conformations that clearly deviated from the all trans conformation usually found in polyamides and polyesters. However, the molecular packing had common features of both families (i.e. a rectangular unit cell in chain axis projection like polyesters and the establishment of

intermolecular hydrogen bonds along a single direction that coincides with the preferred crystal growth direction like polyamides).

Thermal degradation studies indicated that polymers could be processed from the melt since the start of decomposition took place at higher temperatures than fusion. Decomposition occurred according to two degradation steps, the second one of which involved the decomposition of the polymethylene segment, and consequently became more important for samples with longer ω-amino acid units.

The new PEAs were hydrolytically degradable through the cleavage of ester bonds. Polymers were also susceptible to the enzymatic attack of proteases like proteinase K and became more resistant to lipases like *P. cepacia* [86]. Cytotoxycity, cell adhesion and cell proliferation studies were carried out using either L929 (fibroblast type) and Hep-2 (epithelial type) cell lines with a representative PEA derived from 6-aminohexanoic acid [87]. Results were promising for future biological applications of such materials.

The polycondensation reaction based on the elimination of a metal halide as a driving force was also applied to prepare PEAs derived from a diamine, a dicarboxylic acid and glycolic acid (Figure 15b) [81,88]. These polymers were previously patented because of their potential applications in the field of bioabsorbable surgical sutures [89-91]. This previous synthesis was based on a controlled thermal polyesterification between diacid chloride and diamide-diol monomers, using toluene as solvent. The new method provided samples with adequate molecular weight to ensure fiber-forming properties. New polymers were able to be processed from the melt since thermal decomposition started up to 200 ºC and consequently at a higher temperature than the melting temperature. As the above polymers, thermal degradation followed a process that involved two degradation steps. Samples were semicrystalline, being detected a glass transition temperature that decreased with the methylene content and a melting peak which appeared at a maximum temperature for the succinic acid derivative (157 ºC). Samples were also hydrolytically and enzymatically (proteinase K and *P. cepacia*) degradable.

2.2.5. Poly(Ester Amide)s Prepared by Chain Extender Reaction from 2-Oxazolines

It is well known that high molecular weights can be achieved by adding highly reactive coupling agents (chain extenders) during the last steps of melt polycondensation reactions. Bisoxazolines (Figure 16) have been revealed as highly efficient coupling agents for polyesters and polyamides. Furthermore, they can be commercially available at reasonable prices.

PEAs with relatively low molecular weights were firstly synthesized by Douhi *et al.* [92] when carboxyl-terminated polyamides were coupled with dioxazolines. Chalamet *et al.* [93] reported the synthesis of PEAs with high molecular weights by the coupling reaction of carboxyl-terminated polyamide 12 with 2,2'-(1,3-phenylene)-bis(2-oxazoline). The analysis of the influence of experimental conditions on the reaction conversion and the structure of the polymer did not show the occurrence of any particular side reaction.

Pó *et al.* [94] synthesized linear PEAs from bisoxazolines (2,2'-(1,4-phenylene)bis(2-oxazoline) and 2,2'-bis(2-oxazoline)) and dicarboxylic acids prepared *in situ* by reacting a diol with a monoanhydride (phthalic anhydride). The polymerization proceeded through the formation of a dicarboxy ester by reaction of two anhydride molecules with one diol molecule and subsequent 2-oxazoline ring opening by attack of the dicarboxy ester. Interestingly, the one-pot reaction between the three monomers led to linear PEAs with ordered structures,

despite anhydrides themselves could be reactive toward 2-oxazolines and gave rise to a crosslinked infusible polymer. The use of diols of different structure like α,ω-diols having up to 12 carbon atoms, ethylene glycol oligomers (two or three repeating units), cyclic diols and monoanhydrides such as glutaric, 3,3-dimethylglutaric and maleic anhydrides has also been evaluated [95]. Polymerization reactions were carried out in bulk between 150 and 200 ºC. A substantial agreement between the structure of the monomers and the glass transition temperature of the polymers was found. By using primary diamines instead of diols the polymerization reaction was unsuccessful due to a competitive imide formation reaction.

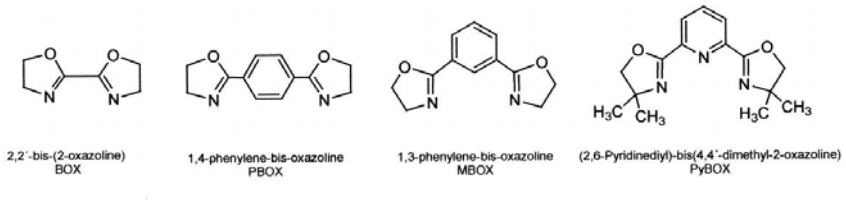


Figure 16. Usual bisoxazolines employed in the synthesis of poly(ester amide)s.

A series of novel aliphatic/aromatic PEAs have been synthesized by condensation reaction of aromatic bisoxazolines (bis(4-(2-oxazolyl-phenyl))phenylphosphine oxide and bis(4-(2-oxazolyl-phenyl))ether) with aliphatic dicarboxylic compounds (1,4-cyclohexane dicarboxylic acid, adipic acid, suberic acid and sebacic acid) [96]. These polymers had a number average molecular weight of 20,000 – 25,000 and were either amorphous or semi-crystalline depending of the aromatic structure of the bisoxazoline precursor. Polymers showed good solubility in aprotic solvents. In general, phosphine derivatives could be interesting as flame-retardant polymers.

Polyaddition reaction of aromatic bisoxazolines with aliphatic dicarboxylic acids were also studied by Luston *et al.* [97]: 1,4-bis(2-oxazolin-2-yl)benzene and 1,3-bis(2-oxazolin-2-yl)benzene were polymerized with aliphatic dicarboxylic acids with a number of methylene groups ranging between 4 and 12. Polymerizations were conducted in melt at temperatures above the melting point of at least one of the reaction components, or in a solution of aprotic high boiling organic solvents. The structure of the formed PEAs was proved by NMR spectroscopy. The effects of the structure of comonomers, reaction time, polymerization temperature, type of solvent, and concentration of monomers were also evaluated. Thermal properties were dependent on the length of the linear link in diacids, structure of bisoxazoline, and final molecular weight. The new materials had molecular weights in the range of potential industrial interest.

Polymers bearing pyridine rings were obtained by polycondensation of glutaric acid with the bis(2-oxazoline) of 2,6-pyridine dicarboxylic acid [98]. The great stability of substituted rings towards acids implied a reaction temperature over 160 ºC. Low molecular weights were attained in bulk polycondensation processes, but new polymers could have applications for metal ion complexation.

Böhme *et al.* [99] studied the thermal polymerization of AB monomers containing a 2-oxazoline group and an aromatic carboxylic group. The use of AB monomers insured the equivalence of reactive groups and diminished mixing problems. Furthermore, the high nucleophilicity of aromatic carboxylic groups gave rise to high molecular weight PEAs (M_n

25,000 - 45,000 g/mol). It was observed that the selectivity of the polyaddition reaction was influenced by the temperature and melt behaviour of the monomers used. Polymers based on fusible monomers were structurally more uniform when the synthesis was performed at lower temperatures. Due to the high mobility of the polymer chains at higher temperatures, the selectivity of the reaction was reduced, resulting in side reactions. Polymerization of the infusible monomers proceeded in the solid state and the mobility of the reacting species was in this case restricted, side reactions could be prevented almost completely. High reactivity and absence of volatile by-products made these new monomers interesting for reactive extrusion and blending.

Lactic acid based polyesters have nowadays a wide range of applications not only in the biomedical field but in packaging, consumer goods, and many other articles of short-term use. However, for many applications, the molecular weight of poly(lactic acid) needs to be relatively high in order to enhance mechanical properties. Alternative polymerization routes for lactic acid are being considered since conventional condensation polymerization of lactic acid does not sufficiently increase the molecular weight (unless long polymerization times were applied) and ring opening polymerization of lactide has the inconveniences of the relatively complicated and expensive monomer synthesis. Sëppäla *et al.* [100] investigated the use of 2,2-bis(2-oxazoline) as a chain extender for a lactic acid based carboxyl-terminated prepolymer (M_n 6,200 g/mol) to produce high molecular weight biodegradable PEAs (Figure 17), and to achieve good thermal and mechanical properties. These PEAs, like the prepolymer, were completely amorphous and the final molecular weight was strongly dependent on the polymerization temperature and molar ratio of end groups. The highest molecular weight was over 300,000 g/mol and the mechanical properties became comparable to selected biopolymers and commercial thermoplastics: the tensile strength was as much as 67 MPa, and the impact strength was about 34 kJ/m^2. These good results could provide an alternative to existing biodegradable lactic acid based polymers.

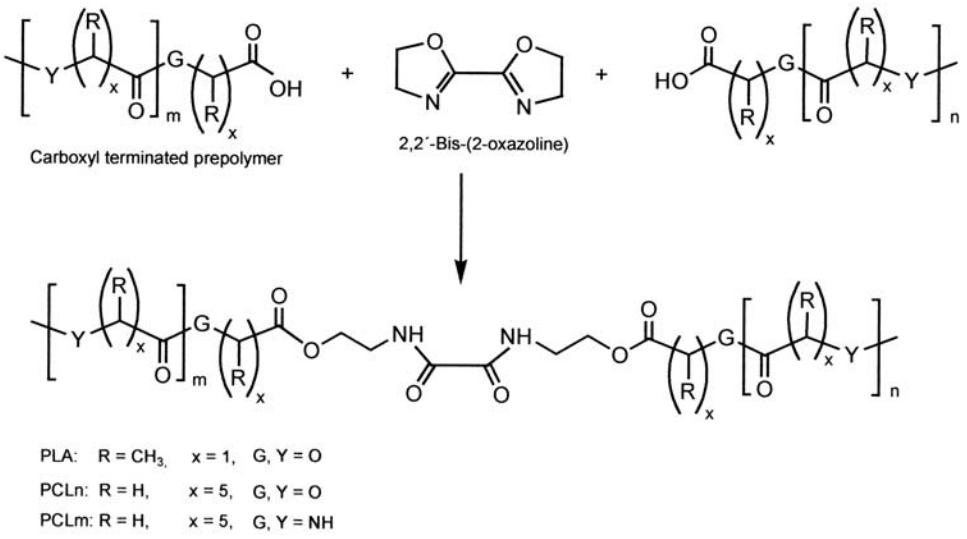


Figure 17. Synthesis of poly(ester amide)s from carboxyl-terminated prepolymers based on lactic acid, caprolactone or caprolactam units and using a bisoxazoline as a chain extender.

2.2.6. Poly(Ester Amide)s Prepared by Microwave Irradiation Polycondensation

Microwave irradiation is an effective, selective, and fast synthetic method to heat molecules directly through the interaction between microwave energy and molecular dipole moments of the starting materials. The microwave radiation penetrates deep into the material, and provides "volumetric" heating, as opposed to surface heating followed by thermal conduction of heat into the bulk. This internal heating is believed to produce an efficient reaction because the reactive sites, which have strong dipole moments, are the primary source of activation in the microwave electromagnetic field. In the last decade, considerable effort has been devoted to investigate the advantages of microwave irradiation over conventional heating techniques.

In the field of synthetic polymer chemistry, microwave energy has been used for addition polymerization (e.g. vinyl monomers), ring opening polymerizations (e.g. caprolactam and caprolactone monomers), condensation polymerization (e.g. synthesis of polyesters, polyamides and polyimides) as well as the curing of epoxy and polyurethane resins. Microwave irradiation has been even employed in the synthesis of PEAs. Specifically, the polycondensation of sebacic acid and α,ω-aminoalcohols (3-aminopropanol, 2-aminoethanol, and 6-aminohexanol) was performed and the results compared to those obtained from conventional melt polycondensation [101,102]. It was found that the reaction proceeded at a much higher rate, had higher energy efficience, had higher yield and rendered higher molecular weight upon microwave irradiation. Furthermore, physicochemical properties of polymers were in good agreement with those of samples obtained by conventional synthesis.

Microwave irradiation was also applied to synthesize poly(ε-caprolactam-*co*-ε-caprolactone)s directly from the anionic polymerization of mixtures of the two cyclic monomers and using tri-tert-butoxyaluminohydride as catalyst [103]. Polymerizations were performed under a low microwave forward power (40–50 W at frequencies varying between 4.19 and 5.19 GHz) due to the high microwave absorption of the starting materials. Results showed that amide composition increased with the increased reaction temperature, time, and catalyst level, while molecular weights of copolymers decreased with the increased catalyst level. Glass transition temperatures of copolymers suggested a random microstructure of copolymers. Compared with the corresponding thermal products, microwave-synthesized copolymers gave higher yield, higher amide composition, higher glass transition temperature and equivalent molecular weight.

3. SPECIFIC FAMILIES OF POLY(ESTER AMIDE)S

3.1. Functionalized Poly(Ester Amide)s

Applications of PEAs can be significantly expanded by incorporation of functional pendant groups since for example they could allow further chemical conjugation with a wide variety of drugs, targeting groups, cell signalling molecules or other biological agents. Furthermore, the presence of built-in functional groups could also provide an efficient and powerful method of tailoring properties of PEAs, such as hydrophilicity, biodegradation rate, and mechanical and thermal properties.

Efforts to get functionalized PEAs were not materialized and reported until the early 2000s when L-lysine copolymers with pendant carboxylic groups were prepared [104,105]. A second approach was based on the use of unsaturated diols and dicarboxylic acids that provided the PEA backbone of reactive double bonds [106-109]. These materials were suitable for preparing hydrogels by fotogelation which were also tested as drug carriers and will be discussed in detail in the next section [110]. Bis(L-lysine) α,ω-alkylene diester was also incorporated into a PEA and the pendant amine group recovered after a deprotection reaction [111]. This process appears expensive due to the starting material and the complicated synthesis and purification steps.

PEAs with a regular sequence and derived from diamine, dicarboxylic acid, and glycolic acid units were easily synthesized by using a thermal polycondensation method based on the formation of metal halide salts as a driving force (section 2.2.4.). This procedure could also be applied when esters of L-lysine were used as a diamine unit since no secondary reactions such as transesterification occurred under the required polymerization conditions (Figure 18) [112]. The possibility of linking compounds with pharmacological activity to the carboxylic acid groups of lysine extended the interest of the referred materials, for example, as drug delivery systems.

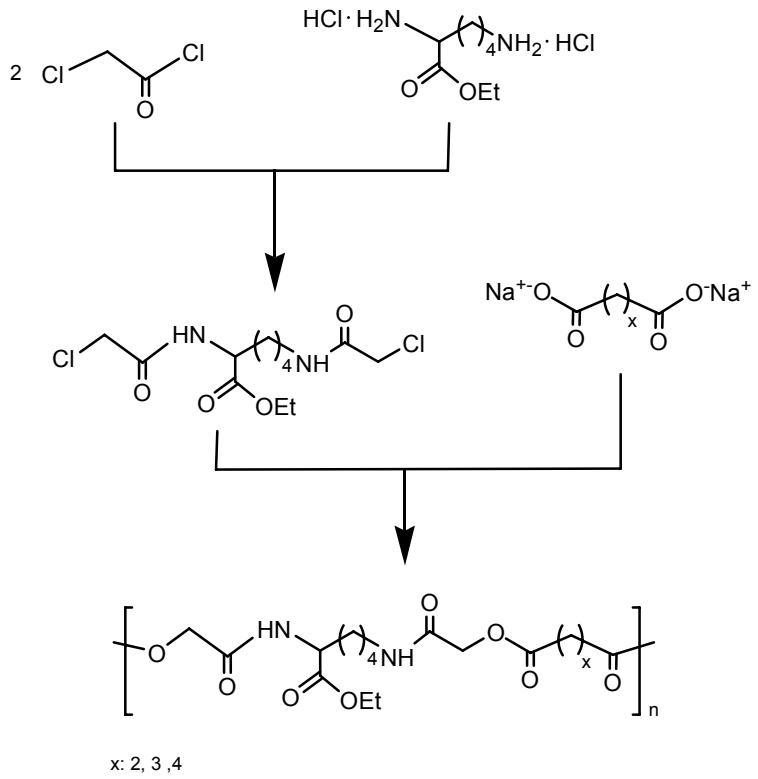


Figure 18. Synthesis of functionalized poly(ester amide)s derived from glycolic acid by a thermal polycondensation reaction induced by the formation of metal halide salts.

A simple and versatile strategy based on orthogonal protecting groups has been proposed by Atkins *et al.* [113,114]. The method allows the incorporation of L-lysine and L-aspartic acid into PEAs based on diacids (succinic and terephthalic acid), diols (1,4-butanediol and

1,8-octanediol) and amino acids (L-alanine and L-phenylalanine) (Figure 19). It was demonstrated that the side chain protecting groups could be readily removed, allowing the pendant amines or carboxylic acids to be functionalized. In particular, the carboxylic acid groups on a polymer containing L-aspartic acid units were converted to *N*-hydroxysuccinimidyl esters, providing a useful template for further derivatization.

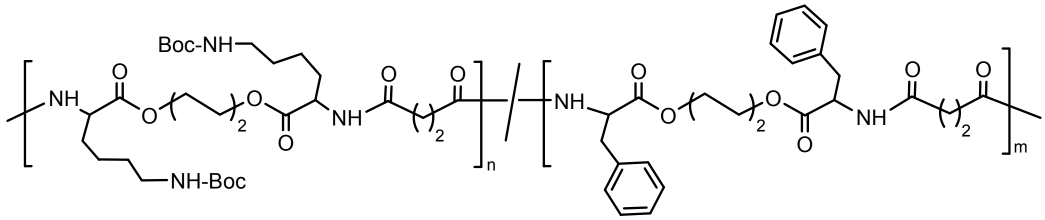


Figure 19. Scheme of functionalized poly(ester amide)s derived from diols, dicarboxylic acids (e.g. succinic acid) and α-amino acids (e.g. L-phenylalanine and protected L-lysine).

Chu *et al.* [115] have reported a new copolymerization method that allows the preparation of PEAs having free amine groups (Figure 20). The procedure involved a ring-opening reaction of a protected amino acid derivative like ε-(benzyloxycarbonyl)-L-lysine *N*-carboxyanhydride (Z-LysNCA) with di-*p*-toluenesulfonic acid salts of bis-L-phenylalanine hexane-1,6 diester (Phe-6), followed by solution polycondensation of di-*p*-toluenesulfonic acid salt mixtures with di-*p*-nitrophenyl sebacoylate. The pendant free amine groups of copoly(ester amide)s were easily regenerated by a subsequent deprotection under a simple acid treatment. The content of amine groups of the resulting functional PEA copolymers was controlled by adjusting the feed ratio of Phe-6 to Z-LysNCA monomers.

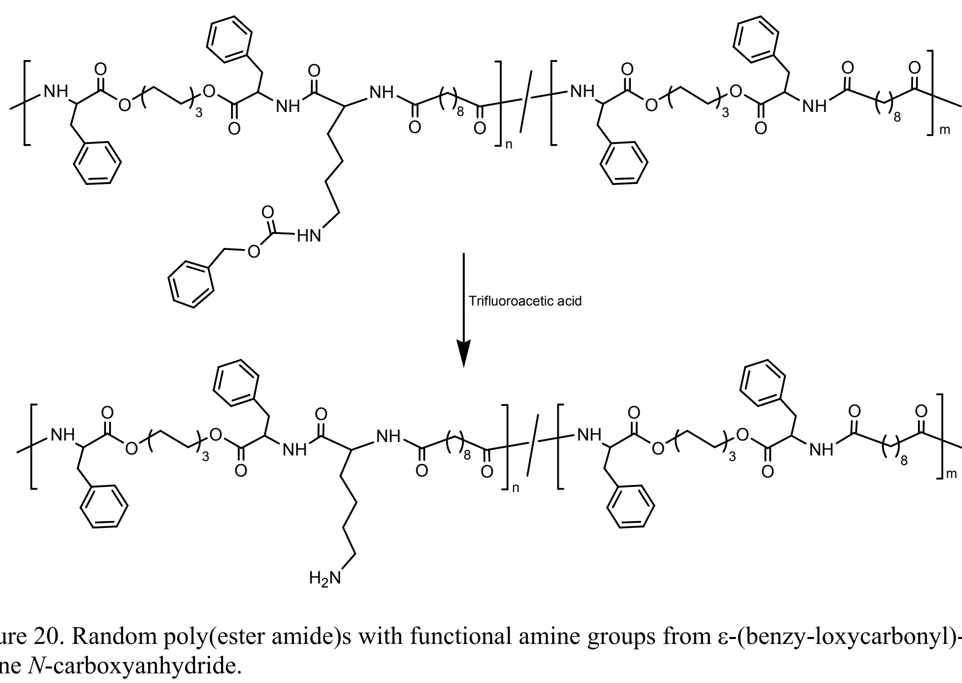


Figure 20. Random poly(ester amide)s with functional amine groups from ε-(benzy-loxycarbonyl)-L-lysine *N*-carboxyanhydride.

All PEAs having L-lysine content were amorphous and exhibited T_gs ranging from 18 to 32 °C. The bulky pendant protective group in the L-lysine unit decreased the glass transition temperature due to its plastizicing effect. After deprotection, the recovered pendant amine groups strengthened intermolecular interactions among PEA chains via hydrogen bonds and increased the glass transition temperature. The preliminary data of cell proliferation and cytotoxicity of these new functional and positive charged PEAs show that they support bovine aortic endothelial cell proliferation without cytotoxicity.

A series of biodegradable functional amino acid based PEAs were designed and synthesized by the solution *co*-polycondensation of amino acid (i.e. L-phenylalanine and DL-2-allylglycine) based monomers and dicarboxylic acid based monomers [116]. Polymers incorporated pendant carbon-carbon double bonds through the DL-2-allylglycine units and consequently the content on these functional groups could be adjusted by tuning the feed ratio of L-phenylalanine to DL-2-allylglycine monomers. The glass transition temperature of PEAs decreased by increasing the methylene chain in both the amino acid and dicarboxilic acid segments. The incorporation of the functional pendant carbon-carbon double bonds along the polymer chains could significantly expand the biomedical applications via either their capability to conjugate bioactive agents or prepare additional useful functional derivatives.

Cytotoxicity, ability to support cell growth, inflammatory properties, and mechanical properties have been investigated for some amino and carboxylic acid functionalized PEAs based on amino acids, diols and dicarboxylic acids [117]. Results indicate that all forms of PEAs were noncytotoxic and noninflammatory *in vitro*. The amino-functionalized PEAs best supported endothelial cell adhesion, growth, and monolayer formation. Data suggested that PEAs could be viable biomaterials for use in tissue engineering applications, particularly for use as vascular grafts.

New biodegradable elastomeric PEAs have been synthesized for tissue engineering applications [118]. These new materials allow overcoming some limitations of conventional crosslinked aliphatic polyesters: a) High crosslink densities, which results in exceedingly high stiffness, b) Rapid degradation upon implantation, or c) Limited chemical moieties for chemical modification. Poly(1,3-diamino-2-hydroxypropane-*co*-polyol sebacate)s formed crosslinked networks through their diamino alcohol (1,3-diamino-2-hydroxypropane) and polyol (glycerol and/or D,L-threitol) units (Figure 21) and featured tensile Young's modulus on the order of 1 MPa and reversable elongations up to 92%. These polymers exhibited *in vitro* and *in vivo* biocompatibility and had projected degradation half-lives up to 20 months *in vivo*.

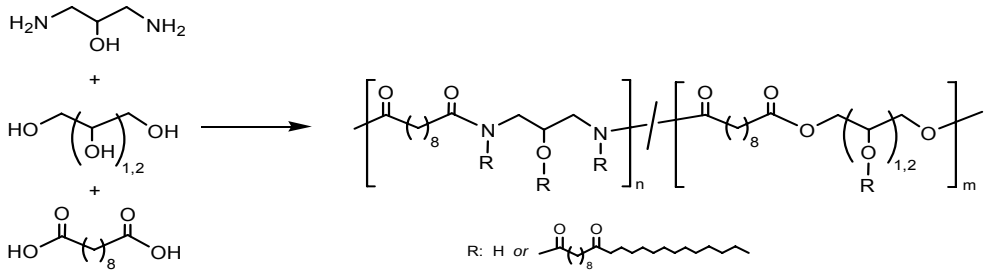


Figure 21. Synthesis of elastomers based on a hydroxy-functionalized diamine (e.g. 1,3-diamino-2-hydroxypropane), a polyol (glycerol or D,L-threitol) and a dicarboxylic acid (e.g. sebacic acid).

Functionalized polymers were also synthesized by ring-opening polymerization of morpholine-2,5-diones derived from α-amino acids like L-aspartic acid, L-glutamic acid, L-lysine, L-serine and L-cysteine which rendered pendant carboxylic acid, amine, hydroxyl and thiol groups, respectively [118-122]. The synthesis involved a protection of functional groups before obtaining the reactive cycle and the subsequent deprotection once the polymerization step took place. In general, substituted morpholine-2,5-diones showed a low reactivity and consequently strategies based on the copolymerization with different lactones (e.g. ε-caprolactone and D,L-lactide) were proposed [8].

An easy way to prepare polydepsipeptides with pendant functional groups consists on the random copolymerization of lactones and amino acid carboxyanhydrides using stannous octoate as a catalyst [123].

3.2. Unsaturated Poly(Ester Amide)S

Unsaturated PEAs containing α-amino acids have been synthesized by the conventional method based on the condensation of bis(α-amino acid) α,ω-alkylene diesters and aliphatic dicarboxylic acids. In this case, unsaturated or even mixtures of unsaturated and saturated dicarboxylic acids have been employed. Incorporation of unsaturated units (e.g. by using bis-*p*-nitrophenyl fumarate) brings C = C double bonds in the backbone that increase rigidity and the glass transition temperature (respect to saturated polymers with a similar chemical structure). Furthermore, double bonds are new reactive sites that could be used to make crosslinked hydrogel networks.

Chu *et al.* studied the polymerization of the *p*-toluenesulfonic acid salt of L-phenylalanine butane-1,4-diester with different mixtures of di-*p*-nitrophenyl esters of saturated and unsaturated dicarboxilic acids [124,125]. Thus, polymers derived from succinic, adipic or sebacic acids as saturated units and fumaric acid as unsaturated unit were considered. Copolymers having different unsaturation levels were easily achieved by the adjustment of the feed ratio of the two dicarboxylic monomers. Copolymers had rather high M_n molecular weights that varied between 14,600 and 36,900 g/mol. The thermal properties, solubility, and biodegradability of copolymers could be controlled within a range between those of pure saturated and unsaturated polymers. The glass transition of copolymers logically increased with the increase of unsaturated units. A preliminary *in vitro* biodegradation test showed that these copolymers could be enzymatically hydrolyzed by α-chymotrypsin even at a low enzyme concentration, although their hydrolysis in a pure PBS buffer medium was very slow. It was also found that the biodegradability of copolymers was affected by the length of the methylene groups in the saturated dicarboxylic units (the increase resulted in a lower hydrolyzable ester bond density and a slower biodegradation rate). The applied methodology seems interesting to tune properties in order to meet the requirements for a wide range of biomedical applications.

A series of biodegradable random unsaturated/saturated poly(ether ester amide)s were synthesized by solution polycondensation of diamine salts of phenylalanine and triethylene glycol with the *p*-nitrophenyl active esters of mixtures between unsaturated (fumaric acid) and saturated dicarboxylic acids (succinic, adipic and sebacic acid) (Figure 22) [126]. These random copolymers were obtained with fairly good yields using *N*,*N*-dimethylacetamide as a

solvent. The M_n molecular weights ranged from 3000 to 27,000 g/mol and the polydispersity index between 1.52 and 2.13. The glass transition temperature was always intermediate between the related pure unsaturated and pure saturated polymers, and increased by increasing the unsaturated content. Copolymers showed a high degradability in α-chymotrypsin enzyme solutions and the biodegradation rates decreased with the unsaturated content. Interestingly, it was concluded that upon adjusting monomers feed ratio, copolymers could have controlled chemical, physical, and biodegradation properties.

A series of hydrogels were obtained from unsaturated PEAs and poly(ethylene glycol) diacrylate and their degradation studied in both PBS and α-chymotrypsin solutions [127,128]. Unsaturations were obtained by using fumaric acid and/or 2-butene-1,4-diol units (Figure 23).

Based on the weight loss data, α-chymotrypsin had a much more profound effect on the hydrolysis (up to 32% weight loss on day 31) than PBS (less than 16%). The changes in elastic moduli and the interior morphology of the hydrogels were monitored during biodegradation and both the crosslinking density and the molecular weight between crosslinks determined. The differences in biodegradation rates showed that hydrogels could have controllable biodegradability by changing the concentration of α-chymotrypsin, the type of unsaturated precursor and the feed ratio (i.e. the ratio between the PEA precursor and the acrylate coupler).

Unsaturated random copoly(ester amide)s were synthesized by reaction of a mixture of phthalic and maleic anhydrides with ε-caprolactam and a mixture of ethylene and neopentylene glycols [129]. The final oligomers (M_n 2100-2600 g/mol) were effectively cross-linked using vinyl acetate and benzoyl peroxide - ascorbic acid as initiator-accelerant agents. The new materials showed a high compressive strength (104.0 MPa) and were hydrolytically degradable. Heat treatment conditions and crosslinker content played an important role to decrease the cumulative mass loss during the hydrolysis process. Measured properties suggested that these copolymers may potentially be used as a new type of bone fixation material. Copolymers with similar characteristics were obtained by the same procedure but changing ε-caprolactam by 1,6-hexanediamine [130] or glycine [131]. In the first case, preliminary biocompatibility in mice skin was evaluated being the results promising for their expected biomedical applications. Mechanical properties of composites constituted by the glycine derivative and calcium polyphosphate fibers were also evaluated. Results indicated that the mechanical strength increased very quickly as the fiber content raised. Flexural and compressive strength achieved maximal values when this content was close to 50-60 wt%.

Insertion of a hydrophilic segment, (e.g. poly(ethylene glycol)) in the main chain of a PEA is an efficient way to favour its hydrolytic degradation since ether linkages can form hydrogen bonds with water and enhance the water uptake [132]. Unsaturated poly(ether ester amide)s are receiving great attention since combine C=C double bonds as functional groups and short ethylene oxide chains as a flexible spacer into the polymer backbone. Tailoring of the properties of such polymers can be achieved by a variation of the length of the hydrophilic blocks, which results in polymer systems with a wide range of properties.

A series of novel biodegradable unsaturated PEAs was successfully prepared through interfacial polycondensation of 1,6-hexanediamine and unsaturated diacylchlorides containing ethylene oxide moieties (from 1 to 4 units) linked to maleic anhydride by ester bonds (Figure 24) [133]. The obtained polymers were amorphous and stable up to 300 ºC under nitrogen.

Synthesized poly(ether ester amide)s showed good hydrophilicity and improved solubility. The degradation results indicated that these polymers were hydrolyzable in a rapid and steady way, increasing the rate of hydrolytic degradation (pH 7.2 phosphate buffer solution at 37 ºC) by increasing the number of ether linkages per repeat unit.

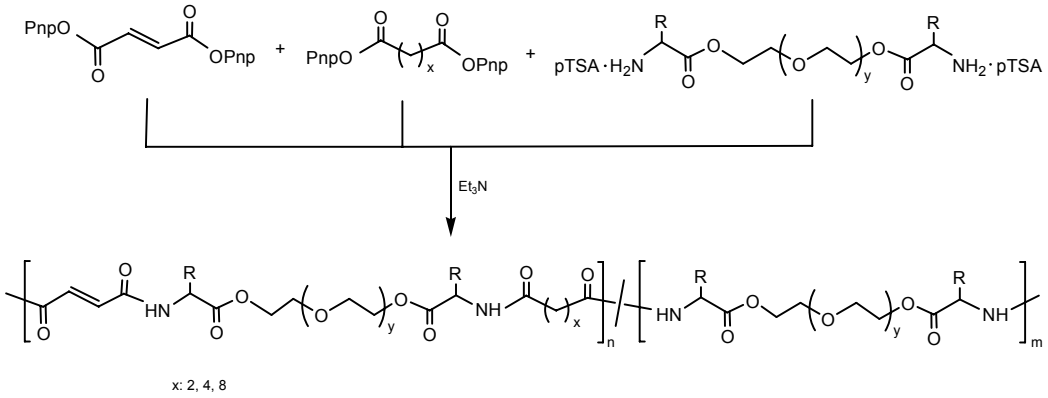


Figure 22. Synthesis of poly(ether ester amide)s constituted by saturated and unsaturated dicarboxylic acid units.

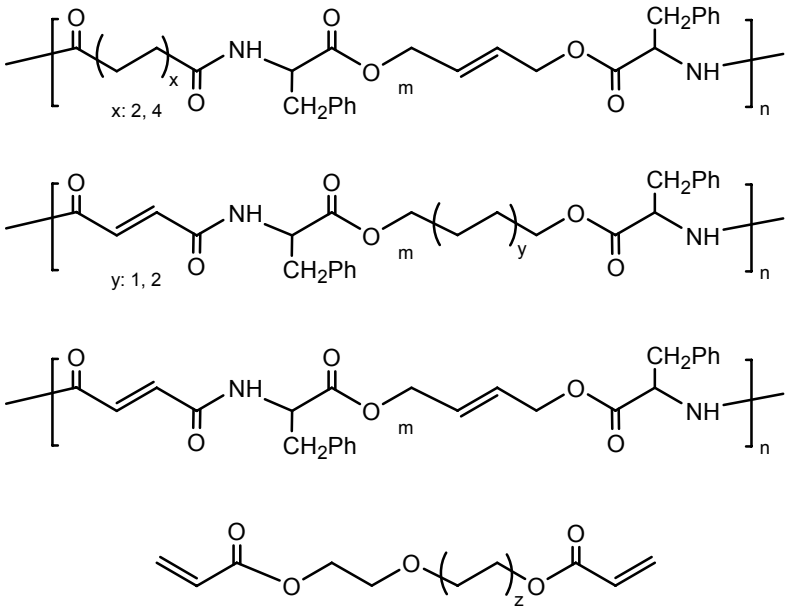


Figure 23. Chemical structure of unsaturated poly(ester amide)s and coupling precursors used for preparing hydrogels.

An unsaturated dicarboxylic-terminated oligoester was prepared by reaction of ethylene glycol lactate diol with maleic anhydride [134] The oligoester was then melt-polycondensed with toluene-2,4-diisocyanate to render a crosslinked resin with unsaturated double bonds (Figure 25). The new polymer showed a porous structure due to the formation of CO_2 in the last synthesis step and was degradable. As a result of introducing isolated C=C double bonds,

the polymer was flexible enough to exhibit shape-memory characteristics. It is worth mentioning that the glass transition temperature was close to human body temperature which meets one of the basic requirements for medical applications.

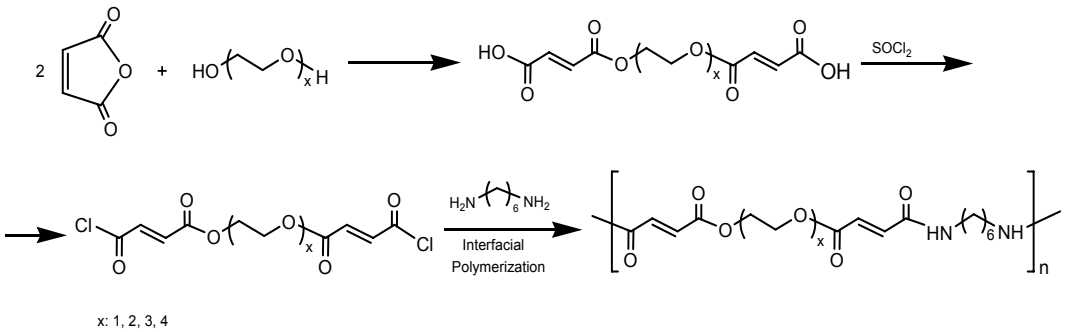


Figure 24. Synthesis of unsaturated poly(ether ester amide)s containing ethylene oxide moieties.

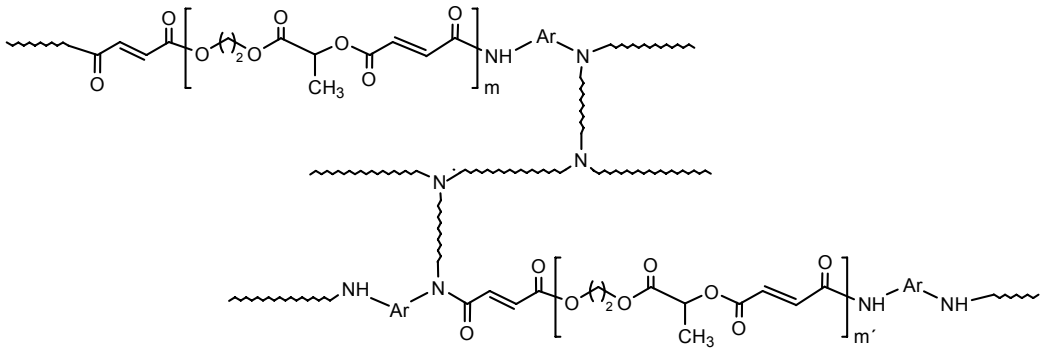


Figure 25. Crosslinked unsaturated poly(ester amide)s containing lactic acid units.

Novel unsaturated PEA resins were prepared by the addition reaction of commercially available epoxy resin (diglycidyl ether) synthesized from bisphenol-A and epichlorohydrin with aromatic unsaturated bisamic acids [135]. Thus, new materials that combine properties of epoxy resins, polyamides, and unsaturated polyester resins could be easily obtained. The curing study of these new resins was carried out by using benzoyl peroxide as a catalyst, according to the curing temperature obtained from DSC thermograms. Moreover, composites were fabricated and characterized using these resins reinforced with glass fibers.

3.3. Poly(Ester Amide)s from Renevable Sources

In concert with the depletion of oil resources, increasingly greater attention has been directed to effective utilization of plant-biomass and carbohydrates as alternative renewable resources that can be steadily supplied and used for polymer syntheses.

3.3.1. Carbohydrate Derivatives

Synthetic polymers containing carbohydrates in the main chain have been considered as a new type of biodegradable and biocompatible polymeric materials. Furthermore and despite limitations derived from their multifunctionality, carbohydrates stand out as highly convenient raw materials for the synthesis of stereoregular polymers containing several stereocenters in the main chain, due to their easy availability and great stereochemical diversity. It has been demonstrated that physical properties and biological activity can be varied by controlling the tacticity and regicity of the samples.

Derivatives of L-Tartaric Acid

Syndioregic and isoregic PEAs containing equal amounts of ester and amide groups have been obtained by polycondensation in solution from di-O-methyl-L-tartaric acid and aliphatic aminoalcohols $H_2N(CH_2)_{(n-1)}CH_2OH$ (n = 5, 6 ,11) (Figures 26 and 27) [136].

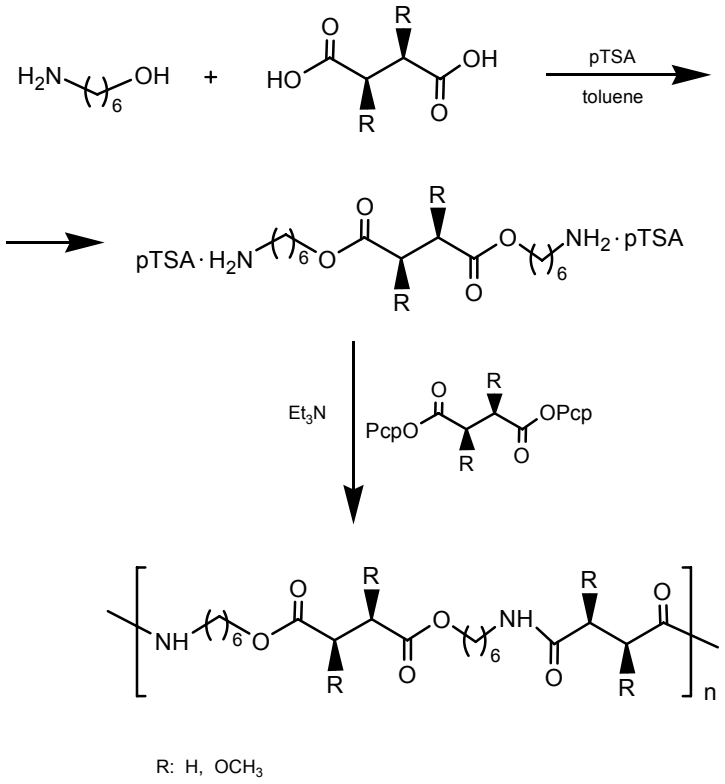


Figure 26. Synthesis of syndioregic poly(ester amide)s derived from α,ω-aminoalcohols (e.g. 6-aminohexanol) and tartaric acid.

These polymers were crystalline (except the syndiotactic sample derived from 5-aminopentanol) with melting points in the 100-150 ºC range and showed glass transition temperatures between 10 and 30 ºC. Thermal decomposition started at a temperature higher than 200 ºC which depended upon both the regicity of the chain and the length of the polymethylene segment. Major differences between syndio- and isoregic samples concerned solubility and hygroscopicity, whereas crystallinity and thermal transitions were found to be scarcely affected by the presence of the methoxy side groups.

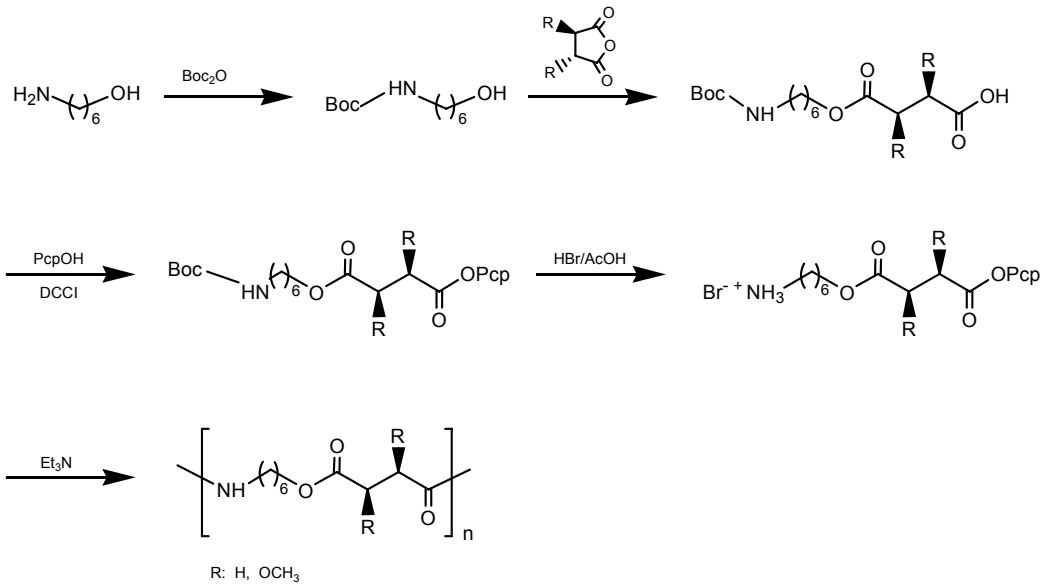


Figure 27. Synthesis of isoregic poly(ester amide)s derived from α,ω-aminoalcohols and L-tartaric acid.

The studied poly(tartarester amide)s adopted crystal packings with chains spaced out by the side methoxy groups and with a contraction in the axial repeat. The structure was described as a stacking of hydrogen-bonded sheets made of chains with the tartaric unit in the gauche arrangement. It was also suggested that the high chain contraction observed could be caused by an additional torsion of the ester group [136].

Solution polycondensation of 1,6-diamine with mixtures of pentachlorophenyl-activated di-O-methyl-L-tartaric and 6-aminohexyl-di-O-methyl-L-tartaric acids (Figure 28) led to a series of aregic PEAs with ester/amide ratios varying from 1:19 to 1:2 and number-average molecular weights between 25,000 and 45,000 [137]. These polymers were highly crystalline, showed melting temperatures ranging from 100 to 230 ºC and glass transition temperatures oscillating between 50 and 100 ºC. Thermal degradation of aregic polymers began above 200 ºC and concluded with a final weight loss between 60 and 90% of the initial mass. The process evolved with the formation of cyclic tartarimide units and extensive main-chain scissions [137].

X-ray diffraction studies on aregic PEAs were also reported and revealed a similar crystal structure than postulated for syndioregic and isoregic samples [138]. Polymers crystallized as complex morphologies displaying heterogeneous texture with axialite-like features. It was indicated that crystallization took place with molecular segregation, probably of those copolymer chain segments enriched in ester groups. The crystallization rate clearly decreased with increasing contents in ester groups and with increasing the isothermal crystallization temperature. Furthermore, solid-state nuclear magnetic resonance (NMR) suggested that ester groups were excluded from the crystal phase.

Hydrolytic degradation studies under physiological conditions were performed with the series of PEAs prepared from α,ω-aminoalcohols and aliphatic dicarboxylic acids including succinic, glutaric, and tartaric acids. It was found that degradation critically depended on the regicity of the polymer chain (aregic > isoregic > syndioregic) and the number of methylenes

of the dicarboxylic unit. Studies on model compounds corroborated that chain scission took place by intramolecular amidolysis with formation of either succinimide or tartarimide units (Figure 29). This mechanism required the presence of four-carbon diacid units in the main chain and was unable to operate if the polymer chain had an entirely syndioregic microstructure. The results seem relevant to the design of sequential PEAs with controlled hydrodegradability [139].

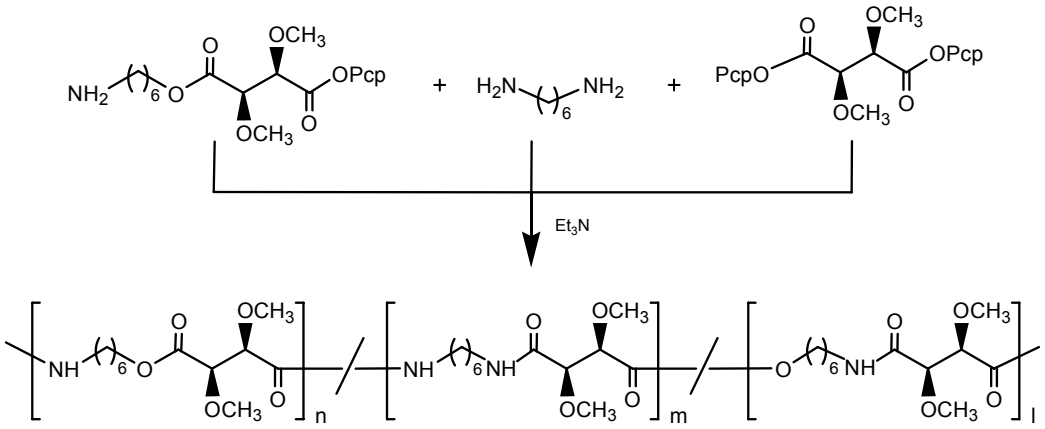


Figure 28. Synthesis of aregic copoly(ester amide)s derived L-tartaric acid, 1,6-hexanediamine and 6-aminohexanol.

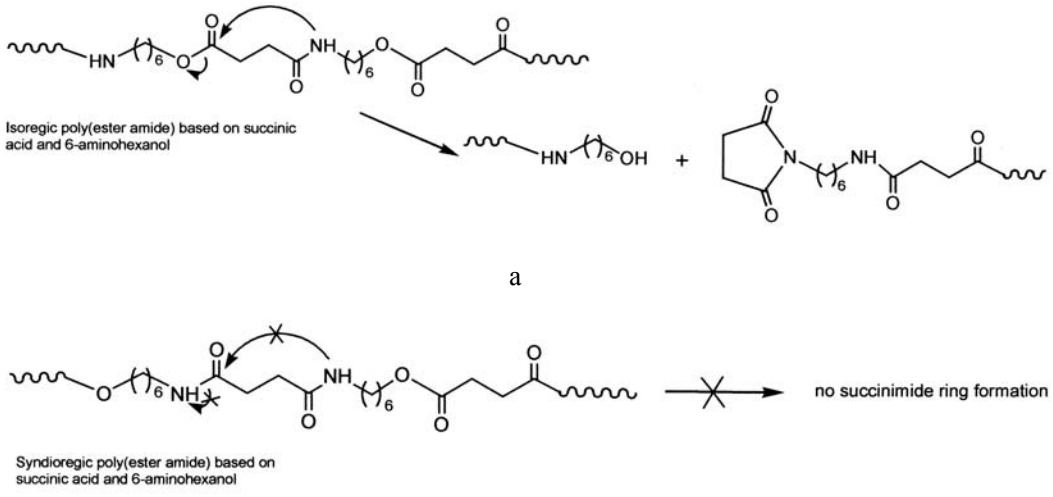


Figure 29. Degradation mechanism through formation of succinimide rings is possible for isoregic PEAs based on succinic acid and α,ω-aminoalcohols (a), but not for the syndioregic derivatives (b).

The hydrolytic (pH 7.4 buffered solution at 37 ºC) and enzymatic (papain) degradation of a series of crystalline copoly(ester amide)s derived from L-tartaric and succinic acids, 1,6-hexanediamine and 1,6-hexanediol (Figure 30) with ester/amide group ratios of 3/97, 10/90, 15/85 and 20/80 has also been investigated [140].

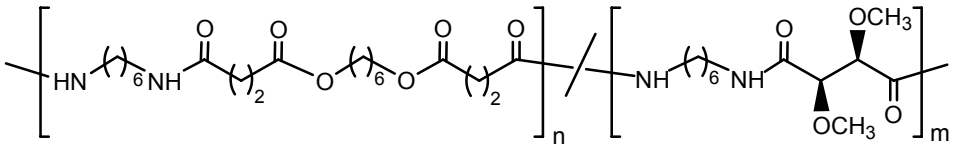


Figure 30. Chemical structure of random copoly(ester amide)s constituted by L-tartaric and succinic acids, 1,6-hexanediamine and 6-aminohexanol units.

Copoly(ester amide)s degraded faster than the parent poly(hexamethylene-di-O-methyl-L-tartaramide) and the rate of degradation increased with the content in ester groups. It was observed that cyclic succinimide units were formed during hydrolytic degradation and thus a scission mechanism involving the occurrence of intramolecular imidation reactions was also postulated. In this way, degradability was enhanced not only by the presence of ester groups in the backbone but also by the strategic position of such groups with respect to the amide groups (i.e. the imide ring formation required the nucleophilic attack of an amide group onto a neighboring ester linkage). Enzymatic degradation of the studied copoly(ester amide)s was strongly dependent on their ester group content. The imide ring formation was in this case low and consequently the preferred reaction mechanism was the cleavage of ester bonds by the action of water, as expected from an enzyme-mediated degradation.

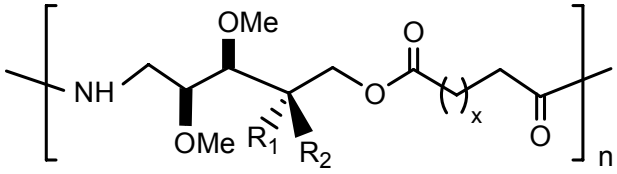
The changes in structure and properties upon hydrolytic degradation were examined for copolymers containing a low percentage of succinic acid units (less than or equal to 10%) [141]. Moisture uptake and hydrolysis induced a noticeable decay in the tensile properties of polymers, being these effects greatly enhanced by the presence of ester groups. Variations in the glass transition temperatures and melting points appeared to be slight, whereas crystallinity clearly increased with incubation time. The latter effect was most apparent in PEAs with a nearly racemic composition, in which a crystal-to-crystal transition was postulated to take place upon degradation.

Derivatives of L-Arabinose and D-Xylose

L-Arabinose and D-xylose were transformed into 1-amino-1-deoxy-2,3,4-tri-O-methyl-5-O-[(pentachlorophenoxy)succinyl]-L-arabinitol and 1-amino-1-deoxy-2,3,4-tri-O-methyl-5-O-[(pentachlorophenoxy)succinyl]-D-xylitol hydrochlorides, respectively, in a seven step synthesis and then polymerized in solution using ethyldiisopropylamine as an acid acceptor (Figure 31) [142,143]. Viscosimetric and GPC data revealed that high molecular weights could be attained. The regular PEA derived from arabinose melted above 135 ºC and was thermally stable up to 250 ºC under nitrogen [140]. The polymer derived from xylose was amorphous indicating a great chain conformational flexibility that may contribute to the decreasing of cohesive forces between the chains [141].

The hydrolytic degradation (37 ºC in bidistilled water and/or pH 7.4 buffered solution) of three stereoregular PEAs obtained by polycondensation of 1-amino-1-deoxy-2,3,4-tri-O-methyl-5-O-[(pentachlorophenoxy)succinyl]-L-arabinitol, 1-amino-1-deoxy-2,3,4-tri-O-methyl-5-O-[(pentachlorophenoxy)glutaryl]-L-arabinitol, and 1-amino-1-deoxy-2,3,4-tri-O-methyl-5-O-[(pentachlorophenoxy)succinyl]-D-xylitol hydrochlorides was also studied and compared [144]. Degradation occurred by hydrolysis of the ester linkages at a rapid rate which was dependent on the crystallinity and hydrophilicity of the samples. PEAs containing

succinic acid units degraded faster according to a mechanism where succinimide rings were formed.



R_1 = OMe, R_2 = H, x = 1
R_1 = OMe, R_2 = H, x = 2
R_1 = H, R_2 = OMe, x = 1

Figure 31. Chemical structure of poly(ester amide)s derived from L-arabinose or D-xylose.

Random copolymers of the arabinose-succinyl monomer and 5-amino-1-O-[(pentachlorophenoxy)glutaryl]pentanol hydrochloride were also prepared (Figure 32) and their hydrolytic degradation studied [145]. Results demonstrated that the degradation rate could be enhanced by increasing the amount of the arabinose-succinyl monomer incorporated in the polymer chain. In this way, small amounts of this monomer were enough to produce a noticeable increase in polymer degradability. Spectroscopic investigations of the hydrolysis products provided evidence for succinimide ring formation, supporting a general mechanism proposed for the hydrolysis of PEAs containing four-carbon diacid units in their structure. The solubility in water of the copoly(ester amide)s containing about 50% of the sugar-based monomer displayed a temperature dependence that was studied and related with the hydrolysis.

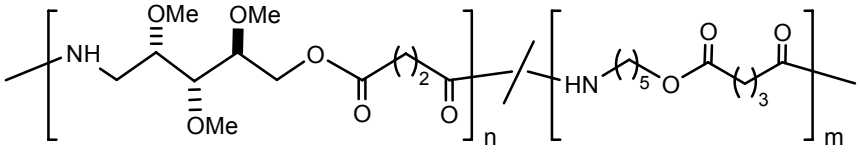


Figure 32. Chemical structure of copoly(ester amide)s contaiming L-arabinose, succinyl and glutaryl units.

Derivatives of Hydrophobic α-Amino Acids and Dianhydrohexitols

Dianhydrohexitols (e.g. 1,4:3,6-dianhydrosorbitol and 1,4:3,6-dianhydromannitol) were used as secondary diols to react with α-amino acids (L-phenylalanine, L-leucine, L-isoleucine, and L-methionine) in the presence of *p*-toluenesulfonic acid [146]. The obtained ester bisammonium *p*-toluenesulfonates were then polycondensed with the *p*-nitrophenyl active esters of even dicarboxylic acids with a number of methylene groups ranging from 4 to 10 (Figure 33).

Polymers appear highly interesting since diols are available in industrial quantities, are derived entirely from renewable resources (starch) and are used in pharmacy (i.e. they are non-toxic). Problems associated to the low reactivity of the sterically hindered secondary hydroxyl groups were avoided with the preparation of O,O'-bis-α-aminoacyl derivatives

which led to sterically unhindered (by the bicyclic fragments at least) and highly active functional amino groups that facilitated the polymer synthesis.

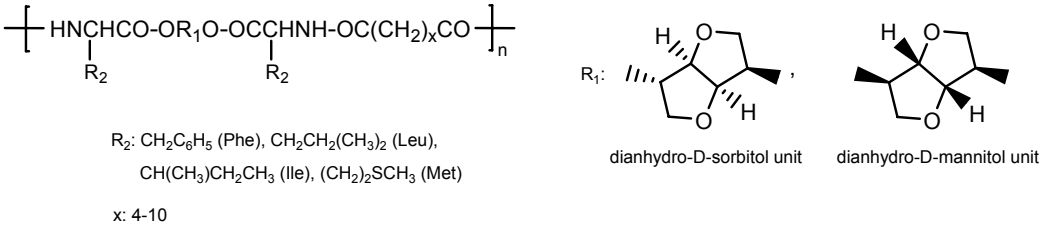


Figure 33. Chemical structure of poly(ester amide)s constituted by dianhydrohexitols, α-amino acids and dicarboxylic acids.

Polymers could be obtained with rather high molecular weights (e.g. 32,000 g/mol for the derivative of phenylalanine, sebacic acid and mannitol) and narrow polydispersities (1.0-1.7). Samples were soluble in common organic solvents like chloroform and tetrahydrofuran and could be cast into films. Polymers had glass transition temperatures up to 60-120 ºC due to the presence of rigid cycles (i.e. higher than related polymers derived from alkylenediols).

Degradation studies performed with α-chymotrypsin and lipase revealed highest tendency towards enzyme catalyzed hydrolysis for the PEAs based on L-phenylalanine probably due to the highest hydrophobicity of the benzyl side groups. Hydrolysis decreased with the length of the diacid unit (i. e. with increasing hydrophobicity of the polymer backbone) since a competitive interaction between the hydrophobic acyl residue and the hydrophobic sites of the enzyme led to a non-productive binding and a decrease on the overall hydrolysis rate. In any case, degradation rates were comparable with those found for related α,ω-alkylenediol derivatives demonstrating that hydrolysis was not prevented by the rigid bicyclic fragments.

A series of PEAs were also synthesized by solution polycondensation of various combinations of *p*-toluenesulfonic acid salts of *O,O*'-bis(α-aminoacyl)-1,4:3,6-dianhydro-D-glucitol and bis(*p*-nitrophenyl) esters of aliphatic dicarboxylic acids with methylene chain lengths of 4–10 [147]. The polycondensations were carried out in *N*-methylpyrrolidone at 40°C in the presence of triethylamine and gave rise to PEAs having number-average molecular weights up to 3.8 10^4 g/mol. Most of these PEAs were amorphous and soluble in a variety of polar solvents. These PEAs were, in general, degraded more slowly than the corresponding polyesters having the same aliphatic dicarboxylic acid units, both in composted soil and in an activated sludge. However, enzymatic degradation tests using papain (an enzyme able to favour ester-bond and amide-bond cleavages) indicated that PEAs degraded faster than the corresponding polyesters. This faster degradation was only observed with PEAs containing dicarboxylic acid components with shorter methylene chain lengths when *Porcine pancreas* lipase was tested.

Intraocular polymer delivery systems based on biodegradable PEAs derived from bicyclic-fragments of 1,4:3,6-dianhydrohexitols such as D-glucitol, D-mannitol or L-iditol have been patented [148]. It has been claimed that the new systems released opthalmologic agents in a consistent and reliable manner into the exterior or interior of the eye by biodegradation of the polymer.

3.3.2. Poly(Ester Amide)s from Vegetable Oils and Fatty Diacids

Synthesis of polymers from vegetable oils is economically, scientifically, and environmentally significant because of their environmentally friendly nature, low cost, abundance, and possible biodegradability. Linseed oil, one of the most widely occurring vegetable oils, has been employed to prepare PEAs with superior characteristics over normal alkyds in terms of hardness, ease of drying, and water vapor resistance. A polymer with fatty lateral chains was easily obtained through condensation polymerization of phthalic anhydride and *N*,*N*-bis(2-hydroxyethyl) linseed oil [149]. The sample exhibited high thermal stability, and good physicomechanical and chemical resistance properties to find application as a corrosion protective coating.

Multiblock copolymers based on oligoamide (M_n, 2000 g/mol) and aliphatic oligoesters from a dimerized fatty acid and 1,4-butanediol were prepared by melt polycondensation under vacuum (~ 400 Pa) at 255–260 ºC, and using a Mg–Ti catalyst [150]. The copolymers showed a wide range of softness and processing flexibility. Calorimetric analysis indicated the existence of segregated amorphous phases corresponding to the oligoester and oligoamide blocks. The tensile properties confirmed a typical thermoplastic elastomeric behaviour of the synthesized PEAs.

3.4. α,ω-Aminoalcohol Derivatives

Although some PEAs containing α,ω-aminoalcohols have been mentioned in the above section, this part is dedicated to PEAs bearing ester and amide functions introduced mainly by reaction of α,ω-aminoalcohols with dicarboxylic acids.

The first derivatives corresponded to the polymerization under reduced pressure of 2-aminoethanol or 3-aminopropanol and succinic, adipic, or sebacic acids [151-152]. Polymers with the additional inclusion of diols and caprolactam were patented in 1959 by BASF [154]. Fibers of 5-aminopentanol derivatives were produced by Kodak [155] in 1962 by polycondensation with diesters at high temperature and vacuum. Since then, different PEAs derived from α,ω-aminoalcohols have been produced and different applications have been considered: photographic emulsions, magnetic tapes, adhesives, dielectric materials, biomedicine, interfacial agents, and additives for the paper industry.

An alternating PEA constituted by 6-aminohexanol and glutaric units has been synthesized by different ways involving solution (ester active method or using *N*-ethyl-*N*-(3,3-(dimethylamino)propyl)carbodiimide hydrochloride as a condensing agent) or melt polycondensation (from both 4-(6-hydroxyhexylcarbamoyl)butyric acid and 4-(6-hydroxyhexylcarbamoyl)butyric acid methyl ester synthesized from glutaric anhydride and 6-aminohexanol) [156]. Results of the synthesis were compared, and the occurrence of a thermal degradation through imide ring formation was demonstrated. The polymer was hydrolytically degradable through the cleavage of ester bonds but not through the formation of imide rings. The degradation was clearly enhanced by using proteolytic enzymes, such as proteinase K. On the contrary, estearases like lipase from *Pseudomona Cepacia* were less effective. The polymer was semicrystalline (degree of crystallinity close to 30%), melted around 125 ºC and showed a glass transition at -18 ºC. A structure based on an arrangement of hydrogen-bonded sheets constituted by an antiparallel disposition of molecular chains was postulated. Consecutive sheets were sheared along both the hydrogen-bonding and the chain

axis directions with progressive and recuperative stackings similar to those reported for aliphatic polyamides.

A series of isoregic semicrystalline PEAs were synthesized by polycondensation of *α*-carboxyl-*ω*-hydroxy amides, which were previously prepared from succinic anhydride and α,ω-aminoalcohols (with a number of methylene groups ranging from 2 to 6) (Figure 34a) [102]. Polycondensation could only be achieved in solution under mild conditions using a carbodiimide for the activation of the carboxyl group. The obtained PEAs had melting points between 136 ºC and 190 ºC, and showed the odd/even effect characteristic of polyamides. Polymerization was not successful in bulk at temperatures above the melting point of the monomers since only the corresponding *N*-(hydroxyalkyl) imides were obtained. Conversion of these imides by ring-enlargement reaction into the isomeric cyclic ester amides could not be achieved experimentally. Theoretical calculations demonstrated that *N*-(hydroxyalkyl) imides were thermodynamically more stable than the corresponding cyclic ester amides.

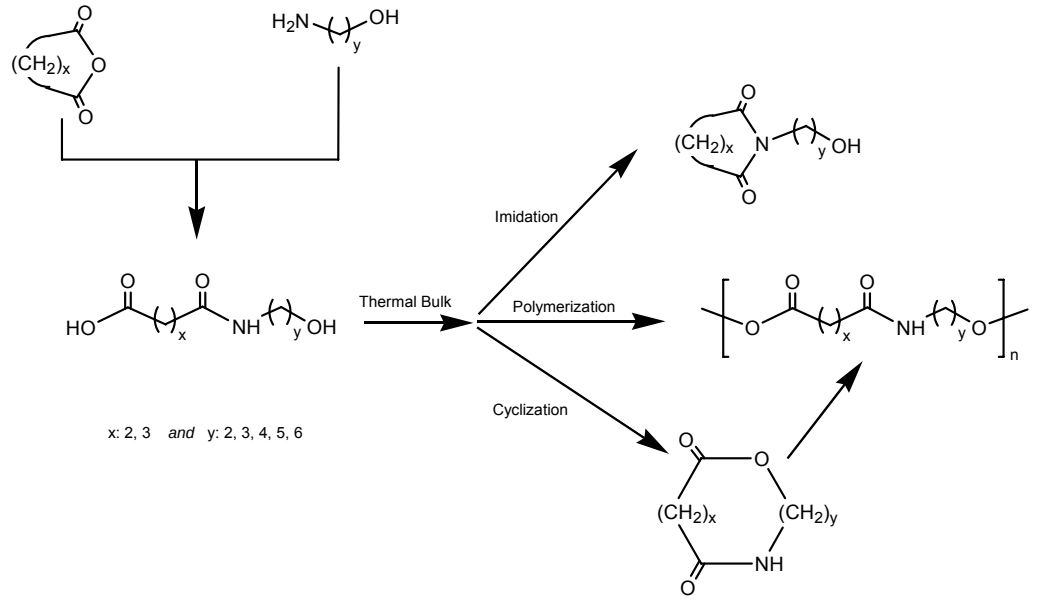


Figure 34. Synthesis of poly(ester amide)s derived from α,ω-aminoalcohols with an isoregic (a) or a random sequence (b). Imidation and cyclization secondary reactions are also indicated for the synthesis of alternating polymers.

Melt polycondensation was also performed with equimolecular amounts of a dicarboxylic acid (sebacic or adipic acid) and an α,ω-aminoalcohol (with a number of methylene groups of 2, 3 and 6) (Figure 34b) [157]. $Sn(Oct)_2$ was used as catalyst and the reaction temperature was kept close to 200 ºC. This one-step synthesis, in which all the monomers were reacted at the

same time, yielded a polymer with a random sequence that surprisingly allowed the ordering and packing in a crystalline structure. These polymers should have higher Young modulus than random copolymers usually obtained from the direct polymerization of a mixture of monomers. M_n molecular weights and glass transition temperatures of the synthesized polymers ranged between 10,000 and 40,000 g/mol and 30 and 58 ºC, respectively. Polymers were semicrystalline (degree of crystallinity and melting temperature ranged from 25 to 34% and 100 to 114 ºC, respectively) and gave rise to spherulitic morphologies by evaporation of formic acid solutions or by melt crystallization.

3.5. Aromatic Poly(Ester Amide)s

PEAs containing *p*-aminobenzoic acid units are interesting as potentially biodegradable and biocompatible polymers since this acid can be synthesized and degraded by enzymes [158].

Alternating PEAs containing *p*-aminobenzoic units were prepared from ethyl bis(*p*-aminobenzoic acid sebacamide) or ethyl bis(*p*-aminobenzoic acid adipamide) and 1,6-hexanediol (Figure 35) [159]. Melt polymerizations were carried out by a two-step reaction with an organometallic catalyst (antimony(III) oxide, tetrabutyl orthotitanate and dibutyltin dilaurate).

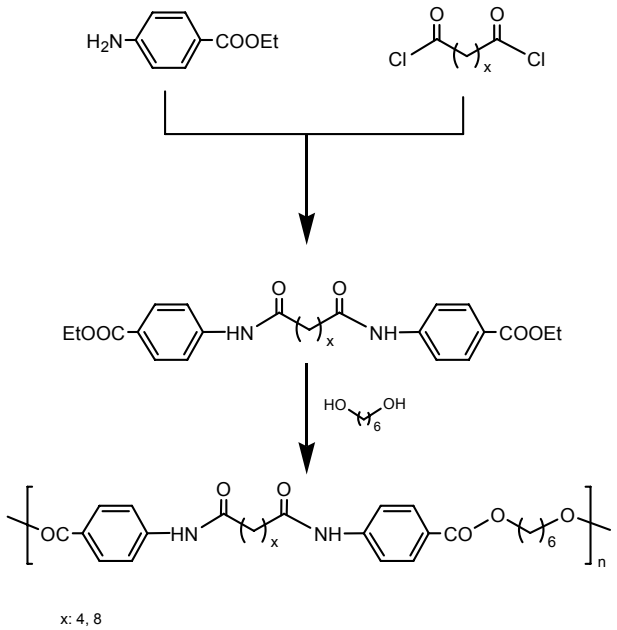


Figure 35. Synthesis by melt polycondensation of aromatic poly(ester amide)s derived from *p*-aminobenzoic acid.

A large excess of diols was used in the first step to make a diol endcapped monomer. The second step involved the removal of diols above the melting point of the polymer and under a high vacuum. The three catalysts showed a similar activity resulting in PEAs with close molecular weights. This was lower than found for polymers prepared by solution

polycondensation, probably as a consequence of ester-amide exchange reactions or insufficient mixing.

Ordered PEAs based on aromatic diamine and dicarboxylic units were synthesized and studied due to their expected liquid-crystalline properties caused by the presence of aromatic groups and the establishment of strong intermolecular hydrogen bonding interactions [160]. The synthesis of PEAs appears a convenient method for reducing the symmetry of intractable fully aromatic homopolyamides and homopolyesters, thus making them melt-processible. New polymers were prepared by melt polycondensation of dimethylterephthalate/ terephthaloyl chloride with aromatic–aliphatic diamide-diols and using titanium tetrabutoxide as catalyst (Figure 36). These diamide-diols were previously obtained by the aminolysis of lactones (γ-butyrolactone, δ-valerolactone or ε-caprolactone) with diamines (*p*-phenylene diamine or *p*-xylene diamine).

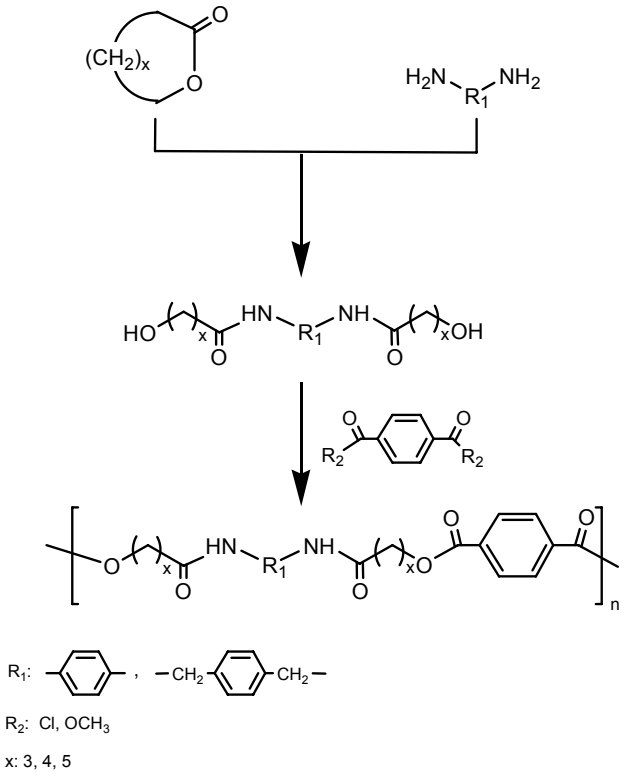


Figure 36. Synthesis of aromatic poly(ester amide)s derived from aromatic diamide-diols and aromatic dicarboxylic acids.

The diamide-diol formation occurred as one of the competitive reactions involving a thermal equilibrium among lactone, amine, hydroxamide, amino acid, and lactam [161]. Aminolysis reaction depended on the size of the ring (δ-valerolactone > ε-caprolactone > γ-butyrolactone) and nature of the diamine used (xylene diamine > phenylenediamine). Solubility was controlled by the structure of the aromatic moiety. Thus, phenylene derivatives had an enhanced rigidity because of the direct attachment of the amide to the aromatic group that led to a lower solubility. The polymers exhibited liquid crystallinity with layered structures formed by self-organization of the hetero intermolecular hydrogen-bonded

networks. Smectic phases were deduced except for the PEAs prepared from 1,4-[bis(4-hydroxy-butyramide) benzene]. In this case, the hydrogen atom of the phenyl-substituent group forced the neighboring carbonyl groups to be out of the plane of the rings preventing formation of layered structures.

Similar polymers were previously obtained by the same procedure but using aliphatic diamines with a number of methylene groups ranging from 2 to 6 [162]. These polymers still had thermotropic liquid crystal properties despite their lower aromatic content. The effect of the number of methylene groups on the mesophase texture, and on the mesophase and isotropization transition temperatures showed odd-even effect. Even PEAs developed threaded nematic textures while PEAs containing odd number of methylene groups developed batonnets or spherulitic textures.

Random PEAs with different adipic acid/terephthalic acid ratios were prepared by melt condensation of 6-aminohexanoic acid, 1,4-butanediol and appropriate mixtures of adipic acid and dimethylterephthalate (Figure 37) [163]. Titanium butoxide was also added as a catalyst for the condensation reaction. These polymers had intermediate compositions between biodegradable commercial polyesters based on the rigid aromatic unit (e.g. EcoFLEX) and PEAs based on amino acids able to establish strong hydrogen bonding interactions (e.g. BAK). Polymerizations took place with high yields and gave rise to samples with high or moderate molecular weights. In general, the degree of polymerization decreased with the aromatic content. Microstructural analysis revealed a deviation from a random distribution for polymers with the higher aromatic content since terephthalic units preferentially established ester bonds with 1,4-butanediol residues rather than amide bonds with 6-aminohexanoic units. Polymers showed a regular increase in glass transition temperature with the aromatic content as well as a slight increase on the melting temperature. The mechanical properties showed also an increase in chain stiffness with the aromatic content. Polymers were degradable, in a process that mainly involved the cleavage of ester linkages. The degradation rate decreased with the aromatic content in aqueous media as well as in those with acid or enzymatic (protease K) catalysis.

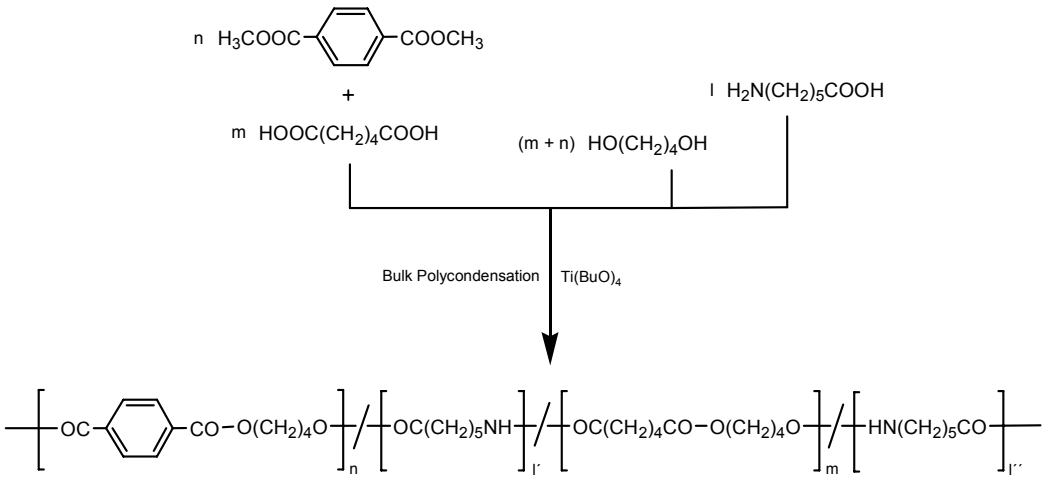


Figure 37. Synthesis of random poly(ester amide)s containing terephthalic acid and ω-amino acid units.

Aromatic PEAs were also prepared using condensing agents like direct phosphorylation [73] and carbonylation reactions [74] as explained in the 2.2.3. section.

3.6. Other Poly(Ester Amide)s

3.6.1. Poly(Ester Amide)s with Poly(Ethylene Oxide) Blocks

Hydrophilic segments provided by poly(ethylene oxide) blocks favour hydrolytic degradation as previously indicated in the section devoted to unsaturated PEAs. Some works merit attention in addition to those described there.

PEAs containing oxyethylene segments have been prepared by polycondensation of activated esters of oligo(ethylene glycol) monoamines (Figure 38) [164]. Amino protected poly(ether) segments constituted by 1-4 oxyethylene units were reacted with succinic anhydride, then activated by esterification with pentachlorophenol and finally unprotected with hydrochloric acid. Polymerizations were carried out at room temperature, both in dichloromethane solution and in bulk, in the presence of a threefold excess of triethylamine. Under these conditions the free amino group quickly reacted with the activated ester to give a mixture of cyclic and linear condensation products.

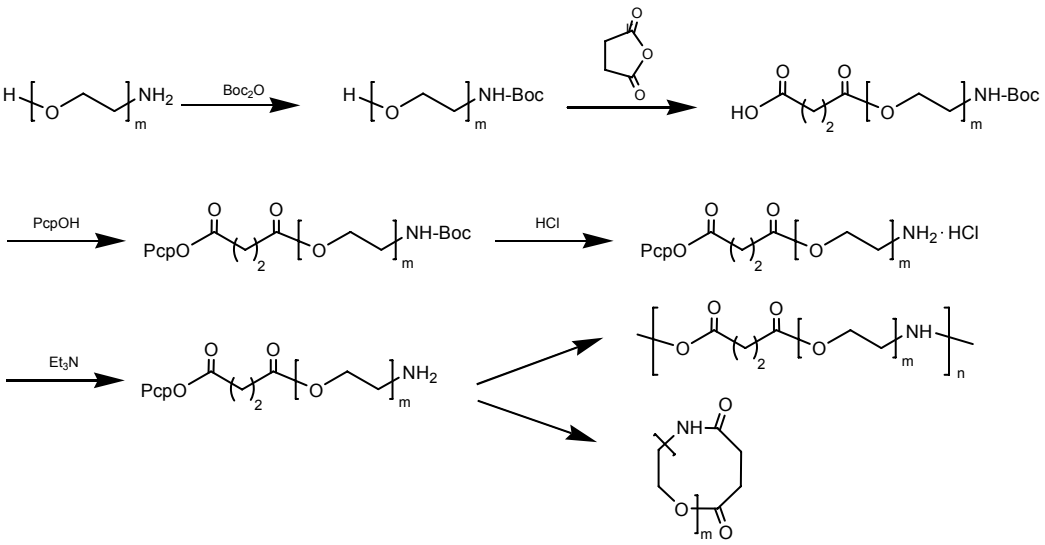


Figure 38. Synthesis of ω-amino oligo(ethylene glycol)pentachlophenyl succinates and subsequent condensation reactions that lead to macrocicles or polymer compounds.

Kinetic reaction was investigated by measuring the variation of the UV absorbance of the polycondensation solution due to the formation of the triethylamonium salt of pentachlorophenol. The results showed that even under the assumption of an identical reactivity of all functional groups, the condensation process was complex due to the occurrence of consecutive as well as parallel reactions. Thus, the reaction of the monomer containing three oxyethylene units followed a first order kinetic typical of the ring-closure reaction, even at a rather high initial monomer concentration (0.05 M). The polymerization of the monomer with two units suggested the occurrence of parallel first and second order

reactions. The latter process was attributed to the dimerization reaction. Finally, the reaction of the monomer with only one unit obeyed a second order kinetics attributable to the polymerization process. This very steep decrease of the cyclization rate was explained in terms of the increasing ring strain (bond angle deformation and bond opposition forces due to eclipsing of atoms).

Bulk polymerization allowed getting polymers with moderate molecular weight (21,000 g/mol) and low polydispersity indices even if monomers with three oxymethylene units were employed. DSC and TGA data showed a different thermal behavior of the investigated PEAs which was related to both the distance among polar amide groups along the polymer backbone and the flexibility of the oxyethylene units.

A series of biodegradable aromatic-aliphatic PEAs containing approximately equal amounts of amide and ester groups (Figure 39) were successfully prepared through the interfacial polycondensation of 1,6-hexanediamine and aromatic diacylchlorides containing ethylene oxide moieties [165]. Polymers combined aliphatic units and ethylene oxide blocks as flexible spacers into aromatic PEA backbones to obtain hydrophilic and processible polymers. Synthesis performed in water/carbon tetrachloride using NaOH as a base rendered polymers with high molecular weights and high yields (69-88%). The diacylchloride monomer was prepared by refluxing the dicarboxylic acid (previously synthesized from poly(ethylene glycol) and phthalic anhydride) in thionyl chloride. The obtained polymers were amorphous and possessed good thermal stability up to 300 ºC. Because of the presence of ethylene oxide units in the polymer chains, the synthesized PEAs showed good and controllable hydrophilicity and excellent solubility in organic solvents. The results of hydrolytic degradation indicated that the PEAs degraded in a rapid and steady way.

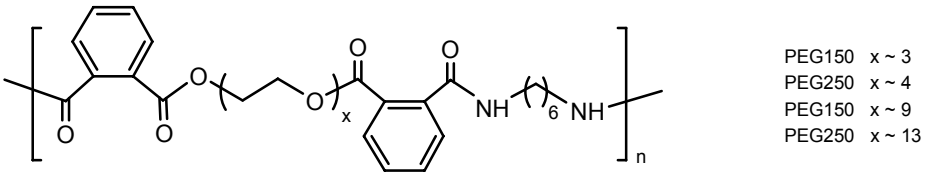


Figure 39. Chemical structure of aromatic-aliphatic poly(ester amide)s containing ethylene oxide moieties.

3.6.2. Aliphatic Poly(Ester Amide)s with Polydimethylsiloxane Blocks

Silicone-based polymers can be used in numerous applications due to their versatile and unique properties. The large bond angle (ca. 145°) and low bending force constant of Si-O-Si linkages endow silicones with high chain flexibility. Moreover, the Si-O bond is characterized by a high bond energy (106 kcal/mol) that led to materials thermally stable over a wide temperature range. Some PEAs containing siloxane segments have been proposed in toner and developer formulations [166].

The synthesis of copoly(ester amide)s containing siloxane units has been performed successfully in bulk at 70 °C via a biocatalytic route that used immobilized *Candida antartica* lipase [167]. Copolymers were prepared from diethyl adipate and mixtures of 1,8 octanediol and α,ω-(diaminopropyl)polydimethylsiloxane (Figure 40) that rendered samples with different amide/ester ratios. For all samples the M_n and PDI values ranged from 6000 to 11,000 g/mol and 1.5 to 2.2, respectively. Formation of amide links occurred more rapidly

than ester repeats, resulting in copolymers that tended toward a block like sequence distribution. The ratio between amide and ester units along the chain strongly affected the physical aspect of copolymers, which varied from hard solid materials with well developed high melting crystal phases (when rich in octamethylene adipate units) to sticky glues (when α,ω-(diaminopropyl)polydimethylsiloxane adipamide was the major component).

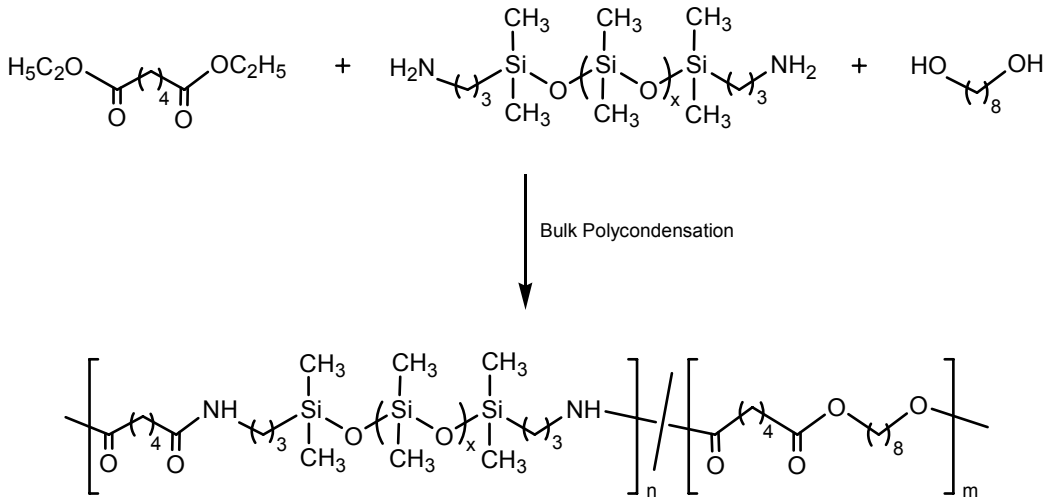


Figure 40. Synthesis of copoly(ester amide)s containing polydimethyl siloxane blocks.

4. SPECIFIC APPLICATIONS OF POLY(ESTER AMIDE)S

4.1. Drug Delivery Systems

Microspheres for Drug Delivery

Development of new synthetic degradable polymers for controlled release of drugs and proteins has focused great attention since 1990s. First polymers were based on lactide and glycolide units due to their biodegradability and safe history as suture materials. Capability for processing into micro- and nanoparticles expanded their pharmaceutical applications for both oral and parenteral administration. The successful use of these polymers led to the evaluation of other aliphatic polyesters such as poly(ε-caprolactone). However, high crystallinity and hydrophobicity may cause an incomplete drug release that justifies the development of new polymers, copolymers and blends. In this way, new series of materials with tailored properties could be achieved.

Poly(ether-ester amide)s has recently been considered for specific applications as drug delivery systems [168]. In particular, biodegradable aliphatic polymers consisting of polyester blocks, low molecular weight hydrophilic triethyleneoxide segments and amino acid residues (Figure 41) were synthesized and characterized in view of their application to the controlled delivery of drugs.

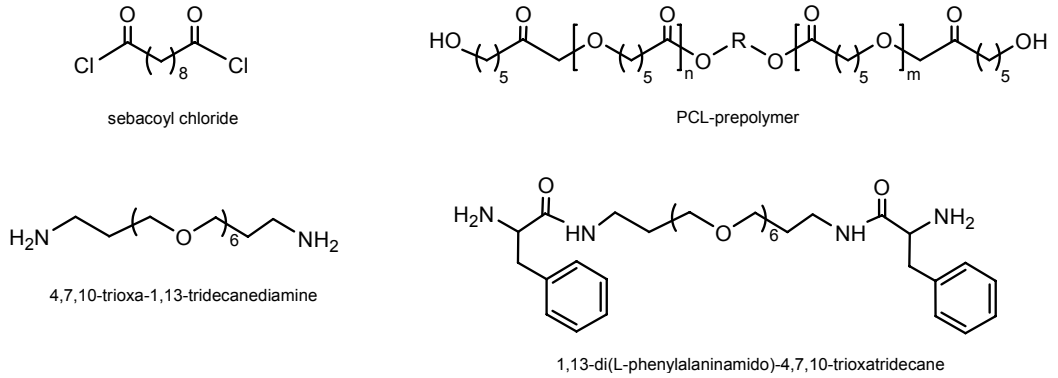


Figure 41. Reagents involved in the synthesis of poly(ether-ester amide)s with applications as drug delivery systems.

Chemical and physical properties of these polymers can be modulated by either varying the composition (i.e. the ester/amide ratio), or the length and nature of both the degradable ester blocks and the hydrophilic segments. Moreover, the introduction of short sequences of appropriate amino acid residues along the chain generated peptide bonds potentially susceptible to enzymatic degradation. The synthesis involved a two step procedure: 1. The reaction between sebacoyl dichloride and an hydroxyl terminated polycaprolactone macromer (2000 g/mol) to give a -COCl end capped oligoester and 2. The chain extension with either 4,7,10-trioxa-1,13-tridecanediamine or 1,13-di(L-phenylalaninamido)-4,7,10-trioxatridecane. The synthesized polymers were semicrystalline, had a poly(ε-caprolactone)-like structure and melting temperatures close to that of high molecular weight poly(ε-caprolactone). Molecular weights were moderate (M_n: 17,000-51,000 g/mol) and the polydispersity index close to 3. Good quality microparticles have been obtained from these polymers by the widely employed emulsification-solvent evaporation technique and drugs with different physico-chemical properties (e.g. diclofenac, dicumarol and nicardipine hydrochloride) were effectively entrapped within microspheres. New poly(ether ester amide)s showed an improved release respect to poly(ε-caprolactone) due to their increased hydrophilicity and lower crystallinity.

Bovine serum albumin release profiles were also obtained from the new poly(ether-ester amide) microspheres potentially considered as carriers for protein oral delivery [169]. The results demonstrated that an increase in polymer hydrophilicity was useful in limiting protein burst effect. Furthermore, the drug delivery rate could be modulated by increasing the polymer degradability. These results demonstrated that a fine-tuning of the hydrophilic/hydrophobic properties of poly(ε-caprolactone) is an essential factor for the formulation of protein-loaded microspheres with specific properties.

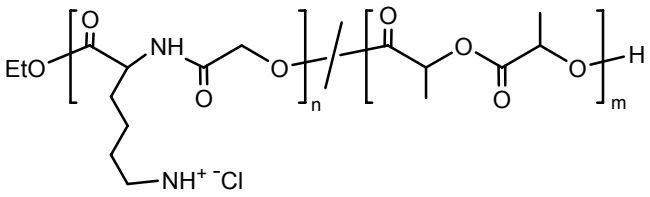
Novel biodegradable submicron microspheres of amino acid based PEAs were fabricated by an oil-in-water (O/W) emulsion/solvent evaporation technique and their morphology and drug loading efficiency examined [170]. A low PEA concentration, a high concentration of emulsifier agent (e.g. poly(vinyl alcohol)), and a high homogenizer speed were the optimal conditions for obtaining smaller microspheres. The biodegradation behavior of these microspheres at 37 ºC were investigated as a function of enzyme (α-chymotrypsin) concentration and incubation time and showed a surface erosion degradation mechanism. High encapsulation efficiency (close to 100%) was obtained when microspheres were loaded

with paclitaxel. This feature raised the potential interest of such microspheres for the injection administration of highly hydrophobic anticancer drugs.

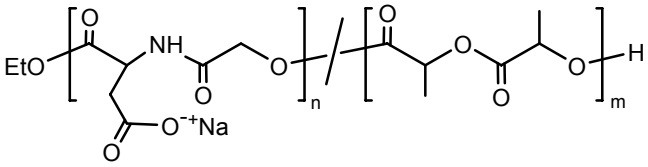
A series of biodegradable PEAs composed of sebacic acid, dodecanediol and different ratios of the stereoisomers of L- and D-alanine were also synthesized for applications in drug delivery systems [171]. Microspheres loaded with diclofenac sodium salt, triclosan and clofazimine were prepared by the solvent evaporation technique. No influence of polymer constitution in the drug release rate was found *in vitro* and no degradation occurred during the period of drug release. It was shown that a sustained delivery of the hydrophilic diclofenac sodium salt in Sorensen media occurred and it was controlled by diffusion. However, exhaustion of microspheres was feasible only from the most porous matrices where channelling had an important contribution.

Microspheres of a biodegradable copoly(ester amide) based on ε-caprolactone and 11-aminoundecanoic acid were also prepared by a simple O/W emulsion solvent evaporation method [172]. Incubation in PBS saline showed a first increase on the particle size and then a decrease associated to degradation as confirmed by scanning electron microscopy.

Random copolymers of lactide and morpholine-2,5-diones with reactive (hydrophilic) side-chain groups such as those derived from glycolic and aspartic acids or glycolic acid and lysine had been used to prepare microspheres with reactive surfaces [173-175]. These showed an efficient entrapment of ionic drugs and a slow drug release because of electrostatic interactions of the drug with the ionic side-chain groups of the polymer matrix. Amphiphilic block copolymers consisting of polylactide as hydrophobic segments and polydepsipeptides with amino or carboxylic acid groups as hydrophilic segments (Figure 42) were also considered. The microspheres of both random and block copolymers showed controlled release of growth factors to promote rapid growth of cells and regeneration of tissues.



PGD(+)-b-PLLA having cationic pendant groups



PGD(-)-b-PLLA having anionic pendant groups

Figure 42. Amphiphilic block copolymers consisting of polylactide and polydepsipeptide with interest as drug delivery systems.

Coatings for Drug Delivery

PEA coatings are characterized by their elastomeric and bioabsorbable characteristics, to which drugs can be covalently conjugated. Furthermore, composition and microstructure can

be easily varied to allow a desired rate of degradation and drug release. Degradation rate of PEAs tends to increase with levels of inflammation, a feature that can be taking into account to control a treatment agent release rate (e.g. when the agent is directly linked to polymer side chains).

PEA coatings have been studied as efficient delivery systems of oxygen free radical scavengers (e.g. tempamine) which reduce tissue injury by neutralizing the toxic free radicals released during inflammation, and have therefore a positive effect on the vascular healing response. In particular, copoly(ester amide)s based on α-amino acids (e.g. L-leucine and L-lysine), diols and dicarboxylic acids were demonstrated to be biocompatible with the arterial walls [176,177]. Furthermore, PEA coatings loaded with a 50% of tempamine had a trend to decrease arterial injury as demonstrated by *in vivo* studies, in contrast with the severe inflammation observed when stents were directly loaded with the drug (i.e. without using the polymer coating) [178]. Several PEA coated stents have been patented for different medical procedures such as treating occluded regions of blood vessels, thrombosis and restenosis [179,180]. Usually, a polymer solution which includes a dispersed therapeutic substance is applied to the stent. The solvent is allowed to evaporate, leaving on the stent surface a coating of the polymer and the therapeutic substance impregnated in the polymer.

4.2. Hydrogels

Hydrogels have great interest for their use as medical implants, biosensors, bioseparators, and matrices for drug delivery and tissue engineering since they have high water content like body tissues and may be highly biocompatible. Specifically, biodegradable hydrogels prepared from biodegradable polymer-based precursors deserve attention since a permanent foreign-body response inside human body is not expected.

Hubbell *et al.* [181] synthesized acrylates based on lactic acid polymers, which after photopolymerization of the acrylate functionality in the presence of cells rendered an hydrogel with encapsulated cells and high interest in tissue engineering. Similar materials have also been reported using PEAs based polymers. Thus, the morpholine-2,5-dione ring constituted by glycolic acid and serine units was copolymerized with L-lactide and the resulting polymer functionalized through the side chain hydroxyl group of serine by reacting with acryloyl chloride. UV-photopolymerization rendered glassy and transparent networks with a gel content close to 90% [182].

PEAs with reactive pendant double bonds susceptible to be photocrosslinked were also synthesized using the amino acid derivative DL-2-allylglycine [183]. The content of the pendant double bond in these unsaturated PEAs was tunable by adjusting the feed ratio of allylglycine to another regular amino acid like L-phenylalanine. Crosslinking was successfully performed using poly(ethylene glycol) diacrylate. All these hybrid hydrogels had a three-dimensional porous network structure. The hydrophobicity, crosslinking density and mechanical strength of these hydrogels increased with an increase in the allylglycine content, but the swelling and pore size decreased. The biodegradation rate was faster in an enzyme (α-chymotrypsin) solution than in a pure phosphate buffered saline solution, and increased with an increase in both α-chymotrypsin concentration and allylglycine content.

4.3. Composites Based on Poly (Ester Amide) S

Commercial success of biodegradable polymers used in commodity applications is limited due to their high cost relative to conventional thermoplastics. Alternatively, starch has been investigated as filler because of its low cost, biodegradability, and renewability. A general difficulty encountered in the use of granular starch as a filler and extender is the reduction in yield and tensile strength as starch content is increased. Furthermore, scanning electron micrographs usually show extensive debonding and void elongation in the assayed materials which mainly belong to the polyester family (e.g. polylactide, polyhydroxyalkanoates and poly(butylene succinate)). Some studies have also been performed with composites based on a PEA matrix, like the random BAK [184-188]. Thus, addition of starch (20 wt%) reduced the tensile strength by approximately 40% [184]. While cryofractured samples showed some adherence of PEA to starch granules, extensive debonding and void elongation were observed in strained samples. Averous *et al.* [185] found that starch/BAK blends had a better interphase compatibility compared to other biodegradable polymers they investigated (e.g. polylactide and poly(ε-caprolactone)). Coextruded films of thermoplastic starch with PEAs have also been reported in which interfacial strength was improved due to mechanical interlocking between adjacent layers [186]. Yield stress of starch-filled PEAs was found to increase in contrast with the decrease typically observed in other starch-filled polymers [187].

The use of agro-fibres as reinforcing components for thermoplastics is also a subject of research because they are renewable, biodegradable and environmentally friendly. Jute is one of the most common agro-fibres having high tensile modulus and low elongation at break. Some studies have been performed on surface chemical modification of jute to improve its suitability as reinforcement in BAK based biocomposites [188]. In this way, the tensile strength of BAK was increased by more than 40% as a result of reinforcement with alkali treated jute fabrics. SEM investigations showed that the surface modifications improved the fibre–matrix interaction.

4.4. Nanocomposites Based on Poly(Ester Amide) Matrices

Preparation of polymer nanocomposites is nowadays an important research subject since polymer properties can be enhanced (e.g. modulus, strength, thermal resistance, permeability, flammability resistance and even biodegradability) and their range of applications extended by using molecular or nanoscale reinforcements rather than conventional fillers. Nanocomposites consist in a combination of two or more phases where at least one of them is in the nanoscale regime and gives rise to a high surface-to-volume ratio. The effects produced by the incorporation of clay structures into biodegradable polymer matrices have been extensively studied. Although very good future prospects exist, the present low level of production and the high costs associated to the biodegradable polymer matrix still restrict them for a wide range of applications. PEAs are recently receiving attention for use as biodegradable matrices in nanocomposite preparation.

The barrier and mechanical properties of biodegradable melt-mixed PEA/octadecylamine-treated montmorillonite clay have been studied [189]. Intercalated structures were attained upon extrusion and shear-induced voids were formed between the clay sheets. The

presence of voids limited the improvement in barrier properties with increasing filler content although they didn't significantly affect stiffness and strength which were largely improved with filler content.

Influence of nanoparticles on the biodegradability of PEAs has also been evaluated [190]. Results indicated that ordinary fillers decreased the degradation rate since particles may act as mechanical obstacles and retard hydrolysis. However, the large increase on the interfacial area between nanofillers and the polymer matrix caused an acceleration of the hydrolysis. As a result of these two inverse effects, the degradation rate showed a maximum depending on the nanofiller concentration.

Nanocomposites of organo-modified montmorillonites and a biodegradable PEA has been obtained by in situ polycondensation of sodium chloroacetylaminohexanoate [191]. Exfoliated or intercalated structures were attained depending on the organo-modifier. Analyses of the polymerization reaction revealed that the kinetics was highly influenced by the presence of the silicate particles which reduced chain mobility and the Arrhenius preexponential factor. Thermal stability and crystallization behavior showed significant differences between the neat polymer and their nanocomposites. In general, exfoliated structures decreased both the primary nucleation and the crystal growth rate whereas intercalated structures increased the density of primary nuclei. Nanocomposites were also prepared by the melt mixing technique which rendered intercalated structures with a higher overall crystallization rate than the neat polymer [192].

Organic–inorganic hybrid materials have been prepared through heat curing of *N*,*N*-dimethylacrylamide solution of unsaturated PEA resin (obtained by ring-opening reaction of diglycidyl ether of bisphenol A and 1,6-hexamethlenediamine bissemimaleamide in the presence of nanoscaled polysilicic acid or its modification with 3-glycidyloxypropyltrimethoxysilane [193]. The presence of nanoparticles enhanced the thermal properties and dynamic mechanical properties, and reduced the curing shrinkage. The effect was more pronounced with the modified polysilicic acid due the existence of additional C–O–C covalent bonding between the organic and inorganic phases.

4.5. Other Applications

Smart Materials

Shape-memory polymers are stimuli-responsive materials, i.e. they have the capability of changing their shape upon exposure to an external stimulus (e.g. an increase in temperature). The shape-memory effect results from the polymer structure and morphology in combination with a certain processing and programming technology. Stimuli-sensitive implant materials have a high potential for applications in biomedicine as for example minimally invasive surgery [194]. These implant materials consists on polymer systems that allow the variation of different macroscopic properties over a wide range by only small changes in the chemical structure.

Feng *et al*. [195] synthesized multiblock copolymers based on oligodepsipeptides with shape-memory properties. These thermoplastic phase-segregated multiblock copolymers were synthesized via coupling of oligodepsipeptides and an oligo(ε-caprolactone) diol using an aliphatic diisocyanate as a coupling agent (Figure 43). The multiblock copolymers showed good elastic properties at 25 and 75 °C and a shape-memory capability. An almost complete

fixation of the mechanical deformation resulting in the temporary shape and a quantitative recovery of the permanent shape with a switching temperature around body temperature were observed. Hydrolytic degradation experiments (pH 7.4 PBS buffer solution at 37 ºC) showed a fast decrease of the molecular weight that mainly occurred through ester bond cleavages in the oligodepsipeptide segments.

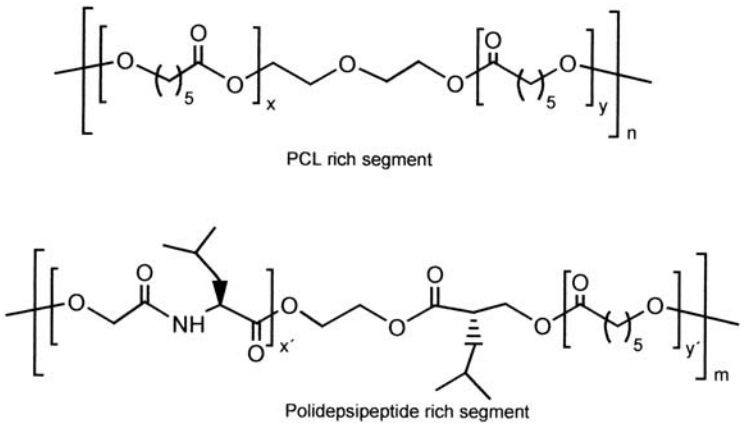


Figure 43. Scheme of multiblock copoly(ester amide)s with shape-memory properties.

Hot Melt Adhesives

Polyamides have higher adhesion strength and a wider application temperature range than the ethylene-vinyl acetate copolymers (EVAs) usually employed as hot melt adhesives. In this way, there is an increasing interest towards the application of polymers with amide groups. A PEA synthesized from dimer acid, sebacic acid, ethylenediamine, and diethylene glycolamine has been evaluated with promising results since high strength (as polyamides) and low-temperature flexibility (as polyesters) were derived [196]. It showed good adhesion to organic polymers like polyethylene and metals like aluminium, and an excellent compatibility with various EVAs that allowed their blending for preparing hot melt adhesives.

Thermosensitive Biodegradable Polymers

Stimuli-responsive polymers (e.g. thermosensitive polymers) have a great interest as advanced materials for biotechnology and the biomedical field due to their wide applications as sensing, pollution control, drug delivery, biomimetic actuation, and catalysis. Poly(*N*-isopropylacrylamide) is a well-known watersoluble polymer capable of undergoing reversible hydration–dehydration changes in response to small changes in the solution temperature [197,198]. The homopolymer and its copolymers are able to be used as intelligent materials [199,200]. However, these compounds are not biodegradable, a feature that may restrict their applications as implantable biomaterials.

The thermosensitivity of any polymeric material can be regulated by controlling the hydrophobic–hydrophilic balance of the polymeric chains. Ohya *et al*. [201] induced thermosensitivity in the polydepsipeptide constituted by glycolic and aspartic acids by attaching the moderately hydrophobic isopropylamine group into its carboxylic side group. The new polymer was fully degradable *in vitro* at room temperature by cleavage of the ester

bonds in the main chain. The polymer and its degradation products were non-toxic and biocompatible. Furthermore, the cloud point at 29°C (between room and body temperature) makes the polymer attractive for implants and other biomedical applications.

5. CONCLUSION

A great efford has been performed on the synthesis and characterization of biodegradable PEAs since 1990's. Nowadays, a considerably body of literature is available concerning polymerization methods and the development of PEAs with different composition and microstructure that make feasible to tune their final properties. PEAs appear as highly promising biodegradable materials since the establishment of hydrogen bonding interactions between amide groups provides mechanical and thermal properties that are not usual in polyesters, the most important family of biodegradable polymers until now commercialized. Incorporation of natural α-amino acids, carbohydrates or poly(ethylene oxide) segments are possibilities that enhance the interest on PEAs and make them suitable for applications that range from their use as low cost commodity materials to their use as highly specialized materials, for example in the biomedical field. However, research is still necessary to reach and ideal biodegradable polymer able to display high performance and to be degraded in a effective way after fulfilling its temporary function. Furthermore, the study of PEAs in applications such as drug delivery systems, hydrogels or thermosensitive materials is still at a preliminary stage that requires great attention but points out to very promising results.

ACKNOWLEDGMENTS

Authors want to indicate the support by CICYT and FEDER grants (MAT2009-11503) and by the Agència de Gestió d'Ajuts Universitaris i de Recerca (2009SGR-1208).

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