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Recent advances in the synthesis of aliphatic polyesters by ring-opening polymerization[*]

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Abstract

Advanced drug delivery systems rely on the availability of biocompatible materials. Moreover, biodegradability is highly desirable in the design of those systems. Consequently, aliphatic polyesters appear as a class of promising materials since they combine both properties. Nevertheless, their use in practical biomedical systems relies on clinical approval which not only depends on the material itself but also on its reproducible synthesis with the absence of residual toxics. The first sections of this review aim at reporting on the evolution of the initiators/catalytic systems and of the synthesis conditions (particularly the use of supercritical CO_2 as polymerization medium) in order to produce aliphatic polyesters with controlled macromolecular parameters by still "greener" ways. In addition, the further development of delivery systems also depends on the synthesis of materials exhibiting novel properties, such as amphiphilicity or pH-sensitivity that are emerging from the active research in macromolecular engineering. Functionalizing aliphatic polyesters is quite tedious due to their sensitivity towards hydrolytic degradation. The last section of this review is discussing several strategies to obtain functional (co)polyesters of various architectures providing them with novel properties.

Keywords: Aliphatic polyesters ; ring-opening polymerization ; enzymatic polymerization ; supercritical carbon dioxide

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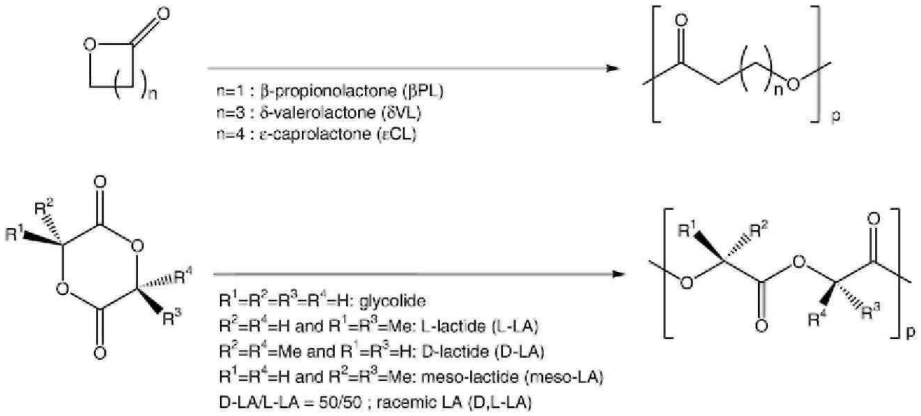
1. INTRODUCTION

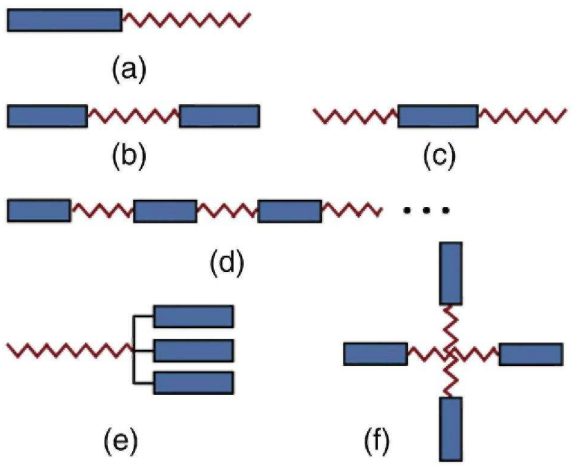
The current development of nano-medicine and particularly polymeric drug delivery systems (DDS) is timely with the advances in understanding the disease-related mechanisms. This relies on the development of novel polymeric architectures and appropriate synthetic methodologies to tailor their physico-chemical properties. However, even if synthetic polymer-based drug delivery systems have been applied in drug delivery for the last 50 years, there are few examples of these macromolecules being used successfully in clinics. Even if the clinical approval of these new materials can seem to be a long way, it is worth to have a look on them and persevere investigating their production by cleaner, more efficient and less expensive ways.

Most of the synthetic polymer DDS are based on biodegradable and biocompatible materials mainly aliphatic polyesters, polyanhydrides, polyethers, polyamides, polyorthoesters and polyurethanes. The present review is going to focus on the family of aliphatic polyesters (Scheme 1). In the first section, we discuss the synthetic strategies evolution of these biodegradable polymers by focusing on the ring-opening polymerization (ROP) mechanism. Indeed, this mechanism allows quite good control of the polymer characteristics (i.e., predictable molecular weight, narrow molecular weight distribution) and is particularly well-suited for macromolecular engineering with the production of homo- and copolymers of various architectures (i.e., palm-tree, diblock, multiblock, star) (Scheme 2). The key role of tin and aluminum alkoxides as initiators of the ring-opening polymerization of lactones, lactides and glycolide will be emphasised. Then the appearance of novel less toxic or more efficient organometallics will be shortly discussed. Since the contamination of the aliphatic polyesters by potentially toxic metallic residues is particularly a concern as far as biomedical applications are envisioned, the possibility to replace organometallic initiators by lipases and full organic systems will finally be described. The second section will be dedicated to the valuable use of supercritical carbon dioxide as novel medium for the ringopening polymerization. Purification and processing as particles of aliphatic polyesters will also be mentioned. The last section will focus on some emergent synthetic reactions particularly promising for the macromolecular engineering of aliphatic polyesters with a particular attention paid to the synthesis of amphiphilic copolymers that are promising materials for advanced DDS.

Scheme 1. *Ring-opening polymerization of unsubstituted lactones, lactides, and glycolide.*



Scheme 2. *Various block copolymer architectures: (a) AB diblock, (b) A-B-A, (c) B-A-B triblocks, (d) multiblock, (e) palm-tree, (f) star-shaped.*



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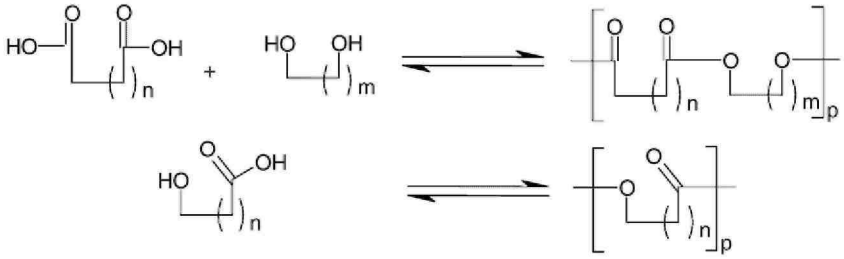
2. SYNTHESIS OF ALIPHATIC POLYESTERS BY LIVING/CONTROLLED ROP

The development of reproducible and efficient DDS requires the fine tailoring of the properties of the used synthetic polymers. As far as aliphatic polyesters are concerned, the control of their biodegradation rate, bioadherence, hydrophilicity, glass transition temperature and crystallinity are of the utmost importance and relies on the availability of suitable synthetic process. Aliphatic polyesters such as poly-ε-caprolactones, polylactides, and polyglycolides can be prepared by two distinct mechanisms: (i) the step-growth polymerization or polycondensation, and (ii) the ring-opening polyaddition (chain polymerization). The step-growth polymerization technique relies on the condensation of hydroxy-acids or of mixtures of diacids and diols (Scheme 3). The major drawbacks of this polycondensation mechanism are the high temperatures and long reaction times generally required that favour the side reactions, together with the deleterious effect on the molecular weight of any short deviation from the reaction stoichiometry. Such reaction is also limited to equilibrium; water must thus be removed from the polymerization medium to increase the conversion and the molecular weight. This can be achieved by azeotropic distillation of high boiling point solvents as used for the industrial synthesis of high molecular weight polylactide (PLA) by Mitsui in Japan [1]. However, the use of high boiling organic solvents, difficult to remove by evaporation, is poorly compatible with production of solvent free PLA.

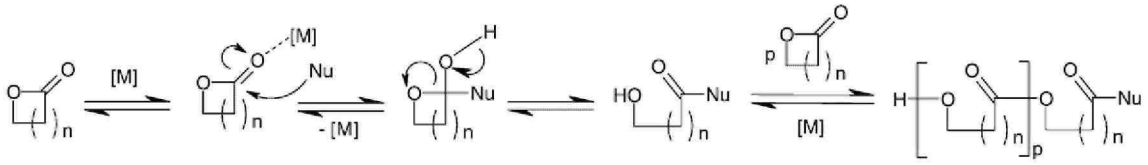
Scheme 3. *Synthesis of aliphatic polyesters by step-growth polycondensation.*



The polymerization of lactides and lactones by the ring-opening polyaddition process is free of these limitations and is thus preferred for their synthesis with tailor-made properties. High molecular weight polyesters can be easily prepared under mild conditions from lactones of different ring-size, substituted or not by functional groups [2,3]. A broad range of anionic, cationic and coordinative initiators or catalysts have been reported for the ROP [4,5]. Generally speaking, ionic (non-bulky ion pairs and free ions) initiators are much reactive and, in case of polyesters, are responsible for detrimental inter- and intra-molecular transesterification reactions lowering the molecular weight and broadening the molecular weight distribution of the polymer. Many organometallic derivatives of metals with d-orbitals of a favourable energy, such as Al, Sn, Nd, Y, Yb, Sm, La, Fe, Zn, Zr, Ca, Ti and Mg, are imparting control to the polymerization in contrast to their anionic counter-part. In the more favourable cases, the ring-opening polymerization of lactones and lactides is a living/controlled process that leads to polyesters of narrow molecular weight distribution with a molecular weight predetermined by the monomer-to-initiator molar ratio.

The ROP proceeds mainly via two major polymerization mechanisms depending on the used organometallics. Some of them acts as catalysts, and activate the monomer by complexation with the carbonyl group (Scheme 4). Polymerization is then initiated by any nucleophile, e.g., water or alcohol, present in the polymerization medium as impurities or as compound added on purpose. In the second mechanism, the organometallic plays the role of initiator and the polymerization proceeds through an 'insertion-coordination' mechanism (Scheme 5). Metal alkoxides are typical initiators, which first coordinates the carbonyl of the monomer, followed by the cleavage of the acyl-oxygen bond of the monomer and simultaneous insertion into the metal alkoxide bond. Other mechanistic proposals can be found in the scientific literature, which are however not general enough to be discussed in this review.

Scheme 4. *Ring-opening polymerization of lactones catalyzed by organometallic species [M] in presence of nucleophiles (Nu).*



Among the wide variety of aliphatic polyesters, PLA and PLGA polymers are the most used materials for drug delivery due to their fast and adjustable degradation rate. The sharp increase of the patents number in this field in the early 90s coincides with the clinical success and commercialization of Lupron Depot, the first parenteral sustained-release formulation using PLA, which was approved in 1989 [6].

High volumes of PLA are produced under the name Natureworks™ by the joint venture between Dow and Cargill in a plant built in North America with a capacity of 0.14 million tones/year [7], mainly for commodity market. Besides, there are four established suppliers of GMP-grade PLA (PLA which complies with the Good Manufacturing Practice regulations (GMP) promulgated by the European Agency for the Evaluation of Medicinal Products) and PLGA: Purac (Purasorb™), Birmingham Polymers (Lactel™), Boehringer Ingelheim (Reso-mer™) and Alkermes (Medisorb™). Other newer suppliers and smaller manufacturers are also catering the local niche markets worldwide.

For the time being, tin octoate and alkoxides were the most widely used organometallic mediators for the ring-opening polymerization of lactones even if novel powerful and interesting metal free catalytic systems are emerging as valuable alternatives.

2.1. Metal-based initiators or catalysts for homogeneous ROP

2.1.1. Aluminum alkoxides

The high selectivity of aluminum alkoxides is the major reason for their choice to produce well-defined polyesters for lab studies. For instance, propagation is 100 times faster than bimolecular transesterification in the ring-opening polymerization of LLA in THF at 80 °C [8] and molecular weight is very well controlled. Advantageously, both chain end-groups are well-defined and predictable (Scheme 5). Indeed, the polyester chains are α-end-capped by an ester group RO-C(=O), where RO is the alkoxy group of the initiator. Because a huge variety of aluminum alkoxides can be prepared by reaction of triethylaluminum with an alcohol ROH (see Eq. (1) with R — Tertiary amine, acrylate, norbornene, alkyl halide, PEG, allyl, ...), polymeric or not, functional or not, the choice of the α-end-group is very flexible. An excess of triethylaluminum is usually used to form the monoalkoxide initiator since the di- and tri-alkoxides, (Eqs. (2) and (3) below) strongly aggregate and are thus not useful in the aliphatic polyester synthesis.

$$AlEt_3 + R\text{-}OH \rightarrow Et_2AlOR + EtH \quad (1)$$

$$Et_2AlOR + R\text{-}OH \rightarrow EtAl(OR)_2 + EtH \quad (2)$$

$$EtAl(OR)_2 + R\text{-}OH \rightarrow Al(OR)_3 + EtH \quad (3)$$

Moreover, the hydrolysis of the propagating chains systematically results in a ω-hydroxyl end-group. Other nucleophiles can also be used to terminate the chains and impose accordingly the structure of the ω-end-group. The very good control imparted to ring-opening polymerization by aluminum alkoxides is a unique platform for the macromolecular engineering of aliphatic polyesters, for instance, making comb-like, star-shaped, graft and hyperbranched (co)polyesters available [9]. This type of initiator can also polymerize other cyclic monomers, such as adipic anhydride and trimethylene carbonate [9],

For safety reasons, residual aluminum must be removed from the material before use in food or biomedical applications. Even if on the lab-scale, aluminum can be efficiently extracted by EDTA complexation, tin (IV) alkoxides is rather used as substitute for aluminum alkoxides, although the polydispersity of the chains is then higher (~1.5).

2.1.2. Tin octoate

Probably the most popular polymerization initiator for ROP of aliphatic polyester is tin(II) bis-(2-ethylhexanoate) also referred as tin octoate ($Sn(Oct)_2$) [10]. It is accepted as a food additive by the US Food and Drug Agency (FDA) and thus no purification of the polymers is needed for applications such as packaging. In the most likely proposed polymerization mechanism, $Sn(Oct)_2$ is converted into tin alkoxide, the actual initiator, by reaction with alcohols (see Eqs. (4) and (5)) or other protic impurities [11,12],

$$Sn(Oct)_2 + ROH \rightarrow Oct\text{-}Sn\text{-}OR + OctH \quad (4)$$

$$Oct\text{-}Sn\text{-}OR + ROH \rightarrow Sn(OR)_2 + OctH \quad (5)$$

As a consequence of the polymerization involves a coordination-insertion mechanism similar to the one described in Scheme 5. Thus again, the deliberate addition of a predetermined amount of alcohol to the polymerization medium is an effective way to control the molecular weight by the monomer-to-alcohol molar ratio. Tin octoate is also efficient in copolymerization of various lactones. Playing on the composition of such copolymers allows tailoring their properties. Controlling the composition, the morphology, the Tg and degradation rate allows regulation of the drug release behaviour [13]. However, even if tolerated in food regulations, due to tin toxicity, it has to be avoided in materials used for biomedical application. When added in stoichiometric amounts for polymerization, careful extraction from the obtained polymer is required before exploitation in the medical field.

2.1.3. Rare earth derivatives

A large variety of rare earth derivatives have been used to initiate ROP of lactones and lactides [14]. Their usually high reactivity must be emphasized, as exemplified by the polymerization of β-butyrolactone which is polymerized by $Y(OCH_2\text{-}CH_2OMe)$ at room temperature [15], in contrast to the long reaction time and high temperature required when aluminum-based initiators are used.

Halo-bridges/Sm(IΠ) complexes ($[Sm(\mu\text{-}X)(N(SiMe_3)_2)_2(THF)]_2$) and non-halo-bridged Sm(III) complexes ($SmCp_3$, Sm $(N(C_6H_5)_3)_3$, $Sm(N(SiMe_3)_2)_3$) promote ROP at room temperature in less than 1 h without the assistance of a cocatalyst. The polydispersity index is rather high (~2.0 and higher) even though "livingness" has been supported by synthesis of a block copolymer [14]. Greiner and co-workers have shown that bimetallic $[Sm_2I(NP(C_6H_5)_3)_5(DME)]$ is an effective initiator for ROP of ε-CL and δ-VL in toluene [16]. At 0 °C, the molecular weight distribution is narrow (PDI ~ 1.2), which indicates a fast initiation compared with propagation and transesterification reactions if any. The experimental molecular weight agrees with the theoretical value on the assumption that two chains are initiated per complex molecule. From the analysis of the chain end groups by ^{1}H NMR, the *in situ* formation of samarium alkoxides is supposed to result from the addition of the bridged nitrogen atom to the carbonyl group of the lactone, followed by the cleavage of the endocyclic acyl-oxygen bond [16].

The ROP of (D,L)-lactide using rare earth (μ-oxo)isopropoxides as initiator systems proceeds rapidly at room temperature [17]. The lanthane initiator is the most reactive with half-reaction time of 45 s, the reactivity range being La>Y>>Yb. With Sm, Yand Yb a narrow polydispersity is observed until high conversions while for La initiator the polydispersity increases with conversion indicating that transesterification reactions occur. Depending on the nature of the metal, the number of active sites is close to 2.6 or 2.0.

Commercially available tris(bis(trimethylsilyl)amido) yttrium ($Y[N(SiMe_3)_2]_3$) added with alcohol is able to initiate ROP by converting *in situ* the inactive yttrium precursor into active Y alkoxide [18]. The rapid exchange between the *in situ-formed* yttrium alkoxide and the alcohol allows the average number of the initiated chains to be controlled by the excess of alcohol with respect to Y. At a molar excess of 50, all the alcohol molecules participate to the exchange and thus to the initiation of ε-CL polymerization at 20 °C. In addition to *M*n, which can be predicted from the monomer/alcohol molar ratio, the molecular weight distribution is narrow even at high monomer conversion.

The use of a catalytic amount of lanthanide alkoxides is a valuable strategy to decrease the polyester contamination by metallic residues as compared to the previously described tin and aluminum based initiators which must be used in stoichiometric amount vs. the alcohol to favour the polymerization kinetics. However, due to low level of tolerance of rare earth metals in the organisms, these catalytic systems are not yet frequently adopted for the preparation of polyesters intended for DDS elaboration.

2.1.4. Friendly metals

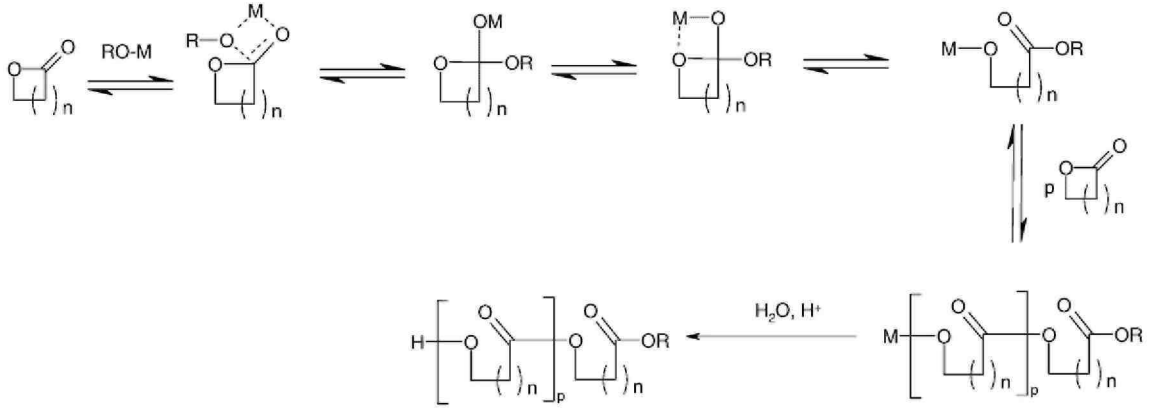
Another approach for producing aliphatic polyesters free from toxic metallic residues is the use of bioresorbable salts for the ROP of polyesters. The LA polymerization at 180 °C has been studied for a wide range of cations [19,20]: Na^+, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}, and Fe^{2+} with a variety of counter-ions: chloride, iodide, oxide, hydroxide, carbonate, acetate and higher fatty acids, lactate, tartrate, citrate, α-amino acids and peptides. Zinc lactate gave the best results.

Although strong Lewis acid metal halogenides are known catalysts for cationic ROP, zinc dichloride can initiate ROP of ε-CL, according to a coordination-insertion mechanism in which the alkyl-oxygen bond of the monomer is cleaved (Scheme 5) [21]. Zinc alkoxides have also been prepared and efficiently used for the controlled ROP of ε-CL [22]. Zinc acetate turned out to be a friendly analogue of tin octoate [23]. $Fe_2(OCH(C_6H_5)_2)_6$ initiates ROP of LA and ε-CL and imparts a good control to the polymerization [24]. A first order in both the monomer and the initiator is the rule.

Although commercially available and highly active in ROP of ε-CL and L-LA, calcium methoxide is of limited interest because of its low solubility and aggregation [25]. Feijen and co-workers used however successfully the strategy implemented for lanthanide alkoxides. The $(THF)_2Ca[N(SiMe_3)_2]_2$ precursor was indeed reacted with isopropanol with *in situ* formation of Ca isopropoxide. ROP of ε-CL and L-LA is then controlled at room temperature as confirmed by the agreement between theoretical and experimental Mn and low *M*w/*M*n(<1.3). Poly(ε-CL)-b-poly (L-LA) was also synthesized with success without racemisation during ROP of L-LA [26]. Remarkably, ROP is much faster when initiated by β-diketonate calcium alkoxides than by aluminum, yttrium and tin alkoxides.

Zirconium derivatives being 10 times less toxic than tin counterparts and Zr-containing drugs and cosmetics being accepted by the Food and Drug Administration [27], they were investigated for the polyesters synthesis. LA and CL were polymerized by Zr (acac)4 in the 100-150 °C range [27,28]. Because Zr complexes usually aggregate (coordination number=6) [29], benzyl alcohol has been advantageously added to $Zr(O\text{-}n\text{-}C_3H_7)_4$ [29,30]. Mn is then determined by the monomer/alcohol molar ratio, with low polydispersities. In contrast to aluminum alkoxides, the propagation rate decreased regularly with increasing benzyl alcohol/Zr molar ratio. Germanium alkoxides because of less toxicity than tin alkoxides have also been studied [31]. However, ROP of ε-CL requires higher temperature, e.g. 140 °C for $Ge(OC_2H_5)_4$], and the molecular weight distribution is quite broad.

Scheme 5. *Ring-opening polymerization of lactones by the "coordination-insertion" mechanism.*



2.2. Supported-metal catalyzed ROP

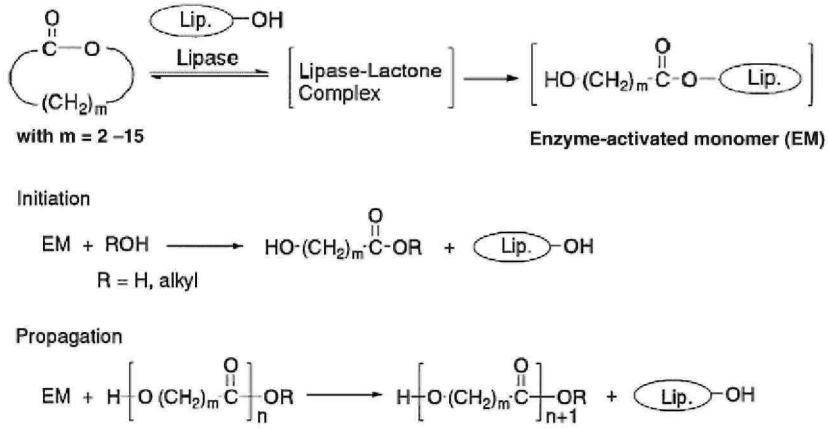
Whenever toxic metallic catalysts is a must, the heterogeneous polymerization by using metal alkoxides grafted onto solid supports is a valuable strategy to produce polyesters free from metallic residues. In addition, these heterogeneous initiators/ catalysts can be used in batch production but their easy recycling/ reactivation is promising for continuous processes [32]. Al, Nd, Y, Sm, Zr metal alkoxides have been grafted onto silica or alumina and successfully used for the synthesis of poly-ε-caprolactone [30-33]. Nevertheless, the alcohol that is released in the reaction medium can react with the silanol groups of silica and form water. Therefore, part of the active species can be lost by hydrolysis. In case of alumina, Al-O-R species can be additionally formed and participate in the polymerization. Jérôme and co-workers tackled this problem by using an Yalkoxide precursor, i.e. $Y[N(SiMe_3)_2]_3$ [34], reacting it with one or two equivalent(s) of isopropanol with formation of mixed yttrium alkoxide/amide. The unreacted amide functions were then used to graft the Y alkoxide to the support. This method, free from side reactions and quite reproducible allows to vary the average number of alkoxides per Y(l or2). The grafted alkoxide can participate in a fast exchange with an alcohol added on purpose in the polymerization medium, at 40 °C. Chains are detached from the support by methanolysis, which restores the Y alkoxides at the surface of the support. Starting with Y amide, rather than with preformed Y alkoxide known for fast association in solution, has the advantage of grafting, well-defined monomolecular species to the support.

2.3. Enzymatic polymerization

As stressed in the previous sections, the availability of aliphatic polyesters uncontaminated with possible toxic metallic residues is essential for biomedical applications. The enzymatic polymerization appears as an alternative technique for producing metal-free polyesters.[35,36] Some lipases are known to catalyze (trans) esterification reactions. A first report on the enzymatic bulk ROP of ε-CL in organic solvents was published in 1993 [37,38]. The *Candida antarctica* Lipase B-mediated polymerization carried out in toluene occurs by catalysis at the active serine residue of the enzyme and not by other chemical or non-specific interactions [39]. Interestingly

enough, lipase-mediated polymerization takes also place in fluorinated solvents [40] and in ionic liquids [41], Since that time, small- to large-sized (4 to 17 membered) lactones were found to be polymerized by lipase catalyzed ring-opening fashion [35] (Scheme 6). In general, similar to chemical catalysts, the lipase-catalyzed ROP of lactones gives both higher molecular weights and higher monomer conversions than the condensation polymerization of hydroxyacids [42]. In organic media, interesting cyclic oligomers are mainly produced [43]. ROP of γ-BL, which is usually a problem by traditional techniques, is oligomerized in the presence of porcine pancreas and *Pseudomonas capacia* [44]. As a rule, large-size lactones react faster than the smaller ones, which is the reverse of what is observed for chemical ROP [45]. Actually, the rate-determining step in enzymatic polymerization is the formation of a lactone-lipase complex, which is more favourable for more hydrophobic large-size lactones. ROP takes place according to an "activated monomer" mechanism (Scheme 6) [46]. The key step is the reaction of lipase with the lactone with formation of an acyl-enzyme intermediate, which further reacts with water, alcohols, or hydroxyl end-capped chains during either the initiation or the propagation step. Most recent insights into the mechanism of lipase-catalyzed ROP of lactones are discussed in details in the review written by S. Kobayashi [47].

Scheme 6. *Mechanism of enzymatic ring-opening polymerization.*

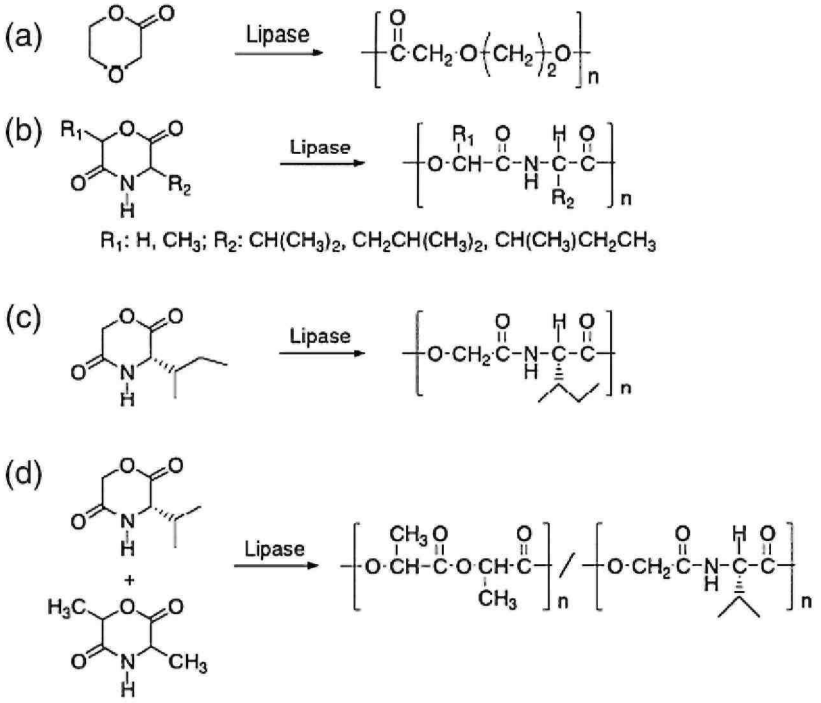


The seven-membered unsubstituted lactone ε-CL is the most extensively studied with respect to lipase-catalyzed ring-opening polymerization. ε-CL is quickly polymerized by various lipases of different origin. Among them, lipase CA appears as the most effective for the polymerization of ε-CL [48,49], and under appropriate conditions PCL with a molecular weight (Mn) greater than 47,000 was produced [50].

Unfortunately, the control imparted to ROP in not as good as the one obtained by chemical ROP, with *M*w/*M*n higher than 2 [35]. One advantage of the enzymatic route is to be found in the optical activity of lipases, which opens up a new route to stereoselective ROP. For example, isotactic (*S*)-enriched poly(4-methyl ε-CL) and poly(4-ethyl-ε-CL) with an enantiomeric purity higher than 95% have been prepared by enantioselective ROP of the racemic mixture, in the presence of lipase Novozym-435 [51],

For medical applications, the metal-free polymerization of l,4-dioxan-2-one by lipase may become the preferred method (Scheme 7a). Poly(1,4-dioxan-2-one) with an *M*w of 41,400 was produced by an immobilized lipase from the *Candida antarctica* (lipase CA)-catalyzed ring-opening polymerization [52]. Different morpholine derivatives can be copolymerized together (Scheme 7d). By the copolymerization of 3(*S*)-isopropylmorpholine-2,5-dione and lactide, the 3(*S*)-isopropyl-morpholine-2,5-dione unit was introduced into the polylactide polymer chain in order to improve the physico-chemical properties of the polylactides. The glass transition temperature (*T*m) of the copolymers decreased with the increasing mole fraction of the DL-lactide residue in the copolymers from 74 to 40 °C [53]. Scheme 7 illustrates various polymorpholines that can be enzymatically obtained.

Scheme 7. *Various monomers and corresponding polymers prepared by enzymatic ROP: (a) 1,4-dioxan-2-one (b) cyclic depsipeptides (c) 3(S)-sec-butylmorpholine-2,5-dione. (d) 3(S)-isopropylmorpholine-2,5-dione and 3-methyl-6-methyl-morpholine-2,5-dione.*



LA is polymerized by lipase as a catalyst in bulk to yield the corresponding polylactide with an *M*w of up to 126,000 with a relatively low yield. The D, L-lactide gives a higher molecular weight compared to the D- and L-lactides [54,55]. The L-, D-, and D,L-lactides can be copolymerized with trimethylene carbonate by porcine pancreatic lipase (PPL) to produce random copolymers having molecular weights of up to 21,000 [56]. Remarkably, catalytic efficiency might be improved by immobilization of the lipase on supports [57] or by using novel solvents [58].

The rapidly increasing number of publications evidences the potential of the enzyme catalysis providing a wide range of polymer structures [59]. In the near future, the development of production systems and feasibility studies for industrial production should provide a novel interesting source of metal free polyesters.

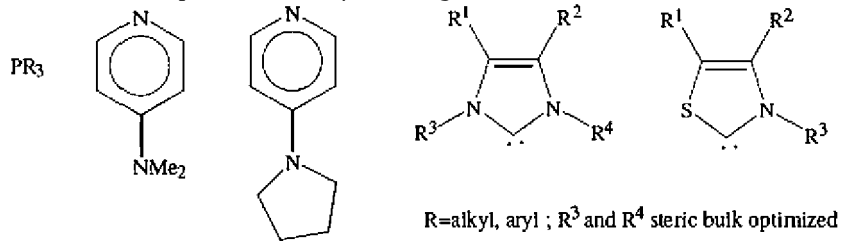
2.4. Metal-free ROP

Last but not least, metal-free polyesters can be prepared by using "all-organic" initiators [60]. A mixture of alcohol and $HCl \cdot C_2H_5O$ is a cationic catalyst for the controlled ROP of ε-CL and δ-VL [61], even if *M*n remains below 15,000 for poly (ε-CL) [62]. Poly(δ-VL) is an exception, with *M*n up to 50,000.

The use of nucleophilic catalyst is also promising (Scheme 8). Indeed, ROP of LA initiated by alcohols is catalyzed by phosphines [63], tertiary amines (eg, 4-dimethylaminopyridine, 4-pyrrolidinopyridine) [64], *N*-imidazolium carbenes [65], thiazaolium carbenes [66]. The mechanism would be similar to the one reported for biocatalysis [67] (Scheme 6) activation of the monomer by the nucleophilic attack of the carbonyl by the catalyst, with formation of an intermediate that reacts further with an alcohol, polymeric or not. *N*-heterocyclic carbenes can be generated *in situ* from the corresponding imidazolium and thiazolium salts, whereas changing the substituents of these compounds is a tool for tuning their reactivity [68]. Remarkably, stereoselecive polymerization of *rac*- and *meso*-lactide was catalyzed by encumbered *N*-heterocyclic carbenes [69]. Alcohol adducts of *N*-heterocyclic carbene function as excellent single-component initiator of the ROP of LA and β-butyrolactone [70], Very recently, the polymerization of L-lactide was also carried out by activation of the alcohol by a base such as 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) [71], *N*-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) [71] and phosphazenes [72]. Interestingly enough, phosphazenes turned out to be efficient to control the polymerization of εCL and δ-VL [72], Conversely, DBU and MTBD were efficient to control the ring-opening-polymerization of εCL and δ-VL only whenever a thiourea was used as a co-catalyst [71]. The role of the thiourea being to activate the monomer, a dual activation of both the monomer and the alcohol was thus implemented. Finally, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) was also prone to control the polymerization of lactide, εCL and δVL in the absence of any other additive, by dual monomer-

alcohol activation [71-73]. This promising process is actively studied at the time being and could be more widely used in the near future.

Scheme 8. *Nucleophiles suitable for all-organic ROP.*



3. TAKING ADVANTAGES OF THE SUPERCRITICAL CO_2 TECHNOLOGY

Environmental concerns have recently prompted the scientific community to investigate new ways to decrease the use of volatile organic solvents. For this purpose, the resort to supercritical fluids appears as a valuable alternative. Indeed, supercritical fluids combine gas-like and liquid-like properties (solvation power and density).

Among the available supercritical fluids, supercritical carbon dioxide ($scCO_2$) is the best candidate because of low toxicity, low cost, non flammability and easily accessible critical parameters (T_c=31.4 °C, P_c = 73.8 bar). Moreover, CO_2 is widely available from commercial and industrial supplies and is also easily recycled.

The low solubility of many polymers, including aliphatic polyesters, in $scCO_2$ may be a drawback. For example, many polymerization conducted in this medium are precipitation polymerizations which is less desirable. Nevertheless, advantage can be taken of the low solubility by using $scCO_2$ as anti-solvent for the preparation of nano- or micro-particles. Plasticization of polymers by $scCO_2$ is also beneficial particularly for drug delivery applications, because it offers the possibility to incorporate guest molecules under mild conditions. These are reasons why the contribution of $scCO_2$ to the ROP of lactones and lactides and their processing has been thoroughly investigated over last few years [74].

3.1. Synthesis of aliphatic polyesters by ROP in $scCO_2$

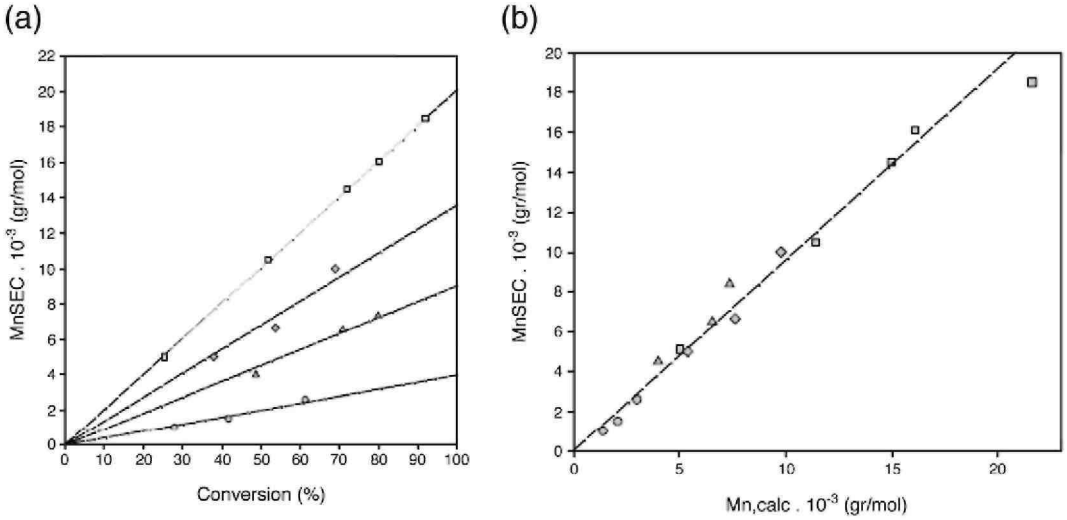
3.1.1. Metal catalyzed/initiated ROP in scCO2

Tin(IV) alkoxides are very efficient initiators for ROP of ε-CL in supercritical CO_2 (40 °C and 210-215 bar) [75] The ^{1}H NMR analysis of the chain-ends has confirmed that ROP proceeds through the coordination-insertion mechanism that commonly operates in organic solvents.

When polymerization starts, the medium is transparent because the monomer and the very short PCL oligomers are soluble. After a few minutes, the medium turns cloudy as result of the precipitation of the non-soluble PCL chains. Nevertheless, the experimental molecular weight increases regularly with conversion and is predetermined by the monomer-to-initiator molar ratio, at least until 20,000 g/mol (Fig. 1), on the assumption that the two alkoxides are active. The first order in ε-CL is observed whereas the first order in initiator indicates that tin species are mostly unaggregated in supercritical CO_2. It has been measured that ROP at 40 °C proceeds ca. 14 times faster in toluene and 33 times faster in bulk than in $scCO_2$. This very slow kinetics has been explained by equilibrium between propagating species and dormant species. The reversible insertion of CO_2 into the Sn-O bond leads to a carbonated tin compound [75]. This mechanism has been substantiated by spectroscopy and the activation parameters for the reaction [76]. When aluminum triisopropoxide is the initiator, ROP of ε-CL is a failure. Only a few percents of oligomers are formed, as result of the high reactivity of aluminum alkoxide towards CO_2. More recently, Howdle and coworkers published a careful study of the PCL precipitation polymerization in $scCO_2$ by using the most popular tin octoate catalyst [77].

Besides the above described ε-CL precipitation polymerization, poly(D,L-lactide)-ran-(glycolide) [78] and poly(L-lactide) [79] have also been successfully synthesized by suspension polymerization in $scCO_2$ in the presence of fluorinated stabilisers.

Fig. 1. *Dependence of Mn (SEC) (a) on the monomer conversion and (b) on theoretical Mn, for the εCL ROP initiated by $Bu_2Sn(OMe)_2$ in supercritical CO_2. [εCL] 0 = 1.39 M, [εCL]0/[Sn]0 = 364 (square), 254 (diamond), 167 (triangle), and 88 (circle). Reproduced with permission from [93]. Copyright Wiley-VCH Verlag GmbH & Co KGaA.*



3.1.2. Enzymatic ROP in scCO2

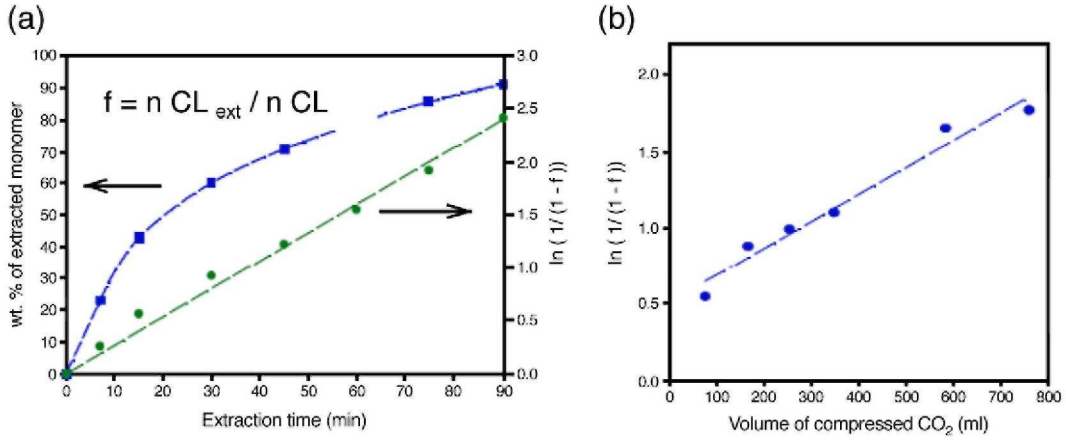
Enzymatic polymerizations have also been performed in $scCO_2$. ε-CL was polymerized by lipase CA to produce the PCL with the highest molecular weight (*M*w) of 74,000. The enzyme and $scCO_2$ were repeatedly used for the polymerization [80], Takamoto et al. reported that the lipase-catalyzed degradation of PCL in the presence of acetone produces an oligomer with a molecular weight of less than 500 in $scCO_2$, which can be polymerized by the same catalyst [81]. Similar results by Matsumura et al. were obtained such that PCL was transformed in $scCO_2$ in the presence of a small amount of water and lipase to produce repolymerizable oligomers having an *M*n of about 500 [82]. The produced CL oligomer was again polymerized with lipase CA to yield a PCL having a *M*n of greater than 80,000 [82-84]. Kinetics measurements were recently reported for the ROP of ε-CL in this medium by using *Candida antartica* lipase B (CALB) as catalyst [83]. High molecular weight (up to 50,000) with polydispersities about 2 were observed. The poor molecular weight control can be attributed to transesterification reactions, as already observed for enzymatic ROP in conventional solvents. The combination of controlled atom transfer radical polymerization (ATRP) with enzymatic ROP in $scCO_2$ is able to produce exceptional graft copolymers, i.e. poly(methyl methacrylate-co-hydroxyethyl methacrylate) (PMMA-co-HEMA) with PCL grafts [84,85], Recently, block copolymers were synthesized by the association of enzymatic ring-opening polymerization and metal free reversible addition-fragmentation chain transfer (RAFT) radical polymerization [86],

3.2. Other advantages of $scCO_2$

3.2.1. Purification of polyesters by $scCO_2$ extraction

$scCO_2$ is a valuable vehicle for extracting residual monomers and catalysts leading to ultra-pure aliphatic polyesters as required for applications in the biomedical field. Fig. 2a shows the first-order kinetic profile for the supercritical fluid extraction (SFE) of ε-CL from a PCL sample containing 15 wt.% of monomer [87]. Based on the extraction constant, 95% of ε-CL is extracted after *ca.* 110 min, while 99% extraction would require *ca.* 175 min. Whenever ring-opening polymerization is initiated by dibutyltin dimethoxide, the extraction of tin from PCL is a more difficult task because PCL bound tin alkoxide. Tin has first to be derivatized into species soluble in $scCO_2$. A possible strategy relies on the reaction of the PCL-alkoxytin end-group with acetic acid and the release of dibutyltin diacetate which is extractable by $scCO_2$ [87]. The kinetic profile is quasi-linear (Fig. 2b) and the slope of the straight line allows the extraction constant to be determined.

Fig. 2. *Kinetic profile for the extraction at 40 °C and 150 bar, of (a) ε-CL from PCL at a flow rate of 6 ml/min (b) dibutyltin diacetate from PCL at a flow rate of ca. 4 ml/min. Reproduced with permission from [93]. Copyright Wiley-VCH Verlag GmbH & Co KGaA.*



3.2.2. Synthesis and drug-loading of micro- and nano-particles

The use of $scCO_2$ has the unique advantage of combining the synthesis of aliphatic polyesters and their processing. For instance, the polyester formed in the high-pressure reactor can be *in situ* loaded by guest molecules, or collected as micro-particles. P(D,L)LA micro-particles loaded by a cholesterol-lowering statin agent have been prepared by "rapid expansion of supercritical solutions" (RESS) [88]. This very simple method consists in dissolving the polymer and the drug into the supercritical fluid followed by the rapidly expansion of the mixture into a low temperature and pressure environment. This leads to a rapid decrease of the solubility of the polymer and crystallization of the solute as micro- or nano-particles of a narrow size distribution. Unfortunately, most polymers and pharmaceuticals have poor solubility in $scCO_2$, which limits the development of such processing strategy.

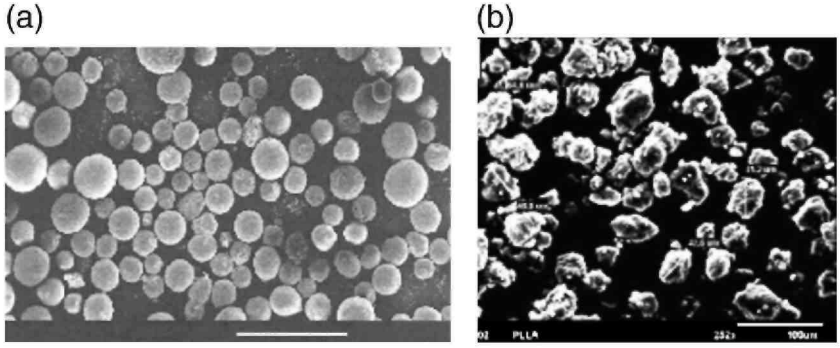
Micro-particles can be produced by a second simple technique that consists of spraying a polymer, e.g., PLLA, solution in dichloromethane (or dimethylsulfoxide), through a nozzle into a reactor filled with supercritical carbon dioxide [89]. This process is known as 'supercritical antisolvent precipitation' (SAS). The experimental parameters have a limited influence on the particle size (~l-4 μm) [90]. A modified version of the process known as "the SAS-EM process", allows nano-particles of a controlled size (3 - 50 nm) to be produced [91].

The effect of $scCO_2$ on many polymers is to lower their Tg and thus, the material is plasticized, or liquefied. This is caused by the very high solubility of the dense gas in the polymer. The scC02 is therefore applied under pressure into the polymer until the gas saturated solution is formed. When depressurized through a nozzle, the gas comes out of the liquefied polymer which forms well-defined particles. This "particles from gas saturated solutions", so-called PGSS process, has the advantages that the starting material does not have to be soluble in $scCO_2$ and that no organic solvents are required during processing. It is thus highly attractive for elaborating particulate DDS, while it is not yet widely developed. Mainly, drug loaded PEG and poloxamers micro-particles are described [92].

Besides these $scCO_2$-based processing methods, a strategy widely implemented for the production of polyester particles relies on ring-opening polymerization in supercritical carbon dioxide in the presence of a block or graft copolymer made of a CO_2-philic block responsible for steric stabilisation and a CO_2-phobic block (PCL) acting as the anchoring block. Because polymers are insoluble in $scCO_2$, the choice of the CO_2-philic component is very limited, and usually restricted to silicones and fluorinated polymers. For instance, ROP of εCL in $scCO_2$ has been carried out in the presence of various poly(tetrahydroperfuorodecylacrylate-b-capro-lactone) diblock copolymers [93]. Micro-spheres have accordingly been prepared with [PCL(20 K)-b-PAC8(40 K)] surfactant, (conditions: 10 vol.% CL, *Mn,th=20* k ; 5 wt.% surfactant, 40 °C, 300 bar, 400 rpm, 15 h) as illustrated in Fig. 3a. In a similar manner, PLLA particles have been obtained by suspension polymerization in $scCO_2$ by using well-defined fluorinated triblock copolymers Fig. 3b [79]. Nevertheless, fluorinated polymers are inappropriate for biomedical applications. Interestingly enough, poly(glycolide) micro-particles were prepared in supercritical carbon dioxide by using a non-toxic hydrocarbon stalilizer, i.e., P (propylene glycol)-b-PEO-b-P(propylene glycol) [94]. Recently, the ROP of L-LA in $scCO_2$ was studied in the presence of different stabilizers architectures based on polydimethysiloxane (PDMS). The stabilization efficiency of amphiphilic block and graft copolymers was compared. While block copolymers were effective giving fine and discrete PLLA micro-particles, the graft copolymer failed to give enough stabilization due to their short polymer-philic chains

resulting in hard agglomerates [95].

Fig. 3. *Various micro-spheres prepared by using the $scCO_2$ technology: (a) PCL (bar: 1 mm) prepared by in situ polymerization in presence of PAC8-b-PCL Reproduced with permission from [93]. Copyright Wiley-VCH Verlag GmbH & Co KGaA. (b) PLA (bar: 100 µm) prepared by in situ polymerization in presence of PCL-PFPE-PCL. Reprinted with permission from [79]. Copyright 2008 American Chemical Society.*



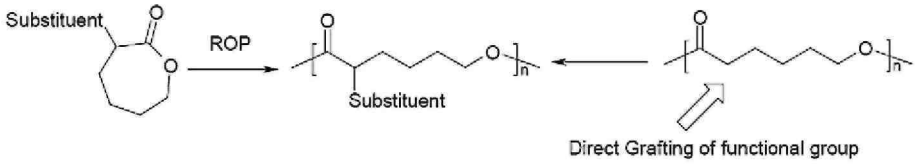
4. MACROMOLECULAR ENGINEERING OF ALIPHATIC POLYESTERS

The previous sections are devoted to the ROP synthesis of the major biodegradable and biocompatible aliphatic polyesters by one-step process from the simplest basic monomers, i.e. ε-caprolactone, lactides and glycolide, all of them being widely used in DDS. Details on the formulations of these aliphatic polyesters as nano- or micro-spheres and their potential applications in the biomedical field are given in recent dedicated reviews [96,97]. Section 4 is rather going to describe several strategies for the attachment of functional groups along the chain to tailor the macroscopic properties of these hydrophobic aliphatic polyesters that are function-free except for the ester group within the main chain. Indeed, in addition to tune physico-chemical properties of the polyesters, these functional groups can be used as anchoring sites for drugs or targeting units, valuable in advanced DDS.

Derivatization of aliphatic polyesters is particularly delicate as compared to non degradable polymers, because any reaction conditions that would cleave the ester bond will be responsible of the premature polymer degradation. A lot of efforts are thus currently devoted to the preparation of tailored-made functional aliphatic polyesters. Even if these novel materials have been only scarcely tested in clinics up to now, their unique properties make them promising for the DDS of tomorrow. In contrast to these functional polyesters, poly(ethylene glycol) (PEG)-based copolymers, developed in response to the need for a variety of formulations for different drugs and delivery pathways [98] are starting to appear on the market thanks to their success in preclinical applications.

For the last few years, two main strategies have been proposed to synthesize aliphatic polyesters with pendent functional groups (Scheme 9). The first one is based on the synthesis and polymerization of lactones substituted in α- or γ-position [99]. The grafting of functional groups in the α-position of the carbonyl of preformed polyester is the second strategy [100].

Scheme 9. *Main strategies for the synthesis of aliphatic polyesters with pendent functional group.*

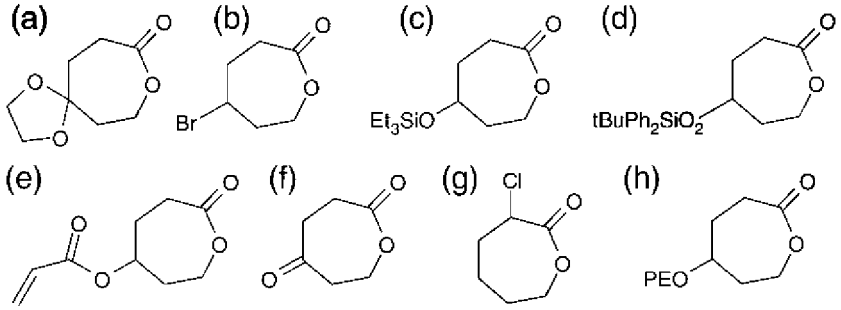


4.1. Polymerization of functional lactones

ε-CL that bears five -(CH_2)-groups beside the ester group can be derivatized in various positions and with a very wide range of functional groups (Scheme 10). The synthesis of 1,4,8-trioxaspiro [4.6]-9-undecanone (Scheme 10a) is reported by Tian et al. This γ-ketal lactone is homo-polymerized [101] and copolymerized [102] with ε-caprolactone. The ketal groups are used as protected ketones, whose reduction by sodium borohydride led to pendent hydroxyl groups, together with an increase of the hydrophilic character of the hydroxy-polyester.

Later on, a series of lactones substituted by bromides [103,104], acrylates [105], protected hydroxyl goups [106,107] protected carboxyl groups [108-115] and terminal olefins [116,117] or containing ketones [118] have been synthesized and homo- or co-polymerized. Interestingly, brominated poly (ε-caprolactone) homo- or copolymers have been successfully quaternized by pyridine [119] and were found to be efficient degradable polycations in gene delivery systems [120]. It must be noted that the synthesis of substituted lactones is most often a multi-step process with a low final yield. For a detailed description of the synthesis and polymerization of these monomers, the reader is referred to a review paper [99].

Scheme 10. *Substituted ε-caprolactones polymerizable by ROP.*



Vert et al. investigated the synthesis and polymerization of 3-(1,2-3,4-tetraoxobutyl-diisopropylidene)dioxane-2,5-dione(DIPAGYL), a derivative of glycolide, substituted by acetonide, which can be partially deprotected into diol [121]. The copolymerization of lactones and lactides with 2,5-morpholinediones substituted by protected acids [122] and amines [123] is also reported.

Recently, the synthesis of novel functionalized dilactones with protected hydroxyl groups, i.e. benzoyloxymethyl Me glycolide and benzoyloxymethyl glycolide was reported [124-126]. These monomers can be homo-polymerized and copolymerized by ROP using conventional tin octoate or ethylzinc as catalyst. After polymerization, the deprotection under mild conditions gives the corresponding hydroxylated polyesters. Another route relies on the copolymerization of non functional dilactones with a functional lactone such as benzyloxyethyl-b-malolactonate [127].

The major drawback of this synthetic strategy is that any functional groups able to react with metal alkoxides (mainly aluminum and tin) involved in the polymerization must be protected prior to polymerization and deprotected after polymerization [128]. The choice of the protecting group is also an important issue because deprotection of too stable protecting groups can result in the polyester degradation. For instance, PCL containing more than 50 mol% of γ-triethylsilanolate (-$OSiEt_3$) could not be quantitatively converted into hydroxyl containing PCL without degradation [106]. Conversely, too labile protecting groups are deprotected at least partly during the synthesis and purification of the monomer.

Epoxides are not compatible with tin and aluminum alkoxides, such that they have to be incorporated by postpolymerization oxidation of pendent double bonds, for instance by *m*-chloroperbenzoic acid (mCPBA) [117-119].

The main advantage of using functional lactones is the possibility to have them purified by distillation or recrystallization processes prior to polymerization. Therefore, the final polymer is not contaminated by potentially toxic catalysts and/ or chemicals as would be the case if the same functionalization reaction was carried out with preformed polymer chains.

A very attractive functional lactone is the poly(ethylene oxide) (PEO) (also called polyethylene glycol-PEG) macromonomer, i.e. a lactone substituted by a PEG polymer chain [129]. Such macromonomer is precursor of graft copolymers, e.g, poly (ε-caprolactone-g-ethylene oxide) (PCL-g-PEO) with a palm-tree architecture due to quite divergent reactivity ratios (Scheme 2e).

Amphiphilic PCL-g-PEO copolymers have been accordingly prepared, that form micelles in water [130]. These palm-tree copolymers have been found more efficient in the stabilization of polylactide nano-particles in water [131], as compared to the more conventional diblock copolymer. Similarly, Park et al. reported on the copolymerization of lactide with poly(ethylene oxide) (PEO) end-capped by an epoxide group [132] having also great potential in DDS.

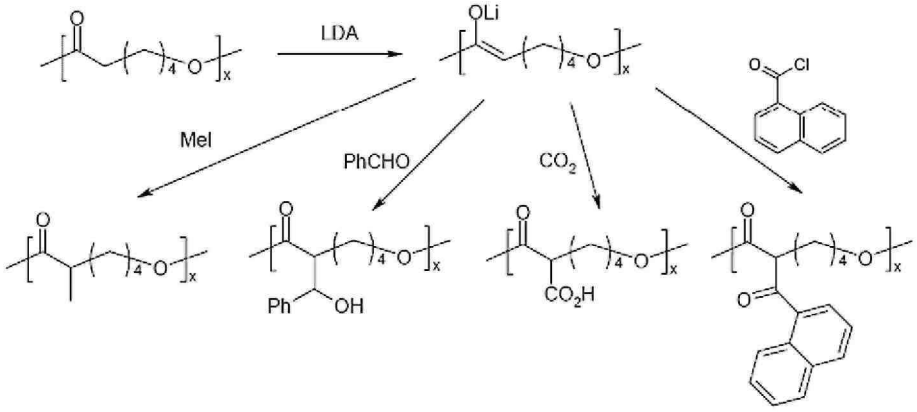
4.2. Derivatization of preformed polyesters

Grafting of functional groups onto preformed aliphatic polyesters chains is an appealing strategy because from a single easily available precursor, a wide range of functional groups can be attached in one further step.

4.2.1. Direct derivatization of poly(ε-caprolactone)

A representative example for the functionalization of PCL or PLA chains along the ester backbone in the α-position of the ester group is reported by Vert et al. [100,133-138] Metallation of PCL by lithium diisopropylamide leads to the formation of a poly(enolate), reactive towards a variety of electrophiles (Scheme 11). For instance, carbon dioxide [135], benzaldehyde [100] and iodine [137], thus precursors of acid, hydroxyl, iodo moieties, have been respectively grafted along the chain. The coupling of bromoacetylated α-hydroxy-methoxypoly(ethyle-neglycol) onto anionically activated PCL is a route to the PCL-g-PEO graft copolymer [138]. The implementation of this strategy is however limited by unavoidable chain scission in competition with chain metallation.

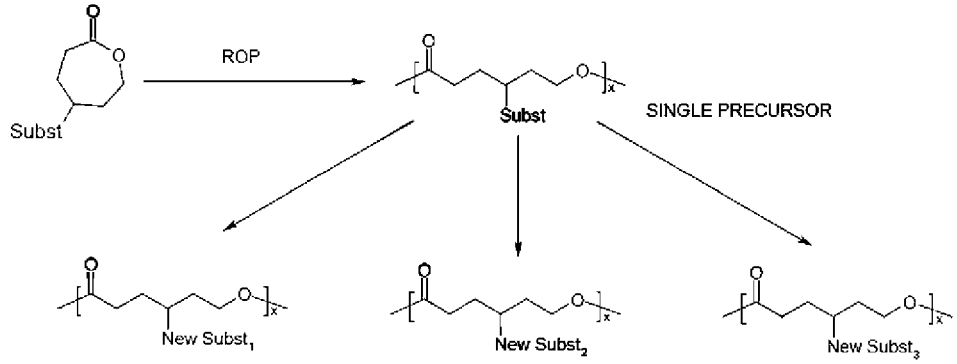
Scheme 11. *Chemical derivatization of PCL by an anionic route.*



4.2.2. Derivatization of suitably substituted aliphatic polyesters

Thanks to the efficiency of synthetic strategies which makes some functional lactones readily available, the combination of the two above-described strategies into a two-step process appears as a valuable alternative (Scheme 12). In the first step, ε-caprolactone is substituted by a properly selected functional group and (co)-polymerized. Then the substituent is derivatized further into a variety of functional groups, polymeric or not, according to any suitable reaction known in the state of the art. A wide range of aliphatic polyesters can accordingly be made available from a single precursor.

Scheme 12. *ROP of substituted ε-caprolactone into a unique precursor followed by its chemical derivatization into various functional aliphatic polyesters.*



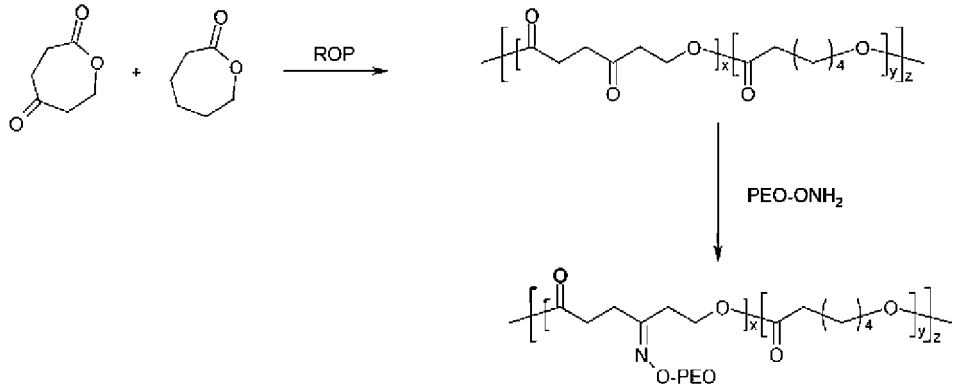
The success of such strategy relies on the fulfilling of the following criteria: (1) as direct synthesis as possible of the substituted monomer to be first polymerized (one or two steps), (2) this monomer should comply with controlled (co)-polymer-ization, (3) the envisioned derivatization reactions should be carried out under mild conditions in order to (i) avoid chain degradation, (ii) avoid protection/deprotection of the functions to be incorporated, (iii) favor quantitative reaction even at high content of functional groups.

Emrick et al. gave a first example of this strategy by copolymerizing ε-caprolactone with an unsaturated derivative, followed by conversion of the pendent double bonds into diols. Esterification of these hydroxyl groups with PEO end-capped by a carboxylic acid generates again amphiphilic graft PCL-g-PEO copolymers [139].

Similar copolymers can also be achieved by the grafting of amino-oxy-terminated poly(ethylene oxide) (PEO) onto the ketone groups of poly(ε-caprolactone-co-oxepane-l,2-dione) [140,141] (Scheme 13). In another work, hydroxyl groups were grafted onto poly(ε-caprolactone-co-oxepane-1,2-dione) by coupling hydroxyethyl hydrazine with pendant ketones [142], Pendant hydroxyl groups were used for further derivatization [142]. Recently, Wooley et al. investigated the derivatization of poly(ε-caprolactone-co-oxepane-l,2-dione) by reductive amination. Nevertheless, this reaction turned out to be not selective enough due to detrimental lactamization side reactions [143], Nevertheless, copolymers with a high content of ketone are insoluble in organic solvents, restricting the content of any functional group to low values.

In the following, we will describe three effective derivatization strategies based on well-known basic organic reactions as a demonstration of the versatility of this third approach. These are all addition-type reactions that have the advantages to be free of side-products of reactions.

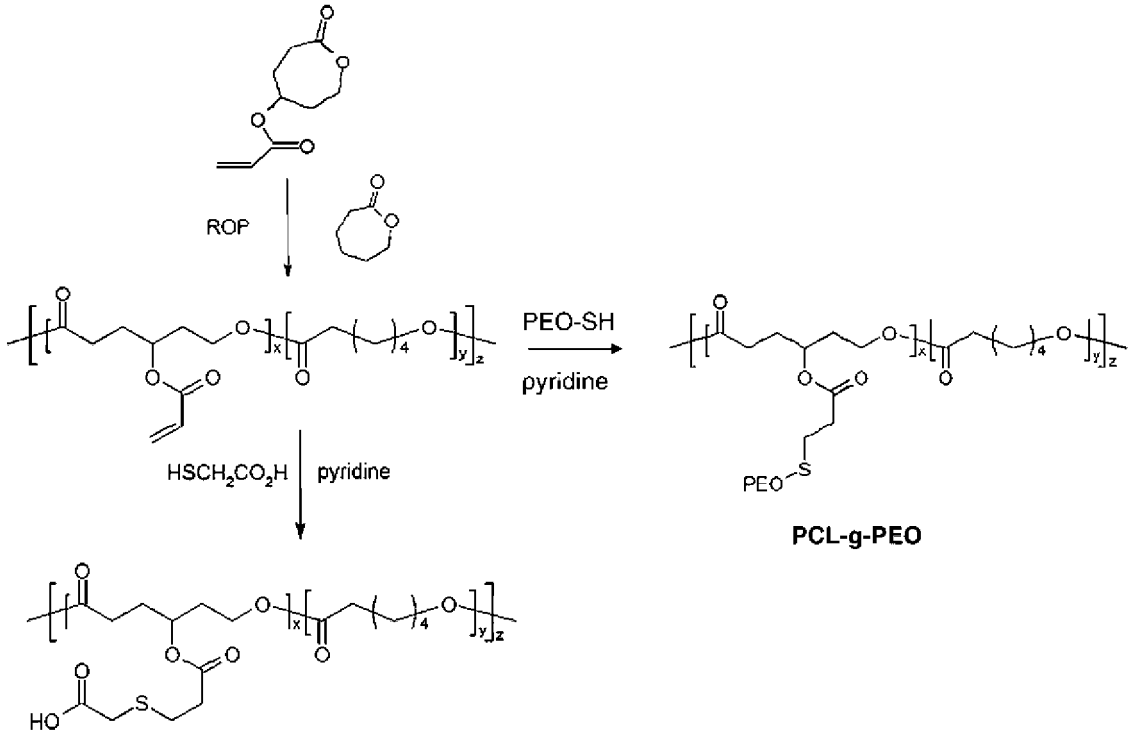
Scheme 13. *Grafting of PEO onto PCL according to Mayes et al. [140].*



4.2.2.1. Michael-type addition.

γ-acrylic-ε-CL can be easily synthesized according to a three-step procedure [144] and copolymerized with εCL into poly (γ-acrylic-εCL-co-εCL) copolymers. Various thiols are efficiently added onto these pendent acrylate groups of PCL (Scheme 14). Thiol end-capped PEO was then added onto the pendent acrylic groups of PCL (content of acrylic units = 18 mol%) in the presence of pyridine (THF, room temperature, 300 h [pyridine]/[thiol]/[acrylate]=15/10/1). [145] The PCL-g-PEO graft copolymer was formed as result of 65% conversion of the acrylic units. These experimental conditions were extended to the addition of mercaptoacetic acid, the acrylic conversion being 71% after 75 h. Remarkably, no cumbersome protection/deprotection reaction was needed for attaching acid groups onto PCL. No degradation was either observed. Nevertheless, the Michael-type reaction is not quantitative; with the risk of cross-linking through the residual acrylic groups. Last but not least, the control of the homo-polymerization of γ-acrylic-ε-CL is limited by a backbiting reaction producing γ-acryloxyethyl-γ-butyrolactone [146]. The main advantage of the Michael addition is that no organometallic catalyst, that might be detrimental to biomedical applications, is needed. In a similar approach, thiols were grafted onto pendent epoxides, prepared by oxidation of unsaturated aliphatic polyesters by mCPBA [117].

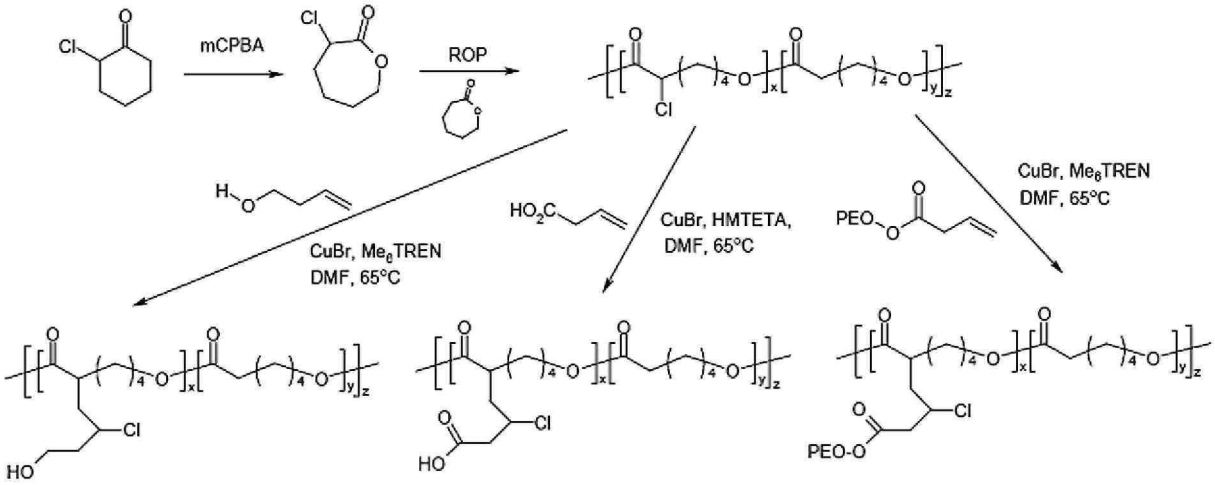
Scheme 14. *Derivatization of pendent acrylic unsaturations of PCL by Michael addition.*



4.2.2.2. Atom transfer radical addition.

Atom transfer radical addition (ATRA) consists in the addition of an activated chlorine to an olefin catalyzed by organometallics. This reaction is known for tolerance towards aliphatic polyesters [147]. α-chlorocyclo-hexanone is easily converted into the parent lactone (αClεCL) by one-step oxidation with *m*-CPBA with high yield, the chlorine atom of the lactone being activated by the proximity of the ester group (Scheme 15) [148,149]. Then, αClεCL is copolymerized with εCL in a well-controlled manner, the initiator being a tin(IV) alkoxide [150]. Finally, 3-buten-1-ol is quantitatively grafted onto chloro-PCL by CuBr/Me_6TREN meditated ATRA in DMF at 65 °C for 4 h [148]. Again, no protection is needed and no chain degradation is observed by SEC [148]. Moreover, ATRA of commercially available α-methoxy, ω-acrylate-PEO (*M*n (PEO = 750) onto poly(αClεCL-co-εCL) (*M*n= 17,500 ; 48 αClεCL units) yields a graft copolymer, with 9 PEO grafts [149]. However, 18 chlorinated units per chain are lost by reduction during ATRA. The situation is even worst when vinyl acetic acid is substituted for 3-buten-1-ol. With this olefin, no all the chlorinated units are reduced and consequently no ATRA occurs. This problem was solved by reducing the activity of the catalyst (HMTETA is used instead of Me_6TREN) leading to ATRA with a moderate yield of 32% after 24 h. To be quantitative, higher temperature (85 °C instead of 65 °C) are needed for ATRA, resulting in chains degradation. As a rule, ATRA does not meet the third criteria of the general strategy shown in Scheme 12. Moreover, the stoichiometric amount of the copper catalyst with respect to activated chlorides, which is needed in ATRA, contaminates the final polyester, prevents its end-use in biomedical field.

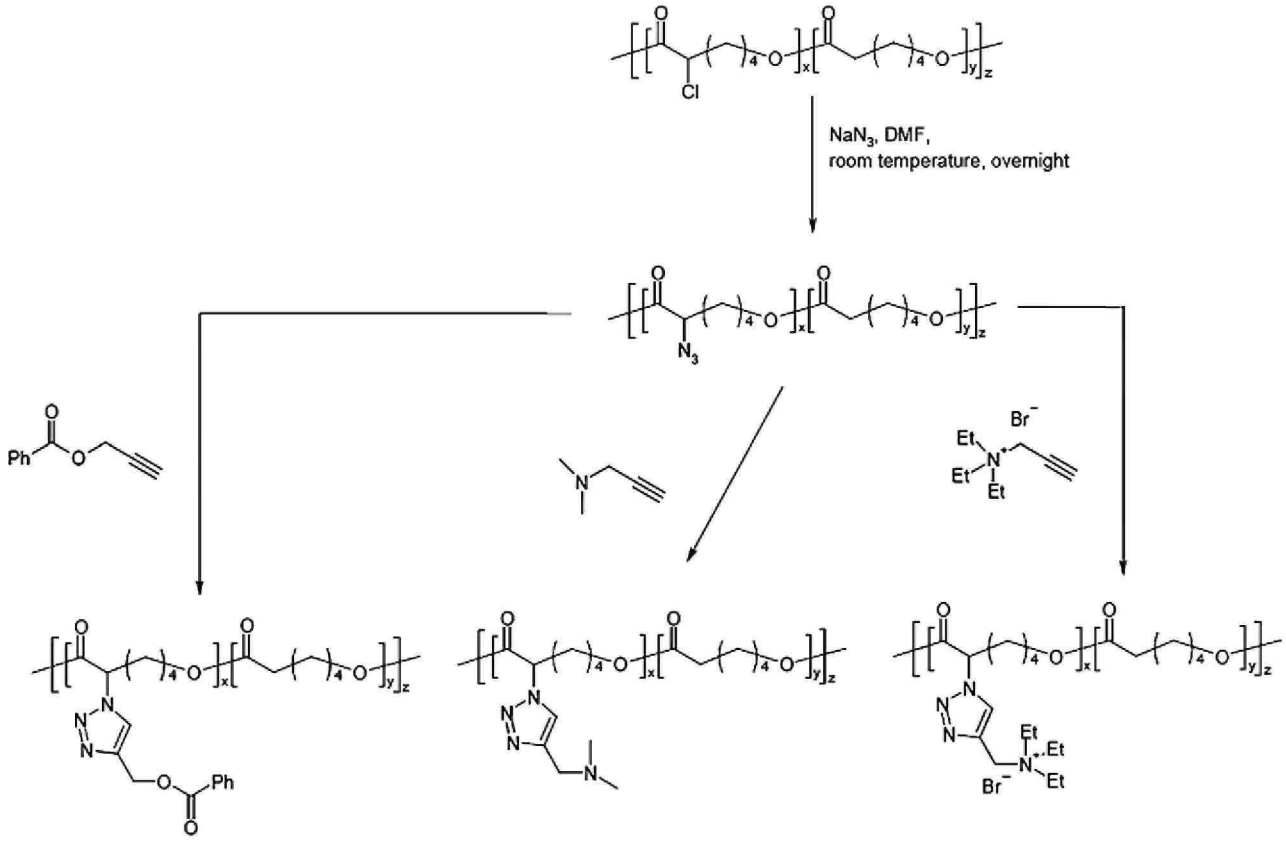
Scheme 15. *Derivatization of the α-chloride pendent groups of PCL by atom transfer radical addition.*



4.2.2.3. Click reactions.

Today, much attention is paid to copper catalyzed 1,3-Huisgen's cycloadditions between azides and alkynes, thus to reactions which are known for quantitative yield, under very mild conditions, from cheap and easily available reagents, i.e. one reaction that falls in the so-called click reactions [151]. This reaction is actively investigated for macromolecular engineering of aliphatic polyesters. Emrick et al. reported on the cycloaddition of an azido-end-capped PEO onto PCL bearing pendent alkynes [152]. The "click" reaction was conducted in water in the presence of $CuSO_4$ and sodium ascorbate as catalyst.

Scheme 16. *Derivatization of pendent azide groups of PCL by "click" reactions.*

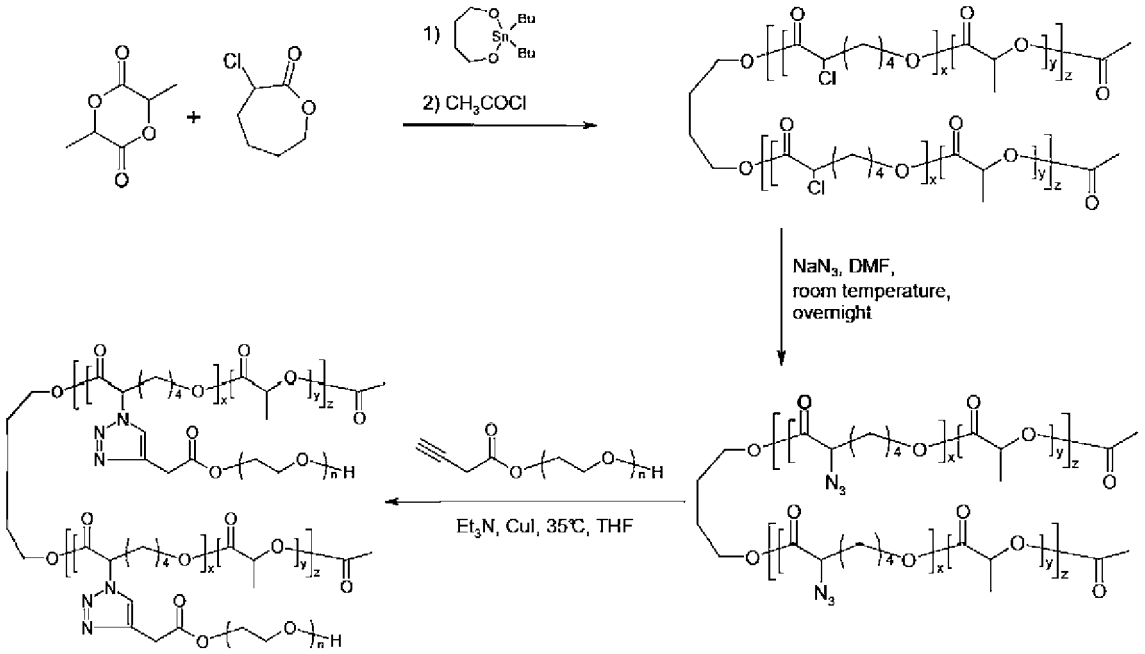


Riva et al. described that poly(αClεCL-co-εCL) can be quantitatively converted into azides, followed by "click" reaction with functional alkynes (Scheme 16) [153]. In order to apply the reaction to more sensitive polyesters such as PLA, the "click" reaction was tested at a low temperature (35 °C) in an organic solvent (THF). Cycloaddition of both propargyl benzoate mediated by CuI and triethylamine (NEt_3) and 3-dimethylaminoethyl-1-propyne mediated by CuI turned out to be quantitative with no significant degradation [153] (Scheme 16). It is worth noting that CuI is used in catalytic amount (0.1 equivalent with respect to the azide groups), which is a significant improvement compared to ATRA, which requires a stoichiometric amount of copper catalyst. An additional advantage of this "click" reaction is tolerance towards many organic functions. Indeed, polycationic polyesters were prepared by using *N,N,N*-triethylammonium propargyl bromide as the alkyne reagent. PCL-g-PEO were also synthesized by reaction of an alkyne end-group of PEO (ω-alkyne-PEO) with poly(αN_3εCL-co-εCL). The grafting efficiency was approximately 30% in line with the yield reported for ATRA. Importantly, no degradation was detected.

"Click" reaction is also superior to other derivatization reactions in that high content of pendent functional groups can be considered. Indeed, the aforementioned cycloaddition was complete in THF when poly(αN_3εCL) homopolymer (Mn=46,000 ; Mw/Mn=1.6) was reacted with propargyl benzoate.

Remarkably, the very mild experimental conditions used in "click" reactions allow them to be extended to the functionalization of polylactide known for higher sensitivity to chain degradation than PCL. ω-alkyne-PEO with poly(αN_3εCL-co-LA), provided that the OH end-groups of the copolylactide chains are previously esterified with acetyl chloride gives PLA-g-PEO graft amphiphilic copolymers (Scheme 17) [154],

Scheme 17. *Synthesis of PLA-g-PEO by combining ROP and "click" chemistry.*



The activated chlorides of poly(αClεCL-co-εCL) can thus be derivatized by either ATRA or 1,3 -Huisgen cycloadditions. Even though the "click reaction" requires an extra step compared to ATRA (comparison of Schemes 15 and 16), it is more effective. This superiority is reinforced by the fact that the additional step, i.e., substitution of chlorides by azides, and the cycloaddition can be carried out in one-pot, thus without isolating the intermediate azide containing copolymer. In a representative example, poly (αClεCL-co-εCL) (Mn=22,000 ; Mw/Mn= 1.5) was reacted with 5 equivalents of sodium azide in DMF at room temperature overnight. 5 equivalents of propargyl benzoate were then added to the reaction mixture, and the "click" reaction was quantitative at 35 °C for 3 h. A slight increase in the polydispersity index was observed (Mw/Mn= 1.7).

The spreading development of click chemistry in polymer engineering leads to very rapidly increasing numbers of papers. For more description on Click reactions applied to polymers, readers can refer to a more complete review paper written by Lutz [155],

4.3. Amphiphilic copolymers, dendrimers and gels

Macromolecular engineering also provides polyesters with a wide variety of architectures and allows their combination of any other polymers. As far as DDS are concerned the developments of copolymer architectures combining polyesters and polyethylene oxide (or polyethylene glycol) is of prime interest. This last paragraph is going to focus on the variation of polyesters architectures (2) and additional strategies for the integration of PEO into them.

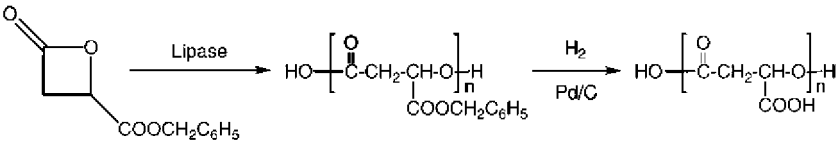
As already mentioned, the hydrolysis of the alkoxide at the ω-end of the polyesters prepared by ROP results in the presence of an hydroxyl group that can be used to prepare various macromonomers, e.g. by reaction with acryloyl chloride.

On the other hand, because aluminum alkoxides can be prepared by reaction of trialkyl aluminum with an alcohol, the variety of alcohols available offers a large choice for the structure of the α end group, including polymerizable end groups of the methacrylate and the norbornenyl types [156,157] These hydrophobic macromonomers can be copolymerized with hydrophilic comonomers, such as 2-hydroxyethylmethacrylate (HEMA), with formation of amphiphilic copolymers [158]. In case of α,ω-acrylate PCL (or PLA), formation of amphiphilic polymer networks can be envisioned. Macroinitiators prepared by reaction of mono- or dihydroxy PEO with triethylaluminum or using tin octoate allow the synthesis of AB diblock and BAB triblock copolymers (Scheme 2 a, c) where (a) is the hydrophilic PEO and (b) the hydrophobic block of biodegradable polyesters (PCL, PLA, PLGA, PGA,...) with a complete control of the copolymer composition and size [159]. Similar copolymers with functional polyesters are also described [160]. Such copolymers are tremendously studied for biomedical applications due to their amphiphilic character and the peculiar properties of the PEO component that makes them unique for injectable DDS [161]. Triblock copolymers are also interesting by their possible formation of physically cross-linked and thermosensitive hydrogels that offer alternative materials of choice in designing DDS [162]. pH-sensitive systems can also be built by introduction of an additional pH-responsive block to the structures leading to the emerging smart DDS sensitive to EPR effect for cancer therapy [163],

The availability of hydroxyl functional lactones used as inimer also opens the way to the synthesis of highly branched or dendritic polyesters valuable for prodrug systems [164],

Even if less developed than the chemical way, the enzymatic ring-opening copolymerization is also effective for some macromolecular engineering. Functional lactones, such as for example the four-membered *β*-lactone benzyl *β*-malolactonate (Scheme 18) [165], were polymerized by lipases to yield the corresponding functional polyesters.

Scheme 18. *Functional polyesters by enzymatic ROP.*



Benzyl β-malolactonate

Biodegradable copolymers, such as poly(ester-co-carbonate)s [166], copolycarbonates [167] and polyethylene glycol-polyester block copolymer [168] have been produced. A series of PCL-PEG and PCL-PEG-PCL block copolymers were successfully synthesized for the first time using lipase CA [168].

Diblock copolymers, polybutadiene-*block*-polypentadecalactone, and polybutadiene-*block*-polycaprolactone were prepared by the monohydroxylterminated polybutadiene-initiated PDL and ε-CL, respectively, using immobilized *Candida antarctica* lipase B [169].

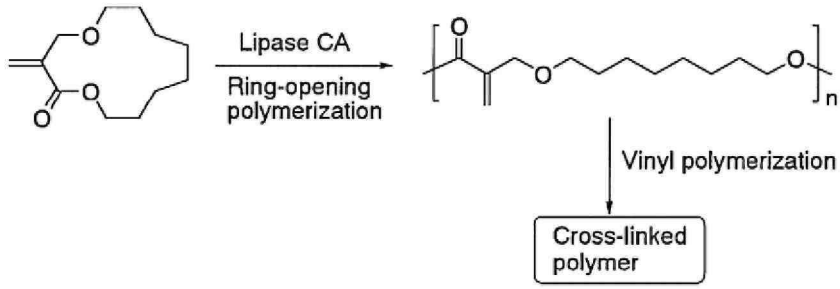
Lactones were also copolymerized with divinyl esters and glycols using lipase to produce the copolyester, not a mixture of homopolymers. Two different modes of polymerization, ring-opening polymerization and polycondensation, simultaneously took place through enzymatic polymerization in one-pot to produce the copolyesters [170].

End-functionalized polyesters are synthesized by the ring-opening polymerization of lactones in the presence of functional hydroxy, carboxy, and methylene groups. An alcohol could initiate the ring-opening polymerization of lactones by lipase [171,172]. The lipase catalysis chemoselectively induces the ring-opening polymerization of 2-methylene-4-oxa-12-dodecanolide yielding a polyester having the reactive exo-methylene group in the main chain. The present polymer cannot be obtained using a conventional chemical initiator [173]. The chemospecific

ring-opening polymerization of α-methylenemacrolides having various groups, i.e., aromatics, ether, and amine, was enzymatically anionically, and radically carried out.

Polymerization with the lipase catalyst successfully yields polymers only through the ring-opening process, whereas vinyl groups were further polymerized by anionic and radical initiators to produce a cross-linked polymer gel (Scheme 19) [173,174].

Scheme 19. *Cross-linkable polyester by enzymatic polymerization.*



5. CONCLUSION

Aliphatic polyesters are emerging materials for the elaboration of drug delivery systems. For such demanding applications, their synthesis has to avoid the use of toxic catalysts and/or initiators and of organic solvents that are difficult to remove. These requirements have driven the evolution of the researches on the ring-opening polymerization of these materials. From the quite toxic aluminum and tin initiating systems mainly used in stoichiometric amount, highly reactive rare earth catalysts leading to lower polymer contamination, initiator/catalysts based on friendly metals have been developed. Presently, all-organic and enzymatic systems for ROP are the hart of tremendous researches since they are totally metal free.

Simultaneously, the spreading of the non toxic $scCO_2$ technology made possible studies not only on the synthesis of aliphatic polyesters in this medium but also on their purification and processing as micro-particles. This technology has been found as a method of choice as far as DDS are concerned.

Finally, the recent discoveries in disease mechanisms are other guidelines for the elaboration of novel materials of tailored properties able to build smart DDS with the appropriate answer to the diseased tissue. Even if the functionalization of aliphatic polyesters is very challenging due to their sensitivity towards degradation, successful strategies have been evidenced and original materials can be synthesized in a highly controlled way. These novel materials, even if they have not yet been tested very much in clinical testing are promising for the advanced DDS of tomorrow.

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