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Polymers from Macrolactones: From Pheromones to Functional Materials

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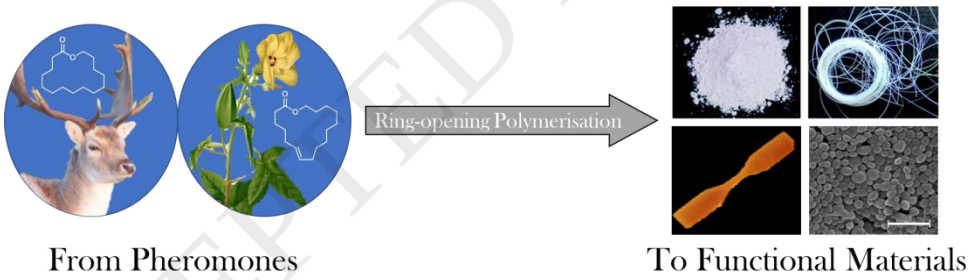
Graphical abstract



Abstract

Recent advances in the ring-opening polymerization (ROP) of macrolactones (MLs) have afforded access to novel, potentially degradable polymeric materials featuring long aliphatic chains. These developments extend the synthetic robustness and versatility of ROP to a greater range of interesting monomers, many of which can be derived from sustainable or renewable

feedstocks, to access polymeric materials boasting a diversity of properties and potential applications. This review discusses current strategies to catalyse the ROP of MLs, comparing and contrasting them with those known for the ROP of small and medium sized lactones, and highlights recent developments in the preparation, functionalization, and application of materials featuring poly(macrolactone)s (PMLs).

Key Words: aliphatic polyesters, macrolactones, ring-opening polymerization, catalysis, renewable polymers.

Introduction

Aliphatic polyesters are widely utilised in biomedical and pharmaceutical applications since they maintain appropriate chemical, thermal and mechanical properties and are frequently both biodegradable and biocompatible (degradation products inclusive). [1-3] Furthermore, polyesters derived from sustainable resources are receiving increasing interest as environmentally-friendly materials. ROP performed on small (up to 6 atom) and medium (between 7 and 11 atom) lactones is well-understood and thermodynamically driven by a negative change in enthalpy during the release of angular or transannular strains, respectively. MLs (consisting of 12 or more atoms), however, possess little or no ring strain and consequently, early attempts to polymerise MLs using conventional ROP catalysts typically proceeded in the absence of control or yielded low molecular weight material. [4-7] Developments in the ROP of MLs since the 1990s have facilitated the preparation of a range of novel polymeric materials that are often challenging to access *via* other synthetic strategies.

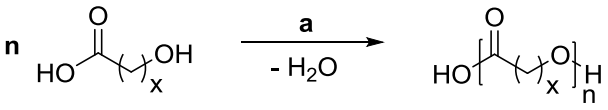
For centuries, MLs have been applied in fragrances for their musky odour. [8, 9] Although originally obtained from animal sources, numerous MLs can be isolated or synthesised from plant oils. [10] The isolation of exaltolide (ω-pentadecalactone, PDL) by Kerschbaum in 1927 [11] generated interest in MLs, which have since been developed into fragrances, pheromones, insecticides, pharmaceuticals, and phytotoxic agents, amongst other applications. [12] Today PDL is FDA-approved for use as an indirect food additive and is widely used as a fragrance in consumer products. [13] Although it is commercially sourced from fossil fuels, PDL can also be extracted

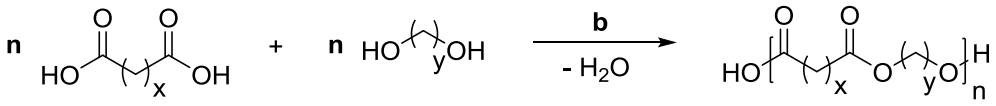
from natural sources including the angelica plant root (*Angelica archangelica*) and musk deer (genus *Moschus*). [8, 9] Interestingly, PDL is a mammalian pheromone secreted by apocrine glands in the human male armpit. [14, 15] As the most commercially available ML, PDL is routinely investigated as a key macrolactone in ROP studies, and the discovery that poly(ω-pentadecalactone) (PPDL) maintains similar properties to low-density polyethylene (LDPE) [16-18] or high-density polyethylene (HDPE), [19] depending on its molecular weight, has attracted considerable interest in PMLs.

Developments in the ROP of MLs have expanded the diversity of properties and potential applications of polyester materials. Furthermore, these developments have led to exciting new processes in polymer science. Herein, recent advances in the ROP of MLs are discussed and developments in the preparation, functionalization, and application of materials featuring PMLs are highlighted.

Ring-opening polymerization of MLs

Aliphatic polyesters were originally prepared *via* condensation polymerization of hydroxyl acids or diacids and diols (Scheme 1). [20] Disadvantages of condensation polymerization, however, include the requirement for stringent monomer purification, precise stoichiometry, and high reaction temperatures that promote undesirable side reactions. Since condensation polymerization proceeds *via* step-growth polymerization kinetics, the ability to both control the reaction and obtain high molecular weight material is challenging to achieve. Nonetheless, condensation polymerization has been reported as a successful strategy to prepare PMLs that are equivalent to those prepared *via* ROP. [21-24] Additional strategies to prepare PMLs include transesterification of diesters and diols, [25] acyclic diene metathesis (ADMET) polymerization, [26-31] acyclic triene metathesis polymerization, [32] ring-opening metathesis polymerization (ROMP) [33], and thiol-ene addition. [29, 31, 34]

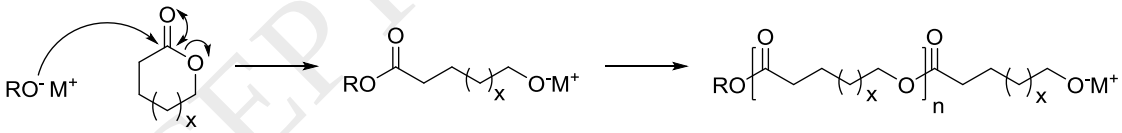




Scheme 1
Preparation of polyesters *via* condensation polymerization of a) hydroxyl acids, and b) diacids and diols.

The modern preparation of aliphatic polyesters *via* the ROP of lactones (*i.e.* cyclic esters) affords excellent control over the polymerization to produce high molecular weight material under relatively mild reaction conditions. ROP techniques are regarded as controlled/living polymerization systems since 1) they proceed *via* chain-growth kinetics, resulting in a linear increase in the molecular weight of the polymer with increasing monomer conversion, 2) the molecular weight of the polymer can be directly controlled by the ratio of monomer to initiator in the initial reaction mixture, 3) the resulting polymer maintains a narrow, monomodal dispersity ($Đ_M$), and 4) high end-group fidelity is preserved throughout the polymerization. The ability to perform a polymerization with living characteristics ultimately enables control over the bulk properties of a material, which is crucial for a number of applications.

Since both nucleophiles and electrophiles can initiate the ionic polymerization of polarised monomers, the range of catalysts appropriate for ROP is vast and includes metal complexes, organic compounds, and enzymes. [35] Initiation in ROP ultimately proceeds *via* either an anionic, cationic, coordination-insertion, or activated monomer mechanism. Alkali and earth-alkaline alkoxides were amongst the first classes of catalysts demonstrated to initiate the anionic polymerization of lactones. Specifically, the alkoxide anion undergoes nucleophilic addition to the carbonyl carbon of the cyclic ester, releasing an alkoxide end-group that propagates in the same manner (Scheme 2).



Scheme 2

Mechanism for the anionic ring-opening polymerization of lactones using metal-based catalysts.

A significant disadvantage of this strategy, however, is that the propagation step is typically accompanied by numerous side reactions, in particular backbiting to regenerate the monomer or yield macrocyclic oligomers. Backbiting results from the reversible nature of the polymerization, and backbiting to form macrocycles is an example of a transesterification side reaction whereby the catalyst coordinates an alkoxide chain-end and an ester linkage within the polymer backbone, the alkoxide attacks the activated carbonyl to form a new ester linkage, and another alkoxide is

eliminated in the process. Transesterification can occur intramolecularly, shortening the linear chain and generating a cyclic species, or intermolecularly, generating two linear polymers of different chain lengths. Consequences of either transesterification reaction, however, include an increase in $Đ_M$ and a loss of control over the system.

The ROP of small and medium sized lactones is driven by a the release of angular and transannular strains, resulting in rapid rates of polymerization at low reaction temperatures. [35] MLs exhibit minimal ring strain and therefore, since the enthalpic gain during ROP is negligible, the main driving force in the ROP of MLs is the entropic gain achieved through ring-opening to attain less hindered chain rotation. [35] Additionally, since the entropic term in the Gibbs free energy equation can be increased with temperature, the polymerization of MLs requires higher reaction temperatures than small and medium sized lactones.

Interestingly, the Jacobsen-Stockmeyer model for reversible ring-formation [37] indicates that, in the ROP of cyclic monomers, cyclic polymers are always produced *in situ* with linear polymerization systems as a consequence of concurrent transesterification side reactions. Generally, the equilibrium for the molar ratio of cyclic to linear polymers is heavily weighted toward the linear side as a consequence of ring-strain. However, given a criteria where the ring strain of the monomeric ring is almost zero, an effective molarity of strainless cyclic oligomers (B) must be attained in order for a polymerization system to generate linear polymers. This is a direct consequence of the molar cyclization equilibrium constant (K_i) being identical to the effective molarity of the monomeric ring (EM_i) in a strainless system, which is inversely proportional to B. This means that at any degree of monomer conversion, a small concentration of cyclic oligomers (B = 0.087 M for ambrettolide) must be reached, even in advance of any linear polymerization. [37] Ultimately, the absence of ring strain in MLs results in similar rates of polymerization and transesterification, and consequently, a lack of control over the ROP process such that cyclic oligomers (2-5 repeat units) are formed, and lower number average molecular masses (M_n) and higher dispersities ($Đ_M \geq 1.5$) are obtained relative to theoretical chain-growth polymerization values based initial on monomer-to-initiator molar ratio. [37] Despite these challenges, numerous catalysts including enzymes, organometallic complexes, and organic compounds have been established in the ROP of MLs.

Enzymatic ROP (eROP)

There is a tremendous amount of interest in utilising enzymes for chemical transformations since they perform biochemical transformations with remarkable precision and efficiency, specifically with a high degree of chemo-, regio-, and enantio-selectivity, all under mild conditions. Furthermore, enzymes are non-toxic, recyclable, and easily removed *via* gravity filtration when immobilised on a solid support. [38] Consequently, enzymes are receiving increasing interest as 'green' alternatives to conventional polymerization catalysts. Beginning in the 1990s, enzymes were explored as catalysts for the ROP of MLs and the success of enzymatic ring-opening polymerization (eROP) has resulted in the preparation of novel polymeric materials and the development of new processes in polymer synthesis. [39]

Initial eROP reactions were attempted on conventional ROP monomers including ε-caprolactone (CL), [40-42] and an initial bulk copolymerization of CL and PDL using the lipase *Pseudomonas fluorescens* reported only trace incorporation of PDL after 10 days. [43] Thereafter, the eROP of ω-undecalactone (UDL), ω-dodecalactone (DDL), and PDL was investigated using various lipases, notably lipases derived from *Pseudomonas fluorescens* (lipase P) and *Candida cylindracea* (Lipase B) in bulk conditions and at various reaction temperatures (Figure 1). Uyama and co-workers [44-46] discovered that the rate of eROP varies depending on the origin of the lipase, increases with temperature and immobilization on Celite®, and proceeds more rapidly for MLs than for smaller lactones. Subsequently, it was discovered that the rate of the eROP of PDL could be increased 100-fold, further increasing monomer conversion and M_n, and improving the $Đ_M$ of the polymer product, by utilising immobilised, surfactant-coated lipases in organic solvents, notably toluene. [35, 46-48]

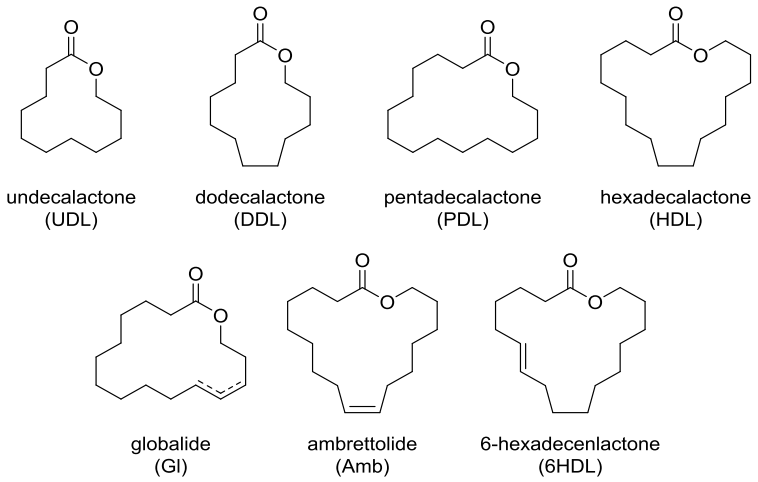


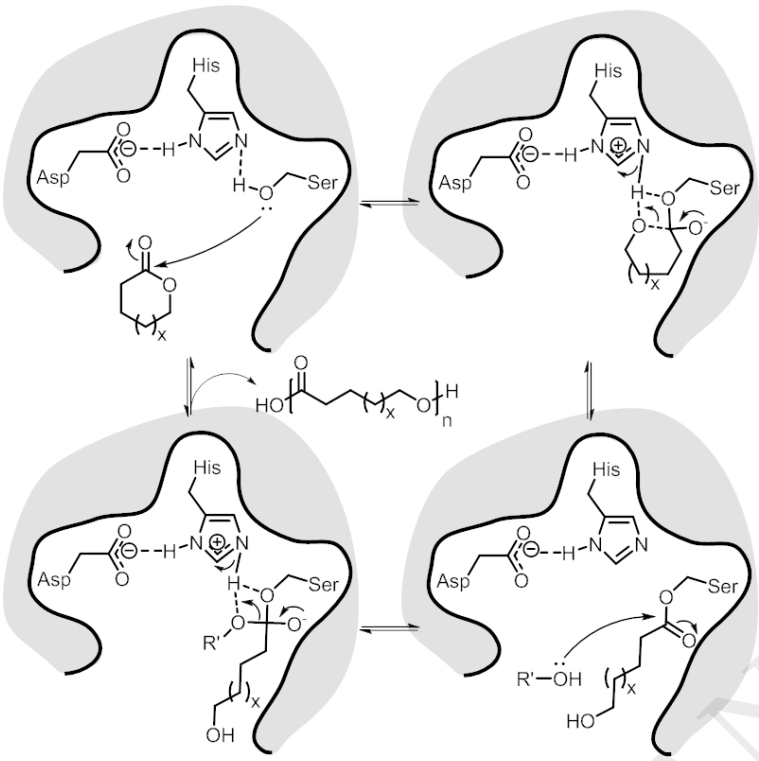
Figure 1. Structures of commercially available macrolactones.

Bisht *et al.* [49] further investigated lipase choice in the eROP of PDL in bulk conditions at 80 °C by screening commercially available lipases over 24 hour polymerization times. Novozyme-435 (N-435), *i.e. Candida antartica* lipase B (CALB) [50] immobilised on an acrylic resin, notably yielded the highest conversion and has since become the enzyme of choice for the eROP of MLs. [51] Although an extensive range of enzymes have been studied for the eROP of MLs, they have all been lipases with the exception of a cutinase from *Humicola insolens*, [52] which exhibits similar kinetics to Novozyme-435. [53] Temperature was determined to be an important factor in the eROP of bulk PDL using N-435, such that increasing the reaction temperature from 60 °C to 80 °C increases both the rate of polymerization and the M_n of the polymer product, however further increasing the reaction temperature to 110 °C decreases both the rate of polymerization and the M_n of the polymer product. [49] Similarly, analysis of PPDL synthesised at 70 °C and 90 °C in toluene using N-435 revealed a significant reduction in the molecular weight and crystallinity of material prepared at 90 °C relative to 70 °C . [54] Therefore, it can be concluded that elevated reaction temperatures denature the native structure of the enzyme, impairing its ability to perform transesterification reactions.

Bisht *et al.* [49] additionally investigated water content, which was found to affect both the rate and M_n such that increasing the water content increases the rate of polymerization, however decreases the M_n of the polymer product. This result is consistent with the conclusion of Matsumoto *et al.* [55] that water is the initiating species. The rate of eROP reactions can be increased by using nucleophilic initiating species such as an alcohol, an amine, or a thiol and it has

been demonstrated that alcohols are more efficient initiators in eROP reactions than thiols since thiols exhibit higher binding affinities to lipases. [56] However, the presence of some water is critical for the enzyme to adopt the correct structure *via* non-covalent bonding, and consequently too little water greatly reduces enzymatic activity. [35] Interestingly, the eROP of PDL affords relatively high weight average molecular weight (M_w) polyesters (M_w = 36,300 g mol^{-1}; $Đ_M$ = 1.44) even where the polymerization is carried out without previously drying reagents and in an open air environment with latent moisture. [57] Performing eROP under inert conditions, however, is desirable to attain precise M_n and end-group control.

Lipases hydrolyse fatty acid esters *in vivo* and eROP is understood to proceed *via* an activated monomer mechanism. [49, 58, 59] The hydrophobic catalytic site consists of a serine, histidine, and aspartate residue and it is proposed that a lactone substrate undergoes nucleophilic addition by the serine alcohol to generate an intermediate that cleaves the monomer acyl bond and releases an alkoxy anion to generate the enzyme-activated monomer (EAM) species. [35, 60] The resulting EAM subsequently undergoes nucleophilic addition of the initiating or propagating alcohol species to generate a new intermediate, the final product of which is released *via* cleavage of the acyl bond to regenerate the enzyme (Scheme 3). Therefore, in eROP, the substrate initially coordinates to the catalyst, unlike with non-enzymatic catalysts, which usually coordinate the initiating species in the first instance. [60] Since the enzyme does not discriminate between ester groups, transesterification side reactions occur, resulting in chain scission and the production of cyclic and linear polymer products, ultimately increasing the $Đ_M$, and decreasing the M_n and end-group fidelity of the polymer product. [18] Furthermore, enzymes such as lipases and proteases only catalyse polymerizations at high monomer concentrations, where the equilibrium favours polymerization. [61, 62] Therefore, eROP cannot be considered a living polymerization process, rather *pseudo*-living, even though reasonable linear molecular mass growth over time, M_n values similar to the targeted degree of polymerization and relatively high end-group fidelity can be achieved using this technique.



Scheme 3

Proposed enzyme-activated monomer mechanism for the enzymatic ring-opening polymerization of lactones. [35], Adapted from Dubois *et al.*

Kinetic investigations into the eROP of various sized lactones determined that eROP proceeds more rapidly for larger rather than smaller lactones since formation of the EAM is promoted by increasing the hydrophobicity of the monomer following the hydrophobic nature of the enzyme active site. [63-67] To date, the eROP of numerous large MLs including nonadecalactone (NDL) and tricosalactone (TCL) has been reported. [68] Furthermore, studies into the enantioselective eROP of substituted lactones report varied selectivities and rates. [67] However, these differences can be attributed to the lactone ester conformation, which can exist in either the higher-energy *cisoid* or lower-energy *transoid* conformation, where the latter exhibits dramatically increased rates of eROP (Figure 2). [35, 67] Critically, seven-membered rings and smaller can only exist in the *cisoid* conformation whereas 10-membered rings and larger exist exclusively in the *transoid* conformation. [35] Although the eROP of monomers that can adopt both ester conformations is non-selective, polymerizations are *S*-selective with exclusively *cisoid* monomers and *R*-selective with exclusively *transoid* monomers in order to afford an *R*-secondary alcohol as a nucleophile, which propagates considerably more rapidly than the *S*-stereoisomer. [35, 63] Since lipases have

a strong preference for *R*-secondary alcohols in the deacylation step, they can be utilised to prepare stereoregular polyesters *via* kinetic resolution polymerization. [35] Interestingly, the rate of eROP decreases for substituted MLs where a methyl group is present in the α-position. [69]

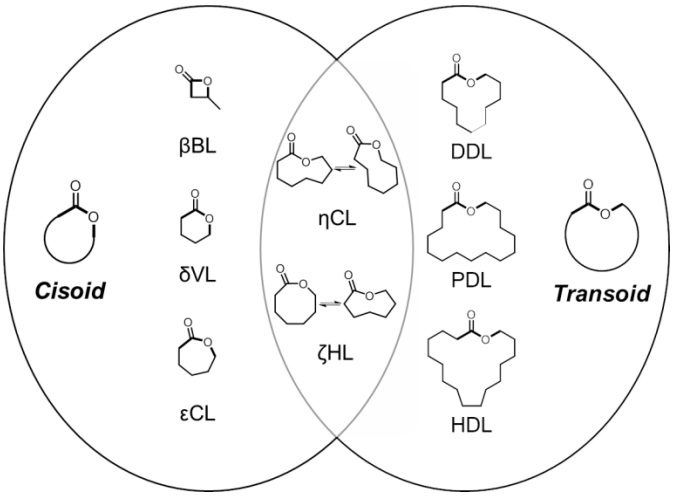


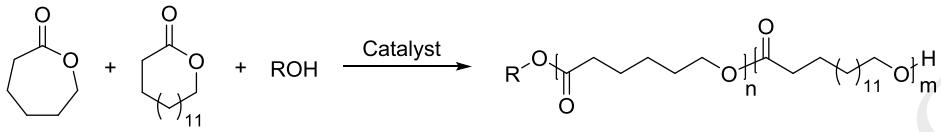
Figure 2. *Cisoid* and *transoid* conformations of ester bonds where bold bonds signify conformationally locked bonds.

The rate of eROP can be further increased by performing the polymerization in a miniemulsion, which is reported as a useful method for preparing PML nanoparticles. [70-73] Furthermore, high M_w PPDL (163,000 g mol^{-1}) was obtained in as little as 15 minutes with high monomer conversion (>99%) *via* eROP by reactive extrusion in bulk and at high reaction temperatures (90 °C – 130 °C) . [74] Aliphatic polyesters including PPDL can additionally be prepared *via* continuous-flow eROP using a packed-bed reactor. [75] This method reduces the amount of solvent required to separate the enzyme from the polymer product, and therefore greatly reduces the amount of solvent consumed during polymer purification. Similarly, a variable-volume view reactor was utilised to evaluate less toxic, lower boiling point solvents for eROP, [76, 77] and supercritical carbon dioxide ($scCO_2$) has additionally been reported as a solvent for the eROP of MLs. [78-80]

Copolymerization of MLs *via* eROP

The majority of copolyesters prepared *via* eROP are statistical, the sequence composition for which can be evaluated by quantitative ^{13}C NMR spectroscopic analysis, following the indiscriminate transesterase activity of lipases. [81] For example, Kumar *et al*. [58] investigated the copolymerization of CL and PDL using N-435, optimizing the reaction temperature (70 °C)

and volume of toluene (1:1 wt./vol.), and obtained a statistical copolymer (M_n = 22,300 g mol^{-1}, $Đ_M$ = 1.97) after 6 h despite the fact that PDL is 13 times more reactive than CL using this enzyme (Scheme 4). This study ultimately highlighted the ability of lipases to not only polymerise lactones but to also perform intermolecular transesterification reactions by combining poly(CL) (PCL) (M_n = 44,000 g mol^{-1}, $Đ_M$ = 1.65), PPDL (M_n = 40,000 g mol^{-1}, $Đ_M$ = 1.71), and N-435 to yield multiblock copolymers (M_n = 18,200 g mol^{-1}, $Đ_M$ = 1.92) within the first hour and statistical copolymers (M_n = 31,200 g mol^{-1}, $Đ_M$ = 1.87) after 30 h. [82]



Scheme 4

Copolymerization of CL and PDL.

ROP of MLs using metal-based catalysts

Duda *et al.* [66] evaluated the polymerization kinetics of various sized lactones in bulk using a zinc 2-ethylhexanoate/butanol catalyst-initiator system at 100 °C and compared the values obtained to those reported by Namekawa *et al.* [64] using *Pseudomonas fluorescens*/octanol in isopropyl ether at 60 °C. A reverse trend was revealed such that the relative orders of polymerization were determined to be 2500 : 330 : 21 : 0.9 : 1.0 : 0.9 : 1.0 for 6-, 7-, 9-, 12-, 13-, 16-, and 17-membered lactones, respectively using zinc 2-ethylhexanoate, compared to 0.1 : 0.13 : 0.19 : 0.74 : 1.0 for 7-, 12-, 13-, 16- and 17-membered lactones using *Pseudomonas fluorescens*. These results corroborate thermodynamic calculations which indicate that the ROP of small and medium sized lactones is accompanied by unfavourable negative change in entropy and driven by a negative change of enthalpy during the release of angular and transannular strains ($\Delta H_p° < 0$, $\Delta S_p° < 0$ and $|\Delta H_p°| > -T\,\Delta S_p°$), effects that decrease with increasing ring size, and that the rate of eROP is promoted by monomer hydrophobicity, which increases with ring size. Therefore, it is not surprising that early attempts to polymerise MLs using conventional, non-enzymatic catalysts were inefficient, yielding relatively low molecular weight material and/or exhibiting poor control over the polymerization. [4-7, 66, 83-86] For example, the anionic polymerization of UDL and DDL initiated from lithium, sodium, or potassium methoxide in bulk and in tetrahydrofuran at temperatures ranging between 90 °C and 150 °C yielded low molecular

weight material ($M_n \leq 11{,}000$ g mol^{-1}). [6] Although the anionic polymerization of PDL initiated from potassium alkoxides in tetrahydrofuran at 35 °C yielded relatively high molecular weight material ($M_n \leq 92{,}000$ g mol^{-1}), no correlation was observed between the monomer-to-initiator ratio and the M_n of the polyesters obtained. [7] Controlled ROP of PDL was achieved using yttrium isopropoxide in bulk and in toluene between 60 °C and 100 °C, proceeding to high monomer conversions within as little as 5 minutes, however only relatively low molecular weight material was obtained ($M_n \leq 32{,}000$ g mol^{-1}). [83] Similarly, the ROP of PDL using both tetrahydroborate complexes of rare earth metals lanthanum, neodymium, and ytterbium [86] at temperatures up to 60 °C, and using aluminium triflate [85] as a catalyst and glycerol as an initiator in bulk at 110 °C yielded relatively low molecular weight material ($M_n \leq 39{,}000$ g mol^{-1} and $M_n \leq 12{,}400$ g mol^{-1}, respectively). Developments in the ROP of MLs using metal-based catalysts nevertheless were pursued in order to overcome limitations of eROP, namely to 1) control the microstructure of the resulting polymer, and 2) polymerise MLs to high monomer conversion in bulk and in melt in order to obtain high molecular weight material.

Catalysts based on Li, [6] Na, [6, 87] K, [6, 7] Mg, [88-92] Ca, [93, 94] Al, [10, 37, 85, 87, 93, 95-102] Sn, [84, 87, 103-118] Bi, [119-124] Zn, [4, 5, 66, 93, 94, 125] Y, [83, 126, 127] La, [86] Nd, [86] and Yb [86] metal centres have been reported to polymerise MLs with varied efficacy (Figure 3). Many of these catalysts proceed *via* a coordination-insertion mechanism whereby coordination of the monomer carbonyl oxygen to the metal alkoxide complex activates the monomer and promotes the nucleophilic addition of the alkoxide to the monomer carbonyl carbon. Acyl bond cleavage ring-opens the monomer and generates a metal alkoxide, from which the polymerization propagates (Scheme 5). [20] Despite following chain-growth kinetics, the $Đ_M$ of polymers obtained *via* ROP using metal-based catalysts is typically similar to that obtained *via* eROP due to transesterification side reactions and the formation of cyclic oligomers.

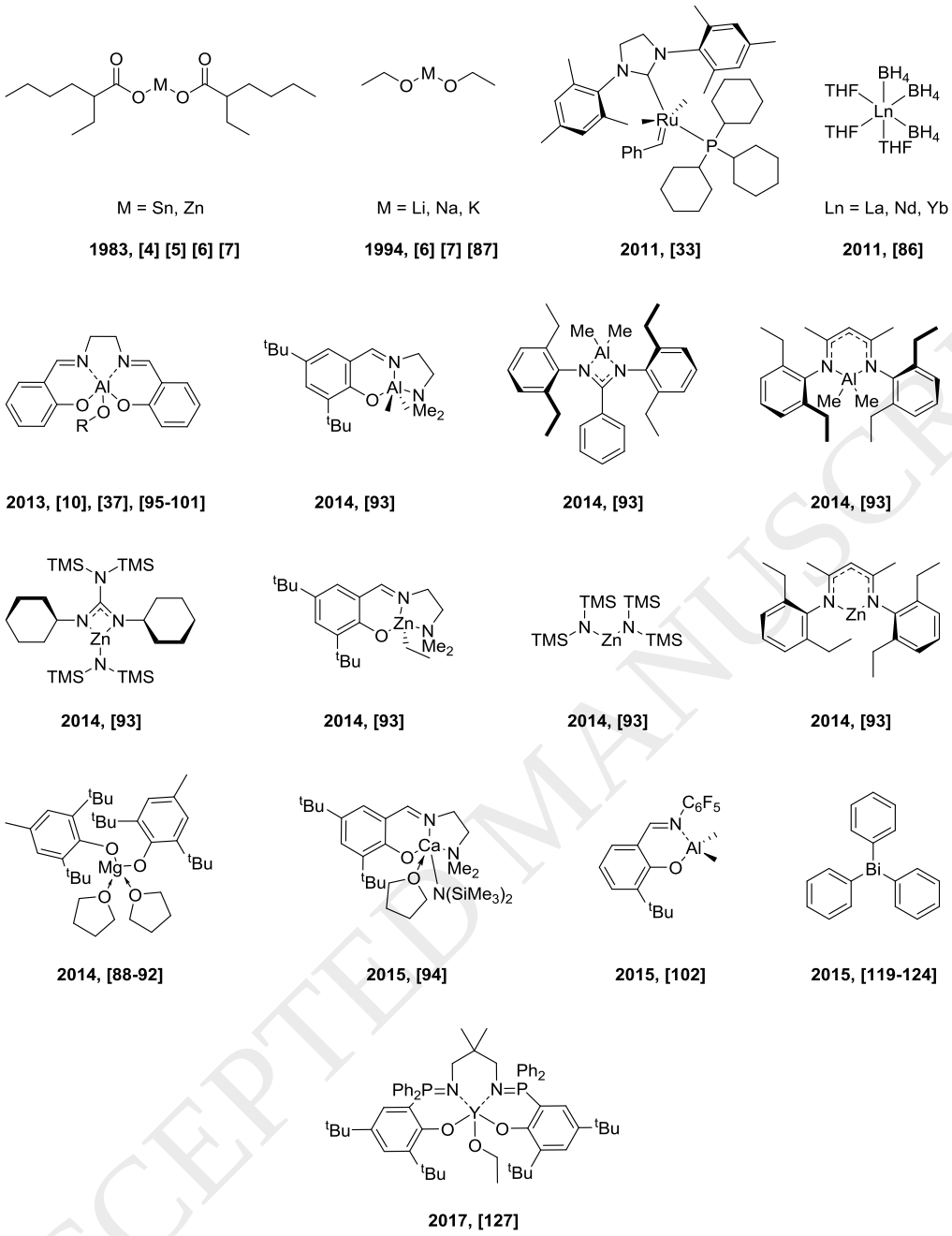
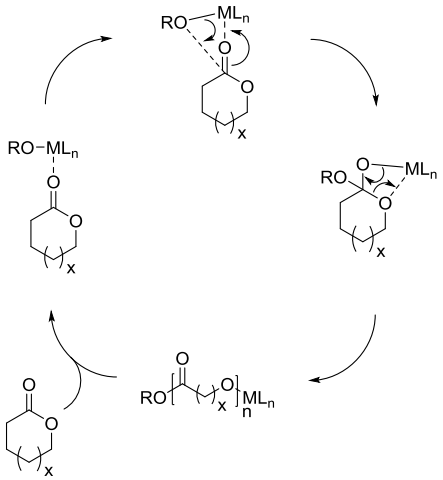


Figure 3. Highly active metal-based catalysts reported in the ROP of MLs.



Scheme 5

Coordination/insertion mechanism for the ring-opening polymerization of lactones using metal-based catalysts.

Several catalysts including tridentate zinc and calcium Schiff base complexes [93, 94, 125] and aluminium-salen complexes [10, 37, 95-101] have been discovered to catalyse the controlled ROP of PDL to both high monomer conversions and high molecular weights (*i.e.* $M_n \geq 150{,}000$ g mol^{-1}). [95] Kinetic investigations into the ROP of PDL, ambrettolide (Amb), butylene adipate (BA), *L*-lactide (*L*-LA), CL, ε-decalactone (DL), and *β*-butyrolactone (*β*BL) were undertaken using various aluminium-salen complexes. [96] It was determined that 1) there is a first order reaction for both the catalyst and the monomer, following the monometallic mechanism, 2) increasing the size of the catalyst diamine bridge dramatically increases the rate of ROP of small lactones, and 3) increasing the steric bulk of the catalyst decreases the rate of polymerization for all lactones. [96] The effect of α-substitution on the ROP of lactones was furthermore investigated using aluminium-salen catalysts and it was determined that α-substitution significantly reduces the reactivity of monomers in the *transoid* and not the *cisoid* conformation, therefore greatly reducing the rate of polymerization of MLs and not small or medium sized lactones. [100] Interestingly, Pepels *et al.* [100] determined that the choice of initiator not only influences the rate of initiation but also the rate of ROP using aluminium-salen catalysts such that a secondary alcohol reduces the rate of propagation and a primary alcohol increases the rate of polymerization, although *via* chain-end transesterification and not ROP. Ultimately, aluminium-salen catalysts have been shown

to be efficient catalysts for the ROP of lactones of various sizes, including lactones as large as NDL and TCL. [10]

'Immortal' ROP (iROP)

'Classical' ROP techniques require interaction between the catalyst and the initiator to form a complex, such as a metal-alkoxide, to initiate polymerization, one chain at a time. [128] Consequently, the resulting polymers are defined not only from the molar ratio of monomer-to-initiator but also the molar ratio of initiator-to-catalyst, and therefore the monomer-to-initiator-to-catalyst ratio. Since 'classical' ROP techniques typically require an equimolar quantity of catalyst and initiator to generate the catalyst/initiator complex, Inoue and co-workers [129, 130] coined the term 'immortal' ROP (iROP) to describe ROP reactions where the quantity of catalyst does not affect the M_n of the polymer product, and a lower than equimolar quantity of catalyst with respect to initiator can be used. Hence, in iROP, one catalytic unit can polymerise multiple chains concurrently, and the M_n of the resultant polymers is defined solely by the monomer-to-initiator ratio (Figure 4). [128] Recently, several catalysts exhibiting 'immortal' characteristics have been reported in the efficient ROP of MLs including bis(phenoxy)magnesium, [88-92] which proceeds with good end-group fidelity in the absence of inert conditions, and a zinc Schiff base complex, [93] which proceeds in the absence of any significant transesterification side reactions.

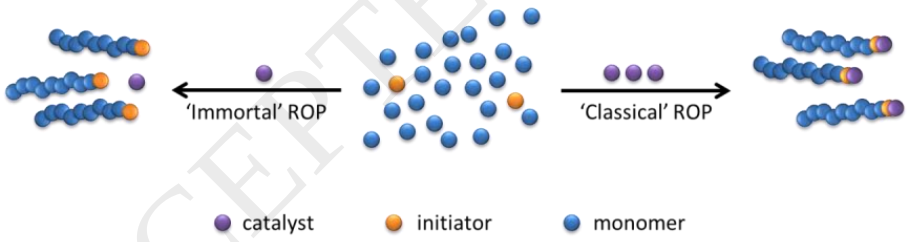


Figure 4. Comparison of 'immortal' and 'classical' ROP.

Copolymerization of MLs using metal-based catalysts

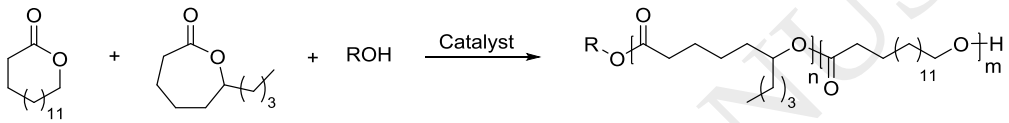
Statistical copolyesters of PDL and CL are readily prepared in one pot *via* ROP using zinc, calcium, and aluminium tridentate Schiff base complexes, [93, 94, 125] bis(phenoxy)magnesium,

[89] and aluminium-salen catalysts. [96, 98] Unlike in eROP, where PDL is polymerised in advance of CL due to the hydrophobicity of the enzyme active site, it is thermodynamically favourable for CL to polymerise in advance of PDL using most metal-based catalysts, after which intra- and intermolecular transesterification randomises the polymer sequence. Statistical copolyesters of PDL have additionally been reported with δ-valerolactone (δVL), η-caprolactone (ηCL), and DDL using bis(phenoxy)magnesium as a catalyst. [89] Similarly, statistical copolyesters of the Amb isomer ω-6-hexadecenlactone (6HDL) and CL have been prepared in one pot using a dimethyl(salicylaldiminato) aluminium complex. [102]

Block copolymers of PDL and CL or *L*-LA, however, have been prepared *via* sequential feed reactions using zinc and calcium tridentate Schiff base complexes, [93, 94, 125] and aluminium-salen complexes. [96, 99] Similarly, block copolymers of 6HDL and CL or *rac*-lactide (*rac*-LA) have been prepared using a dimethyl(salicylaldiminato) aluminium complex and this strategy was extended to prepare poly(6HDL-*co*-CL)-*b*-poly(*rac*-LA). [102] Interestingly, PPDL-*b*-PCL prepared using zinc and calcium tridentate Schiff base complexes [94, 125] did not randomise with further reaction time, indicating the absence of transesterification side reactions, however did randomise with other catalysts including aluminium-salen complexes [96] and an aluminium tridentate Schiff base complex. [93] Therefore, good control over both M_n and sequence composition can be achieved using calcium and aluminium tridentate Schiff base complexes. [93, 94]

Interestingly, Jasinska-Walc *et al.* [94, 125] discovered that the one-pot copolymerization of PDL and *ε*-decalactone (εDL) using zinc and calcium tridentate Schiff base complexes yielded block copolymers that do not randomise with further reaction time, unlike copolymers of εDL and CL (Scheme 6). The one-pot copolymerization of PDL and other *ε*-substituted lactones including menthide (MI), ζ-heptalactone (ζHL), and dihydrocarvide (DHC) has additionally been reported using bis(phenoxy)magnesium as a catalyst, which similarly yielded block-like copolymers with a short graduation between blocks. [90] Investigating the copolymerization of MI with a range of nonsubstituted lactones, specifically 6-, 7-, 8-, and 9-membered rings, Wilson *et al.* [91] determined that sequence composition depends on the relative rates of monomer polymerization such that copolymerization of *ε*-substituted lactones with a 7-membered lactone or smaller resulted in statistical sequencing, whereas copolymerization with an 8-membered lactone or larger resulted in block copolymers. Therefore, in the copolymerization of *ε*-substituted lactones, the smaller

lactone polymerises first, after which transesterification occurs as MI is incorporated. Where the comonomer is an 8-membered lactone or larger, transesterification between resulting blocks is severely retarded since α-substitution prevents transesterification *via* steric hindrance, and insertion of a ML into a branched alkoxide is thermodynamically unfavourable. [91, 94] Transesterification within the ML block, however, still occurs as evidenced with by an increase in $Đ_M$ with increasing reaction times. [91, 125] Statistical copolymers of PDL and εDL [119] or δ-hexalactone (δHL), [120] in addition to the macro(di)lactone ethylene brassylate (EB) and δHL [121], δVL, [123] or *D,L*-LA, [124] however have been reported using triphenyl bismuth as a catalyst. Interestingly, differences in the rate of ROP and transesterification of MI, CL, and PDL were exploited to prepare statistical terpolymers where all reagents were added at the start of the reaction, and triblock copolymers where CL was polymerised sequentially. [91]



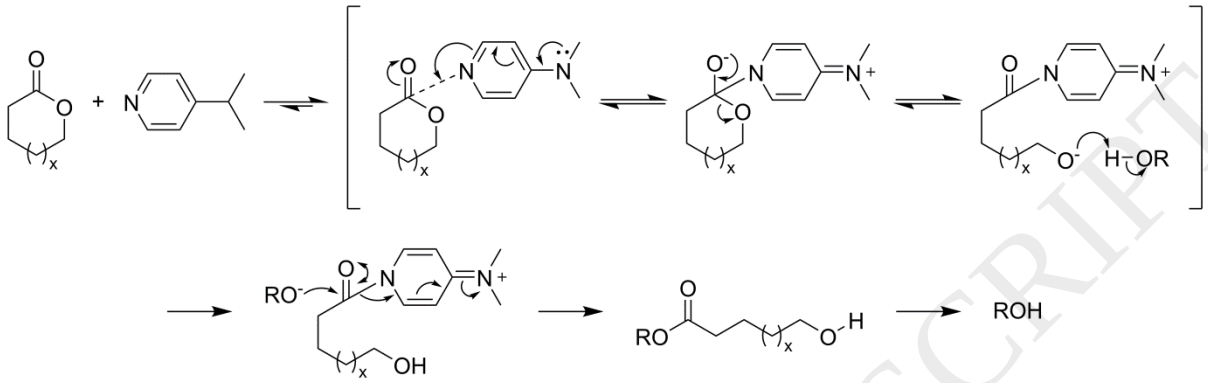
Scheme 6

Copolymerization of PDL with *ε*DL.

ROP of MLs using organo-catalysts

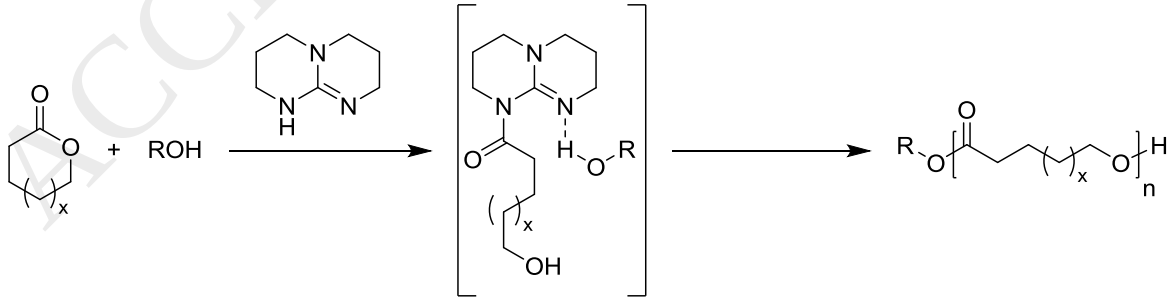
Although several metal-based catalysts efficiently polymerise MLs with living characteristics, the requirement for metal-free processes in biomedical and microelectronic applications, where metals are incompatible even in trace amounts, has driven the development of organic catalysts (Figure 5). An added advantage of most organo-catalysts over metal-based catalysts is that anhydrous conditions are only required to control the molecular weight and end-group fidelity of the polymer product since water is a competitive initiator. [131] The majority of organo-catalysts mediate ROP *via* an activated monomer mechanism (AMM) or an activated chain end mechanism (ACEM). For example, the pyridine-based organo-catalyst 4-(dimethylamino)pyridine (DMAP) undergoes nucleophilic addition to the carbonyl carbon of the monomer to form a zwitterion intermediate, which undergoes ring-opening of the monomer acyl bond (AMM). The resulting alkoxide deprotonates the initiator or propagating alcohol species to generate another anion that undergoes nucleophilic addition to the monomer carbonyl carbon to regenerate the catalyst and yield the hydroxyl-terminated propagating species (Scheme 7). [132] Conversely, the catalyst 1,8-

diazabicyclo [5.4.0]undec-7-ene (DBU) has been shown to work through ACEM, wherein the catalyst associates with the proton of an alcohol moiety. This strengthens the nucleophilicity of the alcohol, enabling a ring-opening nucleophilic attack on a lactone. [133]



Scheme 7
Activated monomer mechanism (AMM) for the ring-opening polymerization of cyclic esters mediated by DMAP. [132], Adapted from Nederberg *et al*.

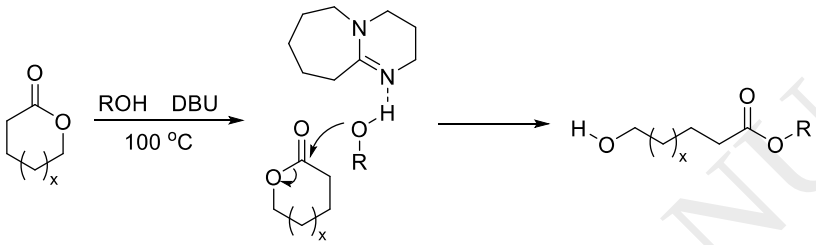
Highly active organic 'superbases' have demonstrated tremendous versatility in the range of monomers they are capable of polymerising. For example, 1,5,7-triazabicyclo [4.4.0]dec-5-ene (TBD) catalyses the ROP of lactones *via* dual activation of the monomer and initiating species (Scheme 8). [134] Since intramolecular transesterification side reactions result as a consequence of the catalytic mechanism, increased dispersities and lower than theoretical M_n values are obtained, however can be reduced by deactivating the catalyst at ≤85% monomer conversion, in addition to altering the polymerization temperature and solvent. The ROP of PDL has been reported in bulk and in toluene at 100 °C using TBD as a catalyst and benzyl alcohol as an initiator (M_n ≤ 108,000 g mol^{-1}; $Đ_M$ = 1.10-1.90). [135, 136] Similarly, the bulk ROP of EB has been reported using TBD at 80 °C. [133]



Scheme 8

Mechanism for the ring-opening polymerization of lactones mediated by TBD. [134], Adapted from Kamber *et al*. [

Phosphazene 'superbases' have also been reported to catalyse the ROP of PDL. The rapid rate of polymerization observed in the ROP of PDL using *t*-BuP_4 and *t*-OctP_4 as catalysts and 3-phenyl-1-propanol as an initiator was decreased by using *t*-BuP_2 instead, affording increased control over the polymerization ($M_n \leq 37{,}500$ g mol^{-1}; $Đ_M$ typically ≤ 2.00). [137] Interestingly, high conversions were achieved both in bulk at 80 °C and in dilute concentrations at ambient temperature. Furthermore, DBU was reported to efficiently polymerised PDL in bulk at 100 °C using benzyl alcohol as an initiator, [135] and 1,2,3-tricyclohexylguanidine (TCHG) and 1,2,3-triisopropylguanidine (TIPG) have been reported to polymerise EB with varied efficacy in bulk at 80 °C using benzyl alcohol as an initiator ($M_n \approx 7{,}000$ g mol^{-1}; $Đ_M = 1.50$) (Scheme 9). [133]



Scheme 9

Activated chain end mechanism for the ring-opening polymerization of lactones mediated by DBU. [133AdaptedAlthough the *N*-heterocyclic olefin (NHO) 2-isopropylidene-1,3,4,5-tetramethylimidazoline has been reported in the ROP of PDL ($M_n = 6{,}300$ g mol^{-1}; $Đ_M = 2.36$), [138] the majority of organic bases ($pK_a < 25$) have been unable to efficiently polymerise MLs in the absence of a Lewis acid. Dual catalyst systems, in which a Lewis acid enhances the catalytic activity of a nucleophile, have been investigated using DBU, DMAP, and *N*-heterocyclic carbenes (NHCs) alongside a range of Lewis acid metal salts in the ROP of PDL and, remarkably, it was determined that cocatalyst reactivity is dictated by the Lewis acid. [139] Similarly, NHO/Lewis acid cocatalyst systems rapidly polymerised PDL to high monomer conversions, with moderate control and reduced transesterification side reactions, where a mildly activating Lewis acid was utilised ($M_n \leq 40{,}800$ g mol^{-1}; $Đ_M = 1.45$-1.79). [140] Furthermore, the DBU/$Zn(C_6F_5)_2$ cocatalyst system has recently been reported to prepare PPDL ($M_w \leq 65{,}500$ g mol^{-1}; $Đ_M = 1.70$-1.90) with minimal transesterification side reactions by performing the polymerization in the absence of an initiator and terminating with a bulky secondary alcohol such as diphenyl methanol. [141] Interestingly, in the absence of a terminating species, high M_w cyclic PPDL can be obtained ($M_w > 100{,}000$ g mol^{-1}; $Đ_M = 1.60$-1.90). [141]

Finally, organic acids have been investigated in the ROP of MLs. For example, dodecylbenzenesulfonic acid (DBSA), diphenyl phosphate (DPP), and trifluoromethanesulfonic acid (TfOH) have been utilised to catalyse the ROP of PDL, Gl, and Amb in bulk using benzyl alcohol as a initiator ($M_n \leq 21{,}000$ g mol^{-1}; $Đ_M$ = 1.65-2.94). [142] The rate of polymerization was dependent on the pK_a of the acid (TfOH > DBSA > DPP) and the broad dispersities obtained indicate the occurrence of transesterification side reactions. Where the reaction was performed in an aqueous miniemulsion, the polymerization proceeded *via* a condensation mechanism and yielded oligo(ester)s ($M_n \leq 1{,}660$ g mol^{-1}). [142, 143] EB has additionally been polymerised with varied efficiency using *p*-toluene sulfonic acid (PTSA) (M_n = 2,000 g mol^{-1}; $Đ_M$ = 2.70), DBSA (M_n = 5,900 g mol^{-1}; $Đ_M$ = 1.90), and DPP (M_n = 7,100 g mol^{-1}; $Đ_M$ = 1.90). [133]

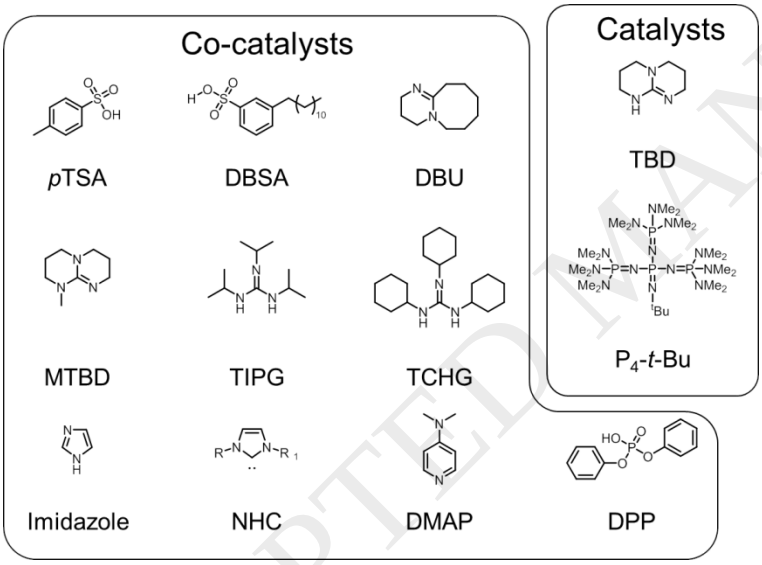


Figure 5. Selected organic cocatalysts for the ROP of MLs.

Copolymerization of MLs using organo-catalysts

One-pot and sequential copolymerization of PDL and CL using TBD yielded statistical PPDL-*co*-PCL copolyesters following the transesterase activity of the catalyst. [136] Interestingly, the transesterase activity of TBD was utilised to randomise PPDL-*b*-poly(DL) and PPDL-*b*-PCL block copolyesters prepared using zinc and calcium tridentate Schiff base complexes that did not

randomise with additional reaction time. [93, 94, 125] Sequential copolymerization of PDL followed by *L*-LA using TBD or DBU as catalysts, however yielded block copolyesters since the rate of ROP of *L*-LA greatly exceeded that of transesterification at ambient temperature. [135] TBD has additionally been utilised to copolymerise PDL and UDL or β,δ-trimethyl-ε-caprolactone isomers in one pot and sequentially to yield both statistical and block-like copolyesters by varying the PDL content such that decreasing the ratio of PDL increased the statistical character of the copolyester. [144]

Statistical copolyesters of MLs DDL, PDL, or HDL and δVL or CL have additionally been prepared both in one pot and *via* sequential polymerization as a consequence of transesterification side reactions using *t*-BuP$_4$ as a catalyst and benzyl alcohol as an initiator. [145] Employing a catalyst-switch method, however, enabled the preparation of block copolymers in one pot whereby the ML was polymerised to high conversion using *t*-BuP$_4$, after which the catalyst was neutralised with DPP and the small lactone polymerised from the PML macroinitiator using *t*-BuP$_2$. [145] Statistical copolymerization of PDL and γ-butyrolactone, δVL, or CL have additionally been reported using a NHO/Lewis acid dual catalyst systems. [140] Interestingly, Wang *et al*. [141] report that relatively high M_w cyclic or linear block copolymers of PPDL can be prepared *via* sequential polymerization of PDL with CL or lactide using the DBU/Zn$(C_6F_5)_2$ dual catalyst system in the absence or presence of a terminating species, respectively.

Functionalization of poly(macrolactone)s

Introduction of functional groups beyond the polyester backbone enables the ability to not only tune polyester properties but also design polymer architecture and function. Furthermore, the introduction of specific functionality such as bioconjugation, biodegradation, or surface wettability enables the design of materials to perform particular functions as medical devices, tissue scaffolds, and drug delivery systems, for example. [146-152] Methods to introduce functionality into polyesters prepared *via* ROP include, however are not limited to using functional monomers or initiators, many of which are available for post-polymerization modification. [20] Combining polymer functionalization with the ability to tune sequence control, stereochemistry, and polymer architecture in some instances *via* catalyst and monomer choice affords access to a multitude of potential polymeric materials featuring PMLs (Figure 6).

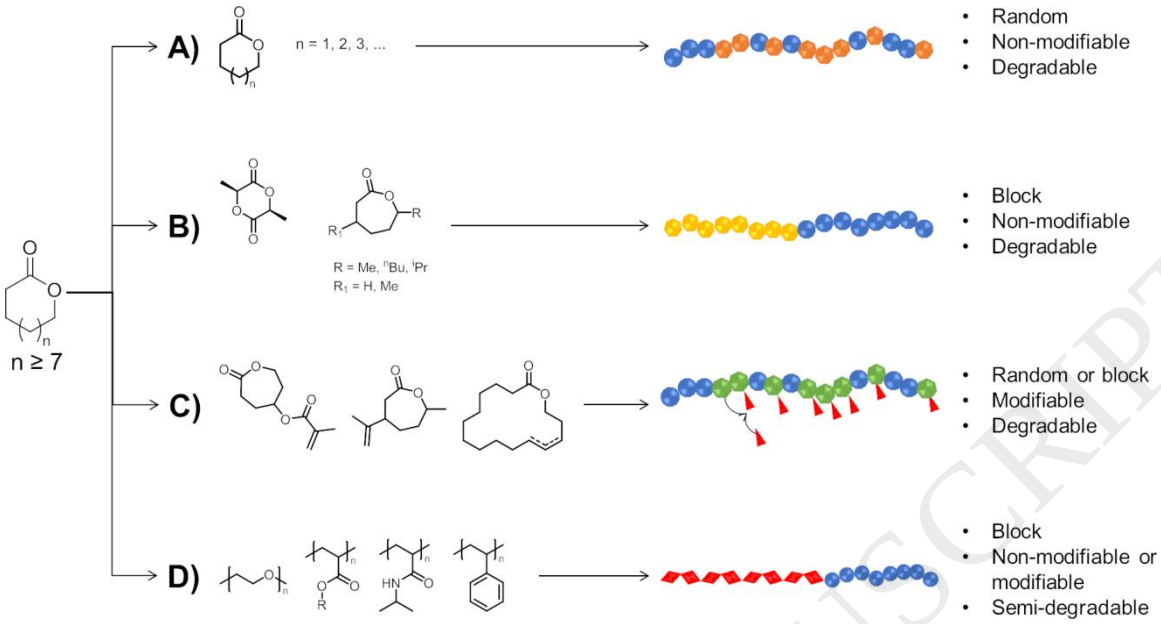
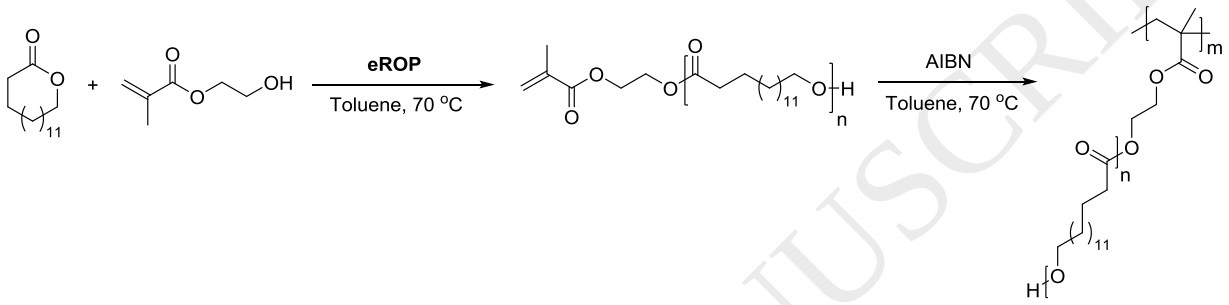


Figure 6. Copolymerization of MLs using a) non-substituted lactones, b) substituted lactones, c) monomers featuring functionalities that may be modified post-polymerization, and d) macroinitiators.

Functional initiation and termination

End-group functionality can be introduced onto PML chain-ends through choice of initiator and/or end-capping compound, enabling the preparation of functional polymers and higher polymer architectures. For example, the eROP of DDL initiated from 5-hexen-1-ol, 5-hexyn-1-ol, and 2-hydroxyethyl methacrylate (HEMA) generated alkenyl, alkynyl, and methacryl ω-functional poly(DDL), respectively. [65, 153] Similarly, alkenyl functional PPDL has been prepared by initiating the ROP of PDL from buten-1-ol. [154] PPDL macromonomers obtained from the eROP of PDL initiated from HEMA or ω-hydroxyl-ω'-methacrylate-poly(ethylene glycol) (PEGMA) (M_n = 360 g mol^{-1}) were further grafted *via* free radical polymerization to prepare PPDL brush copolymers (Scheme 10). [155] Use of initiators featuring cleavable ester bonds in eROP, however can yield polymers with mixed compositions and end-groups. For example, the eROP of PDL initiated from 2-hydroxyl acrylate (HEA) or HEMA has been reported to yield a mixture of polymers with 0, 1, or 2 acrylate or methacrylate end-groups, respectively, following the indiscriminate transesterase activity of lipases. [156, 157] Evidence for the incorporation of the 1,2-ethanediol moiety of HEA or HEMA within the polyester indicates that lipases catalyse two major transesterification side reactions, namely polyester transfer and acrylate/methacrylate

transfer, although transacylation can be minimized by reducing reaction times. [156, 157] Oligoesters prepared *via* the eROP of PDL have additionally been end-capped with 10-undecen-1-ol and linoleic acid to introduce alkene and diene functionality, respectively. [70] Interestingly, the transesterase activity of lipases has been exploited to prepare methacryl and ω-alkenyl macromonomers by performing the eROP of DDL in the presence of vinyl methacrylate and vinyl 10-undecanoate, respectively. [63, 65, 158, 159] Furthermore, end-group functionalization of PMLs has been reported to reduce cyclic oligomer formation. [160]

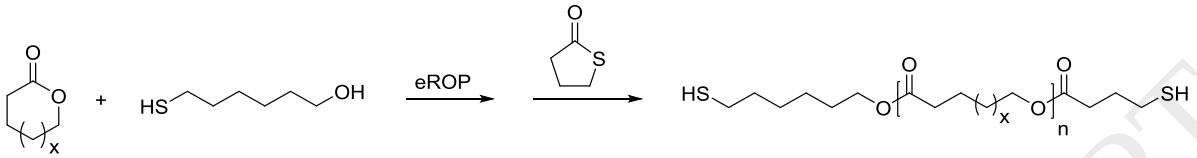


Scheme 10

Preparation of PPDL brush copolymers *via* the eROP of PDL using HEMA as an initiator and radical polymerization of the resultant macromonomer. [155], Adapted from Kalra *et al*.

Telechelic PMLs have been prepared using several combinations of initiators and end-capping compounds. For example, the eROP of PDL initiated from HEMA and end-capped with vinyl methacrylate yielded α,ω-dimethacrylated PPDL. [156] Similarly, α,ω-difunctional PPDL featuring thiol-thiol or thiol-acrylate end-groups was prepared by initiating the eROP of PDL from 6-mercapto-1-hexanol and end-capping with either γ-thiobutyrolactone, 11-mercapto-1-undecanoic acid, or vinyl acrylate (Scheme 11). [161-163] The resultant α,ω-dithiol macromonomer was crosslinked with tetrafunctional norbornene, a trifunctional allyl ether maleate species, or trimethylolpropane tri(3-mercaptopropionate) (TRIS) *via* radical thiol-ene addition using a photoinitiator to generate semicrystalline or amorphous crosslinked films, depending on the crosslinker used. [163] The simultaneous ROP and transacylation activity of lipases has additionally been applied to prepare telechelic PMLs using divinyl esters. For example, α,ω-dicarboxylic acid functional poly(DDL) has been prepared by performing the eROP of DDL in the presence of divinyl sebacate. [63, 65, 159] Similarly, α,ω-diacryl and α,ω-dimethacryl PPDL macromonomers were prepared by performing the eROP of PDL in the presence of ethylene glycol diacrylate and ethylene glycol dimethacrylate, respectively. [162] Furthermore, α,ω-dihydroxy

PPDL has been obtained using tetrahydroborate complexes of rare earth metals as ROP catalysts, [86] in addition to dialkyltin oxide/diol catalyst/initiator systems. [106, 109, 111, 114, 115, 117, 118]



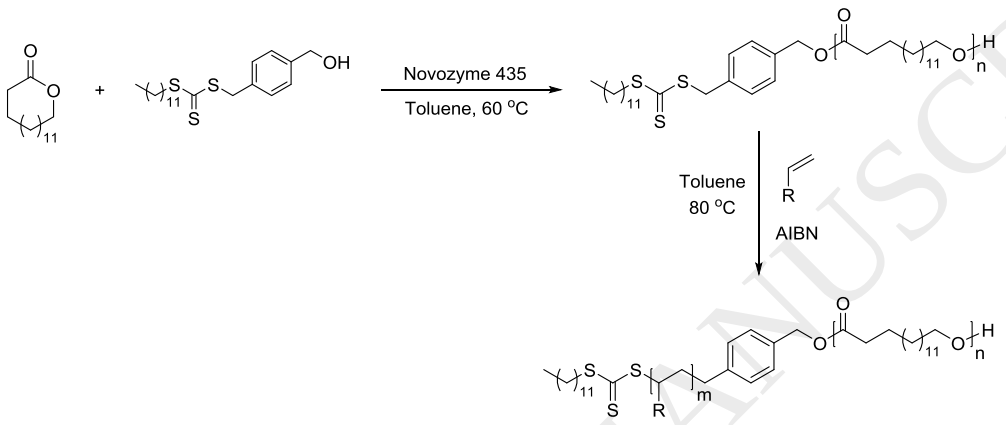
Scheme 11

Preparation of an α,ω-dithiol functional polyester *via* the eROP of PDL initiated from 6-mercapto-1-hexanol and terminated with γ-thiobutyrolactone. [161], Adapted from Takwa *et al*.

Functional initiation can also be employed as a strategy to prepare block copolymers and higher architectures of PMLs. For example, the eROP of MLs was initiated from a monohydroxyl-terminated polymer to prepare poly(butadiene)-*b*-PPDL, [164] methoxyPEG-*b*-PPDL, [137] methoxyPEG-*b*-poly(EB), [165] methoxyPEG-*b*-poly(DL)-*b*-PPDL, [166, 167] and HDPE-*b*-PPDL. [101] Graft copolymers of poly(ethylene) (PE) and PPDL were similarly prepared by initiating the ROP of PDL from randomly hydroxylated HDPE or LDPE, or *via* transesterification of PPDL with randomly hydroxylated HDPE or LDPE. [101] Conversely, using monohydroxyl-terminated PPDL as a macroinitiator for the ROP of *L*-LA using TBD, DBU, and aluminium-salen catalysts yielded PPDL-*b*-poly(*L*-LA) diblock copolyesters following the rapid rate of ROP relative to transesterification, although intrablock transesterification still occurred as evidenced by increased dispersities. [99, 135] Similarly, monohydroxyl-terminated PMLs PPDL, poly(DDL), and poly(HDL) were utilised as macroinitiators to prepare diblock copolymers with δVL or CL using *t*-BuP_2 as a catalyst. [145] Furthermore, exploiting the fact that ε-substituted lactones polymerise in advance of and do not transesterify with MLs, PPDL-*b*-poly(MI)-*b*-PPDL triblock copolymers were prepared in one pot using 1,4-benzenedimethanol as an initiator and bis(phenoxy)magnesium as a catalyst. [91]

Block copolymers and higher architectures featuring PMLs can additionally be prepared by combining functional initiation with other polymerization techniques. For example, PPDL-*b*-HDPE has been prepared *via* cross metathesis of alkenyl end-functional homopolymers. [154] Furthermore, use of a bifunctional initiator has been reported as a strategy to prepare acrylic and styrenic diblock copolymers of PPDL *via* a combination of eROP and reversible addition-fragmentation chain-transfer (RAFT) polymerization techniques (Scheme 12). [168] ROP and

RAFT polymerization techniques have additionally been utilised to prepare 4-armed star copolymers by initiating the ROP of EB from pentaerythritol, condensing the chain-transfer agent (CTA) *S*-1-dodecyl-*S*'-(α,α'-dimethyl-α''-acetic acid)trithiocarbonate onto the resulting hydroxyl-functional chain ends, and polymerising PEGMA from the macro-CTA *via* the RAFT process. [169] Finally, cationic polymerization of α,ω-dihydroxyl functional PPDL with the diepoxide 3,4-epoxycyclohexyl-30,4'-epoxycyclohexane carboxylate yielded switchable shape memory polymers. [170]



Scheme 12
Synthesis of acrylic and styrenic diblock copolymers of PPDL *via* a combination of eROP and RAFT polymerization techniques. [168]

Condensation between hydroxyl-functional PMLs and diisocynates has been utilised as a strategy to prepare a range of polyesterurethane materials. For example, condensation between α,ω-dihydroxyl-PPDL and α,ω-dihydroxyl-PCL using a diisocyanate yielded multiblock copolyesterurethanes. [106, 109, 111, 114, 115, 117, 118] This strategy was extended to prepare copolyesterurethane crosslinked networks from hydroxyl-functional three-armed PPDL and four-armed PCL stars. [104, 105, 107] Where α,ω-dihydroxyl-PPDL and α,ω-dihydroxyl-PCL were condensed with a diisocyanate and *N*,*N*-bis(2-hydroxyethyl) cinnamide, crosslinked copolyesterurethanes could be obtained *via* reversible photoinitiated [2+2] cycloaddition reactions. [171] Furthermore, PPDL surface functionalised magnetic nanoparticles, prepared *via* the ROP of PDL initiated from glycolic acid functionalised nanoparticles, [110] were subsequently polymerised with CL to prepare bilayer coated magnetic nanoparticles [116] or condensed with hydroxyl-functional three-armed PPDL stars using 1,6-hexane diisocyanate to form hybrid nanocomposite materials. [112, 113] Finally, condensation between mono-hydroxyl functional

PPDL and 2-isocyanatoethyl methacrylate was utilised to prepare methacrylate-functional PPDL, which was radically copolymerised with *N*-vinyl-2-pyrrolidone and oligo(ethylene glycol)dimethacrylate using 2,2-azobis(2-methylpropionitrile) (AIBN) to prepare hydrogel networks. [108]

Functional monomers

Main-chain and pendant functionality is readily introduced into polyesters *via* the polymerization of lactones with added functionality. [172] For example, numerous homopolymers prepared from functional MLs including Amb, [37, 96, 173-175] the corresponding epoxide of Amb (AmbE), [173] Gl, [174, 175] 6HDL, [102] BA, [96] 2-oxo-12-crown-4-ether (OC), [176] and crown-ether-like macrocyclic dilactones 15,15-dimethyl-1,4,7,10,13-pentaoxacyclohexadecane-14,16-dione [177] and 5,8,11,14,17-pentaoxaspiro [2,15]octadecane-4,18-dione [177] have been reported. Furthermore, macrocycles containing up to 84 atoms and featuring significant in-chain functional moieties including steroid residues have been successfully polymerised *via* eROP. [178] Copolymerization of PDL with *p*-dioxanone (*p*DO), [179, 180] γ-methacryloyl-ε-caprolactone (McrCL), [173] γ-benzoyl-ε-caprolactone (BnzCL), [173] β,δ-trimethyl-ε-caprolactone isomers, [144] 1-oxa-8-aza-cyclotetradecan-9,14-dione (cEA), [173] DL, [90, 94, 119, 125] MI, [90, 91] ζHL, [90] δHL, [119] DHC, [90] OC, [176, 181] Amb, [97, 173] AmbE, [173] and cyclic butylene terephthalate oligomers [182] has additionally yielded copolymers with main-chain or pendant group functionalities, many of which are accessible for post-polymerization modification (Figure 7, Table 1). Interestingly, the eROP of cEA proceeds exclusively *via* the lactone and not the cyclic amide, and not all γ-substituted ε-lactones can copolymerise with MLs since many, including γ-acetyloxy-ε-caprolactone and γ-acryloyloxy-ε-caprolactone, rearrange to form γ-butyrolactones, which cannot copolymerise. [173]

Additional functional copolyesters that have been reported include poly(Gl)-*co*-PCL, [79] poly(6HDL)-*co*-PCL, [102] poly(6HDL)-*co*-poly(*rac*-LA), [102] and poly(EB)-*co*-poly(δHL), [121] for example. Interestingly, a novel series of poly(hydroxyalkanoate)s was reported *via* the copolymerization of (*R*)-βBL with several MLs including PDL, HDL, ethylene dodecanedioate, ethylene tridecanedioate, and 11-oxa-16-hexadecanolide using 1-ethoxy-3-chlorotetrabutyldistannoxane as a catalyst. [103] Furthermore, α,ω-dihydroxyl functional poly(OC)-*co*-PCL statstical copolymers, prepared by initiating the ring-opening copolymerization

from 1,6-hexanediol, were condensed with diisocyanatobutane using dibutyltin dilaurate as a catalyst and chain extended with 1,4-diaminobutane to yield poly(urethane urea)s. [183] Finally, copolymerization of MLs alongside other monomer classes suitable for ROP has been demonstrated. For example, PDL has been copolymerised with TMC *via* eROP and using sodium ethoxide to yield statistical copolymers, and other metal-based catalysts to yield block copolymers with limited incorporation of PDL. [87, 184]

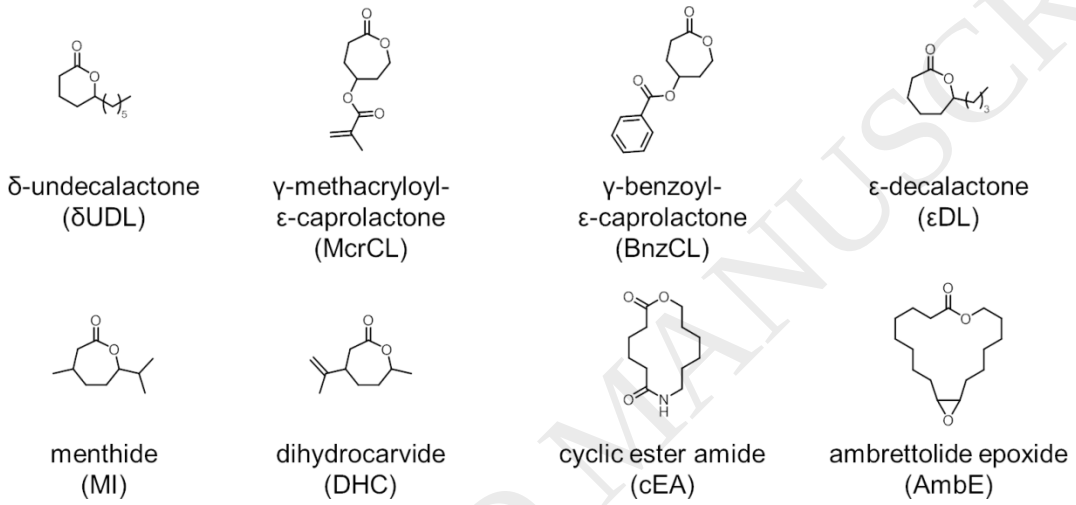


Figure 7. Examples of substituted lactones copolymerised with MLs.

Table 1PML homopolymer and copolymer properties.

Macrolactone	**Comonomer**[a]	**Catalyst**[b]	**Sequencing**[c]	T_m (°C)[d]	T_c (°C)[d]
PDL	- [33]	E/I/O	-	95.7	81.2
	γBL [140]	I	Statistical[e]	85	70
	δVL [89]	I	Statistical	74.1	58.9
	*p*DO [106]	E	Statistical	57	42
	δHL [120]	I	Statistical	63.2	-
	δUDL [144]	O	Block/Statistical	61/67	-
	εCL [89]	E/I/O	Statistical	74.9	58.2
	BnzCL [173]	E	Statistical[e]	80.1	-
	DHC [90]	I	Block	-	-
	εDL [119]	I	Block	84.0	56.3
	εHL [90]	I	Block	-	-
	McrCL [173]	E	Statistical[f]	82.9	-

	MI [90]	I	Block	-	-
	ηCL [89]	I	Statistical	77.7	60.2
	cEA [173]	E	Statistical	80.3	-
	Amb [173]	E	Statistical	72.5	-
	AmbE [173]	E	Statistical	72.5	-
Gl	- [174]	E/O	-	46.2	29.8
	εCL [194]	E	Statistical	39[g]	20
	DXO [31]	E	Statistical	26.6	5.6
	4MeCL [31]	E	Statistical	36.5	18.3
HDL	- [174]	E	-	96.2	76.6
Amb	- [174]	E/I/O	-	54.9	37.7
	cCO [33]	I	Statistical	105.0	89.8
	DXO [31]	E	Statistical	-	-
6HDL	- [102]	I	-	72.9	-
	εCL [102]	I	Statistical	44.1	-
NDL	- [10]	E/I	-	103	84
TCL	- [10]	E/I	-	104	88

[a] Reference for DSC values only. [b] Where E = enzyme, I = inorganic catalyst and O = organic catalyst. [c] Determined by quantitative ^{13}C NMR spectroscopy. [d] Determined by DSC for a 50 : 50 molar ratio of comonomers unless otherwise stated. [e] Maximum ratio of incorporated PDL : comonomer achieved is 78 : 22. [f] Maximum ratio of incorporated PDL : comonomer achieved is 85 : 15. [g] Double T_m as a consequence of low cocrystallinity.

Alkenes are versatile sites for pre- and post-polymerization modification. For example, Baeyer-Villiger oxidation has been utilised to epoxidise Amb, which was subsequently homopolymerised, [173, 185] and poly(6HDL), which was subsequently crosslinked *via* ring-opening the resultant epoxides using $NaCNBH_3$. [102] Furthermore, the eROP of α-(alkyoxymethyl)acrylate 2-methylene-4-oxa-12-dodecanolide and copolymerization with DDL yielded polyesters with *exo*-methylene groups along the main chain. [186] Additional MLs featuring α-methylene groups, including a selection containing aromatic, ether, and amine groups, have been polymerised *via* eROP and subsequently crosslinked *via* radical polymerization to yield polymeric gels. [187] Interestingly, radical and anionic polymerization *via* the α-methylene group of these MLs has been reported to generate polymers with macrocyclic moieties along the main chain. [187-189] Poly(Gl) (PGl) and poly(Amb) homopolymers [174] and statistical copolymers [175] with CL, 4-methyl caprolactone (4MeCL), and 1,5-dioxepan-2-one (DXO) have additionally been thermally crosslinked using dicumyl peroxide to yield amorphous networks (Figure 10). Similarly, PPDL-

co-poly(Amb) latexes were crosslinked using benzoyl peroxide to prepare polyester films. [142] Furthermore, ring-opening metathesis copolymerization of Amb and *cis*-cyclooctene, followed by hydrogenation, was utilised as a strategy to prepare aliphatic long chain polyesters. [33]

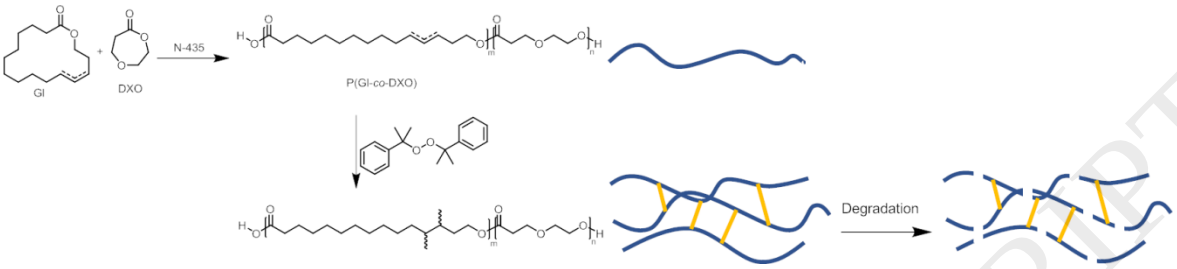


Figure 8. Copolymers from unsaturated MLs GI and Amb, and their thermal cross-linking with dicumyl peroxide (poly(Gl-*co*-4MeCl) (75:25); films before (left) and after (right) thermal cross-linking). [175], Adapted from van der Meulen *et al.*

Thiol-ene addition to monomer and polymer alkenes has additionally been investigated. For example, thiol-ene addition of 6-mercapto-1-hexanol, butyl-3-mercapto propionate, and *N*-acetylcysteamine to Gl and PGl has been reported using AIBN (Figure 9). [190, 191] Similarly, thiol-ene addition of 6-mercapto-1-hexanol to poly(6HDL) has been reported using AIBN, [102] and thiol-ene addition of mercaptoethanol, benzyl mercaptan, and dodecanethiol to block-like PPDL-*co*-poly(DHC) has been reported using a photoinitiator. [90] Additionally, PGl [191-193] and PGl-*co*-PCL [194] were crosslinked *via* the thiol-ene addition of ethylene glycol bis(3-mercaptopropionate), [191-193] 1,5-pentanedithiol, [193] or trimethylolpropane tris(3-mercaptopropionate) [194] using a photoinitiator. PGl crosslinked films were further reacted with 6-mercapto-1-hexanol using a photoinitiator, and the resulting hydroxyl groups reacted with α-bromoisobutyryl bromide to form ATRP macroinitiators from which *tert*-butyl acrylate was grafted, deprotected, and conjugated to biological molecules. [192] Additionally, thiol-ene addition of 1-pentanethiol and 6-mercapto-1-hexanol to Amb using AIBN, and subsequent copolymerization with PDL yielded substituted linear and branched copolymers, respectively. [97] Finally, α,ω-dimethacryloyl terminated PPDL-*co*-PCL and PCL, prepared *via* post-polymerization modification of the dihydroxylated polymers with methacryloyl chloride, were reacted with pentaerythritol tetrakis(3-mercaptopropionate) using a photoinitiator to yield a reversible shape memory crosslinked polymer network. [195]

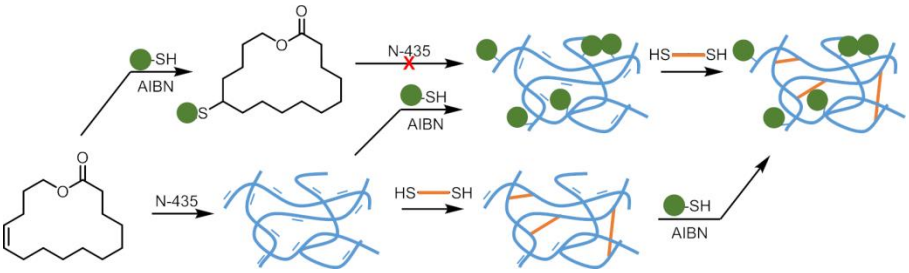


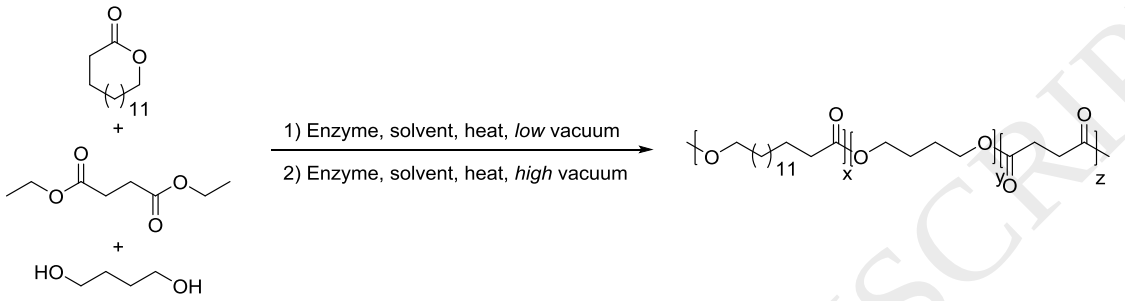
Figure 9. Synthetic routes to functional crosslinked films from MLs using thiol–ene chemistry. [191], Adapted from Ates *et al.*

Simultaneous ROP and condensation polymerization

An additional method of introducing functionality into PMLs is to perform simultaneous eROP of MLs and condensation polymerization [59, 196] of diols with diesters in one pot to generate statistical copolyesters. For example, aliphatic copolyesters have been prepared *via* simultaneous eROP of MLs UDL, DDL, or PDL and condensation of divinyl esters of adipic or sebacic acid and α,ω-glycols. [63, 197-208] This strategy has been extended to prepare PEG-*co*-polyesters and methoxyPEG-*co*-polyesters through copolymerising PEG or monomethoxyPEG with PDL, divinyl adipate, and glycerol. [209, 210] Similarly, the copolymerization of PDL, diethyl succinate, and 1,4-butanediol has been reported. [211-213] The latter reaction was performed in the following two stages: 1) oligomerization under low vacuum to prevent monomer evaporation, followed by 2) polymerization under high vacuum to drive the equilibrium of transesterification to high conversion (Scheme 13). [211]

Simultaneous eROP and condensation polymerization has also been reported in the preparation of 1) copolyesters from PDL and ethyl glycolate, [214] 2) poly(amine-*co*-ester)s [215, 216] from DDL, PDL, or HDL, diethyl sebacate, and *N*-methyldiethanolamine, 3) poly(PDL-*co*-butylene-*co*-3,3'-dithiodipropionate) copolyesters [217] from PDL, 1,4-butanediol, and dimethyl 3,3-dithiodipropionate, 4) poly(carbonate-*co*-ester)s [218, 219] from PDL, diethyl carbonate, and 1,4-butanediol, 5) poly(PDL-*co*-β-amino ester)s [220] from PDL and ethyl 3-(4-(hydroxymethyl)piperidin-1-yl)propanoate (EHMPP), and 6) poly(amide)s [221] *via* simultaneous ring-opening and aminolysis-condensation polymerization between EB and various diamines using TBD as a catalyst at 100 °C. Furthermore, this strategy has been extended to prepare PEGylated poly(amine-*co*-ester)s, [217, 222, 223] poly(PDL-*co*-butylene-*co*-3,3'-dithiodipropionate) copolyesters, [224] and poly(PDL-*co*-β-amino ester)s [225] by

copolymerising the respective monomers with PEG or monomethoxyPEG. Finally, telechelic PMLs have been obtained *via* simultaneous eROP and condensation polymerization by performing the eROP of PDL in the presence of divinyl adipate and glycidol to yield α,ω-diepoxy functional PPDL. [226] Cationic photopolymerization of α,ω-diepoxy macromonomers and crosslinking using cycloaliphatic diepoxide formed durable crystalline films. [226]



Scheme 13
Two-stage process for the copolymerization of PDL, diethyl succinate, and 1,4-butanediol. [211], Adapted from Jiang.

Functional materials from PMLs

The long aliphatic backbone in PMLs gives rise to thermal and mechanical properties comparable to PE, [16-19] attracting interest in PMLs for numerous applications. Since properties of PMLs, including hydrophobicity and degradability, can be tuned through copolymerization, functionalization, and post-polymerization modification, for example, the range of potential applications for materials derived from PMLs is extensive. Importantly, the discovery that PPDL is biocompatible and nontoxic to cell activity [174] has enhanced interest in PMLs for biomedical applications, which is a significant area of research for polyesters derived from small and medium sized lactones, [227-229] and ultimately expands the scope of materials that can that can be prepared *via* ROP.

PMLs as polyethylene-like materials

PPDL is highly crystalline [230] and its thermal [5, 16, 17, 83, 231] and mechanical properties [18, 19, 232] are comparable to those for LDPE [16-18] or HDPE, [19] depending on its molecular weight. For example, the melting temperature (T_m) and glass transition temperature (T_g) of PPDL (M_n = 64,500 g mol^{-1}; $Đ_M$ = 2.00; T_m = 97 °C; T_g = -27 °C) [18] are comparable to values reported for PE (T_m = 136 °C; T_g = -120 °C) (Figure 10). Molecular weight profoundly affects the properties

of PPDL, particularly *via* chain-end effects, which reduce the crystallinity and T_m of lower molecular weight material. [16, 17, 231] Since crystallinity influences the Young's modulus and stress at break, the mechanical strength of PPDL can be increased by using high molecular weight material, which reduces the number of plasticising chain ends, and applying processing procedures that maximise lateral chain interactions. [19, 232]

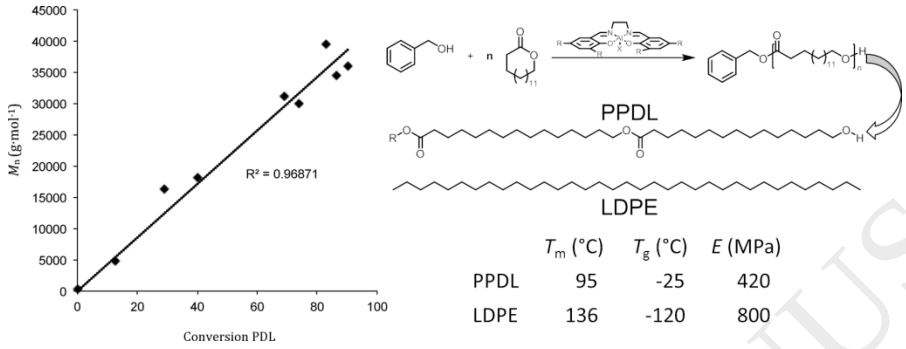


Figure 10. Plot of M_n versus monomer conversion for the bulk polymerization of PDL using an aluminium-salen catalyst (X = Et) and benzyl alcohol as initiator ([M]/ [I] = 100). M_n values were obtained from HT-SEC chromatography in trichlorobenzene. [95], Copyright 2011. Reproduced with permission from the American Chemical Society.

Samples prepared by press-moulding high M_w PPDL (189,000 g mol^{-1}) revealed a Young's modulus of 450 MPa, up to 650% elongation at break, and tensile strengths of up to 60.8 MPa since, at high molecular weights, the strength of the entanglement network is enhanced and results in strain-hardening prior to break (Figure 11). [19, 233] Furthermore, analysis of high M_w PPDL (143,000 g mol^{-1}) melt processed into fibres that were elongated 9-10 times their original length through various processing conditions yielded tensile strengths of up to 740 MPa for fibres with the highest degree of crystal orientation, and elongations at break exceeding 1200%. [232] Interestingly, the increased crystallinity observed in poly(NDL) (M_n = 80,000 g mol^{-1}) and poly(TCL) (M_n = 120,000 g mol^{-1}) reduced the elongation at break of these materials (270% and 210%, respectively) relative to PPDL of similar molecular weights despite having recorded higher Young's moduli (647 MPa and 612 MPa, respectively). [68] Ultimately, the mechanical performance of these PMLs is approaching values for HDPE (Young's modulus = 900 MPa; elongation at break ≈ 900%). [234]

Interestingly, the tensile performance of melt-drawn PPDL fibres reinforced *in situ* with a vanillic acid-based thermotropic liquid crystalline polyester (LCP) was enhanced with increasing LCP orientation and concentration (up to 30 wt.%) *via* interfacial crystallization, which delocalises stress between the PPDL/LCP interface (Figure 12). [235] Furthermore, PPDL and statistical PPDL-*co*-PCL copolyesters were demonstrated to be effective nucleating agents for commercial PCL, increasing the number of spherulites, accelerating the nonisothermal rate of crystallization, increasing the T_c, and enhancing the tensile strength of the material by 12.4% while maintaining the same elongation at break. [236] Blending PPDL (up to 30 wt.%) into poly(*L*-LA) (PLLA) films increased the Young`s moduli of these materials from 670 MPa to 1010 MPa, [57] and PPDL-*b*-PLLA copolymers were shown to be efficient compatilising agents in blending PLLA with high carbon content polymers such as poly(ω-hydroxytetradecanoate), HDPE, and LDPE. [99, 135] Similarly, PPDL-*b*-HDPE diblock copolymers were demonstrated to compatilise HDPE/PPDL polymer blends. [154] Finally, Pepels *et al*. [97] demonstrated that it is possible to prepare short- and long-chain branched LDPE-like polyesters *via* the ROP of Amb modified *via* radial thiol-ene addition in the presence and absence of PDL.

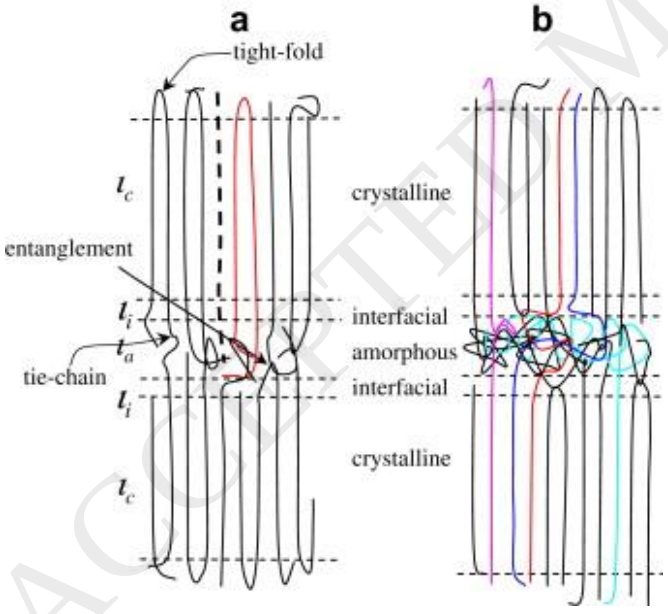


Figure 11. Possible mechanism responsible for the brittle-to-ductile transition in: (a) lower molecular mass PPDL and (b) higher molecular mass PPDL. [19], Copyright 2010, Reproduced with permission from Elsevier Ltd.

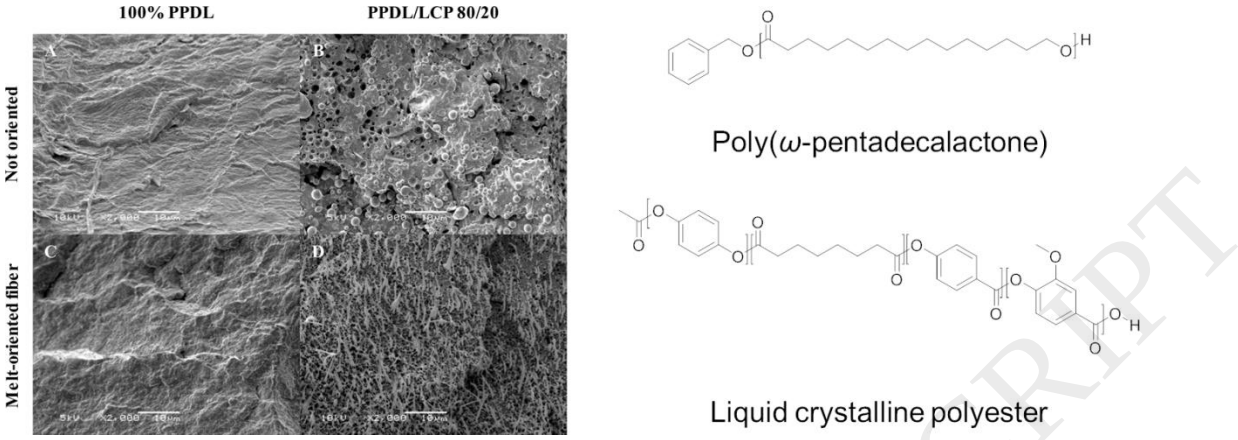


Figure 12. Morphology as observed with SEM after blending and extrusion of (A) PPDL, (B) PPDL : LCP 80 : 20 blend, (C) PPDL after melt drawing, and (D) PPDL : LCP 80 : 20 after melt-drawing (draw-ratio of 400). [235], Copyright 2016. Reproduced with permission from the American Chemical Society.

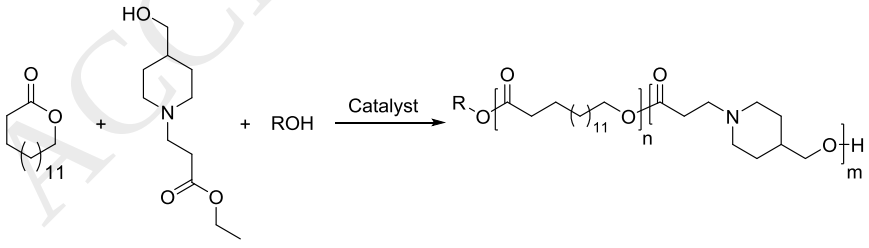
Although the recurring ester linkage in PMLs are sites for hydrolytic degradation, [237] hydrophobicity and a high degree of crystallinity limit the accessibility of ester linkages in PPDL. Consequently, PPDL is stable to hydrolytic and enzymatic (*Pseudonomas cepacia*) degradation in phosphate buffer solution (PBS) at 37 °C. [174] Biodegradation of PPDL in compost at 60 °C, however, has been reported, although only 18 wt.% degradation was observed after 280 days. [86] Numerous factors influence polymer degradation including environment, crystallinity, molecular weight, surface chemistry, mechanical properties, and morphology, [238] however since the molar ratio of ester bonds in the polymer backbone directly affect polymer degradation, copolymerization of PMLs with other monomers including smaller lactones can potentially increase the degradability of these materials.

Tuning the thermal, mechanical, and degradation properties of PML-based materials

The crystallinity, thermal and mechanical properties, hydrophobicity, and degradability of PMLs can be tailored through copolymerization. Although the crystal structure and lamellar thickness of PMLs and copolyesters of MLs are only moderately affected by the inclusion of ester groups, since ester groups reduce the stability of the crystal lattice, the melting temperature (T_m)

of these materials varies according to the ratio of methylene-to-ester units. [33, 98] For example, as the ratio of methylene-to-ester units is increased, the T_m of a PML can approximate that of HDPE ($T_m \approx 130$ °C). [33] Conversely, statistical copolyesters of MLs, which are highly crystalline over the entire composition range due to cocrystallization in a common lattice *via* comonomer isomorphic substitution, maintain reduced T_m values relative to those of the PML homopolymers. Interestingly, in the copolymerization of PDL and CL, varying the molar ratio of PDL to CL revealed a linear relationship between the comonomer molar ratio and the T_m/T_c such that as the ratio of one lactone increases, the copolyester T_m and T_c shift linearly towards values for the corresponding homopolymer. [89, 136, 239] This trend has also be observed in the copolymerization of PDL with other non-substituted lactones including δVL, ηCL, and DDL. [89] Furthermore, this trend has also been reported in the copolymerization of several functional MLs with smaller lactones, although the T_m values for PGl (T_m = 46 °C), poly(Amb) (T_m = 55 °C), and poly(AmbE) (T_m = 73 °C) are significantly lower than that for PPDL. [173, 175] Interestingly, the T_m of poly(cEA) (140 °C) greatly exceeds that of PPDL. [173] Additional monomers that have been determined to cocrystallise with PPDL include *p*DO, [179, 180] TMC, [87, 184] and ethyl glycolate, [214] for example.

Several monomers including DL, [94, 119, 125] δHL, [120] UDL, [144] OC, [176, 181] and EHMPP [220] do not cocrystallise with PDL despite their semicrystalline properties (Scheme 14). Similarly, poly(EB-*co*-δHL) [121] copolyesters do not cocrystallise. Varying the monomer feed ratio of these copolymers alters the crystallinity of the resulting material to a minimum T_m observed near equimolar incorporation. Interestingly, many of these copolymers rapidly crystallise from melt, which prevents physical aging during their application, and are easier to process as a consequence of their low T_g values. [119-121]



Scheme 14
Copolymerization of PDL with EHMPP.

Copolymerization of MLs with other monomers also affects the mechanical properties of the resultant materials. For example, PPDL-*co*-PCL copolyesters maintain significantly reduced yield stress values relative to PPDL due to the increased mobility of the crystalline phase following irregular stacking of the ester groups in the crystal lamellae. [98] Copolymerization of MLs with other monomers, however is utilised to tune the mechanical properties of these materials for specific applications. [103, 119-121, 124]

Finally, copolymerization of MLs with smaller lactones enhances the degradability of the resultant copolyesters relative to PML homopolymers. For example, degradation of statistical copolyesters with varied molar ratios of PDL, δVL, CL, and ηCL (42:58 PPDL-*co*-poly(δVL); 41:59 PPDL-*co*-PCL; 25:75 PPDL-*co*-poly(ηCL)) and identical T_m and T_c values (T_m = 70 °C; T_c = 54 °C) were monitored in 5 M $NaOH_{(aq)}$ solution at 37 °C. [89] Interestingly, it was determined that the rate of degradation is independent of thermal properties, however increases with increasing ester-to-methylene unit ratios (PPDL-*co*-poly(δVL) = 50 days; PPDL-*co*-PCL = 65 days; PPDL-*co*-poly(ηCL) = 10 wt.% mass loss after 120 days). [89] However, PPDL-*co*-poly(DL) copolyesters, where the molar content of PDL was varied from 30-78%, [119] and PPDL-*co*-poly(δHL) copolyesters, where the molar content of PDL was varied from 39-82%, [120] were determined to be stable to hydrolytic degradation in PBS at 37 °C for 182 days.

Biomaterials derived from PMLs

Biocompatible scaffolds and implants

Although PPDL, poly(HDL), PGl, and poly(Amb) homopolymers are neither enzymatically nor hydrolytically degradable, an MTT assay for metabolic cell activity in a 3T3 mouse fibroblast cell line indicated that these polymers are not cytotoxic. [174] Numerous PML-based materials have additionally been determined to be biocompatible. For example, subcutaneous implantation of copolymer films in mice determined PPDL-*co*-poly(DO) copolymers to be biocompatible, [180] and metabolic activity and cell morphology studies determined that poly(EB-*co*-δHL) is compatible with human dermal fibroblasts. [121] The requirement for biodegradability in a biocompatible material is application dependent. For example, biodegradation is an essential feature of *in vivo* tissue scaffolds and drug delivery devices, however is not desirable for biomedical implants.

Several PML-based materials have been investigated for biomedical scaffold and implant applications. For example, PPDL, [160] electrospun PPDL fibrous scaffolds, [240] and PPDL-*co*-PCL [80] copolyesters were prepared as potential porous scaffolds for tissue regeneration applications. Furthermore, poly(EB-*co*-δHL) has been investigated as a potential material for degradable scaffolds, however rates of hydrolytic degradation at 37 °C in PBS ($t_{½}$ = 169-248 days) were determined to be too long for this application. [121] Interestingly, simultaneous *in situ* photoinitiated thiol-ene crosslinking and electrospinning of Gl yielded biocompatible and swellable crosslinked amorphous PGl microfibers. [193] Hydrolytic degradation of these microfibers (up to 34 wt.% after 90 days in PBS at 37 °C), in addition to loading and subsequent release of rhodamine-B, demonstrates their potential for drug loading applications. [193] Furthermore, electrospun PLLA fibres compatilised with PPDL-*co*-PLLA were determined to enhance neurite outgrowth of chick dorsal root ganglia *in vitro* relative to PLLA fibres, potentially due to differences in fibre diameter and surface nanotopology. [241] Finally, PPDL-based shape memory materials [104-117, 171] have been developed with potential applications as stimuli-responsive implant devices or nanocomposite materials for regenerative therapies. For example, electrospun PPDL-*co*-PCL polyesterurethane non-woven fabrics consisting of PPDL hard segments and PCL switching segments were demonstrated to be shape memory materials with potential applications as responsive textiles or devices. [111]

Biofunctional crosslinked films

Functional PML-based polymers have been utilised to prepare a range of crystalline, semicrystalline, and amorphous crosslinked films. [142, 163, 174, 175, 187, 191, 192, 194, 226] Although crosslinked PGl and poly(Amb) films do not undergo degradation using *Pseudomonas cepacia* in PBS at 37 °C due to the high crystallinity and hydrophobicity of these materials, [174, 191] a 20 wt.% degradation of PGl crosslinked with ethylene glycol bis(3-mercaptopropionate) was reported after 50 days under the same conditions. [191] Since polyester degradation predominantly takes place in amorphous regions and progresses into crystalline regions at a reduced rate, [242] integration of hydrophilic comonomers such as DXO was determined to enhance enzymatic degradation by up to 90 wt.% after 100 days. [175] Biofunctional films derived from PMLs have been reported, including conjugation of green fluorescent protein and chitobiase onto poly(acrylic acid)-functionalised crosslinked PGl films. [192]

Biodegradable particles

Biodegradable polyesters are routinely investigated as nano-carriers for controlled drug delivery and the incorporation of MLs increases the hydrophobicity of these systems, which influences drug loading and degradation behavior, for example, and can be tuned by varying the size and molar ratio of the ML. PEG-stabilised PPDL and polyHDL nanoparticles were amongst the first PML-based nanoparticles prepared *via* eROP in miniemulsions between 45 °C and 90 °C, [70, 71] and PPDL and PGl nanoparticles have since been prepared between 45 °C and 60 °C. [73] The ability to polymerise at lower temperatures reduces thermal stress on any potential drug load, however reaction temperature was determined to affect particle morphology such that non-spherical aggregates were produced at lower temperatures as a consequence of crystallization, and at higher temperatures, lemon shaped particles were obtained instead of spheres following post-polymerization cooling and crystallization. [70, 73] PPDL-*co*-poly(DO) nanoparticles prepared using a modified oil-in-water single emulsion technique were reported to degrade hydrolytically over 60-70 days under physiological conditions. [180] Doxorubicin loaded PPDL-*co*-poly(DO) nanoparticles exhibited continuous controlled release over 20-60 days *in vitro* and siLUC encapsulated nanoparticles inhibited luciferase gene expression in LUC-RKO cells. [180] Additionally, amphiphilic methoxyPEG-*b*-poly(DL)-*b*-PPDL terpolymers self-assembled into micelles have been reported to incorporate Nile Red [166] and curcumin [167] *via* a nanoprecipitation method. Similarly, methoxyPEG-*b*-poly(EB) diblock copolymers assembled into multimorphological aggregates [165] and 4-armed poly(EB)-*b*-poly(PEGMA) copolymers assembled into micelles [169] were reported to encapsulate and release doxorubicin *in vitro*.

Numerous microspheres prepared *via* simultaneous eROP and condensation polymerization have been investigated for encapsulation and drug delivery applications. For example, PPDL-*co*-poly(glycolate) nanoparticles have been prepared using an oil-in-water single emulsion system with average particle sizes ranging from 174 nm to 190 nm, and poly(PDL-*co*-butylene-*co*-succinate) nanoparticles [212, 213] prepared *via* a similar method were reported to deliver camptothecin to tumour cells *in vivo* following intravenous administration (Figure 13). [213] The encapsulation and controlled release of ibuprofen from copolyester nanospheres prepared from the copolymerization of PDL, divinyl adipate, and propane-1,3-diol or glycerol have also been evaluated. [198] Interestingly, the efficacy of doxorubicin-loaded PEGylated poly(PDL-*co*-butylene-*co*-3,3’-dithiodipropionate) copolyester micelles was determined to be enhanced against

HepG2 cancer cells by intracellular glutathione following internalization of the micelles by the cells *in vitro*. [217]

PDL-*co*-(glycerol adipate), PEG-*co*-(PDL-*co*-glycerol adipate), and methoxyPEG-*co*-(PDL-*co*-glycerol adipate) copolyester nanoparticles have similarly been investigated for numerous drug delivery applications. [199-205, 207-210] For example, bovine serum albumin adsorbed PDL-*co*-(glycerol adipate) copolyester nanoparticles with *L*-leucine micro-carriers were investigated for vaccine delivery applications *via* dry powder inhalation. [206] Furthermore, α-chymotrypsin and DNase I loaded PEG-*co*-(glycerol adipate-*co*-PDL) microparticles prepared *via* spray drying from double emulsion were investigated as a potential dry powder inhalation treatment for local pulmonary diseases. [209] Additionally, poly(amine-*co*-ester) nanoparticles prepared from DDL, PDL, or HDL, diethyl sebacate, and *N*-methyldiethanolamine were investigated as non-viral carriers for gene transfection and copolymers containing PDL were determined to be effective for luciferase gene transfection of HEK293 cells *in vitro* [215] and targeted gene delivery to tumour cells *in vivo*. [216] Finally, PEGylated poly(amine-*co*-ester), [222, 223] poly(lactone-*co*-β-amino ester), [225] and poly(amine-*co*-disulfide ester) [224] block copolymer micelles featuring PDL have been determined to be promising new pH and/or redox responsive vectors for drug and gene delivery applications.

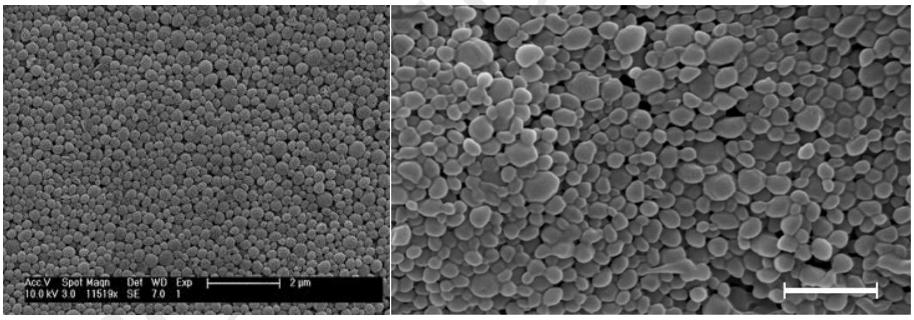


Figure 13. SEM micrograph of poly(PDL-*co*-butylene-*co*-succinate) copolymer (20 mol% PDL) nanoparticles (187 ± 37 nm; Scale bar: 1 µm; right) and of poly(PDL-*co*-GA) copolymer (21 mol% GA) nanoparticles (181 ± 45 nm; Scale bar: 2 µm; left). Left: [214], Copyright 2011. Reproduced with permission from Elsevier Ltd; Right: [212], Copyright 2009. Right image reprinted with permission from the American Chemical Society.

Conclusions

Advances in the ROP of MLs have afforded access to novel polymeric materials featuring aliphatic polyester moieties. The range of catalysts investigated to date for the ROP of MLs enable the ability to tune sequence control, stereochemistry, and polymer architecture in some instances *via* catalyst and monomer choice. Furthermore, polymer functionalization *via* functional initiation, termination, copolymerization, and post-polymerization modification enables the ability to not only tune polymer properties but also design polymer architecture and function. Ultimately, a diversity of polymeric materials featuring PMLs have been prepared to date and hold promise as functional materials for biomedical applications and beyond.

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B.

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