Controlled ring-opening polymerisation of cyclic esters: polymer blocks in self-assembled nanostructures

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The state of the art with respect to the application of poly(ester)s, obtained by living/controlled ring-opening polymerisation as components of block copolymers, in self assembly is discussed in this *feature article*. Poly(ester) synthesis is outlined by metal and metal free catalysts (including both small molecule organic catalysts and enzymatic catalysts) and the properties of the polymers, including access to poly(lactic acid) stereocomplexes are detailed. Methods for the combination of ring-opening polymerisation with controlled radical polymerisation are reviewed to provide an overview of the many methodologies applied in the synthesis of poly(ester) containing functional block copolymers. Their self-assembly in both solution and the solid phase are discussed, with particular attention focused on the properties and characteristics of the nanostructured materials resulting from the inclusion of poly(ester) components.

Introduction

Block copolymer self-assembly is a powerful means to access complex soft materials in both the solution and bulk phases.[1–3] In turn, the enhanced availability of both the block copolymer materials and self-assembly techniques has led to a wide array of investigations into their potential applications in the emerging field of nanotechnology.[4] As a consequence of their feature sizes, these materials have received attention in a range of biomedical/pharmaceutical applications such as hydrogel materials and micelles for drug and gene delivery applications[5] as well as in the synthesis of nanoporous materials,[4] particularly for use in nanoscale microelectronics, separation technologies and photonic applications amongst others. In many of the proposed and studied applications of these materials, either biocompatibility, degradability or both are highly desired properties. Indeed there has been a great deal of focus in this respect with the use of polymer segments to aid biocompatiblisation (*i.e.* poly(ethylene glycol), PEG, or poly(peptide)s) and/or incorporation of selectively removable blocks (*i.e.* poly(isoprene), PI, or poly(methyl methacrylate), PMMA).

Poly(ester)s are interesting candidates in this field as a consequence of being both biocompatible and (bio)degradable under mild conditions, properties that have led to significant investigations into their applications in tissue engineering, drug and gene delivery and even as environmentally friendly packaging materials.[6–11] Synthetically, poly(ester)s are commonly obtained by either condensation polymerisation of dicarboxylic acids and bifunctional alcohol units or by ring-opening polymerisation (ROP) of lactones and cyclic diesters such as lactide. While the application of condensation polymerisation techniques undoubtedly allows access to a wider range of functional polymers than ROP through a greater choice of monomer feedstocks, application of ring-opening polymerisation techniques provides greater control over the molecular characteristics of the polymers. Indeed, ROP displays many of the characteristics of a living polymerisation enabling the synthesis of poly(ester)s that display predictable molecular weights (from the monomer to initiator ratio), narrow molecular weight distributions, end-group control and the ability to access block copolymers by chain extension. Furthermore, application of readily available stereopure monomers in cooperation with stereocontrolled ROP has enabled the facile manipulation of the tacticity of the resultant polymers, greatly affecting their properties.

This *feature article* will focus on the synthesis of poly(ester) containing block copolymers by ROP in combination with other controlled polymerisation techniques and their application in self-assembling and self-ordering systems. A great deal of work has focused on the use of PEG di- and triblock

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copolymers with poly(ester)s (these polymers can be easily obtained by using the residual hydroxyl-chain end from the epoxide ROP to initiate ROP of cyclic ester monomers) and provides a range of biocompatible amphiphilic block copolymers that have received extensive study as polymeric micelles as drug delivery vehicles amongst others. However, in order to increase the functionality of these systems and hence potentially increase their application, the combination of poly(ester)s with other readily tuneable functional polymers is required. Obviously a comprehensive review of all of these aspects is beyond the scope of this *feature article* and to this end this review will focus on the synthesis of poly(ester) containing block copolymers by mechanistically distinct polymerisations, primarily the combination with controlled radical polymerisations to access multifunctional block copolymers that are able to self assemble/order, with a focus on work that has taken advantage of the properties of the poly(ester) blocks such as facile degradability and crystallinity. Specifically, this *feature article* will focus on providing an overview of the literature considered by the author to be the most relevant for those wishing to conduct investigations into this area of research.

Polymer synthesis and properties

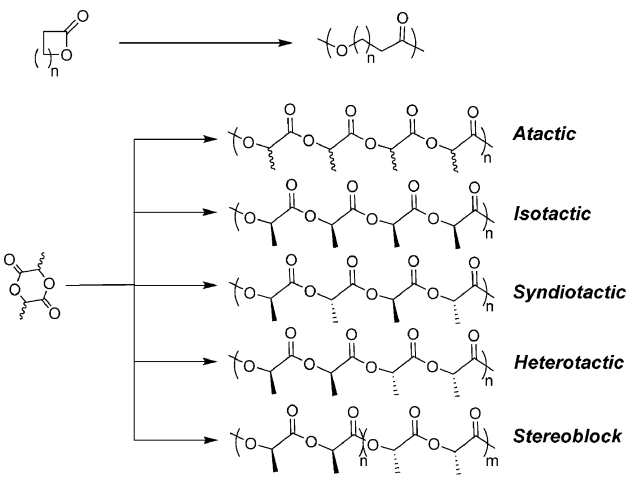
Ring-opening polymerisation enables the synthesis of predictable and high molecular weight polymers.[6–8,12–14] Judicious choice of initiating species enables the preparation of polymers with specific end groups. A great deal of research has focused on improved synthetic techniques and catalyst discovery to more efficiently mediate the ROP processes. The living characteristics of many of these catalytic polymerisation methods, in combination with an appropriate initiating species, enables either functional polymer synthesis or for the realisation of block copolymer structures that contain poly(ester) segments. A wide range of poly(ester)s that display different thermal and degradative properties can be synthesised in this manner (Table 1), controlled by structure and composition of the repeat unit, flexibility of the chain, presence of polar groups, molecular mass and crystallinity.[6,7,9,10,15] Monomers such as ε-caprolactone, δ-valerolactone, β-butyrolactone and the cyclic diesters, lactide and glycolide, are typically used for poly(ester) synthesis as a consequence of their ready polymerisability arising primarily from their ring strain.[12,16] The less strained 5-membered γ-butyrolactone and larger macrolide lactones are much less readily polymerised although their polymers can be prepared (primarily by enzymatic routes).

Table 1 Thermal properties of poly(ester)s

Polymer	Tacticity	T_g/°C[a]	T_m/°C[b]
Poly(ε-caprolactone)[c]	—	−60	65
Poly(δ-valerolactone)[c]	—	−63	60
Poly(γ-butyrolactone)[c]	—	−59	65
Poly(β-butyrolactone)[c]	Atactic	−2	—
Poly(β-butyrolactone)[c]	Isotactic	5	180
Poly(β-propriolactone)[c]	—	−24	93
Poly(glycolic acid)[c]	—	34	225
Poly(lactic acid)[c]	Atactic	45–55	—
Poly(lactic acid)[c]	Isotactic	55–60	170
Poly(lactic acid)[d]	Syndiotactic	34	151
Poly(lactic acid)[e]	Heterotactic	<45	—
Poly(lactic acid)[d]	Stereocomplex	65–72	220–230

[a] Glass transition temperature. [b] Melting temperature. [c] Figures quoted from Jérôme *et al.*[17] [d] Figures quoted from Tsuji.[10] [e] Figures quoted from Nozaki *et al.*[18]

Poly(ester)s generally degrade through a bulk erosion mechanism whereby the initial molecular weight of the polymer chains decreases, most likely as a result of random chain scission throughout the polymer matrix.[6,15] Further degradation can be additionally autocatalysed by the formation of carboxylic acid groups within the polymer matrix and leads to elimination of oligomers and monomers that continues until all regions of the polymer have been fully degraded. Degradation can take place through the action of a range of enzymes such as proteinase K, pronase and bromelain, as well as chemically through both transesterification and hydrolysis in either acidic or basic solutions. Poly(ε-caprolactone) and poly(δ-valerolactone) are both tough and flexible polymers, a consequence of melting temperatures (T_m) ~ 60 °C that result largely from the crystalline domains within the polymers, and glass transition temperatures (T_g) well below room temperature.[17] Poly(glycolide), PGA, is highly crystalline and thus displays a high melting point and T_g, these characteristics also result in relatively poor solubility of the polymer. Poly (lactic acid), PLA, displays slower degradation rates than poly(glycolide) as a consequence of both crystallinity and steric inhibition in the polymer; as such PGA is often applied in copolymers with PLA (to produce PLGA) to moderate the degradation rates.[6,17,19] PLA provides a further interesting possibility as a consequence of the presence of two stereocentres per monomer unit (Scheme 1).[8,18] Lactide, LA, is readily commercially available as the L-isomer and a racemic mixture of LL- and DD-LA (*rac*-LA); enantiopure D-LA can also be obtained and *meso*-LA (containing one L- and one D-stereocentre) is also known. While ROP of either enantiopure lactide enantiomer in the absence of epimerisation reactions enables synthesis of the highly crystalline poly(L-(or D-)LA), ROP of *rac*- or *meso*-lactide with catalysts able to mediate the addition of monomers based on their stereochemistry has allowed the synthesis of stereoblock copolymers, heterotactic and syndiotactic PLAs. Both atactic



Scheme 1 Ring-opening polymerisation of lactones and lactide.

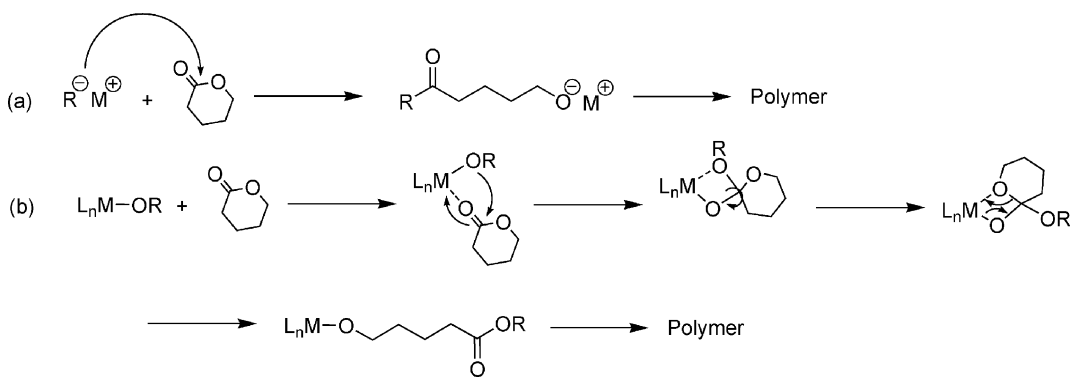
and heterotactic PLA are amorphous and display no melting point, however, poly(L-(or D-)LA) is a semicrystalline material and as a consequence of this has a $T_m \sim 170$ °C, the stereochemistry of the polymer has little effect on T_g. Notably, stereoregular PLAs display much lower rates of degradation than the amorphous atactic polymer. Interestingly a 1 : 1 mixture of poly(L-LA) and poly(D-LA) results in the formation of a stereocomplex whereby the opposite chiralities of the polymer chains lead to a complementary supramolecular interaction between the two helical polymers.[10] The PLA stereocomplex can be realised in solution or the bulk state from the melt or during polymerisation and results in much greater levels of crystallinity and a polymer that displays an increase in T_m of ~50 °C (to *ca.* 220–230 °C) in comparison to either homopolymer. Furthermore, the stereocomplex displays higher hydrolysis resistance and thus retains its tensile properties for much longer than the homochiral polymers. While the synthesis of the pure stereocomplex requires individual chains of poly(L-LA) and poly(D-LA), synthesis of stereoblock copolymers from *rac*-LA provides a more accessible method for the realisation of polymers that display very similar properties. Stereoblock copolymers can be synthesised as either discrete diblock, tapered or multi-block copolymers and commonly display high melting temperatures comparable to those obtained for the pure stereocomplex.

Catalysis of the ROP process[7,8,13,14,20–22] is possible with a range of species including metal coordination complexes,[8,14,18,20,21,23] enzymes[24] and simple organic molecules.[21,25–27] Several reviews have focused entirely on this subject, in this part of the *feature article* only those advances that are considered to be of high interest to a synthetic polymer chemist for the facile realisation of these structures are discussed.

Metal-based catalysts/initiators

The ROP of cyclic esters has been demonstrated to proceed readily through the application of metal-based salts and coordination complexes by both anionic polymerisation and coordination–insertion mechanisms. Simple initiators such as butyl lithium, lithium/potassium *tert*-butoxide and potassium methoxide have all been demonstrated to mediate anionic ROP in which the polymerisation principally proceeds *via* attack of the initiating or propagating alkoxide at the carbonyl group of the cyclic ester with ring-opening occurring quantitatively at the acyl–oxygen bond (Scheme 2a).[14,28–30] Such an approach provides poly(ester)s with high levels of chain end functionalisation (determined by the initiating alkoxide). While a range of poly(ester)s can be readily prepared by the ROP of lactones such as ε-caprolactone and δ-valerolactone, the high reactivity of the propagating species is known to lead to low levels of racemisation of the stereocentres in the ROP of lactide such that PLLA is obtained (from enantiopure L-LA monomer) with an isotacticity of up to 95%.[30] It is worthy of note that the ROP of β-lactones cannot be readily achieved by these common anionic initiators, requiring the addition of macrocyclic ligands, bulky counterions or highly polar aprotic solvents to obtain well controlled polymerisations, carboxylate ions are also preferable for these polymerisations.[28] It is also noteworthy that the heightened acidity of the protons at the β-position of the lactone ring also lead to crotonate α-chain ends and carboxylate ω-chain ends (a result of *O*-alkyl cleavage) reducing the level of end-group fidelity possible by this approach.[31]

The use of metal salts and well defined single site metal complexes has enabled the exploitation of coordination insertion mechanisms in ROP. Coordination of monomer by the carbonyl oxygen to the metal centre leads to initiation and subsequently propagation by a metal alkoxide species, either isolated or generated *in situ* by addition of an alcoholic initiator to a suitable metal precursor, to result in the formation of a new chain-extended metal alkoxide species (Scheme 2b). These approaches have enabled the facile syntheses of poly(ester)s with both molecular weight and molecular weight distribution control, chain end control and an absence of epimerisation reactions. Additionally, many of these salts and complexes display a much greater tolerance of protic impurities than those applied for anionic polymerisation. One of the most commonly applied catalysts for the ROP of cyclic esters is tin(II) octanoate, $SnOct_2$, providing a simple and effective means for effecting synthesis of poly(ester)s by ring-opening polymerisation.[32,33] This simple complex, in combination with an alcoholic initiator, enables the synthesis of poly(ester)s with good control over molecular weights and high levels of end-group fidelity (arising from the added initiator). While the exact mechanism of this transformation has been under debate, it is generally accepted that a coordination–insertion mechanism is active in this case.[32] Tin(II) octanoate has been demonstrated to be an efficient catalyst for the ROP of a wide range of cyclic esters although it is generally only active at elevated temperatures and is



Scheme 2 Metal-catalysed ring-opening polymerisation of lactones. (a) Anionic polymerisation; (b) coordination insertion polymerisation.

well-documented to undergo transesterification side reactions (both inter- and intramolecularly) throughout the polymerisations that lead to decreased control over the polymerisations, manifested by broad polydispersities ($\sim$2). Other tin(II) salts have been demonstrated to provide improved activity and selectivity for ROP reactions, most notably tin(II) triflate.[34] In the ROP of ε-caprolactone, this complex has been noted to display higher activities than tin(II) octanoate, enabling the use of lower polymerisation temperatures with accurate control over polymer molecular weights and narrow PDIs.

Aluminium complexes have also been shown to be highly efficient catalysts for the ROP of cyclic ester monomers. Of particular note is the application of aluminium tris-(isopropoxide), receiving extensive study as a catalyst for the ROP of cyclic esters.[35,36] While ROP of ε-caprolactone is most commonly achieved at 0 °C, these species are much less reactive towards the ROP of lactide, with this polymerisation requiring temperatures of 70 °C to proceed efficiently. The polymers produced are of predictable molecular weights and narrow polydispersities and transesterification side reactions are maintained at a minimum until high monomer conversions are realised. It is worthy of note that these polymerisations are complicated by the aggregation to A3 and A4 aggregates (of which only the A3 is highly active) resulting in loss of predictability of molecular weight determined by the monomer : initiator ratio.[37] While this can be overcome by fresh distillation of the catalyst species, the nature of the alkoxide ligands acting as initiators for ROP results in the chains being capped by an isopropoxide α-chain end. This has been overcome by the application of triethyl aluminium as the catalyst species with an initiating alcohol and has been shown to produce very well controlled polymers under comparable conditions to those applied for $Al(O^iPr)_3$ that are end-capped with a variety of α-chain ends derived from the chosen initiating alcohol.[35,38,39]

The ROP of cyclic esters can be readily achieved with these simple metal salts and *in situ* derived initiators to provide poly(ester)s with well defined molecular weights and narrow polydispersities. However, there has been a great deal of interest in the development of single-site homogeneous metal catalysts. Such complexes, supported by carefully designed ancillary ligands, offer the potential to tune the reactivity and selectivity of the catalyst thereby both increasing polymerisation activity and decreasing their propensity to catalyse side reactions. In addition, in the case of lactide ROP, these systems offer the potential to control the stereochemistry of the polymers hence moderating their properties. The tin(II) based complexes have seen some development, although it has been suggested that their ROP chemistry is dominated by the lone pair on the metal centre. In contrast, aluminium complexes have received a great deal of attention as catalysts for ROP with these studies resulting in a wide variety of easy to synthesise and easy to use complexes that provide a great deal of options to the synthetic polymer chemist. One of the first reports in this area was the application of tetraphenylporphyrinatoaluminium (TPP–Al) complexes for the immortal polymerisation of lactones (Fig. 1).[40] Inoue demonstrated that a range of TPP–Al complexes were able to mediate the ROP of cyclic ester monomers with good control over molecular weights and narrow

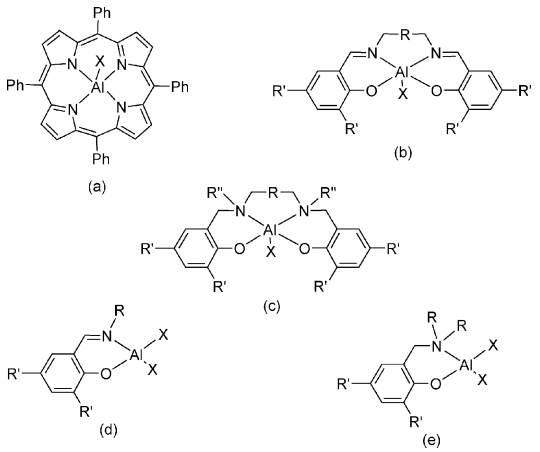


Fig. 1 Aluminium complexes supported by (a) tetraphenylporphyrin; (b) salen; (c) salan; (d) half-salen and (e) half-salan ligands for ROP.

polydispersities. The polymerisations are termed immortal as the addition of protic agents, usually applied to quench/terminate the polymerisation reactions actually leads to the formation of new polymer chains.

More recently the application of tetradentate salicaldimine (salen)aluminium complexes has received a great deal of attention (Fig. 1). Commonly used at 70 °C in solution, these complexes have proved to have a rich array of ROP chemistry. The facile manipulation of the steric and electronic nature of the ligands has enabled a great deal of study with derivatives being discovered that are highly active catalysts as well as demonstrating the ability to control the stereochemistry of the ROP of lactide. Both chiral and achiral salen ligands have been successfully applied in ROP. While initial work in 1993 by Spassky and co-workers[41] demonstrated the ROP of β-butyrolactone and lactide by an achiral (salen)aluminium complex, the application of a single (+)-*R* enantiomer of a binaphthyl derived chiral (salen)aluminium complex in the ROP of *rac*-lactide was demonstrated to result in the preferential incorporation of the D-lactide units into the polymer chain such that after 19% monomer conversion a polymer was observed with an 88% enantiomeric enrichment of D-lactate units, ultimately resulting in a tapered stereoblock copolymer.[42] Further studies into the application of this ligand system demonstrated that syndiotactic PLA could be readily obtained from the *meso*-diastereomer of the monomer and that application of a racemic mixture of catalyst led to the synthesis of an alternating stereoblock copolymer that displayed an increased melting temperature greater than that of the homochiral PLA.[43,44] Majerska and Duda also elegantly manipulated this system using a ligand exchange mechanism to produce a true poly(L-LA)-*b*-(D-LA) stereoblock copolymer with a melting temperature of 210 °C.[45] A more simply derived chiral (salen)aluminium complex was reported by Feijen and co-workers in which the application of the commercially available Jacobsen's ligand resulted in excellent probabilities of isotactic enchainment, P_m, (up to 0.93 in toluene solution at 70 °C and 0.88 under melt conditions at 130 °C).[46]

High levels of stereocontrol have also been achieved with achiral (salen)aluminium complexes. In the initial reports by Spassky and co-workers, PLAs displaying multi-stereoblock

structure were obtained at 70 °C in dichloromethane.[47] Nomura,[48,49] Gibson,[50,51] Chen[52] and their co-workers have performed extensive investigations into comparable catalytic species that have resulted in a library of highly active and selective catalysts. These studies, carried out at 70 °C in toluene solution, revealed that more highly withdrawing ligand substituents attached to the phenoxy donor, small *ortho*-phenoxy substituents and more flexible linkers between the imino nitrogen donors led to increased rates of polymerisation.[48,50] More interestingly this study also revealed that the isoselectivity of the catalysts in the ROP of *rac*-lactide was favoured by the combination of a flexible aliphatic propyl linker and sterically demanding *ortho*-phenoxy substituents; furthermore, the propylene linker was found to further reduce transesterification at high monomer conversions. While the precise mechanistic pathways for this high selectivity are not straightforward,[53] Nomura and co-workers reported that the multi-stereoblock PLA can be synthesised with a $P_m = 0.98$ when a propylene-bridged salen ligand with *tert*-butyldimethylsilyl groups at the *ortho* position of the phenoxy ring is employed.[48,54] Gibson *et al.* also demonstrated that the application of reduced salicaldimine (*i.e.* phenoxyamine or salan ligands, Fig. 1) enabled facile tuning of the stereoselectivities of the catalysts such that either multi-stereoblock or heterotactic PLA could be synthesised depending on the exact ligand substitution, providing the ability to readily tune the tacticity of the polymeric product by judicious ligand choice.[55] In most cases, the active aluminium initiating species are formed *in situ* by addition of the appropriate alcohol to the corresponding alkyl–aluminium complex. The alcohol is incorporated as the α-chain end of the polymer and is present quantitatively. The ability to readily tune polymer tacticity and α-end group in a synthetically accessible system that produces polymers with narrow polydispersities and an almost complete absence of transesterification provides attractive options in the synthesis of advanced polymer architectures. Similar half-salen aluminium complexes (Fig. 1) have been shown to display good activities for the ROP of caprolactone.[56]

Other metal complexes bearing Schiff base ancillary ligands such as the salen, salan and half-salen/salan ligands have also found a great deal of success[57] with reports of tin,[58] zinc,[59,60] yttrium,[43,61,62] titanium[63,64] and zirconium[63] complexes being highly active for ROP. Indeed, the more electrophilic nature of particularly zinc and yttrium furnishes much more highly active complexes than the aluminium examples outlined above. The zinc complexes supported by a trifunctional phenoxy-amine ligand reported by Hillmyer, Tolman and co-workers are amongst the most active catalysts for the ROP of *rac*-lactide converting 650 equiv. to atactic PLA with molecular weights that are slightly lower than predicted based on the monomer : initiator ratio and polydispersities *ca.* 1.4 within 5 min at room temperature in $CDCl_3$ solution ([catalyst] = 0.7 mM). The deviation of polymer molecular weight from that predicted was attributed to the presence of impurities that acted to deactivate some of the catalytic species.[60]

A wide range of additional metals and ligands have been applied for ring-opening polymerisation, with work focusing across the whole periodic table including lanthanum, zirconium, titanium, scandium and calcium supported by a wide range of ligands which have all been demonstrated to provide highly efficient catalytic species.[8,23] Several of these species are additionally able to mediate the stereospecific ROP of lactide with excellent control over the polymer molecular weights and polydispersities. Notably, (β-diketiminatato)-zinc,[65] tris(pyrazolyl)calcium,[66] amino-alkoxy(bisphenolate)-yttrium[67,68] and bis(phenolato)scandium[62,69] complexes (Fig. 2) under solution conditions resulted in the heterospecific ROP of *rac*-lactide. Of these, the alkoxy(bisphenolate)yttrium complexes have also been reported to display immortal polymerisation behaviour enabling the synthesis of microstructurally controlled PLAs with low catalyst concentrations, thereby minimising the contamination of the polymer with metallic residues.[67] The control of the polymerisation process is not compromised by the addition of >1 equiv. alcohol to yttrium catalyst and the polymers produced are of predictable molecular weight (from the monomer : alcohol initiator ratio) and of narrow polydispersity (~1.1). Davidson and co-workers have also demonstrated that a range of germanium, zirconium and hafnium complexes supported by a C_3-symmetric amine(trisphenolate) ancillary ligand (Fig. 2) are able to mediate the heterospecific ROP of *rac*-LA under both solution and melt conditions at ~130 °C.[70] While in all cases the polymers produced are of predictable molecular weight and narrow polydispersity, the highest levels of stereocontrol are achieved with the Zr analogue (probability of heterotactic enchainment, $P_r = 0.98$). Furthermore the amino-alkoxy(bisphenolate)yttrium,[71] (β-diketiminate)zinc[72] and (salen)chromium[73] complexes have also been reported to display notable activity and selectivity in the ROP of β-butyrolactone.

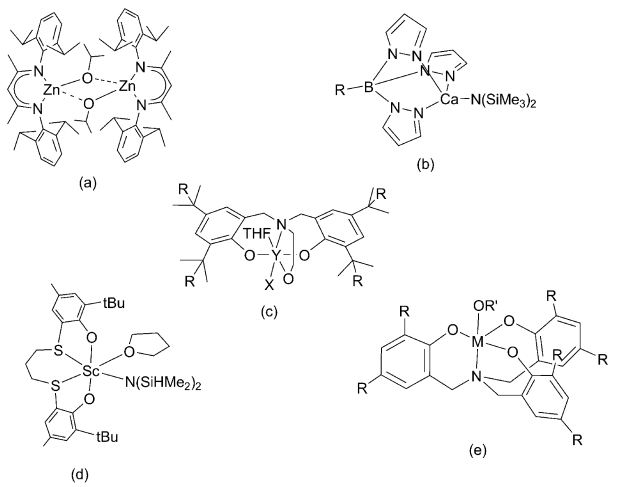


Fig. 2 Metal-based single-site catalysts for heterospecific ROP. (a) (β-Diketiminatato)zinc; (b) tris(pyrazolyl)calcium; (c) amino-alkoxy (bisphenolate)yttrium; (d) bis(phenolato)scandium complexes and (e) germanium, zirconium and hafnium complexes supported by a C_3-symmetric amine(trisphenolate) ancillary ligand.

Metal-free ROP catalysts/initiators

Metal free polymerisation including enzymatic, nucleophilic/supramolecular organocatalysis and cationic polymerisation

has recently received a great deal of interest, providing facile synthetic methodologies for the synthesis of poly(ester)s in the absence of metals. This research negates the requirement for the costly removal of the often highly toxic heavy metals from the resultant polymers, especially relevant for the biomedical and microelectronics fields, and has led to a wide range of catalysts that bring high activities, high selectivity for ROP over transesterification side reactions and stereocontrol in the ROP of lactide. Such approaches also offer the advantage that the catalytic species are often air stable, thus aiding their preparation and storage. These species only require removal of water to ensure end-group functionality and molecular weight control over the polymerisation.

The field of enzyme catalysed ROP (eROP) of cyclic ester monomers has received a large amount of interest. Enzymes do not require the exclusion of water or air and catalyse the degradation as well as the synthesis of poly(ester)s. While enzyme solubility *in vivo* is only possible in aqueous solvents, *in vitro* enzyme catalysed reactions are commonly carried out in organic solvents (including supercritical fluids) or in bulk monomer. Under these conditions enzymes exhibit different properties to those observed in water such that the activity and selectivity of the process is highly dependent on the method of enzyme preparation, type of solvent and the temperature of the reaction.[74,75] Enzymes remain in suspension in organic solvents potentially rationalising their apparent lower activity under these conditions. Nonetheless, the presence of water is required to enable enzyme activity by providing a partial hydration layer around the enzyme thus providing flexibility to its structure. Several lipases have been reported to be active for poly(ester) synthesis and all contain structurally similar conformations that include a hydrophobic pocket containing serine, histidine and aspartate or glutamate as the key residues. Esterification is believed to happen by acylation of the serine residue with subsequent esterification (or hydrolysis) by alcohol (or water).[76]

The first reports of enzyme catalysed ROP of cyclic esters appeared in 1993[77,78] with Uyama and Kobayashi reporting the highest % monomer conversion in the ROP of ε-caprolactone by applying *Pseudomonas fluorescens* in bulk for 10 days to result in poly(ε-caprolactone) with M_n = 7700 g mol^{-1}.[78] While a range of lipases have been investigated for ROP, probably the most commonly applied in the non-aqueous ROP of cyclic ester monomers is *Candida antarctica* lipase B (CALB). CALB is often immobilised on a macroporous support available as Novozym 435. Immobilisation of the enzyme has led to greater solubility in organic solvents, resulting in greater catalytic activity. Other supports have been utilised including sol–gel and aero–gel dispersions and more recently immobilisation of CALB on 68 nm nanoparticles with a poly(gycidyl methacrylate) outer region led to a notable increase in activity in the ROP of ε-caprolactone.[79] Gross and Kumar have performed investigations into the concentration of CALB, the effect of temperature, choice of organic media and presence of water in the ROP of ε-caprolactone.[75] It was shown that the highest activities and polymer molecular weights were obtained in toluene or isooctane solution, more polar solvents were shown to deactivate the enzyme resulting from conformational changes. Furthermore, the volume ratio of monomer to solvent proved to be an important factor in optimising the polymerisations with the highest molecular weights being obtained at 70 °C with a 2 : 1 ratio of toluene : ε-caprolactone. Higher temperatures led to increased reaction rates such that polymerisations could be carried out at 90 °C reaching 90% monomer conversion within 2 h. The water content of the solvent was shown to be critical to controlling the molecular weight of the polymer, not reaction temperature, believed to be a result of the increased stabilisation of the enzyme by the more abundant carboxyl chain ends that result from initiation from water. More recently, Howdle *et al.* have investigated the CALB catalysed ROP of ε-caprolactone in supercritical carbon dioxide ($scCO_2$), demonstrating this to be a highly effective solvent.[80] These studies revealed that molecular weights comparable to those obtained in organic solvents could be realised but with both more narrow polydispersities (between 1.4 and 1.6) and higher yields of products (up to 98%). In all these cases, large numbers of enzyme catalysed transesterification reactions result in a mixture of cyclic and linear polymers being produced throughout the polymerisation reaction and incomplete control of the chain ends when alcohol or amine functional initiators are applied. However, notably Albertsson and Srivastava have recently demonstrated that removal of water from the lipase by drying over P_2O_5 resulted in the ability to achieve complete end-group fidelity, in this case with 4-pentene-2-ol in the ROP of 1,5-dioxapan-2-one and ε-caprolactone in bulk, thus enabling the synthesis of block copolymers by chain extension.[81]

Enzyme catalysed ROP reactions can be extended to a range of cyclic ester monomers including the usual highly strained monomers such as β-butyrolactone, δ-valerolactone and ε-caprolactone (4-, 6- and 7-membered rings, respectively). More remarkably, enzyme-mediated ROP can readily be extended to less strained rings such as γ-butyrolactone (unstrained 5-membered ring)[82] and much larger macrolides (up to 17-membered rings).[83] While in the case of γ-butyrolactone polymers of up to 10–11 monomer units could be readily obtained,[82] in contrast to metal catalysed ROP, the polymerisation of the larger low strain rings proceeded with increased activity than smaller more strained lactones such that modest molecular weight polymers could be obtained.[83] This reaction is thought to be driven by the increased hydrophobicity of the larger monomers, rather than by monomer ring strain, thus providing a greater driving force for the essential lactone–lipase acylation reaction. Notably, while quantitative control over chain end functionality from an additional alcohol initiator is hard to realise in the ROP of ε-caprolactone, polymerisation of the 13-membered rings, τ-dodecalactone and ω-pentadecalactone, has been shown to be achieved with full incorporation of methacrylyl end-groups.[84] Enzyme catalysed ROP reactions also provide excellent selectivities towards alcohols over thiols enabling the chemoselective synthesis of thiol end-capped polymers.[85–88] Three approaches were examined including application of 2-mercaptoethanol as initiator[86,88] and termination with either 3-mercaptopropionic acid or γ-thiobutyrolactone.[87,88] Up to 90% thiol end group functionalisation was achieved by the latter method and the combination of incorporation of initiating and terminating groups has resulted in α,ω-thiol substituted

poly(ω-pentadecalactone).[87] Lipase catalysts are also known to display a preferential selectivity for primary over secondary alcohols. This has led to the ability to selectively initiate polymerisation from a primary alcohol in the presence of secondary alcohols exemplified by the ROP of the 17-membered epoxide functional ambrettolide and ε-caprolactone.[89] Furthermore, it is known that increased steric effects also have a significant effect on the efficiency of the initiation of the ROP reaction. To this end, Howdle and co-workers have demonstrated that the synthesis of brush copolymers initiated from hydroxyalkyl (meth)acrylate copolymers prepared by atom transfer radical polymerisation (ATRP) produces a polymer with a grafting density *ca.* 30–40% in a block copolymer; these grafting densities could be improved by initiation from random copolymers (up to 80%); application of a longer chain alkyl spacer enabled 100% grafting to be achieved.[90,91] The enzymatic ROP of lactide has been much less well studied than that of the related cyclic mono esters.[92,93] Lipase *Pseudomonas fluorescens* has been shown to be an efficient catalyst for lactide ROP able to produce PLAs of up to 270 000 g mol^{-1} with molecular weight distributions around 2.[93] Furthermore, porcine pancreatic lipase and *Pseudomonas cepacia* have been shown to be able to mediate ROP copolymerisation with trimethylene carbonate and glycolide respectively.[94] While stereoregular enzymatic ROP has not been realised with lactide, some substituted lactones have been demonstrated to be polymerised with modest enantioselectivities.[91,95]

Simple organic molecules have also received a great deal of attention as catalysts for the ROP of cyclic esters. Many of these organocatalysts have the advantage of being commercially available or readily synthesised in a few steps. Simple nucleophiles such as 4-dimethylaminopyridine (DMAP), 4-pyrrolidinopyridine (PPY) and several phosphines have shown significant promise in this respect.[96–98] ROP catalysed by DMAP provided an excellent method for the ROP of lactide in dichloromethane solution at 35 °C.[97] While polymerisation proceeded slowly (for example 60 : 2 : 1 LA : DMAP : EtOH, complete conversion in 50 h) the polydispersity of the polymer remained very low (<1.10) even at extended reaction times, suggesting that transesterification was negligible, although Hedrick *et al.* also demonstrated that in the presence of excess alcohol, DMAP performed as a highly efficient PLA depolymerisation catalyst.[99] Phosphine catalysed ROP required melt conditions to obtain good activities and produced well-controlled PLAs.[96] The methodology was not extended to the polymerisation of other less strained cyclic ester monomers although DMAP has been shown to be an excellent catalyst for the ROP of *O*-carboxyanhydrides as a route to PLA and functional poly(ester) synthesis.[100,101] A major breakthrough in this field was reported by Hedrick and co-workers in which they demonstrated that the more nucleophilic *N*-heterocyclic carbenes (NHCs) were able to perform the ROP of LA at ambient temperature in a few hours.[102] In later reports, these times were reduced to a few minutes for the ROP of 100 equivalents of lactide to initiator, also enabling the application of sub-stoichiometric amounts of catalyst (relative to initiator) to be applied.[27,103,104] Imidazolium (most commonly the commercially available 1,3-bis-(2,4,6-trimethylphenyl)-imidazol-2-ylidene, IMes), imidazolinium, thiazolium and

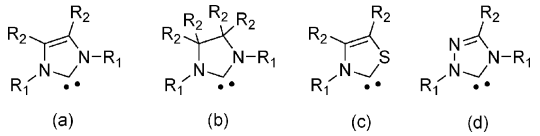
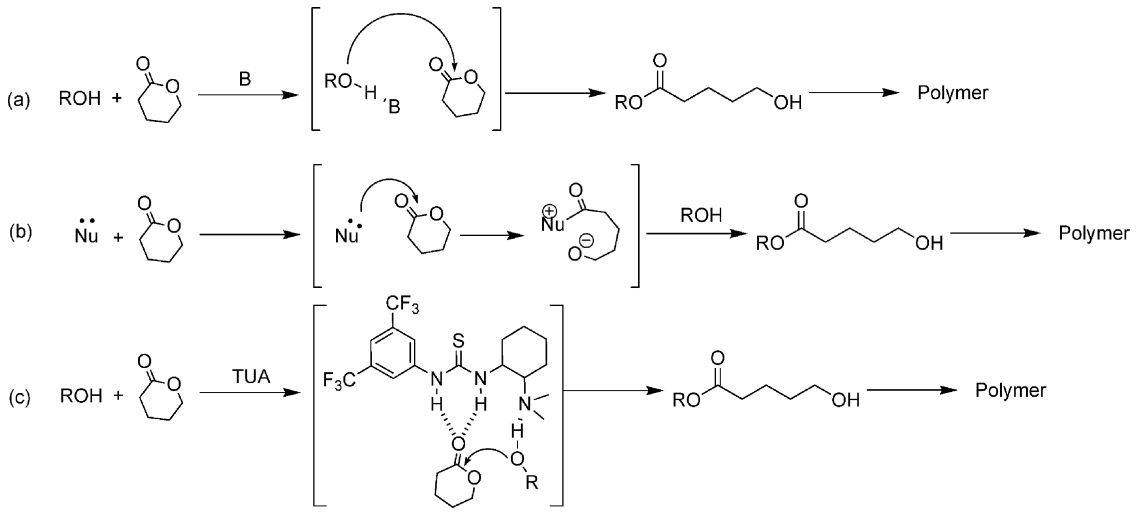


Fig. 3 *N*-Heterocyclic carbene catalysts for organocatalytic ROP. (a) Imidazolium; (b) imidazolinium; (c) thiazolium and (d) triazolium.

triazolium carbenes (Fig. 3) have all been demonstrated to be highly active catalysts, although the triazolium catalysts are less active than the other NHC derivatives, largely a result of the strongly bound alcohol adducts formed under polymerisation conditions. Nonetheless this resulted in the ability to switch 'on' and 'off' their activity as a function of temperature.[105] NHCs are also highly active for the ROP of less strained cyclic ester monomers such that they have also been shown to efficiently polymerise ε-caprolactone, δ-valerolactone and β-butyrolactone.[104,106,107] Of particular note is the application of 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene in the ROP of β-butyrolactone in which the synthesis of poly(hydroxybutyrate)s up to DP200 could be achieved without loss of end-group fidelity at 80 °C in toluene solution in the presence of 20 vol% *tert*-butanol as cosolvent, believed to favour adduct formation thus reducing the amount of free triazolium NHC in solution.[106,107] Although highly air sensitive, many carbene precursors are not and as such several methods of generating NHCs *in situ* from air stable precursors have been reported including silver or acid salts,[104,108] thermally cleavable haloalkane adducts,[109] and reversibly cleavable alcohol and amine adducts.[103,105,107,110] Of these, the alcohol adducts of the imidazolinium and triazolium carbenes have enabled the isolation of single-component catalyst initiator species.[103,105,107,110] The high activities of these catalysts have also enabled polymerisations to be carried out at low temperatures. Hillmyer, Tolman and co-workers demonstrated the application of the IMes NHC at −20 °C in dichloromethane solution for the ROP of *rac*-LA to produce a strong preference for isotacticity (such that $P_m = 0.75$).[111] Hedrick, Waymouth and co-workers subsequently demonstrated that the application of the more hindered 1,3-bis-(2,4,6-trimethylphenyl)-4,5-diphenylimidazol-2-ylidene NHC demonstrated a $P_m = 0.90$ for the synthesis of multi-stereoblock PLA from *rac*-LA at −70 °C in dichloromethane solution and a $P_m = 0.83$ for the synthesis of heterotactic PLA from *meso*-LA at −40 °C in dichloromethane solution.[112] While there is some ongoing debate between proposed nucleophilic monomer activated and H-bonding alcohol activation/general base mechanisms (Scheme 3),[101,104,113] these catalysts provide a powerful means of synthesising poly(ester)s.

There have also been several reports of organic catalysis for the ROP of cyclic esters mediated by compounds that activate monomer, initiating/propagating species or both by supramolecular interactions. Harada *et al.* demonstrated that β-cyclodextrin (βCD) is able to efficiently polymerise ε-caprolactone, δ-valerolactone and β-butyrolactone in bulk at 100 °C, proposed to proceed *via* monomer activation through formation of an inclusion complex within the βCD and ring-opening by a hydroxyl group on the face of the βCD, chain extension occurring by insertion into the propagating



Scheme 3 Organocatalysed ring-opening polymerisation of lactones. (a) Chain-end/general base, B; (b) nucleophilic monomer activated; (c) concurrent monomer and chain-end activation by thiourea-amine (TUA) catalyst.

chain.[114] Hedrick, Waymouth and co-workers reported the application of a conjoined thiourea–tertiary amine catalyst in the ROP of LA by supramolecular activation of both chain end and monomer (Scheme 3).[115] At ambient temperature complete monomer conversion was demonstrated for 100 : 10 : 1 LA : catalyst : initiator within 48 h in dichloromethane solution. Interestingly, even at greatly extended reaction times no evidence of transesterification was observed. This observation was later attributed to the selective activation of cyclic esters over linear esters by the thiourea moiety.[116,117] Disconnection of the tertiary amine and thiourea moieties did not disrupt polymerisation activity and enabled a thorough assessment of the catalyst components. Whilst the requirement for a highly electron withdrawing thiourea was confirmed, the ability to increase the basicity of the tertiary amine enabled large increases in activity to be obtained such that with the combination of bis(3,5-trifluoromethyl)phenylcyclohexyl-thiourea and (−)-sparteine a DP100 polymer could be obtained within 2 h (5 mol% thiourea, 2.5 mol% sparteine, [LA] = 0.7 M) while maintaining the excellent control of the conjoined catalyst system.[116] This increase in catalyst activity also enabled the ROP of less strained lactones such that in combination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the thiourea catalyst was highly active towards the ROP of δ-valerolactone and ε-caprolactone. Interestingly, DBU proved to be a highly efficient catalyst for the ROP of LA without added thiourea, as did 7-methyl-1,5,7-triazabicyclo[4.4.0]-dec-5-ene (MTBD), Fig. 4; proposed to mediate ROP through a chain-end activation/general base catalysed mechanism.[117] Extension of this work to the study of guanidines and phosphazenes resulted in some of the most active catalysts in this class.[117–119] While guanadinium acetate was demonstrated to be a mildly active LA polymerisation catalyst operating by a coordination-insertion mechanism,[120] 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) at a 0.1 mol% loading (to monomer) was shown to polymerise 500 equivalents of LA to 95% monomer conversion within 1 min at ambient temperature to produce a polymer with M_n = 62 600 g mol^{-1} and PDI = 1.11.[119] This catalyst also demonstrated remarkable activities for the ROP of δ-valerolactone although it was less active towards ε-caprolactone such that the polymerisation was complicated by the onset of transesterification reactions. Initially a mechanism involving acylation of the monomer followed by transesterification with the initiation/propagating species was proposed, although recent computational studies propose that polymerisation occurs through chain end activation through hydrogen bonding to the catalyst.[119,121] Phosphazene bases such as 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), *N*′-*tert*-butyl-*N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethylphosphorimidic triamide ($P_1{}^tBu$) and 1-*tert*-butyl-2,2,4,4,4-pentakis(dimethylamino)-2Λ,5^{4}δ5-catenadi(phosphazene) ($P_2{}^tBu$), Fig. 4, have also demonstrated extremely high activities.[118,122] At room temperature in dichloromethane solution, 1 mol% $P_2{}^tBu$ is able to quantitatively convert 100 equiv. *rac*-LA (to initiator [LA] = 0.32 M) in 10 s. Furthermore, application of this sterically hindered catalyst system at −75 °C resulted in a polymer that displayed a P_m = 0.95.[122]

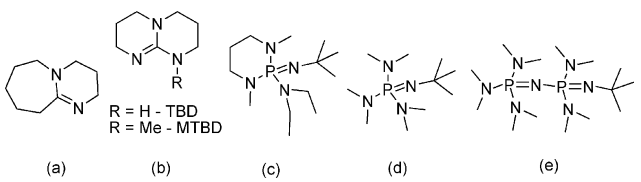


Fig. 4 Organic catalysts for ROP. (a) DBU; (b) (M)TBD; (c) BEMP (d) $P_1{}^tBu$ (e) $P_2{}^tBu$.

The polymerisation of cyclic ester monomers through cationic ROP has been demonstrated with a wide range of strong mineral and organic acids.[123–125] Trifluoromethanesulfonic acid (HOTf), methane sulfonic acid (MSA), HCl·OEt$_2$, trifluoro- and trichloroacetic acids have been applied in this respect. While polydispersities of the resultant poly(ester)s synthesised in this manner tend to be slightly broadened, Bourissou and co-workers have recently demonstrated that MSA and HOTf are able to mediate the well controlled polymerisation of ε-caprolactone and lactide to result in polymers of predictable molecular weight and narrow

polydispersity (ε-CL: PDI ~ 1.07; LA: PDI ~ 1.13) in a few hours at room temperature.[123] Triflic acid has also been demonstrated to mediate the ROP of β-butyrolactone, producing polymers with predictable molecular weights and low PDIs (<1.12).[125] ROP was shown to occur by acyl–oxygen cleavage and occurred with retention of stereochemistry.

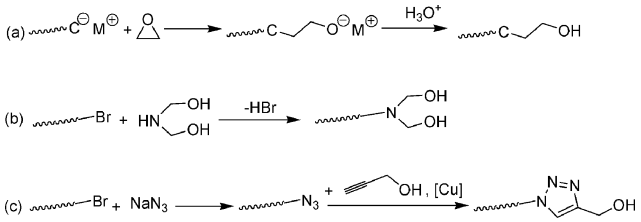
Mechanistically distinct block copolymer synthesis

Block copolymer structures have been the subject of a great deal of study as they provide interesting opportunities to construct objects with controlled feature size on a nanometre scale. A key aspect of this research field is the ability to synthesise polymers with blocks that are tuneable in functionality as well as molecular dimensions. While poly(ester)s offer intriguing possibilities in nanoscale assemblies, the introduction of functional non-degradable blocks enables a much greater array of potential applications. Living and controlled polymerisation methodologies such as anionic polymerisation and controlled radical polymerisations (CRP) including atom transfer radical polymerisation (ATRP),[126] nitroxide mediated polymerisation (NMP)[127] and reverse addition fragmentation chain transfer polymerisation (RAFT)[128] offer excellent synthetic pathways into functional polymer blocks. Anionic polymerisation offers excellent control of the polymer characteristics as a consequence of its living nature however, the high sensitivity to moisture and oxygen make it less practical than the CRP techniques. As opposed to conventional free radical polymerisation techniques, CRPs moderate the concentration of radicals in solution by reversible activation/deactivation processes to maintain excellent control over polymer molecular weight, polydispersity and end-groups. The versatility offered by these approaches has resulted in several syntheses of block copolymers by these mechanistically distinct routes from both sequential and simultaneous '*grafting from*' chain growth as well as by '*grafting to*' approaches to combine two preformed polymer chains.

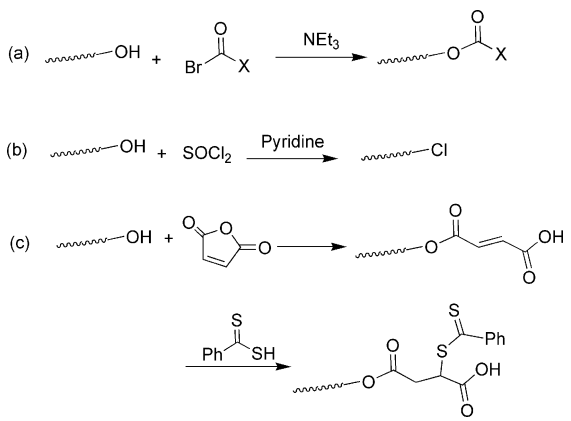
'Grafting from' approaches. The preparation of poly(ester) containing block and graft copolymers *via* 'grafting from' methodologies can be examined from three points of view whereby ROP is carried out first, second or simultaneously with the other polymerisation strategy. In the event of sequential polymerisation strategies, either the polymer end group can be modified after the first polymerisation or a dual-headed initiating species can be applied; the latter approach is essential in simultaneous polymerisations. In order to synthesise a block copolymer in which the poly(ester) segment is synthesised second, a hydroxyl functional polymer is required. While this is relatively straightforward for poly(ethylene glycol) polymers, where the propagating chain end is a hydroxyl group upon quenching of the polymerisation, many other polymers require tailoring to present a hydroxyl group, either at the chain termini or along the polymer backbone.

The synthesis of hydroxyl end-functional polymers *via* anionic and controlled radical polymerisation techniques has been reported. Anionic polymerisation methodologies can be quenched by the addition of an epoxide. As a consequence of the strong lithium–alkoxide interactions, propagation of the epoxide monomer is not possible and upon termination of the polymerisation a hydroxyl functional polymer can be obtained (Scheme 4a).[129] ATRP has also been employed to grow poly(styrene) before end-group conversion with diethanolamine in DMF to result in a hydroxyl functional polymer (Scheme 4b).[130] More recently, the bromide end group resulting from polymerisation by the ATRP technique has been transformed into an azide functional group by reaction with sodium azide. Further conversion of these azide functional polymers using the Huisgen copper catalysed cycloaddition reaction with a functional alkyne has enabled the synthesis of hydroxyl-functional polymers (Scheme 4c),[131] although to date these techniques have not been extended to the further growth of ROP polymers from these macroinitiators. In sequential polymerisation strategies, a great deal more work has focused on synthesis of the poly(ester) block first, probably a result of the ease of functionalisation of the alcohol end group through a range of methodologies. Most commonly the application of acid halide functional compounds to convert the hydroxyl chain end to an initiator for a different polymerisation mechanism has been studied. In this way initiators suitable for chain propagation by ATRP and RAFT polymerisation have been readily incorporated onto the polymers (Scheme 5a).[132–137] While this is commonly performed by post-polymerisation modification of the hydroxyl chain end in the presence of a suitable base (*e.g.* triethylamine), the chain end modification can also be performed directly following anionic polymerisation[134] or aluminium catalysed coordination insertion polymerisation.[39]

Alternatively, the secondary hydroxyl end group resulting from the ROP of lactide has been converted to a secondary



Scheme 4 Transformation of anionic and controlled radical polymerisation end groups to hydroxyl groups.



Scheme 5 Transformation of polymer hydroxyl end-groups into suitable initiating species for controlled radical polymerisation.

β-chloroester by reaction with thionyl chloride in the presence of pyridine (Scheme 5b) and has subsequently been applied as a macro initiator for the polymerisation of *tert*-butyl acrylate *via* ATRP methods.[138] Hydroxyl end groups have also been converted to malate monoesters by the ROP of maleic anhydride. Conversion of the alkene functionality to a dithiobenzoate, suitable for RAFT polymerisation, can be achieved by reaction with dithiobenzoic acid (Scheme 5c).[139]

A great deal of work has been carried out with dual-headed initiators (Table 2).[140] These species, bearing suitable initiating sites for ROP as well as CRP, have been applied either in sequential polymerisations or as initiators for simultaneous ROP/CRP. In 1998, Jerome, Hedrick and Hawker *et al.* reported both the stepwise and simultaneous ROP of ε-caprolactone with both the NMP of styrene at 125 °C and the $[NiBr_2(PPh_3)_2]$ catalysed ATRP of methyl methacrylate at 80 °C in bulk monomer.[141,142] The NMP/ROP copolymerisation was realised by the application of a hydroxyl-benzyl functional TEMPO derivative (entry 11, Table 2) with ROP being mediated using $Sn(Oct)_2$ or $Al(O^iPr)_3$. In the same way, 2,2,2-tribromoethanol (entry 1, Table 2) was applied as a dual-headed ATRP/ROP initiator; ROP was catalysed by $Al(O^iPr)_3$. In both cases the ROP was found to proceed more rapidly than the CRP, resulting in reduced mole fractions of the caprolactone blocks with increased reaction time. Sequential polymerisations led to a greater degree of control being exerted over the polymerisations as evidenced by generally more narrow polydispersities, attributed to both less adequate kinetic control and the presence of side reactions. Several other dual-headed initiators have been reported and have been used to synthesise a wide range of mechanistically distinct di- and triblock copolymers. With respect to ROP, $Sn(Oct)_2$ either in toluene solution or bulk monomer at elevated temperatures and Al based catalyst species have been most commonly applied, most likely a consequence of the their ready availability, simplicity of application and literature heritage. Matyjaszewski *et al.* noted that simultaneous ROP/ATRP catalysed by $Sn(Oct)_2$ and Cu(I) sources, respectively led to a great disparity in polymerisation rates (ATRP ≫ ROP).[143,144] In an attempt to correct this Cu(II) was added to the system to reduce the ATRP rate, however an increase in the rate of ATRP was in fact observed. It was concluded that the $Sn(Oct)_2$ was acting as a reductant for Cu(II) to Cu(I) thus causing further imbalance in the relative rates of polymerisation. More recently, examples in which metal-free catalysts have been applied to effect both poly(ε-caprolactone) and poly(lactic acid) blocks have been reported. Howdle and co-workers reported that both sequential and simultaneous enzymatic ROP and Cu catalysed ATRP in supercritical CO_2 of ε-caprolactone and methyl methacrylate or a semifluorinated methacrylate monomer was possible.[145] Interestingly, the authors found that the caprolactone acted as a highly efficient cosolvent for the methacrylate monomers preventing precipitation of the polymers. Furthermore, the authors suggest that the application of $scCO_2$ provided an increased level of control over the copolymerisation by comparison to synthesis in standard organic solvents. Meijer, Palmans and co-workers demonstrated a one-pot cascade approach to the synthesis of poly(4-methyl-ε-caprolactone)-*b*-poly(methyl methacrylate) was possible. In this study the authors first used Novozym 435 to effect the enzymatic enantioselective ROP.[146] In the second step, ATRP of MMA was carried out by injection of $[NiBr_2(PPh_3)_2]$ to both effect ATRP and inhibit the enzyme activity to further prevent polymerisation or transesterification side reactions.

NMP and RAFT polymerisations have also been applied in dual-headed polymerisation strategies. In the application of a TEMPO derived benzylic alcohol NMP–ROP initiator (entry 11, Table 2), Hedrick, Hawker and Jerome *et al.* showed that both sequential and simultaneous polymerisation of ε-caprolactone and styrene was possible.[141,142] Again, the sequential polymerisation strategy yielded polymers with more narrowly dispersed molecular weights. Yoshida and Osagawa demonstrated that hydroxyl-TEMPO (entry 13, Table 2) was also able to act as an efficient bifunctional initiating species.[147] In this case, it was noted that combination of hydroxy-TEMPO with one equivalent of $AlEt_3$ to generate an aluminium alkoxide *in situ* resulted in very little poly-(ε-caprolactone). This was tentatively attributed to the incompatibility of TEMPO with strong bases such as the aluminium alkyl species and was overcome by treating the $AlEt_3$ with 3 equivalents of hydroxy-TEMPO to result in the trisubstituted aluminium tris(alkoxide). Polymerisation was able to be effectively mediated by the resultant Al complex and generated polymer with a high degree of TEMPO end groups that were applied as macroinitiators for the NMP of styrene. More recently, the hydroxymethyl functional alkoxyamine initially reported by Hawker *et al.* (entry 11, Table 2)[148] was applied as a dual-headed initiator for NMP and metal-free ROP.[116,118,149,150] Heise and co-workers reported the sequential and one pot cascade polymerisation of ε-caprolactone/4-methyl-ε-caprolactone with styrene[149] and Hedrick and Waymouth *et al.* demonstrated the application of this initiator to synthesise hydroxy-functional poly(styrene) and poly(dimethylacrylamide) that was chain-extended with poly(lactic acid) using organocatalytic methods.[116,118] Bifunctional RAFT chain transfer agents have been applied in a similar manner, with both organic and Al/Sn salt catalysis. Notably, Hedrick, Waymouth and Wade and their respective co-workers used a hydroxy-functional RAFT initiator (entry 19, Table 2) to synthesise a range of poly((alkyl)acrylate) and poly(vinylpyridine) polymers that were chain extended using either the thiourea–tertiary amine or phosphazene organic catalysts.[116,118] Interestingly, the Hedrick group extended this methodology using $P_2{}^tBu$ at low temperature to prepare poly(dimethylacrylamide)-*b*-poly(lactic acid) in which the PLA block was itself a stereoblock copolymer.[162] Howdle *et al.* also reported the enzymatically catalysed ROP of ε-caprolactone simultaneously with the AIBN initiated RAFT polymerisation of methyl methacrylate or styrene in supercritical CO_2.[150,163]

These methodologies have also been applied to the synthesis of more complex polymer architectures such as miktoarm stars,[159,165–167] star-shaped polymers initiated from dendritic initiators,[171] H-shaped polymers[169,172] and graft copolymers.[90,91,173–178] There have been several reports of the latter type of graft copolymer which can be synthesised by simultaneous or sequential polymerisations ('grafting from') or by

Table 2 Dual-headed initiators for CRP–ROP copolymerisations

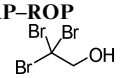
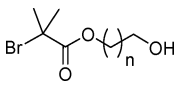
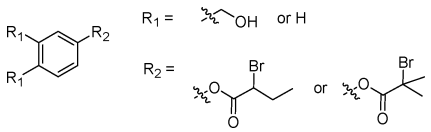
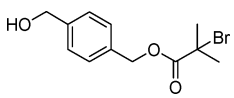
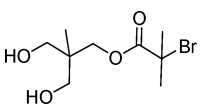
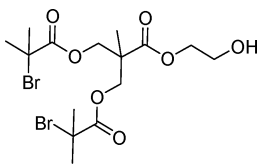
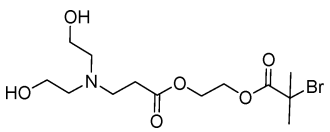
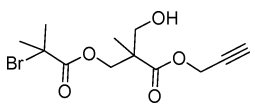
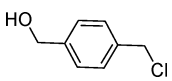
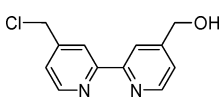
Entry	Dual-headed initiator	Comments
ATRP–ROP		
1		$[NiBr_2(PPh_3)_2]$ catalysed ATRP of methyl methacrylate then AlO^iPr_3 catalysed ROP of ε-caprolactone and *vice versa*.[141] Also applied in simultaneous polymerisations using the same systems.[142]
2		n = 1: Poly(styrene) and poly(styrene)-*b*-poly(methyl methacrylate) macroinitiators prepared by Cu(I)–bpy catalysed ATRP followed by ROP of L-LA by $Sn(Oct)_2$ in toluene solution.[151] Either CuBr–bpy catalysed ATRP (both MMA and fluorinated monomer) first then eROP of ε-caprolactone or *vice versa* and simultaneous in $scCO_2$.[145] Sequential ATRP (CuBr–bpy) and ROP ($Sn(Oct)_2$ bulk) polymerisations of styrene or methyl methacrylate and ε-caprolactone. Also extension to bifunctional monomers to synthesise partially degradable core-crosslinked star polymers.[152,153] Two step and simultaneous ROP ($Sn(Oct)_2$, toluene) of ε-caprolactone and ATRP (CuCl–bpy) of octadecyl methacrylate,[143,144] and ATRP of dimethylaminoethylacrylamide.[144] Sequential ATRP of methyl methacrylate (CuBr–bpy) then ε-caprolactone catalysed by $AlEt_3$; ε-caprolactone was used as the solvent.[154] n = 3: Simultaneous copolymerisation of ε-caprolactone catalysed by $AlEt_3$ and *tert*-butyl methacrylate catalysed by CuBr–bpy in toluene at 60 °C.[155]
3		Several isomers applied in the sequential ATRP of styrene using a CuBr–bpy catalyst system then ROP of L-LA by $Sn(Oct)_2$ in toluene solution. Notably, the *m*-benzyl alcohol derivatives systematically gave better yields than the *p*-isomers in ATRP.[135]
4		Cascade approach to the eROP of 4-methyl-ε-caprolactone using Novozym 435 and ATRP of methyl methacrylate catalysed by $[NiBr_2(PPh_3)_2]$[146]
5		Sequential polymerisation of styrene, *tert*-butyl acrylate by CuBr–PMDETA catalysed ATRP followed by ROP of ε-caprolactone using $Sn(Oct)_2$ in bulk monomer (PMDETA = pentamethyldiethylenetriamine).[156]
6		ROP of ε-caprolactone using $Sn(Oct)_2$ in bulk monomer then CuBr–bpy catalysed ATRP of *tert*-butyl acrylate, styrene and butylacrylate.[157] Further reaction of the alcohol chain ends with bromoisobutyroyl bromide provided more complex block copolymers. Also, ROP of ε-caprolactone using $Sn(Oct)_2$ in bulk followed by CuBr–bpy catalysed ATRP of dimethylaminoethyl methacrylate.[158]
7		ROP of ε-caprolactone using $Sn(Oct)_2$ then CuBr–bpy catalysed ATRP of dimethylaminoethyl methacrylate.[158]
8		After 'click' conjugation of an azide terminated poly(ethylene oxide), sequential ATRP (CuBr–PMDETA catalysed) of styrene was followed by ROP of ε-caprolactone using $Sn(Oct)_2$ in bulk monomer.[159]
9		Applied in the synthesis of chlorobenzyl-functional bis(phenoxy)aluminium and lithium alkoxide complexes. Polymerisation of ε-caprolactone or lactide in DCM solution at ambient temperature was followed by ATRP (CuBr–bpy) of acrylonitrile.[160]
10		Sequential polymerisations (either ATRP or ROP first) of styrene (CuBr–HMTETA, anisole) and ε-caprolactone ($AlEt_3$, THF). Bipyridine moiety subsequently applied for metal chelation to produce star-shaped polymers (HMTETA = hexamethyltriethylenetetraamine).[161]

Table 2 (*continued*)

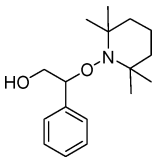
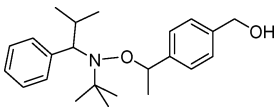
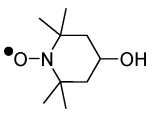
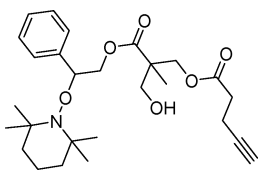
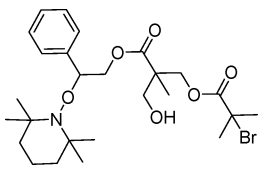
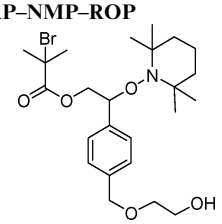
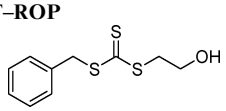
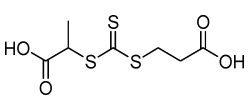
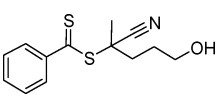
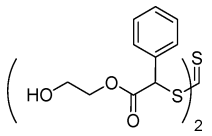
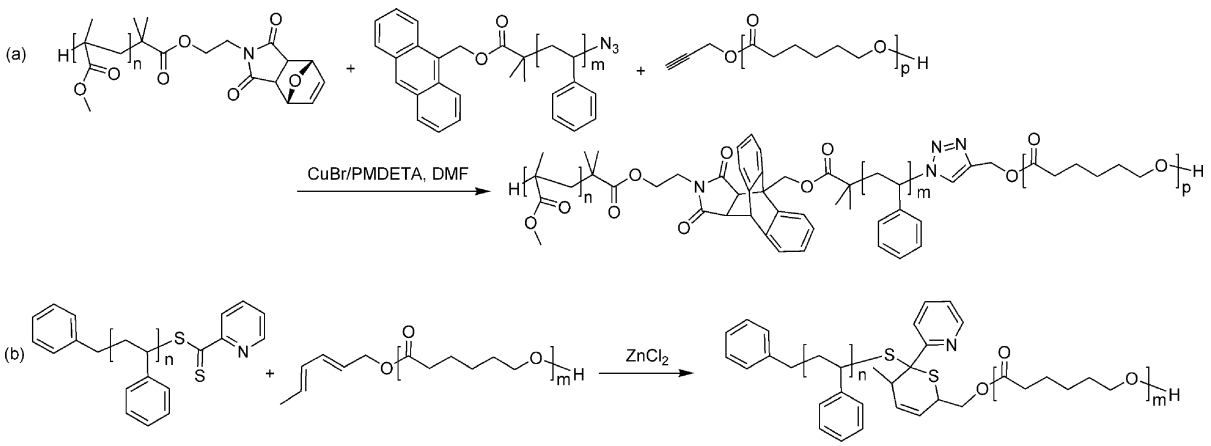
Entry	Dual-headed initiator	Comments
NMP–ROP		
11		Sequential (either way) and simultaneous polymerisation of styrene or methyl methacrylate with ε-caprolactone, catalysed by AlO^iPr_3; ε-CL first increased the reactivity of alkoxyamine.[142] Also, sequential ROP, using $AlEt_3$, of ε-caprolactone in THF then NMP of styrene in bulk.[141]
12		Sequential or one pot cascade polymerisation of ε-caprolactone or 4-methyl-ε-caprolactone by eROP (Novozym 435) in bulk then NMP of styrene in bulk.[149] Also sequential NMP of styrene or dimethylacrylamide followed by ROP of lactide catalysed by thiourea–sparteine or phosphazene base.[116,118]
13		Addition of 3 equivalents to $AlEt_3$ to produce initiator *in situ* for ROP of ε-caprolactone followed by benzoyl peroxide initiated NMP of styrene in bulk.[147] Also, isolation of Ti–TEMPO complex by addition of 4 equivalents to TiO^iPr_4 for ROP of ε-caprolactone followed by NMP of styrene in bulk; led to broad molecular weight distribution (TEMPO = 2,2,6,6-Tetramethylpiperidine-1-oxyl radical).[164]
14		One pot NMP, ROP and click of styrene, ε-caprolactone ($Sn(Oct)_2$ catalysed) and azide functional poly(ethylene glycol) (CuBr–PMDETA catalysed).[165]
15		As part of miktoarm star polymer synthesis, simultaneous NMP of styrene and ROP of ε-caprolactone catalysed by $Sn(Oct)_2$ were carried out in bulk at 120 °C.[166]
ATRP–NMP–ROP		
16		Three step sequential preparation of miktoarm stars. ROP of ε-caprolactone catalysed by $AlEt_3$ in toluene followed by ATRP of methyl methacrylate catalysed by CuCl–PMDETA at 75 °C then NMP of styrene in chlorobenzene.[167]
RAFT–ROP		
17		Simultaneous eROP (Novozym 435) of ε-caprolactone and AIBN initiated RAFT of methyl methacrylate or styrene at 65 °C in $scCO_2$.[163] Also sequential polymerisation by preparation of macro-RAFT agent by ROP of lactide by $Sn(Oct)_2$ in toluene solution then AIBN initiated RAFT of *N*-isopropyl acrylamide.[168]
18		ROP of ε-caprolactone catalysed by AlO^iPr_3 then applied as macro-chain-transfer agent (macro-CTA) for the AIBN initiated RAFT of *N*-isopropyl acrylamide.[169]
19		Sequential RAFT of 2-vinylpyridine, *tert*-butyl acrylate, methyl methacrylate and dimethylaminoethyl methacrylate using functional radical initiator then ROP of lactide from macro-initiator using thiourea–sparteine or phosphazene base catalysts.[116,118] Stereoblock PLA was synthesised at −78 °C.[162]

Table 2 (*continued*)

Entry	Dual-headed initiator	Comments
20		ROP of lactide catalysed by $Sn(Oct)_2$ in toluene solution followed by AIBN initiated RAFT of *N*-isopropyl acrylamide to produce the ABA triblock copolymer.[170]

CRP of poly(ester) macromonomers ('grafting through') that in turn can be synthesised by initiation from a hydroxy-functional vinyl monomer or post-polymerisation modification of the alcohol chain end. Graft copolymers have been obtained by the polymerisation of hydroxyethyl acrylate (HEA), hydroxyethyl methacrylate (HEMA) or hydroxyethyl acrylamide (HEAAm) monomers or copolymerisation with other (meth)acrylate or styrenic monomers. Such polymers have been obtained by all three main methods of CRP and have been applied as macroinitiators for the ROP of ε-caprolactone and lactide. In a notable deviation from this strategy, Janata and co-workers described the post-polymerisation Friedel–Crafts acylation of poly(styrene) followed by reduction to present a secondary alcohol functional poly(styrene) that was used to initiate ROP of ε-caprolactone and lactide.[179] Moderation of the hydroxy-functional to non-functional monomer ratio enables control over the graft density of the polymers and is particularly useful in enzyme catalysed graft-copolymerisation whereby steric blocking of the initiator due to its poor access to the enzyme active site results in incomplete side-chain grafting. Synthesis of PMMA-*co*-PHEMA-*g*-PCL has also been achieved in a simultaneous one-pot manner. Hedrick, Hawker and Jerome *et al.* reported the combination of Rh catalysed ATRP with AlO^iPr_3 catalysed ROP.[142] Howdle and co-workers reported comparable copolymers by the combination of Novozym 435 catalysed ROP with CuBr–bpy catalysed ATRP in $scCO_2$[90,173] and most recently Barner-Kowollik *et al.* reported the simultaneous copolymerisation of HEMA and ε-caprolactone using RAFT and $Sn(Oct)_2$.[175] In all cases free poly(ε-caprolactone) that was not incorporated into the chain could be easily removed by precipitation. The further functionalisation of the remaining free hydroxyl groups (either on poly(ester) chain ends or unfunctionalised hydroxyethyl groups on the acrylate backbone) to halide groups by reaction with bromoisobutyroyl bromide to facilitate further polymerisation by ATRP mechanisms has also been reported.[176] Furthermore, in an interesting reversal, Jerome *et al.* utilised an poly(α-chloro-ε-caprolactone) to initiate the graft polymerisation of styrene by Cu(I) catalysed ATRP.[180]

'Grafting to' approaches. The grafting/conjugation of two polymers displaying complementary functionalities can provide a simple and modular approach to block copolymer synthesis. Furthermore, this approach allows the separate synthesis of the polymers by distinct mechanisms thus enabling the maximum efficiency in their synthesis to be achieved. For this to yield well defined polymers that are not significantly contaminated with excesses of either homopolymer the coupling chemistry that is applied has to be highly efficient. The recent application of 'click' chemistry to block copolymer synthesis has enabled the facile coupling of two complementally functionalised polymers.[181–183] Tunca and co-workers have demonstrated that the coupling of an alkyne functional poly(ε-caprolactone), synthesised by the bulk polymerisation of ε-caprolactone by $Sn(Oct)_2$ and initiated by propargyl alcohol, to an azide functionalised poly(styrene), prepared by the conversion of the residual bromo end group resulting from its synthesis by ATRP with sodium azide, could be achieved efficiently in the presence of CuBr and PMDETA in DMF to perform the Huisgen cycloaddition reaction.[182] The work also applied the Diels–Alder conjugation of the



Scheme 6 'Grafting to' approach for the synthesis of poly(ester) containing block copolymers.

other anthracene functionalised chain terminus of the poly(styrene) with a maleimide-functional poly(methyl methacrylate) to simultaneously synthesise the triblock copolymer (Scheme 6a). Stenzel, Barner-Kowollik and co-workers also demonstrated that an efficient hetero-Diels–Alder cycloaddition reaction was able to be applied for the synthesis of poly(ester) containing block copolymers.[181] Here, a butadiene end functional poly(ε-caprolactone) was synthesised under enzymatic conditions, initiated by *trans,trans*-2,4-hexadien-1-ol, and directly reacted with dithioester functional poly(styrene)s prepared by RAFT polymerisation. The conjugation reactions were shown to be highly efficient, operating at 50 °C in chloroform solution and the presence of $ZnCl_2$, when a dithioester with an activating Z-group (such as *o*-pyridine or phosphoester) was used resulting in the dithioester functionality acting as both RAFT agent and heterodienophile (Scheme 6b). Metal–ligand interactions can also be applied towards the synthesis of block copolymers. Fraser, Schubert and others have demonstrated that bipyridine, terpyridine and dibenzoylmethane based initiators can be applied successfully in the polymerisation of ε-caprolactone and lactide and subsequently applied as macroligands to bring together two or more chains at a metal centre, including miktoarm star polymers bearing PMMA and PCL/PLA.[161,184]

Poly(ester)s in self-assembly

The application of block copolymers in self assembling systems has been well studied. By taking advantage of phase separation of polymers by either their incompatibility or selective solvation, tying together two (or more) polymers by their ends forces the polymers to adopt interesting morphologies and structures. The high degree of control offered by the application of controlled or living polymerisation techniques presents the ability to precisely predict and control the length scale, morphology, functionality and properties of self assembled and self ordered polymer structures. A wide range of polymers have been applied in such studies, however, by comparison to vinyl-based polymers, poly(ester)s have received relatively little attention in block copolymer self assembly. Despite this, poly(ester)s offer many potential advantages over styrenic and other hydrophobic vinyl polymers in self-assembled and self-ordered polymeric nanostructures, including biocompatibility, crystallinity, degradability under mild conditions and the ability of homochiral polymers to form stereocomplexes.

Solution self-assembly

The self assembly of di- and triblock copolymers in solution to create nanoscale organic particles has been an area of great interest in recent years.[167–171] The high degree of control over the polymer structure, length and functionality available through use of living or controlled polymerisation strategies has enabled specifically designed copolymers to be constructed to enable the realisation of a range of self-assembled nanoparticles with tailored properties. The use of noncovalent interactions to drive this assembly process is well documented and in solution is most commonly driven by the hydrophobic effect whereby the selective solvation of one polymer block in water drives the polymers to arrange in a manner that most efficiently reduces their free energy, *i.e.* whereby the water soluble blocks are solvated in the aqueous phase and the hydrophobic blocks are protected in the core of the particle. While here this is described with amphiphilic block copolymers, the same principles can be extended to other selectively soluble block copolymers. The dimensions of the resultant self-assembled particles are largely controlled by the molecular weight of the polymer blocks whereas the mole fraction of the blocks has a significant effect on the morphology of the resultant particles.[185] Manipulation of the hydrophilic fraction, f, dictates the morphology of the aggregates such that when f is large (typically $>50\%$) a spherical micellar morphology[168,171] is observed and when f is small ($f \sim 25$–40%) bilayer structures form, with spherical vesicles/polymersomes being commonly observed.[171,173] In the intermediate region ($f \sim 40$–50%), worm-like cylindrical micelle morphologies are known to form.[186] The use of polymeric materials in these self-assembling systems has enabled the facile tuning of the properties and functionality of the polymers. Manipulation of the assembly conditions and properties of the block copolymers has been demonstrated to enable access to other more complex morphologies while the use of functional polymers has allowed specific properties such as responsive behaviour to be introduced into the particles.[168] Furthermore, micellar assemblies are dynamic by their nature and hence under a change of conditions can be forced to revert back to the individual unimers. The enhanced control over functionality within the polymers and hence micelles enables the selective crosslinking of a particular domain that results in the stabilisation of the nanoparticles.[187]

The construction of poly(ester) containing nanoparticles requires their copolymerisation with functional polymers. Typically these polymers and subsequently nanoparticles are constructed from PLA or PCL blocks with poly(*N*-isopropylacrylamide),[151,153,157,160,175] poly(dimethylaminoethyl methacrylate),[132] poly(*N*,*N*-dimethylacrylamide),[143,176–178] poly(*tert*-butylacrylate),[188] poly(2-methacryloyloxyethyl phosphorylcholine),[134] poly(glycidyl methacrylate)[136] and poly(styrene)[140,141,143] being applied as the other block. In several of these examples, the poly(ester) block is used simply to render the micelle or particle fully biocompatible. In some of these cases, the application of poly(*N*-isopropylacrylamide), PNIPAAm, or poly(dimethylaminoethyl methacrylate), PDMAEMA, results in the formation of biocompatible responsive particles as a result of the responsive behaviour of the PNIPAAm which undergoes a thermal response with a lower critical solution temperature, LCST, at 32–34 °C and PDMAEMA which is responsive to pH. Several groups have reported the synthesis and micellisation of these polymers, commonly demonstrating that the responsive nature of the particles is present and that it can be applied to trigger the release of small molecules.[123,151,153,157,160,175,177] Stenzel and co-workers reported a thermally responsive PLA–PNIPAAm block copolymer that was assembled into vesicles.[168] Crosslinking stabilisation in this system was achieved by chain extension of the PNIPAAm block with hexamethylene diacrylate, possibly as a consequence of the RAFT chain transfer agent being located at the PLA–PNIPAAm interface (Fig. 5).

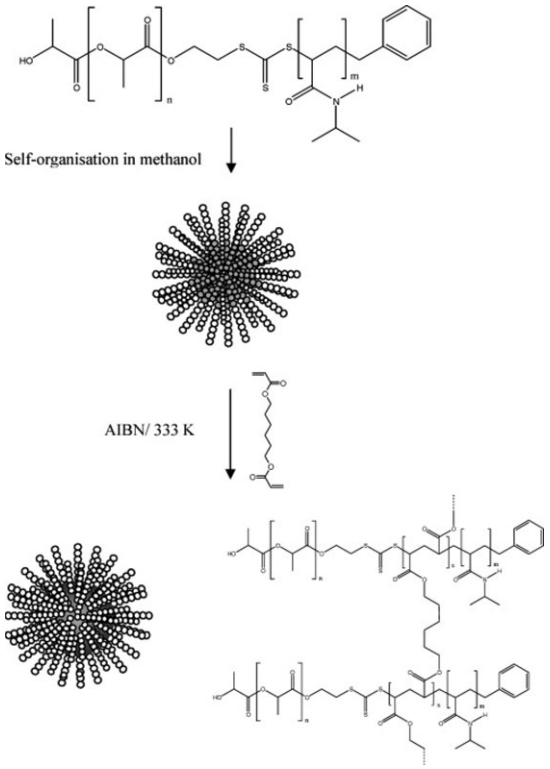


Fig. 5 Synthesis of crosslinked PLA–PNIPAAm vesicles by chain extension with hexamethylene diacrylate *via* RAFT. Figure reprinted with permission from Stenzel *et al.*[168] Copyright (2004) American Chemical Society.

Lazzaroni and co-workers have demonstrated a pH based size dependence of PCL–PDMAEMA based micelles in solution, with larger micelles observed under acidic conditions resulting from less favourable interactions between the positively charged amine groups in the polymer corona.[132] A further potential advantage of applying mechanistically distinct polymerisation strategies is the more facile synthesis of miktoarm star polymers through a dual-headed initiator approach. To this end Liu *et al.* have reported PCL–$PDMAEMA_2$ and PCL_2–PDMAEMA copolymers and studied their self-assembly into micelles.[158] In accordance with other studies in which miktoarm star polymers were applied, their results showed that the properties of these micelles were highly dependent on the chain morphology such that at comparable PCL to PDMAEMA ratios increasing the number of DMAEMA arms led to decreased micelle density and *vice versa.*

Poly(ester) containing nanoparticles have also been synthesised in which the application of the poly(ester) is specifically designed to take advantage of its degradability. This concept was first taken advantage of by Wooley and co-workers in 2000 who reported the synthesis of a poly(ε-caprolactone)-*b*-poly(*tert*-butylacrylate) copolymer.[188] After removal of the *tert*-butyl groups by selective hydrolysis either thermally or with trimethylsilyl iodide, the resultant poly(ε-caprolactone)-*b*-poly(acrylic acid) (PCL-*b*-PAA) was self-assembled in H_2O–THF and stabilised by crosslinking by amidation to yield globular shell-crosslinked (SCK) nanoparticles. Interestingly, it was noted that the size of the SCKs was largely

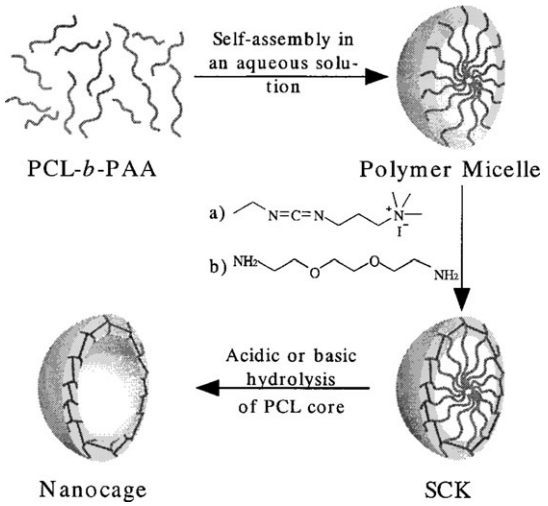


Fig. 6 Synthesis of PAA nanocages by self assembly of PCL–PAA block copolymers, crosslinking by amidation of the shell layer and core removal by hydrolysis. Figure reprinted with permission from Wooley *et al.*[188] Copyright (2000) Americal Chemical Society.

insensitive to the degree of crosslinking in the shell domain, a finding that was attributed to the reinforcement of the shape and structure of the particle resulting from the high crystallinity of the PCL core. Removal of the degradable PCL core was also possible by either acidic or basic hydrolysis and enabled the synthesis of globular 'nanocage' structures (Fig. 6). It is worthy of note that these nanocage structures have more recently been realised by the excavation of SCKs by ozonolysis of a poly(isoprene) core[189] and removal of a poly(styrene) core from a non-covalently linked SCK by

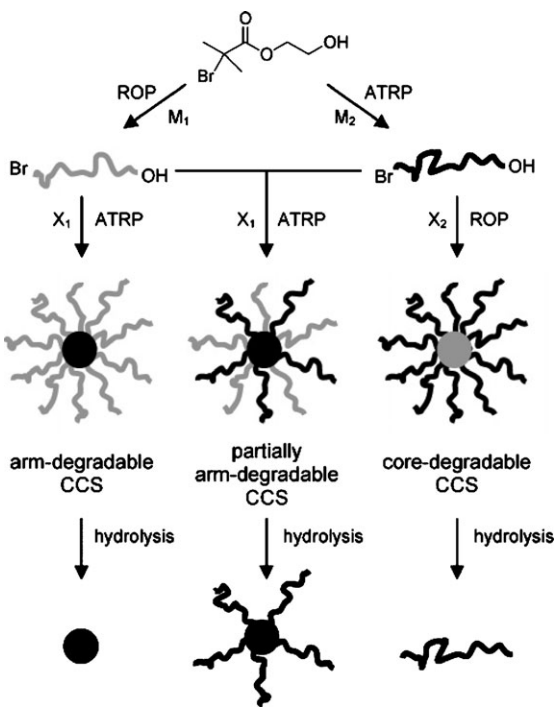


Fig. 7 Synthesis of core crosslinked star polymer particles containing degradable segments. Figure reprinted with permission from Wiltshire and Qiao.[153] Copyright (2006) American Chemical Society.

cleavage of the metal–ligand bonds at the hydrophobic/hydrophilic block interface.[190] Wiltshire and Qiao have demonstrated the synthesis of core crosslinked star (CCS) copolymers in which different domains can be selectively degraded to produce either arm-degradable, partially arm-degradable, core-degradable or fully degradable CCS polymer particles (Fig. 7).[152,153] The syntheses were achieved by the combination of ROP and ATRP to polymerise ε-caprolactone and styrene/MMA, respectively *via* a dual-headed initiator. Degradable crosslinked cores were realised by ROP of the bis-lactones 4,4′-bioxepanyl-7-7′-dione or 2,2-bis(ε-caprolactone-4-yl)-propane with non-degradable cores being achieved by copolymerisation with divinylbenzene, DVB, or ethylene glycol dimethacrylate, EGDMA. Following homopolymerisation of the polymers to form the arms by either ROP or ATRP, bifunctional monomer was added to the polymerisation mixture to result in the synthesis of CCS polymers in a two step one pot process. In the case of different arm–core combinations, different optimal ratios were required although, in accordance with other findings, short arm lengths resulted in a higher CCS yields. Furthermore, the synthesis of partially arm-degradable polymers was affected by the different reactivities of the PMMA and PCL macroinitiators such that the PCL macroinitiator was found to be more active and thus led to a greater incorporation of PCL in the final polymer. Hydrolysis of either arms or cores was performed under acidic conditions and resulted in the mild extraction of the poly-(ester) segment to leave either crosslinked nanoparticles (d_h DVB particle = 11 nm, d_h EGDMA particle = 37 nm), crosslinked nanoparticles with a tuneable number of remaining arms or liberation of the non-degradable arms. Extension of this work examined the synthesis of more complex particles with tuneable coronal degradability enabling manipulation of properties such as the size, density and chemical composition of the CCS particles. More recently, the group of Hedrick has applied poly(lactic acid) containing block copolymers to provide a simple method for the synthesis of templated inorganic nanostructures. In this study the authors synthesised a poly(*N*,*N*-dimethylacrylamide)$_{70}$-*b*-poly(lactic acid)$_{150}$, PDMA–PLA, block copolymer using a dual headed NMP–ROP initiator.[191] Under standard self-assembly conditions, the block copolymer applied would normally be expected to result in the formation of spherical micelles, however, in this study the authors examined the self assembly of the block copolymer in the presence of methyl silsesquioxane (MSSQ) in propylene glycol propyl ether (a good solvent for MSSQ and PDMA), followed by vitrification of the MSSQ to form the inorganic network and subsequent degradation of the polymer. By variation of both the concentration in solution (wt%) and the weight fraction of block copolymer to MSSQ a range of morphologies were observed by atomic force microscopy (AFM) resulting from templation by the block copolymer micelles in solution. Four distinct morphologies are observed: isolated toroids, linear wormlike features, densely pack toroids and contiguous nanoporous films (Fig. 8), with the isolated toroids and worm-like particles being observed at the low and intermediate concentration regimes. In the case of the worm-like particles, they are noted to have a continuous open channel down their length, suggesting that these features are formed by the fusion of the individual toroidal particles.

The application of poly(lactic acid) blocks also enables the synthesis of polymer blocks with specific stereochemistry. Of particular note in this respect is the application of the PLA stereocomplex, formed by the supramolecular interactions of a chain of poly(L-LA) and a chain of poly(D-LA) to provide enhanced stability to nanoscale polymer structures.

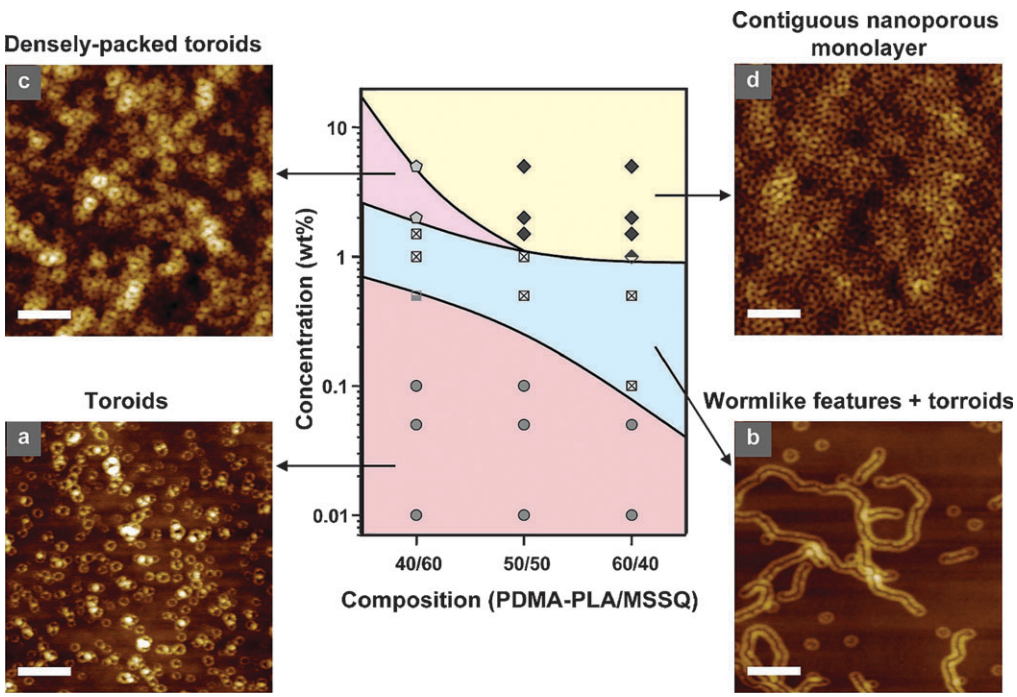


Fig. 8 AFM images of nanoparticles obtained from PLA–PDMA–MSSQ solutions after vitrification and annealing. XY scale bar on images = 300 nm, z = 10 nm (a, c, d) and 40 nm (b). Figure reprinted with permission from Hedrick *et al.*[191] Copyright (2006) American Chemical Society.

In combination with poly(ethylene glycol) and dextran these inter-chain interactions have been shown to be sufficiently strong to effect stabilisation of the physically crosslinked pluronic hydrogel materials.[192] Such polymers have also been demonstrated to be applicable in the synthesis of micellar assemblies in solution, with stereocomplexation within the micellar core demonstrated to increase the kinetic stability of the micelle in water, decrease their propensity for aggregation and decrease the size of the micelles by comparison to the homochiral PLA containing micelles.[193,194] In turn, these micelles demonstrated a higher loading capacity and encapsulation efficiency than the homochiral micelles.[194] Jing and co-workers demonstrated that the incorporation of PDLA into copolymer micelles formed from *N*-isopropylacrylamide and oligomeric enantiopure hydroxyethyl methacrylate terminated PLLAs was also able to significantly affect the size and stability of the resultant micelles.[174] In this study, micelle size was noted to be highly dependent on the incorporation of both enantiomers of PLA such that even with the incorporation of 11 wt% PDLA into the system, a decrease in the average micelle diameter from 140 to 100 nm that decreased further at 20 wt% PDLA to 80 nm was observed. A decrease in size was also observed with added PLLA (20 wt% resulting in 110 nm particles) demonstrating that the effect is partly a consequence of increased hydrophobic chain proportion and drawing the chains together by crystallisation. The additional decrease in particle size upon addition of PDLA is attributed to additional core compaction by the formation of PLA stereocomplex crystallites. Furthermore, the critical micelle concentration was also demonstrated to decrease with increased amounts of added PDLA. In contrast, Hedrick and co-workers observed an increase in dimensions of their toroidal PDMA–PLA nanoparticles upon addition of the opposite enantiomeric homopolymer to the block copolymer (*i.e.* PDLA to PDMA–PLLA).[162] The same study however, has taken advantage of stereocomplexation between PLA chains to affect association of nanoparticles bearing opposite PLA enantiomers. Solution self-assembly of PDMA–PLA block copolymers, in the presence of MSSQ was performed before spin casting the solution onto silicon wafers and organosilicate vitrification by thermolysis. Examination of the toroidal nanoparticles formed on the surface showed that those formed using a racemic mixture of PDMA–PLLA and PDMA–PDLA block copolymers displayed around a 3× increase in vertical height, measured by AFM, in comparison to single enantiomer or atactic PLA containing particles, with a concurrent decrease in surface density of the toroids (Fig. 9). This height increase was attributed to vertical stacking of multiple toroidal nanoparticles indicating that the stereocomplexation between PDLA and PLLA containing nanoparticles induces their preferential stacking.

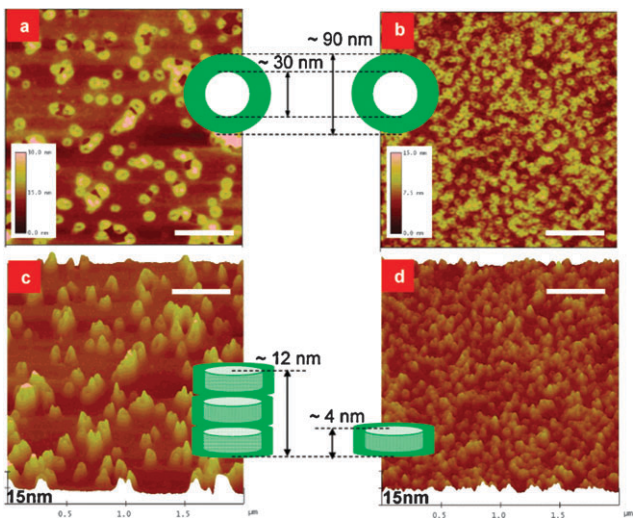


Fig. 9 Top view (a, b) and side view (c, d) AFM images of particles prepared with mixtures of poly(D-LA)-*b*-PDMA and poly(L-LA)-*b*-PDMA (a, c) and atactic-poly(LA)-*b*-PDMA, respectively. Scale bars on images = 500 nm. Figure reprinted with permission from Hedrick *et al.*[162] Copyright (2008) American Chemical Society.

Solid state self assembly (phase separation)

In the absence of solvent, block copolymers in which the blocks are chemically distinct, and commonly immiscible, are known to undergo self-assembly into a range of microphase separated structures both in bulk and in thin films. While both regimes have potential important applications, thin films have received greater attention than bulk polymers, most likely as a consequence of the increased interest in their application in nanotechnological devices. In the case of the most simple class of block copolymers, AB copolymers, the thermodynamic incompatibility between the two blocks is responsible for driving the blocks to phase separate in order to maximise the interaction between like blocks and hence minimise the free energy of the system. In these cases, the covalent tether between blocks prevents the macrophase separation of the individual aspects and leads to some interesting and useful features both in bulk and thin films. The morphology of the microphase separated systems is defined by the molecular weight of the blocks, the mole fraction of the two polymers, f_a and f_b, respectively, and the temperature dependent Flory–Huggins interaction parameter, χ. Commonly these block copolymers phase separate into body centred cubic spheres in a matrix of the opposite block, cylinders of one polymer in a matrix of the opposite block as well as bicontinuous gyroidal and lamellar phases (Fig. 10).[2–4,195] While other phases can be observed, these are generally less stable. Triblock copolymers add a further level of complexity to the system and are known to phase separate into a wider range of structures. In thin film and bulk phase separation, poly(ester)s have been primarily applied as a 'soft etch' porogen to generate nanoporous materials, whereby their application is desirable due to their facile removal from the microphase separated polymer.[4] While several other polymers can be selectively degraded from mixtures, commonly poly(methyl methacrylate) or poly(isoprene), the conditions for their removal can require demanding chemistries such as ozonolysis or UV irradiation that can also cause unwanted side reactions. Conversely, poly(ester)s are both easy to synthesise and can be readily degraded under mild acidic or basic conditions, thereby not adversely affecting other embedded functionality. In addition, hydrolytic degradation methodologies also lend

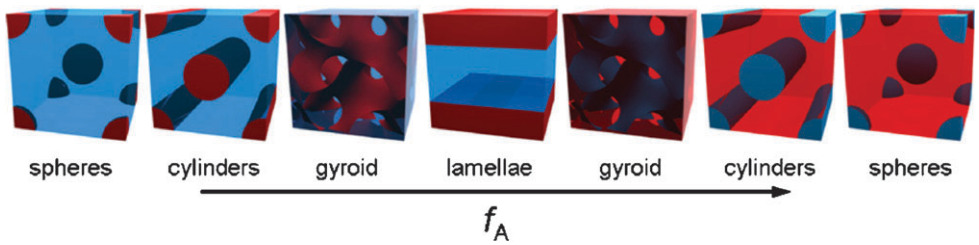


Fig. 10 Schematic representations of the stable diblock copolymer phases, each colour represents one polymer block. Figure reprinted from Darling.[2] Copyright (2007) with permission from Elsevier.

themselves more readily to degradation in thicker/bulk samples, a potential limitation of the other degradation methodologies.

Several di- and triblock copolymers containing poly(ester)s have been reported for use in solid state phase separation. Most commonly these are copolymers of PLA or PCL with poly(styrene), PS,[147,178,196–201] although a range of other copolymers have also been reported including poly(isoprene), PI,[202–204] PLA-*b*-poly(dimethylacrylamide),[205] PCL-*b*-poly(dimethylethylamino methacrylate),[132] PLA-*b*-poly(acrylonitrile),[160] PLA-*b*-poly(PEG methacrylate),[206] PLA-*b*-poly(cyclohexylethylene),[207] PLA-*b*-poly(3-alkylthiophene)[208] and PLA-*b*-poly(butadiene).[209] Triblock copolymers have included PI-*b*-PS-*b*-PLA210 and PLA-*b*-poly(dimethylacrylamide)-*b*-PS.[137] Hillmyer *et al.* have demonstrated the application of PS–PLA materials in the generation of nanoporous templates in bulk polymers and thin films.[196–198] The facile degradation of the PLA segments in methanol–water sodium hydroxide solution above the T_g of the PLA resulted in removal of the poly(ester) evidenced by NMR spectroscopy and GPC. Under these conditions the PS showed no alteration in its morphology, notably in the absence of any crosslinking of the PS component, and was shown to be a nanoporous material by small angle X-ray scattering, SAXS, and scanning electron microscopy, SEM (Fig. 11).[196] Further investigations by this group demonstrated that the morphology map for PS–PLA copolymers was as expected for simple coil–coil copolymers.[197] Furthermore, this report details the alignment of the pores by both reciprocating shear and channel die alignment, type and density of defects in the materials, tuneability of pore size and high temperature stability of the PS matrix. Ho *et al.* examined the effect of the helicity of pure poly(L-lactic acid) in PS–PLLA block copolymers on the self-assembling structures thereby formed.[199] The authors report that well organised, hexagonally packed PLLA nanocylinders were formed in the bulk under specific volume ratios *i.e.* $f_{PLLA}{}^{v} = 0.35$. The diameters of the nanohelices (imaged by transmission electron microscopy, TEM) were determined as 43.8, 31.9 and 25.3 nm on average. This behaviour was tentatively attributed to the formation of specific configurations of PLLA chains due to interactions of chiral entities comparable to the formation of helical crystals from chiral liquid crystalline polymers. The nanohelical structure was retained upon removal of the PLA. At higher PLLA volume fractions ($f_{PLLA}{}^{v} = 0.65$) this behaviour expresses itself to present a core-shell through a bilayered microstructure brought about as a result of the helicity of the PLLA fraction.[200] Hydrolysis of the PLLA resulted in the formation of hollow PS cylinders. PI–PLA block copolymers have a very high χ (approx. 5 times that of PI–PS) and therefore provide a system that should enable the attainment of block copolymer monoliths and films in which phase separation is possible at lower molecular weight; thus enabling the realisation of smaller PLA domains (and hence pores) and a greater pore density.[202–204] Russell *et al.* have demonstrated that PI–PLA diblock copolymers are able to provide films that display improved long range ordering after solvent annealing.[202,203]

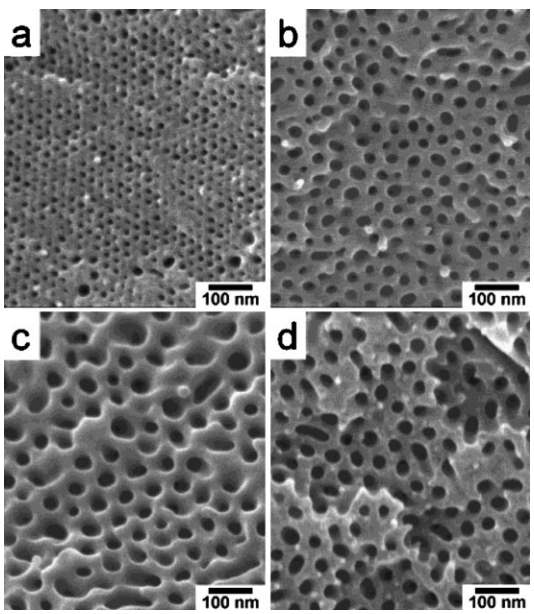


Fig. 11 SEM images perpendicular to the cylinder axes of nanoporous materials prepared from PLA–PS block copolymers. Figure reprinted with permission from Hillmyer *et al.*[197] Copyright (2002) American Chemical Society.

The further introduction of functionality to the walls of the nanoporous polymer matrices is possible using a range of methodologies. The most simple is the post-degradation modification of the walls of the nanostructured materials. The mild degradation methodologies applied are anticipated to result in the presence of free hydroxyl groups present on the walls of the structures (Fig. 12a).[197] This functionality can be tailored to control the nature of the chemical groups at the surface of the polymer structures. Hillmyer *et al.* estimated from the BET-determined surface area that the resultant areal density of the OH groups on the pore walls was 0.25 nm^{-2} (*i.e.* 1 OH

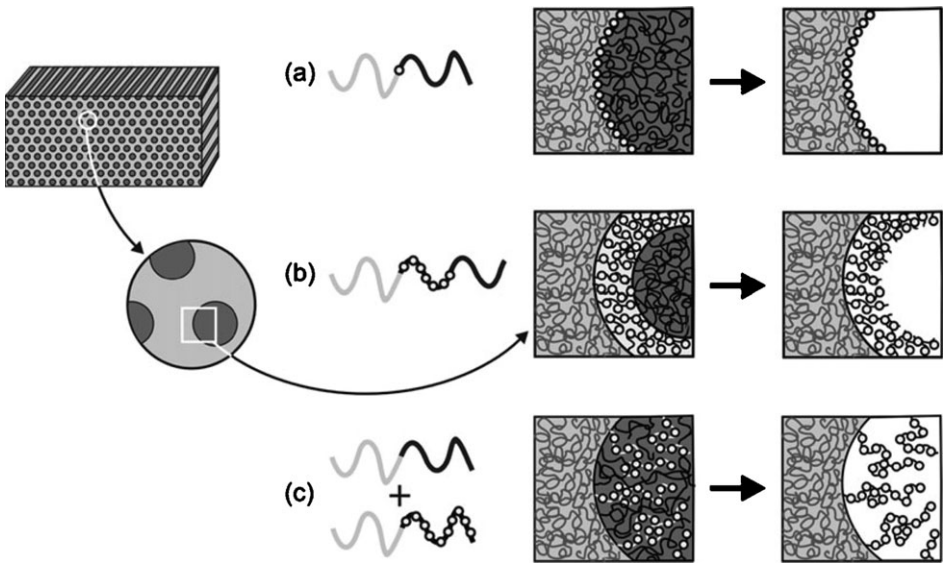


Fig. 12 Schematic representations of routes to wall-functionalised nanoporous materials. (a) Manipulation of the wall functionality post-degradation; (b) from diblock mixture approach whereby one block remains after degradation; and (c) application of triblock copolymers. Figure reprinted with permission from Hillmyer *et al.*[211] Reproduced by permission of The Royal Society of Chemistry.

group per 4 nm^2), assuming that all OH groups remain at the pore surface. The accessibility of that functionality was determined by submersion of the nanoporous monolith in trifluoroacetic anhydride (a non-solvent for PS). Functionalisation was confirmed by the observation of the carbonyl stretch of the trifluoroester by IR spectroscopy and the maintenance of the nanoporous structure confirmed by SAXS.[197] Both diblock copolymer blends or triblock copolymers can be applied to produce nanoporous polymers with selected functionality at the air–polymer interface (Fig. 12b and c). Self-ordering of PS–PLA and PS–PEO (up to 12 wt% poly(ethylene oxide) PEO) blends led to cylindrical domains of PLA/PEO in PS, a result of the miscibility of the PLA and PEO components.[211] Upon degradation of the PLA segments, a nanoporous poly(styrene) remained in which the pores were coated with poly(ethylene oxide). Synthesis of triblock copolymers with a terminal PLA block also enables the synthesis of nanoporous materials with tailored pore surface chemistry. Hillmyer and co-workers have demonstrated that PS–PDMA–PLA and PS–PI–PLA triblock copolymers provide ABC block copolymers that in the correct ratios can be phase separated to form cylindrical matrices such that the A block provides the matrix, B block the pore lining and C block the degradable porogen.[137,210] In the case of the PS–PDMA–PLA copolymer matrix,[137] basic hydrolysis selectively removed the poly(ester) whereas acidic hydrolysis also resulted in the conversion of PDMA to PAA. Furthermore, the PDMA or PI wall coatings could be readily altered to display a range of functionalities.

In common with all nanoporous materials, the stabilisation of the nanoporosity is of great concern. Despite the mild conditions applied for removal of the poly(ester) component, heating a nanoporous monolith or thin film above the T_g of the polymer or exposure to a good solvent for that polymer destroys the porosity. Obviously the application of a higher T_g or less soluble polymer is a good option for the synthesis of more stable nanoporous networks. Wolf and Hillmyer demonstrated this by the synthesis of poly(cyclohexylethylene)-*b*-poly(lactic acid) copolymer monoliths with the subsequent removal of the PLA. The more thermally stable poly(cyclohexylethylene) (T_g 147 °C *vs.* 100 °C for PS) was also more resistant to organic solvents such as pyridine, ethyl acetate and acrylic acid.[207] The introduction of crosslinking into the matrix domain of the block copolymer can also be applied to increase the stability of the nanoporous films. To this end, Cavicchi and Russell showed that the crosslinking of the poly(isoprene) domain of a cylindrical PLA in a PI matrix with sulfur monochloride vapour led to films that were insoluble in organic solvents.[202] Hillmyer *et al.* adopted an alternative approach in which bicontinuous gyroidal phases of PLA–PS were stabilised by the combination of polymerisation induced phase separation (PIPS) and the application of a doubly reactive block copolymer.[201] In this study, a PLA-*b*-poly(styrene-*co*-*p*-norbornenylethylstyrene) was synthesised. Upon combination with dicyclopentadiene and the second generation Grubbs metathesis catalyst, gel formation was observed that after curing resulted in an optically transparent film. Removal of the PLA component by degradation resulted in a stable nanoporous film.

The crystallinity of the poly(ester) segments can also have an effect on the morphology of the polymeric structures in the solid state. Lazzaroni and co-workers have studied the supramolecular organisation of PDMAEMA–PCL block copolymers.[132] While casting thin films onto mica from acidic (pH 4) micellar solutions, conditions under which the PDMAEMA corona will be positively charged, leads to a continuous deposit, casting films from basic solutions (pH 7.4–8) results in a more complex morphology. Under these conditions the PDMAEMA coronas are expected to be uncharged, thus exhibiting less repulsion leading to aggregation of the spherical micelles present in solution into micrometre long cylindrical objects, postulated to be driven by the more favourable packing of the crystalline poly(ε-caprolactone) core. Zhu *et al.* described the application of mixed poly(L-LA)-*b*-poly(ethylene oxide) and poly(D-LA)-*b*-poly(ethylene-*co*-1-butene)

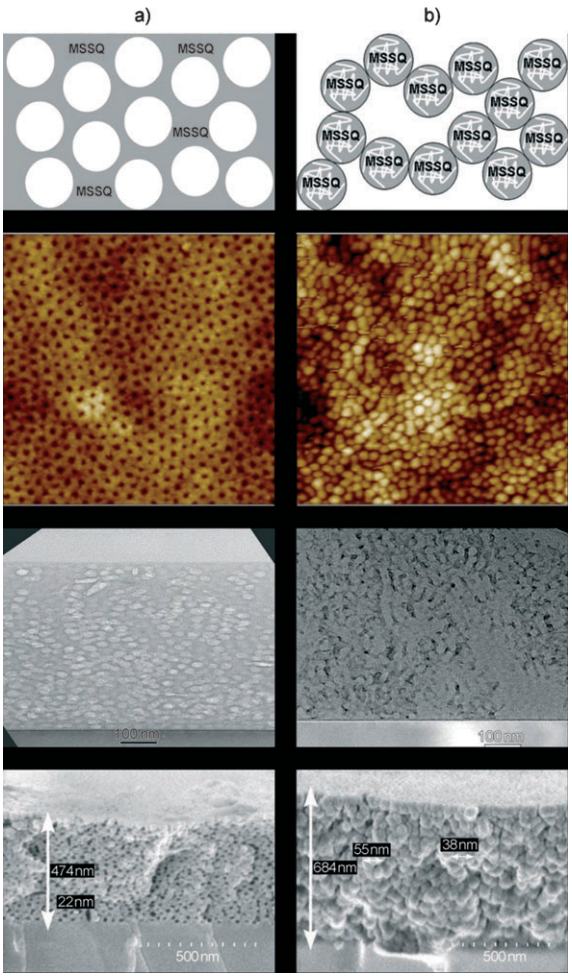


Fig. 13 AFM (2nd from top), TEM (3rd from top) and SEM (bottom) images of (a) micellar and (b) inverse micellar nanostructured materials prepared from PLA–PDMA–MSSQ mixtures. Figure reprinted with permission from Hedrick *et al.*[205] Reproduced with permission of Wiley-VCH.

to control lamellar curvature. Blending the polymers and annealing above the melting point of the stereocomplex led to the observation of onion-like crystal domains being formed with a curved non-centrosymmetric lamellar structure.[209]

Nanoporous polymer synthesis in this manner provides access to a range of interesting materials. Phase separation followed by removal of the PLA from a PLA-*b*-poly(acrylonitrile)[160] film potentially provides an interesting route to mesoporous carbon materials whereas PLA-*b*-poly(thiophene) materials offer interesting opportunities in the field of organic electronics.[208] Hedrick *et al.* have taken advantage of the affinity of the organosilicate precursor, methyl silsesquioxane (MSSQ), towards polar, basic polymers that display an ability to hydrogen bond, thus promoting strong interactions between organosilicate precursor and polymer to form silica based, low dielectric constant materials. Hedrick, Miller and co-workers have applied dendritic initiators for the synthesis of star shaped PCL-*b*-poly(PEG methacrylate) block copolymers.[206] These star shaped copolymers do not display the same complex self-assembly behaviour as diblock copolymers, forming unimolecular micellar morphologies in solution that generate highly porous silicates upon casting films after mixing with MSSQ in propylene glycol propyl ether, vitrification and PLA removal. Hedrick *et al.* have also taken advantage of the affinity of MSSQ for PDMA to produce highly porous silicate materials from PDMA–PLA block copolymers.[205] In this way, pre-mixing the MSSQ with diblock copolymers of PDMA–PLA in propylene glycol propyl ether (a good solvent for PDMA but a poor solvent for PLA) or butyl acetate (a good solvent for PLA but a poor solvent for PDMA), spin-coating the solution onto silicon wafers, annealing at 50 °C to vitrify the silica then thermally degrading the PLA, resulted in the formation of porous silica films and packed silica nanoparticles, respectively (as evidenced by TEM, SEM and AFM, Fig. 13). SAXS analysis of the films indicated that propylene glycol propyl ether cast films were relatively ordered well-defined spheres whereas the butyl acetate cast films were

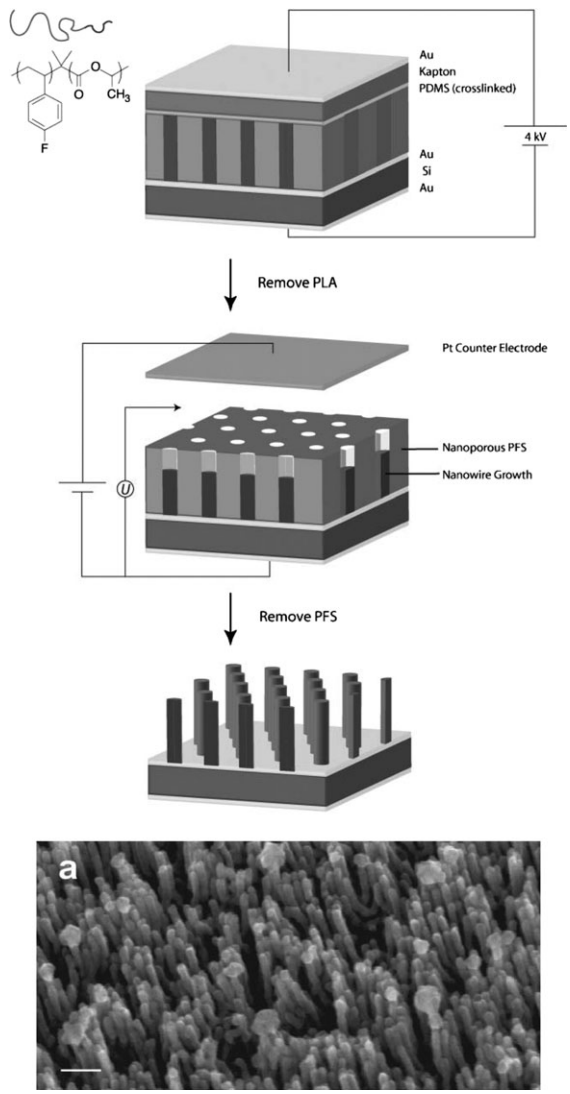


Fig. 14 Top: schematic of Cu_2O/Cu nanowires formed by degradation of PLA from a cylinder forming PLA–PFS block copolymer, nanowire growth and removal of remaining polymer by dissolution. Bottom: SEM images of freestanding Cu_2O/Cu nanowires. Figure reprinted from Steiner *et al.*[212] Reproduced by permission of The Royal Society of Chemistry.

relatively disordered spheres that displayed little long range ordering. Further application of this chemistry also led to the formation of nanoporous silica thin films formed from contiguous monolayers of toroidal particles using high polymer/MSSQ concentrations.[191] Steiner *et al.* have applied a cylinder forming poly(4-fluorostyrene)-*b*-PLA to synthesise Cu/Cu_2O nanowire arrays (Fig. 14).[212] Following annealing and alignment of the PLA cylinders by applying an electric field, the PLA was removed by basic hydrolysis to yield a nanoporous poly(4-fluorostyrene), PFS, thin film. Cu_2O was electrochemically deposited into the pores before the poly(4-fluorostyrene) matrix was removed by simple dissolution to leave the Cu/Cu_2O nanowire arrays.

Conclusions and outlook

The potential for the application of poly(ester) containing block copolymers in nanotechnological devices is clear. Such polymers provide unique opportunities as a consequence of their 'soft etch' degradability, controllable crystallinity including access to stereocomplexes, as well as their biocompatibility. The many recent advances in methodologies for their synthesis are making poly(ester)s more accessible and in combination with the potentially unique features offered by this class of polymer are beginning to deliver new methodologies and technologies. While at present, little functionality is introduced through the poly(ester) segment of the nanostructured materials, the increasing interest and exciting developments in the synthesis of functional degradable materials[17,26,213] is creating opportunities for more complex or entirely poly(ester) based nanoparticles and nanostructured materials.[214]

Acknowledgements

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