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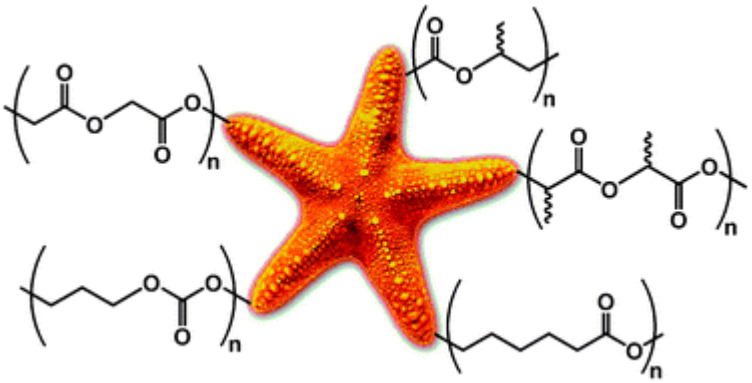
Aliphatic Polyester Polymer Stars: Synthesis, Properties and Applications in Biomedicine and Nanotechnology**

Donald J. A. Cameron[1] and Michael P. Shaver[1,*]

[1]Department of Chemistry, University of Prince Edward Island, 550 University Avenue, Charlottetown, PEI, Canada.

[*]Corresponding author; (current address): Michael.Shaver@ed.ac.uk, EaStCHEM, School of Chemistry, Joseph Black Building, University of Edinburgh, West Mains Road, Edinburgh, EH9 3JJ, UK.

Graphical abstract:



Abstract

A critical review. The ring-opening polymerization of cyclic esters provides access to an array of biodegradable, bioassimilable and renewable polymeric materials. Building these aliphatic polyester polymers into larger macromolecular frameworks provides further control over polymer characteristics and opens up unique applications. Polymer stars, where multiple arms radiate from a single core molecule, have found particular utility in the areas of drug delivery and nanotechnology. A challenge in this field is in understanding the impact of altering synthetic variables on polymer properties. We review the synthesis and characterization of aliphatic polyester polymer stars, focusing on polymers originating from lactide, ε-caprolactone, glycolide, β-butyrolactone and trimethylene carbonate monomers and their copolymers including coverage of polyester miktoarm star copolymers. These macromolecular materials are further categorized by core molecules, catalysts employed, self-assemby and degradation properties and the resulting fields of application.

Introduction

Star polymers are branched, multi-armed polymeric materials in which the branches radiate from a central core. They have attracted significant attention across multiple fields of chemistry, biochemistry and engineering because they exhibit useful rheological, mechanical and biomedical properties that are inaccessible in linear polymers.[1,2] Polymer stars offer an increased concentration of functional end groups for polymers of equal molecular weight, have improved solubility and exhibit differences in hydrodynamic volumes. They often have lower melt viscosities, different thermal properties and improved physical processing, as viscosity and other properties are more influenced by arm molecular weight than the total molecular weight of the polymer star.[3] These star polymers were first developed in 1948 by Flory *et al.* who synthesized four- and eight-arm star polymers of ε-caprolactam,[4] eventually ushering in a robust age of research in this area.

Three methods may be employed for star polymer synthesis, as shown in Figure 1.[2] The core-first method involves the living polymerization of a reactive monomer in the presence of a multi-functional initiator. In this instance the polymer chains are grown directly on the core. The arm-first method will couple linear polymer chains with a reactive core molecule. This method can operate by using a multi-functional reagent to terminate linear living polymers, or can exploit the latent reactivity of telechelic linear polymers to chemically attach the polymer arms to the core.

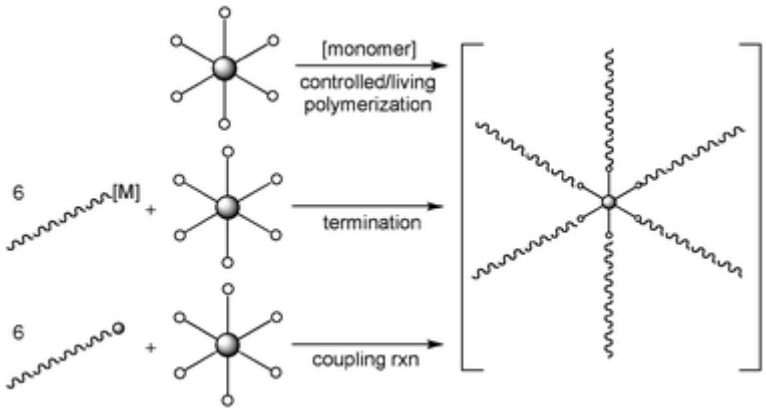


Figure 1. Synthetic methodologies for the synthesis of polymer stars.

One of the most important classes of polymer stars are built from aliphatic polyesters. Their prevalence is partially derived from their relative ease of synthesis, with multi-functional alcohols providing readily available reagents to initiate the ring-opening polymerization (ROP) of cyclic esters in a core-first approach to polymer synthesis. Polymer stars have been prepared from the monomers lactide (**1**), caprolactone (**2**), glycolide (**3**), β-butyrolactone (**4**) and trimethylene carbonate (**5**) as well as other, more esoteric cyclic esters (Figure 2). Ring-opening polymerization of these monomers is initiated by an alcohol and catalyzed by a metal complex to form an active metal alkoxide that follows a coordination-insertion mechanism.[5,6]

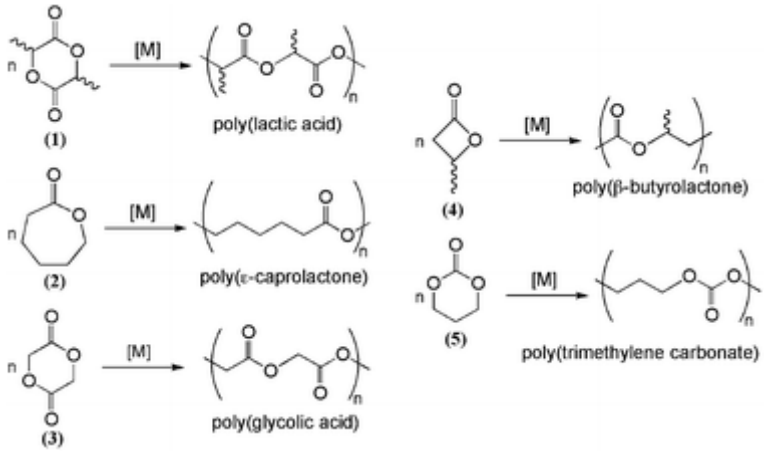


Figure 2. Cyclic ester monomers and their homopolymers.

Interest in the corresponding linear polymers is derived primarily from their renewability, biodegradability and bioassimilability. The polymers are readily hydrolyzed to form the corresponding hydroxyacids,[5,6] many

of which are metabolized through the citric acid cycle. Poly(lactic acid), PLA, is derived from the ring-opening polymerization of lactide, a monomer which exists in three diastereomeric forms. The most common, and least expensive form is *rac*-lactide, a racemic mixture of the *R,R* and *S,S* forms. When polymerized, atactic, heterotactic and isotactic chains exhibit strikingly different crystallinity, thermal properties and degradability. Similarly, poly(β-butyrolactone), PβBL, is derived from a chiral source. While isotactic PβBL is produced via a bacteria-mediated polymerization, metal mediated-ring opening polymerization provides access to an array of microstructures.[5] In addition, the γ-butyrolactone monomer posesses no stereocentres but has found some application in this field as poly(γ-butyrolactone), PγBL. Poly(ε-caprolactone), PCL, polyesters have low melting points (T_m) and glass transition temperatures (T_g) and have found significant applications in hobbyist and biomedical fields.[7] Poly(glycolide), PGL, polyesters are readily degraded and have found less use as a homopolymer, appearing predominantly as copolymers with lactide, glycolide and trimethylene carbonate monomers.[8] Poly(trimethylene carbonate), PTMC, is an elastomeric material with predominantly biomedical applications.[8] For each of these homopolymers and their copolymers, materials properties and applications change significantly when the macrostructure is altered into a star polymer.[1] Aliphatic biodegradable star polymers have found particular utility as controlled release drug delivery systems and in nanotechnology applications.

In the organization of this review, polymer stars are first separated by monomer type. Poly(lactic acid), poly(ε-caprolactone), poly(glycolic acid), poly(β-butyrolactone) and poly(trimethylene carbonate) homopolymers are presented first followed by copolymers containing multiple polyesters. For each monomer, discussion materials are divided by the nature of the core molecule, the catalyst employed and the properties of the material. Finally, polymer stars are delineated based on their aggregation behaviour and physical properties. While the focus is on the synthesis and properties of these stars, the review highlights key applications in biomedicine and nanotechnology but does not cover solely applied work. This review concerns star polymers and purposefully avoids comprehensive coverage of dendronized[9] and hyperbranched[10] polymers, both of which have been recently reviewed. This review is focused on recent advances in the ring-opening polymerization of cyclic esters to form star polymers and is meant to be a comprehensive review of work published since 1995, with particular emphasis on the seminal advances which form the foundation for future discoveries.

Poly(lactic acid) polymer stars

Poly(lactic acid) is a biodegradable polymer traditionally synthesized from the ring-opening polymerization of lactide monomers. While this polymer can be produced through a condensation polymerization of lactic acid,[5,6] this is an uncontrolled process requiring a high energy input. Driven by the release of ring strain, and

catalyzed by a Lewis acidic metal or organic mediator, the ROP of *rac*- or l-lactide accesses controlled molecular weight, low PDI macromolecules.

Although star polymers were first reported in 1948, the first such PLA macromolecule was prepared in 1989,[11] and intenstive research in this area has only taken place during the past decade. The marked rise in interest with respect to star-shaped PLAs and other macromolecular PLA frameworks is due to their unique properties when compared to linear homopolymers. Specifically, star polymers exhibit lower melting temperatures (T_m), glass transition temperatures (T_g), and crystallization temperatues (T_c) than their linear counterparts.[6,12] In addition, star-shaped polymers of PLA exhibit coiling, have lower hydrodynamic volumes and have higher viscosity than linear PLA.[12] A stronger correlation between viscosity and temperature is also noted, with the entanglement of arms suppressing longitudinal motion.[13]

PLA polymer stars are categorized with respect to core, differentiated into discrete, polymeric, miktoarm and dendritic/hyperbranched cores. In almost all systems presented the classic tin(II) ethylhexanoate (stannous octanoate, $Sn(Oct)_2$) is used. It is a ubiquitous catalyst in aliphatic polyester synthesis that produces atactic PLA chains.

Discrete cores

In this context discrete cores are small molecules containing multiple hydroxy functionalities used to initiate the ring opening polymerization. These initiators are often termed polyols if derived from sugar alcohols. The simple polyols pentaerythritol (PE) and dipentaerythritol (DPE) are most commonly used and produce four- and six-armed polymer stars respectively. The field is certainly not limited to these cores, with many other simple polyols, cyclodextrins, cholic acids and metal-centred cores employed.

A comprehensive list of the polyols for PLA stars includes PE,[12,14-24] DPE,[17,19,20,25-29] 3-armed stars based on trimethylolpropane (TMP) and glycerol,[15,17,22-25,30-31] 4-armed stars based on diTMP and erythritol,[17,30] 5-armed stars based on xylitol,[30] 6-armed stars based on inositol and sorbitol,[22,30] and 8-armed stars based on tripentaerythritol (TPE) and a modified diTMP.[17,32] These cores are shown in Figure 3.

The polymeric and thermal characterization for polyol PLA stars is summarized in Table 1. For the purposes of brevity we have only included PLA star polymers that report thermal data. These stars with extensitve thermal characterization were all generated from the isopure l-lactide using the $Sn(Oct)_2$ catalyst. The table includes phase transition temperatures along with percent crystallinity (X_c).

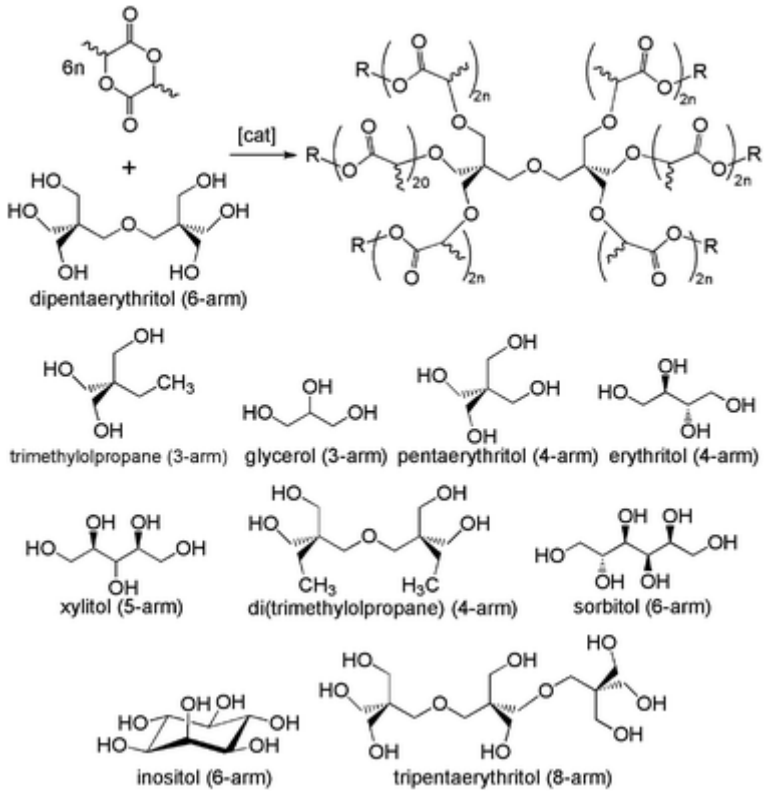


Figure 3. Polyol cores in PLA star polymer synthesis.

Table 1. Characterization data for PLA polymer stars. [a]

Core	**M_n**	**PDI**	**T_g (°C)**	**T_c (°C)**	**T_m (°C)**	**X_c (%)**	**Ref**
Glycerol	17400	1.78	55.9	109.5	160.2	-	25
Glycerol	21200	1.56	53.7	100.8	157.2	38.7	15
Glycerol	8600	1.19	-	-	126.6	-	30
PE	1940	1.97	60.6	107.3	179.1	51.9	12
PE	20200	1.94	50.5	115.2	160.2	-	25
PE	31700	1.75	58.2	98.0	162.1	44.4	15
PE	165000	1.90	53.0	93.0	172.0	-	12
PE	13250	1.05	51.4	105.4	153.2	48.3	20
Erythritol	8300	1.12	-	-	112.5	-	30
Xylitol	8300	1.10	-	-	113.1	-	30
DPE	29800	1.43	55.3	118.3	152.4	-	25
DPE	12700	1.10	49.3	100.5	147.7	41.0	20, 26
Sorbitol	8500	1.09	-	-	114.8	-	30
TPE	52800	1.81	57.6	101.4	166.3	-	25

[a] l-lactide, $Sn(Oct)_2$ catalyst

A few trends can be garnered from the reported data. We can see that the molecular weight distributions of selected samples are often very good with significant deviations at the low and high extremes of molecular

weight evidenced by narrow PDIs (<1.2). This is a strong indication of the concurrent initiation of ROP at all OH groups present in the core and the good control offered by $Sn(Oct)_2$. Catalyst loading correlates to deviations from ideal molecular weight distributions, with both low and high catalyst:initiator ratios resulting in anomalous PDIs.[9,12] Confirmation that all alcohol functionalities have initiated is verified by ^{1}H NMR spectroscopy in most cases.

Trends in thermal properties are also observed. The value of T_g more closely correlates to molecular weight than the specific core or the number of arms present in the PLA star. For PlLA stars prepared under similar conditions the T_g ranges from 49 °C (M_n = 12700) to 58 °C (M_n = 31700), although significantly lower temperatures would be expected for *rac*-lactide stars when correlating to the behaviour of linear PLA systems.[6] In addition, increased control over the ROP results in lower T_g indicating that polymer star uniformity has an important role in controlling the thermal properties.

The crystallization behaviour of some stars has also been studied. Here it can be noted that the choice of core has a larger effect on the values of T_c. PE-based PlLAs have lower T_c values than DPE-based PlLAs, even when PE-based stars have higher molecular weights.[15,25] For a specific core, however, an increase in molecular weight will lead to an enhancement of T_c. The same holds true for melting temperatures of star PlLAs. An increase in M_n will lead to an enhancement of the melt properties of the material. A report detailing the preparation of 3-, 4-, 5- and 6-armed PlLA star polymers suggests little impact on the number of arms and T_m.[30] While the number of arms had a significant impact on crystallization rates, no other thermal data was reported. Even less work has been reported about the crystallinity of these polyol stars.

One challenge in bringing together this data is that there seems to be little batch-to-batch consistency amongst star PlLAs. This is predominantly due to differences in experimental design, catalyst loadings and monomer:initiator ratios. A more systematic approach to understanding the impact of core, catalyst, molecular weight and and molecular weight distribution is needed to systematize these materials.

Towards this end, a recent report details the role of polymer tacticity and monomer feedstock on the properties of DPE-based PLA star polymers.[29] The report is focussed on the synthesis of PLA stars using $Sn(Oct)_2$ and *rac*-lactide to produce atactic stars, $Sn(Oct)_2$ and l-lactide to produce isotactic(l) stars, the catalyst ^{Cl}[salan]AlMe (^{Cl}[salan] = *N,N′*-ethylenebis(benzyl)bis(3,5-di-chlorosalicylamine)) to produce heterotactic stars and the catalyst ^{tBu}[salen]$AlMe_3$ (^{tBu}[salen] = *N,N′*-ethylenebis(3,5-di-*tert*-butylsalicylimine)) to produce isotactic(*rac*) star polymers. The important data are summarized in Table 2. T_g values varied across 11 °C between atactic, heterotactic, isotactic(*rac*) and isotactic(l) samples, while T_m and T_c values for isotactic-biased samples showed significant differences between isopure stars and those with stereoerrors. Significant differences were also noted in the crystallite size and d-spacing determined from powder-XRD. Small differences attributable to changes in sample M_n were noted, but differences associated with stereochemical changes were significantly larger in each case.

Table 2. Microstructure control in PLA polymer stars. [a]

Bias	**M_n**	**PDI**	**T_g (°C)**	**T_c (°C)**	**T_m (°C)**
Atactic	8873	1.14	39.9	-	-
Atactic	9058	1.18	37.3	-	-
Heterotactic	8755	1.26	41.5	-	-
Heterotactic	8240	1.19	41.4	-	-
isotactic(*rac*)	8501	1.22	43.7	84.2	114.5, 134.4
isotactic(*rac*)	8688	1.22	43.3	-	117.2, 128.5
isotactic(l)	8771	1.18	48.2	96.9	132.0, 142.9
isotactic(l)	8691	1.08	47.7	-	122.9, 137.4

[a] Dipentaerythritol core, 60:1:0.6 monomer:initiator:catalyst ratios.

This report highlights the importance of the catalyst on the control of ROP of cyclic esters in polymer star synthesis. While nearly all reports use $Sn(Oct)_2$ to promote star formation, alternatives do exist. Enzymatic catalysis using lipase *Pseudomonas fluorescens* was used to produce four- and six-armed polymer stars based on pentaerythritol and inositol respectively.[22] Spirocyclic tin initiators based on tin-substituted polyethylene ethoxylate[33,34] and a cyclic stannoxane[35] have also been used successfully. *N*-heterocyclic carbenes[36] and dimethylaminopyridine (DMAP)[37] were used as organic catalysts in PLA star synthesis to prepare four-armed stars from amine substituted poly(ethylene glycol)s and six-armed stars from a luminescent ruthenium complex respectively. The aforementioned aluminum salen and salan complexes access stereocontrolled PLA stars[29,38] while zinc amino- and thio-phenolate[39,40] and bis(calcium)pentaeryth-ritol[41] catalysts expand the range of metal-based mediators of PLA star synthesis.

While the nature of the core and catalyst play an important role in PLA star polymer properties, the terminating end-group of star arms has a significant effect, especially on hydrolytic degradation stability. The hydrolyic degradation of star-shaped PLAs is a key factor to control in utilizing these materials in controlled release drug delivery systems. Solution stability of star-shaped polymers and their resistance to hydrolytic degradation was studied by comparing OH, Cl, NH_2 and COOH terminated PLAs.[15] The cold crystallization temperatures of Cl-, NH_2- and COOH-terminated PLAs were higher than OH counterparts. The same star polymers also possessed enhanced thermal stability when compared to hydroxy terminated chains. Cl and NH_2 end-groups were the most resistant to hydrolytic degradation. In addition, as the number of end groups increased, moving from small star to hyperbranched and dendritic systems, the end-group trends were enhanced. This work is summarized in Table 3.

Table 3. Terminating end-group effect on PLA polymer star properties. [a]

Term.	Core	M_n	PDI	T_g (°C)	T_c (°C)	T_m (°C)	ΔH_m [b]
OH	Glycerol	21200	1.56	53.7	100.8	157.2	40.9
Cl	Glycerol	21300	1.56	57.1	126.8	159.1	33.9
NH_2	Glycerol	20200	1.56	52.3	111.5	156.9	42.0
COOH	Glycerol	18800	1.76	53.2	121.9	155.3	32.9
OH	PE	31700	1.75	58.2	98.0	162.1	47.4
Cl	PE	32400	1.73	58.3	128.5	163.5	39.4
NH_2	PE	33700	1.61	55.2	123.2	161.7	40.3
COOH	PE	33200	2.14	53.7	125.0	159.4	34.6

[a] $Sn(Oct)_2$ catalyst, l-lactide. [b] Enthalpy of melting (J/g).

End-group functionalization has also been used to generate succinic acid terminated PE-based PLA stars.[24] These succinic acid groups can be cross-linked with succinic anhydride to form complex polymer networks. These networks maintained similar T_g and T_m values while exhibiting much lower crystallinity than the prepolymers.

Researchers are not limited to simple polyols to initiate the ROP of LA (Figure 4). Cholic acid, a natural crystalline bile acid, has been used an initiator in the ROP of lactide to produce 4-armed star-PLAs[42-47] and PLLA-PEG-PLLA block copolymers.[46] While little information is reported on the polymeric materials, their application in substrate mediated gene delivery and cell transfection is explored. The PLA star polymers act as a support for DNA co-precipitate complexes as well as *in vitro* drug delivery vectors. They can also be linked through condensation of multiple cholic acid oligo-PLA macromolecules to form PLA-*co*-cholate chains.[47] The PLA stars were found to have relatively fast degradation times and their benign nature and bioassimilability are key requirements of transfection systems.

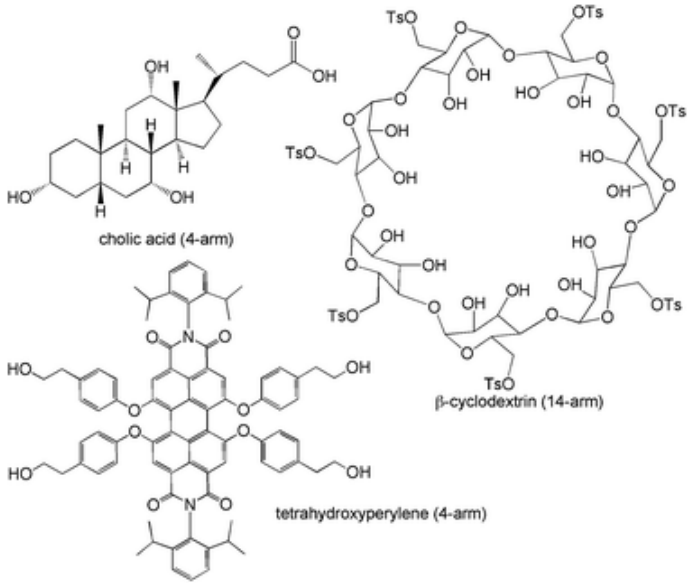


Figure 4. Discrete cores for PLA star polymers.

Tosylated β-cyclodextrins (β-CD) were used as multi-functional macroinitiators for the ROP of LA.[48] Seven latent tosyl functionalities on the β-CD ring were used to subsequently initiate the ROP of 2-ethyl-2-oxazoline to form PLA-β-CD-POX star-shaped block copolymers. These materials were extensively studied for the loading capacity for the dye Congo Red, tracking the maximum loading capacity and the degradation and release profiles were studied by UV-visible spectroscopy.

A hexahydroxy triphenylene core (2,3,6,7,10,11-hexa(10′-hydroxy decanoxyl triphenylene) was used to synthesize 6-armed star PLA polymers and co-polymers with styrene and *N*-acryloxysuccinimide (NAS).[49] Hydroxy terminated PLA stars were reacted with α-bromo-isobutyric chloride to generate bromine-terminated stars. These materials were then used as macroinitiators for the atom transfer radical polymerization (ATRP) of styrene and NAS. Micelle formation and cross-linking afforded nanospheres, as shown by TEM imaging. The nanospheres could be hollowed out by hydrolysis of the PLA core.

Novel tetra- and hexa-hydroxy functionalized perylene chromophores[50] have introduced a rigidity to star PLA architecture. The more rigid cores show improved thermal stability compared to flexible polyol cores, minimizing the destabilization when switching from linear architectures to stars. The system was also investigated for its potential to encapsulate small molecules with the encapsulation potential heavily dependent on star arm length.

Finally, discrete transition metal complexes have been employed as cores for PLA nanoparticles (Figure 5). Discrete cores based on iron, ruthenium and europium with hydroxy-substituted dibenzoylmethane (dbm) and bipyridine (bpy) ligands. For dbmOH, ROP of LA was followed by complexation to the metal centre[51,52] while bpyOH systems[37,53-55] must first be complexed to create a transition metal macroinitiator core. While broader PDIs were observed when metals were present in the cores during ROP, activities and conversions increased, especially in the case of iron-based cores. The materials are designed with a specific function in mind, as stimuli-responsive materials, luminescent materials for drug delivery and imaging or responsive chromophores.

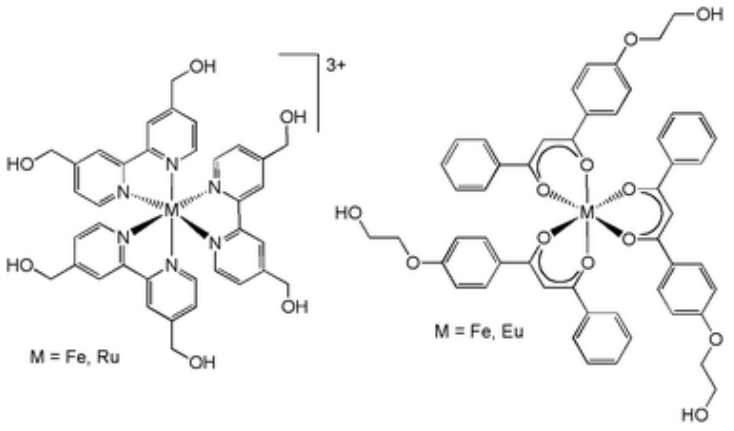


Figure 5. Metal-based cores for PLA star polymers.

Polymeric and oligomeric cores

Simple polyols have also been modified to achieve a specific function. Pentaerythritol ethoxylates are employed as macroinitiators in the polymerization of lactide.[56-58] Oligomeric ethylene oxide blocks promote enhanced water solubility for the PLA materials without adversely affecting the non-toxic, non-immunogenic and biodegradable properties of PLA. Derived from *rac*-LA, these PLA star polymers are then end-derivatized with methacrylate and urethane end groups.[56,58] Photo cross-linking of these samples yield polymer networks with high gel content (>95%). These networks, formed from lower molecular weight oligomers, were more rigid, with the urethane-terminated stars possessing higher tensile strength and Young's modulus, presumably due to the hydrogen bonding ability of the end-groups. This work can be extended by functionalizing PE ethoxylate-P(*rac*-LA) stars with the complementary DNA base pairs adenine and thymine.[57] Increased hydrogen-bonding gave higher solution viscosities and improved physical properties while VT-NMR studies showed the hydrogen-bonding to be thermoreversible.

PE ethoxylates have also also been utilized in conjunction with the aforementioned spirocyclic tin initiators.[33,34] These polymerizations showed no temperature or solvent dependence for M_n or PDI and had no induction period, offering an improvement over traditional $Sn(Oct)_2$ polymerizations. The thermal properties were maintained, however, as the typical dependence of T_g on polymer arm length was observed.

Other star-shaped PLAs that are based on polymer-type cores include polyhedral oligomeric silsesquioxanes[34] and poloxamine T1107-supported, collagen-containing cross-linked remoldable networks.[59] With degradable, oligomeric PLA arms, and synthesized under traditional conditions, these materials have been investigated for their potential in modular tissue engineering, displaying promising cellular confluence and adhesion.

PLA star polymers based upon multi-armed poly(ethylene glycol) backbones have been studied for their potential biomedical applications[22,60-65] while epoxidized soybean oil has been studied as a model biodegradation system.[66] Star polymers of 3, 4 and 8 arms have been synthesized and readily form hydrogels. Improved hydrogel properties are achieved through aqueous mixing of equimolar solutions of star PEG-PdLA and PEG-PlLA to create stereocomplex interactions between stars,[63,64] and through the threading of cyclodextrins onto biodegradable polymers.[61] The effect of the linker group, in these copolymers has also been studied, with ester functionalities allowing for rapid cleavage into two distinct homopolymers and amide functionalities requiring chain hydrolysis to break the copolymer linkage.[62] The versatility of this system (# of arms, tunable linkers) coupled with the increased water solubility improves the properties of these hydrogels with potential micellar drug delivery and tissue engineering biomedical applications.[65]

Miktoarm stars from discrete and polymeric cores

Miktoarm star polymers are asymmetric polymers where various types of polymer arms emanate from the core. Polymer arms should vary by chemical identity or molecular weight and impart unique properties for

self-assembly and micellization, stimuli-responsive materials (pH, temperature, light, solvent) and small molecule controlled release. The general field of miktoarm star polymers has been recently reviewed.[67]

While poly(ε-caprolactone) stars have a much more robust research history in this subfield than other aliphatic polyesters, PLA polymer stars have seen recent interest. Miktoarm polyester polymers often overcome problems with brittleness and access new morphologies and solution properties for these stars. For LA, polymer synthesis requires multifunctional initiators possessing reactive tags for both ROP and an additional living polymerization technique, including reversible addition-fragmentation chain transfer (RAFT)[68] and atom transfer radical polymerization (ATRP).[69] ABC-type miktoarm star polymers of poly(l-lactide)/poly(ethylene glycol)/polystyrene/ have been synthe-sized in a three step process.[70] First, PEG-macroinitiators are prepared with two dithiobenzoate and two hydroxy functionalities. Second, hydro RAFT polymerization of styrene activates the dithiobenzoate functionalities and accesses PEG-PS macroinitiators. Subsequent ROP of l-LA onto latent hydroxy functionalities provides the ABC star-polymers. This high conversion technique produced low PDI (~1.1) polymers with molecular weights ranging from 15-50 Da. Similarly, (PLA)(PEG)(PS) ABC star copolymers can be produced from a polystyrene substituted diphenylethene which serves as an initiator for anionic and ring opening polymerization.[71]

Similarly, RAFT was employed in the copolymerization of ethyl acrylate (EA) and hydroxyethylacrylate (HEA) to form poly(EA-*co*-HEA) oligomers. These oligomers were used as macroinitiators for the ROP of l-lactide to produce the desired miktoarm star polymers.[72] These macromolecules were further derivatized by first chain-extending the poly(EA-*co*-HEA) oligomers with styrene before the ROP of l-lactide. While this method produced polymers with moderately high PDI (1.3-1.9), it represents a production method that circumvents much of the rigorous reaction conditions associated with RAFT processes.

Finally, AB_2 type miktoarm PLA polymers have been synthesized where the A-block consisted of poly(*t*-butylacrylate), poly(ethylene oxide) and poly(*N*-isopropylacrylamide).[73] These star polymers were synthesized with an azide-functionalized RAFT agent *S*-1-dodecyl-*S*′-(□,□′-dimethyl-□″-acetic acid)trithiocarbonate, adding the potential application of cross-linking agents in biomedical, biodegradable and environmentally-sensitive applications.

Dendritic cores

Dendritic-type cores, while not a focus of this review, are hyperbranched cores containing a greater number of arms than polyol and polymeric cores. They have lower percent crystallinity than discrete cores, as their morphology makes a regular packing arrangement challenging. Some dendritic cores with a relatively small number of branch points maintain star-like behaviour and are often self-identified by authors as such. These examples are included herein, but this section should not be assumed to be comprehensive. Star-like dendritic

cores include hyperbranched poly(amidoamine)s (PAMAM),[74-77] polyamines,[78] bis(hydroxymethyl)propionic acid derivatives (bMPA),[36,79-81] polyglycerines,[16,82,83] poly-esters,[84,85] poly(ethyleneimine)s (PEI),[86] poly(arylether)s,[87,88] and polyhedral oligomeric silsesquioxanes.[89]

As with other cores, a typical synthesis involves initiation of ROP from a multifunctional hydroxy or amine substituted initiator. In dendrimer synthesis, however, incomplete initiation is often observed due to the close packing of growing chains. As this area has been recently reviewed,[9,10] an extensive coverage of the physical properties and applications of these materials is not necessary, although it is important to note that dendritic PLAs have found utility in the embedding and controlled release of bovine serum albumin,[76] chlorambucil[85] and Rose Bengal[86] as models of controlled release drug delivery systems.

Applications of PLA polymer stars

Biodegradable polyesters have played an important role in many biomedical applications, especially in drug delivery where the monomer, polymer composition and polymer architecture are instrumental in controlling properties and tuning delivery profiles.[90] Many reports on PLA star polymers investigate their potential effectiveness as drug delivery vectors and self-assembled micelles. The morphology,[26,31,49,53] solution properties[12,15,25,35,60,62,79] and loading potential[18,22,42,48,75,77,85,86] have been investigated. Dyes, small molecules and model drugs have been successfully encapsulated with release profiles generally exhibiting fewer burst defects and lower initiation times when compared to analogous linear systems. Further control over degradation rates is offered by stereoregular PLA architectures,[29] offering great potential for further tuning these systems for *in vivo* controlled release biomedical applications. Polyester substituted prodrugs of Norfloxacin were also prepared by covalently linking the drug to PLA and PCL frameworks.[22] Other applications including luminescence and nanoparticle formation have been previously highlighted as appropriate.

Poly(ε-caprolactone) polymer stars

PCL stars may also be classified into convenient groups based upon the type of multifunctional initiator used as a core. The relative ease of PCL synthesis and initiation as well as improved properties for biomedical applications has led to an increased breadth of studies.

Discrete cores

Polyol-based PCL stars have been synthesized utilizing similar polyol cores to the aforementioned PLA work: glyercol,[22,91-94] TMP,[23,95-97] PE,[22,23,92,95,96,98-111] erythritol,[93] xylitol,[92,93] DPE and modified DPEs,[95,102,103,109,111-114]

and bis(2-hydroxyethyl)amino-tris-(hydroxymethyl)methane[115] (HAHM) have all been extensively studied (Figure 3). Other discrete cores include: bis(ε-caprolactone) crosslinkers,[116-117] 1,3,5-benzenetricarboxylic acid and 1,2,4,5-benzenetetracarboxylic acid,[118] hexakis(*p*-hydroxymethylphenoxide)cyclotriphos-phazene (PZ),[119-120] tetrahydroxyperylenes (Figure 4),[50] propionic acid (PA) derivatives,[121-125] silsesquioxanes,[126-128] azide functionalized cyclodextrins,[129,130] C_{60} fullerenes,[131,132] porphyrins,[133-137] chlorins[138] and resorcinarenes (RES).[139-141] Selected cores are shown in Figure 6. The thermal data accumulated on PCL stars is more complete and gives a clearer understanding of thermal and chemical relationships. Table 4 highlights this data.

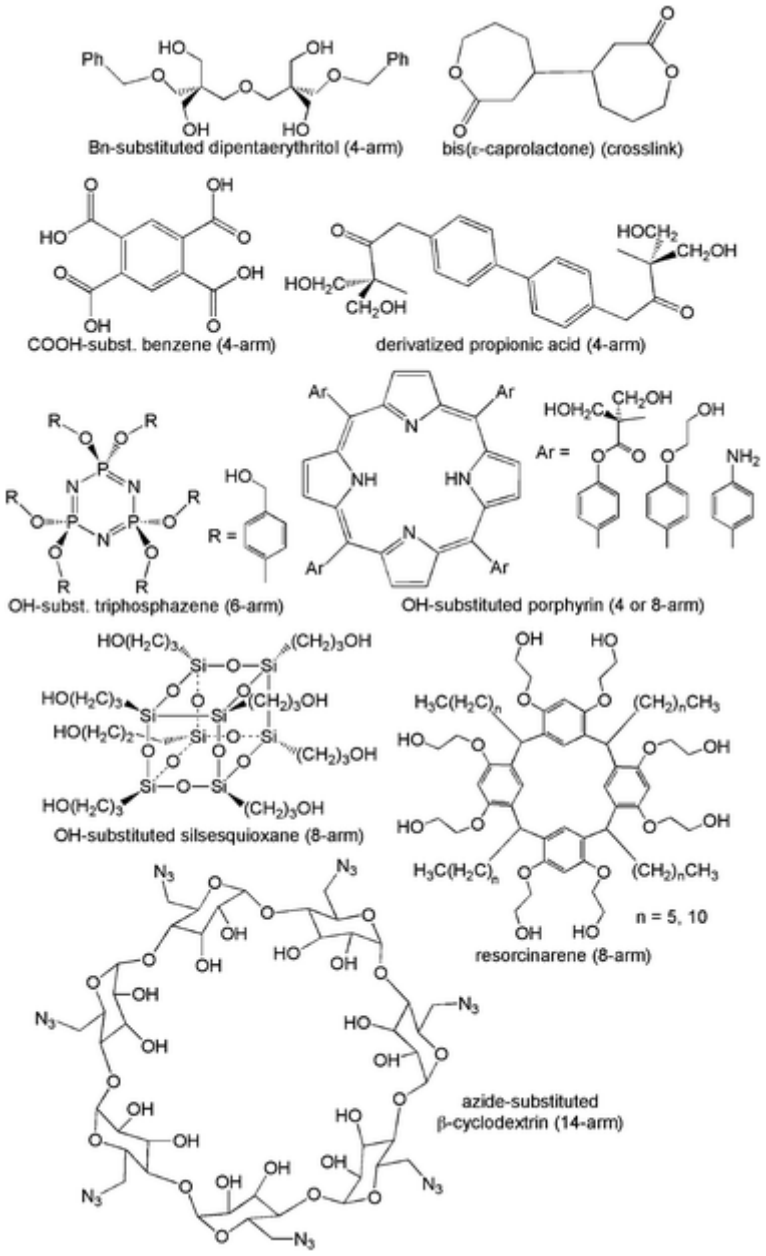


Figure 6. Additional cores used in PCL star polymer synthesis.

Table 4. Characterization data for ε-PCL polymer stars.

Core	Catalyst	M_n	PDI	T_g (°C)	T_c (°C)	X_c (%)	Ref
Glycerol	Novo[a]	2900	1.46	46	109.5	57	94
Glycerol	Novo	4900	1.42	53	100.8	68	94
Glycerol	$Sn(Oct)_2$	2500	1.49	44.2,49.2	-	-	91
Glycerol	$Sn(Oct)_2$	6280	1.54	51.7,54.5	-	-	91
Glycerol	$Sn(Oct)_2$	18900	1.45	56.5,57.5	-	-	91
TMP	$Sn(Oct)_2$	4900	1.42	50.2	-	56.1	94
TMP	$Sn(Oct)_2$	21800	1.30	62.5	-	-	101
TMP	$Sn(Oct)_2$	28500	1.23	61.6	-	-	97
TMP	$Sn(Oct)_2$	47100	1.27	60.2	-	-	97
PE	$Sn(Oct)_2$	5200	1.46	50.5	-	55.5	95
PE	$Sn(Oct)_2$	6070	1.07	50.1	26.1	68.2	103
PE	$Sn(Oct)_2$	12540	1.10	53.6	30.8	80.8	103
PE	$Sn(Oct)_2$	17140	1.22	56.4	31.4	70.0	103
PE	$Sn(Oct)_2$	23600	1.28	61.3	-	-	101
DPE	$Sn(Oct)_2$	6400	1.50	51.2	-	-	95
DPE	$Sn(Oct)_2$	7160	1.05	48.6	20.1	58.2	112
DPE	$Sn(Oct)_2$	11820	1.08	54.5	28.3	60.9	112
DPE	$Sn(Oct)_2$	13410	1.15	55.7	31.0	76.2	112
PA	$Sn(Oct)_2$	26016	1.60	47.0	-	-	123
PA	$Sn(Oct)_2$	106765	3.13	57.7	-	-	123
Porphyrin	Sn/Mg[b]	6400	1.74	57.2	22.8	70.6	148
Porphyrin	Sn/Mg	15100	1.80	60.9	29.5	74.8	148
Porphyrin	Sn/Mg	15100	1.80	62.5	30.6	76.8	148
β-CD	$Sn(Oct)_2$	13300	1.04	32.7	-	34.4	126
β-CD	$Sn(Oct)_2$	65100	1.11	53.6	-	43.1	126
RES	$Sn(Oct)_2$	15000	2.00	60.6	-	67	139
RES	Y(dbmp)[c]	18800	1.28	54.7	-	49.7	140
RES	Y(dbmp)	25300	1.43	57.2	-	56.6	140
RES	Y(dbmp)	55000	1.50	60.4	-	63.4	140

[a] Novo = Novozym 435, [b] Sn/Mg = $Sn(Oct)_2$/Mg(porphyrin), [c] Y = Yttrium tris(2,6-di(*t*-butyl-4-methyl-phenolate)

T_g and X_c are affected by molecular weight, as increasing the length of polymer arms leads to enhanced thermal properties and percent crystallinity, especially for systems with a larger number of polymer arms. Little effect on crystallinity or glass transition temperature is noted when increasing the number of polymer arms. In one study, switching from TMP to PE to DPE increased the T_g by only 1 °C.[95] Reproducibility across different studies is much improved when compared to PLA systems; three studies of PE stars show a consistent correlation between T_g and M_n.[95,101,103] With no stereocentres imparting tacticity, the nature of the catalyst has little effect on star properties, although the catalyst can have a significant effect on reaction control, as evidenced by variable PDIs.

Polyol-based PCL stars exhibit a unique ability to be readily modified for specific biomedical and materials applications. PCL stars have been modified through end-functionalization and converted into block copolymers. This is most frequently accomplished through conversion of the hydroxy end-group into a RAFT, NMP or ATRP active functionality. These copolymers typically form core-shell arrangements and can provide improved hydrophilicity, crystallinity, drug loading and, in the case of amphiphilic polymers, form self-assembled micelles in solution or bulk.[142]

TMP-initiated PCL stars were copolymerized with bis(4-methoxyphenyl)oxycarbonylstyrene,[97] while PCL stars with PE cores have been combined with *N*-(2-hydroxypropyl)methacrylamide,[98] styrene,[101] ethylene glycol,[104] 2-ethoxy-2-oxo-1,3,2-dioxaphospholane,[105] 2- lactobionamido-ethyl methacrylate,[106] gluconamidoethylmeth-acrylate,[108] and ethylene glycol methacrylate.[109] Control of the length of the blocks had a significant effect on the polymer properties including T_m,[101] crystallinity,[108] degradation rate,[105] and micelle size and shape.[106]

Many of these PCL star block copolymers have been further investigated as drug delivery vectors. They have been loaded with indomethancin,[98] paclitaxel,[105] and Concanavalin A.[108] Toxicity studies in both red blood and HeLa cells confirmed the benign nature of these macromolecules, including their capacity to escape the reticuloendothelial system once injected.[104]

PCL star systems have also been modified for specific applications. Glycerol-based PCL stars have been modified to form 3-armed PCL poly(ester-urethanes) that have potential shape-memory polymer applications,[94] exhibiting 99% shape recovery within 10 s. PE- and DPE-initiated PCLs have been used to create host-guest inclusion complexes with α-cyclodextrins.[100,111] Branch arm number and molecular weight had a large effect on the stoichiometry of the inclusion complexes. In all cases, crystallinity was suppressed and therma stability enhanced. Similarily, octakis(3-hydroxy-propyldimethylsiloxy)octasilsesquioxane initiated PCL was also used to form inclusion complexes with α- and γ- CDs.[128] Poly(N-isoproylacrylamide)-functionalized cholic acid has also been used for ROP of caprolactone to create a block copolymer.[143] The stars were loaded with methotrexate and their release profile was found to be temperature dependent and highly controlled. This concept could be extended to $(AB)_2(BA)_2$ block copolymer stars where careful protection and deprotection steps allowed for asymmetric PE(PS-*b*-PCL)$_2$(PCL-*b*-PS)$_2$ star polymers to be produced.[144] The intricate structure limits the movement of PS and PCL segments, leading to a decrease in T_g and crystallinity compared to PE(PCL-*b*-PS)$_4$ macromolecules.

Unlike PLA stars which are almost universally prepared through a core-first approach, several arm-first coupling methodologies have been used to prepare PCL star polymers. Core cross-linking allows polymer stars to be prepared by the addition of a cross-linking agent to linear polymer chains. These macrostructures have star-like properties and are gaining popularity with emerging applications in drug delivery, membrane formation and paint additives.[145,146] Core cross-linked stars of PCL have been prepared with

bis(caprolactone)[116] and 2-hydroxyethyl-2′-methyl-2′-bromopropionate.[131,132] Modification of these structures is also possible, installing methyl methacrylate[131] or poly(propargyl methacrylate)[132] end-groups onto the polymer chains.

Click chemistry strategies have also been used to access PCL star morphologies via an arm-first approach.[121,125,129,147] Copper-catalyzed azide alkyne coupling has been used to couple acetylene functionalized PCL chains to azide functionalized β-CDs.[129] This system trapped the copper out of the reaction mixture, forming 2×2 grid-like copper containing macromolecules. Azide-alkyne coupling and Diels-Alder reactions have been used to create PCL stars, providing the possibility of employing both arm-first and core-first synthetic methodologies.[121,147] Specifically, this double click reaction was used to synthesize PS-*b*-PCL 3-armed stars. First, α-diene-ω-alkyne functionalized PCL was used to couple PS homopolymers to form the blocks. Subsequent coupling of these polymers to 1,3,5-tris((3-azidopropoxy)methyl)benzene through a copper-catalyzed reaction formed the desired star polymers. Alternatively, the reactions could be reversed, first forming a PCL star by coupling to the azido-functionalized core followed by Diels-Alder cycloaddition attaching the PS blocks to complete the formation of the macromolecule. While both processes were very effective, the arm-first methodology was more efficient (94% vs 81% yield).

Macrocyclic multifunctional cores are popular cores for PCL macrostructures. Alcohol, propionic acid and aniline substituted cores have all been used to create 4- or 8-arm PCL star polymers.[133-138] Encapsulation of these photoactive cores within biodegradable polymer shells enhances site isolation of the core and is controlled through the length of the polymer arms.[133] Zinc-centred porphyrins protected by PCL arms are also resistent to the fluorescence quencher methyl viologen.[136] These porphyrin-PCLs can be combined with α-CDs to create inclusion complexes that behave as polypseudorotaxanes with channel-type crystalline structures being investigated in photodynamic therapy and peptide-polymer compatibility.[134] Chlorin cores have been used to form amphiphilic PCL-*b*-PEG copolymers that self-assemble into micelles. Hydrophobic paclitaxel was trapped in the inner micelle core providing a delivery vector with lower cytotoxicity.[138] Magnesium-centre porphyrazines support 8-armed PCL stars with broad PDIs and enhanced thermal properties.[148]

Other complex cores have also been used to support PCL star formation. Polyhedral oligomeric silsesquioxanes improve melting temperatures while maintaining PCL crystalline properties and increasing the crystallization rate.[127] Resorcinarenes form 8-armed PCL stars with distinct thermal properties, slower crystallization and irregular crystallization patterns.[139-141] The RES framework has also supported the synthesis of triblock terpolymers of the form PCL-*b*-poly(acrylic acid)-*b*-PCL. Naturally forming spherical micelles of these macromolecules possessed a large range of sizes (20 to 60 nm).[141]

In parallel to PLA star polymers, metal-centred cores have also been prepared. Supplementing the Zn and Mg porphyrin PCL stars, the aforementioned dbm[149,150] and bpy[54,55] systems feature prominently, with complexes

of Eu, Fe, Ni and Cu reported. This approach has also been expanded to produce asymmetric stars that include PS and PEG chains.[55] Post-synthetic demetallation is also possible.[150]

While most reports of PCL stars discuss the thermal properties and/or stability of the materials, little work exists on the mechanisms of pyrolysis. One key paper investigates this mechanism for a series of discrete stars built from erythritol, xylitol and glycerol cores.[93] These samples were analyzed by thermogravimetric analysis with the results suggesting that (a) the ester bonds of PCL pyrolyze into alkene and carboxyl functionalities or (b) the ester linkages pyrolyze into ketene and hydroxyl groups. Independent of mechanism, thermal stability enhancement was observed upon increasing molecular weight and number of star arms. In addition, Grazing Incidence Small Angle X-ray Scattering (GISAXS) is used to determine the mechanism of thermal pore generation in organosilicate thin films loaded with PCL star polymers,[151] while the rheology of these PCL stars is modelled with the Milner-McLeish methodology.[152]

As in the ROP of lactide, the ROP of ε-caprolactone is widely mediated by a $Sn(Oct)_2$ catalyst. Alternative catalysts for the preparation of PCL star polymers include: (a) lipase enzyme Novozym 435 from *Candida antarctica*,[94,153,154] (b) metal-based catalysts $Sm(PPh_2)_2$,[107] SmI_2,[107] $Bi(O(CH_2)_5CH_3)_3$,[110] $Al(O^iPr)_3$,[117] $AlEt_2(O(CH_2)_{12}Br)$,[131,132] and $Y(dbmp)_3$,[140,141] and (c) organic catalysts including aromatic acids,[118] fumaric acid[123] and DMAP.[147]

Polymeric and oligomeric cores

Polyols can be converted into polymeric and oligomeric macroinitiators that act as cores for PCL star polymers. Ethoxylated-pentaerythritol is used as a base for oligomeric macroinitiators for the preparation of PCL stars that mimic the zero concentration diffusivities of amorphous poly(vinyl alcohol)s.[155] Ethoxylated PEs can also be used to produce spirocyclic tin initiators as PCL ROP mediators, accessing novel figure-eight or tadpole type macrostructures.[156-159] PE can be brominated to form ATRP initiators that facilitate the production of $PE(PS)_4$ macroinitiators.[160] From these species eight-armed star shaped block copolymers of the form $(PS\text{-}b\text{-}(PCL)_2)_4$ were prepared by a divergent approach involving functionalization of the PCL chains with pyrene groups. These fluorescent macromolecules have potential applications as biological fluorescent probes, photodynamic therapy agents and optoelectronic components.[160]

Polyglycerine-based PCL star polymers provide intriguing architectures for post-synthetic cross-linking.[83,153,161,162] Functionalization of the polymer using maleic,[161] itaconic,[161] or succinic[162] anhydrides was an effective method to install unsaturations along the glycerine backbone and permit cross-linking of polymer stars with epoxides. Toughened coatings with reduced brittleness could be produced by tuning the epoxy to oligomer ratio.[162]

Cross-linking was also employed in creating oligoglycerin-based PCL stars for use in shape-memory networks.[163] Lower molecular weights gave improved temperature-sensitive shape recovery. When loaded with theophylline the system affected the controlled release of the model compound with sustained release observed over the period of 1 month in phosphate buffer solution.

Differences in the effectiveness of chemical and enzymatic initiated ROP for polymeric initiators has also been investigated.[154] Polyglycidol-initiated ROP with zinc(II) 2-ethylhexanoate gave quantitative initiation; only 15-20% of initiation sites were activated by the Novozym 435 catalyst. The difference in efficiency produced two completely different structures: For zinc, a typical core-shell polymer with hydrophilic polyether core and hydrophobic polyester shell forms while for the enzyme a hydrophilic polyglycidol-headed coil with hydrophobic PCL-tails was produced.[154]

Multi-armed PEGs are also common initiators of PCL star polymers. Systems with 3,[164] 4[165,166] and 5[167,168] arms have been reported. These stars have been developed for nanoparticle synthesis,[164] temperature dependent sol-gels,[166] polyurethanes,[167] air/water interface modifiers,[169] tissue engineering[170] and Pd- and Au-containing nanoparticles.[167-168] The polymer star substituted palladium nanoparticles showed improved stability and decreased aggregation, resulting in efficacy in Heck coupling reactions.[167]

Miktoarm stars from discrete and polymeric cores

Miktoarm star polymers containing PCL are an extensively studied sub-field of PCL star macromolecules. As with LA, these materials combine often conventional ROP with controlled radical polymerization. The versatility of these combined methodologies has led to a huge range of architectures. For clarity purposes, these miktoarm PCL polymers are all classified with A representing the PCL block and include: AB,[171,172] A_2B,[73,173-176] AB_2,[177-179] AB_4,[180] A_2B_2,[181-186] A_3B_3,[173] AB_8,[187] ABC,[77,188-194] $(A\text{-}b\text{-}B)_3(C)_3$,[195] ABCD[196-198] and ABCDE.[199]

AB miktoarm polymers are prepared by the core cross-linking approach and thus often contain a random number of A and B arms attached to the core, dependent upon reaction conditions and polymer ratios. 2-Bromoisobutyryl functionalized PCL was copolymerized with divinylbenzene to form a cross-linked star core to which PS was grafted via Cu-catalyzed ATRP.[171] Similarly, a PCL-PMMA miktoarm polymer was prepared through cross-linking 2-hydroxyethyl-2′-methyl-2′bromopropionate terminated PCL and PMMA homopolymers with ethylene glycol dimethacrylate.[172] Variation of the extent of cross-linking and the length and composition of star arms allowed for the preparation of an extensive family of stars which can be selectively degraded and serve as platforms for the preparation of monodisperse lead sulfide nanoparticles.[171]

A_2B-type miktoarm polymers and, in fact, all other miktoarm PCL stars discussed, are built from a core-first approach with multifunctional initiators. Discrete multifunctional initiators may be derived from propargylamine diol,[73] TMP,[173] (1,1-dihydroxymethyl-1-(2-bromoisobutyryloxy)methylethane,[174] and 2-ethyl-2-hydroxymethyl-propane-1,3-diol.[175]

An elegant methodology can generate $(PCL)_2$(PS) and $(PCL)_2$(PMMA) miktoarm stars in a one-pot process with initiators, catalyst and both monomers combined simultaneously.[173] Extension of this method permits synthesis of miktoarm stars bearing block copolymer arms, forming PS-*b*-PCL_2, (PS-*b*-poly(^{n}butylacrylate))(PCL-*b*-PS-*b*-poly(^{n}butyl-acrylate)$_2$ and (poly(^{t}butylacrylate)-*b*-PS)(PCL-*b*-poly(^{t}butyl-acrylate)-*b*-PS)$_2$ polymers.[174] Improved reaction efficiency was afforded by performing ROP prior to ATRP. $(PCL)_2$PS have also been prepared using a titanium catalyst[175] and pentaerythritol-derived initiators.[180]

Polymeric $PEO(OH)_2$ initiators were prepared through selective hydrolysis of α-methoxy-ω-epoxy-poly(ethylene glycol) as scaffords for $(PCL)_2$(PEG) A_2B-type miktoarm stars.[176] Changing the length of the hydrophobic PCL block relative to constant length PEO blocks permitted modulation of micelle size upon self-assembly.

AB_2-type miktoarm polymers containing only a single PCL arm have also been reported. The simplest methodology involves the termination of linear PCL chains with a bifunctional reagent like 2,2-dichloroacetyl chloride. This species can then be used as a macroinitiator for the ATRP of glycidyl methacrylate to form Y-shaped 3-armed stars.[177] Discrete multifunctional initiators derived from propanoates offer one alcohol site for ROP and two halogen sites for ATRP initiation. This technique has been used to generate (PCL)(poly^{t}butylacrylate)$_2$ and (PCL)$(PMMA)_2$ stars.[178] Polyethers functionalized with a single benzylic alcohol and two or four TEMPO-derived alkoxyamines were used to prepare miktoarm polymers with AB_2 and AB_4 structures through the ROP of CL and the NMP of styrene.[179] These reactions produced well-defined macrostructres with low PDIs.

It is worthwhile to compare the related A_2B and AB_2 star polymers formed from CL and ^{t}butyl methacrylate (Figure 7).[173,179] While both polymers were generated from a multifunctional core and had similar arm lengths, the presence of two alcohol functionalities prevented efficient initiation with aluminum catalysts, requiring the use of $Sn(Oct)_2$. While reaction **A** can generate product in a one-pot process, the incompatibility of NMP and ROP conditions in **B** prevent this simplification. Both methodologies offer good control over the reaction, but the combination of ATRP and ROP can afford PDIs as low as 1.1. Unfortunately, the authors do not investigate the self-assembly or physical properties of these materials, thus highlighting the need for a more systematic understanding of this field.

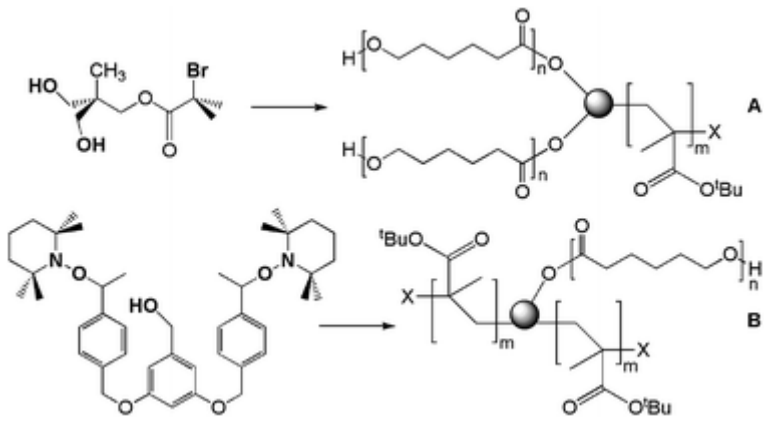


Figure 7. AB2 and A2B miktoarm star copolymers of PCL and PtBuMA.

A_2B_2 miktoarm stars are the most common framework for PCL based systems. The simple polyol PE can be modified to provide a framework for PCL stars with PS, PMMA, poly(dimethylaminoethyl methacrylate) and poly(2-hydroxy-ethyl methacrylate).[180-182] Compared to linear block copolymers, the macromolecules were entropically restrictred and resisted chain stretching. Packing also reorganized, as linear PCL-*b*-PS chains took a lamellae form while the $(PCL)_2(PS)_2$ stars formed hexagonally packed cylinders.[182]

$(PCL)_2(PS)_2$ miktoarm stars have also been prepared using dibromodihydroxybenzene[183] and substituted pentynoates[184] through core-first and arm-first synthetic strategies respectively. $(PCL)_2(PEG)_2$ stars were prepared from 2,2-bis(bromomethyl)propane-1,3-diol cores.[185] The latter of these A_2B_2 stars was directly conjugated to ibuprofen molecules and tested for controlled release drug delivery. The ibuprofen functionalized stars showed dramatically improved efficiency for drug loading and encapsulation. A_3B_3 stars of the form $(PCL)_3(PMMA)_3$ were grown from a bis(hydroxymethyl)propionic acid core.[186] DSC analysis indicated that the materials properties were independent of the order of polymerization. Finally, 9- and 17-armed miktoarm stars have also been prepared from a multi-functional core with 8 TEMPO-derived alkoxyamines, generating $(PCL)(PS)_8$ and $(PCL)(PS)_{16}$ stars through the successive ROP of CL and NMP of styrene.[187] GPC analysis revealed low PDIs of 1.18-1.28 indicating surprisingly good control for a dendrimer-like core.

Inclusion of a third monomer allows for ABC-type miktoarm stars to be prepared. The synthetic challenges of preparing these macromolecules is often heightened by the need to exploit three different polymerization mechanisms and access trifunctional discrete initiators or bifunctional polymeric macroinitiators (Figure 8). Discrete cores combine ROP, ATRP and NMP to activate hydroxy, bromo and TEMPO functionalities respectively.[188,189] These techniques were used to prepare (PCL)(PS)(P^{t}BuA) and (PCL)(PMMA)(PS) ABC-stars. The well-defined nature of these stars was confirmed through analysis of cleaved polymer arms.[189] Alternatively, end-functionalized poly(ethylene glyc-ol)s can be used to generate (PCL)(PEG)(PS) through

ROP and ATRP or ATRP and the anionic polymerization of ε-caprolactone.[190-192] In the case of anionic polymerization, a PS-*b*-PEG block copolymer is prepared with a protected anionic initiator at the junction point. Deprotection followed by activation with a weakly basic carbanion initiates the ROP of CL.

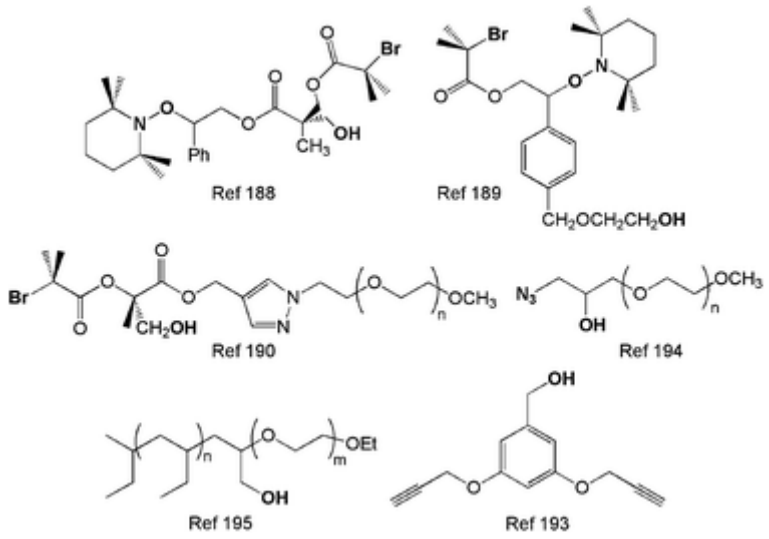


Figure 8. ABC miktoarm initiators.

Double click reactions with a bis(alkynyl) substituted benzyl alcohol yield (PCL)(PS)(poly(*N*-isopropylacrylamide)) from the ROP of CL and the reaction of azide-functionalized PS and polyacrylamide homopolymers.[193] Self-assembly resulted in the formation of macrostructures with polystyrene/poly(ε-caprolactone) centred micelles and a thermoresponsive acrylamide shell. A similar strategy was employed in the synthesis of (PCL)(PEG)(polyphosphoester) ABC miktoarm stars where propargyl-substituted PCL homopolymers were coupled onto a bifunctional PEG macroinitiator followed by ROP of 2-eth-oxy-2-oxo-1,3,2-dioxaphospholane to form the desired terpolymer.[194]

Substituted caprolactones have also been utilized in the formation of ABC miktoarm stars of form (γ-methyl-ε-PCL)(PEG)(poly(ethylethylene).[195] Two successive living anionic polymerizations form a hydroxyl-functionalized PEE-*b*-PEG which serves as a macroinitiator for the $AlEt_3$-catalyzed ROP of γ-methyl-ε-caprolactone. Self-assembled micelles were thermoresponsive, transitioning from micelle to worm to sphere morphology, an observation attributed to the connection of three immiscible blocks at one junction.

More complex miktoarm macrostructures have also been prepared. Dendrimer-like $(A\text{-}b\text{-}B)_3(C)_3$ polymers $(PCL\text{-}b\text{-}PS)_3(P^tBuA)_3$ have been prepared from ATRP, ROP, NMP and a Huisgen cycloaddition to click the components together.[195] Limited differences in arm polarity prevented self-assembly. ABCD and ABCDE miktoarm stars have also been prepared.[196-200] Multifunctional initiators including 2-hydroxyethyl-3-(4-(prop-

2-ynyloxy)phenyl)[198] were used to prepare (PCL)(PS)(PMMA)(PEG) and (PCL)(PS)(P^{t}BuA)-(PEG) by combining ROP, RAFT polymerization and click cyclizations. Click reactions were also used to prepare (PCL)(P^{t}BuA)(PS)-(PMMA) stars.[199] Linear PCL was synthesized with an anthracene initiator, while P^{t}BuA was prepared with a furan-protected maleimide terminus. These homopolymers were linked via a Diels-Alder click reaction to give the PCL-*b*-P^{t}BuA copolymer subsequently used as a macroinitiator for the NMP of styrene and the uncontrolled free-radical photopolymerization of MMA. The greatest combination of distinct monomers is observed in the preparation of ABCDE type miktoarm stars combining a (PCL)(PS)(P^{t}BuA) terpolymer with a PEG-*b*-PMMA copolymer through an azide-alkyne click reaction to form the desired H-shaped quintopolymers with 60% efficiency.[200]

As in other areas of aliphatic polyester synthesis, alternative catalysts have been used to facilitate the ROP of CL including Cp($TiCl_2$)(OR) (R = polystyrene),[175] Novozym 435[177] and $AlEt_3$.[179,187,189,195]

Dendritic cores

As with lactide, we provide here the PCL dendritic stars employing hyperbranched cores that self-identify as having star-like characteristics. Derivatives of bMPA,[81,201-220] PEG,[60,221,222] polyglycerols,[83,223,224] PAMAM,[77,225-228] polyamines,[78,229] hyperbranched poly(hydroxyethylmethacry-late),[230] poly(ether)amides,[231,232] poly(ester)amides,[233] and PEIs.[234-236] Dendritic star polymer architectures with PCL date back to 1998.[201] The first report focuses on 6-armed star PCLs synthesized from a 2,2-bis(phenyldioxymethyl)prop-ionic acid core. Amphiphilic block copolymers possessing a hydrophilic outer layer were prepared by installing hydroxyethylmethacrylate or methacrylate terminating functional groups. These new macromolecules were well defined (M_n = 96000, PDI = 1.1). End-group functionalization is a common route to new dendritic stars; methacrylate,[202] poly(acrylic acid)[203] and poly(ethylene glycol)[204] functionalized stars have been reported. Other factors such as the presence of amorphous regions between crystalline lamellae,[205] restriction of arm movement[206] and the placing of branching junctures[207] in these stars has been shown to have pronounced effects on morphology, hydrodynamic volume and form-factor of these materials.

These dendritic stars have seen extensive application as drug delivery vectors. They have been loaded with volatile hydrophobic fragrance molecules,[203] 5-fluorouracil,[204] etoposide,[77,225] Concanavalin A,[227] organic dyes,[233,235,236] diadzein,[232] and prednisone acetate.[226]

Alternative catalysts used for synthesis of PCL dendrimers are l-lactic acid,[216] tartaric acid,[216] $HfCl_4(THF)_2$,[202] and diphenylammonium trifluoromethanesulfonate.[202]

Other aliphatic polyester polymer stars

Aliphatic polyester homopolymer stars

A surprising paucity of reports of homopolymer stars of glycolide (GLY), trimethylene carbonate (TMC) and β-butyrolactone (βBL) exists. While this fact correlates strongly with the extent of research on the same range of linear polyesters, it is clear that much remains to explore.

Poly(trimethylene carbonate) star polymers have been prepared from the simple polyols glycerol[237] trimethylolpropane[23] and pentaerythritol[23] using $Sn(Oct)_2$, $ZnEt_2$ or the zinc catalyst [(BDI)Zn($N(SiMe_3)_2$] (BDI =$CH(CMeNC_6H_3$-2,6-$^iPr_2)_2$).[237] With zinc catalysts, these stars can be prepared under solvent-free conditions at relatively low reaction temperatures (60 °C). Lipase enzyme Novozyme 435 has also been effective in mediating TMC star synthesis.[154] While conversions were high, polydispersities between 1.6-1.9 indicated a loss of control. Spirocyclic initiators derived from dibutyltin and ethoxylated PE have been used to prepare stars based upon β-butyrolactone.[157,159]

Star polymers containing multiple aliphatic polyesters

The most common polymer star copolymers are PCL-*b*-PLA[22,159,238-250] and PLA-*co*-poly(glycolic acid) (PGA)[252-259] although there are also reports of PCL-*b*-PβBL[157] and PGA-*co*-poly(dioxanone).[260] These efforts are focused on developing materials with unique physical properties and self assembly that maintain the total biodegradability of the parent homopolymers.

PCL-*b*-PLA stars

PCL-*b*-PLA star polymers are an important target due to their elastomeric properties. For these stars, discrete cores including glycerol,[22,238-243] PE,[22,159,243] DPE,[239,244] cyclotriphosphazenes,[245] HAHM,[115] and dbm[150] and bipyridine macroligands[246,247] have been implemented. These star PCL-*b*-PLA macromolecules have been utilized in the preparation of cross-linked networks. The elastomeric properties can be varied through altering the ratios between the polymer and the dilactone monomer bis(ε-caprolactone-4-yl)propane in the cross-linking step.[238] These elastomers possess a glass transition temperature independent of the polymer molecular weight before cross-linking, which is independent of the prepolymer molecular weight. Degradation studies in phosphate buffered saline found that little mass loss, little strain at break, but appreciable mechanical strength loss occurred over 12 weeks.[239]

Alternatively, acrylated PCL-*co*-PLA stars were photo-crosslinked.[240,242] *In vivo* degradation in rats after subcutaneous implantation was measured over a twelve week period and compared to *in vitro* degradation

profiles. Elastomers possessing a high cross-link density exhibited a profile that fit a surface erosion mechanism and no differences were detected between *in vivo* and *in vitro* samples. However, samples with a low cross-link density exhibited a bulk erosion profile, whereby mechanical strength markedly decreased after the fourth week of sampling.[240] Similar acrylated PCL-PLAs based on PE were used as a scaffold microstructured chamber for enhanced albumin production.[243]

Polymer blends of LA and CL were prepared from glycerol and stearyl alcohol.[241] Thermal analysis of these materials showed a single glass transition temperature and an onset of the melting transition close to biological temperatures. The star architecture was noted for inducing a decrease in T_m and increases in melt viscosity and degradation rate. Polymer functionalized predrugs of norfloxacin have also been prepared from glycerol, PE and PEG-centred PCL-*b*-PLA polymers.[22]

The composition ratio of DPE-centred PCL-PLA polymers controls sphericulite growth.[244] An increase in the PCL concentration led to the formation of banded sphericulites, attributed to the progressive dilution of PLA sphericulites in molten PCL at elevated temperatures. The isothermal crystallization of PCL segments was mainly templated by existing sphericulites of PLLA.[244] Bipyridine macroligands bearing a PEG-*b*-PCL-*b*-PLA terpolymer have been prepared and complexed with Fe and Ru.[246,247] These materials were shown by TGA to have distinct decomposition profiles for each monomer present and typical melting transitions.[246] These macromolecules show great potential as sensors, with strong chemo- and thermo-chromic bleaching observed upon exposure to various stimuli.[247] PCL triols were also used as macroinitiators to ring-open l-lactide, serving as a polymeric initiator for this polymer synthesis.[248]

PCL-*b*-PLA star copolymers have also been built from dendritic bMPA polyester cores.[249] The dendritic and block architectures had no effect on the crystallization properties of the PCL and PLA blocks. These cores have also been used to prepare complex star-block-comb copolymers of PCL-*b*-PLA that are outside the scope of this review.[250] Selective capping of 1-ethyl-6-oligo(CL)-glycopyranoside with vinyl acetate created macroinitiators for the preparation of PCL-PLA copolymers with three LA arms and one CL arm.[251]

Numerous monomer ratios have been utilized to prepare PCL-b-PLA star copolymers with different properties. The simplest method is to utilize a previously synthesized hydroxy terminated PCL[120,244,246,248-250] or PLA[54] star as an initiator in the ROP of the other monomer. For those systems containing an inner PCL block, it was found that the crystallization rate of the PCL block was greatly reduced when compared to the parent PCL star. This observation is attributed to the confinement of the dendritic core and PLLA blocks upon crystallization of the PCL.[248] Similarly, the melting transition of sPCLs has been observed to shift to a lower temperature when combined to form PCL-b-PLLA copolymers. A shoulder appearing on this transition is attributed to the lamellar rearrangement of PCL being affected by the PLLA block.[249]

Alternatively, both lactide and caprolactone monomers can be mixed simultaneously to produce star shaped PCL-PLA copolymers. Typically an equimolar 50:50 ratio of ε-caprolactone and lactide is employed[22,110,238-

[240] but other ratios have been reported.[238,241] NMR analysis of these samples show that CL:LA enchainment closely resembles the monomer ratio as a molar percentage.[238] Interestingly, most chains, ~90% or greater are capped with LA, indicating a strong preference for an inner PCL:outer PLA arrangement.[238] An increase in the PCL content of the stars has been observed to speed up the rate of degradation when compared to equimolar copolymers.[241]

PLA-*co*-PGA stars

PLA-co-PGA star copolymers have also been prepared. The poor hydrolytic stability of poly(glycolic acid) is improved through incorporation of another lactone.[252] Discrete cores include TMP,[252] tris(hydroxymethyl)ethane,[253,254] PE,[252,254] DPE,[255] and glucose.[256] The structural similarities between lactide and glycolide monomers provide straightforward copolymerization. Often samples are later chain-extended with a PLA block.[261]

These macromolecules are versatile: PLA-*co*-PGA properties can be tuned through alteration of the composition ratios.[255] Hydolytic degradation was enhanced through an increase in the glycolide content, while mechanical properties improved with increasing PLA content. Star blends retained their mechanical properties longer when compared to linear analogues of similar composition.

Cross-linking is also common for these PLA-*co*-PGA stars. Linking with diisocyanates yields degradable shape-memory polymer networks.[253] Loading the drugs enoxacin, nitrofurantoin and ethacridine lactate into the networks provides a controlled release drug delivery vector with 90% release observed over a period of 80 days. Glucose centred PLA-*co*-PGA stars have been loaded with bovine serum albumin.[256] Co-encapsulation of $Mg(OH)_2$ and the acidic microclimate of the stars caused aggregation of the bovine serum albumin into insoluble products.

PLA-*co*-PGA stars have also been built from polymeric cores including 4- and 8-armed PEGs.[257] Stars built on these multibranched PEG cores were loaded with recombinant human erythropoietin (EPO) and fluorescein isothiocyanate labelled dextran, although the materials did not provide a sustained release profile.[258]

PLA-co-PGA stars have also been synthesized with various molar ratios, including equimolar[256] and variable[253,255,257,258] ratios. With respect to thermal properties, an increase in PGA content was found to reduce the T_g and T_m values of these stars. Differences in the PLA:PGA composition have been found to have little effect on the drug loading capacity of these stars.[258] An extension of this method has allowed for the preparation of PLA-co-PGA stars that have been utilized as macroinitiators for the ROP of l-lactide to prepare poly(lactic acid)-co-(glycolic acid)-*b*-poly(l-lactic acid) polymer stars.[252]

Other aliphatic polyester copolymers

Star copolymers of the form PCL-*b*-PβBL and PCL-*co*-PβBL have been prepared using spirocyclic tin initiators derived from PE and dibutyltin.[157] Glass transition temperatures for the block copolymers were between 63 and 66 °C depending upon arm length. While block copolymers contained crystalline blocks of ε-CL, the random copolymerization creates an entirely amorphous macromolecule.

Star copolymers of type PGA-*co*-poly(dioxanone) have been synthesized from a PE core.[260] These stars were endcapped with biocompatible lysine-based diisocyanate crosslinkers. Mixing these stars with inorganic fillers such as hydroxyapatite or $Ca_3(PO_4)_2$ followed by the cross-linking reaction formed hardened materials as potential bioassimilable bone growth substrates.

Finally, star terpolymers have also been prepared of the form PCL-*b*-(PLA-*co*-PGA) from a cyclotriphosphazene core.[262] The stars were found to possess a two-phase structure with crystalline PCL regions and amorphous PLA-*co*-PGA domains. The incorporation of these 3 monomers has led to the creation of star polymers with very low crystallinity (X_c) in the range of 2-7%, a marked decrease from conventional PCL stars.[262]

Conclusions

It is apparent from writing this review that there is a wealth of dynamic research on aliphatic polyester polymer stars. Much of the work is focussed on poly(l-lactic acid) and poly(ε-caprolactone) presumably due to the availability and ease of use of these two key cyclic esters. Thermal, physical and self-assembly properties can all be tuned by altering the polymer composition, the number of arms, the polymer tacticity and the length of the polymer arms. Further control over macromolecular properties is offered by combining polyester arms with others of complementary characteristics in miktoarm macromolecular structures.

It is also apparent that much work remains. A concrete understanding of how each variable affects polymer properties needs to match our production of new-to-the-world materials to provide better guidance for the preparation of next-generation materials. Research projects galore can also be found in the relatively unexplored poly(β-butyrolactone), poly(glycolic acid) and poly(trimethylene carbonate) polymer stars. With a deep set of applications in the biomedical and nanotechnology industries it is hoped that this review provides a framework from which directed and purposeful research in this field can build.

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