Synthesis of functionalized biodegradable polyesters

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Received 14th March 2007
First published as an Advance Article on the web 13th July 2007
DOI: 10.1039/b614342n

This *tutorial review* summarizes recent developments in the syntheses of functionalized aliphatic polyesters. These polymers are attracting attention as sustainable alternatives to petrochemicals and for applications in medicine. Two main syntheses are described: step polymerization using mild chemo/enzymatic catalysis and ring opening polymerization, which is usually initiated by metal complexes. The methods are compared and their utility illustrated with reference to interesting new materials.

Introduction

The 'plastic age' dominates modern materials to such an extent that it would be difficult to imagine life without them. Their manufacture is a growth industry with worldwide production exceeding 150 million tons per year. However, concerns are now arising about their environmental footprint and in particular the impact of resource and energy utilization and disposal. These concerns have spurred investigations into the development of renewable, biodegradable and biocompatible polymers; of these, aliphatic polyesters are promising sustainable alternatives to commodity plastics such as polypropylene. The most commercially viable material to date is polylactide (PLA), produced by the ring opening polymerization of lactide, which itself derives from biomass such as corn or wheat. Polylactide has good mechanical and physical properties and therefore is suitable for use in disposable consumer articles as well as fibre applications, a key advantage being its hydrolysis to lactic acid, a metabolite in the carboxylic acid cycle. The success of polylactide highlights the commercial and environmental potential for plastics sourced from plants, with renewable life cycles and which are carbon neutral (Fig. 1).[1]

PLA is currently manufactured on a large scale in the US and by smaller enterprises in the EU and Japan.[2] The applications for polylactide are enhanced by its biocompatibility and its ability to be absorbed and degraded *in vivo*; furthermore, it is an FDA approved substance for use in therapy. It has been used for some time in biomedical applications such as sutures, stents, dental implants, vascular grafts, bone screws and pins. It has also been investigated as a vector for drug delivery, for example in the long-term delivery of antimicrobial drugs, contraceptives and prostate cancer treatments.[3] PLA has been widely used in the field of tissue engineering as a scaffold material to support cell and tissue growth. However, for many applications, PLA is not an ideal material due to its high crystallinity, brittleness, lack of total absorption and thermal instability. Further drawbacks are that it is unfunctionalized and hydrophobic; these properties

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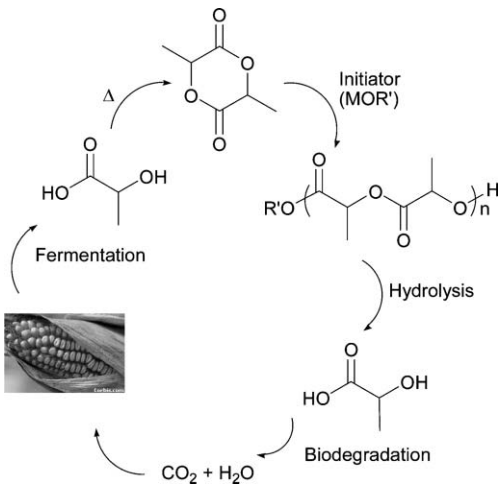


Fig. 1 The life cycle of polylactide (PLA).

impede its biodegradation and prevent targeting of the treatment.

It is important to develop strategies toward and syntheses of functionalized aliphatic polyesters and in particular to develop routes to functionalize them with biologically relevant and compatible molecules. There are two types of synthesis used: condensation/step polymerization of functionalized diols and diacids and ring opening polymerization of functionalized lactones. This review will summarize the salient features of these two syntheses, highlighting recent advances with reference to selected examples of interesting materials rather than providing a comprehensive overview of all functionalized aliphatic polyesters.

Condensation polymerizations

The first syntheses of aliphatic polyesters were by condensation or step polymerization, *i.e.* the reaction of a diol with a dicarboxylic acid (AA + BB) or the condensation of a hydroxy-acid (AB); both reactions result in the elimination of stoichiometric equivalents of water. The major drawback of step polymerizations is the need to achieve very high conversions to produce polymers and this places stringent requirements on the position of the esterification equilibrium, the absence of cyclization reactions, and for AA + BB type polymerizations the use of precise reagent stoichiometry. Therefore, condensation polymerizations are often carried out in a driven system, accomplished by the use of vacuum, temperature or gas to remove the water produced. Another disadvantage of step polymerization is the broad molecular weight distribution that results from the inability to accurately control the polymer's molecular weight. Aliphatic polyester synthesis presents further problems as the monomers are often thermally unstable and side reactions such as dehydration or decarboxylation readily occur. Therefore, traditional methods to drive the polymerization equilibrium are frequently not suitable for aliphatic polyester synthesis.

In the light of the limitations of traditional step polymerization techniques, there is considerable drive to discover mild, chemo- or biocatalytic routes to prepare functionalized aliphatic polyesters. The syntheses highlighted will illustrate some of these milder step polymerization techniques and will focus on the incorporation of carbohydrates into the polyester backbone. Carbohydrates are of interest due to their high degree of chemical functionality, in the form of hydroxyl or protected hydroxyl groups, and for their plethora of easily accessible regio- and stereoisomers. They are also renewable resources that are both abundant and relatively inexpensive; as an example of their economic potential, D-glucose is produced at 5 million metric tonnes per annum and at a cost of \$0.76 kg^{-1}, which compares with methyl methacrylate production at 2.1 million tonnes per annum and a cost of \$1.32 kg^{-1}.[4,5] Carbohydrates are already established biodegradable materials, many of which have well defined degradation pathways (*via* the Krebs cycle) with a very wide range of medical and biological applications. For example, cell surface carbohydrates are involved in numerous biological functions, including cellular recognition, adhesion, growth regulation and cancer cell metastasis. However, the natural glycopolymers displaying these cell surface carbohydrates are heterogeneous and their structures are ill-defined. Synthetic carbohydrate-based polymers are emerging as useful tools for investigating carbohydrate interaction processes as well as interesting materials for biomedical applications.[6] However, their application in drug delivery or tissue engineering requires the design and efficient synthesis of materials incorporating well defined carbohydrate moieties and degradable, biocompatible backbones.

The chemical syntheses of aliphatic polyesters with carbohydrate incorporation require methods to protect the secondary hydroxyl functional groups and prevent formation of highly branched polymers. Guan and co-workers have recently described a seven step synthesis of a highly methyl ether substituted polyester derived from dulcitol; the polymerization step is shown in Fig. 2.[7] The polyester was unusual as it was both highly functionalized and degradable; it also behaved like a side chain poly(ethylene glycol) (PEG). Surface plasmon resonance spectroscopy was conducted to study protein adsorption and it was found that the material has excellent resistance to fibrinogen.

Galbis *et al.* have synthesized a series of copolymers from alditols and aromatic dicarboxylic acids that serve as renewable analogues for PET and PBT.[8] Recently, the same group described the synthesis of aliphatic polyesters by condensation of alditols with adipic acid or aldaric acids with 1,4-butanediol.[9] They contrasted several synthetic methods and found reasonable M_n were obtained by combining the diol and diacid with diisopropyl carbodiimide and 4-(dimethylamino)-pyridinium tosylate in methylene chloride at room temperature. The decomposition temperatures of the resulting polyesters were moderate (around 220–230 °C) and they displayed a T_g below room temperature in most cases. The degradation time appeared to depend on the stereochemistry of the alditol, with those derived from D-arabinitol taking significantly longer to degrade at 60 °C than those from D-xylitol. Generally, all the chemical condensation methods are hampered by the lengthy syntheses of the monomers, which involve the use of several protecting groups and provide only modest overall yields.

An alternative approach was to use biocatalysts, such as lipase enzymes, to catalyze the condensation of diol and diacid or diester monomers. This approach is especially useful for highly functionalized carbohydrates as it circumvents the need

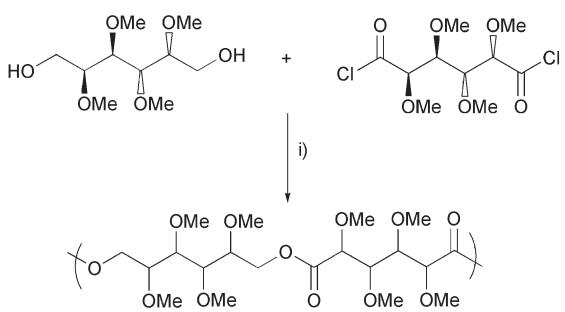


Fig. 2 Condensation polymerization to produce carbohydrate-derived side chain polyether.[7] Reagents and conditions: (i) NEt_3, CH_2Cl_2.

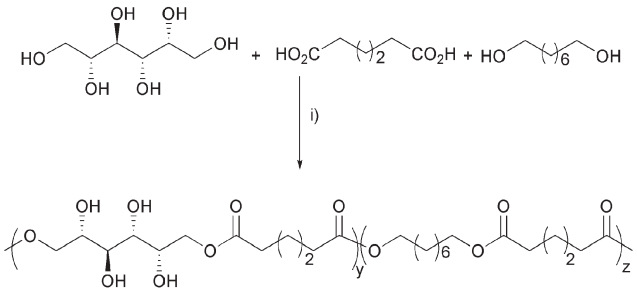


Fig. 3 Copolymerization of sorbitol, octanediol and adipic acid. Reagents and conditions: (i) Novozyme 435, 90 °C, bulk, 42 h, vacuum.

for elaborate protection–deprotection strategies because the lipase enzymes are selective for the primary over secondary hydroxyl groups in esterification reactions. Several groups have outlined methods to incorporate highly functionalized carbohydrates into polyester backbones by using lipases such as Novozyme 435—a lipase B from *Candida antarctica* immobilized on a Lewatit resin. This was attractive as they were regioselective, reacting faster with the C-6 hydroxyl group on the glycosides; they also required mild reaction conditions, which favored the thermally sensitive monomers required in aliphatic polyester synthesis (Fig. 3). Initially, attention focused on the condensation of activated esters with alditols, for example Kim and Dordick used a combinatorial approach to discover that Novozyme 435 was a good catalyst for production of poly(sorbitol adipate) of M_n 20 kDa.[10] A divinyl ester, *e.g.* divinyl adipate, was used as the monomer because the condensation product is vinyl alcohol, which undergoes a rapid and irreversible isomerization to acetaldehyde, which was used to drive the polymerization. In a recent development, Gross and co-workers carried out Novozyme 435 catalyzed copolymerizations under mild conditions and without needing to use activated esters; instead they combined sorbitol, octanediol and adipic acid to produce high molecular weight copolyesters incorporating up to 50% sorbitol (Fig. 3).[11] These copolyesters showed an increased thermal stability and a decreased melting temperature as the weight fraction of sorbitol increased.[12]

Very recently, Gross *et al.* have extended this condensation polymerization method to include other alditols, *e.g.* erythritol, xylitol, ribitol, glucitol, mannitol and galactitol.[13] They observed that precise vacuum control was of key importance in obtaining reproducible results and also that the stereochemistry at the β-carbons influenced the rate and M_n of the polyester; an *R*–*R* relative stereochemistry, as observed for mannitol, resulted in the fastest polymerization but also led to increased branching due to polymerization occurring from secondary as well as primary hydroxyl groups. Whilst these approaches are versatile and have yielded a range of new materials, they still require the preparation of AA and BB type monomers and the subsequent tight control of the reaction stoichiometry to access high molecular weight polymers. Furthermore, the polymerizations are not controlled and the polydispersity indices (PDI) of the resultant polymers are broad.

Ring opening polymerizations (ROP)

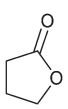
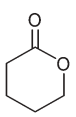
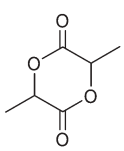
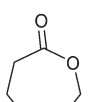
The ring opening polymerization of lactones is an attractive method to synthesize aliphatic polyesters because it enables living polymerizations to be conducted and therefore provides a route to tightly control the polymers' physical properties and polydispersity indices. The thermodynamic driving force for the polymerization is the relief of ring strain, which enables the entropy, unfavorable in all polymerizations, to be overcome. A range of simple lactones of varying ring size and strain have been investigated, as shown in Table 1.[14]

Four or seven membered rings have greater ring strain than five or six membered rings and therefore there is a greater thermodynamic driving force for their ROP. Generally, the influence of substituents on the rings is to decrease the ring strain and thereby the polymerizability of the rings. Thus, the ring strain decreases in the order glycolide > lactide > tetramethyl glycolide. This is attributed to interactions between substituents being more pronounced in the linear *versus* the cyclic molecules.

The generally accepted mechanism for ring opening polymerization involves initiation by either an anionic, cationic, coordination–insertion or an activated monomer mechanism. The coordination–insertion mechanism (Fig. 4) is commonly used as it is a living polymerization, enables access to high molecular weight polymers and does not epimerize stereocentres such as those found in lactide.

The mechanism operates *via* the coordination of the lactone to a Lewis acidic metal alkoxide complex, which activates and attacks the lactone at the carbonyl carbon. Acyl bond cleavage results in ring opening and the generation of a novel metal alkoxide species from which the cycle can re-initiate. Many metals have precedent for initiating the coordination–insertion polymerization, the common features being that they are Lewis acidic with a labile metal alkoxide or amide bond from which

Table 1 Enthalpy and entropy of ROP for selected lactones (298 K)

Ring size					
	β-Propiolactone	γ-Butyrolactone	δ-Valerolactone	Lactide	ε-Caprolactone
ΔH/kJ mol^{-1}	−82.3	5.1	−27.4	−22.9	−28.8
ΔS/J mol^{-1} K^{-1}	−74[a]	−29.9[a]	−65.0[a]	−25.0[b]	−53.9[a]

[a] [Monomer] = 10 M, conducted in liquid monomer. [b] [Monomer] = 1 M, conducted in solution. The values are taken from ref. 14.

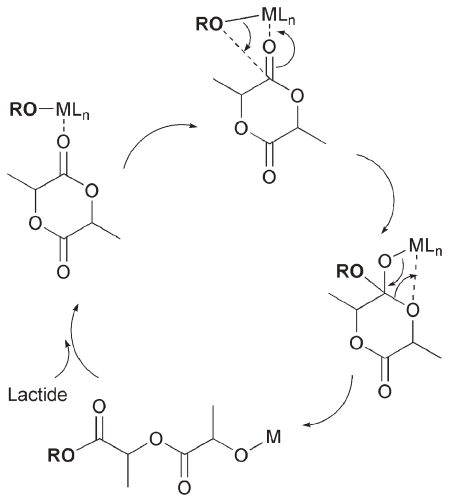


Fig. 4 Coordination–insertion mechanism for lactide ROP.

to initiate the polymerization; several excellent reviews already cover the selection and range of initiators tested.[15,16]

More complex lactones can also be polymerized by ROP, including those with functional substituents; the most explored class were those derived from ε-caprolactone with substitution at the 3-, 4- or 5-positions. Other rings have also been investigated, including substituted β-propiolactones, valerolactones, lactides and glycolides. The ROP of functionalized lactones has recently been comprehensively reviewed;[17] here attention will focus on selected classes of functionalized lactones and their use to moderate the physical and chemical properties of the polyesters.

Carbonyl functionalized poly(ε-caprolactone)

The ROP of 5-keto-ε-caprolactone has attracted attention for several reasons: the monomer can be synthesized in high yield, it has sufficient ring strain to enable homopolymerization and either the monomer or polymer can be further derivatized. The efficient monomer synthesis was a very important factor and the overall synthetic scheme is shown in Fig. 5, whereby 1,4-cyclohexanedione was oxidized using the Bayer–Villiger oxidation in good yield. The novel monomer was polymerized to produce a highly crystalline polyester with a T_m of 150 °C, which compares with the T_m for ε-caprolactone of 59 °C.[18]

Further to this work, Mayes *et al.* recently demonstrated the chemoselective grafting of aminoxy terminated PEG to copoly(5-keto-ε-caprolactone-ε-caprolactone).[19] Although the coupling reaction was slow and did not always go to 100% conversion, it was still a useful method to install PEG functionality onto the polyester backbone due to the mild conditions employed and the lack of backbone polyester degradation. PEG confers hydrophilicity to the polyester and at substitutions greater than 50% the polymer becomes water soluble, which is of potential utility for drug delivery or medical applications.

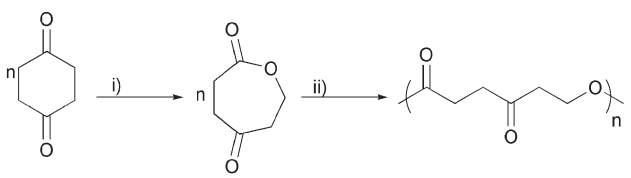


Fig. 5 Synthesis of poly(5-keto-ε-caprolactone). Reagents and conditions: (i) *m*-CPBA; (ii) $Bu_2Sn(OMe)_2$.

Halide functionalized poly(ε-caprolactone)

6-Chloro-ε-caprolactone was also prepared *via* a Bayer-Villiger oxidation, from 6-chlorocyclohexanone in reasonable yield. Jérôme *et al.* recently published an interesting study using 6-chloro-ε-caprolactone (Fig. 6).[20] It was polymerized or copolymerized with ε-caprolactone to produce novel polyesters with pendant chloro groups. The chloro groups were subsequently converted into azido moieties by reaction with sodium azide. Building upon previous work by Emrick and his group,[21] the azido functional group was applied in the 'Click' chemistry reaction with an alkyne group, to form a triazoline. Key to the success of this method was the development of non-aqueous coupling conditions (using CuI, THF and DBU), which enabled coupling of a range of alkynes without any backbone degradation being observed. By changing the base to NEt_3, copoly(6-azido-ε-caprolactone-*b*-lactide) could be derivatized without polylactide degradation, for the first time. The Click coupling chemistry is useful due to its biocompatibility; indeed, it is a ubiquitous method to install functionality into biological molecules.

Hydroxyl functional groups

The hydroxyl group is a useful substituent because it increases hydrophilicity, aids solubility in water and undergoes many reactions compatible with biological substrates. However, the direct attachment and ROP of hydroxyl substituted lactones is not always feasible due to their instability and propensity to

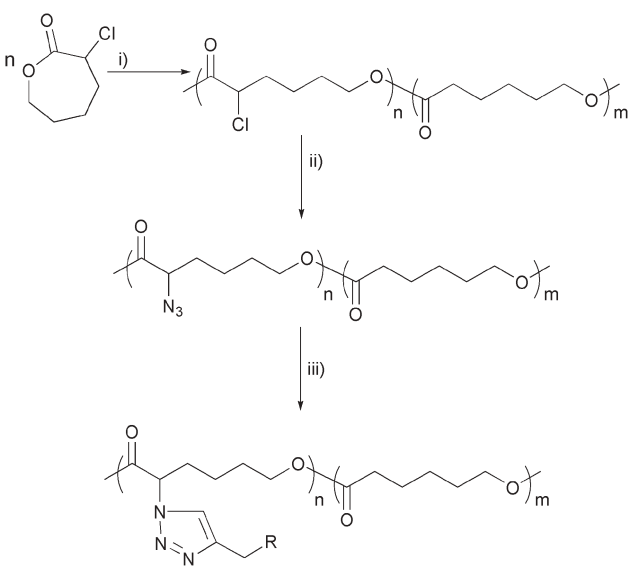


Fig. 6 Synthesis of azido substituted poly(ε-caprolactone) and subsequent Click coupling reactions. Reagents and conditions: (i) 2,2-dibutyl-2-stanna-1,3-dioxepane, *m* ε-caprolactone; (ii) NaN_3, DMF, 25 °C, 20 h; (iii) CuI, DBU, THF, 35 °C, $CHCCH_2R$, where R is OCOPh, NEt_4Br, NMe_2.

undergo side reactions, *e.g.* transesterification or ROP. Thus 5-hydroxyl-ε-caprolactone is unstable and undergoes a rearrangement to 4-ethylhydroxyl-γ-butyrolactone, which is not a polymerizable monomer. Furthermore, even if hydroxyl substituted lactones are stable, they cannot be reacted with metal initiators to form linear hydroxyl substituted polyesters due to their ability to initiate the ROP—if unprotected hydroxyl groups are present, highly branched polyesters are formed. Indeed, this strategy has been deliberately used by Fréchet and co-workers to prepare hyperbranched polyesters.[22] Thus 4-(2-ethylhydroxyl)caprolactone was polymerized to produce a hyperbranched polymer with M_w 65–85 kDa (Fig. 7). The hyperbranched polymer had a high density of hydroxyl functionalities at the chain ends, which could be further derivatized. Parzuchowski *et al.* have synthesized related hyperbranched aliphatic polyesters but using 5-hydroxymethyl-1,4-dioxan-2-one, which was synthesized from the renewable resource glycerol.[23]

Linear polyesters with pendant hydroxyl groups can be prepared by protection of the hydroxyl groups followed by a post polymerization deprotection. One successful example is the reduction of poly(5-keto-ε-caprolactone), discussed earlier, with $NaBH_4$ at room temperature, which produced poly-(5-hydroxyl-ε-caprolactone) without any chain scission, as detected by GPC or ^{1}H NMR spectroscopy.[24] A protecting group strategy has also been applied to functionalize poly-(valerolactone). 3-Allylvalerolactone was synthesized in excellent yield by reaction of valerolactone with lithium diisopropylamide (LDA) and allyl bromide.[25] It was polymerized using $Sn(OTf)_2$ to produce a polymer with a degree of polymerization of 60, which was totally amorphous and in fact was a liquid at room temperature. It was also copolymerized with ε-caprolactone or valerolactone. Then, the allyl group was dihydroxylated using *N*-methylmorpholine *N*-oxide (NMO) and OsO_4 to yield copoly[(3-(2,3,-dihyroxypropyl)-valerolactone)-*b*-(ε-caprolactone)] without significant chain degradation. However, it was noted that a slow degradation occurs over time (the M_n decreased by ⅙ over seven days) and this was due to attack by the hydroxyl groups on the polyester backbone. The degradation was much more rapid for the homopolymer and, in fact, precluded isolation of the dihydroxylated product.

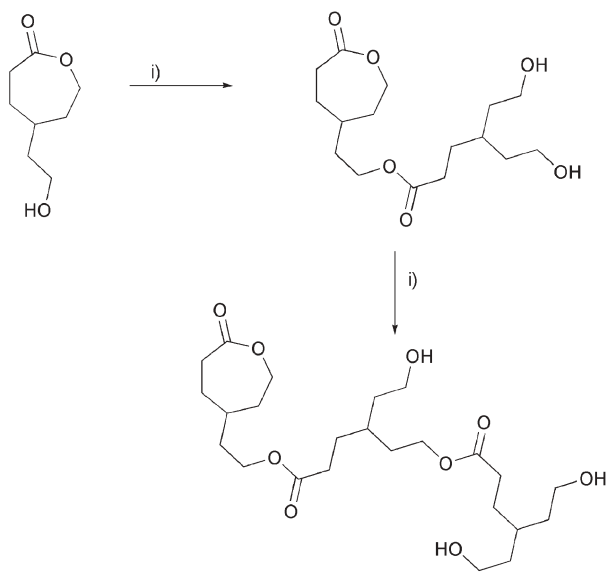


Fig. 7 Synthesis of hyperbranched poly(ε-caprolactone) by ROP of 4-(2-ethylhydroxyl)caprolactone. Reagents and conditions: (i) 0.01 $Sn(Oct)_2$, 110 °C, 1 h.

Unsaturated groups

Unsaturated ε-caprolactone derivatives can be polymerized using ring opening polymerization or metathesis polymerization to yield polyesters with unsaturated moieties in the main chain. Jérôme *et al.* polymerized 6,7-dihydro-2(5*H*)-oxepinone using $Al(O^iPr)_3$. The unsaturated monomer was slower to polymerize than ε-caprolactone, the reactivity being reduced by conjugation of the carbonyl group with the internal double bond. The unsaturated group is potentially useful for cross linking or epoxidation reactions.[26]

Functionalized end groups

Ring opening polymerization controls the polymer's end group according to the type of initiator used; therefore, by judicious choice of initiating alcohol or amine group it is possible to install functionality to the chain ends as ester or amide groups (Fig. 4). The majority of ROP studies focus on the use of 'simple' alcohols such as ethanol or benzyl alcohol, however, some have addressed the application of functionalized initiators. An interesting synthesis was reported by Kricheldorf and Kreiser-Saunders, and later applied by Stupp *et al.*, using vitamins, hormones and drugs to initiate lactide polymerization.[27,28] Thus, cholesterol functionalized oligo(lactide)s were synthesized by initiating the ring opening polymerization of lactide from cholesterol using either $AlEt_3$ or $Sn(Oct)_2$ (Fig. 8).[28] The oligomers were fully characterized, including by DSC, which showed a T_g of 32 °C and two phase transitions at 57 and 88 °C resulting from the liquid crystalline behaviour of the oligomers. The same paper describes an alternative method to functionalize the chain ends, which involves coupling the secondary alcohol terminus of the PLA with carboxylic acids using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 4-(dimethylamino)pyridine or diisopropylcarbodiimide (DDC) and 4-(dimethylamino)pyridinium tosylate (Fig. 8).[28] The coupling methods were useful due to the mild conditions and excellent yield, which enabled attachment of bioactive substituents such as drugs or fluorescent tags that might not have been compatible with metal initiators.

Using functional end groups to initiate ROP is a well established and large research area, so this section is restricted to the incorporation of carbohydrates at the end of aliphatic polyester chains. This is relevant as they are biocompatible, renewable resources with large numbers of functional groups and also provides an interesting contrast to the methods applied for incorporating carbohydrates into condensation polymerizations. Alkyl glycosides or acetal protected monosaccharides were investigated by a number of groups as initiating groups for either metal or enzyme initiated lactone ring opening polymerization.[29–34] Kricheldorf and Stricker synthesized stannylated glycosides as cyclic initiators for

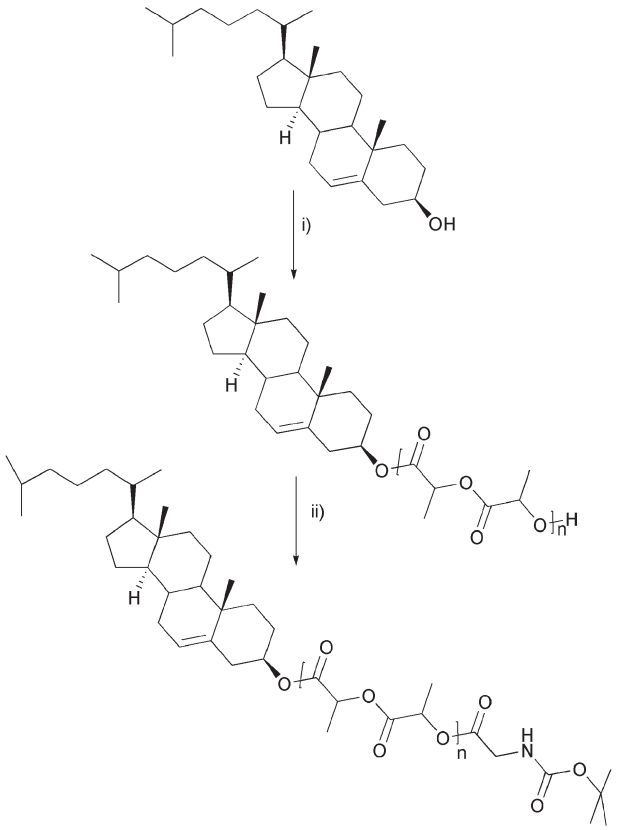


Fig. 8 Synthesis of PLA end-capped with cholesterol and *N*-(*tert*-butoxycarbonyl)glycine. Reagents and conditions: (i) *n* (*S*)-lactide, $AlEt_3$, toluene, 80 °C, 5 h; (ii) EDC, *N*-(*tert*-butoxycarbonyl)glycine, DMAP, CH_2Cl_2, 0 °C, 4 h.

ε-caprolactone polymerization; they discovered regioselective insertion of the lactone into the six membered ring at the Sn–O bond in the C-6 position.[35] However, there are only limited examples of lactide polymerizations initiated by carbohydrate groups and very few of these are controlled.[33] Gross and co-workers used lipases and ethyl-D-glycoside as initiators for the C-6 regioselective polymerization of ε-caprolactone.[29] The ethyl-D-glycoside terminated oligo(caprolactone) was subsequently used as an initiator in the tin octanoate polymerization of lactide and proved an interesting method to synthesize a multiarm copolymer. Katoaka *et al.* reported regioselective polymerization initiated at C-3 for D-glucose and the C-6 for D-galactose, by using isopropylidene acetal protected carbohydrates (Fig. 9).[30] The initiators were *in situ* generated potassium alkoxides, which were used to produce PEG–PLA block copolymers with a protected sugar end group at the PEG end. The protecting group was cleaved using mildly acidic conditions, which did not degrade the PLA backbone, and the copolymer with D-galactose installed showed selective lectin binding.[36]

Ouchi and co-workers reported the synthesis of PLA grafted to polysaccharides using the polysaccharide as a degradable and hydrophilic backbone with TMS protecting groups to selectively initiate lactide polymerization. The PLA grafted polysaccharide gave a microphase separated structure and showed faster biodegradation than PLA.[37] In a recent report, Ouchi *et al*. showed that PLA end-functionalized with amine

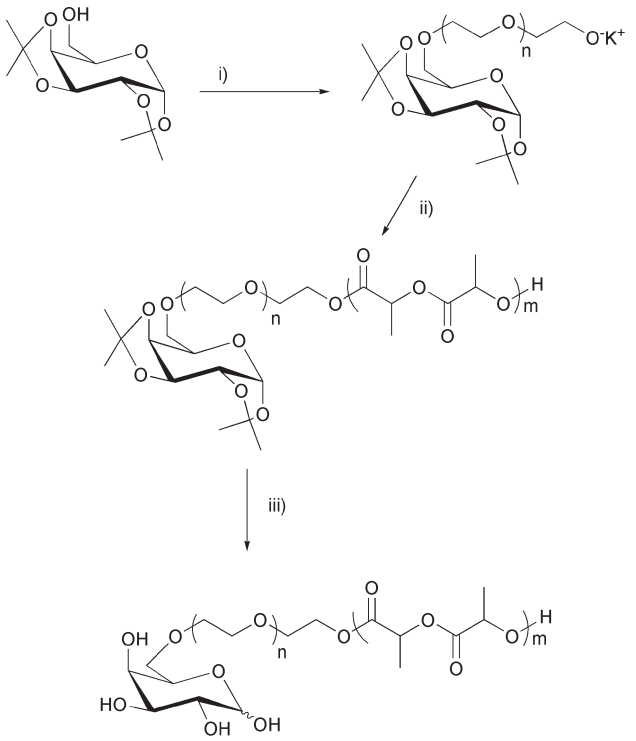


Fig. 9 Synthesis of D-galactose end-functionalized copoly(ethylene glycol-*b*-lactide). Reagents and conditions: (i) potassium naphthalenide, *n* ethylene oxide; (ii) *m* (*R*,*S*)-lactide, H^+; (iii) 80% CF_3CO_2H.

groups could react with lactonolactone, without the need to protect any of the hydroxyl groups, to produce a lactose end-capped PLA (Fig. 10).[38]

We recently reported a highly unusual oligomerization of carbohydrate derived lactones.[33,34] Thus 2,3,4,6-tetra-*O*-acetyl-D-gluconolactone was oligomerized by reaction with catalytic quantities of $Sn(Oct)_2$ and alcohols to yield oligoesters of up to three repeat units (Fig. 11). The oligoesters were interesting products in their own right, but were also used to initiate lactide ROP to produce PLA with highly functionalized oligoester end groups.

Iversen *et al*. investigated the cationic ring opening oligomerization of ε-caprolactone, catalyzed by lactic acid and initiated with methyl-β-D-glucopyranoside, sucrose or

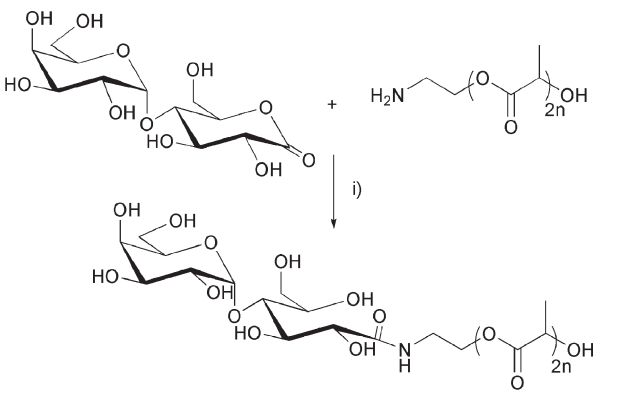


Fig. 10 Synthesis of PLA end-capped with a lactose derivative. Reagents and conditions: (i) DMF, 80 °C, 24 h.

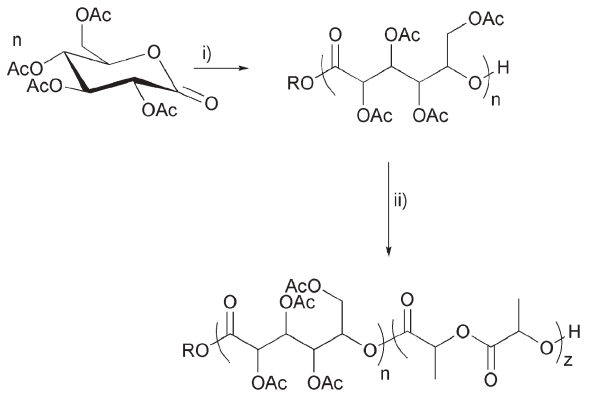


Fig. 11 Synthesis of highly functionalized oligo- and copolyesters from sugars. Reagents and conditions: (i) $Sn(Oct)_2$, 3ROH (ROH = butanol, benzyl alcohol, butanediol), 80 °C, 8 h; (ii) (*R*,*S*)-lactide, LZnEt, CH_2Cl_2, 25 °C, 20 h.

raffinose.[32] The M_n was limited to less than 5 kDa using this route and initiation was shown to mostly occur from the primary alcohol groups on the carbohydrates. Recently, cyclodextrins were found to initiate lactone polymerization without the need for any catalyst or additive. This is an intriguing result, not least due to the unusual mechanism which must be operating.[39]

Grafting to polyester surfaces

An alternative strategy to functionalize polyesters is to graft functional monomers/polymers to their surfaces. This strategy is superior to physical adsorption or coating due to the improved environmental stability. Conventional grafting techniques for polymers are based on γ, electron beam, X-ray or UV light irradiation, which generate free radicals in the substrate that initiate the radical polymerization of vinyl monomers. However, only a few biodegradable polymers can be grafted using this technique (*e.g.* poly(ε-caprolactone)) and it is not a viable route for polylactides due to their susceptibility to degradation. Recently, Albertsson *et al.* reported a novel, mild mutual irradiation technique whereby PLA surfaces were subjected to gaseous acrylamide, maleic anhydride or *N*-vinylpyrrolidone and polymerization was photo-initiated with benzophenone, under solvent-free conditions.[40] The modified surfaces exhibited higher wettability and the grafting was verified using X-ray photoelectron spectroscopy, ATR-FTIR, contact angle measurements and SEM.

Conclusions

The synthesis of functionalized aliphatic polyesters is attracting considerable attention due to their applications as sustainable alternatives to commodity plastics and their specialist applications in niche medical markets. The introduction of functionality is especially important as it enables control of the physical and chemical properties of the resultant polyesters, for example the T_g or degradation rate. The two major methods to synthesize functionalized biodegradable polyesters are by mild step polymerization techniques or by ring opening polymerization of functionalized lactones. The step polymerization method has proved particularly effective for the introduction of a large number of substituents per repeat unit (*e.g.* copolymerization with alditols) using chemo-enzymatic methods that are both mild and regioselective. However, it suffers from the drawbacks of requiring high monomer purity, precise control of monomer stoichiometry and an inability to control the polymer's M_n or PDI. The ring opening polymerizations of functionalized lactones, on the other hand, are highly controlled and therefore offer accurate control of the polymer's M_n, PDI, structure of the repeat unit, tacticity and morphology. Thus, a wide range of functional groups have been introduced using this method, including keto-, halo-, hydroxyl- and alkene. It suffers from the drawbacks of complex monomer syntheses and the need to protect certain functionalities (*e.g.* hydroxyl) to prevent side reactions. Finally, if a lower degree of substitution can be tolerated, then the end groups of conventional biodegradable polyesters (*e.g.* PLA) can be easily functionalized. There are two main methods to accomplish this functionalization: by initiation of a controlled polymerization from a functionalized alcohol initiating group, *e.g.* vitamins, hormones, carbohydrates, or by the post-polymerization coupling of functional groups to the hydroxyl end group of PLA. Although the end group is unlikely to influence the bulk properties of the material, it can influence the surface properties and even the morphology of the polymers. Post-polymerization functionalization by grafting to PLA is generally unsuccessful but it has recently been reported using a very mild irradiation technique. In general, this method is not widely applicable due to problems with backbone scission and the requirement for volatile co-monomers.

The outlook for the synthesis of functionalized biodegradable polymers is good due to an ever increasing demand for well characterized and defined functionalized materials for biomedical studies and for versatile, inexpensive and general methods to make new materials for packaging and commodity plastics applications. There is still much potential for the development of novel polymerization methods, in particular those that are mild, use easy to synthesize monomers, use renewable resources and are generally applicable will be very useful. More research is also required to delineate the structure–activity relationships for functionalized aliphatic polyesters so that in future the required properties of the material can be easily selected from a range of functionalized monomers.

Acknowledgements

The EPSRC is gratefully acknowledged for funding (EP/C544846/1, EP/C544838/1, GR/T17960/1). Anita Haider is thanked for the graphical abstract image.

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