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Branched polyesters: Preparative strategies and applications☆

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ABSTRACT

In the last 20 years, the availability of precision chemical tools (e.g. controlled/living polymerizations, 'click' reactions) has determined a step change in the complexity of both the macromolecular architecture and the chemical functionality of biodegradable polyesters. A major part in this evolution has been played by the possibilities that controlled macromolecular branching offers in terms of tailored physical/biological performance. This review paper aims to provide an updated overview of preparative techniques that derive hyperbranched, dendritic, comb, grafted polyesters through polycondensation or ring-opening polymerization mechanisms.

Contents

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1. Nomenclature

It is worthwhile summarizing the IUPAC-recommended nomenclature [1–3] in terms of branched macromolecules:

- star polymers: characterized by the presence of one single point of branching, from which linear chains originate. The functionality of this point is referred to as the number of arms (linear chains) departing from it. Star polymers are prepared either through convergent ("arm-first", "arm-in") or divergent ("core-first", "arm-out") approaches (Fig. 1). The independent synthesis of the arms ("arm-first") allows for their better characterization, but steric hindrance may make functionalization of the core far from quantitative, above all when the arms are many and/or have a large molecular weight. The resulting uncertainty in the actual number of arms makes this approach considerably less common than the "core-first". A star polymer is defined as miktoarm (or μ-star) when some arms are chemically different from others.
- graft polymers: when side chains of any architecture are connected to a main chain that differs in chemical composition. Graft polymers are prepared by coupling pre-formed side chains onto the main chain (*grafting on* also referred to as *grafting to*), (co)polymerizing appropriate macromonomers (*grafting through*) or producing side chains in situ via initiation from pendent groups of the main chain (*grafting from*). A special case of *grafting through* occurs when a macromonomer bears multiple polymerizable groups along its main chain; in a copolymerization with low molecular weight monomers, the latter are technically *grafted from* the polymer chains; here we will refer to this hybrid mechanism as *cross-linking through*.
- comb polymers: when regularly or irregularly spaced linear side chains depart from branch points on a main chain. Comb polymers are therefore a special case of graft macromolecules (more commonly obtained via *grafting through*), and in this review we will refer to all grafted macromolecules with linear polymeric side chains as combs; however, if the comb is only a block of a more complex structure, the latter will be generically referred to as a grafted polymer. Occasionally the expression 'brush polymer' is used for combs where branching points have a functionality > 3.
- dendritic and hyperbranched polymers: in both cases the macromolecule presents a nested structure of branch points that has a regular and cascade-like architecture for dendritic polymers, and is randomly organized for hyperbranched polymers, which have a statistically identical number of subchains in any direction. It is possible to differentiate the two categories based on the distribution of the branch point 'seniority'; seniority is a concept expressing the increasingly slow relaxation behaviour of branch points with their internal character [4], and while dendritic polymers present a topologically ordered seniority (higher at the origin), hyperbranched ones present no such order. In the preparation of dendritic polymers, one can adopt the same divergent and convergent approaches seen for star polymers; however, please note that in the latter case complex and multifunctional dendrons (as opposed to linear arms) are synthesized before their linkage to the core.

A final nomenclature note: high molecular weight macromolecules with the CH_2CH_2O repeating unit are often referred to as poly(ethylene oxide), PEO, or poly(oxyethylene), POE. Here we will refer to them only as poly(ethylene glycol), PEG.

2. Introduction: peculiarities introduced by branching

Aliphatic polyesters are ubiquitous in the biomedical field. Their defining point is the controlled degradability, i.e. the hydrolytic conversion of polyester backbones into compounds that present a low toxicity and in most cases are already part of our metabolic processes. We refer the reader to more specialized reviews in order to appreciate the breadth of the applications of biodegradable polyesters, which includes screws and other forms of orthopaedic fixators [5,6], macroscopic fibres/sutures [7], nanofibres [8], scaffolds [9,10] etc., and notably their use also extends to matrices for controlled release, e.g. as injectable microparticles [11,12], as thermally gelling systems [13], as nano-carriers [14,15].

Traditionally, biodegradable polyesters have been employed in the form of linear polymers. In this review we focus on branched structures, whose peculiarities have attracted much interest in the last 25 years. The following list reports the key points of a branched vs. linear comparison, having specifically in mind applications as carriers for drug release

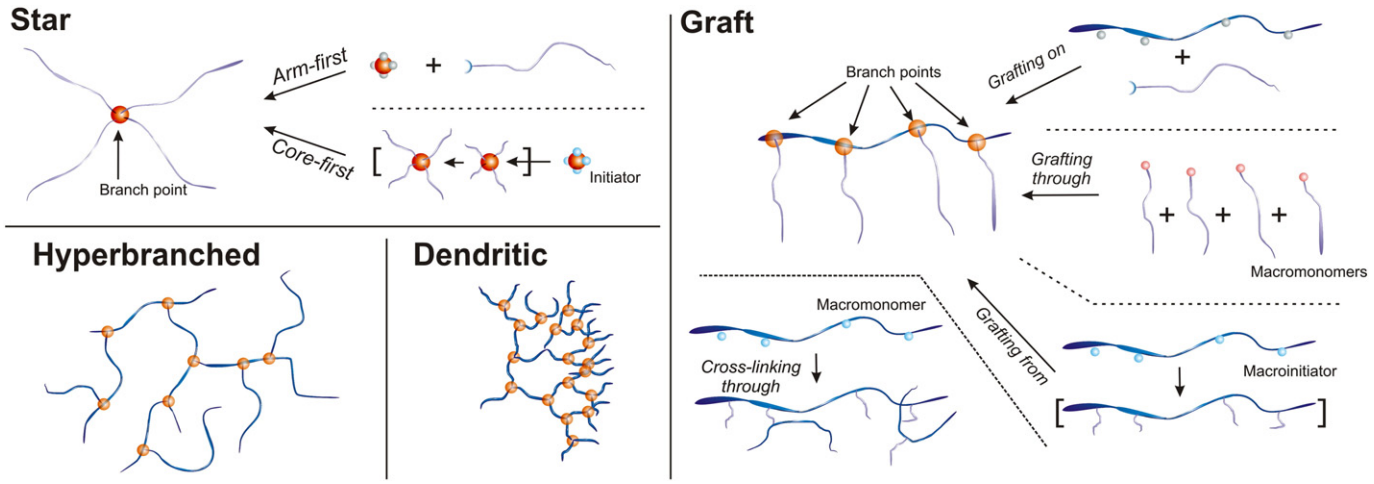

Fig. 1. Summary of the most common branch polymer architectures.

(as opposed to load-bearing ones); please note that the comparison implies a comparable degree of polymerization.

A) lower viscosity. The likelihood of entanglements between macromolecules is inversely proportional to their branching degree: at high densities of branching points the coils assume a more compact character, approximating globules/"hard spheres" (= decrease in radius of gyration; parameter a in the Mark–Houwink equation < 0.5, and even approaching 0 → invariance of intrinsic viscosity with molecular weight [16]). As a result, at any given concentration the viscosity of branched polymer solutions is typically much lower than that of their linear counterparts; this can be highly advantageous in the administration of therapeutics e.g. via injection of concentrated liquid formulations, as it has been demonstrated in the use of polyPEG (bottlebrush PEG) in protein conjugation [17].

B) chemical multifunctionality and presentation of functional groups. Branching inherently multiplies the number of chain ends, which can be engineered to bear chemically or biologically reactive functionalities. Increasingly with the density of branch points these functional end groups localize at the surface of the polymer coil.
For a more extended discussion of A) and B) we refer the reader to a seminal paper of Fréchet [18].

C) attractive aggregation behaviour. Nano-carrier structures often self-assemble under thermodynamic control, which implies that their stability depends not only on the interactions between their components but also (strongly) on the concentration of the latter. An appropriate example is the disappearance of micelles below their Critical Micellar Concentration (CMC). Upon injection into systemic circulation a micellar dispersion would experience a strong (1:100 or more) dilution, which, by bringing its concentration close or below its CMC destabilizes the system, thus resulting in a loss of control over the release of any encapsulated drug. However, as first stated by Hawker [19] and then confirmed by many others in the late '90s including Fréchet [20], in a core cross-linked micelle (i.e. an amphiphilic polymer branched in its hydrophobic block(s)) the hydrophobic cavities exist independent of dilution/concentration. The application of such internally cross-linked/hyperbranched carriers in drug delivery has been recently reviewed by Haag et al. [21].

D) effect of local polymer density on biological interactions. Branching implies a closer proximity between polymer segments. The vast literature describing the effect of crowding on the conformation of PEG chains ("PEG brushes") and on their biological interactions (reduced protein adsorption and cell adhesion with increasing density [22,23]) is an example of how these effects may play a major role in the performance of a biomaterial. It is also noteworthy that the polymer coil compaction induced by branching may influence the passive diffusion of macromolecules through bodily barriers, such as the renal endothelium; the impossibility of reptation may thus be the reason for the decreased renal clearance and longer circulation for polyester-PEG star polymers with increasing number of arms (2–8) [24].

E) effect on degradability. Branching can largely decrease the possibility of crystallization and self-association. Indeed it has been demonstrated that poly(L-lactic acid) (PLLA) increases both its chemical and enzymatic degradability proportionally to its degree of branching [25], and poly(glycolic acid) (PGA) increases its solubility [26], but it is important to note that these effects are obtained through rather short-chain branching, whereas long-chain branching may promote the opposite behaviour: for example, it induces accelerated nucleation and crystallization in star PLLA [27]. It is worth pointing out that loss of crystallinity can be a problem in structural terms, e.g. for the development of macroscopic and load-bearing devices such as screws; however, the materials considered in this review are predominantly applied as colloidal carriers, whose mechanical properties are less critical for their operational behaviour. Therefore the decrease/absence of crystallinity is not necessarily a weakness.

F) effect on molecular weight distribution. In comparison to a linear polyester, branching may lead to a sizeable increase in the breadth of the molecular weight distribution; this is later discussed in some depth for hyperbranched polymers obtained via step growth. In the perspective of obtaining regulatory approval, this can be seen as a disadvantage, due to the chemical heterogeneity of the material and the potential differences in performance of its differently sized components. However, these issues stem from the difficult reproducibility of a broad distribution rather than from its breadth per se.

With the above points as a motivation, we seek here to provide an up-to-date overview of the preparative methods for making branched polyesters, organizing them according to the nature of the monomers and polymerization mechanisms used. Firstly, we will focus on step growth (polycondensation) methods, continuing on to chain growth mechanisms; in this second part, we will also provide considerable information about the synthesis of functional monomers when their chemical functionality is instrumental to achieve branching.

3. Step growth (polycondensation) methods

3.1. Generalities

- The direct melt polycondensation of α-hydroxyalkanoic acids (AHAs, Fig. 2A) such as glycolic acid (GA) or lactic acid (LA) generally results in polymers with low molar masses (<10 kDa) and high dispersity values, which are inherent to step growth processes, but here is further complicated by the propensity to parasite processes, such as hydrolysis (from the water produced in the condensation), transesterification, back-biting/macrocyclization [28]; further, relatively low temperatures (<200 °C) are required to minimize the formation of cyclic dimers (glycolides, lactides), hence the resulting high melt viscosity becomes problematic. Among the solutions provided to alleviate the above problems, one can mention the use of:
  A) chain extenders, e.g. bis-2-oxazolines or diisocyanates that are reactive respectively towards carboxylic acids and alcohols [29].
  B) azeotropic removal of water through the use of solvents such as anisole or diphenyl ether [30]; the azeotropic polycondensation is compatible with a variety of catalysts, including Sn powder, SnO, $SnCl_2$ or *p*-toluenesulfonic acid (*p*TsOH), and has allowed to prepared poly(lactic acid) with molar masses exceeding 100,000 g/mol.
- Enzymatic catalysis has become increasingly popular; typically it is not directly performed on AHAs (converted only to oligomers [31]) but rather on their esters, most commonly alkyl lactates (through expulsion of alcohols), using lipases in a D-isomer-selective fashion [32] and proteases with the opposite L-isomer selectivity [33]. We direct the reader to a recent article of Kobayashi for a more in-depth review in the state of the art of lipase-catalysed polymerization chemistry, both for polycondensation and ring-opening polymerization mechanisms [34].
- Polyesters can also be produced through polycondensation of di-acids (or diesters) and diols, e.g. using succinic, adipic or fumaric acid in combination with ethylene glycol, 1,3-propanediol or 1,4-butanediol (A-A + B-B reactions, whereas the above examples referred to are A–B reactions), and some of these materials have reached the stage of sizeable industrial production [35]. These polycondensation reactions can be performed also under lipase catalysis as demonstrated by Kobayashi in the middle '90s [36]. However,

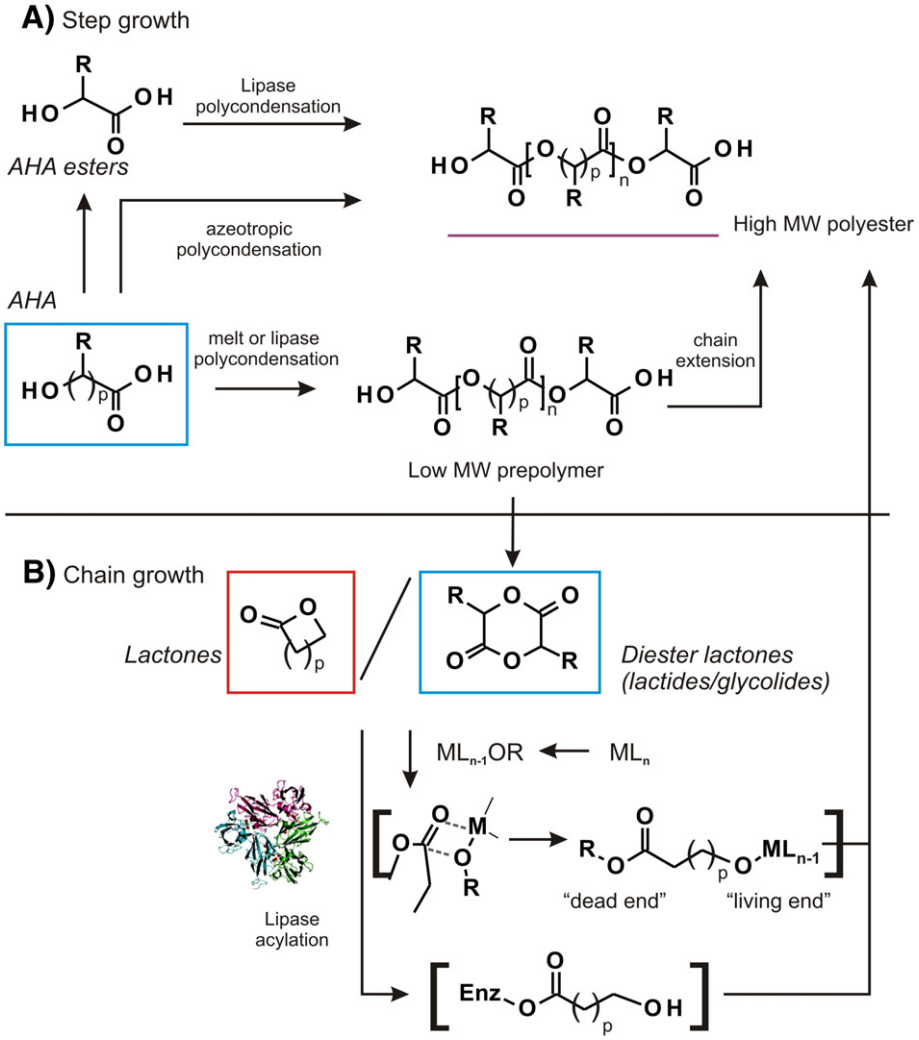

Fig. 2. Summary of the most common preparative strategies for aliphatic polyesters. Please note that for convenience the condensation reactions between diacids and diols have been omitted, since they follow the same paths described in A for AHAs. *A.* Chemically or enzymatically catalysed polycondensation of hydroxyacids provides oligomers that may only be converted into high MW products via chain extension. Alternatively, the azeotropic removal of water can suffice to push the polycondensation to high molar masses. Reasonably high masses can also be obtained using lipase on AHA esters. *B.* Better results, both in terms of molecular weight and of its dispersity, are obtained using the ROP of cyclic monomers, which in cases of lactides and glycolides are prepared via thermal depolymerization of low MW polyesters; lactones are on the contrary are produced through more classical organic means such as the Baeyer–Villiger reaction. In the case of chemical catalysis, M represents a Lewis acid metallic centre such as Sn, Mg or Ca, and L represents a generic ligand such as a 2-ethylhexanoate for Sn; the structures in square brackets represent the activated form of the monomer (left) interacting with an alcoholate complexed M, and the propagating species (right), with the linear ester showing a terminal M alcoholate. In the case of enzymatic catalysis, the key step is represented by lipase acylation leading to the so-called enzyme-activated monomer (in square brackets).

they are either performed through enzymatic processes or catalysed melt polycondensation, the major limitation of these processes is again the low molar masses of polymerization products, typically below 1–2 $*$ 10^4 g/mol [37].

3.2. Hyperbranched and dendritic polymers

3.2.1. Synthesis

In the preparation of hyperbranched polymers, the key point is to adjust the degree of branching and the concentration of unpaired reacting groups to avoid the formation of a macroscopic network, whereas at a nano-scale the macromolecule has a high volume density of branch points. Although eventually reduced to practice in the second half of the '90s, this idea was considerably older: in 1952 Flory pointed out that an AB_n type of monomer (where A and B are complementary reaction species such as carboxylic acids and alcohols) would give rise to highly branched polymers [38]. By far, the most common preparative process is the acid catalysed polycondensation, although recently also enzymatic processes have been attempted.

Among the former products, the so-called Boltorn™ polymers have been most extensively characterized and applied in drug delivery, since they were first described in 1995 by the group of Hult [39]. In analogy to dendritic structures, a core unit (typically a polyol such as tris(methylol)propane for a B_3 monomer/initiator, or pentaerythritol or its ethoxylated derivatives for a B_4) is employed at the beginning of the acid-catalysed polymerization and amounts of AB_2 monomers (typically 2-bis(methylol)propionic acid (bis-MPA)) are sequentially added to it (Fig. 3A). This "pseudo-one-step" process was performed with the aim to minimize the self-condensation of the AB_2 monomers, which would increase the molecular weight dispersity, reduce the control over the average molar mass and also increase the morphological heterogeneity of the sample. Always in analogy to dendrimers, polymers like Boltorn™ were initially categorized in generations, with each generation corresponding to the addition of a stoichiometric amount of the AB_2 monomer.

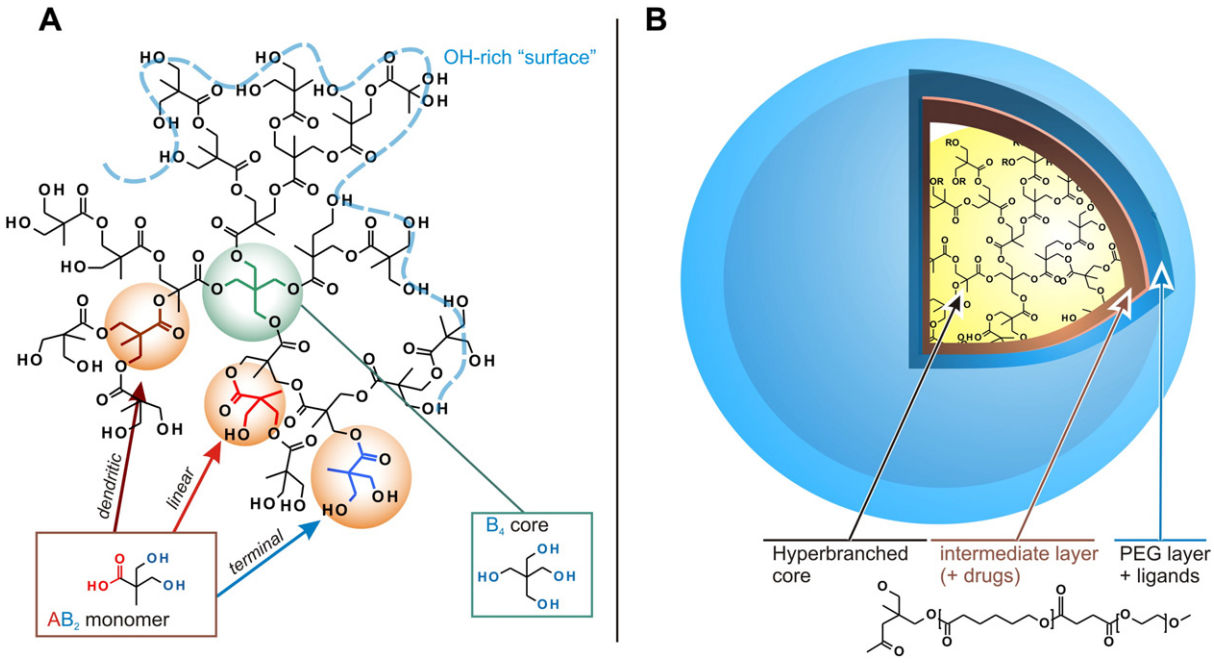

Fig. 3. *A.* An idealized structure of hyperbranched Boltorn™ polyesters obtained through the use a tetrafunctional core unit; the latter here is considered as completely reacted, although this typically is not the case. The example could correspond to a third pseudo-generation polymer (H30, according to Boltorn™ nomenclature); please note that the real H30 structure would comprise a significant number of intramolecular cycles, and also molecules missing the core unit. In an aqueous environment, the molecule would reorganize to reduce the water exposure of hydrophobic esters and increase that of alcohols, leading to a rather globular and OH-covered morphology *B.* Scheme of the multi-layer structure that could be achieved using a Boltorn™ core, a PCL intermediate layer and a PEG external shell. Also in this case, the picture represents an idealized structure; the different domains phase separate within the same molecular structure and would provide an onion-like structure due to the globular morphology (rather than molecular spherical shape) of the hyperbranched core.

Despite this hoped analogy, however, the structure of Boltorn™ polymers, turned out to be substantially undefined and a number of careful characterization studies (summarized e.g. in a review by Zagar and Zygon [40]) have progressively recognized important weaknesses in the preparative approach. Among them, it is worth mentioning that A) a large fraction of the hyperbranched polyester chains lacked a core unit, increasingly at low core/monomer molar ratios [41,42]; since these polymers are typically produced in the later stages of polymerization, they are predominantly to be found in the low molar mass end of the molecular weight distribution. B) The condensation reactions are far from quantitative, and the polymers comprise large amounts of linear units that do not contribute to the degree of branching. C) As shown by Frey in 2000 [43], intramolecular cyclization is also a common problem, limiting the maximum molecular weight achievable (please note that GPC/SEC was shown to provide unreliably high estimates) and also the degree of branching. Simulations demonstrated that a slow, in principle continuous monomer addition considerably improves the degree of branching obtained with the repeated addition of stoichiometric amounts of monomer [44]; however, this does not overcome the generation of cycles due to intramolecular transesterification, which is an inherent problem due to the reversibility of ester linkages under acid catalysis. D) It is also noteworthy that (irreversible) acid-catalysed ether formation takes place in the process and this can occur both intramolecularly (→decrease in molar mass) and intermolecularly (→increase in molar mass) [45].

Due to all the points above, the structural analogy to dendrimer generations is substantially not valid, and thus it is more appropriate to refer to the Boltorn™ products obtained via sequential additions of AB_2 monomer as pseudo-generations (as opposed to 'real' generations).

It is worth mentioning that Hult also developed dendrimeric analogues to the hyperbranched Boltorn™ [46]; please refer to Section 3.2.3 for their applications. Although less common, other AB_2 or also A_2B monomers have also been used to produce hyperbranched polyesters through the acid-catalysed polycondensation mechanism; for example, 3-[bis(2-hydroxyethyl)amino]propionic acid ethyl ester (AB_2) yields OH-terminated hyperbranched constructs with a tertiary amine-rich bulk [47], thus cationic and suitable for encapsulation of polyanions such as cytochrome C [48], whereas 2-(4-hydroxybutyl)malonic acid (A_2B) produces carboxylate-terminated polymers, with a more hydrophobic core than Boltorn™ [49].

Finally, although less common, lipase-catalysed polycondensation can also be used to prepare hyperbranched polyesters, e.g. by copolymerizing a diester [50] as an A_2 monomer, with glycerol as a branching monomer; glycerol bears three alcohols, two primary and a slower reacting secondary, thus acting as a $B'B_2$ monomer where only a fraction of B′ groups give rise to branching. The introduction of a flexible diol comonomer, 1,8-octanediol (bifunctional, a B_2 monomer), has apparently allowed to increase the degree of branching and the overall molecular weight of the polymer [51], which may be due to a lower likelihood of ring formation. Similarly, the AB_2 units of 2,2-bis(hydroxymethyl)butyric acid (structurally analogous to the bis-MPA at the basis of Boltorn™) also lead to hyperbranched polymers under lipase catalysis, although only in a mixed polymerization mechanism with ε-caprolactone ROP [52].

3.2.2. Hyperbranched polyesters (core–shell systems)

Despite the drawbacks just described, the Boltorn™ polyesters have been extensively employed as building blocks in the design of materials for various biomedical applications, taking advantage of the fact that in a water environment they behave as hydrophobic globules with a functional, poly-hydroxylated surface. For example, H40 (="4th generation") Boltorn™ polyesters have been employed as the cross-linked core of 'unimolecular' aggregates built by attaching hydrophilic PEG chains directly to the core [53,54] or through intermediate hydrophobic chains of poly(L-lactide) [55], poly(ε-caprolactone) (PCL) [56–58], poly(L-aspartate) [59] or poly(L-glutamate) [60], which are typically obtained via ROP using the Boltorn™ OH groups as initiators (Fig. 3B). PEG chains are used to provide long circulation times in vivo and offer the possibility of decoration with well-exposed targeting groups such as folate [56,61], alendronate [54] or RGD peptides [60];

the role of intermediate chains is, on the contrary, to provide an environment conducive to drug loading, as it is apparent when e.g. doxorubicin is covalently attached to them through pH-sensitive links [59,60]. The advantage is possibly less clear in the case of physical loading of drugs, since hydrophobic compounds such as paclitaxel could be physically loaded also in PEGylated H40 devoid of intermediate chains [53]; nevertheless their solubility in their hyperbranched core is likely considerably lower than in the intermediate chain region, whose presence therefore would allow for higher drug loading.

This general scheme also accepts several variations. For example, single PEG chains at the end of the intermediate block, have been replaced with a poly(PEG methacrylate) (polyPEG) produced via Atom Transfer Radical Polymerization (ATRP) (*grafting from*) [62]. In another recent example, the terminal PEG was linked to the intermediate PCL chain through multiple uracil-adenine complementary hydrogen bonds, which in principle allows the amphiphilic structure to dissociate in response to external stimuli without the cleavage of covalent bonds [58]. Similarly, disulphides have been used as the reversible connection between poly(L-lactide) intermediate chains and hydrophilic poly(2-ethoxy-2-oxo-1,3,2-dioxaphospholane), thus providing a REDOX responsive means to shed the hydrophilic shell [62]. As a final example, poly(acrylic acid) has been used as an additional intermediate layer, connecting either H40 and PEG in a tri-, or H40-PCL to PEG in a tetralayer morphology [63].

It is debatable whether these core-hyperbranched structures have a truly unimolecular character; a quantitative comparison of literature results is often difficult, because the molecular characteristics of the polymers are variable: these constructs are typically characterized via GPC/SEC, although, as previously pointed out, this technique is often unreliable on Boltorn™ derivatives; additionally, some authors prefer to remove low MW fractions in a fractionation procedure [55,64]. Very low values of Critical Aggregation Concentration (CAC), typically in the range of a few μg/mL [57–59], are commonly observed and they may simply reflect the lack of sensitivity of the analytical methods (typically pyrene fluorescence) than a real de-aggregation, which would support the concept of hydrophobic domains with very little if any dependency on concentration. On the other hand, these systems have dimensions commonly ranging from a few tens to up to 100 nm, which would nevertheless suggest a multimolecular nature of the colloidal species.

The dense functionality of H40 has also been employed to develop amino-functionalized systems as cationic carriers for nucleic acids [65], similarly to what was studied using hyperbranched poly(aminoester)s [66,67]. In comparison to one of the best polymer-based transfection agents, the hyperbranched polyethylenimine (PEI), the amino-functionalized H40 in general appears to be less efficient in transfection but considerably less cytotoxic; for example, it has been used at concentrations up to 1 mg/mL without producing any significant loss in cell viability [65].

3.2.3. Dendritic polyesters

Bis-MPA dendrimers and dendrons can be produced through controlled, step-by-step condensation reactions, as recently and very comprehensively reviewed by Malkoch [68]. The main advantage of such structures is a much better control over the degree of branching and the topology of the polymer, e.g. the end groups are predominantly to be found at the external spherical surface. On the other hand, this control is not absolute due to the possibility of back-folding, which in dendritic structures depend on a number of environmental parameters [69]; additionally the preparation of dendritic structures is considerably more laborious and difficult to scale-up.

Among these structures, it is worth mentioning the bow-tie constructs developed by the group of Fréchet [24] (Fig. 4A), which have been used as biodegradable and compact (because of the branched structure) macromolecular prodrugs [70]. Of note is that bis-MPA dendrons have been developed to undergo also degradation through non-hydrolytical processes, e.g. through photodegradation of *o*-nitrobenzyl esters embedded in the polyester structure [71].

Such bis-MPA dendrons have recently found application in the preparation of dendrimersomes; these structures are broadly analogous to polymer vesicles (aka polymersomes), but the use of asymmetric and amphiphilic dendritic macromolecules [72](Fig. 4B) allows dendrimersomes to have a narrower size distribution than polymersomes [73]. Of note is that the availability of a polyhydroxylated surface makes the bis-MPA dendrons usable as hydrophilic elements, whereas its absence (OH used up in chemical reactions) made hyperbranched MPA a part of the hydrophobic interior of core–shell systems. These bis-MPA-based dendrimersomes have been recently used as MRI contrast agents, with gadolinium complexes either

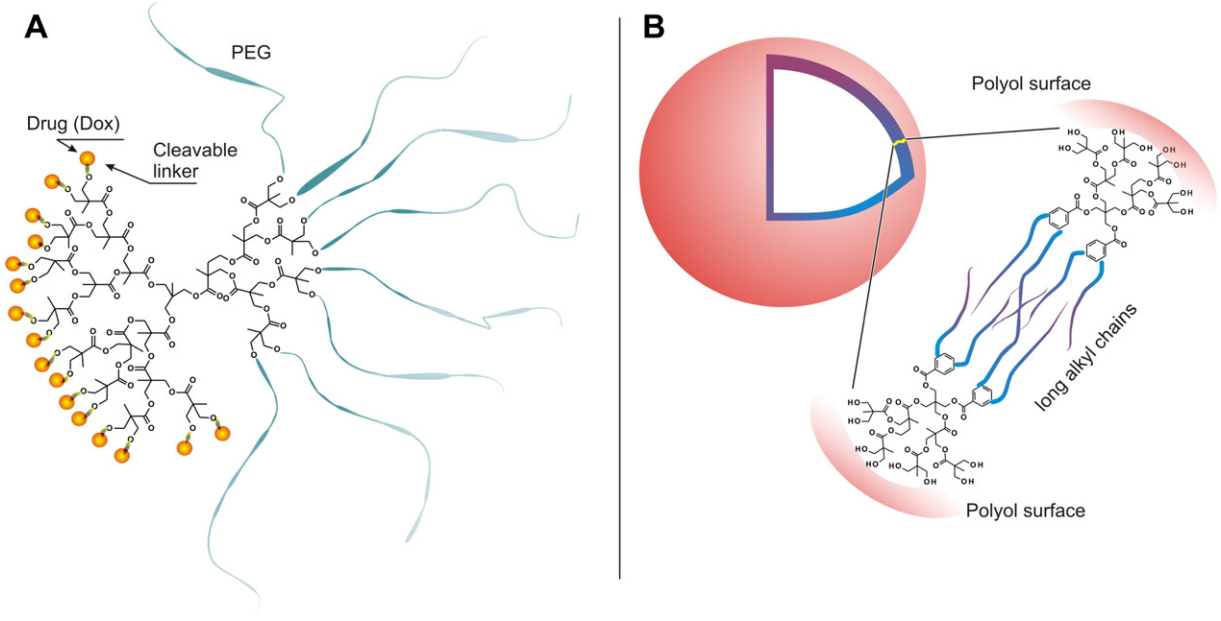

Fig. 4. *A.* Asymmetric dendritic polyesters bearing PEG chains (green) on one side and drug molecules (orange) on the other have been used for the responsive release of doxorubicin using hydrazone linkers [70]. *B.* Alcohol-terminated dendritic polyesters have been used as the hydrophilic building block of amphiphiles which assemble into vesicular carriers (dendrimersomes) [73].

loaded in the hydrophobic membrane or entrapped in the water cavity [74,75].

3.3. Graft polymers through polycondensation

Besides hyperbranched polymers, the recent literature offers only few examples of branched polyesters produced via polycondensation reactions. Among them it is worth mentioning the *grafting on* preparation of amphiphilic polymers, which leads to self-assembled, biodegradable nano-carriers; for example, azide groups are introduced in a hydrophobic polyester backbone prepared through lipase catalysis, and then reacted with alkynyl PEG to provide an amphiphilic comb structure (Fig. 5) [76,77].

In water, such structures may or may not provide unimolecular micelles, but nevertheless they are likely to be more stable against dilution than linear polymers, due to the entanglements in the micellar core being more difficult to resolve.

4. Chain growth methods: ring-opening polymerization of cyclic esters/diesters

4.1. Generalities

In the synthesis of aliphatic polyesters, undoubtedly the most common polymerization mechanism is the ring-opening polymerization (ROP) of cyclic diesters or monoesters; the most common monomer structures are illustrated in Fig. 6. Probably the earliest reference to ROP in polyester synthesis is from 1932 [78], but it took more than 40 years to re-enter the main-stream of polymer synthesis [79], contemporaneously to a similar but readily abandoned mechanism, the ROP of hydroxyacid anhydrosulfites [80].

It is worth mentioning that cyclic diesters are industrially obtained via thermal decomposition of low MW polyesters (Fig. 2B); for example, lactides are obtained from lactic acid (commonly produced via fermentation from glucose sources [81,82]) first by oligomerizing it, and then decomposing the oligomers under catalysis of SnO or ZnO at temperatures > 180 °C, using pressures as low as 0.01 atm to facilitate the lactide distillation [83–85].

The ROP may be accomplished through ionic (cationic or anionic) mechanism, via enzymatic catalysis or via metal-catalysed coordination-insertion; among the chemical methods, the latter is the most common due to the lower number of side reactions (backbiting, transesterification and racemization).

It is worth highlighting some basic points of these mechanisms:

A) in coordination-insertion polymerization, catalysts are most typically carboxylates or alkoxides of Sn or Al, for example tin(II) 2-ethylhexanoate (aka tin octoate; hereafter referred to as $Sn(Oct)_2$). Environmental/health concerns have been raised with regards to the permanence of these species in the polyesters; for example, although $Sn(Oct)_2$ is approved for medical use, the US Food and Drug Administration (FDA) has also imposed a limit of 20 ppm of tin in medical polymers [86]. As a result, considerable research has been devoted to the development of catalysts based on potentially less toxic metallic centres, such as Zn [87], Mg [88,89], Ca [90,91], Li [92], and Fe [93].

B) anionic/nucleophilic ROP processes are metal-free and typically employ organic bases. N,N-dimethylaminopyridine (DMAP) [94] is among the most commonly used, but better performances (less parasite reactions) are typically offered by more sterically hindered bases such as (1,8-diazabicyclo[5.4.0] undec-7-ene) (DBU) [95] 2-((2,6-diisopropylphenyl)amido)-4-((2,6-diisopropylphenyl)-imino)-2-pentene] (BDI) N-$(TMS)_2$, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) [96] and 1-[3,5-bis(trifluoromethyl)phenyl]-3-[(1R,2R)-(−)-2-(dimethylamino) cyclohexyl]thiourea (TU-amine) [97]. It is noteworthy that compounds other than strong, non-nucleophilic bases, e.g. salicylic acid, are capable of providing a controlled and substantially living character to lactone ROP [98].
Finally, it is worth pointing out that the approaches described in point A and B are not mutually exclusive and, as Dove has recently demonstrated, can successfully be combined (i.e. the metal activating the ester, and the organic base the alcohol); for example, this combination has allowed to polymerize the rather recalcitrant ω-pentadecalactone (PDL) [99], even with bases such as DBU which do not typically polymerize PDL on their own. A similar mechanism is probably at the basis of L-lactide polymerization by the DBU/benzoic acid combination, with the latter possibly acting as a Lewis acid [100].
In all the above mechanisms, primary alcohols are the most popular initiators. Of note, they may be presented by a molecule with a specific activity, e.g. a drug; examples comprise the use of alcohols that are part of the drug molecular structure [101], or are introduced via derivatization [102], therefore yielding drug-polyester (in these cases poly(L,D-lactide) (PDLLA)) conjugates. However, depending on the catalyst employed, the presence of secondary alcohols on the same molecule may give rise to branched (star) polymers; for example, when using (BDI) N-$(TMS)_2$ as a catalyst only the primary alcohol of doxorubicin appears to be active in the initiation, whereas with (BDI)MgN$(TMS)_2$ initiation also involved the daunosamine alcohol and with Zn(N-$(TMS)_2)_2$ all the three non-phenolic alcohols participated in initiation [103].
For a more in-depth review on the chemical polymerization of lactides and lactones we refer the reader to a recent review [104].

C) the enzyme-catalysed ROP was initially developed in the early '90s [105,106], and is most typically conducted by using lipases in organic solvents. The key step of such reactions is the

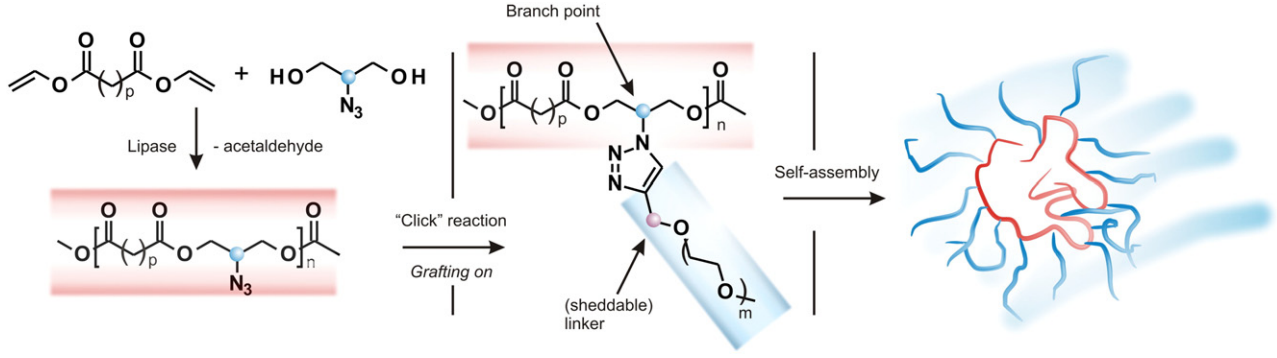

Fig. 5. Branched polymers produced via *grafting on* reactions to polyesters containing azide groups in their side chains. Please note that other diols can be added as comonomers in the lipase-catalysed polycondensation. The polymers would assemble into colloids where chains in the core would connect multiple hydrophiles, i.e. a form of core-branched micelles.

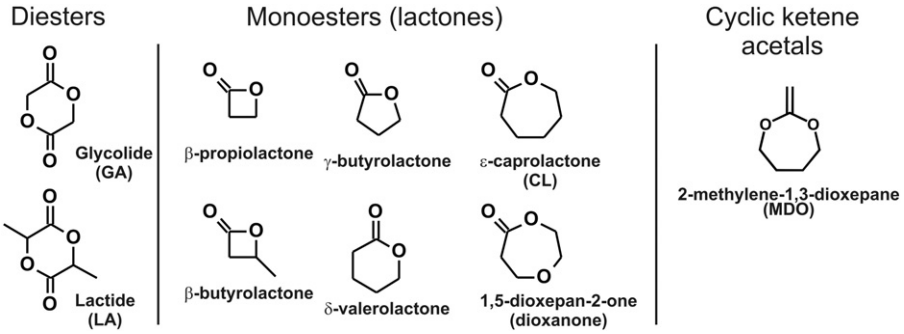

Fig. 6. Most common monomer structures used to prepare polyesters via ROP mechanism. Please note that this review article predominantly focuses on LA and CL.

formation of an enzyme-monomer complex (the enzyme-activated monomer, Fig. 2B), which is more favoured for larger rings (e.g. macrolides); this is to the contrary of what is observed in the classical ROP, where the ring strain governs the polymerizability of monomers [107].

D) the radical ROP (rROP) is a recently developed method, which we believe is worth a more in-depth illustration than other better known methods. rROP employs cyclic ketene acetals (CKAs) as monomers, which are typically synthesized by first reacting chloroacetaldehyde dimethyl acetal with a diol under acid catalysis (Fig. 7A); Bailey et al. [108] first demonstrated that CKAs can be polymerized via a free-radical polymerization leading to mixtures of ring-opened (RO) and ring-closed (RC) repeating units (Fig. 7B); the ratio between RO and RC is monomer dependent: smaller rings (5- and 6-membered rings) had ~15% of RC whereas 7-membered rings had 100% RO. Since the end of the 90s [109, 110], controlled/living mechanisms have substantially replaced free radical polymerization.

CKAs can be copolymerized with traditional vinyl/(meth)acrylic monomers, offering the potential to incorporate degradability into polymer backbones which were traditionally non-degradable. However, the reactivity ratios of CKAs are very different from those of most monomers, which hampers the synthesis of statistical copolymers. Vinyl acetates are a lucky exception, with reactivity ratios similar to CKAs, such as 2-methylene-1,3-dioxepane (MDO)(the CKA equivalent of CL, i.e. identical repeat unit). Dove and O'Rielly have recently pioneered the use of xanthate chain-transfer agents in the RAFT co-polymerization of CKA and VAc [111]. This method allows for the controlled and near random insertion of MDO and vinyl-acetate into the polymer chain; when a N-vinylpyrrolidone block was first polymerized using a xanthate chain transfer agent followed by the copolymerization of MDO, vinyl-acetate and divinyl adipate, degradable cross-linked nanoparticles could be readily prepared.

4.2. Star polymers through ROP

4.2.1. 'Core-first'; small polyols as initiators

Hydrophobic core/hydrophilic shell systems (theoretically unimolecular micelles) are typically prepared through the same three-layer scheme previously discussed for Boltorn™ polymers (Fig. 8A; see also Section 3.2): a polyol initiates the ROP to generate hydrophobic polyesters that are finally end-capped with a hydrophilic derivative such as PEG [56–59]). In regards to the influence that the number of arms has on material properties, it has been recently shown that 3-, 4- and 6-armed star PLGA-PEG block copolymers (respectively initiated by trimethylolpropane, pentaerythritol and dipentaerythritol) exhibit decreasing CMC values, slower release of encapsulated doxorubicin and a certain enhanced internalization in HeLa cells [112]; these star polymers likely do not form unimolecular micelles: the average size of their aggregates in water is in the range of 80–200 nm, and increases with the degree of branching, which suggests that the colloids are formed via polymer aggregation and that this may become more stable due to more permanent entanglements as a result of the presence of branching points (hence the lower CMC values).

Variations to this scheme include the use of:

A) more complex polyols. For example, the octafunctional polyhedral oligomeric silsesquioxane (POSS) has been employed as an initiator, e.g. to yield an 8-armed star PCL that contained an equal number of core azides that were further exploited to link alkyne-terminated polymer chains through the [3 + 2] Huisgen 'click' reaction [113].

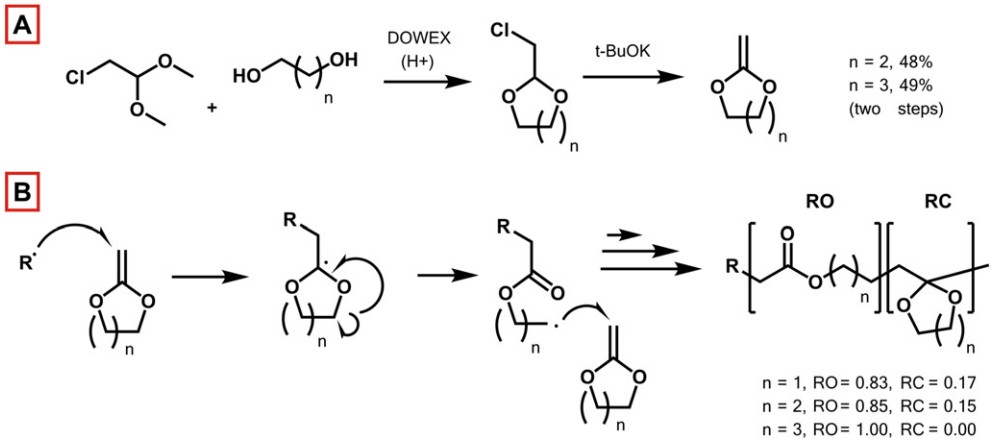

Fig. 7. *A.* Synthesis of CKAs [108]. *B.* Mechanism of the rROP of CKAs [108].

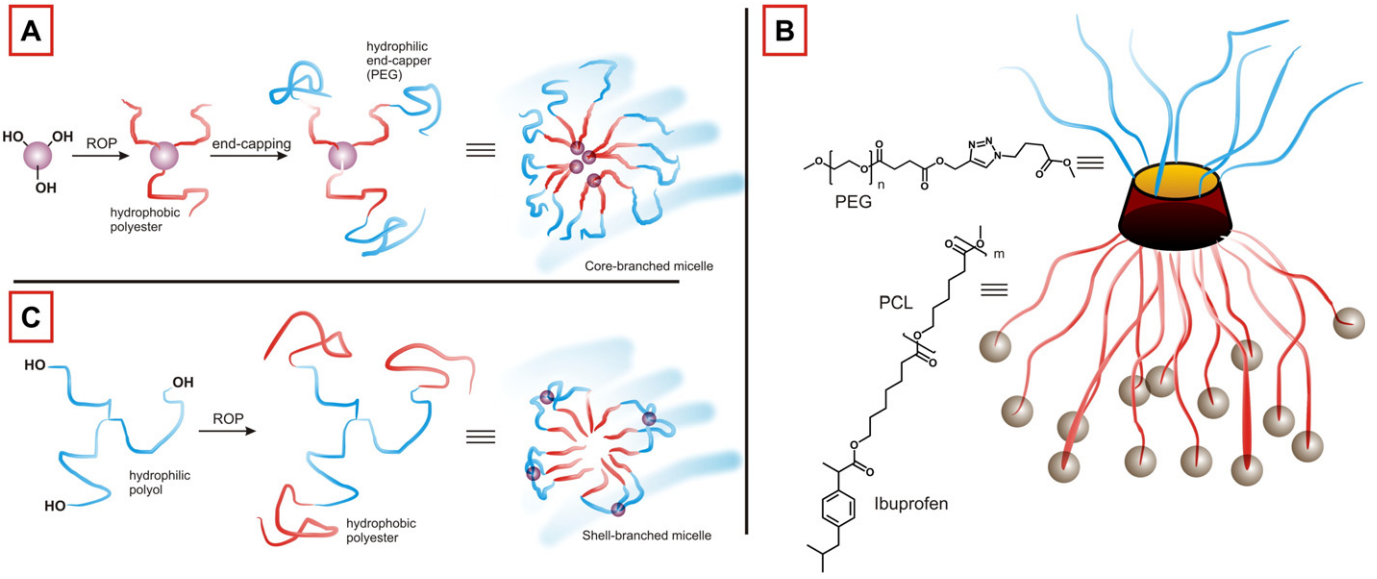

Fig. 8. *A.* Star block copolyesters produced via a core-first approach typically feature a hydrophobic core and a hydrophilic periphery, with an architecture that in water would produce core-branched micelles. *B.* A 'Janus' miktoarm morphology can be obtained by differentiating the reactivity of the 14 secondary from the 7 primary alcohols of β cyclodextrin; the first were used to produce PCL chains (red) end-capped with ibuprofen, the second for a 'click' reaction with alkyne-terminated PEG (blue). *C.* A core-first morphology based on hydrophilic polyols is likely to produce shell-branched micelles.

B) sequential activation of alcohols in the core molecule, resulting in the formation of mikto-armed star constructs, e.g. two branches of PCL and one of a CL functional copolymer [114].

C) different hydrophilic terminal segments. For example, Leroux prepared pentaerythritol-initiated 4-armed PCL, converted its terminal alcohols into thiols via carbodiimide-mediated coupling with 3-mercaptopropionic acid (in its disulphide form, later reduced) and finally used the thiols as chain transfer agents in the free radical polymerization of *N*-(2-hydroxypropyl)methacrylamide (HPMA); the resulting pHPMA chains then allowed for the water dispersion, and the resulting systems (nanoparticles rather than unimolecular micelles: size 100–150 nm) were used for indomethacin solubilization [115]. Similarly, Dai transformed the terminal OH groups of 4-armed star PCL terminal OH groups into ATRP initiators to create terminal poly(gluconamidoethylmethacrylate), whose open saccharidic structures allowed the colloidal aggregates formed by these block copolymers to be recognized by concanavalin A [116].

D) monomers other than cyclic esters, e.g. O-carboxyanhydrides [117].

A last and arguably most intriguing variation was developed by the group of Zhu: β-cyclodextrin was regioselectively functionalized to act as a 14-functional initiator (for CL) at its secondary alcohols, and at the same time as a support for seven PEG chains at the primary alcohols present on the opposite face of the barrel-shaped cyclodextrin structure [118]. The resulting construct is a miktoarm star polymer with a Janus morphology, which (Fig. 8B); in order to provide the means for a prolonged drug release, ibuprofen was covalently linked to the chain-ends of PCL, in order to release it upon biodegradation of the polyester chains. In most other cases, drugs were simply physically loaded, and it is noteworthy that even a relatively polar model drug like etoposide (logP = 0.6) showed higher solubility in PCL-PEG stars than in PLLA-PEG stars [119].

We also refer readers to the recent review article by Smet for complementary readings in this area [120].

4.2.2. 'Core-first'; hydrophilic and polymeric polyols (single branch point) as initiators

A number of reports have used an opposite approach, where the hydrophilic element is provided by a large and polar initiator, and not by end-cappers (Fig. 8C). For example, Venkatram employed a 4-armed PEG to initiate L-lactide polymerization (DP > 35) [121], Nagahama et al. used 8-armed PEG for the same purpose but aiming at shorter PLLA chains (DP ≈ 11) [122]; the latter amphiphilic polymers, in water, showed thermal responsiveness (increase in viscosity or gelation at concentrations > 16 wt.% by raising the temperature in a physiologically relevant temperature range), but did not form real gels unless the PLLA hydrophobicity was further enhanced by cholesterol end-capping. A similar system investigated by the group of Feijen, i.e. 8-armed PEG terminated with short (DP = 10–14) PLLA chains, micellized in water (most likely flower micelles) and provided relatively soft gels; interestingly, their gelation was greatly facilitated by the formation of stereocomplexes with corresponding PDLA-terminated star polymers [123]. A *caveat* about the comparison of these two papers with regards to the thermal properties of seemingly identical or very similar 8-armed PEG-PLLA stars: small variations in LA degree of polymerization which can lead to the very significant effects on the gel point, e.g. using a PEG with $M_n \approx 20{,}000$ g/mol the critical gel concentration at room temperature decreased from 40 to 15 wt.% by increasing the PLLA DP from 10 to 14 [123]. Therefore, it is noteworthy that a) often apparently incongruent data may simply refer to slight variations in the size of either blocks, but b) the general trend is that this class of polymers does exhibit inverse thermal gelation and this is improved by increasing the hydrophobicity/length of the hydrophobic block and also its degree of association (stereocomplexes but also hydrogen bonds, see next section).

Again using star PEGs as initiators, CL and several of its functional derivatives can also be polymerized, as recently reviewed by Stefan [124]. Among these star PEG-PCL structures, it is worth mentioning the miktoarm constructs obtained via initiating CL polymerization from a diol-terminated PEG (DP = 45); the branch point allowed these polymers to switch from a spherical micelle to a cylindrical micelle morphology with increasing PCL size (already with two PCL chains at DP =

20), whereas the micelles formed by a linear diblock copolymer with the same PEG/PCL ratio would maintain the spherical shape [125]. The cylindrical micelles were also shown to allow for a larger doxorubicin loading and a higher uptake in HeLa cells.

Similar approaches where, however, the initiator has not a single branch point, but e.g. is a hydrophilic polyol with a hyperbranched structure are reviewed in Section 4.3.1.

4.2.3. 'Core-first', amines as initiators

Although less commonly employed, primary amines can also be used for initiating the ROP of lactones. For instance, the group of Feijen [126] has used amine-terminated 8-armed PEG stars to polymerize L-lactide; the resulting polymers were shown to exhibit the same inverse gelation as those obtained from the OH-terminated PEG stars, but formed harder gels and at considerably lower concentrations, for example, at the same concentration (20 wt.%) PEG-amide-$(PLA_{13})_8$ formed gels with a G′ of 17 kPa, and PEG-ester-$(PLA_{13})_8$ with a G′ of only 7 kPa. The effect was postulated to derive from the higher rigidity of the amide bond linking the two blocks. A substantial effect was recorded also on the degradability with complete solubilization in 5 days for PEG-ester-$(PLA_{13})_8$ vs. 15 days of PEG-amide-$(PLA_{13})_8$. This was attributed to the preferential hydrolysis of the surface ester in the PEG-ester-$(PLA_{13})_8$ samples, as the surface amide is insensitive to hydrolysis under conditions used.

More recently, Alba et al. [127] have synthesized star-PLA from primary and secondary amines, but by first allowing them to react fully with L-lactide without catalyst, and thus generating OH groups of the first ring-opened lactide unit, and only then adding catalyst (DBU) to initiate the polymerization from these alcohol groups. Well-defined star-PLA with low dispersity values ($Đ = 1.07–1.18$) could be obtained using this method, which was also used in a resin-supported fashion to scavenge residual monomers from lactide polymerization experiments.

4.2.4. Arm-first

As discussed in Section 1, the main weakness of the "arm-first" approach is the possibly poor yield of the arm-to-core coupling reactions, due to crowding and steric hindrance. Some authors choose to perform rather uncontrolled reactions, such as radical oligo/polymerizations of terminal groups [128] or the use of double- or multifunctional monomers (di- or multilactones) as the last step of the ROP [129] yielding structures with a large and cross-linked core rather than a single branch point. The latter can be obtained with a good control only through the use of 'click' reactions, such as the photoinduced, copper-catalysed [3 + 2] Huisgen cycloaddition to link alkyne-terminated PCL to an octa-azide-terminated POSS [130], or of highly reactive groups. For example, acid chlorides, which have been employed to link PCL-PEG arms to the amine-terminate tetrapyrrol macrocycle chlorin (similar to porphyrin). The central and thus hindered position of this photosensitizer in the resulting amphiphilic tetra-armed star polymer reduced its own dark cytotoxicity while retaining its photoactivity [131]. It is also noteworthy that a similarly high-yielding reaction (Williamson reaction between terminal aluminium alkoxides on PCL or PLLA chains and trimesic acid trichloride) was employed for one of the first controlled syntheses of (3-armed) star PCL and PLLA [132].

4.3. Graft/comb polymers through ROP

4.3.1. Use of multifunctional macroinitiators (grafting from)

Analogously to what seen in Section 4.2, branched polymers can be produced using multifunctional ROP initiators also if they present multiple (e.g. hyperbranched polyols) or no branching points (e.g. linear polyols).

The first class of polymers are sometimes referred to as 'hyperstars' (star polymers from a hyperbranched/dendritic core), and as examples of their preparation one can mention the use of mannan (a polyol) [133] or PEI (a hyperbranched polyamine) [134] to initiate lactide ROP and reportedly produce inverse micelles capable of entrapping polar molecules such as rose bengale, or poly(ester amides) as the initiator for ε-caprolactone (CL) ROP to produce phase transfer agents [135], or OH-terminated polyamidoamine (PAMAM) dendrimers to polymerize L-lactide [119] and ε-caprolactone [136] followed by PEG end-capping, or most interestingly hyperbranched polyglycerol [137] or hyperbranched PEG [138] to produce PLLA based arms with low molecular weight dispersity.

For what attains to linear polyols as ROP initiators, possibly the best known system makes use of poly(vinyl alcohol) (PVA), which has been extensively used by Kissel as a platform to further develop cationic polymers for the delivery of nucleic acids. This approach is based on the functionalization of PVA alcohols with tertiary amines, most commonly diethylaminopropylamine (DEAPA) through carbonylbisimidazole, and of the further use of PVA OH groups for the initiation of lactide/glycolide polymerization [139]; the latter point is analogous to the use of polyols as initiators (vide supra) and had been previously used by the same group also to prepare anionic PVA-*g*-PLGA copolymers, which can provide nanoparticles through a solvent displacement method [140]. The amine-containing polymers have been produced in nanoparticle form through the same method and then extensively and successfully used to complex and deliver DNA [139,141] and RNA [142,143], also in combination with lung surfactant to improve their transfection efficiency [144].

Also, PEG derivatives have been used as linear ROP macroinitiators: in this case, OH groups were generated via the chain extension of PEG-bis-epoxide with glutaric anhydride. They have been used in the $Sn(Oct)_2$-catalysed grafting polymerization of D,L-lactide and glycolide mixtures, thereby yielding PLGA branches sprouting from a mainly PEG backbone (PEG-*g*-PLGA) [145]. The resulting amphiphilic polymers self-assembled into micelles and underwent inverse thermal gelation in water at concentrations > 16%wt. and in the physiologically relevant region of 20–40 °C; this prompted their use as in situ gelling injectable formulation, similarly to what is observed in analogous linear triblock (PEG-PLGA-PEG) copolymers [146]; for example, PEG-*g*-PLGA has been applied for both the delivery of proteins (insulin) and cells (chondrocytes in cartilage defects) [147]. It is noteworthy that although branching likely reduced the viscosity of the formulation, its main advantage appeared to be the control over its dissolution behaviour: where PEG-*g*-PLGA (branched with a hydrophilic backbone and hydrophobic side chains) likely assembled into flower-like micelles and exhibited an accelerated dissolution in excess water, its mirror image PLGA-*g*-PEG (hydrophobic backbone and hydrophilic side chains from the ROP of PEG epoxide with glycolide and lactide, as in Section 4.3.3) shows a much more extended stability [145,148]. Of note, by replacing PLGA with PCL as the grafted chains, thermally gelled formulations showed increased modulus and decreased critical gel concentration [149].

A number of other linear polymers have also been used as ROP macroinitiators, e.g. homo and copolymers of 2-hydroxyethyl methacrylate (HEMA) obtained via ATRP [150,151].

4.3.2. Telechelic polyesters

A) Polyesters *grafted to* other substrates. Carboxy-terminated polyesters can be obtained via uncatalyzed ROP of cyclic (di)esters [152], the use of acidic initiators such as methanesulfonic acid [153], or the end-capping with cyclic anhydrides such as succinic anhydride [103]. Either through promoted coupling (e.g. carbodiimide [153], carbonylbisimidazole [152]) or via preliminary activation of the acid in the form of N-hydroxysuccinimide (NHS) esters [154,155], these end-functional polyesters can be reacted with nucleophilic side groups (alcohols, amines) on other macromolecules, therefore yielding graft/comb constructs. Although occasional cases are reported [156], the use of alcohol terminal groups is considerably less common for the end-functionalization of polyesters. Typically, the backbone is a

polysaccharide such as dextran [152], hyaluronic acid [154,155] or chitosan [153], and the resulting amphiphilic structures (hydrophobic polyester branches-hydrophilic polysaccharide backbone) have been employed to produce nano-carriers through the self-association of the polyester chains in a water environment (Fig. 9A) [152,153,156,157]. It is noteworthy that, despite all polysaccharides being polyols and therefore also usable as macroinitiator in *grafting from* ROP, many authors prefer the *grafting to* method, because it avoids side reactions during polymerization and therefore provides better defined branches. For example, with chitosan well-defined grafts are obtained only via protection of its primary amines [158], whereas when used in a free-amine form conflicting reports exist also in relation to the nature of the initiating species, whether amines [159] or alcohols [160].

B) Polyesters from *grafting through* reactions. Among the *grafting through* approaches, well known is the use of a (meth)acrylic alcohol, which will deliver polyester chains sporting a polymerizable group at one end and an OH at the other. Early attempts used HEMA as a ROP initiator in the form of an aluminium alkoxide ligand [161], but more recently the attention has then polarized on more stable acrylamide derivatives, such as N-(2-hydroxyethyl)methacrylamide (HEMAm) [162] or HPMA [163] (Fig. 9B). The comb structures resulting from oligo(L-lactide)-methacrylamide polymerization with PEG-containing free radical initiators have shown thermal gelation, self-assembly into spherical micelles and fast degradability; when the terminal OH groups of the oligo(L-lactide) branches were converted into methacrylic esters, the micelles can be covalently cross-linked in their core (Fig. 9C), which has been shown to provide a major increase in their circulation times [164]. After some initial studies, the group of Hennink appears to have preferred HPMA to HEMAm as the lactide ROP initiator, extensively studying the resulting core-cross-linked micelles; the latter have been used as carriers of covalently bound drugs such as doxorubicin [165,166] or leuprolide [167], which are incorporated in the core during the polymerization of their methacrylic derivatives.

4.3.3. Epoxides as functional comonomers (grafting to)

Epoxides can participate in the ROP of cyclic (di)esters; this copolymerization is possible only at high temperature, due to the different ring strain of the two classes of monomers (epoxides are unreactive at temperatures as low as 80 °C [168]); it must be pointed out that the very likely different reactivity of the two classes of monomers is conducive to the formation of gradient rather than random copolymers. In the best known example, allyl glycidyl ether has been copolymerized with a variety of monomers (e.g. lactide, CL), yielding olefinic side groups that have been converted to carboxylic acids and then further functionalized [169]; for example, they have been linked to PEG chains yielding amphiphilic structures later used to stabilize PDLLA nanoparticles [170,171] and to reduce their unspecific uptake by macrophages [172].

4.3.4. Functional cyclic diesters and related monomers (various forms of grafting)

A) Methylene lactide (ML). Direct functionalization of cyclic lactides can be performed, as demonstrated by Scheibelhoffer et al. in 1969, by first reacting with N-bromosuccinimide (NBS) to produce the monosubstituted (3R,6S)-3-bromo-3,6-dimethyl-1,4-dioxane-2,5-dione which was then subjected to an elimination reaction to form ML, i.e. (6S)-3-methylene-6-methyl-1,4-dioxane-2,5-dione (red box in Fig. 10). ML readily undergoes radical polymerization (Fig. 10A), but not ROP using conventional catalysts due to the methylene rearranging with the terminal alcohol forming a ketone [173] (Fig. 10B); the monomer may however prove to be a useful end-capping molecule where a single terminal ketone functionality is desired, but this possibility has not been explored to date.

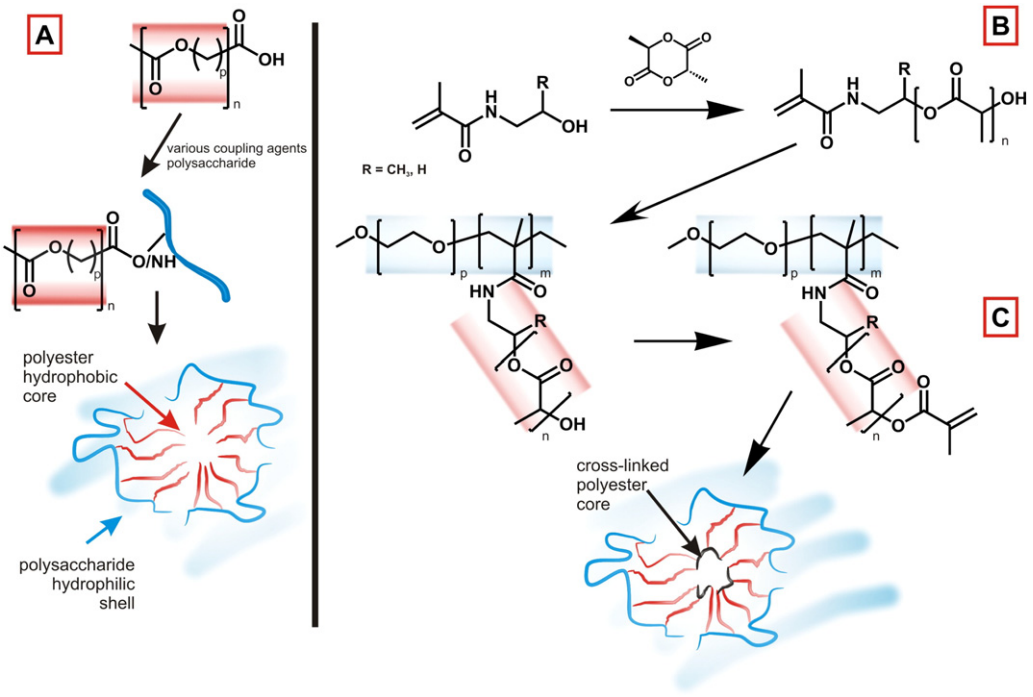

Fig. 9. *A.* Grafting carboxy-terminated hydrophobic polyester chains onto polysaccharide backbones allows the formation of amphiphilic combs that self-assemble into micelles where each hydrophile branches several hydrophobes, effectively cross-linking them. *B.–C.* α-Methacrylic-ω-hydroxy-terminated PLLA can be used as a macromonomer and then further derivatized to allow the cross-linking of the hydrophobic chains once they assemble into micelles; in comparison to case A, the hydrophobes are therefore inter-connected both directly and through the hydrophiles.

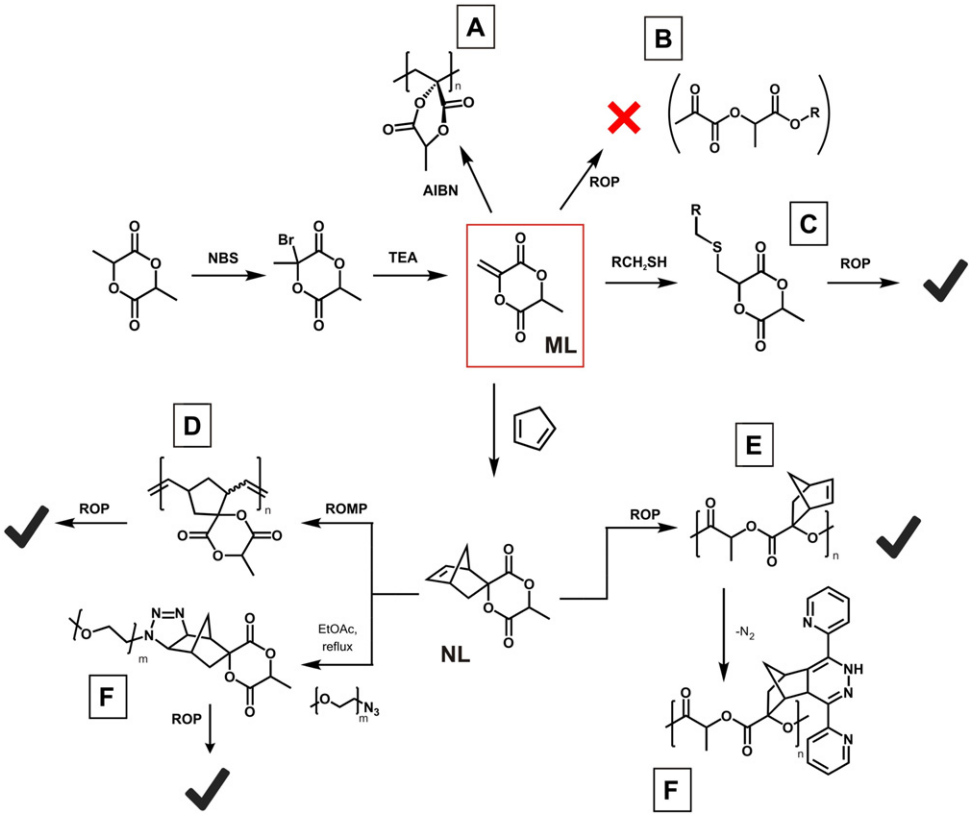

Fig. 10. Sketch of the possible polymerization or end-capping reactions based on the use of ML.

ML also readily reacts with thiols through Michael-type addition (Fig. 10C), which also restores the capability of the lactide to polymerize via ROP. In a study by Bowden and co-workers [174], ML was reacted with 1,3-propanedithiol to form a thiolated lactide followed by the reaction with a thiolated H_2S releasing moiety to form a disulphide-linked thiobenzamide lactide. When the above lactide was polymerized through ROP, the polymers displayed a slow but sustained release of the H_2S releasing molecule thiobenzamide therefore highlighting the promise of the system. As demonstrated by Hillmyer and Jing [175], ML is also a substrate for Diels-Alder reactions, e.g. using cyclopentadiene as the diene to form norbornene lactide (NL). NL could be polymerized either by ROMP at the norbornene unit (using a 3rd generation Ru Grubb's catalyst, Fig. 10D; please note that this is a *cross-linking through* hybrid) or by ROP of the lactide (Fig. 10E). Further, NL could also be copolymerized, e.g. using 1,5-cyclooctadiene (COD); such a copolymer with 3:97 (NL:COD) mol ratio was then used in a subsequent ROP of the lactide, the product of which displaying considerably improved toughness values as compared to either PLA, PCOD or PLA-PCOD binary blends. In a separate study by Weck [176], NL was used as a cycloaddition substrate with oligoEG/PEG_{40}-azides. The resulting oligoEG/PEG-lactides can undergo ROP, e.g. by using the organocatalyst TBD, but suffer from the most typical drawback of the *grafting through* approach, i.e. the steric repulsion between bulky reactants (both monomers and propagating species), which leads to decreasing yields with increasing EG size: 99, 82 and 50 wt.% respectively for PEG_3, PEG_7 and PEG_{40} after 24 h. Finally, it is worth mentioning a study by Dove and co-workers [177], where they were able to polymerize NL and then functionalize the pendant norbornene moieties through a tetrazine-strained alkene 'click' reaction (Fig. 10F), thereby further demonstrating the versatility of norbornene moiety for either *grafting-to* (tetrazine) or *grafting-through* (ROMP).

B) Functional monomers from α-hydroxyacids (AHAs). AHAs are typically prepared through diazotization (decomposition of aliphatic diazonium ion, Fig. 11A) of amino acids [178,179], or through the Bi^0 (from in situ reduction of $BiCl_3$ with Zn)-catalysed Barbier-type addition of a functional bromide onto glyoxylic acid (Fig. 11B) [180,181]. Besides these approaches, a number of interesting although less trodden alternatives exist, such as 1) the reduction of α-keto esters produced from in situ generated oligo(ethylene glycol) Grignard reagents reacted with diethyl oxalate (Fig. 11C) [182]; 2) the use of bromoacetaldehyde diethyl acetal as a building block, either through first its Williamson substitution with an alcoholate and then its transformation into a cyanohydrin intermediate (Fig. 11D) [183], or through its conversion into a isocyanide undergoing a multicomponent Passerini-type condensation (camphorsulfonic acid catalysis) to yield N-acylindole intermediates (Fig. 11E) [184].

AHAs can be used to provide ROP monomers through three main avenues:

1) Difunctional cyclic diesters can be obtained via *AHA azeotropic distillation* under *p*TsOH catalysis (Fig. 11F), but the rather poor yields [185] have not made this method particularly popular.
2) AHA may also be directly reacted with *2-haloacetyl halides* to form mixed cyclic lactide/glycolide derivatives (Fig. 11G); this route allows the preparation of monofunctional cyclic diester, and has been specifically employed to produce protected monofunctional monomers, e.g. monobenzylated lactide, which has been later

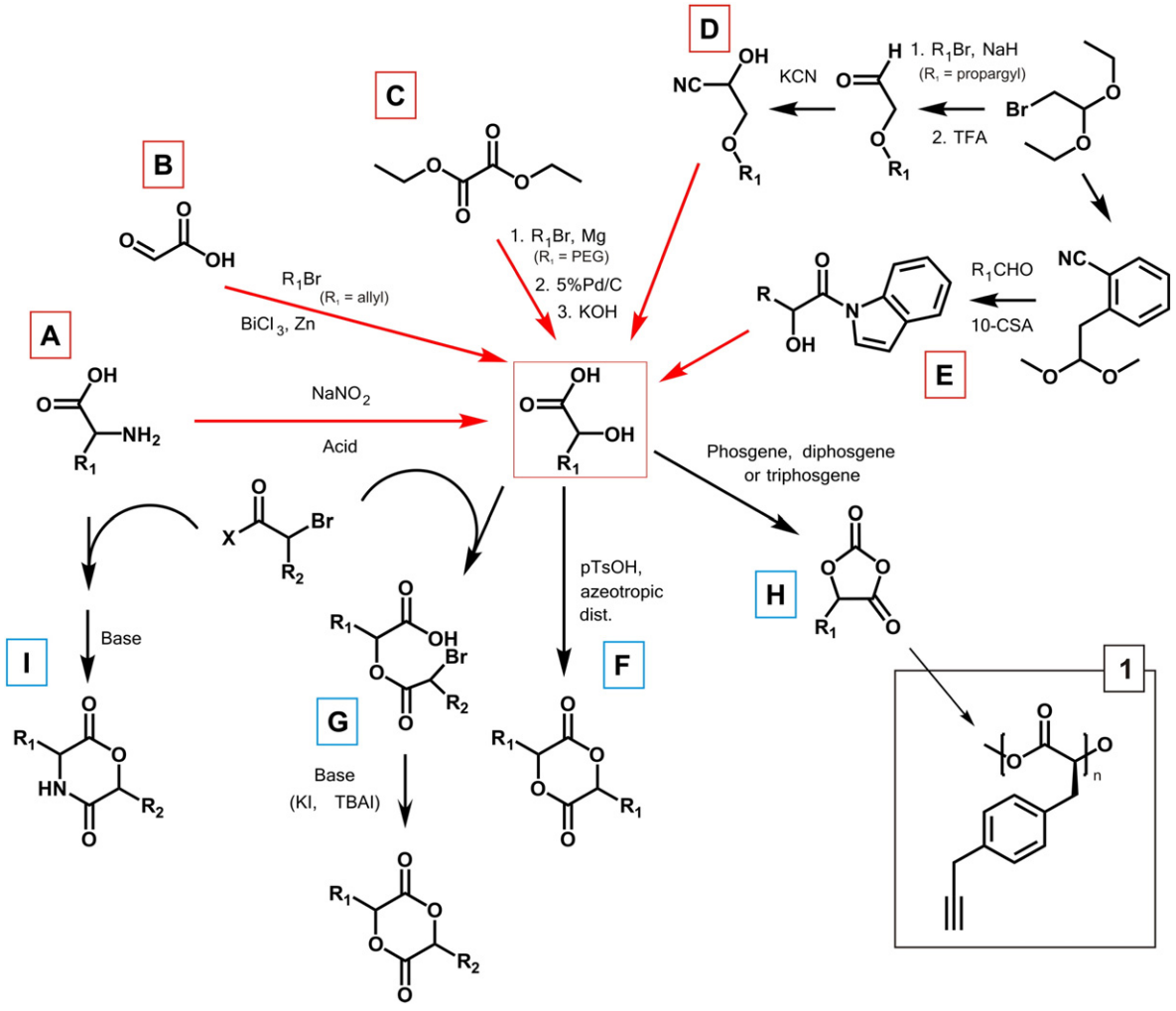

Fig. 11. The pathways to the synthesis of α-hydroxyacids (AHA) are highlighted by red arrows and correspond to the letters A to E. Those leading to the preparation of cyclic esters from AHAs (or directly from aminoacids) correspond to the letters F to I.

employed to provide the copolymers of hydroxymethyl glycolic acid [178,186–188], or monobenzyloxycarbonyl glycolic acid, which yields side-chain carboxylated polylactides [179,189]. In these 2-step processes, the ring-closure reaction (attack of the carboxylic acid onto the alkyl halide) is the weak point with rather low yields, typically ≤40–50%, although it has been reported that the in situ generation of more reactive iodides using KI [190] or tetrabutyl ammonium iodide [179] can increase the ring closure yield. Among the examples of these reactions specifically used to yield branched structures, one can mention the synthesis of propargyl-bearing lactide later used for the preparation of comb polymers through the *grafting on* 'click' reaction with PEG azide [191], or for that of allyl-bearing lactide, which is used for the preparation of thiol-ene reactive polymers yielding hyperbranched/cross-linked nanoparticle systems through free radical reaction with dithiols [181].

In the latter case, the polymers can also be pre-functionalized with (2-diethylamino)ethanethiol (aka diethylcysteamine, a cationizable thiol) [192]; the resulting positive charges allow to load nucleic acids on the surface of the then dithiol-cross-linked nanoparticles. The latter have been successfully used to deliver siRNA for IL-8 in prostate cancer PC3 cells [193] (also in combination with doxorubicin loaded in the nanoparticle core [192]), and pancreas cancer Panc-1 and MiaPaCa-2 cells [194], or K-Ras oncogene in Panc-1 [195]. Interestingly, increasing the degree of amine functionalization appears to lead to accelerated polymer degradation, with the concomitant increase in cytotoxicity and knockdown efficiency [193].

Always exploiting the allyl-functionalized lactide, Weck and co-workers have synthesized graft copolymers [196], where an α-thiol-ω-azido tri(ethylene glycol) converted this monomer into an azido-lactide, which after ROP (benzyl alcohol as the initiator and $Sn(Oct)_2$ as the catalyst) was finally linked to a phosphine-terminated RGD peptide via Staudinger ligation. In a separate study, the azide groups were linked to a tracking fluorophore using the [3 + 2] Huisgen 'click' reaction, whereas the use of an aldehyde-bearing initiator allowed for the orthogonal introduction of a peptide as a terminal group through reductive amination [197]. A last example of this approach to the synthesis of 'branch-able' monomeric units has been recently provided by Gianneschi, who synthesized and then copolymerized a norbornene-functionalized lactide in a 5-step synthesis with an overall yield of 14% starting from norbornenecarboxylic acid and exploiting the Passerini-type reaction (vide supra) [198]. Similarly to the previously mentioned Jing/Hillmyer study [175], the norbornene-functionalized PLA was copolymerized via ROMP (also here a *cross-linking through* hybrid) with other norbornene monomers containing either oligo(ethylene glycol) chains, or a dual light/pH-sensitive unit (caged imidazoles), whose response allows for a double control of the morphology of the nanoparticles formed by these amphiphilic graft copolymers in water.

3) AHA can also be used to produce *O-carboxyanhydrides* (Fig. 11H), which owing to their structural analogy to both lactides and N-carboxyanhydrides, readily undergo ROP. The reaction of AHA with

phosgene derivatives normally retains their stereochemistry, has higher yields than the methods of point 1 and 2, and the liberation of CO_2 provides a powerful entropic driving force for polymerizations, which also gives narrow dispersities (typically $Đ < 1.2$) [199,200]. As an example of OCA-based polymers, it is worth mentioning those obtained from Tyr(alkynyl)-OCA (Fig. 11, inset 1); these hydrophobic polymers can be endowed with an amphiphilic structure and functionality, respectively by using a hydrophilic initiator such as PEG-OH, and employing the [3 + 2] Huisgen 'click' reaction on the triple bonds to introduce targeting peptides [201]; the latter reaction can also be employed to stabilize and at the same time provide responsiveness to the micellar core by cross-linking it with disulphide-containing diazides [195]. Both effects of water solubilization and functionalization can also be obtained in one step, via the double addition of 2-aminoethanethiol through the thiol-yne radical addition [202]; the latter allowed DNA complexation and efficient endosomal disruption in HeLa cells.

4) It is worth to mention another connected synthetic method, i.e. the synthesis of *morpholine-2,5-diones* from aminoacids (Fig. 11I). Such compounds were first pioneered by Feijen and co-workers [203–205] in the 80s and can be seen as both a lactone and a lactam, leading thus to poly(ester amide)s, also known as polydepsipeptides. Unlike their lactide analogues, morpholine-2,5-diones are formed in one step by reacting aminoacids and haloacetyl halides, although typically with yields lower than the corresponding two-step reaction of AHAs, which may be due to the higher rigidity of the cyclic amide bond. Indeed, one of the few examples of multi-step morpholine-2,5-dione synthesis showed a total yield of 69% (with the amide formed last) as compared to the direct cyclization of amino acid derivatives with haloacetyl halides that is generally 16–31% [206]. Morpholine-2,5-diones undergo polymerization under conditions virtually identical to those of cyclic (di)esters and therefore can be easily copolymerized with them, as witnessed by an extensive literature spanning a few decades [207,208]. Besides the physico-chemical peculiarities of polydepsipeptides (e.g. the higher stability of hydrophobic domains due to hydrogen bonding [209]), there is a distinct key advantage in using morpholine-2,5-diones as building blocks: the majority of their commercially available parent aminoacids bear additional (protected) functional groups that can be used for purposes of both branching and functionalization. For example, Morita and co-workers synthesized 3-(O-benzyl)-L-serinylmorpholine-2,5-dione [210], whose post-polymerization deprotection into serine alcohols and their further reaction with acryloyl chloride allows to form polydepsipeptide macromonomers cross-linkable via UV light. Similarly, the side-chain amine groups of poly(lactic acid-*co*-lysine) [207] have been used as initiators for N-carboxyanhydride ROP, generating poly(aspartic acid) branches that could be methacrylated and eventually photochemically cross-linked [211].

4.3.5. Functional lactones (various forms of grafting)

Lactone rings are typically produced through Baeyer–Villiger oxidation of a cyclic ketone, ring-closure reactions or cycloadditions. Most functional monomers used for the preparation of branched polymers are produced through the former method, or through the derivatization of existing lactones.

A) The Baeyer–Villiger oxidation (Fig. 12A) is a very popular synthetic method, and examples of its use include the industrial synthesis of CL conducted with peracetic acid, although in academic literature *meta*-chloroperbenzoic acid (*m*-CPBA) is more commonly used. This reaction is most typically employed as the last step in the synthesis of functional lactones, with other groups being introduced on the parent cyclohexanone structure; this approach is best known for the production of CL-based ATRP initiators. For example, α-bromo-ε-caprolactone, α-chloro-ε-caprolactone and γ-(2-bromo-2-methylpropionyl)-ε-caprolactone (αBrCL, αClCL and γBMP-εCL) have been prepared in this way (Fig. 12B to D) and are then often copolymerized with CL. For example, the αBrCL and αClCL copolymers have been employed as macroinitiators for the ATRP of styrene [212] and HEMA [213], or that of N-isopropylacrylamide [214]. An interesting variant to this approach has been proposed by Albertsson who has employed α-bromo-γ-butyrolactone as a co-monomer for CL and L-lactide ROP [214]. Unlike αBrCL, α-bromo-γ-butyrolactone (as with many other 5-membered ring lactones)

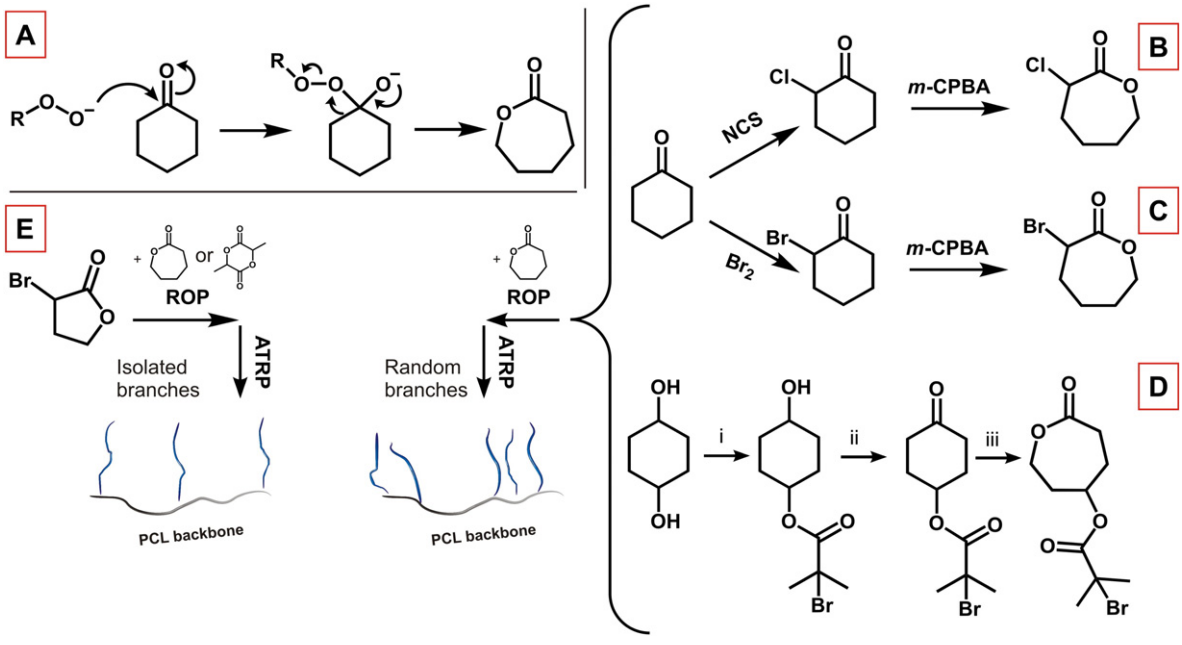

Fig. 12. *A.* Mechanism of Baeyer–Villiger oxidation. *B.–D.* Synthetic paths to the production of caprolactone-based ATRP initiators. In D, the γ-(2-bromo-2-methyl propionyl)-ε-caprolactone (γBMP-εCL) was prepared through (i) the monoesterification of 1,4-cyclohexanediol, (ii) the oxidation of the remaining alcohol with pyridinium chlorochromate (PCC) and finally (iii) the Baeyer–Villiger oxidation with mCPBA [215,216]. *E.* The lack of α-bromo-γ-butyrolactone homopolymerization allows it to be included in an isolated fashion throughout the PCL backbone, as opposed to statistical sequences as for e.g. γBMP-εCL.

hardly homopolymerizes, and is thus incorporated as isolated functional repeating units in the PCL or PLLA backbones, a highly desirable trait for graft copolymers.

It is worth mentioning that αClCL has also been employed to introduce branching on PCL chains via nucleophilic substitution reactions. For example, by replacing chlorides with azides and performing the [3 + 2] Huisgen 'click' reaction with propargyl-terminated chitosan oligosaccharides [217] or protected PEG aldehydes (for further functionalization with biomolecules) [218]. Similar reactions can also be performed under topological control by introducing αClCL in selected parts of amphiphilic block copolymeric structures and therefore in selected regions of the micelles that they form in water: in this way, the chloride-azide conversion followed by reaction with a disulphide-containing (bis)alkyne cross-linker in PEG-*b*-PCL-*b*-PαClCL, PEG-*b*-PαClCL-*b*-PCL and PEG-*b*-P[CL-*co*-αClCL) polymers respectively afforded core-cross-linked, shell-cross-linked and core–shell-cross-linked micelles [219], which all showed an accelerated drug release performance in the presence of thiols (Nile Red as a model drug, DTT as a reducing agent) [220].

γBMP-εCL has probably been more extensively employed than αBrCL and αClCL for the purpose of ATRP initiation, and has been used both in *grafting through* or *grafting from* approaches. For example, in its first description by Hedrick in 1999 [215], it was both used to initiate methyl methacrylate ATRP and then co-polymerized with CL via ROP, or vice-versa. It is noteworthy that the *grafting from* approach has also been extended to surface-initiated ATRP, by polymerizing oligo(ethylene glycol) methacrylate from films of CL/γBMP-εCL copolymers [216]. Arguably, the best known use of γ2B2MP-εCl/CL copolymers (Fig. 13A) is the production of polycationic combs based on 2-(dimethylamino)ethyl methacrylate (DMAEMA, Fig. 13B) [221].

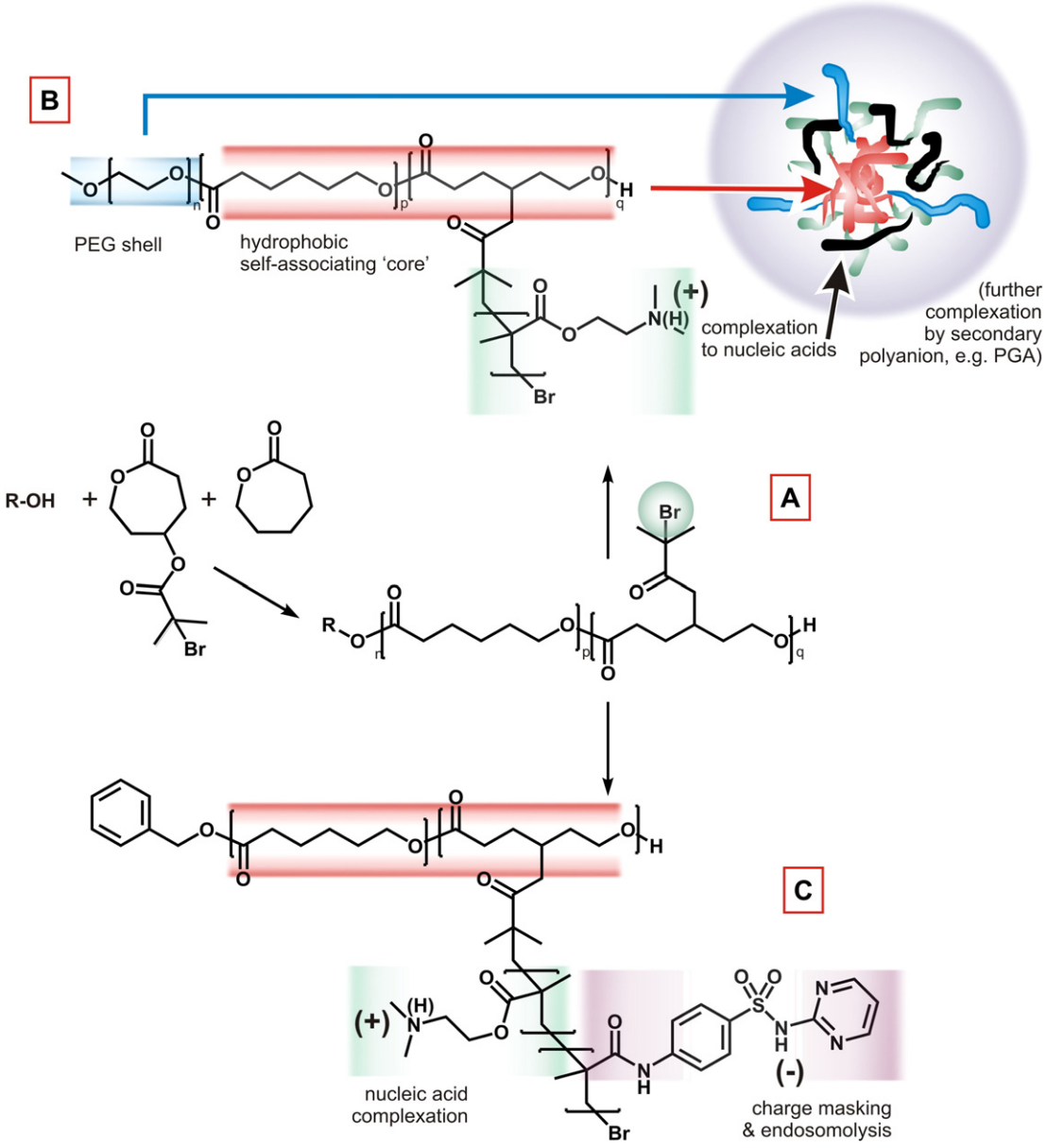

Fig. 13. *A.* General structure of macroinitiators obtained via CL/γBMP-εCL copolymerization; the green circle highlights the ATRP-initiating 2-bromoester. *B.* Structure of PCL/PDMAEMA graft copolymers, where the different components are colour-coded: red for the hydrophobic polyester backbone, blue for the PEG chains, and green for PDMAEMA chains (black for a nucleic acid payload). The toxicity of these constructs have been improved by further complexation with a secondary polyanion (the primary polyanion being the nucleic acid of choice), such as PGA-*g*-PEG. *C.* the copolymerization of DMAEMA with SDZMA (in purple) allows at the same time to improve the toxicity profile at physiological pH and improve the endosomolytic behaviour.

These polyamines allow the use of these constructs for nucleic acid release; when complexed with plasmid DNA, they have showed transfection efficiencies comparable to those of PEI or Lipofectamine over three different cell lines. When used in combination with siRNA, these branched copolymers showed a slight reduction in cytotoxicity and a significant increase in transfection and knockdown efficiency (~85% knockdown, similar to Lipofectamine), when compared to the PEG-PCL-PDMAEMA triblock-copolymer controls [222]. The siRNA polyplexes were not found to be significantly removed by the ReticuloEndothelial System (RES), therefore indicating a good protection from opsonisation by PEG chains. In terms of tumour accumulation, the graft-PDMAEMA performed better than either the triblocks controls or PEI. Interestingly, when PCL was exchanged for PDLLA and co-polymers of PCL-PDLLA, the high-PDLLA polyplexes displayed lower uptake but equivalent silencing [194]. The authors interpreted this result as a consequence of a different internalization mechanism, which appears to involve more *caveolae* (inhibition through the use of genistin) for PCL-rich particles and possibly determines a slower degradation and thus a slower siRNA release. The high toxicity is, however, a well-known problem of PDMAEMA-based systems; as a solution to this, polyanionic poly(glutamic acid)-*g*-PEG bearing or a folic acid as a terminal group was added to the positively charged siRNA polyplexes, effectively providing a protective coating. The resulting nanoparticles were found to have a significantly reduced in vitro toxicity, however at the cost of a lower knockdown efficiency [223]. In vivo, the FA-functionalized particles were able to deliver fluorescently labelled-siRNA into the cytoplasm of Hela-Luc tumour cells in BALB/C nude mice with a higher efficiency than particles without FA. Always aiming to reduce cytotoxicity without detrimental effects on transfection efficiency, in an alternative approach DMAEMA has been copolymerized with sulfadiazine methacrylamide (SDZMA, Fig. 13C). As previously shown in different studies [224], the negative charge exhibited by N-diazine-bearing sulfonamides (sulfadiazines) at physiological pH (pKa ≈ 6.5) allows them to form polyelectrolyte complexes, whereas their hydrophobic character at endosomal pH make them potentially endosomolytic. Therefore, PDMAEMA-*co*-SDZMA branches are self-complexing at physiological pH (= sulfonamides partially counterbalance the cationic character of DMAEMA units), lowering the cytotoxicity of the constructs: for example, in 293 T and MFC-7 cells the cell viability improved from <20 to up to ~80% (1 μg/well of DNA, N/P ratio = 10); moreover, the SDZMA copolymers displayed considerably higher transfection efficiencies and expression of the plasmid vectors (typically double) [225]. It is worth noting that also other functionalities have been introduced via DMAEMA copolymerization, such as with 2,2-dimethyl-1,3-dioxolane-4-yl)methacrylate (the ketal-protected form of glycerol monomethacrylate). The resulting polymers showed an accelerated solubilization due to the protonation of tertiary amines (pH < 6.8) catalysing the deprotection of diol groups, and thereby uncovering further hydrophilic groups [226]. In other works, PDMAEMA was replaced with poly(methacrylic acid) (PMAA) in order to deliver hydrophobic drugs such as ibuprofen into the digestive tract and avoid burst release of drug in the stomach (= PMAA working as an enteric coating agent) [227].

The use of the Baeyer–Villiger oxidation, however, is not limited to the preparation of ATRP-initiating lactones. Among the numerous cases, this reaction has been employed as the last synthetic step in the preparation of CL derivatives featuring oligo(ethylene glycol) chains [228], protected carboxylic (3-oxy-(*tert*-butylpropanoate)) [229] or ketone (5-ethylene ketal) [230] groups. We limit this discussion to only one example of application to the preparation of branched polymers for each of these monomers. PCLs featuring oligo(ethylene glycol) branches have shown thermoresponsive aggregation in a physiological range of temperature [231]. In a clever approach, cisplatin has been used both as a payload and as branching agent for the side-chain carboxylic groups deriving from the second monomer: by the use of $AgNO_3$, cisplatin chlorides can be replaced by water molecules, which can then be easily inserted into the side chains of an amphiphilic PEG/carboxylated CL block copolymer. The resulting nanoparticles acted as prodrugs for cisplatin, which is released in media containing Cl^- ions, as well as in the presence of esterases [232,233]. Finally, ketone-containing PCLs have been employed to introduce photopolymerizable groups (reaction with hydroxylamine-containing acrylate) [234] or sheddable polycationic branches (reduction to alcohol and conversion into thiols and then disulphides) for siRNA complexation [235].

B) The derivatization of pre-formed CL is a considerably less common preparative method. An example is offered by Lavasanifar [236], who prepared an alkyne-functionalized monomer by activating CL with lithium diisopropylamide (LDA) for nucleophilic substitution onto propargyl chloroformate, and copolymerized with CL using mPEGOH as an initiator (Fig. 14A). The micelles formed in water by the resulting amphiphilic block copolymer were stabilized through core-cross-linking using the [3 + 2] Huisgen cycloaddition of a tetraethylene glycol (bis)azide; it is noteworthy that the cross-linked nanoparticles displayed significantly reduced protein (BSA) adsorption.

4.3.6. Other ROP-based approaches to branched polymers

A) rROP. The nitroxide-mediated copolymerization of CKAs with oligo(ethylene glycol) methacrylate has been employed to prepare PEG combs, which are effectively a degradable alternative to polyPEGs (Fig. 14B, top) [237,238]. Similar, degradable PEG combs obtained via free radical polymerization had been previously produced with photoactive side chains to yield core-cross-linked micelles [239].

MDO is the most popular CKA and its polymerization product is a PCL chain. In a recent study, MDO has been used to prepare branched PCL making use of vinyl bromobutanoate (VBr) as a functional comonomer (Fig. 14B, bottom); MDO and VBr were found to have near identical reactivity ratios ($r_{MDO} = 0.964$ and $r_{VBr} = 1.03$) indicating the randomness of monomer insertion [240]. The post-polymerization substitution of bromides with azides made the polymers amenable to further functionalization through the [3 + 2] Huisgen "click" reaction [240].

B) Self-condensing ring-opening polymerization (SCROP). This approach is conceptually analogous to the possibly better known self-condensing vinyl polymerization (SCVP) introduced by Fréchet in the 90s [241]; as SCVP, also SCROP is based on the use of inimers, i.e. compounds capable of acting at the same time as initiators and monomers. Possibly, the simplest inimer used in SCROP is HEMA [242], which can initiate a base-catalysed ROP through its primary alcohol, but can also react as a Michael-type acceptor for alcoholates; HEMA, however, may also experience side reactions (e.g. homopolymerization due to the high temperature of the reaction).

More recent studies have used alcohol-containing cyclic esters; the first known example employed mevalonolactone (4-hydroxy-4-methyl-valerolactone), which provided relatively little branching possibly due to steric hindrance of its secondary alcohol [243]. Primary alcohols such as 6-hydroxymethyl-1,4-di-oxane-2-one (6HDON) [244] or 5-hydroxymethyl-1,4-dioxane-2-one (5HDON) [245] were more effective inimers, and their homopolymerization provides alternating polyester/ether hyperbranched structures. In probably the most complete

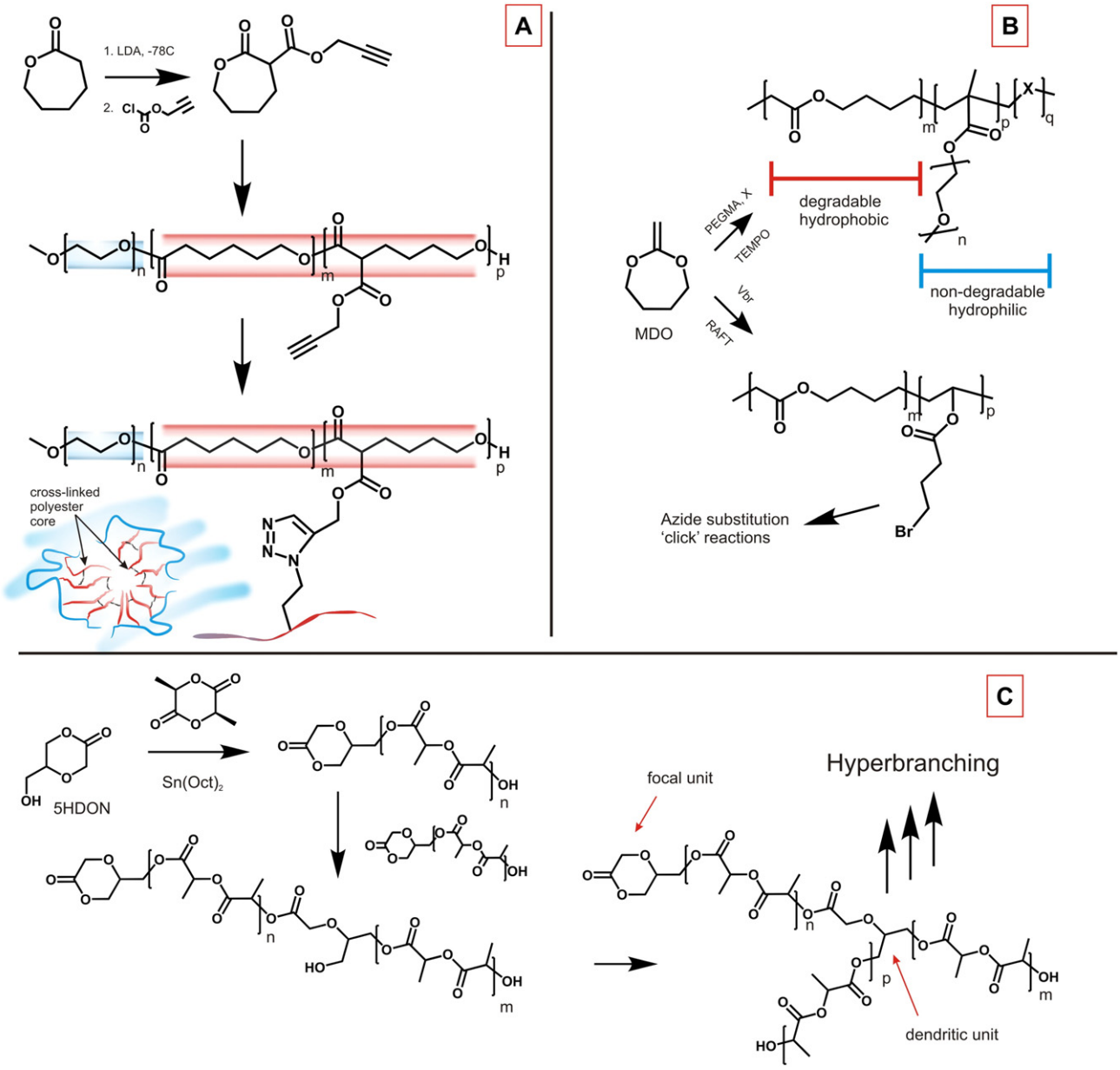

Fig. 14. *A.* Core-cross-linked aggregates can be obtained by performing 'click' reactions between diazides and PCL blocks bearing alkynes as side groups. The latter can be introduced directly on the CL structure. *B.* Top: MDO is a prototypical CKA that can be copolymerized with PEG methacrylate and other radically polymerizable comonomers (X; e.g. acrylonitrile or styrene [237]), yielding copolymers where the macromolecular chain can be eroded in correspondence to the ester units. Bottom: the random copolymerization between MDO and VBr allows for an even distribution of side-chain functional groups that can be functionalized in a *grafting to* approach. *C.* 5HDON can initiate L-lactide polymerization, providing polymers with lactone terminal groups (corresponding to focal units in the final polymer), that would react during the process and then provide additional initiators at the reaction site (corresponding to dendritic units in the final polymer).

work in the area of SCROP to date, Frey has employed 5HDON as an inimer during the polymerization of L-lactide [246], showing the formation of a well-defined dendritic structure under $Sn(Oct)_2$ catalysis(Fig. 14C); notably, TBD catalysis suppressed the formation of dendritic units.

It is worth mentioning a parallel approach to hyperbranched polyesters used by the group of Frey; glycolide was polymerized using 2,2-bis(hydroxymethyl)butyric acid (BHB) as a difunctional initiator (at the two alcohol groups) under $Sn(Oct)_2$ catalysis, and then condensing the terminal OH groups with BHB-derived intrachain carboxylic groups via a thermal treatment at reduced pressure [247].

C) Enzymatic catalysis. Although mechanistically different (e.g. not governed by ring strain), enzyme catalysis does not conceptually alter the overall scheme of ROP: alcohols and polyols [25] (or carboxylic acids, or even polyamines such as chitosan [248]) can be used as initiators for the opening of cyclic esters. For example, Frey and Smet demonstrated that 2,2′-bis(hydroxymethyl)butyric acid (an AB_2 monomer analogous to bis-(MPA)) could be used for both initiating and branching the lipase-catalysed polymerization of CL [52], and Howdle used the OH side-groups of poly(MMA-*co*-HEMA) to graft CL on a methacrylic backbone [249]. The most important difference between chemical and enzymatic polymerization is possibly the efficiency of initiation, which in the second case is probably more influenced by steric hindrance: when using both linear and hyperbranched polyglycerols as initiators, Möller showed a quantitative use of their alcohol groups when employing zinc(II) 2-ethylhexanoate

in CL polymerization, but only a very fractional (15–20%) when employing lipase B [250], and a low grafting efficiency was also recorded by Howdle [249].

In this context, it is also worth mentioning the enzymatic synthesis of a PCL-based macroinimer presented by Heise: 2-hydroxyethyl α-bromoisobutyrate was used as a CL initiator under lipase catalysis, employing vinyl acrylate to terminate the polyester chain (always through enzymatic catalysis). The resulting polymer thus featured an ATRP initiator at one end, and a ATRP-polymerizable acrylate at the other, allowing therefore the preparation of a hyperbranched construct through SCVP [251].

5. Conclusions

Branching encompasses a variety of architectures, which are obtained through a large and often disparate number of preparative methods. Yet, despite this morphological and chemical diversity, some trends can be recognized. For example, most of these branched constructs have an amphiphilic character; many can be simply summarized as attempts to produce polymers where the topological (core, shell, etc.) control of branching/cross-linking confers stability and/or irreversibility to water-driven, nano-scale self-assembly. Another common point is that only occasionally materials and processes have been designed and/or developed in view of their industrialization/scale-up, Boltorn™ being the most noticeable exception, despite the many problems with its characterization. This reflects a translational perspective that focuses on nano-materials and thus privileges small-scale/high-value applications such as those in nanomedicine (drug delivery/diagnostics). It is also of note that often insufficient attention is paid to the precise characterization of the molecular weight distribution, which may later cause issues for regulatory approval.

Finally, it is noticeable that, although with some exceptions, considerably less attention has been paid to other peculiarities of branched materials, chiefly the control over the presentation of chemical groups (as in dendrimers).

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