Cyclic polymers: Advances in their synthesis, properties, and biomedical applications

Romain Liénard1,2 | Julien De Winter2 | Olivier Coulembier1

1Laboratory of Polymeric and Composite Materials (LPCM), Center of Innovation and Research in Materials and Polymers (CIRMAP), University of Mons, Mons, Belgium
2Organic Synthesis and Mass Spectrometry Laboratory (S2MOs), Interdisciplinary Center for Mass Spectrometry (CISMa), University of Mons, Mons, Belgium

Abstract
Since the time first synthetic macrocycles were observed as academic curiosities, great advances have been made. Thanks to the development of controlled polymerization processes, new catalytic systems and characterization techniques during the last decades, well-defined cyclic polymers are now readily accessible. This further permits the determination of their unique set of properties, mainly due to their lack of chain ends, and their use for industrial applications can now be foreshadowed. This review aims to give an overview on the recent progresses in the field of ring polymers to this day. The current state of the art of the preparation of cyclic polymers, the challenges related to it such as the purification of the samples and the scalability of the synthetic processes, the properties arising from the cyclic topology and the potential use of cyclo-based polymers for biomedical applications are as many topics covered in this review.

KEYWORDS
cyclic polymer, macromolecular engineering, polymers, ring expansion, ring-closure

1 | INTRODUCTION

Intensive research has been conducted on the synthesis and physical properties determination of cyclic polymers over the last decades.1–4 Although the first report on a synthetic cyclic polymer was released by Ruggli over a hundred years ago,5 the cyclic topology only attracted interest when its presence in various natural biomacromolecules was highlighted and proved of importance.

Jacob and Wollman first suggested the existence of cyclic genetic elements in the form of plasmids in Escherichia coli in 1958.6 A few years later, Freifelder et al. demonstrated the circularity of deoxyribonucleic acids (DNA) of bacteriophage φX174 by electron microscopy.7 Cozzarelli et al. quickly followed with cyclic DNA synthesized by E. coli, verifying the hypothesis of Jacob and Wollman.8 Since then, circular DNA has been observed in different bacteria and viruses, as well as knotted and concatenated DNA.9 This topology has been assigned to a set of unique properties in comparison with linear DNA molecules, such as enhanced chemical and thermal stabilities.10 Similar observations have been made for other biomolecules, as natural11 and synthetic12 cyclic peptides.

Until the early 1980s, there has been very little advances in the preparation and the study of the properties of synthetic ring polymers. This is partly because, when Carothers and Flory elaborated the theoretical basis of step-growth polymerizations (SGPs), they did not take the cyclization reaction into account even though they themselves observed the formation of trace amounts of cyclic material.13,14 For a while, this omission hindered chemists to further investigate macrocycles. Later, the development of controlled polymerization processes and characterization techniques such as size-exclusion chromatography (SEC), nuclear magnetic resonance (NMR), and mass spectrometry (MS) permitted the
synthesis of well-defined ring polymers. The progresses made on the preparation of these structures allowed the subsequent determination of their physical and biological properties.\[1-4\] Since then, a steady flow of publications related with cyclic polymers is reported in the literature.

This review attempts to compile these information and is divided in two main sections:

1. Section 2 summarizes in a historical way the development of synthetic pathways for the preparation of ring polymers. The current challenges in relation with these syntheses are also discussed.
2. Section 3 deals with the physical and biological properties of cyclic polymers and their foreshadowed applications, with a focus on the field of medicine.

2 | ADVANCES IN THE SYNTHESIS OF CYCLIC POLYMERS

Since the time first synthetic macrocycles were observed as oligomeric by-products from SGPs and considered at that time as laboratory curiosities,\[15,16\] the controlled synthesis of ring polymers and related cyclo-based structures became a hot topic for synthetic polymer chemists around the world because of the unique properties those structures exhibit due to their “endless” topology.\[1-3\]

The first historical approach to their synthesis took benefit of the ring-chain equilibrium during an SGP. In such polymerization, two chemical processes are indeed competing: (a) the coupling of two linear precursors to form a larger linear chain and (b) the “end-biting” and “back-biting” reactions yielding a cyclic product. Stepto and coworkers and Gordon and Temple have been the first to take the cyclization reaction into account in their calculation on the SGP process,\[17-19\] after Carothers and Flory had deliberately omitted it when they defined the fundamental principles of polycondensation reactions in order to simplify their theory.\[13,14\] Doing so, Stepto and Gordon showed that, during an SGP, the cyclization reaction is observed no matter the initial monomer concentration. Their calculation also showed that cyclic structures constitute the main products of the reaction only at high conversion. By a fine-tuning of the experimental conditions, the synthesis of cyclic polymers could be achieved through this approach with, however, a limited success.\[20\] In fact, these materials would inescapably present a high dispersity, a low molecular weight, and, since a 100% conversion cannot be reached in real experiments, they would also be contaminated by nonnegligible amounts of linear structures.

These first synthetic efforts have laid the foundations of a whole new branch of materials science, namely topological polymer chemistry.\[21\] Since then, alternative cyclization strategies have been introduced, allowing the preparation of high purity macrocycles: the ring-closure (RC) and ring-expansion (RE) approaches. The former is a two-step process involving the (a) preparation and (b) closure of a linear precursor, while the latter permits the direct obtention of cyclic structures by the insertion of the monomer units into an activated (pseudo-)cyclic chain or initiator.\[1-4,22,23\] As will be discussed later, each approach demonstrates its own advantages and drawbacks. While RC techniques are generally compatible with most monomers and offer the possibility to introduce functionality in the polymer backbone, the molecular weight of the as-generated macrocycles is limited (<20,000 g.mol\(^{-1}\)) and the yields are low (usually a few hundreds of milligrams).\[22\] In contrast, RE techniques permit the production of higher molecular weight ring polymers (up to \(10^5\) g.mol\(^{-1}\)) on a larger scale but are compatible with less polymer backbones.\[23\] The following section focuses on the turning points in the history of the preparation of cyclic structures.

2.1 | Bimolecular RC approach

The bimolecular RC strategy was the first modern cyclization technique to be developed following the initial investigations on the ring-chain equilibrium. It refers to the reaction between an \(\alpha,\omega\)-homotelechelic polymer and a bis-functional coupling agent. The bimolecular RC takes place in two steps: (a) the intermolecular reaction between one extremity of the polymer chain and one complementary functional group of the coupling agent and (b) the intramolecular reaction between the remaining available functional groups of both the polymer and the coupling agent. The main issue with this strategy is the absolute need to be in exact stoichiometric conditions. If in the presence of an excess or a lack of difunctional linking agent as compared to the linear precursor, the formation of linear polymer chains with “dead” chain ends, unable to cyclize anymore, is observed.\[1\]

The bimolecular RC strategy also presents a paradox in its concept: while the first step (i.e., the intermolecular coupling) is kinetically favored in concentrated conditions, the second step (i.e., the intramolecular cyclization) is favored in diluted conditions. In order to minimize the formation of acyclic by-products, the concentration of both the \(\alpha,\omega\)-homotelechelic polymer and the bifunctional coupling agent should therefore be kept as low as possible.

Even though this strategy is not flawless, its great compatibility with the anionic polymerization has led to
its application for the cyclization of polymers with well-defined molecular weights and low dispersities ($D_M < 1.2$). In the late 1970s-early 1980s, three research groups, namely those of Rempp and coworkers, Höcker and Geiser, and Vollmert and Huang, reported independently and almost simultaneously the preparation of cyclo-poly(styrene) (c-PS) by bimolecular RC of a linear PS (l-PS) prepared by anionic polymerization using $a,a'$-dihalo-$p$-xylene as coupling agent. Each of these groups, however, observed the contamination of c-PS by large amounts of by-products from intermolecular couplings (>50%) by SEC. Chromatographic fractionation of the sample was therefore required to isolate the monocycles from these impurities.

In 2000, Tezuka and coworkers proposed an elegant method to address one of the issues encountered with the bimolecular cyclization approach, that is, the paradox between the first intermolecular step and the second intramolecular step of the cyclization, in the name of the electrostatic self-assembly and covalent fixation (ESA-CF).

In their study, the ESA-CF process involved a reaction between a poly(tetrahydrofuran) (PTHF) end-capped with $N$-phenylpyrrolidinium cationic moieties on both chain ends and a dicarboxylate anionic coupling agent. Under high dilution conditions, the polymer and the linking agent self-assemble into a pseudo-cyclic structure maintained by the electrostatic attraction between the two. Thanks to this strong interaction, the issue with the intermolecular step of the cyclization is suppressed. Then, upon heating at roughly 66°C for few hours, the pyrrolidinium ring undergoes a ring opening by the carboxylate anion, leading to the formation of a stable covalent bond (Scheme 1).

Using this method, Tezuka and Yamamoto not only prepared c-PTHF with a high purity and high yields, but also a wide range of complex (multi-)cyclic structures such as fused-, spiro-, and bridged macrocycles by variation of the linking agent (e.g., with trifunctional or tetrafunctional carboxylates). The ESA-CF process was also later adapted to other polymers such as PS and poly(ethylene oxide) (PEO).

The unimolecular RC strategy refers to the reaction between the two chain ends of the same polymer chain under dilute conditions. The two extremities can be whether of the same or different nature. We then speak, respectively, of homodifunctional or heterodifunctional unimolecular RC.

The unimolecular approach was rapidly adopted because it solves some of the main flaws of its bimolecular counterpart. In fact, as long as a quantitative functionalization of the polymer is reached, there is no more issue with the stoichiometry of the reaction. Chain-end modification is a well-known issue in material science. It was shown that the extremities of a polymer chain play a crucial role in the properties of the material, and intense research has been devoted to the development of strategies permitting to reach a high chain-end fidelity. Also, as the chain bears the two functional groups required for the cyclization, there is no need of bimolecular reaction. The cyclization is, thus, conducted in highly dilute conditions to suppress the oligomerization, while the rate of cyclization is not impacted.

However, this strategy still shares one common issue with the bimolecular approach: for the polymer chain to cyclize, it is required for both chain ends to be in a capture volume for them to meet and react. As the length of the chain increases, it may sound trivial that the probability for the two chain ends to be in that capture volume decreases, and therefore the cyclization reaction of very long polymer chains becomes highly improbable. This entropic penalty was actually demonstrated by Jacobson and Stockmayer as early as 1950, and they showed that the probability of cyclization of a polymer chain decreases as $n^{-2.5/2}$, where $n$ is the number of repeating units constituting the backbone of the chain. This is commonly referred in the literature as the Jacobson–Stockmayer theory and has been verified experimentally numerous times since then. For that reason, RC methods are usually limited to the preparation of relatively small macrocycles ($<20,000$ g.mol$^{-1}$).
2.2.1 Homodifunctional unimolecular RC

The homodifunctional approach was, at first, preferred over the heterodifunctional one, probably due to the relative ease of introducing two identical functional groups on the chain ends of a polymer.

In 2002, Tezuka and Komiya reported the cyclization of an allyl end-capped PTHF by olefin ring-closing metathesis using a ruthenium-based Grubbs first generation catalyst. In 2007, they later adapted this method to poly(methyl acrylate) by combination with atom transfer radical polymerization (ATRP). Using an H-shaped telechelic precursor, they were also able to produce molecules and θ-shaped cyclo-based structures via double metathesis condensation.

In 2006, Monteiro and coworkers reportedly developed the first example of reversible cyclization using the coupling/cleavage of thiol/disulfide groups. By oxidation under highly diluted conditions and in the presence of an oxidizing agent such as FeCl₃ of a linear dithiol-functionalized PS prepared by reversible addition–fragmentation chain transfer (RAFT) polymerization, the corresponding c-PS was obtained. The linear polymer could then be recovered by reduction in the presence of Zn and acetic acid (Scheme 2).

Other notable works could also be cited, such as the use of the isocyanates homocoupling by Chen et al. in 2006, Monteiro and coworkers reportedly developed the first example of reversible cyclization using the coupling/cleavage of thiol/disulfide groups. By oxidation under highly diluted conditions and in the presence of an oxidizing agent such as FeCl₃ of a linear dithiol-functionalized PS prepared by reversible addition–fragmentation chain transfer (RAFT) polymerization, the corresponding c-PS was obtained. The linear polymer could then be recovered by reduction in the presence of Zn and acetic acid (Scheme 2).

Finally, in 2015, Ji et al. reported the use of cucurbit [8]uril (CB[8]) to assist the light-triggered intramolecular cycloaddition of the naphthalene or anthracene end groups of an α,ω-homotelechelic PEO (Scheme 3). Even though this is not the first occurrence of a photo-induced cyclization in the literature (as it will be discussed later), this was the first time supramolecular chemistry was applied for the purpose of cyclic polymers synthesis. Yet, the as-generated c-PEO was contaminated by a significant amount of undesired by-products.

2.2.2 Heterodifunctional unimolecular RC

Because organic chemistry counts very few efficient homocoupling reactions, many more examples of the heterodifunctional unimolecular RCs have been reported in the literature. These methods, however, require the precise synthesis of an α,ω-heterotelechelic linear precursor, which represents a challenge on its own.

Schappacher and Deffieux, in 1991, provided a very early example of successful cyclization of poly (2-chloroethyl vinyl ether) (PCEVE) by heterocoupling. The α-styrenyl, ω-iodo linear PCEVE precursor was prepared by cationic polymerization of the corresponding monomer from a vinyl ether-functionalized styrene initiator. In the presence of SnCl₄, a carbocation can be formed by abstraction of iodide. That carbocation further reacts with the styrenyl end group to afford a benzylic cation. Quenching with an alkoxide ultimately leads to the desired c-PCEVE (Scheme 4). They estimated the sample to be composed of 80% of monocycles by SEC. Rique-Lurbet et al. applied a similar method for the preparation of c-PS in 1994.

Following this work, several other heterodifunctional cyclizations have been reported in the literature. One noteworthy advance in the preparation of macrocycles was made by Lepoittevin et al. in 2001, with the integration of controlled radical polymerizations (CRPs). CRPs are particularly attractive for that purpose because they allow easy modification of the chain ends, and the polymers obtained by these methods have very well-defined molecular parameters. Lepoittevin et al. utilized the nitroxide-mediated polymerization (NMP) of styrene using a dicarboxylic acid and 4-hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy (hydroxy-TEMPO) as initiator and radical mediator, respectively. The α-carboxylic acid and ω-hydroxy end groups can then react under highly diluted conditions and in the presence of 2-chloro-1-methylpyridinium iodide to activate the carboxylic acid, affording c-PS with a very high degree of purity (>95%) (Scheme 5).

In 2006, Laurent and Grayson were behind what could arguably be considered the greatest breakthrough in the field. In fact, they have been the first to report the efficient cyclization of a polymer using the so-called “click” chemistry reactions. “Click” chemistry is a concept defined in 2001 by Sharpless and coworkers to describe very efficient reactions. In order to be considered as a “click” reaction, a chemical process must fulfill different requirements, among which: be modular, wide in scope, give very high yields, generate only inoffensive by-products that can be removed by nonchromatographic methods and be stereospecific. Even though most of the reactions meeting these criteria were long known before

![Scheme 2](image-url) Preparation of cyclo-poly(styrene) (c-PS) by reversible oxidation/reduction of thiols/disulfide.
Sharpless and coworkers put it into words, the introduction of this concept definitely revolutionized modern organic chemistry and materials science.\[49–51\] Today, the three major representatives of this chemistry are the copper-catalyzed azide–alkyne cycloaddition (CuAAC), the Diels–Alder cycloaddition and the thiol–Michael addition (also known as thiol–ene reaction).

Laurent and Grayson had the idea to combine the ATRP of styrene with the CuAAC (Scheme 6). Because the ATRP process is compatible with the use of initiators bearing a variety of functional groups, such as alkynes, and the terminal bromide of the polymers produced by ATRP can be turned into an azide group by reaction with sodium azide, the \( \alpha \)-alkyne, \( \omega \)-azide linear precursor could be obtained quite easily. The linear polymer was then slowly injected by a drop-wise addition into a catalytic solution of copper (I) complex in order to keep the instant concentration of linear polymer very low so oligomerizations are suppressed, and limit the amount of solvent used for the cyclization. This is referred to as pseudo-high dilution conditions. The cyclization appeared to be nearly quantitative, as verified by Fourier transform infrared spectroscopy (FTIR), \(^1\)H NMR, and SEC, and no further fractionation of the c-PS was

**Scheme 3**  Schematic representation of the CB[8]-assisted cyclization of poly(ethylene oxide) (PEO) by anthracene photodimerization

**Scheme 4**  Preparation of cyclo-poly(2-chloroethyl vinyl ether) (c-PCEVE) by heterocoupling

**Scheme 5**  Preparation of cyclo-poly(styrene) (c-PS) by intramolecular esterification

**Scheme 6**  Preparation of c-PS by copper-catalyzed azide–alkyne cycloaddition (CuAAC) “click” coupling
required.\textsuperscript{[47]} Since then, a wide range of (co)polymers obtained by ATRP, NMP, RAFT, ring-opening polymerization (ROP), and cationic polymerization have been cyclized by means of CuAAC.\textsuperscript{[52–67]}

Because of potential toxicity concerns for biomedical applications, metal-free cyclizations have been investigated. Some examples have been provided by Mizawa et al.,\textsuperscript{[68]} Durmaz et al.,\textsuperscript{[69]} and Glassner et al.,\textsuperscript{[70]} who utilized the Diels–Alder cycloaddition with more or less success. All these methods, however, have in common that they use a metal catalyst at some point in the route, would it be Zn, Ni, or Cu, even though the cyclization step only requires heat. The cyclization using Diels–Alder coupling was also, at the time, limited in scope because of how hard the introduction of the chain ends was for polymer backbones other than those produced by radical polymerization.

In 2013, Monteiro and coworkers reported on the use of the thiol-Michael reaction, the third major representative of “click” chemistry, for the cyclization of different polymers obtained by RAFT polymerization.\textsuperscript{[71]} They used an acryloyl-functionalized RAFT initiator to polymerize styrene, 2,4,6-trimethyl benzaldehyde (tBA), N-isopropylacrylamide (NIPAm), and N,N-dimethylacrylamide. One-pot aminolysis of the RAFT agent in the presence of hexylamine followed by the base-catalyzed thiol-Michael addition of the newly formed thiol on the acryloyl group yielded the corresponding cyclic polymer.

In 2014, another notable advance has been made by Josse et al. who reported the first example of catalyst-free photo-induced cyclization.\textsuperscript{[72]} They prepared poly(lactide) (PLA) and poly(ε-caprolactone) (PCL) by organocatalyzed ROP of lactide (LA) and ε-caprolactone (ε-CL), respectively, using an initiator bearing a photosensitive group, namely o-methylbenzaldehyde, as diene precursor. Subsequent functionalization of the ω chain end with acryloyl chloride afforded the linear precursor. By irradiation with ultraviolet (UV) light (\(\lambda_{\text{max}} = 315\) nm) in dilute conditions, the o-methylbenzaldehyde isomerizes into a very reactive photoenol-diene that is prone to react by Diels–Alder cycloaddition with the ω end group, yielding the corresponding cyclic polyesters near quantitatively (Scheme 7). This approach presents the major advantage of requiring no purification other than the evaporation of the solvent, due to the absence of any catalyst or reactant beside the linear precursor itself. Josse et al. further demonstrated the efficiency of their approach using the sun as UV light source, under a variety of weather conditions (high/low UV index, cloudy weather, hot/cold weather), making it accessible to a larger number of groups as no specific equipment is required anymore.\textsuperscript{[73]}

Following this initial report, a number of different photo-induced cyclizations quickly arose in the literature.\textsuperscript{[39,74–77]} In 2015, Sun et al. published a particularly interesting demonstration of the use of a metal-free variant of the CuAAC for the preparation of cyclic structures, the strain-promoted azide–alkyne cycloaddition (SPAAC).\textsuperscript{[75]} They prepared a linear PS precursor by ATRP of styrene from an initiator bearing a dibenzocyclooctyne group, in which the alkyne moiety is protected as a cyclopropenone, followed by postpolymerization modification of the ω chain end with a TEMPO derivative functionalized with an azide group. Under UV irradiation, the highly reactive (due to the cyclic strain) alkyne group is released and reacts with the free azide function to produce c-PS with a high purity (Scheme 8). Sun et al. also successfully designed a “batch-wise” procedure to try to overcome the low yields that are inherent to high dilution conditions, in which a quantity of l-PS is evenly divided in three batches that are added to the solution one after each other, each addition being followed by 5 hr of UV irradiation. Inspired by this success, the same group later made this approach compatible with other polymers such as poly(vinyl acetate) and poly(N-vinylpyrrolidone),\textsuperscript{[78]} and also adapted the SPAAC into a “self-accelerating” bimolecular homodifunctional RC technique.\textsuperscript{[79]}

To conclude on the RC approach, much progress has been made during the last 30 years. The combination of RC methods with living polymerization processes, the use of the highly efficient “click” reactions, and the development of the recent catalyst-free and light-induced cyclizations, all of these contributed to the step-by-step improvement of the cyclization efficiency, the suppression of oligomerization reactions, the increase of the yields and the simplification of the work-ups. To this day, synthetic pathways for the RC cyclization of most

\textsc{scheme 7} Preparation of cyclo-poly(lactide) (c-PLA) by Diels–Alder cycloaddition using o-methylbenzaldehyde as photoactivated diene
polymer backbones exist, usually providing a high degree of purity. However, some flaws remain. As demonstrated by Jacobson and Stockmayer, the cyclization of linear chains becomes increasingly difficult as the chain lengthens because of the entropic constraint to which the RC methods are subjected.\(^3\) For this reason, the RC approach is limited to the production of relatively small macrocycles (<20,000 g.mol\(^{-1}\)). Also, due to the highly diluted conditions required to favor the intramolecular reaction over the oligomerization, regular RC techniques are limited in yields, usually in the range of tens to a few hundreds of milligrams.

2.3 | RE approach

In an attempt to suppress the entropic penalty that is inherent to RC techniques, different approaches have been developed such as the use of solid supports,\(^{42}\) interfacial condensation\(^{80}\) or the previously discussed ESA-CF process.\(^{27,29,30}\) In this context, the RE appeared as an attractive strategy. The RE involves a polymerization reaction during which the monomers are inserted into a weak bond of a (pseudo-)cyclic chain. Because the cyclic structure is maintained all along the process, the RE methods do not suffer from the entropic constraint related to the closure of the chain. The RE approach is, thus, more suitable when it comes to the preparation of high-molecular-weight macrocycles. For the same reason, RE techniques do not require high dilution conditions, allowing the preparation of cyclic structures on a larger scale. Finally, as long as the initiator/catalyst and the monomer are free of any linear contaminant, pure cyclic structures are obtained.\(^8\) However, this approach has some drawbacks, as it usually provides poor control over the molecular parameters. It is also compatible with fewer monomers than the RC, typically, strained cyclic olefins and lactones, even though recent examples of the application of the RE to other kinds of monomers have also been reported, such as alkynes\(^8\) and episulfide monomers.\(^23,83\)

2.3.1 | RE using cyclic tin alkoxide initiators

Early efforts from Kricheldorf and Lee, in 1995, demonstrated the possibility to use the RE as an efficient route to cyclic polymers. In their initial study, they investigated the use of cyclic tin-based initiators (2,2-dibutyl-1,3-dioxa-stannanes) for the polymerization of different lactone monomers, namely \(\beta\)-butyrolactone (\(\beta\)-BL) and \(\epsilon\)-CL. This process involves the coordination-insertion of the lactone monomer into the labile tin alkoxide bond, resulting in the formation of the corresponding cyclic poly(\(\beta\)-BL) and PCL, respectively (Scheme 9).\(^84\)

The cyclic structure of the polymers provided by RE techniques is not always as straightforward to highlight as it may seem. In fact, in contrast with the RC methods, the RE does not provide any linear precursor to compare with. In addition, because of the lability of the tin-oxygen bond, the cyclic polymers produced by this method are very susceptible to cleavage. However, Kricheldorf and Lee remarkably turned this weakness into a strength, and used it to generate the corresponding linear analogues by a ligand exchange reaction with 1,2-ethanediithiol (Scheme 9), therefore permitting the comparison of the SEC chromatograms to assess the cyclic nature of the as-obtained cyclic polyestiers.

Following their studies, different strategies have been proposed to eliminate the labile tin-oxygen bond while keeping the cyclic topology.\(^85,86\) Li et al., for instance, suggested adding a small amount of an \(\epsilon\)-CL derivative bearing an acrylate side chain after the initial polymerization, yielding an ABA-type triblock copolymer. Under UV irradiation, the acrylate side chains would crosslink, therefore maintaining the cyclic structure of the polymer after hydrolysis of the tin moiety.\(^86\) In a very recent work, Kricheldorf et al. employed 2,2-dibutyl-2-stannan-1,3-dithiolane for the polymerization of \(\epsilon\)-LA.\(^87\) Because of the increased stability of the Sn—S bond as compared with the Sn—O bond, this initiator presents a lower
activity than the previous tin alkoxide initiators and the resulting cyclic polymers are more stable.

### 2.3.2 | RE metathesis polymerization

In 2002, Bielawski et al. demonstrated the use of a cyclic Ru-based Grubbs catalyst for the RE metathesis polymerization (REMP) of cyclooctene. During the process, the Ru catalyst inserts itself into the cyclooctene by alkene metathesis, yielding a larger cycle. The propagation reaction occurs the same way, but it is in competition with the intramolecular metathesis reaction. The latter takes place, mainly, at low monomer concentration, that is, high conversion. After the intramolecular reaction, the initial catalyst and cyclic poly(octenamer) are released (Scheme 10). Bielawski et al. reported the preparation of cyclic poly(octenamer) with $M_n$ up to $1.2 \times 10^6$ g.mol$^{-1}$ and $D_M$ around 2.0.[88] Similar results were described for the REMP of 1,5-cyclooctadiene and 1,4,9-trans-cis-trans-cyclododecatriene. High molecular weight cyclic polymers ($\sim 30,000$ g.mol$^{-1}$) could be obtained in roughly 15 min.[81] After this initial study, Grubbs and coworkers further reported on the influence of the structure of the catalyst, and demonstrated its significant impact on the polymerization kinetics.[89] Recently, Veige and coworkers released a series of reports on the use of tungsten-based alkylidyne catalysts for the REMP of phenylacetylene[82] and norbornene,[90,91] resulting in the formation of unique cyclic poly(phenylacetylene) and highly stereoselective cyclic poly(norbornene), respectively, in high yields.

### 2.3.3 | Radical RE polymerization

Similarly, the mechanism of CRPs (i.e., homolytic bond cleavage, addition of a monomer unit, radical recombination) makes them suitable to be adapted into RE techniques by using a cyclic initiator. In 2003, Pan and coworkers utilized a cyclic RAFT agent to perform such RE polymerization of methyl acrylate. The difference with traditional RAFT polymerizations is that they used $^{60}$Co γ-ray irradiation to induce the initiation of the polymerization, which was conducted at low temperature ($-30^\circ$C), instead of the usual temperature-induced initiation (Scheme 11).[92] The purpose of this was to diminish the thermal diffusion of the chain ends in order to avoid intermolecular recombination, which would lead to linear chains. Several other radical RE polymerizations have been reported since then.[93–98]

### 2.3.4 | Zwitterionic ROP

The zwitterionic ROP (ZROP) implies the ROP of a cyclic monomer, typically four to seven-membered (di)lactones, generating an ionic propagating species whose counterion is carried by the same chain. It is assumed that the cyclic structure is retained during the process thanks to
the electrostatic interaction between the two charged end groups. ZROP can, thus, be considered as an RE. ZROP methods can be further divided in three distinct mechanisms: the nucleophilic ZROP, the Lewis-pair-mediated ZROP and the electrophilic ZROP.

The nucleophilic ZROP was the first to be reported and is probably the most employed. Many different neutral nucleophilic species have been employed as ZROP initiators to produce macrocycles, including pyridines, N-heterocyclic carbenes (NHCs), amidines, and sparteine. During the process, the nucleophile opens a cyclic monomer, typically strained cyclic lactones, generating a zwitterionic species with an anionic propagating chain end. Further propagation followed by intramolecular cyclization yields the corresponding cyclic polymer with regeneration of the initiator. Interestingly, most of these nucleophiles can also be used as organic catalysts for the preparation of linear polymers when used in the presence of a protic initiator.

Perhaps, the most representative example of nucleophilic ZROP is that of Waymouth and coworkers, who, in 2007, employed a NHC catalyst for the preparation of c-PLAs with $M_n = 8-26 \times 10^3 \text{ g.mol}^{-1}$ and narrow molar mass dispersities ($D_M < 1.3$) (Scheme 12). NHC catalysts were also utilized for the preparation of cyclic polymers from $\beta$-lactones, $\varepsilon$-CL, $\delta$-valerolactone ($\delta$-VL), and N-substituted N-carboxyanhydrides. The Lewis-pair-mediated ZROP involves the catalysis of the ZROP by a Lewis pair, that is, the combination of a Lewis acid and a Lewis base. These catalytic systems were initially investigated by Stephan and Erker, who introduced the concept of “frustrated Lewis pairs” (FLPs), that is, a pair of a sterically hindered Lewis acid/base. FLPs differ from usual Lewis pairs in that they do not react to form a Lewis acid/base adduct, but instead, they can activate small molecules and catalyze reactions that were previously known to need transition metal complexes, such as catalytic hydrogenation. In 2013, Bourissou and coworkers demonstrated the use of an FLP composed of $\text{Zn(C}_6\text{F}_5)\text{2}$ and 1,2,2,6,6-pentamethylpiperidine for the ROP of LA, generating c-PLA with $M_n$ as high as $50 \times 10^3 \text{ g.mol}^{-1}$ and $D_M < 1.5$. In the same report, they also prepared c-(PCL-b-PLA) by sequential polymerization of $\varepsilon$-CL and LA.

The electrophilic ZROP is the most recent of the three mechanisms. During this process, an electrophilic catalyst activates a strained cyclic monomer to promote the ring opening of the latter by another monomer, generating the zwitterionic species that further undergoes cyclization. A notable example of electrophilic ZROP has been provided by Asenjo-Sanz et al. in 2014, who used a Lewis acid, B($\text{C}_6\text{F}_5)_3$, to catalyze the polymerization of glycidyl phenyl ether (GPE). Cyclic polyethers with $M_n = 3-12 \times 10^3 \text{ g.mol}^{-1}$, $D_M = 1.5-1.9$ and a high monomer content (>95%) were generated. When in the presence of water, however, linear polymer chains with a hydroxy terminal group were obtained.

Finally, the RE addresses some of the issues encountered with RC techniques such as the entropic penalty or the requirement of diluted conditions, but it also suffers from its own flaws. While the RE provides access to high-molecular-weight cyclic polymers in a short time, the RC offers more versatility and a better control over the molecular parameters. These two approaches are
therefore perfectly complementary. Even though some challenges remain, the field of cyclic polymers synthesis has developed in such a way that, nowadays, synthetic polymer chemists have access to a large panel of strategies to pick from, based on their needs (Table 1).

<table>
<thead>
<tr>
<th>Approach</th>
<th>Technique</th>
<th>Monomer family</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC</td>
<td>Anthracene photodimerization</td>
<td>Cyclic ethers</td>
<td>[77]</td>
</tr>
<tr>
<td></td>
<td>Epoxides</td>
<td>[39,77]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactones</td>
<td>[76,134]</td>
<td></td>
</tr>
<tr>
<td>CuAAC</td>
<td>Acrylics</td>
<td>[52–54,63,192,193,198,210,218]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epoxides</td>
<td>[65]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactones</td>
<td>[57,59,60,65,66,197]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxazolines</td>
<td>[67,137]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vinils</td>
<td>[47,55,56,61,62,64,192]</td>
<td></td>
</tr>
<tr>
<td>Diels–Alder</td>
<td>Acrylics</td>
<td>[68–70,74,141]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactones</td>
<td>[69,72]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vinils</td>
<td>[69,74,140]</td>
<td></td>
</tr>
<tr>
<td>ESA-CF</td>
<td>Cyclic ethers</td>
<td>[27]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epoxides</td>
<td>[30]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vinils</td>
<td>[29]</td>
<td></td>
</tr>
<tr>
<td>RCM</td>
<td>Acrylics</td>
<td>[34,204]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclic ethers</td>
<td>[33,35]</td>
<td></td>
</tr>
<tr>
<td>SPAAC</td>
<td>Vinils</td>
<td>[75,78,79]</td>
<td></td>
</tr>
<tr>
<td>Thiol-Michael addition</td>
<td>Acrylics</td>
<td>[71]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vinils</td>
<td>[71]</td>
<td></td>
</tr>
<tr>
<td>RE</td>
<td>CRPs with cyclic initiators</td>
<td>1,2-Dithianes</td>
<td>[93–95]</td>
</tr>
<tr>
<td></td>
<td>Acrylics</td>
<td>[92]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vinils</td>
<td>[96–98]</td>
<td></td>
</tr>
<tr>
<td>REMP</td>
<td>Alkynes</td>
<td>[82]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclic alkenes</td>
<td>[81,88–91]</td>
<td></td>
</tr>
<tr>
<td>ROP using cyclic tin alkoxide initiators</td>
<td>Lactones</td>
<td>[84,86,87]</td>
<td></td>
</tr>
<tr>
<td>ZROP</td>
<td>Acrylics</td>
<td>[111]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epoxides</td>
<td>[114,130]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactones</td>
<td>[100,104–106,112,113]</td>
<td></td>
</tr>
<tr>
<td>NCA</td>
<td></td>
<td>[107]</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CRPs, controlled radical polymerizations; copper-catalyzed azide–alkyne cycloaddition (CuAAC); ESA, electrostatic self-assembly and covalent fixation; NCA, N-carboxyanhydride; RC, ring-closure; RCM, ring-closing metathesis; RE, ring-expansion; REMP, RE metathesis polymerization; ROP, ring-opening polymerization; SPAAC, strain-promoted azide–alkyne cycloaddition; ZROP, zwitterionic ROP.

Therefore perfectly complementary. Even though some challenges remain, the field of cyclic polymers synthesis has developed in such a way that, nowadays, synthetic polymer chemists have access to a large panel of strategies to pick from, based on their needs (Table 1).

2.4 | Current challenges

It is indisputable that the synthesis of cyclic polymers has been drastically improved over the last decades, thanks to the combined efforts of numerous chemists all around the world. However, there is still some room for improvement on some aspects of it. In the few following lines, the current remaining challenges in the synthesis of cyclic macromolecules will be discussed.

2.4.1 | Elimination of cyclization by-products

As discussed previously, the presence of impurities in a cyclic sample is almost inescapable. For the RC techniques, the most common ones are uncyclized chains due
to an inefficient cyclization reaction or an incomplete functionalization of the chain ends of the linear precursor, and cyclic or linear oligomers generated by an intermolecular coupling rather than intramolecular due to inappropriate experimental conditions (i.e., when the cyclization is performed under a too high concentration).\[22\] The RE methods are usually less concerned by this issue, because the cyclic structure is maintained throughout the whole process and there is no linear intermediate.\[23\] However, if the initiator/catalyst or the monomer involved in the RE are unfortunately contaminated by linear species, it is possible to observe the formation of linear chains instead of the expected cyclic product.\[81\] Other factors, such as the presence of water in the reaction medium, may also instigate the formation of undesired by-products.\[114\] As polymers are characterized by a very close structure–property relationship, in solution as well as in bulk, the elimination of these impurities is crucial when determining the properties of cyclic polymers.\[2,115–117\]

The most traditional technique used to get rid of these impurities is the preparative SEC. In fact, because of its limited conformational freedom, a cyclic polymer will present a lower hydrodynamic volume when compared to its linear analogue.\[2,118,119\] The monocyclic product will therefore elute after a longer time than the linear precursor or the possible oligomers, and fractionation is made possible.\[120\] However, because of the relatively low sensitivity and resolving power of the SEC, small amounts of linear contaminants (<5%) can barely be detected.\[41\] Other liquid chromatography techniques such as the liquid chromatography at the critical conditions (LCCC) can be employed for the fractionation of cyclic samples.\[121,122\] The LCCC is another high-performance liquid chromatography technique, just like the SEC, in which the chromatographic parameters (i.e., the stationary phase, the mobile phase, and the temperature) are fine-tuned in such a way that a balance between the entropic exclusion and the enthalpic adsorption interactions between the polymer chains and the stationary phase is reached. This results in the simultaneous elution of polymer chains of different molecular weights, provided they have the same structure and the same chain ends.\[123\] However, if the chains bear different functional groups (in this case, if they have actual chain ends or not), they will present different retention times.\[124,125\] The LCCC is also used for the characterization of block copolymers, functionalized polymers, polymer blends, and so on.\[126–129\] Even though this technique allows a highly efficient separation of the cyclic polymer from the linear impurities, the determination of the experimental conditions is a very tedious task and each different polymer backbone requires the different parameters to be readjusted, hence why, to date, the few examples that have been reported in the literature only concern PS samples. This is even more true for the smaller cyclic samples (e.g., those prepared by RC techniques), for which the resolution of the LCCC becomes too poor.\[122\]

In 2011, Touris and Hadjichristidis suggested the use of a Merrifield resin modified with azide groups for the purification of a c-PS-block-poly(isoprene) (c-[PS-b-PI]) sample (Figure 1).\[62\] This method was also employed by Haque et al., who reported on the preparation of c-GPE by electrophilic ZROP following the procedure of Asenjo-Sanz et al. discussed above,\[114\] the identification of the cyclization by-products by MS and the elimination of these.\[130\] To do so, they functionalized the noncyclic impurities with propargyl bromide and utilized the azide-modified resin for the “click-scavenging” of the noncyclic impurities. After reaction of the crude mixture of cyclic polymer and cyclization by-products with the resin in the presence of Cu(I), the said impurities are covalently linked to the resin and can be removed by a simple filtration, yielding the pure cyclic product. This method is brilliant in the fact that, as mentioned earlier, following the work of Laurent and Grayson, the CuAAC has been the main route for the preparation of cyclic polymers by RC.\[52–67\] Therefore, the use of this modified resin can easily be applied to any cyclic polymer prepared via the CuAAC route, as the potential linear impurities present in the sample already bear an alkyne moiety.

Recently, Hövelmann et al. proposed a similar technique using a basic ion-exchange resin for the purification of cyclic poly(ethylene glycol) (PEG).\[131\] The terminal hydroxyl groups of the residual linear PEG chains are oxidized into carboxylate groups by reaction with NaClO and TEMPO. The newly generated

**FIGURE 1** “Click-scavenging” of noncyclic impurities using an azide-functionalized resin
α,ω-dicarboxylate PEG chains are then removed by elution of the sample through an ion-exchange resin bearing ammonium groups. The linear chains are strongly adsorbed on the stationary phase due to the electrostatic interactions between the carboxylate and the ammonium groups and the cyclic product is recovered.

2.4.2 Quantification of linear impurities

In cases where all the cyclization by-products, and mainly the linear chains, cannot be eliminated, it is important to be able to evaluate the contribution of these impurities to the sample. In fact, when studying the properties of cyclic polymers, one should know if the experimental results are attributed (or not) to the presence of unycyclized chains in the sample.[132]

Quantification methods using traditional polymer characterization techniques, such as 1H NMR and FTIR present a low sensitivity and are based on signals that are specific to the chain ends of the linear contaminants. These signals are usually overwhelmed by those of the polymer backbone, leading to a very inaccurate estimation. Due to their spectroscopic nature, they also only provide an averaged overview of the sample and, for instance, an oligomer generated by intermolecular reaction cannot be differentiated from a mixture of cyclic polymer and its corresponding linear precursor. The case of chromatographic techniques such as SEC and LCCC was discussed in the previous paragraphs, and an accurate quantification method can hardly be developed using these, mostly because of their low resolving power. Over the last decades, MS has become a “must-have” technique for the characterization of polymers thanks to the development of soft ionization sources, such as matrix-assisted laser desorption/ionization (MALDI) and electrospray ionization, as represented by the growing number of papers devoted to polymer synthesis combined with MS each year.

In 2015, Josse et al. reported a method to quantify as little as 2% of linear contaminants in a c-PLA sample prepared via the CuAAC route using tandem MS (MS–MS).[66] MS–MS is an MS technique in which the ions are separated by a first mass analyzer, with selection of ions of a specific mass-to-charge ratio (m/z). The selected ions are then activated, for instance, by collision-induced dissociation, leading to the fragmentation of the so-called “precursor ions.” The fragment ions are finally discriminated by a second mass analyzer before being detected. Josse et al. adapted the survival yield (SY) method developed by Memboeuf et al. for isobaric species.[133] The SY method takes benefit of a significant difference between the energy thresholds at which the isomeric ions (e.g., in this case, the cyclic and linear polymer ions) dissociate. The SY is defined as the ratio of the intensity of the precursor ions and the total intensity of all the ions (SY (%) = (I_{precursor}/I_{total}) × 100). If the SY is determined at different collision voltages, a SY curve can be plotted (Figure 2). If the SY curve is recorded for mixtures containing different linear-to-cyclic polymer ratios (from pure l-PLA to “pure” c-PLA), a calibration curve can be determined by plotting 1-SY versus the fraction of linear polymer voluntarily added to the mixture. The x-intercept of that curve gives the fraction of residual linear polymer in the initial c-PLA sample for the corresponding degree of polymerization (DP). The interest of this method, besides from being extremely sensitive when compared to the more traditional techniques, is that, thanks to MS, each DP can be discriminated and individually investigated. Doing so, Josse et al. have been able to confirm, once more, the Jacobson–Stockmayer theory predicting a decreasing probability of cyclization for the longer chain,[32] as they determined an increasing fraction of linear impurities for higher DPs.

Inspired by this method, Liénard et al. recently attempted to combine the standard addition method with ion mobility–MS in a similar way.[134] During an IM–MS analysis, the polymer ions are generated just like in a regular MS analysis, before being separated in a mobility cell based on their 3D structure. Since the cyclic ions are more compact than their linear analogues, the two isomers can be readily separated.[135,136] However, they encountered issues because the cyclic and the linear isomers feature different ionization efficiencies. The percentage of linear contaminants in the cyclic sample could nonetheless be roughly estimated.

**FIGURE 2** Survival yield (SY) curves of linear poly(lactide) (PLA) ions and cyclic PLA ions obtained by cyclization via copper-catalyzed azide–alkyne cycloaddition (CuAAC).[66]
2.4.3 Scaling-up processes

The last major challenge concerns the development of processes that permit the production of cyclic polymers in high yields. As will be discussed in details in the next section, cyclic polymers, and especially those prepared by RC, feature unique properties that may lead to potential industrial applications. However, because the RC requires high-dilution conditions to foster the intramolecular reaction, and because most of the strategies that have been developed to this date are batch-wise processes, only small quantities of cyclic polymer are produced.

In this context, Zhang and coworkers, well-known for their work on photo-induced cyclizations, suggested the use of a continuous-flow reaction technique to substantially increase the yields of the cyclization. They prepared a l-PS precursor by RAFT polymerization of styrene from a RAFT agent bearing the same o-methylbenzaldehyde group that has been used by Josse et al. In this case, the o-methylbenzaldehyde acts as a photoactivated diene that is prone to react with the carbon-sulfur double bond of the dithioester group of the RAFT agent. The linear precursor is then dissolved in a large quantity of a mixture of acetonitrile and dichloromethane, and the linear precursor solution pushed through a coiled glass tube with a UV lamp in its center. The solution of cyclized product is then conveniently recovered at the other extremity of the glass tube.

As a result of the large surface-to-volume ratio of the flow reactor as compared to batch reactors, the UV irradiation is more uniform, leading to a significant increase of the efficiency of the reaction. Thanks to this method, large quantities of solution can potentially be processed in a relatively short time. In fact, Zhang and coworkers determined experimental conditions such that they have been able to produce 1 g of c-PS in only 3 hr. An arguable drawback is that large amounts of solvents are consumed during the process (17 L of solvent for 1 g of c-PS). Nonetheless, as the photo-induced cyclization involves no other reactant than the linear precursor, the solvent can be easily recycled by distillation. Baeten et al. further improved this aspect of the cyclization by the use of a looped-flow system, therefore reducing the required solution volumes by a factor of 43. To this day, the combination of light-induced cyclizations and continuous-flow reactions can probably be considered as the most promising and greenest alternative when it comes to the preparation of functional cyclic polymers on an industrial scale.

Recently, Shen and Wang introduced a cyclization procedure using microreactors. A solution of linear α,ω-dialkyne PEO precursor is injected into a micromixer, where it is mixed with a solution of copper (I) complex that catalyzes the Glaser coupling. The flow rate is set such that the concentration of linear precursor in the microreactor is kept very low to avoid any intermolecular reaction. Interestingly, the final revision of their setup forms a closed loop and the resulting mixture of c-PEO and catalytic complex is recycled, thus drastically reducing the amount of solvent consumed in the process.

Finally, Bonnet and coworkers have provided a very unique example of reactive extrusion polymerization of t-LA in bulk using borohydrides-lanthanide complexes as catalysts, which, in the absence of alcohol, results in the formation of cyclic poly(t-lactide) (c-PLLA) as the main product. The PLLA macrocycles are generated by intramolecular “back-biting” transesterification reactions during the polymerization. These catalysts permit a surprisingly good control over the molecular parameters, as the as-obtained ring polymers exhibit pretty high molecular weights (3 × 10^4 g mol\(^{-1}\), as determined by SEC) and low molar mass dispersities (\(D_M < 1.30\)). High yields can furthermore be reached, as they could process 2 g of t-LA in 20 min.

A potential concern when using closed loop reactors and bulk polymerizations to scale-up the production of cyclic polymers generated by RC is the formation of catenanes. In fact, catenanes are generated by the threading of a ring chain by a linear one, and further closure of the latter. Hence, this process becomes more probable when in the presence of a high concentration of cyclic chains, such as when using the above described systems. In addition, catenanes are hardly differentiable from larger macrocycles and their elimination from the sample can be tedious. However, none of the authors mentioned in the previous paragraphs did comment or highlight the presence of such structures in the resulting cyclic polymer samples.

3 CYCLIC POLYMERS FOR THE DESIGN OF NEW MATERIALS

3.1 Properties of cyclic polymers

The synthetic efforts discussed in the previous section were motivated by the unique properties exhibited by ring polymers and resulting from their topology. In the first papers dealing with the synthesis of these polymers, a comparison with their linear homologues in (semi-)dilute solution was already established. The first characteristic of cyclic polymers that quickly arose is their lower hydrodynamic radius when compared to linear polymers of the same nature and molecular weight. Alberty et al. showed that for PS, which is...
the polymer that was the most investigated, the ratio of the hydrodynamic radius of the cyclic polymer and that of its linear analogue varies from 0.92 for polymer chains of roughly \(10^3 \text{ g.mol}^{-1}\) to 0.7 for polymer chains of \(3 \times 10^4 \text{ g.mol}^{-1}\).\(^{[119]}\) This property of ring polymers greatly facilitates the identification of cyclic structures since, as mentioned previously, it is possible to take advantage of it for the separation of the two species by SEC.\(^{[120]}\)

Differences in the dynamic properties of cyclic polymers are also observed. In fact, chain ends play a crucial role in the reptation mechanism of linear polymer chains, which is their fundamental mode of motion.\(^{[146]}\) In the absence of chain end, it is suggested that ring polymers diffuse in a speculative amoeba-like motion, but this is still subject to controversies.\(^{[147–149]}\) Using single-molecule fluorescence imaging of c-PThF labeled with a fluorescent dye, namely perylene diimide, Yamamoto and coworkers showed that ring polymers in a linear polymer matrix exhibit a multimode diffusion.\(^{[150,151]}\) These modes were ascribed to the presence of both threaded and unthreaded cyclic chains within the linear chains matrix. Additionally, they also observed that unthreaded cyclic chains diffuse faster than linear ones.

Concerning the rheological properties of ring polymers, the earliest data reported on their melt viscosity, all recorded on c-PS samples, were contradictory. While some studies indicated that cyclic and linear polymer chains show similar viscosities and dependencies to the molecular weight,\(^{[152]}\) others demonstrated a lower melt viscosity and a significantly reduced dependency to the molecular weight for the cyclic chains.\(^{[153,154]}\) This was later attributed to the poor or good purity of the samples, respectively, as it was found that the presence of even small amounts of linear chains in the melt drastically impacts the rheological properties of cyclic chains due to threading.\(^{[132,150,155]}\) Recent works on high purity c-PS samples have reported values of intrinsic viscosities ratio \((g' = [\eta]_{\text{cyclic}}/[\eta]_{\text{linear}})\) of 0.57 \(\leq g' \leq 0.63.\)\(^{[132]}\) The lower viscosity of ring polymer melts is attributed to the reduced entanglement of the polymer chains resulting from the absence of chain ends.

Because of the constraints induced by the cyclic topology, the free volume in ring polymers is lower than in their linear analogues, thus impacting the thermal properties such as the glass transition temperature \((T_g)\). The \(T_g\) of a polymer is affected by multiple factors like the monomer units, the nature of the chain ends, the architecture of the chains or the molecular weight.\(^{[156–159]}\) Even though it is now globally accepted that cyclic chains exhibit higher \(T_g\) values than their linear counterpart of the same molecular weight, early studies on PS, poly(dimethylsiloxane) (PDMS), poly(phenylmethylsiloxane), and poly(2-vinyl pyridine) (PVP) showed some inconsistencies.\(^{[160–163]}\) These were recently ascribed to the poor quality of the samples by Gao et al., similarly to what was observed for viscosity measurements, and can be fully explained using the Fox equation \((1/T_g = w_{\text{linear}}/T_g \text{ linear} + w_{\text{cyclic}}/T_g \text{ cyclic})\), where \(w_{\text{linear}}\) and \(w_{\text{cyclic}}\) are the weight fractions of linear and cyclic polymers in the sample, respectively). Gao et al. further demonstrated that, while the \(T_g\) of cyclic polymers shows a much weaker dependence to the molecular weight than linear ones, the \(T_g\), \(\infty\) values \((T_g \text{ extrapolated to infinite molecular weight})\) are nearly the same.\(^{[117]}\) The variation of the temperature of melting \((T_m)\) and the temperature of crystallization \((T_c)\), however, seems to be a lot more dependent on the nature of the polymer, as increases\(^{[105,164,165]}\) and decreases\(^{[105,166–168]}\) have both been reported.

The equilibrium temperature of melting \((T_m^0)\) refers to the transition temperature between the isotropic melt and the 100% crystalline phase for a crystal of infinite size and is defined as the ratio of its enthalpy of fusion \((\Delta H_m)\) and its entropy of fusion \((\Delta S_m)\) \((T_m^0 = \Delta H_m/\Delta S_m)\). While it is agreed that cyclic and linear polymers have similar \(\Delta H_m\) values, the entropy of fusion is still a controversial point and two points of view have been suggested in the literature.\(^{[169]}\)

1. According to Tezuka and coworkers, the arrangement of the chains in the crystalline phase is more restrained for ring polymers and a larger difference of entropy between the crystalline phase and the melt is therefore expected, resulting in a lower \(T_m^0\) in comparison with their linear analogues.\(^{[170,171]}\)
2. According to Müller and coworkers, cyclic chains have a lower conformational entropy in the molten state because of the constraints induced by their topology. If we assume that cyclic and linear polymers have similar entropies in the crystalline state, a higher \(T_m^0\) is then expected.

Since both types of deviation have been reported depending on the polymer system that is investigated, this is still a highly debated topic.\(^{[172,173]}\) Computational chemistry was employed to help elucidating this contentious issue, and recent studies seem to validate Tezuka and coworkers’ hypothesis, as these work showed that pure cyclic polymer free of any impurities should exhibit a lower \(T_m^0\).\(^{[174,175]}\)

The crystallization from the melt is also affected by the ring topology. First, nucleation kinetics have been investigated for polymers of different natures, namely PThF,\(^{[170,176]}\) poly(ethylene) (PE),\(^{[166]}\) PCL,\(^{[165,173]}\) PLA,\(^{[177]}\) and PCL-b-PLA.\(^{[178]}\) They all concluded on an increased nucleation rate and a higher density of nuclei for the cyclic polymers with respect to their linear
counterpart, which can be easily observed using polarized light optical microscopy (Figure 3). This is attributed to the lower viscosity and the faster diffusion of the cyclic chains. In addition, Tezuka et al. reported differences in the morphology of the spherulites of linear and cyclic PTHF, which they suggested being due to the speculative double-layer adsorption mode on the growth face of the crystal for c-PTHF whereas l-PTHF can crystallize in a monolayer adsorption mode.\[170] As for the growth rate of the spherulites, opposite trends have once more been observed depending on the nature of the polymer. When compared to the linear analogues, c-PTHF\[170,176] and c-PE\[166] exhibit a slower spherulitic growth, while c-PEO\[179] and c-PCL\[164,172,173,180] reportedly present an increased growth rate. Another unique example is that of cyclic poly(3-hexylthiophene) (P3HT) that exhibits both slower nucleation and overall crystallization rates.\[168] This observation was attributed to the very rigid character of P3HT, which is even more pronounced for the cyclic isomer. At this point, and from the many contradictory data reported in the literature, we should conclude that it is still very difficult to fully explain the influence of the cyclic topology on the crystallization and the thermal transitions of polymers and further investigation is therefore required. In this regard, molecular dynamics simulations are being employed and have already provided helpful additional information.\[181–183]

Other properties have been assigned to the cyclic topology in bulk, and notably in polymer thin films. Albert and coworkers recently showed that c-PCL thin films are less prone to melt-induced dewetting with respect to films of the same thickness but made from linear analogues.\[184] This is a very interesting and unexpected finding, considering the characteristics of ring polymers (e.g., increased mobility and lower viscosity), and the mechanism responsible for this enhanced stability has not been elucidated yet. Polymer thin films are also usually subject to a confinement effect (i.e., a modification of the physical properties of a material below a certain film thickness due to the conformational restriction of the polymer chains at the free surface). For instance, Zhang et al. measured a decrease of the $T_g$ of as much as 10°C for l-PS ($M_n = 9.1 \times 10^3 \text{ g.mol}^{-1}$) thin films of 21 nm, while this effect was almost completely suppressed for the cyclic counterpart.\[185] This was attributed to a better and less perturbed packing efficiency of the cyclic chains at the surface of the film.

Block copolymer thin films are seen as a very promising alternative to the current well-established lithography processes in the semiconductor industry. Due to their ability to self-assemble into nanoscopic structures by phase segregation, they could allow patterning at a sub-30 nm scale, which is an inherent limitation of the currently employed photolithography process.\[186] As early as 1993, Marko predicted that the use of ring diblock copolymers could lead to a reduction of the domain spacing between the two phases down to 0.63 times that of the corresponding linear analogue for symmetric diblock copolymers in a lamellar morphology.\[187] The decrease of the domain spacing was quickly confirmed by Lescanec et al., in 1995, who compared cyclic block copolymers based on PS-PVP and PS-PDMS with varying

**Figure 3** Polarized light optical microscopy (PLOM) micrographs of spherulites of linear (left) and cyclic (right) poly(tetrahydrofuran) (PTHF) at $T_c = 11$°C after the indicated times. (Reproduced from ref. \[176\], with permission from Elsevier)
segments lengths to their linear triblock counterparts and measured an experimental ratio of domain spacing ($D_{\text{cyclic}}/D_{\text{linear}}$) of 0.91–0.95. Since then, many other groups reported a similar behavior for other polymer systems.\cite{188,189,190} Zhu et al. reported on the comparison of cyclic and linear triblock copolymers of PS and poly(butadiene) (PBD). By gradually increasing the percentage of PS in the copolymer, they could not only study the lamellar morphology, but also random PS spheres and cylinders in a PBD matrix and the gyroid morphology. For all of these, they determined $D_{\text{cyclic}}/D_{\text{linear}}$ values comprised between 0.84 and 0.89.\cite{188} Lecommandoux et al. investigated a cyclic copolymer of PS and PI, cyclo-(PS$_{290}$-b-PI$_{110}$), and observed a reduction of the domain spacing by a factor $\sqrt{2}$ using small-angle X-ray scattering as well as different morphologies for the linear and the cyclic polymers (cylindrical vs. sphere-like, respectively).\cite{190} Hawker and coworkers reported a decrease of 33% for c-(PS$_{257}$-b-PEO$_{113}$), resulting in a domain spacing of 19.5 nm, that is, in the sub-20 nm regime. Interestingly, this regime cannot be reached using linear polymers with shorter chain length, as the thermodynamic driving force for phase segregation is insufficient to achieve well-defined domains.\cite{191} A last example was recently provided by Gartner et al. who measured a 20% reduction of the domain spacing for c-[poly(styrene)-b-poly(ethylene glycol)methacrylate)] in comparison with its linear analogue.\cite{192}

In solution, ring polymers also exhibit interesting properties. Different groups synthesized cyclic polymers bearing fluorescent functional groups, either as pendant groups\cite{61,193} or included in the polymer backbone,\cite{194} and they all observed a significant increase of the fluorescence with respect to the linear analogues, whatever the polymer system that is employed. Even though the reason for this enhanced fluorescence is not completely understood yet, Mu et al. speculatively attributed this effect to an aggregation-induced emission phenomenon. In other words, because of the constraints related to the cyclic topology, the excited molecules cannot release the energy through bond rotation as compared to linear molecules. This energy is therefore released as light.\cite{193}

Finally, Hoskins and Grayson demonstrated that the acid-catalyzed hydrolytic degradation of c-PCL presents a significant delay in comparison with that of its linear counterpart. The hydrolysis reaction was followed by measure of the $M_n$ using MALDI-MS. This can be accounted to the absence of chain ends and the fact that, while the first bond cleavage of a linear chain results in a dramatic modification of its molecular weight, that of a cyclic chain does not induce any. A modification of the topology, from cyclic to linear, could nonetheless be observed by SEC during the hydrolysis, thanks to an initial increase of the apparent molecular weight due to the larger hydrodynamic radius of the linear chains. Once the cyclic polymer is opened, its kinetic of hydrolysis follows the same trend as that of the linear polymer. However, the cyclic topology did not seem to have any influence on the thermal degradation of the polymer in bulk, as determined by thermogravimetric analysis (TGA).\cite{60} Grayson et al. further observed a similar phenomenon for c-(PEG-b-PCL).\cite{65}

### 3.2 Biomedical applications

Even though some early reports on the bioactivity of cyclic oligomers can be found in the literature,\cite{195,196} cyclo-based polymers were only really considered for biomedical applications following the work of Szoka and coworkers, in 2009.\cite{197,198} Their study reported on the effects of the architecture on the pharmacokinetics (i.e., the fate of a substance in a living organism, including its absorption, metabolism, biodistribution, and elimination from the body) of polymers in mice. They synthesized amphiphilic cyclic graft copolymers made of a hydrophobic cyclic core of PCL and hydrophilic arms of PEG ([c-PCL]-g-PEG) with different sizes, about 30, 50, and 90 kDa. What they observed is that, above the renal filtration threshold (30–40 kDa), the cyclic polymer presents a longer plasma circulation time than its linear analogue with the same molecular weight. This was attributed to the different mode of motion of cyclic polymers, which, unlike their linear counterparts, cannot reptate through the nanopores of the kidneys (Figure 4). In addition, the cyclo-based polymers showed a highly different biodistribution profile in comparison with linear ones, with a drastically increased accumulation in organs such as the heart, the lungs, the liver, or the spleen.\cite{197} In a second paper published quickly after their initial report, they studied graft copolymers of poly(acrylic acid) (PAA) and PEG ([c-PAA]-g-PEG). In addition to the same effects as for (c-PCL)-g-PEG, they also reported a higher tumor uptake for cyclic polymers.\cite{198}

The development of drug delivery systems allowing the controlled release of a compound in time and space as well as a high loading capacity is one of the biggest challenges in the field of medicine nowadays. In this regard, amphiphilic biocompatible block copolymers are materials of interest due to their ability to self-assemble into polymeric micelles in solution. These micelles represent a viable alternative for the encapsulation and the administration of poorly soluble drugs, and linear block copolymers have been widely investigated in this context.\cite{199,200,201} In early works comparing micelles of cyclic and linear block copolymers, Hadjichristidis and coworkers showed that micelles of c-(PS-b-PBD) are
characterized by a smaller size and aggregation number (i.e., the number of polymer chains constituting the micelles) than micelles of PS-b-PBD-b-PS. A similar observation on the size of micelles of c-(PS-b-PI) and PS-b-PI was reported almost simultaneously by Lazzaroni and coworkers. Although these polymers are not of relevant interest for biomedical applications, these studies have paved the way for further investigations on the use of cyclic polymers for such purpose.

Yamamoto and coworkers reported on block copolymers of PEO and poly(butylacrylate) (PBA), namely c-(PBA10-b-PEO70) and PBA5-b-PEO70-b-PBA5. Even though their study did not highlight any influence of the topology on the size of the micelles and the critical micelle concentration, they observed a drastic elevation (over 40°C) of the cloud point (i.e., the temperature at which the polymer micelles aggregate, ultimately leading to a phase transition). The authors further demonstrated, in another report, a remarkably higher resistance to the salting-out effect (i.e., effect where, when the salt concentration increases, the water molecules interact with the salt ions, thus decreasing the number of available water molecules to interact with the micelles, leading to the precipitation of the micelles at high salt concentration) for the cyclic polymer micelles by a twofold increase ([NaCl] = 130 and 260 mg/ml for PBA5-b-PEO70-b-PBA5 and c-[PBA10-b-PEO70] micelles, respectively). By mixing linear and cyclic block copolymers with various ratios, they were able to tune both the cloud point temperature and the salting-out concentration of the micelles. The enhanced salt and thermal stabilities of cyclic polymer micelles were ascribed to the fact that, in linear polymer micelles, one end of a chain constituting the micelle can get loose from the core and bridge two micelles. This crosslinking movement is not possible for the cyclic polymer micelles.

Grayson et al. prepared cyclic and linear PCL-b-PEG amphiphilic block copolymers. In addition to the retarded hydrolytic degradation of the cyclic polymer that was discussed previously, they confirmed once more the smaller size of the micelles self-assembled from the cyclic block copolymer.

Liu et al. synthesized a cyclo-based copolymer constituted of a cyclic poly(NIPAm) (c-PNIPAM) linked to a l-PCL segment ([c-PNIPAM45]-b-PCL60). l-PNIPAM is known to be a thermoresponsive polymer with a lower critical solution temperature (LCST) (i.e., temperature at which the PNIPAM turns from hydrophilic to hydrophobic) of 32°C in aqueous solution. c-PNIPAM, on the other hand, reportedly possesses a lower LCST than its linear analogue. When the temperature is raised above the LCST, a drastic conformational change is observed and the PNIPAM coil collapses on its own. This feature makes PNIPAM a very interesting polymer in the context of triggered/stimuli-responsive drug delivery systems. In aqueous medium, micelles of the tadpole-shaped (c-PNIPAM45)-b-PCL60 exhibit a higher drug loading capacity than micelles of the linear PNIPAM45-b-PCL63 copolymer, as attested by the encapsulation of doxorubicin (Dox), an anti-cancer drug. In addition, the release of Dox in vitro appeared to be substantially faster and more efficient using the cyclo-based copolymer. This was attributed to the absence of entanglements in the c-PNIPAM corona, facilitating the diffusion of the drug out of the micelle. Finally, the in vitro cytotoxicity of (c-PNIPAM45)-b-PCL60 micelles on HeLa cells is insignificant.

Recently, O’Reilly et al. designed original nanoparticles self-assembled from (c-poly[5-methyl-5-ethoxycarbonyl-1,3-dioxan-2-one])-g-poly(N-acryloylmorpholine) for triggered drug delivery. The cyclic core can encapsulate small hydrophobic molecules such as a drug or imaging agent and includes a sensitive disulfur bond. When the nanoparticles of the cyclic graft copolymer are subjected to a stimulus, like a pH increase in tumor cells, the disulfur bond is cleaved, therefore inducing a topology switch from cyclic-linear to linear-linear. This topology modification leads to the disassembly of the nanoparticles and, thus, the release of the encapsulated molecule (Figure 5).

Gene therapy is another topic of interest in modern medicine, as it is believed that the delivery of “healthy” nucleic
acids into the nuclei of target cells may help to cure or prevent some genetic disorders.\cite{212–215} Polycationic polymers have been widely investigated for that purpose, as they are able to complex DNA by electrostatic interactions to form the so-called “polypexes.”\cite{216} In this regard, Pun and coworkers studied poly(2-dimethylaminoethylmethacrylate) (PDMAEMA)-based polymers,\cite{217,218}\[217,218]\ and Grayson and coworkers reported on cyclic poly(ethylene imine) (PEI).\cite{67} In both cases, a significant reduction of the toxicity was observed with respect to the linear analogues. While no improvement of the in vitro transfection efficiency was observed for c-PDMAEMA\cite{217}, the graft copolymer constituted of a cyclic poly(2-hydroxyethyl methacrylate) core with polycationic PDMAEMA arms ([c-PHEMA]-g-PDMAEMA) performed significantly better than its linear PHEMA-g-PDMAEMA counterpart.\cite{218} In contrast, c-PEI exhibited a greatly improved transfection efficiency and even outperformed the 25 kDa branched PEI gold standard. Grayson et al. ascribed this to the increased charge density resulting from the more compact structure of cyclic polymers.\cite{67}

As a last example, Benetti and coworkers recently published a series of reports on the surface modification of inorganic substrates with cyclic poly(2-ethyl-2-oxazoline).\cite{137,219,220} The authors concluded on an increased grafting density of the ring polymers at the surface, resulting in enhanced steric barrier, antifouling, and lubricating properties in comparison with the linear analogues, which they believe to be of great interest for biomedical applications such as the stabilization of inorganic nanoparticles used as contrast agents. These properties were attributed to the smaller size of cyclic polymers and the absence of interdigitation between the cyclic chains.

4 | SUMMARY AND OUTLOOK

To conclude, in the recent years, cyclization techniques have kept evolving to provide more pure products with substantially more important yields. These improvements did not only concern the cyclization reaction itself, but also how they were performed with the development of more efficient experimental setups, apparatus, and work-up procedures. Furthermore, the cyclic topology possesses many unique properties, mainly related to the absence of chain ends. The use of ring polymers for biomedical applications such as controlled delivery vehicles for contrast agents, drugs, or genes seems very promising, even though all the mechanisms responsible for these enhanced performances are not fully understood yet. Regarding the use of cyclic polymers for other kinds of applications in materials science, the recent literature provides very few examples of gels,\cite{221} self-healing, and shape-memory systems\cite{222} based on cyclic chains yet. While not long ago, cyclic polymers could hardly be considered for industrial purposes because of the difficulties encountered in their preparation, the field is now mature enough so that the integration of these one of a kind polymers for the design of new promising materials is finally conceivable, and there is no doubt that cyclic polymers are promised to a bright future.

ACKNOWLEDGMENTS

R. L. thanks F.R.I.A. for a PhD thesis grant. O. R. C. is a research associate for the F.R.S.-FNRS of Belgium.

ORCID

Romain Liénard \(\text{https://orcid.org/0000-0002-2696-3046}\)
Julien De Winter \(\text{https://orcid.org/0000-0003-3429-5911}\)
Olivier Coulembier \(\text{https://orcid.org/0000-0001-5753-7851}\)

REFERENCES


FIGURE 5 Triggered drug release by stimulus-induced topology switch

**AUTHOR BIOGRAPHIES**

**Romain Liénard** received his MSc degree in Chemistry from the University of Mons, Belgium, in 2016. He is currently a graduate research student in the Laboratory of Polymeric and Composite Materials (LPCM) and the Laboratory of Organic Synthesis and Mass Spectrometry (SMOs) at the University of Mons, under the supervision of Dr Olivier Coulembier and Dr Julien De Winter. His work focuses on the synthesis and characterization of cyclic polymers obtained by means of ring-closure.

**Julien De Winter** obtained his PhD degree from the University of Mons in 2011 under the supervision of Prof Pascal Gerbaux and Prof Philippe Dubois. His main research areas are the synthesis of original polymers and their in-depth studies by mass spectrometry. He is currently a junior lecturer at the University of Mons in the laboratory of Prof Pascal Gerbaux and is responsible for the use and development of mass spectrometry methods for macromolecular characterization.

**Olivier Coulembier** graduated from the University of Mons-Hainaut in 2005 and moved to Stanford University and the IBM Almaden Research Center to undertake periods of postdoctoral research under the supervision of Prof Robert M. Waymouth and Dr James L. Hedrick. Olivier is currently a research associate of the Belgian F.N.R.S. in the Laboratory of Polymeric and Composite Materials (LPCM) at the University of Mons. His research focuses on the (non)-organometallic ring-opening polymerization of cyclic monomers.

**How to cite this article:** Liénard R, De Winter J, Coulembier O. Cyclic polymers: Advances in their synthesis, properties, and biomedical applications. *J Polym Sci.* 2020;58:1481–1502. https://doi.org/10.1002/pol.20200236