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The Synthesis, Properties and Applications of Bio-based Cyclic Aliphatic Polyesters

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ABSTRACT: Cyclic polymers have long been reported in literature, but their development has often been stunted by synthetic difficulties such as the presence of linear contaminants. Research into the synthesis of these polymers has made great progress in the past decade, and this review covers the synthesis, properties and applications of cyclic polymers, with an emphasis on bio-based aliphatic polyesters. Synthetic routes to cyclic polymers synthesized from bio-derived monomers, alongside mechanistic descriptions for both ring closure and ring expansion polymerization approaches are reviewed. The review also highlights some of the unique physical properties of cyclic polymers together with potential applications. The findings illustrate the substantial recent developments made in the syntheses of cyclic polymers, as well as the progress which can be made in the commercialization of bio-based polymers through the versatility this topology provides.

Introduction

Aliphatic polyesters are one of the most promising bio-based commodities and consequently huge progress has been made in recent decades in their synthesis using well-defined metal and organic catalysts.[1-3] Polymers with properties tailored to a range of commercial applications from packaging to biomedical materials are now accessible.[4,5] This is well evidenced by the increasing use of polymers such as poly(lactic acid) (PLA) which now sees large-scale production of around 190,000 tonnes per year as of 2019.[6] In spite of this progress, bio-based polymers still only constitute a small fraction of global polymer production (~1%), which remains dominated by commodity polymers derived from fossil feedstocks.[7] To achieve greater market penetration, bio-based polymers with a wider range of properties are required to give access to a wider range of applications.

Recently, significant developments in the synthesis of cyclic polymers have highlighted marked differences in physical properties such as thermal degradation, crystallization, glass transition temperature (T_g) and intrinsic viscosity.[8-14] Realization that their topology can result in unique properties has led to a renewed interest in exploiting cyclic polymers as a means to further enhance the benefits of bio-based polymers such as aliphatic polyesters. The field of cyclic polymers has seen much development in the past decade, and questions of how they work and where they can best be applied are now being investigated. The next decade of cyclic polymer research is open to a number of possibilities.

Recent developments in cyclic polymers

While the knowledge around their synthesis and properties has greatly improved, investigations into the nature of cyclic polymers as well as possible applications have frequently been marred by purity issues.[15] In addition, producing high molecular weight cyclic polymers reliably has not been a possibility until the last decade or two, and the field of cyclic polymers has been underrepresented as a result.[16,17]

While purity remains an issue, progress has been made in the synthetic routes to cyclic polymers and a renewed interest in the field has been highlighted in recent reviews.[8,9,18,19] In addition, the development of purification methods such as Liquid Chromatography at the Critical Condition (LCCC) have allowed some researchers to produce highly pure cyclic polymers (less than 0.1% linear contaminants)[20] with substantial molecular weights. A variety of newer synthetic methods (such as zwitterionic polymerization, atom transfer radical polymerization (ATRP), Reversible Addition Fragmentation Chain Transfer (RAFT) etc)[10,21,22] have been employed to great effect while the use of LCCC has allowed for separation of polymer products based solely on their end-group topologies (i.e. not molecular weight dependent). This has been well illustrated in various reports detailing "ultra-pure" cyclic polymers.[15,18,23] The cyclic purity of polymers can be confirmed through differences in viscosity, T_g and MALDI-TOF spectra (among others) when compared to linear counterparts, although identification of small quantities of linear impurities can be challenging with these methods. Recently, it was reported by Shi et al. that cyclic purity could be

accurately analyzed by Size Exclusion Chromatography (SEC) combined with the Log Normal Distribution method as the two topologies have different hydrodynamic volumes.[24] This may allow for accurate, accessible analysis of cyclic polymers and is a good example of the progress being made in this area.

What has progressed to a lesser extent is our understanding of how these polymers behave in terms of their rheology and physical conformations. Linear and branched polymers have defined conformations and are able to relax stress applied to them via chain reptation or branch retraction respectively, but cyclic polymers have yet to be conclusively defined in such ways. It is established that they do not reptate but there are multiple studies suggesting opposing behaviour types. There has been a lot of attention on this topic in the form of both theoretical and experimental studies, but aforementioned purity issues have so far hampered definitive conclusions as contaminants (i.e. linear polymers) have substantial effects on rheology, even at low concentrations. [20,25–29]

Scope of Review

In this context of synthetic development coupled with the desire to provide sustainable materials with enhanced properties, it is timely to highlight the distinct properties afforded by cyclic polymers and how this can be applied to bio-based materials. Reviews to date have focused on improvements in synthetic methodologies (such as the use of ATRP and developments in Ring Expansion strategies) as well as on potential biological applications.[9,10,18,19,22,30,31]

In this review we present an up-to-date account of the synthesis, physical properties and applications of cyclic aliphatic polyesters with a specific emphasis on the use of bio-based monomers. The intention is to highlight the examples where these promising monomers have been used in the formation of cyclic polymers. These have been summarised in two tables which detail the methods and catalysts used along with basic characterization. The review will aim to highlight the extent to which the cyclic topology can affect physical properties, as well as possible applications for these polymers, which include catalysis, adhesive and thermoset applications, self-healing and shape-memory materials and rheology modification. Biological applications, which have been reviewed elsewhere will be addressed only to a small extent.

The term "bio-based" requires specific definition in this context. The review is referring to polymers made using monomers which are derived from renewable natural sources as opposed to from fossil-based petrochemical sources.

ε-caprolactone, although typically fossil-based is included as an important monomer for future developments using related bio-based feedstocks such as ε-decalactone. Beyond aliphatic polyesters, isosorbide and isomannide-based poly(acetals) are included as recent work using these monomers highlights a replated area where bio-based monomers can be used to exploit this new topology.

General Synthetic Approaches: Ring Closure and Ring Expansion

Conventional polyester syntheses (such as the polycondensation of dicarboxylic acid dichlorides and diols by Kricheldorf et al.[32]) can give solely cyclic products in some cases, and cyclization has been shown to be an inherent part of any step growth polymerization under ideal conditions. However, cyclic polymers are typically synthesized via ring closure or by ring expansion polymerization. In a ring closure approach (RC), a linear polymer with functionalized end groups is synthesized and a separate cyclization step generates the cyclic polymer (Figure 1). RCs are based on a homo- or hetero- difunctional linear polymer, depending on the method. The most common RC method uses a copper-catalyzed azide-alkyne reaction to cyclize the linear polymer.[15,33] It is worth noting that RC is not literally a polymerization process (polymerization is one step in the ring closure synthesis strategy).
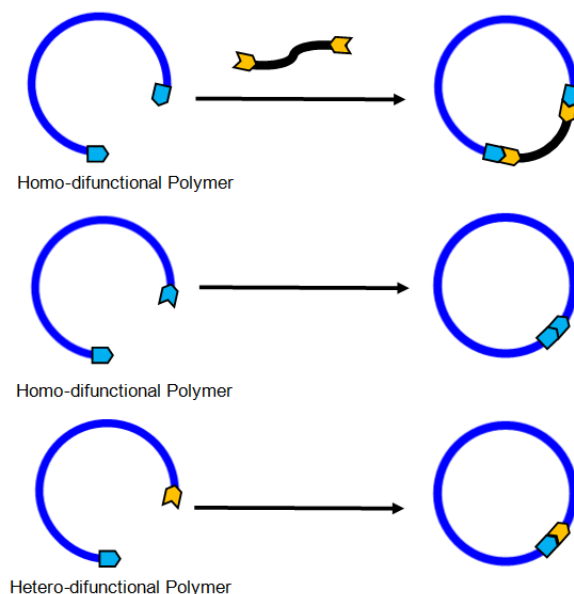

Figure 1: Scheme showing the different routes to cyclization in ring closure polymerizations

Cyclic polymers synthesized using RC tend to have low polydispersity indexes (Đ) because the product of the polymerization stage is linear. Linear polymers can be synthesized using techniques such as ATRP,[10] where the linear polymer formed has a very low Đ due to kinetic favourability of the deactivation reaction, meaning that (in theory although not entirely in practice) termination between two reactive polymer ends does not occur. The resulting polymer has a halogen end group allowing for modification suitable for ring closure.[34] Similar control of the initial polymer can also be achieved via RAFT polymerization.[22]

RCs can have issues with purity in the cyclization step as an intramolecular reaction is not the only possibility. Reactions at only one end of the polymer or between two different linear polymers can lead to linear contaminants, regardless of reaction stoichiometry. To minimise the formation of linear products, the cyclization step is often conducted in highly dilute conditions.
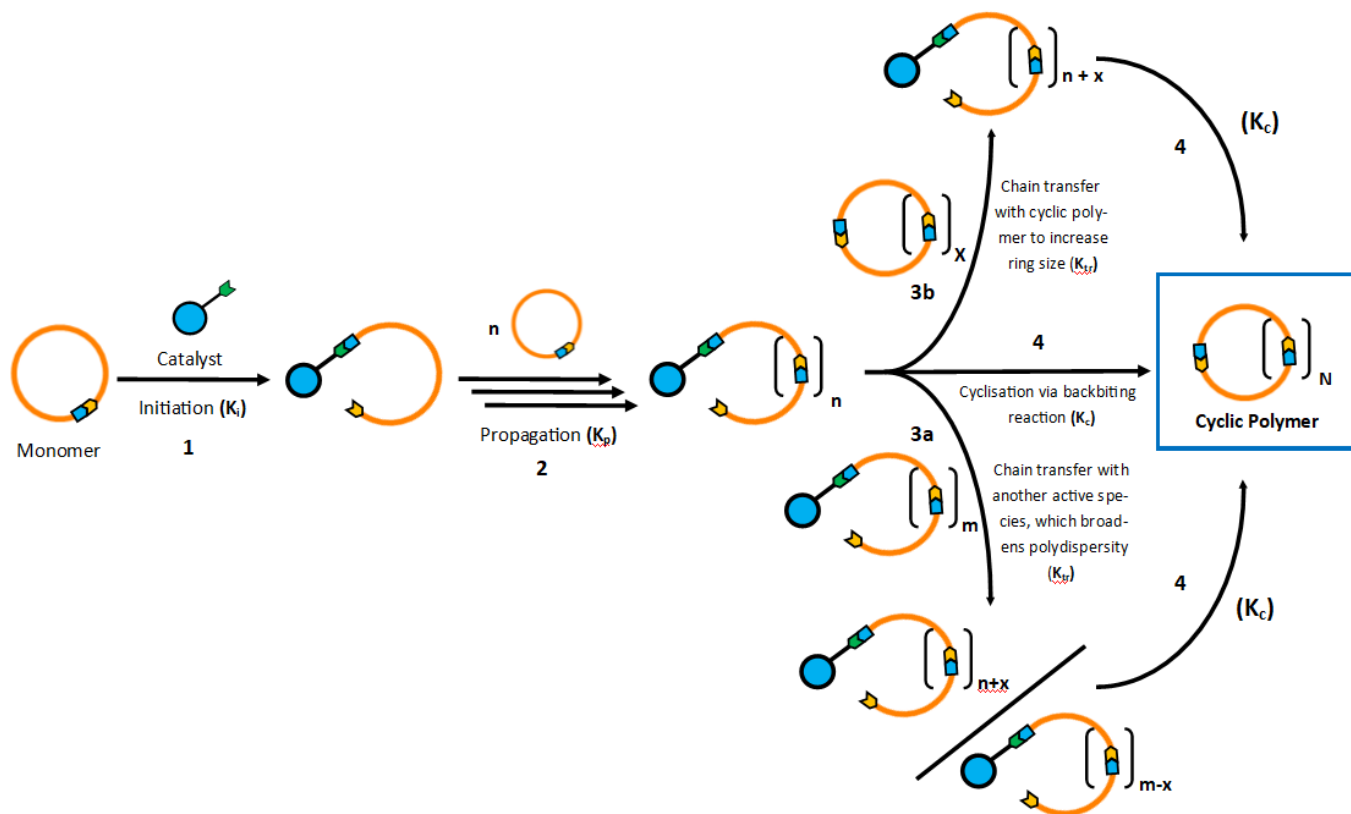
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Figure 2: Scheme of ring expansion polymerization, including possible chain transfer reactions with cyclic polymers and other active species. n denotes the number of monomers in the propagated ring species in question, m denotes the number of monomers in other propagated ring species, N denotes the number of monomers in the finished cyclic polymer and X/x denotes the number of monomers gained or lost from chain transfer reactions. In most cases, $K_p \gg K_{tr} > K_i \sim K_c$.

It has recently been reported that the formation of linear contaminants can be negated using Electrostatic Self-Assembly and Covalent Fixation (ESA-CF), in which the homo-difunctional polymer has metal salt end groups and the linkers have counterions to help give a preference for the cyclic product only.[35]

The high degree of control in RCs means that they are frequently employed for studies of properties such as crystallization behaviours of cyclic polymers.[36] In addition, the number of options in their synthesis (i.e. choice of linker and ring closure route) allow for the synthesis of larger structures based off of cyclic polymers, like the tadpole-shaped polymers reported by Zhou et al.[34]

Another route to cyclic polymers is ring expansion polymerization (REP) (Figure 2). REP is a single step process in which the monomer and catalyst form an active ring species into which more monomer can be added to grow the cycle. The termination step for this polymerization removes the catalyst and cyclizes the polymer, typically via a backbiting reaction. Some of the first examples of REPs came from the seminal contributions of Kricheldorf and co-workers using various tin catalysts.[37–40] Among other metal catalysts, *N*-heterocyclic carbenes (NHCs) can also be used to synthesis cyclic polymers via a zwitterionic REP.[41]

In REP, the cyclic topology is maintained throughout the polymerization and the process does not require highly dilute conditions. Polymers made from REPs usually have higher Đ values compared to those made using RCs due to the possibility of chain transfer reactions.

The kinetics of REPs have been studied in detail, particularly for the zwitterionic method using NHCs.[41–43] For instance, Brown and co-workers reported a detailed investigation into the kinetics of the zwitterionic polymerization and compared their results with Monte Carlo simulations to propose a mechanism.[42] This report (and other studies) found the initiation step to be slow and reversible and the propagation to be rapid. The cyclization process was slow, which enabled the possibility of chain transfer reactions. These reactions can involve cyclized polymers which allows access to cyclic polymers with higher molecular weights (3b in Figure 2) as well as other un-cyclized species resulting in a variety of cycle sizes and broadening the dispersity of the polymerization (3a in Figure 2).

While REPs do not consistently give low Đ values, they do allow for easier access to high molecular weight cyclic polymers and would be more appropriate for industrial-scale cyclic polymerizations due to the absence of dilute conditions and the single step nature of the REP. This approach has been developed substantially over the past decade and an array of options are now available which provide controlled (Đ < 1.5) cyclic polymers.[41,44] In particular, the recent use of metal catalysts with NHC ligands has led to incredibly fast, controlled polymerizations which is

another advantage considering the lengthy reaction times involved in ring closure approaches.[45,46]

While rapid progress has been made in the synthesis of cyclic polymers over the past decade, some synthetic questions remain. For instance, the possibility of catenanes being produced in these polymerizations has yet to be discussed in depth to our knowledge. Given the need to open and close active ring species in REPs for propagation, as well as the presence of linear and cyclic species in RC cyclization steps, there is a clear potential for mechanically interlocked cyclic polymers. Such cases have not been reported to our knowledge, although this would likely have a profound effect on the polymer rheology and the molecular weight distribution may be bimodal. Future experiments regarding this topic would be very interesting and would help to further expand the knowledge of cyclic polymer syntheses.

Synthetic Details and Review (cPLA)

While cyclic aliphatic polyesters have been synthesized from multiple bio-based and/or biodegradable monomers, cyclic poly(ε-caprolactone) (cPCL) and cyclic poly(lactide) (cPLA) are by far the most commonly reported. The linear forms of these polymers have been heavily studied and have been used in biomedical applications (among others).[47] Table 1 displays the reported methods to synthesize cPLA and cPCL respectively as well as the basic properties reported (M_n, M_w, Đ).

The data in Table 1 shows that it is possible to synthesize cPLA with relatively low Đ values across a range of molecular weights. The use of the IMes carbene by Culkin et al. (entry 1 in Table 1) in a zwitterionic REP was one of the first examples of a successful cyclic polymerization via an organic catalyst. Using the carbene nucleophile, NHCs can open lactone rings to form a zwitterionic species in which the opposing charges promote cyclization after rapid propagation (Scheme 1). This allows for rapid reactions

Scheme 1: Mechanism of the Zwitterionic REP of lactide using NHC catalysts reported by Culkin et al.[41]
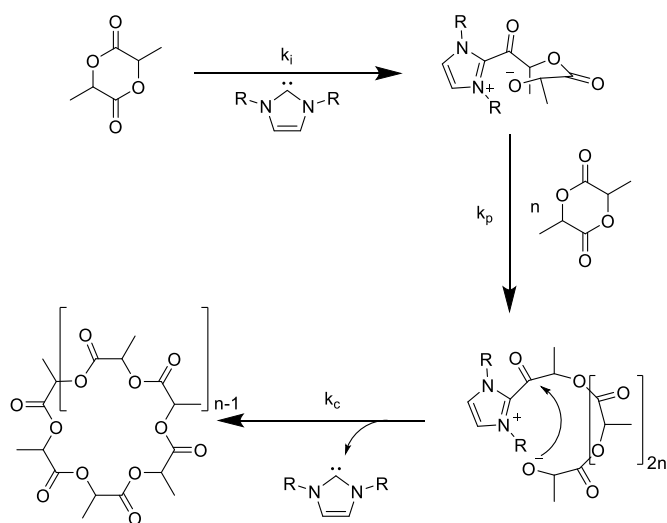
(5-900 s) at room temperature and cyclic polymers with low Đ values, especially compared to other REP methods.

Polymers made using NHC catalysts often have lower molecular weights compared to metal-catalyzed approaches due to the reactive cationic and anionic chain ends. The choice of NHC catalyst is important for achieving desired molecular weights as they are influenced by the proximity of the anion and cation in the active ring species. Other NHC catalysts have been tested for cyclic polymerizations of lactide, such as in the report by Prasad and co-workers (entry 2). In this example, the air-sensitive NHC was generated in situ from the air-stable salt via reaction with potassium tert-butoxide.

During polymerization, the NHC catalysts are highly sensitive to air and moisture which can lead to linear products, although this sensitivity is common with many REP methods and lactone polymerizations. The MALDI data in the report by Prasad et al. showed impurities in the form of polar polymers with potassium/sodium adducts attributed to the reaction environment and the use of potassium tert-butoxide in situ.[44]
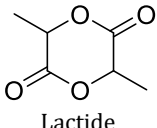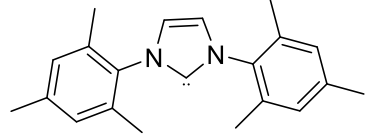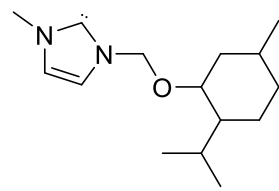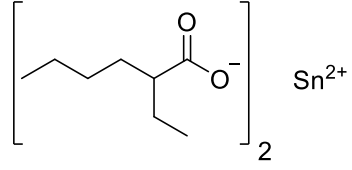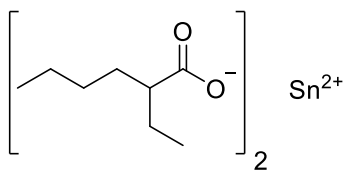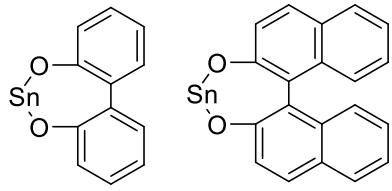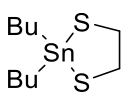
The reported use of other organic catalysts for cyclic polymerizations of lactide have been limited to the use of imidazole by Kricheldorf et al. (entry 14), and iterative polymerizations catalyzed by carbodiimides (entry 15).
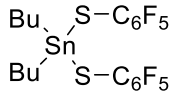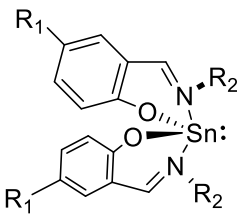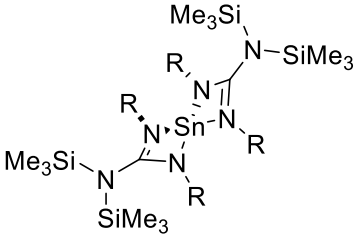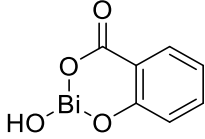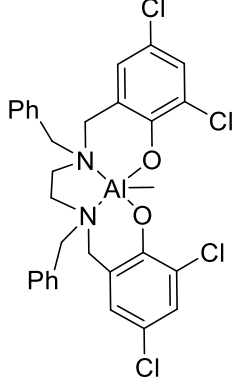
While NHCs are an effective option for cyclic polymerizations, most of the reported cPLA syntheses have used REPs with metal catalysts. For example, Kricheldorf and co-workers have experimented with many tin (and other metal) complexes (see entries 3,4,5,6,7,8, and 11) in cyclic polymerizations of L-lactide. These polymerizations typically yielded high molecular weight cyclic polymers with relatively high Đ values.
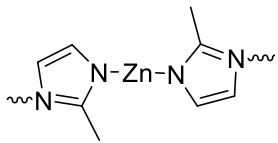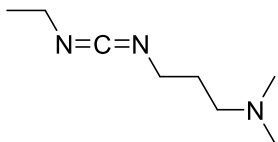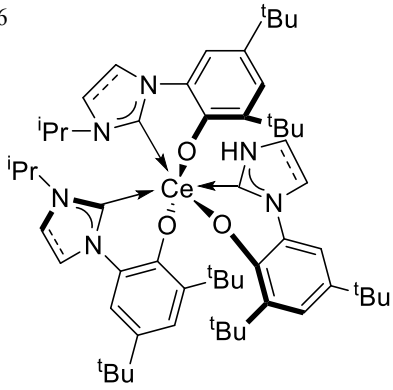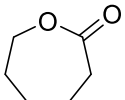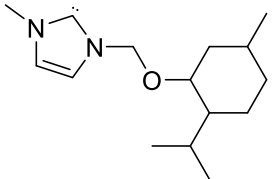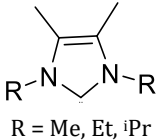
Relative to the NHCs, REPs using metal catalysts usually require higher temperatures (120 – 160 °C) and longer reaction times. The advantage of these catalysts lies in their ease of use as many are stable under ambient conditions and easy to synthesize. Some of the catalysts were reported to form cycles without racemization, which allowed the product to retain stereochemistry.[39] While early reported cyclic polymerizations using tin catalysts were conducted in chloroform at lower temperatures of around 60 °C,[48] most of the recent reports of metal-catalyzed REPs have been bulk processes which have allowed access to cyclic polymers with higher molecular weights. As NHC-catalyzed polymerizations are typically done in solution, the lack of solvent in these metal-catalyzed REPs may be advantageous in the possible commercialization of cyclic polymers. Overall, NHC and metal catalysts are some of the most promising and popular for cPLA syntheses, and the work by Culkin, Waymouth and Kricheldorf et al. has greatly advanced the synthesis of cyclic polymers over the last decade.
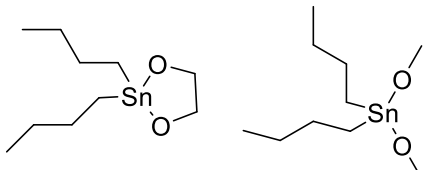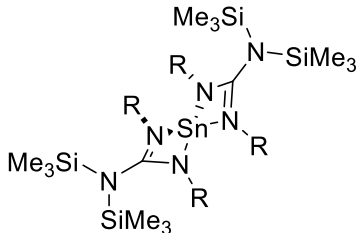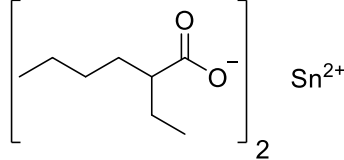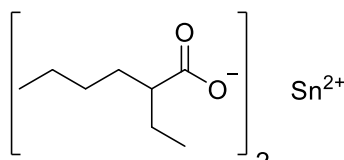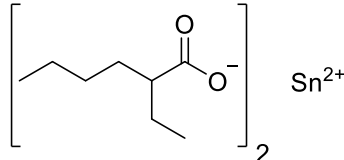
The ease of use of metal catalysts in cyclic polymerizations is typified by the use of Sn(Oct)$_2$ by Kricheldorf and co-workers. This is a standard catalyst for formation of linear PLA,[49] and by using catechol co-initiators the polymerization can be tuned to exclusively favour a cPLA

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Table 1: Table showing various methods used to synthesize cPLA and cPCL with basic characterization, notes and references

Monomer	Catalyst/method	M_n (kDa)	M_w (kDa)	Đ	Notes	Reference/s
Lactide	1	7.30 – 26.0	8.50 – 35.0	1.16 – 1.35	Zwitterionic REP using NHC catalyst – specifically IMes carbene.	[41]
	2	12.0 – 36.0	18.0 – 74.0	1.44 – 2.02	Zwitterionic REP using NHC catalyst.	[44]
	3	23.0 – 70.0	59.5 – 170	2.00 – 2.70	Tin(II) 2-ethylhexanoate (Sn(Oct)$_2$) with a catechol as co-initiator in REP method.	[38]
	4	13.0 - 165	25.0 - 315	1.80 – 2.50	Reaction using neat Sn(Oct)$_2$.	[50]
	5	23.0 - 112	57.0 - 305	2.10 – 4.60	Cyclic Tin(II) bisphenoxides used in a REP.	[51]
	6	13.0 – 34.0	53.0 - 146	2.40 – 5.60	Bulk REPs using neat dibutyl-2-stanna-1,3-dithiolane.	[39]
	7 Bu$_n$SnCl$_n$ and Ph$_2$SnCl$_2$ n = 1,2,3	13.5 – 55.0	34.5 - 132	1.90 – 3.00	Use of alkyl- and aryl- Tin Chlorides in a ring opening polymeriza-	[52]

				tion (ROP) terminating with end-to-end cycliza-tion.	
8	45.0 – 88.0	131 - 198	1.70 – 3.00	Similar to the previous entry.	53
9	13.6 - 132	18.9 - 245	1.39 – 1.96	REP of racemic and L-lactide using bis(salicylaldi minato)tin(II) complexes. R_1 = H or Br, R_2 = various ali-phatic or aro-matic substit-uents.	54
10	10.3 – 41.9	14 – 64.1	1.36 – 1.53	Tin catalyst designed to mimic activity of NHC Car-bene, R = iPr. REP method.	46
11	17.0 – 57.0	57.0 – 122	1.90 – 3.80	Bismuth cata-lyst used in conjunction with Salicylic acid in REP.	11
12	1.71 – 8.12	1.98 – 8.85	1.06 – 1.16	RC using a maleimide-di-functional poly(lactide) cyclized using a thiol-ene reaction. Polymeriza-tion catalyst is an Salen Alu-minium com-plex.	55

#	Structure					
13		8.35 – 24.5	10.9 – 39.7	1.22 – 1.94	ROP using Zeolitic Imidazole Framework (ZIF-8) which results in cyclic products.	56
14		13.0 – 41.0	20.8 – 71.8	1.60 – 1.75	ROP using Imidazole in which end-to-end cyclization provides a cyclic polymer.	57
15		2.40 – 41.8	2.43 – 42.6	1.02 – 1.03	RC method using azide-alkyne click reaction with poly(rac-lactide). Polymers made using iterative process with carbodiimide catalyst.	58
16		61.0 – 253	102 – 402	1.53 – 1.85	REP using cerium catalyst with NHC ligands. Very short reaction times (15 – 60 s) at room temperature in solution (THF).	45
ε-caprolactone						
1		22.4 – 31.9	56.1 – 72.6	2.27 – 2.50	REP using NHC catalyst generated in situ.	59
2	R = Me, Et, ⁱPr	41 – 114	126 – 232	1.29 – 2.60	Alternative NHC methods using different catalysts.	42,60

#	Structure				Description	Ref
3	Bu₃Sn(ethylene glycolate) and Bu₂Sn(OMe)₂ structures	45.0 – 69.0	72.0 – 145	1.60 – 2.10	REP method using Tin catalysts.	[61]
4	Me₃Si, N–SiMe₃, R, N, N, R, N·Sn·N, R, Me₃Si–N, N, R, SiMe₃ structure	15.7 – 58.6	28.1 – 110	1.77 – 1.88	Tin catalyst designed to mimic activity of NHC Carbene, R = ᶦPr. REP method.	[46]
5	[2-ethylhexanoate]₂ Sn²⁺ structure	2.00 – 22.0	2.14 – 25.7	1.07 – 1.17	RC cyclized using copper-catalyzed azide-alkyne "click" chemistry. Ring closures of this polymer have been done with homo- and hetero-difunctional polymers.	[13,33,34,62]
6	[2-ethylhexanoate]₂ Sn²⁺ structure	23.6 – 53.9	48.6 – 121	2.06 – 2.26	Sn(Oct)₂ polymerizations with Anthracene initiator in which the di-functional polymer chain is closed with UV light, causing the anthracene units to photodimerise (RC).	[63]
7	[2-ethylhexanoate]₂ Sn²⁺ structure	3.20 – 6.40	3.52 – 7.36	1.03 – 1.60	RC using ring closing metathesis with 1st generation Grubbs catalyst. Undecylenyl alcohol and acid were used to give two vinyl end groups to allow for metathesis.	[64]

product (entry 3). This process was successful with unsubstituted and 4-*tert*-butyl catechols, although the former gave higher molecular weights and less discolouration. The *tert*-butyl catechol may have been a less effective co-initiator for this polymerization due to the steric bulk of the tert-butyl group, although the electron donating effect of this substituent should help to form the catecholate complex and initiate the polymerization with lactide.

Compared to other metal catalysts, relatively large cyclic polymers with low Đ values were synthesized using this method. A preference for an even number of lactic acid units was reported and the extent of this favourability was increased when lower temperatures and shorter reaction times were employed. While catechol is suspected of being genotoxic, the method yields high molecular weight cyclic PLA and catechol is no more toxic than $Sn(Oct)_2$; It is often found in the polymer industry as a radical scavenger.[38] The use of less bulky electron donating substituents such as methyl groups may improve this polymerization. For instance, 4-methyl catechol, is classified as non-hazardous and may give similar (or better) results.

More recently, Kricheldorf and co-workers showed that neat $Sn(Oct)_2$ was also capable of producing cyclic polymers.[65] The authors found a small fraction of linear chains with octanoate and COOH end groups, however. Using $Sn(Oct)_2$ alone means the polymer propagates from the tin catalyst and is terminated via end-to-end cyclization as opposed to the catechol method which cyclizes via a back-biting interaction.

Other researchers have reported the use of tin(II) catalysts for cyclic polymerizations of lactide, such as the use of various bis(salicylaldiminato)tin(II) complexes by Piromjitpong et al. (entry 9). These catalysts were relatively active in cPLA synthesis and some polymerizations were completed in 25 minutes. As expected, catalysts with less bulky, electron donating substituents were more active. This system was tested with racemic lactide as well as the typically reported L-lactide, and the catalyst imparted a slight stereoselectivity on the racemic polymer. Using homonuclear decoupled 1H NMR, the polymer was shown to have a slight heterotactic preference. While only slightly heterotactic, this is the only reported instance of some stereocontrol over cPLA. The other reports of cyclic polymerizations of racemic lactide mentioned in this review did not show any stereoselectivity. The stereo-control of linear PLA has been the topic of many publications, and more cyclic polymerizations using racemic lactide would be useful. For instance, polymerizations of racemic lactide have not been reported using the zwitterionic method which may impart a preference for either stereoisomer.

The use of a Bismuth Subsalicylate/Salicylic acid system by Kricheldorf et al. (entry 11) yielded some of the largest reported cPLA samples with lower Đ values than many of the prior tin catalysts. Bismuth (III) is the least toxic heavy metal ion and its use in conjunction with a co-catalyst such as salicylic acid provided a catalytic system with low toxicity; both reagents are already widely present in the pharmaceutical industry.[11] Bismuth salts have an equally low tendency to cause racemization of the lactide monomer as tin salts, which makes them better suited to lactide polymerizations compared to other non-toxic alternatives such as zinc compounds.

While REPs using NHCs and metal catalysts are good options for the synthesis of cyclic polymers, both of these approaches have opposing flaws. It has recently been shown that combining these two systems can result in efficient and precise cyclic polymerizations up to very high molecular weights. The use of metal catalysts designed to mimic the activity of the carbene catalysts has been reported twice in the past year for the cyclic polymerization of lactide. Ungpittagul et al. (entry 10), reported the cyclic polymerization of lactide (and ε-caprolactone) via novel guanidinate tin(II) complexes. Compared to most metal catalysts, these rapid polymerizations (10 – 60 mins) occurred at lower temperatures (100 – 120 ºC) and produced polymers with relatively low Đ values.

The authors synthesized homoleptic and heteroleptic tin(II) complexes, but the latter were described as unstable and degraded into the homoleptic counterpart (Scheme 2). The isopropyl variant was found to be the most active in polymerizations due to the minimal steric hinderance.

Scheme 2: NHC-like Tin (II) complexes for use in REP of lactide and ε-caprolactone by Ungpittagul et al. [46]
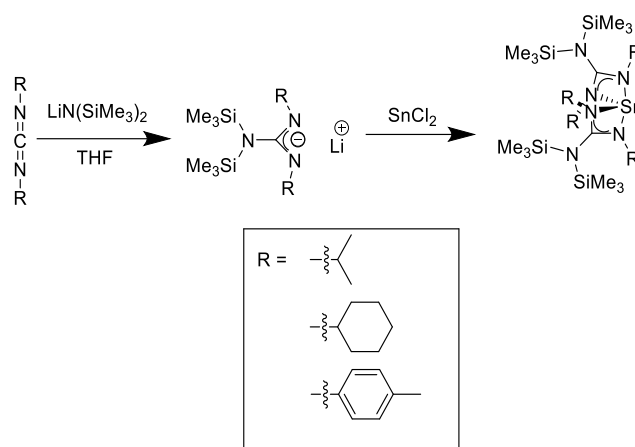
A similar approach by was reported by Kerr and co-workers, who polymerized racemic lactide using cerium(III)-NHC catalysts with emphatic results (entry 16). The combination of the Lewis acidic cerium (III) and the NHC functionalities led to exceptionally fast polymerizations (15 – 120 s), very high molecular weights and low Đ values. When used in the absence of any co-initiator, these catalysts had a very high preference for the cyclic product. The suitability of the catalyst for cyclic polymerization of lactones was hypothesised by the ability of the complex to insert CO_2 exclusively between the Ce-NHC bond. Catalysts with saturated and unsaturated NHC ligands were tested and the former was found to be more active in the cyclic polymerization of lactide due to increased Lewis basicity and steric bulk of the NHC moieties. The polymerization was also successful with L-lactide, ε-caprolactone and β-butyrolactone, which is highly encouraging, and it would be very useful to see other catalysts applied to multiple monomers.

Luo and co-workers reported the use of a zeolitic imidazole framework to synthesize cPLA (entry 13). ZIF-8 has typically been shown to be active in transesterification and Knoevenagal reactions[56] but provided cPLA of low molecular weight. This was the only reported instance of a cyclic polymerization using a heterogenous catalyst, and the further exploration of such methods could be hugely beneficial. For example, the ZIF-8 catalyst was recyclable following filtration and washing with dichloromethane. The polymer product from a heterogenous polymerization would also not contain any metals from the catalyst. More research on these methods would be very useful as a result.

The work by Koo et al. (entry 15) is the only report of the azide-alkyne RC method being used to synthesize cPLA (this method is far more common with ε-caprolactone) and the polymers are incredibly well controlled, with very narrow Đ values. This level of control was due to the use of iterative process of forming the linear polymer (via successive esterification reactions with carbodiimide catalysts to form dimers, tetramers, octamers etc). While the polymers are very controlled, the method for making them is lengthy and it would be useful to see more work done on both the alkyne-azide ring closure.

RC of lactide can also be achieved by the use of Aluminium Salen complexes followed by a thiol-ene reaction (entry 12), as was reported by Stanford and co-workers (Scheme 3).

Scheme 3: Scheme of the Ring Closure synthesis of cyclic poly(lactide) using thiol-ene click chemistry reported by Stanford et al.[55]
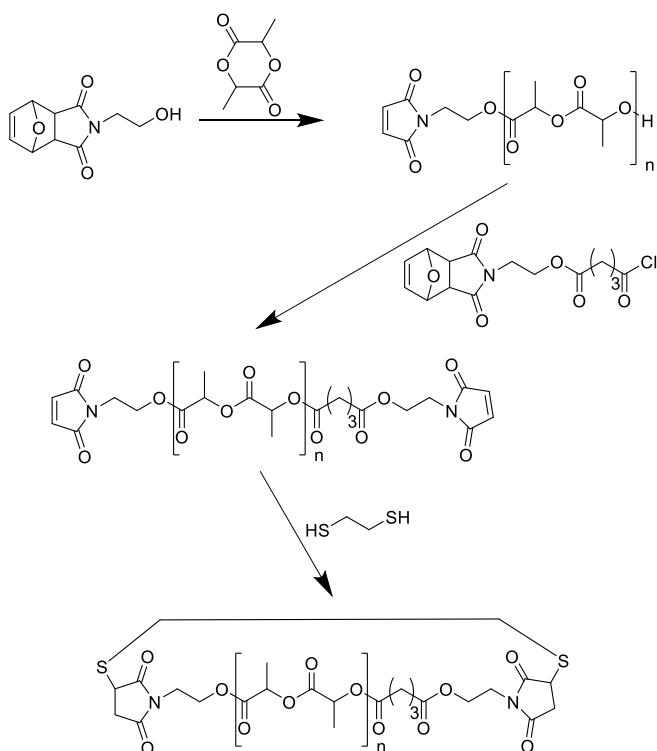
The use of a maleimide functionalized initiator in the initial linear polymerization allowed for subsequent closure with the addition of a dithiol. This ring closure method does not require the use of a copper catalyst, like the typical alkyne-azide method for instance. The reaction times reported were lengthy, however.

While reports of cPLA syntheses have been relatively extensive and efficient, controlled cyclic polymerizations are now accessible, some questions remain. For instance, the use of stereoisomers of lactide other than the L-variant would be welcome, especially given the aforementioned interest in this for linear PLA. It would also be highly interesting to see how cyclic polymers of different lactide stereoisomers (i.e. a mixture of L- and D- cyclic polymers) would interact. The ease with which a typical cyclic polyester could be converted to the linear form (and possibly back to the original cycle) is another open question. Such conversions have been done with polymers specially designed with UV-activated end groups, but a study of how labile these polymers are with regards to topology conversions has yet to be reported.[66] Due to the distinctly different properties of cyclic and linear topologies, efficient conversion between the two may allow for unique applications and a better insight into the chemical stability of cyclic polymers compared to linear counterparts.

Synthetic Details and Review (cPCL)

Syntheses of cPCL have been reported using similar catalysts as those of cPLA. For instance, NHC-catalyzed REPs of ε-caprolactone have been reported on multiple occasions (entries 1 and 2 in Table 1). Shin et al.[60] experimented with alkyl substituted NHCs and reported high molecular weights considering the method (over 100 kDa). The ethyl and methyl-substituted carbenes appeared to be more active than the isopropyl variant, presumably due to reduced steric bulk.

Unlike reported cPLA syntheses, there have been frequent reports of RC methods being used to polymerize ε-caprolactone. This is due to the desire to study the crystallization behaviour of PCL (which is better able to crystallize than PLA), and the highly controlled polymers needed for such studies. The most common example of RC of ε-caprolactone is the copper-catalyzed alkyne-azide ring closure approach (entry 5). Typically, linear PCL was synthesized using Sn(Oct)$_2$ and a diol co-initiator. This polymer was then functionalized with alkyne groups, before cyclization occurred using a difunctional azide linker (Scheme 4). Depending on the linker used to cyclize the linear polymer, this method can give cycles with reactive functional groups (e.g. the hydroxyl groups in the product of Scheme 4) which can be further modified to create larger structures. As expected with RCs, the cPCL synthesized using this method had very low Đ values with relatively low molecular weights. As a result, the alkyne-azide method the been the favoured choice for the synthesis of crosslinked polyurethanes from cPCL and of tadpole-like cPCL-structures for applications in drug delivery as well as shape memory and self-healing materials.[33,34]

Scheme 4: Scheme showing the RC method for cPCL using alkyne-azide ring closure reported by Chen and co-workers[34]
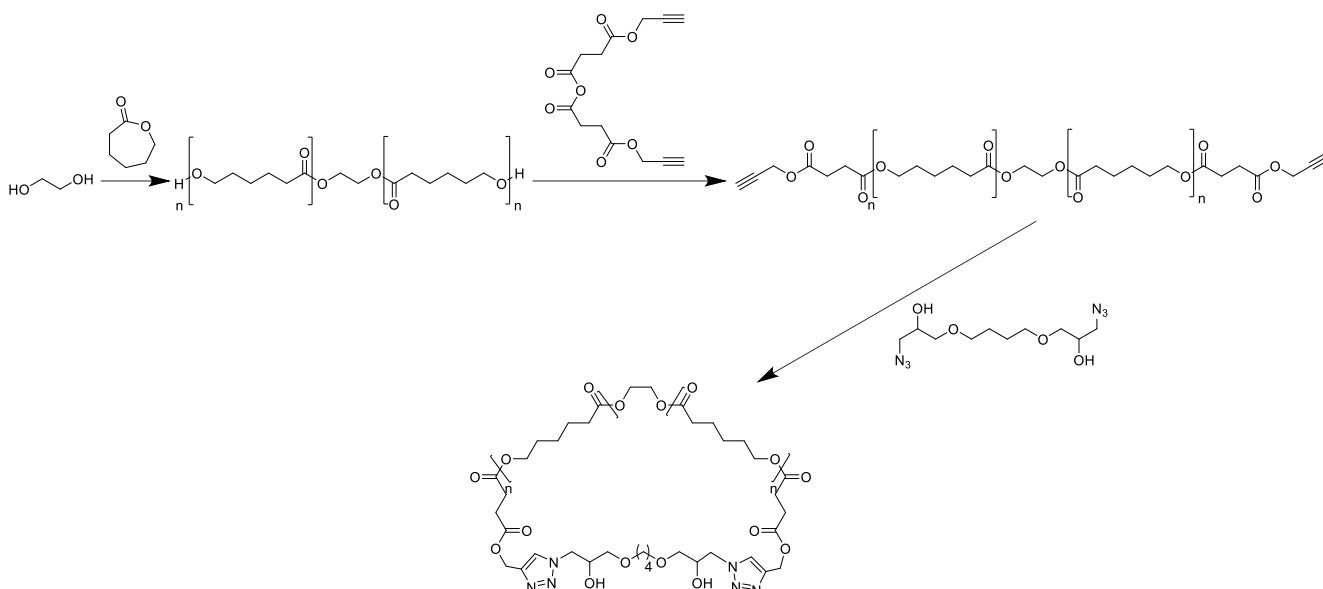
Other RC approaches have been reported using ε-caprolactone, including ring closing metathesis (RCM) via Grubbs catalyst by Xie et al. (entry 7). While this method was less efficient than the alkyne-azide reaction due to the presence of dimers, trimers and tetramers in the cPCL samples, the RCM worked under more mild and less dilute conditions. RC approaches typically allow for easier identification of cyclic products in the NMR spectra, such as in this case where peaks for an expected vinyl pendant group could be seen. However, the reaction times for RC methods tends to be rather long (24 – 48 hrs per step).

Another RC approach for cPCL was the UV-induced cyclization of anthracene-functionalized PCL using the photodimerization of two anthracene units by Wang et al. Relative to other reported RCs of ε-caprolactone, this approach gave cPCL samples of high molecular weights and Đ values. The cyclization was partly reversible (45.9%) when the sample was heated to 160 °C. It was also found that the cPCL molecular weights could be tuned based on the concentration of linear polymer in solution at the cyclization stage.

Synthetic Details and Review (Cyclic polymers from other bio-based Monomers)

Cyclic polymerizations have been reported on other bio-monomers to a lesser extent than cPLA and cPCL. The basic characterization and notes for these polymers can be found in Table 2.

The polyacetals of isosorbide reported by Hammami et al. are a great example of how non-lactone monomers can be polymerized to form cyclic products (entry 1 in Table 2). Isosorbide is a sugar derived diol that has been touted as a promising bio-monomer in recent years due to its rigid bicyclic structure which often provides favourable physical properties.[67,68] The polyacetals were synthesized using a base (KOH) and dichloromethane (DCM) to link isosorbide units, and the difunctional monomer was then able to undergo ring closure via the same methods (Scheme 5).

The resulting cyclic polymer was fairly polydisperse due to the potential for inter- and intramolecular ring closure, but the molecular weight was substantial. The use of DCM as a reagent may not be the "greenest" option, but this is a good example of a different way to synthesize cyclic polymers from bio-based monomers. This approach could be tested with other bio-based diols such as 1,3-propane diol and the stereoisomers of isosorbide. The authors did report substantial differences between their linear and cyclic polyacetals (such as a 10°C difference in T_g), but the cyclic polymer was of a much higher molecular weight which would exaggerate this comparison.

The use of polyacetals may also allow for easy recycling. Klankermayer et al.[78] recently reported the efficient degradation of polyacetals using an acid catalyst to give useful

Scheme 5: Scheme for synthesis of poly(acetals) from Isosorbide reported by Hammami et al.[69]

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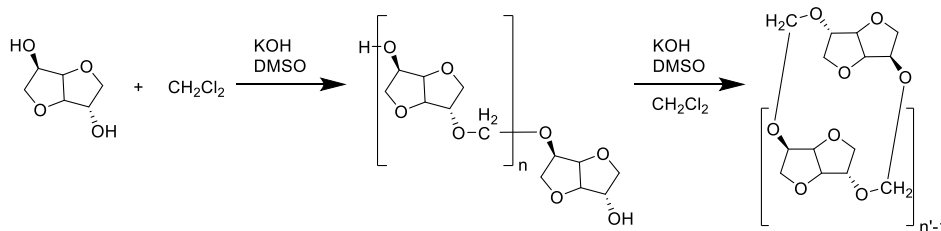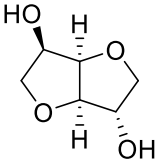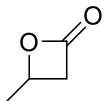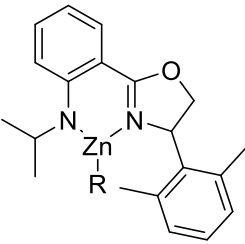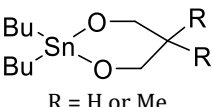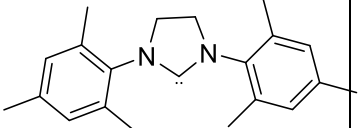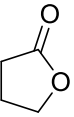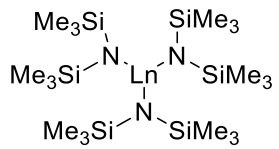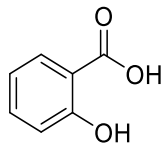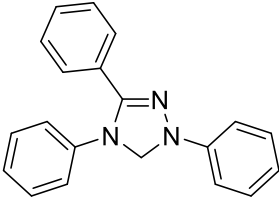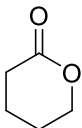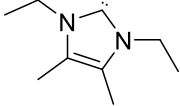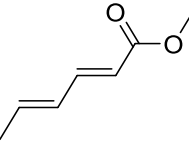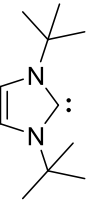
Table 2: Table showing methods used to synthesise cyclic polymers from a variety of bio-based monomers, with basic characterisation, notes and references

Monomer	Catalyst/Method	M_n (kDa)	M_w (kDa)	Đ	Notes	Reference/s
Isosorbide (HO H O, O, H OH)	1 KOH	21.1	55.6	2.60	Polyacetal via one step process using CH$_2$Cl$_2$.	[69]
	2 K$_2$CO$_3$	11.8	61.0	5.17	Polycondensation with tri-fluorobenzophenone and 1,3,5-tris(4-fluorobenzoyl) benzene.	[70]
β-butyrolactone	3 (Zn complex, R = N(SiMe$_3$)$_2$)	2.80 – 197	3.40 – 388	1.08 – 1.97	REP in toluene at 100 °C. R = N(SiMe$_3$)$_2$.	[71]
	4 Bu-Sn-O / O, R R R = H or Me	18.8	32.0	1.70	Early report of a REP in which the catalyst remained in the cyclic product.	[40]
	5 (IMes carbene)	4.89	6.94	1.42	Zwitterionic REP using saturated IMes carbene.	[72]
	6 Via Lipase catalysis	0.26 – 3.84	0.37 – 7.30	1.30 – 3.00	Polymerizations were also tested with other enzymes.	[73]

O (γ-butyrolactone)	7	Me$_3$Si, SiMe$_3$, N, Ln, N catalyst structure	8.37 – 10.0	14.3 – 21.0	1.71 – 2.10	REP using Lanthanum, Yttrium and Samarium catalysts. [12]
Salicylic Acid	8	triaryl triazoline catalyst structure	Up to 4.00	Not reported	Not reported	Zwitterionic REP. The paper also used imidazole also although little data is given. [74]
δ-valerolactone	9	diethyl dimethyl imidazolylidene catalyst	85.0	94.0	1.11	Zwitterionic REP using in-situ generated catalyst. [59,75,76]
(E,E)-Methyl Sorbate	10	di-tert-butyl imidazolylidene catalyst	1.10 – 28.7	2.20 – 37.3	1.10 – 2.10	Zwitterionic REP with NHC and aluminium Lewis acid. [77]

cyclic acetal products such as 1,3-dioxane in strong yields. Such products could be used as solvents, fuel additives or monomers. While the recycling process did not return the starting monomer, the process worked with real polymer waste which included additives and contaminants. The dyes and additives were unaffected by the degradation and could be removed by filtration. It would be interesting to see if and how the cyclic topology could affect this degradation process.

Polycondensation of isosorbide can also give cyclic products, as was shown by Bennour and co-workers who reported polycondensations with trifluorobenzophenone (TFB) and 1,3,5-tris(4-fluorobenzoyl) benzene (TFBB) (entry 2). Similar to the polyacetals of isosorbide, these cyclic polymers were sizeable and highly polydisperse, but some linear products were also detected. When isomannide was used in this process, there was a greater preference for the cyclic polymer and multicyclic species were detected as major products using MALDI-TOF (Figure 3). This was due to both hydroxyl groups of isomannide being in the endo position, which gives a V-like conformation and increases cyclization tendency. The rigid polymer products had Tg's of up to 200 °C. By varying monomer ratios, the polymerization was tuned to strongly favour hyperbranched structures or multicyclic ones, although some ratios resulted in gelation.
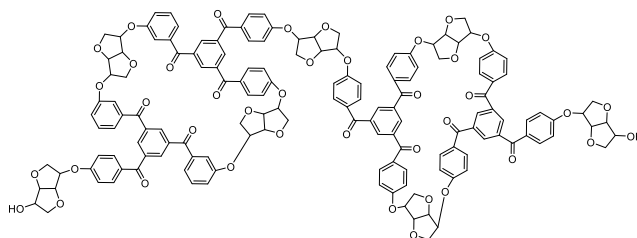
Figure 3: Example of the multicyclic species formed by polycondensations of isosorbide and isomannide reported by Bennour et al.[70]

While lactones have received substantial attention, the development of diols such as isosorbide and 1,3-propane diol in polymerizations is imperative in order to replace petroleum-derived options such as neopentyl glycol (NPG). The exploration of cyclic polymerizations of these monomers may allow for more favourable properties, especially considering that NPG is used in applications where properties such as viscosity and T_g are crucial (i.e. paints and coatings). The cyclic topology obviously influences these properties greatly.

The use of lactones in cyclic polymerizations is not limited to lactide and ε-caprolactone. Shaik et al. reported the use of a zinc catalyst in a zwitterionic REP similar to the NHC approach to synthesize cyclic polymers of β-butyrolactone across a wide range of molecular weights (entry 3). The linear form of this polymer could be used in various applications such as in packaging and drug delivery, although issues such as thermal instability currently limit its competition with petroleum-based plastics.[79] The different physical properties of cyclic polymers (namely greater thermal stability and faster crystallization rates than linear counterparts) would help in the commercialization of poly(3-hydroxybutyrate) (PHB). This is a great example of how the cyclic topology can improve the versatility of current bio-based properties and their ability to compete with traditional plastics.

Cyclic polymerizations of β-butyrolactone have been reported by Kricheldorf and co-workers using tin catalysts, by Jeong et al. using the saturated IMes carbene and by Matsumura et al. who used lipase as a catalyst (entries 4, 5 and 6). While some of the cyclic products did contain substantial amounts of linear polymer, they illustrate a history of interest in cyclic PHB.

In contrast, polymerizations of γ-butyrolactone have been severely limited due to the unfavourable nature of the ROP.[80–82] The monomer has a low strain energy and the enthalpy of its polymerization is often not enough to counter-act the large negative entropy change.

Efficient homo-polymerization was not possible under ambient pressure until recently and polymerizations under ultra-high pressure yielded polymers of limited molecular weights (up to 8 kDa).[83] γ-butyrolactone is a known petrochemical product and promising biomaterial which can be produced from succinic acid.[84] It has variety of applications such as in the enhancement of the capacity and conductivity of lithium ion batteries, and in the synthesis of solvents such as N-Methyl-2-Pyrolidone (NMP).[85]

Hong et al. reported the first successful polymerizations of γ-butyrolactone under ambient pressure using a lanthanum catalyst (entry 7), which yielded cyclic and linear polymers depending on the [monomer]:[catalyst]:[co-initiator] ratios. Sub-zero temperatures (around -40 °C) reduced the entropic penalty of the reaction and different lanthanide metals were tested. The activity of the catalysts decreased with the ionic radius of the metal (Lanthanum > Samarium > Yttrium). Polymers with M_n's of up to 10 kDa were reported using this approach.

Due to the thermodynamics favouring depolymerization, complete conversion of the polymer (in either cyclic or linear form) to the starting monomer was achieved by heating for an hour, making it completely recyclable. This process was shown to be even quicker with a catalyst at room temperature. The cyclic polymer required higher temperatures to depolymerize, but also had a much higher thermal stability so this was to be expected. These results represent a substantial development in both cyclic and bio-based polymers, although the greater thermal stability of the cyclic form may be a disadvantage in terms of post-use

as more heat (80 °C higher) was required to convert it back to the original monomer.

Kricheldorf and co-workers reported a zwitterionic polymerization of salicylic acid but did not specifically isolate a cyclic product and linear chains could be seen in the MALDI-TOF spectra. Small cyclic oligomers were formed by heating the monomer alone and larger homopolymers were obtained using imidazole or an NHC catalyst, though these were still fairly small.

The cyclic polymerization of δ-valerolactone has been reported on multiple occasions using NHC methods (entry 9). There is little data on the cyclic homopolymers, as the monomer has been used more in cyclic co-polymerizations with ε-caprolactone due to favourable reactivity ratios. Shin and co-workers experimented with cyclic gradient copolymers of the two,[76] which contained both a sharp comonomer interface and a gradient interface. While limited, the data on cyclic homopolymers of δ-valerolactone shows that cyclic polymers of high molecular weights are very accessible.

Scheme 6: Scheme of NHC polymerization of Methyl Sorbate reported by Hosoi et al.[77]
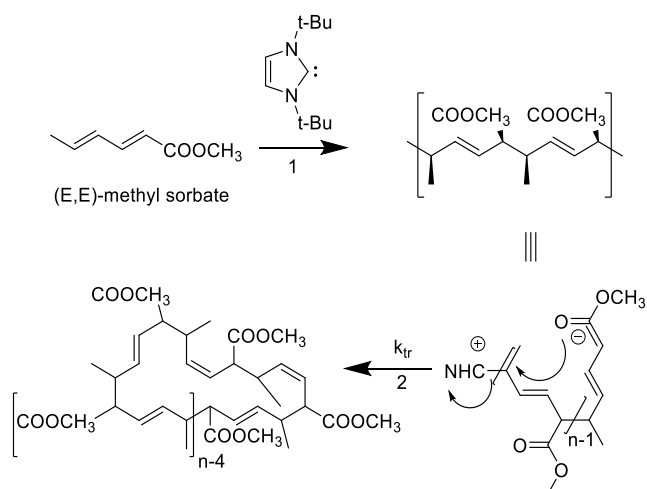
Finally, Hosoi and co-workers reported the zwitterionic REP of (E,E)-methyl sorbate using an NHC catalyst (entry 10). This monomer is derived from fatty acids and can react with an NHC to form a zwitterionic species in the same way as lactones (Scheme 6). Unlike other NHC-catalyzed REPs, a bulky aluminium Lewis acid was used to accelerate monomer consumption and to make the reaction favour ring closure as opposed to linear enamine formation.

This effect was due to the steric presence of the Lewis acid only and it was not directly involved in the polymerization mechanism. These results are a good example of how the NHC approach can be adapted to non-lactone monomers.

Physical Properties

The cyclic topology has been shown to provide substantial differences in physical properties when compared to linear polymers. The purpose of this section is to highlight these differences to show the extent of the impact of the

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cyclic architecture, and to provide context for some of the potential applications.

Viscosity

The lack of free end groups in cyclic polymers means that they have fewer entanglements and are therefore less viscous than their linear counterparts. The difference in viscosity is often used as evidence for a successful synthesis. For instance, papers on cPLA often include plots of intrinsic viscosity against molecular weight (Mark-Houwink plots), allowing for comparisons with known linear PLA samples of the same molecular weights. One such example can be found in the paper by Culkin et al., which uses a logarithmic plot to compare their synthesized cPLA with a commercial sample of linear PLA (Figure 4).[41]
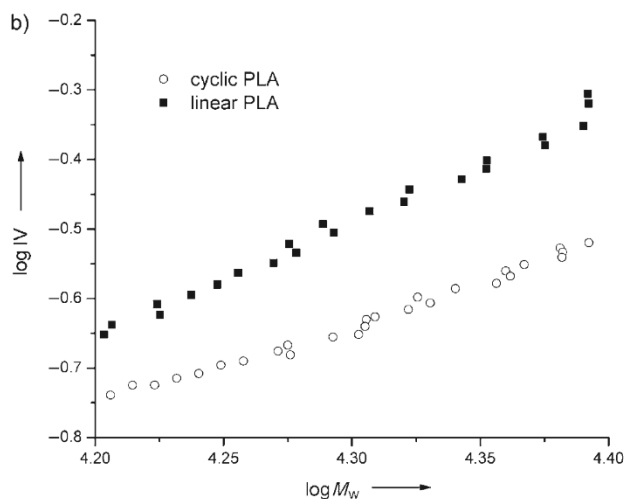

Figure 4: Logarithmic plot of intrinsic viscosity against molecular weight of cyclic and linear PLA samples reported by Culkin et al.[41] Figure reproduced with permission from Angew. Chem. Int. Ed. 2007, 46, 2627–2630.

The ratio of the viscosities ([ηcyclic]/[ηlinear]) can be obtained from the Mark-Houwink plot and compared with other literature on cPLA. This ratio is specifically known to be between 0.66 and 0.7.[38,41]

In the work done on cyclic polyacetals from Isosorbide, mixtures of linear and cyclic polymers were shown to give viscosities between those of each pure form, suggesting that rheological properties could be tuned by doping one form with the other in different ratios; the polymers in this example were noted to be miscible.[69] In one paper, it was reported that a linear polybutadiene sample doped with a certain volume fraction (0.4-0.6) of the cyclic variant exhibited a viscosity increase of up to 2.3 times that of the sole linear polymer. The researchers claimed the increase was comparable to that caused by the relaxation of linear polymers and that the cyclic topology may be causing such an effect, but this result is an outlier to the norm and should be viewed as such.[86]

Glass Transition

In addition to a lower viscosity, the lack of free ends in cyclic polymers results in reduced flexibility and a higher glass transition temperature. In practice this difference is usually around 5 °C or so, but in applications like powder coatings - where having a Tg suitably above room temperature to prevent curing of the coating when in storage is crucial – even small differences in Tg can be hugely beneficial. An example of this difference can be seen in the paper by Hosoi and co-workers on cyclic polymers from (E,E) methyl sorbate (see entry 9 in Table 2), where the Tg of the cyclic polymer was shown to be 7°C higher than the corresponding linear polymer (Figure 5).[77]
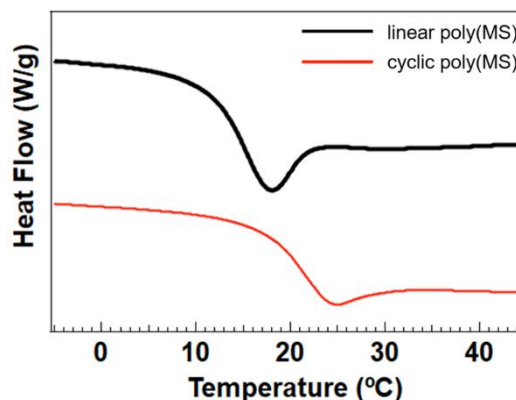
Figure 5: Comparison of DSC curves of cyclic and linear polymers of (E,E)-Methyl Sorbate reported by Hosoi and co-workers.[77] Figure reproduced with permission from J. Am. Chem. Soc. 2017, 139, 15005–15012

Thermal Stability

Owing to the extra energy needed to break the cycle, cyclic polymers also are typically more stable with regards to thermal degradation. The potential extent of this is best evidenced in the work on γ-butyrolactone by Hong and co-workers, in which the cyclic polymer displayed a much higher onset degradation temperature compared to the linear form, differing by 72 °C.[12] TGA analysis is often used to distinguish between cyclic and linear forms due to these noticeable changes. The authors also tested a sample which contained significant amounts of both forms, which resulted in a less smooth plot due to the presence of two different polymer architectures.

This example is on the extreme side, and other papers have reported much more mild variations. For instance, Hoskins et al. reported a 10 °C difference in inflection points from TGA results between their PCL and cPCL samples.[47]

Crystallization Behaviour

Crystallization properties of cyclic polymers have been investigated in detail, with the majority of studies being done with cPCL samples. The overall consensus from these is that while there is minimal difference in the morphology of the crystals formed, the crystal growth rate is significantly affected by the cyclic topology. Varying conclusions have been found depending on molecular weight, conditions and analysis techniques.

For example, a study by Shin and co-workers focused on high molecular weight cPCL using DSC and time-dependant Small angle X-ray Scattering (SAXS) to look at isothermal crystallinity rates.[60] The authors used DSC to compare the enthalpy of melting after crystallization by annealing relative to the maximum enthalpy of heating achieved under experimental conditions. By varying the time the samples were annealed for, the authors produced a plot showing the time dependence of the relative crystallinity (χc), which shows the cyclic samples crystallising in a shorter timeframe than linear counterparts of similar weight (Figure 6).

The SAXS results confirmed this difference. The variation in crystallization rates is likely linked to the differences in intrinsic viscosities, as the lower cyclic viscosity (and less entanglement) would allow faster diffusion from the melt and faster polymer crystallization in the melt.[87] This enhanced mobility provides access to faster crystallization.

Figure 6: Relative crystallinity as a function of time for cyclic and linear PCL samples during isothermal crystallization at 45°C reported by Shin et al.[60] Figure reproduced with permission from Macromolecules 2011, 44, 8, 2773–2779.

The report by Shin et al. also mentioned using the electron density correlation function (derived from SAXS data) to look into long period spacing and lamellar thickness.[60] The authors found these to be very similar for both types of sample, which led them to suggest that th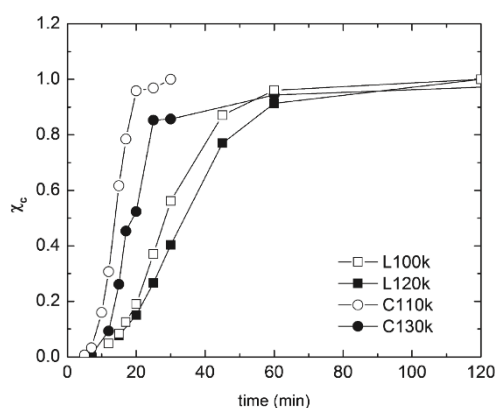e morphology of the crystals was insensitive to the topology. WAXS patterns shown helped to further support that the crystal structures adopted were very similar to each other.

Another paper by Schäler and co-workers investigated crystallinity using lower molecular weight samples (50 to 80 kDa) and reported similar results.[61] It was also mentioned that the cyclic form showed a higher degree of crystallinity. The cyclic samples were reported to have reached a more perfect morphology allowing for this higher crystallinity. The authors of this paper employed different methods to reach their conclusions, including free induction decay to study the crystallization behaviour of its samples.

The molecular weight dependence of crystallization rates for these polymers was explored in another paper by Li et al., where they found it to be non-monotonic, decreasing with higher molecular weights due to the chain entanglement effect (i.e. the more a polymer is free of entanglements, the more able it is to diffuse and crystallize).[13] This technique is quite novel and provides faster heating and cooling rates compared to DSC. Curiously, the authors found that linear PCL crystallized faster than cyclic PCL in a limited low temperature range between -40C and -20C. This was said to be as a result of the mobility produced by the free chain ends, which is dominant at this temperature range over the higher equilibrium melting points and faster diffusion of the cyclic PCL. Li and co-workers found the highest crystallization rates to be at the mid-point of their temperature range covered (-80 to 80 C). A recent report by Zaldua et al. confirmed the trend of faster cyclic crystallization with cyclic and linear PLA samples.[88] The faster crystallization rates of cyclic polymers overall may prove useful in passive heating and cooling applications, where crystallization rates are imperative.[13]

There are other, less studied areas where cyclic polymers are noticeably different to their linear counterparts such as stronger fluorescence behaviours and lifetimes, stronger redox behaviours and improved solution properties. There are no studies of these properties using bio-based polymers but Molecular Dynamics simulations have been used to study redox and solution behaviours, and work on polymers with strong fluorescence (such as Poly(4-vinylbenzyl-carbazole)) have shown this to be the case.[89,90]

Potential Applications

While the focus of research so far has been on synthetic developments to prepare controlled, high molecular weight cyclic polymers, there have been some reports on the potential applications of certain bio-based cyclic polymers. Some of these studies are limited but give a good idea of the areas where these polymers could be advantageous. Certain reports of potential applications of polymers outside of the scope of this review will also be mentioned to better cover the possible applications for future work.

Catalysis

Prasad and co-workers reported the use of a cyclic PLLA-clay hybrid to support metal catalysis.[91] They polymerized L-lactide with clay particles (Scheme 7), before palladium particles were deposited throughout the system to create a nanocomposite structure. Clay is considered to be ideal for this role due to its high intercalation chemistry and aspect ratio.[92]

The cyclic polymer was deemed more applicable for this setup as the palladium particles were unable to disperse properly when using the linear form, resulting in bulk palladium particles in the composite. The cyclic polymer did not have this issue and the Pd nanoparticles were found to be between 5 and 10 nm in size using TEM.

The nanocomposite successfully catalyzed aminocarbonylation reactions with a variety of bases and amines at a catalyst loading of 1 mol%. Following the reaction, the nano-Pd catalysts were retrieved by filtration and washed

Scheme 7: Scheme for synthesis of Cyclic PLLA-clay palladium (Pd) nanocomposite reported by Prasad and co-workers[91]

Clay   NHC precursor enriched clay (in situ)   Cyclic PLLA-clay hybrid

(1) n-BuLi
(2) L-lactide

-MCl, M = Na, K

(1) $Na_2PdCl_4 \cdot 3H_2O$
(2) $NaBH_4$

ꕥ = cyclic PLLA

● = Pd nanoparticle

Pd^0 on cyclic PLLA-clay
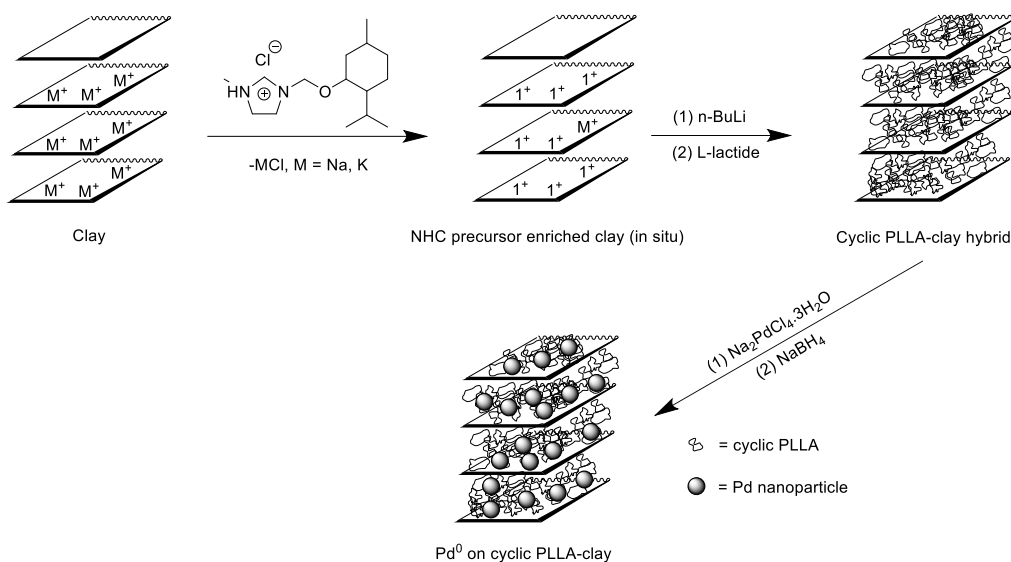
with ethyl acetate and de-ionized water. They could then be loaded and reused at least four times with near-identical yields. The reason for the better suitability of the cyclic PLLA for this application was not discussed, but the structure of the cyclic polymer may have allowed for better encapsulation and separation of individual Pd particles, functioning in a similar way to a crown ether.

Given the extensive use of palladium in C-C and C-N coupling reactions, the potential for cyclic polymers to better support and allow reuse of this catalyst metal would be very desirable, and it would be interesting to see this catalyst tried with other reactions.[93] Unfortunately, the whole metal/polymer composite was not recyclable as it resulted in partial dissociation of the non-supported cyclic PLLAs. There were no reports of depolymerization or scission of the cycles by the metal catalyst, but the authors found difficulty in assessing the quality of intercalation between the clay and polymer during synthesis.

Adhesive and Thermoset Applications

Potential applications as adhesives and thermosets for cyclic polymers made from isosorbide and isomannide were mentioned in both papers found in Table 2. [69,70] In the case of the poly-condensates with TFB and TFBB (entry 2), the thermoset capabilities were tested to a small extent. The authors heated some of their samples containing multicyclic species (i.e. those rich in OH end groups which may promote cross-linking) to 220 °C between two aluminium plates under slight pressure and found that the plates were fixed together in 10 minutes.

The multicyclic species are said to be prone to these types of applications as they can form bi-radicals and cross-links easily, although comparisons with samples that had fewer OH end groups, fewer multicyclic polymers present or with linear polymers were not reported. It was also mentioned that the multicyclic polymers tended to have

better solubility, which would be useful in any further physical and chemical studies.[70]

The potential for adhesive applications is mentioned in the paper by Hammami et al on polyacetals from iso-sorbide (entry 1).[69] The paper noted a very high viscosity during the synthesis of both the linear and cyclic polymers, and a lack of crystallinity in the final sample. This could combine well with the known tuneable rheology of cyclic and linear polymers in an adhesive application that warrants further investigation.

Tuneable Rheology through mixing with linear polymers

The difference in rheology between cyclic and linear polymers is particularly interesting, and the rheology of cyclic polymers is still yet to be fully defined, even though there has been lot of interest in this topic. This is because results have been markedly skewed by tiny quantities of linear impurities. As a result, the effects of mixing linear and cyclic polymers may be useful in applications such as rheology modification.

A paper by Kapnistos et al. studied highly pure cyclic polystyrene samples to ascertain their rheological nature (i.e. conformations, method of relaxing stress). [25] In order to test how linear contaminants affected the rheology of the cyclic polymers, the authors added small amounts of linear polystyrene of the same molar mass.

The polymers were doped with different concentrations of linear polymers of the same molar mass to see how this affected the zero-shear-rate viscosities. The difference in viscosity was substantial even at low concentrations of linear contaminant (the lowest dopant concentration was 0.0007 g cm^{-3}). Properties like the overall stress relaxation were also affected more than expected. The marked changes at a concentration well below the overlap concentration of the linear polymers implied that the isolated

17

Scheme 8: Scheme of the synthesis of cross-linked polyurethanes reported by Chen and co-workers[33]

cPCL via alkyne-azide ring closure method

(=M)

R =

or

Cross-linked polyurethane
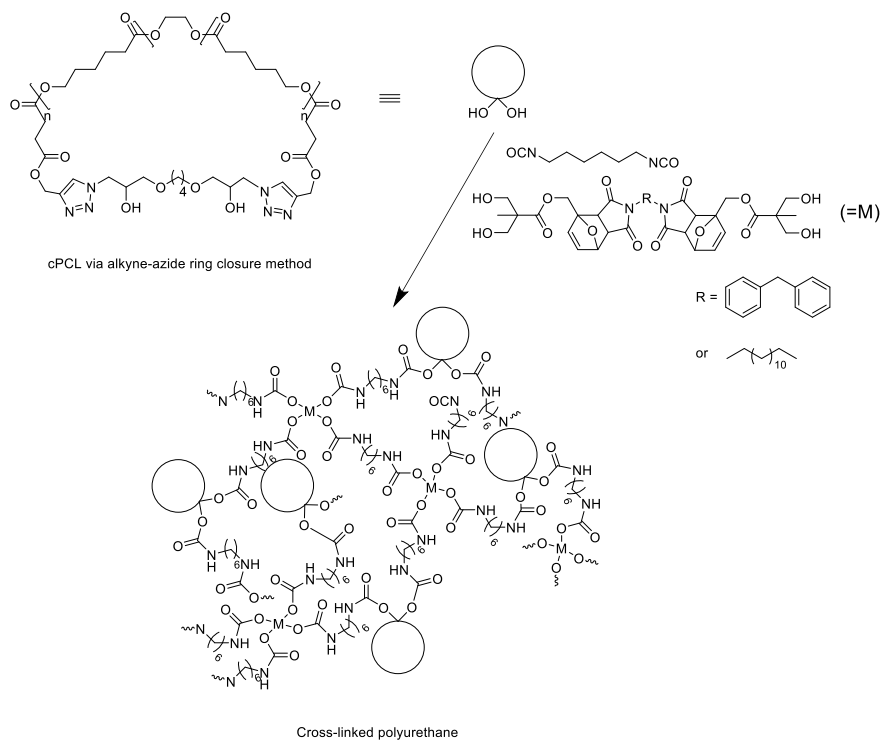
slow linear chains must have had to couple with each other substantially to produce this viscosity increase. It was proposed that the linear chains at this concentration were "bridged" by the cycles. The authors tested the effect of linear dopants on two samples and the sample of a larger molecular weight appeared to be much more affected by linear contaminants.

Linear contaminants have been reported to have had a substantial influence on the viscosity of cyclic polymers in other studies.[20] So far, the effects of the contrary approach (i.e. small amounts of cyclic "contaminants" in a linear polymer) have yet to be reported and doing so may help to rationalize the results seen here. These initial findings open up the possibility of tuneable rheology via mixtures of cyclic and linear polymers, as well as the possibility of quick access to viscosity changes by conversion between the two topologies provided the difference in their viscosities was significant. These would be useful features for biobased rheology modifiers.

Converting between cyclic and linear architectures could allow rapid access to different viscosities and properties, provided the effect on molecular weight was not substantial. Recently, Honda and co-workers developed a method of repeatedly converting between cyclic and linear architectures based on the photochemistry of hexaarylbiimidazoles (HABIs), but the ease with which a typical cyclic polyester could be converted to the linear form has yet to be studied and reported.[66] For the lactones, conversion to linear topology could likely be done with an alcohol capable of opening the cycle.

The lower viscosity and generally more lubricious nature of the cyclic topology may also provide general advantages in terms of processing and mass production areas. Viscosity is a crucial property when using equipment such as extruders for instance (although a lower viscosity does not necessarily mean the polymer is more applicable for this) and the ability to vary this among other properties through topology changes may help in the processing of products.[94] In addition, lower viscosity cyclic polymers are easier to stir and, if substantially different, the higher thermal stability means they could be used in higher temperature conditions.

Self-healing and Shape Memory Applications

Chen and co-workers tested the self-healing and shape memory abilities of polyurethanes based on cPCL, which were already well-documented for linear PCL. They synthesized cyclic PCL through azide-alkyne "click" chemistry, before forming the cross-linked polyurethanes as seen in Scheme 8.[33]

The shape memory capabilities were tested by heating films of these polymers, and it was found that the polyurethanes from both cyclic and linear PCL were able to form a temporary new shape when heated, as well as to recover the original shape when heated again. The only difference was that the authors found that the cyclic-based films were able to maintain their temporary shape for longer than the linear counterpart.

DMA was used to quantify this and the cyclic film tested had a higher fixing ratio compared to the linear version (95% to 80%). These results were rationalized by the dif-

ferent conformations of the two polymers, as the cyclic polymer chains could impose more positional restrictions compared to linear chains. The networks were thought to be more compact as a result.

The authors tested self-healing properties by making a crack in each film using a surgical blade before putting them in the oven. The crack had disappeared when the film was heated at 130 °C for 4 hrs and at 60 °C for a further 48 hours. The samples were able to recover their mechanical strength almost entirely after healing. The authors found no obvious differences in the self-healing capabilities between linear and cyclic films, although their sample was subjected to a substantial amount of heating. Using more varied temperatures and times to push the limits of the self-healing behaviour may uncover some differences between the two topologies.[33]

Bio-applications

The topic of bio-properties and applications has been mentioned in previous reviews and is not the focus of this paper, but it is important to note due to the well-known capabilities of polymers like PLA and PCL in bio-applications. The cyclic topology has been shown to provide improvements in an array of bio-applications, and the work on such properties for bio-based polymers is a promising avenue of research.[9,18,95]

Cyclic Polymers as Drug Carriers

It has been suggested that the cyclic topology would be superior in drug delivery applications (i.e. drug delivery time and solubility). Fox and co-workers looked at the effects of architecture on the ability of a polymer to act as a carrier for drug treatments in cancer, using PVA as an example.[96] The cyclic form showed longer blood circulation times in comparison to equivalent linear polymers due to the lack of chain ends and an increased resistance to deformation, which hindered reptation through pores of the kidney. However, branched polymers also showed drastic increases in blood circulation times and a direct comparison between branched and cyclic polymers was not men-

tioned in detail. A similar conclusion was reached by Nasongkla et al. in their studies of PCL-PEG cyclic copolymers.[97]

Elsewhere, Zhou and co-workers used azide-alkyne chemistry to synthesize tadpole shaped copolymers from PEG and PCL units, (Scheme 9). These were then compared to 4-arm star and linear variants with regards to drug loading capacities and in vitro cytotoxicity.

The tadpole polymer was the only variant containing a cPCL unit, and all 3 of the polymers were found to self-assemble into spherical nano-particles in aqueous solution, which could make them effective as potential nanoscale drug delivery systems; They also exhibited minimal cytotoxicity. The polymeric nanoparticles were loaded with a control drug to test release rates and behaviours. The release rates and behaviours were similar for both the tadpole and linear architectures, showing no obvious advantage to using the cyclic form.[34]

Micelle Studies

There have frequently been studies comparing micelles from cyclic and linear polymers, due to the differences in thermal stability and diffusion properties which would be useful for drug delivery applications. For instance, Honda et al.[98] tested micelles based on acrylic copolymers and reported significantly improved thermal stability for the cyclic topology by around 50 °C.

The authors also found that mixes of linear and cyclic copolymers gave micelles with a tuneable cloud point. It was suggested that this could be used in heat responsive applications to collect and release guest molecules (i.e. drugs).

The cyclic topology has also been seen to affect the aggregation of micelles, which could further aide in drug delivery applications. Yang and co-workers reported micelles of cyclic poly(N-vinylcaprolactam), a well-known thermoresponsive polymer which could have potential applications in catalysis, drug discovery and tissue engineering.[21] The cyclic variant had a lower LCST (Lower Critical Solu-

Scheme 9: Scheme of twin-tadpole shaped PCL/PEG copolymers synthesised via azide-alkyne click chemistry by Zhou et al.[34]

cPCL via alkyne-azide ring closure method
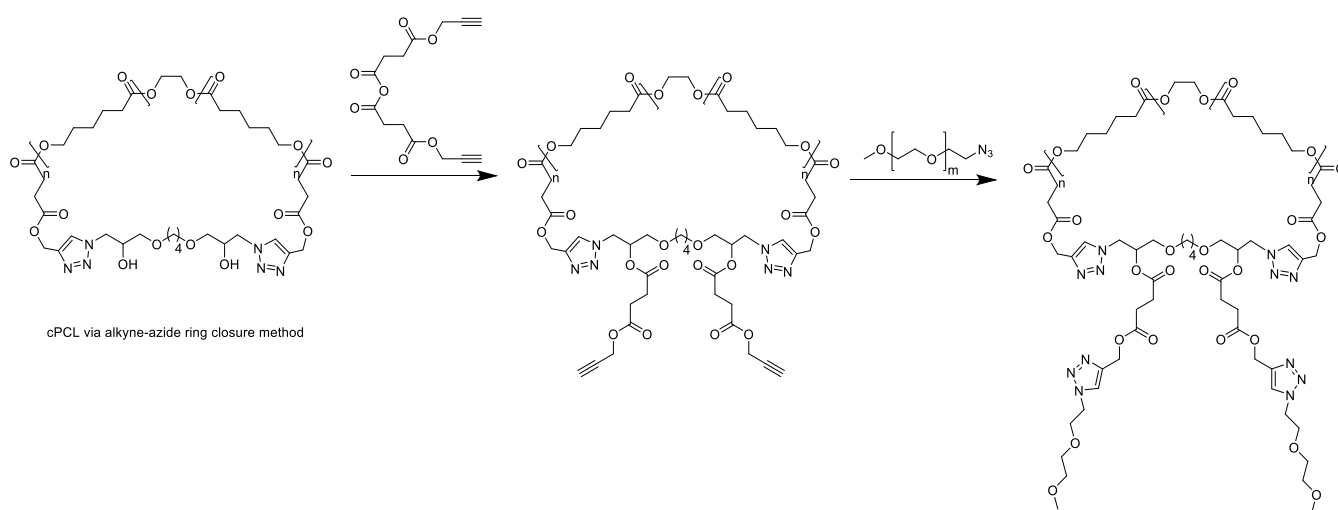
tion Temperature) and a narrower thermal phase transition range. Both linear and cyclic polymer samples formed nano-spherical micelles in water but the cyclic polymers able to form substantially smaller aggregates. This more compact form could potentially help with diffusion into the body.

Recently, Kang et al. reported the synthesis of micelles with cPCL moieties which were found to be more stable and to have a higher drug loading capacity. A tadpole shaped copolymer of cPCL and poly(ethylene oxide) was synthesized using the azide-alkyne RC method, similar to the tadpole-shaped polymers reported by Zhou et al. (Figure 15). The cyclic polymer micelle exhibited a two-stage degradation process due to an additional step required to open the cyclic polymer. This, as well as the stronger steric hinderance of the cyclic moiety, gave the cyclic micelle a greater stability.[99]

The advantage of greater stability is true for other physical forms of cyclic polymer, as was shown by Kelly and co-workers in their report of thin films of cPCL.[100] Interestingly, using cyclic films resulted in the suppression of the common problem of film dewetting. This was in spite of the fact that the physical property differences of the cyclic topology (i.e. lower viscosity, greater chain mobility than linear counterparts) should promote film dewetting processes.

Applications of Other Cyclic Polymers

Bio-based polymers have yet to be tested extensively in many cases and the number of studies on applications is limited. Cyclic polymers from other sources have received attention in different applications and, although the examples in the following section are not of polymers within the scope of this review, they have been included to cover more areas where the cyclic topology has been shown to be advantageous.

Photo-Responsive Applications

Cyclic azobenzene polymers by Xu and co-workers showed how topology can influence polymers with a chromophore. Azobenzene polymers have unique reversable photoisomerization properties, which can be useful in photo-responsive applications like optical data storage and liquid crystal displays. In the paper cited, the authors used azide-alkyne click chemistry to synthesize the first cyclic azobenzene polymer.[101]

The report compared the photoisomerization behaviours of the cyclic and linear forms under UV light of ~365 nm. The authors found that the cyclic polymer was slightly faster in terms of the rate of isomerization, potentially making it more suitable for these photo-responsive applications. This was specifically attributed to the lower degree of inter-chain entanglements that exist in the cyclic polymer samples.[101] The photoisomerization of azobenzene causes substantial changes in the properties of its polymers (such as size, shape, polarity etc), due to the motions involved in the isomerization process.[102,103]

Surface Functionalisation and Cartilage Repair

A study by Morgese et al. looked at the effects of polymer topology on the properties of polymer brushes for functionalisation of surfaces. The authors assembled grafts of poly-2-ethyl-2-oxazoline on titanium oxide surfaces and found that the smaller hydrodynamic radius afforded by the cyclic topology allowed for denser brushes. This is favoured in this application as it generates a better barrier to biological contamination from protein mixtures. This steric effect combines well with the lower viscosity of the polymer to give surfaces a "super-lubricating" character upon shearing.[104]

The same authors studied the methyl variant of this polymer and found the above advantages to also be useful for protection of cartilage against enzyme degradation. They used graft copolymers of hydroxybenzaldehyde-functionalized poly(glutamic acid) with cyclic poly(2-methyl-2-oxazoline) side chains. The polymer was able to chemisorb onto degraded tissue and form a film on the cartilage. As with the previous example, these films were more lubricious compared to the linear counterpart, and the resistance to biological entities helped to protect against degradation.[105] The superior lubricity and biorepellency may be advantageous various coatings applications, such as the hulls of ships.[106]

Conclusions and Future Outlook

In recent times, researchers have overcome a multitude of synthetic challenges for cyclic polymers, and there has been increasing attention paid to those made from some of the most promising bio-based monomers. High molecular weight cyclic polymers with reasonable purity are now accessible, and several synthetic methods are available depending on the goal of the user (i.e. the use of alkyne-azide click chemistry to give lower Đ values or more complicated structures,[33,34] or the use of metal catalysts to form very high molecular weight cyclic polymers).[11] While the RC approach is currently imperative for the production of polymers with extremely low Đ values, for studies of properties such as crystallization behaviours, we would expect to see it used less frequently as the open questions regarding cyclic polymers are answered, especially given the huge developments in REPs which can now give similarly low Đ values themselves. Initial reports of metal catalysts with NHC ligands have shown fantastic results,[45] and this approach may be the future of efficient, controlled syntheses of large cyclic polymers.

So far, the cyclic topology has been briefly tested using bio-based aliphatic polyesters in a range of possible applications, and they have been found to be uniquely advantageous in catalysis, shape memory and various bio applications. There are still key areas that remain to be studied, such as rheology modification, and some of the applications have only been assessed crudely and require more attention (e.g. thermoset and adhesive applications).

The future outlook for cyclic polymers is bright, and the synthetic developments have advanced to a point where practical applications and properties can now seriously be considered. Exploring polymers in cyclic form offers potential for wider application and sustainability of bio-based and related aliphatic polyesters, as the distinct properties

afforded by this unique topology may help to give bio-based polymers the versatility needed to transition into more mainstream use. The level of attention on lactide and caprolactone is very encouraging, and there is an array of other bio-based monomers which merit further attention (i.e. butyrolactones and isosorbide). The possibility to generate materials with different properties from the same monomer via polymer topology is also key to reducing the number of different components in a material which need to be recycled.

The use of bio-derived polymers combined with the work towards better end-of-life options for all polymers is the type of approach that is needed to tackle the global problem of plastic pollution. With the ever-increasing interest in cyclic polymer research, we expect to see this variation in topology to soon be considered in the same way as a novel monomer or different polymer tacticity is considered as an option for new and unique materials. In addition, the optimisation of cyclic polymers from other monomers (as highlighted in table 2) is a clear next step in the synthesis of cyclic polymers, and the challenges posed by these endeavours will further expand our knowledge and proficiency in their synthesis. This has become especially apparent in the past few years given the ease with which cyclic products can now be accessed (e.g. the use of $Sn(Oct)_2$ with a catechol co-initiator by Kricheldorf and co-workers).[38]

However, there are still challenges to be addressed if we are to see cyclic polymers in commercial use, as the advantages they provide are not yet worth the difficulties of mass-production. Obtaining cyclic polymers which are highly pure has been an issue from the beginning, and many of the papers highlighted here merely present evidence for the cyclic structures from MALDI-TOF and NMR, but these methods may not be able to see trace impurities. For instance, MALDI-TOF may not give a bulk analysis of the polymer and NMR is not sensitive enough to see trace end groups if they are present. The introduction of new purification methods such as LCCC (and previously mentioned SEC analytical method by Shi et al.[24]) have shown great promise meaning highly pure polymers are now more within reach, although it remains to be seen if efficient purification could be implemented on an industrial scale. Other purification methods have been reported with encouraging results as well, such as temperature gradient chromatography and electrospray ionization tandem mass spectrometry.[107–109] Developing these methods in addition to ways of quantifying purity is key to consistent, large-scale production. The unique nature of cyclic polymers compared to linear impurities means that there are many possible opportunities to separate and quantify the two in a given mixture (i.e. by differences in thermal stability, rheology, Tg etc).

The further combination of novel analytical techniques and cyclic polymers should be encouraged as further characterization and identification of these materials is needed. For instance, the use of Diffusion-Ordered NMR spectroscopy (DOSY) may be particularly useful given the differences in hydrodynamic radii of cyclic and linear polymers.

This, among other differences, may allow for better analysis and characterization of cyclic polymers. So far, DOSY experiments have only been reported in one instance with cyclic polystyrene by Zhao and co-workers.[110] This study revealed a non-free draining effect in very small cycles in which the cycle shows a larger hydrodynamic radius to the linear counterpart. Diffusion NMR experiments have also been reported on cyclic biomacromolecules such as peptides, and further use of this technique with cyclic polymers would be useful.[111]

These challenges and questions remain despite the substantial improvements and interest in the field of cyclic polymers, and the fact that researchers can now look to issues such as commercial scale-up and applications is highly promising, especially considering the basic synthetic challenges that were present only a decade ago. The new developments in synthesis coincide nicely with the ever-increasing attention on environmentally friendly polymers, and a combination of the two could prove to be very beneficial as concerns over plastic pollution are pushed further to the forefront.

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Author Contributions

The manuscript was written through contributions of all authors.

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ABBREVIATIONS

cPLA, cyclic Poly(Lactide), cPCL, cyclic Poly(ε-caprolactone), REP, Ring Expansion Polymerization, RC, Ring Closure Polymerization, $Sn(Oct)_2$, tin(II) 2-ethylhexanoate, Đ, Poly dispersity index

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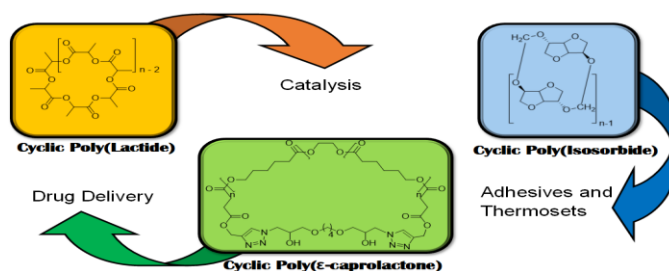
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