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Advanced Developments in Cyclic Polymers: Synthesis, Applications, and Perspectives

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Due to the topological effect, cyclic polymers demonstrate different and unique physical and biological properties in comparison with linear counterparts having the same molecular-weight range. With advanced synthetic and analytic technologies, cyclic polymers with different topologies, e.g. multicyclic polymers, have been reported and well characterized. For example, various cyclic DNA and related structures, such as cyclic duplexes, have been prepared conveniently by click chemistry. These types of DNA have increased resistance to enzymatic degradation and have high thermodynamic stability, and thus, have potential therapeutic applications. In addition, cyclic polymers have also been used to prepare organic–inorganic hybrids for applications in catalysis, e.g. catalyst supports. Due to developments in synthetic technology, highly pure cyclic polymers could now be produced in large scale. Therefore, we anticipate discovering more applications in the near future. Despite their promise, cyclic polymers are still less explored than linear polymers like polyolefins and polycarbonates, which are widely used in daily life. Some critical issues, including controlling the molecular weight and finding suitable applications, remain big challenges in the cyclic-polymer field. This review briefly summarizes the commonly used synthetic methodologies and focuses more on the attractive functional materials and their biological properties and potential applications.

1 Introduction

Polymers can be structurally classified as linear or cyclic. Due to their topology and lack of chain ends, cyclic polymers are more compact and, thus, display smaller hydrodynamic volumes than their linear analogues. Therefore, cyclic polymers generally display unique physical properties such as higher glass-transition temperatures (T_g), lower intrinsic viscosities, and longer retention times (t_R) by gel permeation chromatography (GPC).[1–3] Following advanced developments in analysis technology, structures of the cyclic polymer can now be well characterized by GPC, NMR spectroscopy (no end groups can be identified), matrix-assisted laser desorption/ionization–time of flight mass spectrometry (MALDI-TOF MS) and Fourier-transform infrared spectroscopy (FT-IR) besides the conventional measurement of intrinsic viscosities and UV absorption. Although it has been more than 100 years since the first report on a cyclic polymer,[4,5] this special area still hasn't been well explored, both in synthetic technology and applications in comparison with the linear counterparts. Although most of the existing functional materials are based on linear polymers, increasing effort is now given to cyclic polymer research in order to develop new synthetic protocols and new functional materials with unique properties and potentially important applications.

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2 Generalization of Existing Synthetic Styles

Two existing styles, namely ring-closing and ring-expanding polymerizations, are commonly used to prepare cyclic polymers.[1–3] Between them, ring-expansion technology is recognized as more attractive and practical because it generally produces highly pure cyclic polymers from a relatively high concentration of monomers. Therefore, this protocol might be more suitable for industry processes. On the other hand, ring-closing polymerization usually needs to be carried out in an extremely dilute solution of monomers, which limits their scale-up capabilities. Recent reviews have summarized the two methods well.[6–10] This review shortly summarizes the synthetic methodology by amending it with fresh reports and mainly focusing on special properties and potential applications.

2.1 Ring-closing technology

Various methods have been explored to chelate the two ends of a linear polymer and, thus, form the corresponding cyclic polymer.

2.1.1 Click reaction

The catalytic azide (N_3)–alkyne (–C≡CH) 1,3-dipolar cycloaddition, commonly called the "click" reaction, usually occurs in

mild reaction conditions with high yields and good functional group tolerance. It was first introduced to cyclic polymer chemistry by Laurent and Grayson in 2006.[11] Significant achievements have been made following the introduction, and plenty of cyclic polymers have since been reported.[6,12–26] The click reaction has also been applied to construct multiring complex topologies from azide–alkyne multifunctional cyclic polymers.[26–30] Complex polymer structures such as bridged and spiro-tricyclic, tetracyclic, pentacyclic and heptacyclic topologies with 1,2,3-triazole links, as shown in Figure 1a, have

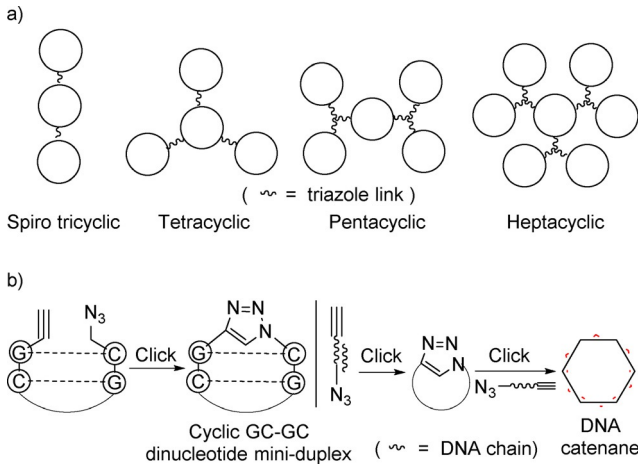

Figure 1. Multicyclic polymers prepared by click cycloaddition. 1a reproduced with permission from Ref. [26]. Copyright 2014, American Chemical Society. 1b reproduced with permission from Ref. [33]. Copyright 2012, American Chemical Society.

been synthesized.[26–30] Alkynes and azides can also be conveniently attached to linear nucleic acids to undergo click reactions to form cyclic mini-DNA duplexes and DNA catenane as described in Figure 1b. Nucleic acid ligations by click reaction have been well summarized in recent reviews,[31–33] and, therefore, a similar detailed description in this report is repetitive and unwarranted. However, the inherit drawbacks, such as requirement of a highly dilute reaction medium and presence of Cu^{I} catalyst species during the reaction course, may limit its commercial applications such as in drug delivery or gene delivery.

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2.1.2 Electrostatic-assembly-oriented tandem cyclization (backbiting and covalent fixation)

In this method, electrostatic assembly occurs oriented by interaction between a quaternary ammonium cation and a carboxylic anion to form a cyclic ionic complex which further undergoes either substituted or covalent formation reactions to generate the cyclic polymers as shown in Figure 2.[29,34–45] Cyclic polymers produced from this method also have been functionalized with $-C{\equiv}CH$ and $-N_3$ groups, and thus enable constructing topologically different cyclic polymer composites, such as bridged and spiro multicyclic topologies, via click cycloaddition reactions.[29]

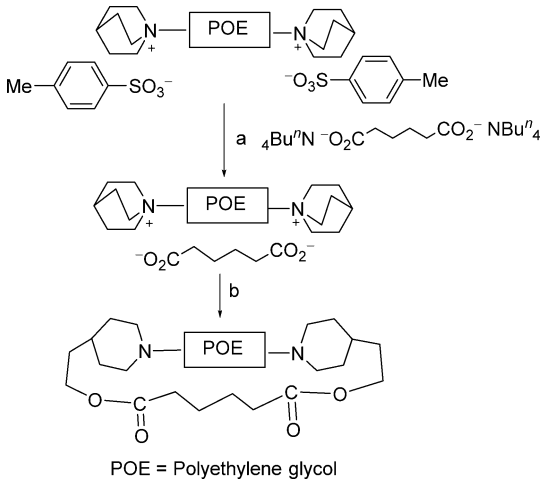

Figure 2. Cyclization via backbiting and covalent fixation. *Reagents and conditions*: a) acetone, 0°C, 0.5 h, 99%; b) toluene, reflux, 30 h, 100%. Reproduced with permission from Ref. [39]. Copyright 2002, American Chemical Society.

2.1.3 Self-condensation

Intermolecular condensation of N-benzylated phenyl *p*-aminobenzoates in the presence of lithium bis(trimethylsilyl)amide (LiHMDS) could form a three-membered triangular cyclic aramide (Figure 3).[46] After deprotection of *N*-(*o*-alkoxybenzyl) protecting groups, cyclic tri(*p*-benzamide) was obtained. The macro cycle exhibited a highly ordered two-dimensional orientation on calcite surfaces.[46]

2.1.4 Diels–Alder (*D–A*) addition ([4+2])

Intramolecular [4+2] reaction of a linear α-maleimide-ω-cyclopentadienyl-functionalized polymer results in a well-defined highly pure cyclic polymer upon heating at high dilution.[47] The more convenient UV-induced [4+2] cycloaddition between end groups of photoenol and dithioester has also been reported, as shown in Figure 4.[48] The method combined a reversible addition–fragmentation chain transfer (RAFT) polymerization and UV-induced Diels–Alder addition.[48] The authors claimed the method was a powerful and convenient ring-closure technique.

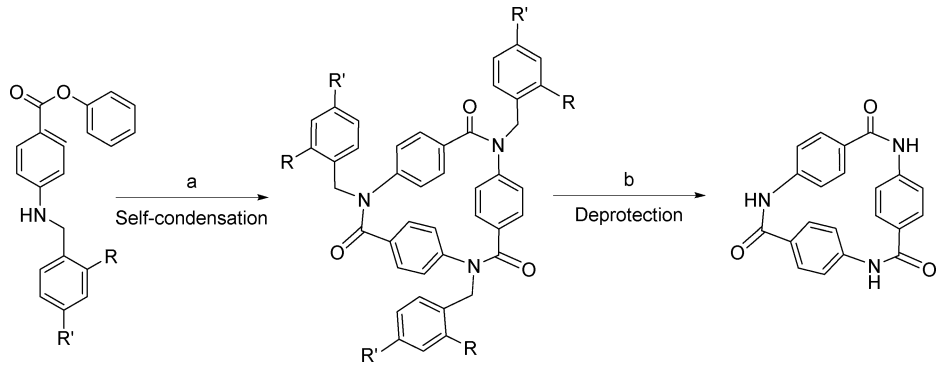

Figure 3. Condensation reaction to synthesize cyclic polymers. *Reagents and conditions*: a) lithium bis(trimethyl silyl)amide, tetrahydrofuran (THF), rt, 18 h, 33—52%; b) trifluoroacetic acid, triisopropylsilane, 65 °C, 18 h, 43%. Reproduced with permission from Ref. [46]. Copyright 2014, American Chemical Society.

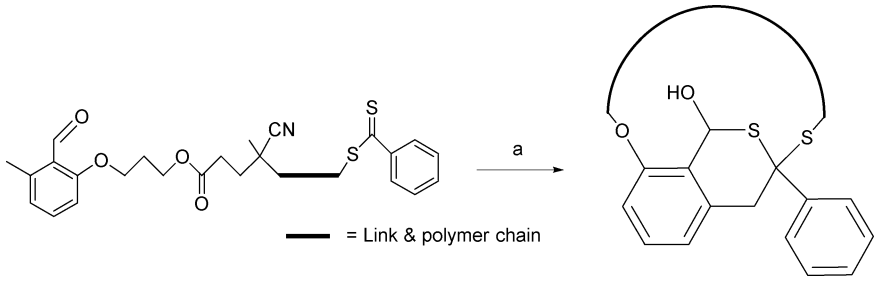

Figure 4. Light-induced D–A reactions to synthesize cyclic polymers. *Reagents and conditions*: a) UV light, 2:1 CH_3CN/CH_2Cl_2 (*v/v*), rt, 9 h, 100%. Reproduced with permission from Ref. [48]. Copyright 2014, American Chemical Society.

2.1.5 Intramolecular oxidation of thiol telechelics to form a disulfide bridge (S–S) and thus close the ring[49,50]

$FeCl_3$ and air were used as oxidants to carry out the reactions.[49,50] Interestingly, the S–S link in cyclic polymers could be easily broken via a reduction reaction by zinc powder to form linear polymers, as shown in Figure 5.[49]

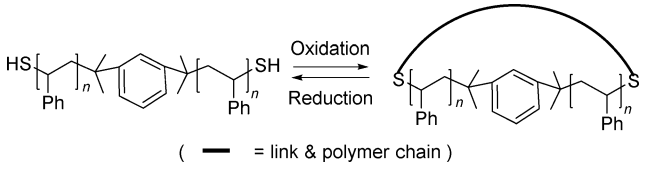

Figure 5. Formation of S–S bond for cyclization. Reproduced with permission from Ref. [49]. Copyright 2006, American Chemical Society.

2.1.6 Formation of the CO–NH bond

The classical intramolecular amidation of a linear polymer with $-NH_2$ and $-CO_2H$ end groups leads to the formation of a cyclic peptide (Figure 6).[51,52] Microwave irradiation has been used to promote formation of the CO–NH bonds. For example, microwave irradiation allows the efficient conversion of the amide of maleic acid to cyclic poly(aspartic acid), with a reaction efficiency of above 93%.[53]

2.1.7 Cyclization-cleavage cyclization

A polymer support enriched with functional groups such as $-NH_2$ and –OH is commonly used in this method (Figure 7). After an intramolecular cyclization, the cyclic polymer can be released into the solution phase. However, due to other competing reactions, the obtained products require further purification.[54–56]

2.1.8 Intra and intermolecular electrophilic substitutions

Bifunctional linear polymers that have a general structure of A–polymer chain–B (A and B represent functional groups e.g. halide, carbon anion, or amine) may react with bifunctional links, such as C–link–D (C and D being functional groups e.g. amino, halide), in a stoichiometric amount to form a cyclic polymer.[57–64] For example, Br–polymer chain–Br reacts with H_2N–link–NH_2 to generate covalently bonded cyclic [–HN–link–NH–polymer chain–] and release two HBr molecules, as shown in Figure 8.[63]

2.1.9 Atom-transfer radical coupling (ATRC)

Chen and co-authors reported that a star-shaped polymer with bromine terminal groups may conduct intramolecular end–end coupling to form cyclic polymers. As shown in Figure 9, two

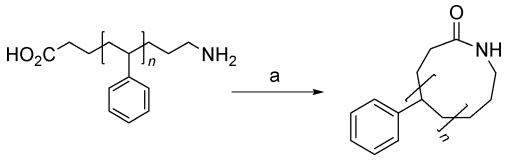

Figure 6. Formation of CO–NH bond for cyclization. *Reagents and conditions*: a) high dilution (1.4×10^{-4} M), 1-methyl-2-chloropyridinium iodide, NBu^n_3, 62%. (Reproduced with permission from Ref. [51]. Copyright 1997, American Chemical Society.

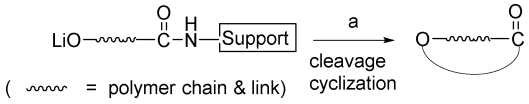

Figure 7. Cyclization cleavage for cyclic polymer synthesis. *Reagents and conditions*: a) benzene, rt, 18 h, 22%. Reproduced with permission from Ref. [55].Copyright 2006, The National Academy of Sciences.

topological isomers could be prepared. In addition, the bridge S–S bonds could be further broken to generate new cyclic polymers.[65]

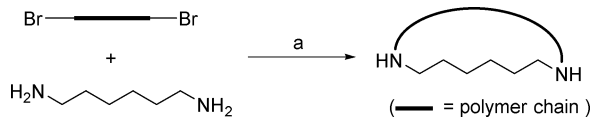

Figure 8. Preparation of cyclic polymers by bromomaleimide-thiol substitution reaction. *Reagents and conditions*: a) dimethyl formamide, 100 °C, 46 h, 83–100 %. Reproduced with permission from Ref. [63]. Copyright 2001, American Chemical Society.

2.1.10 Ring-closing olefin-metathesis coupling

The method is applicable to a bisallylic-ended polymer (CH_2=CH–polymer chain–CH=CH_2→[=CH–polymer chain–CH]). In the procedure, the reactions were carried out with Grubb's catalysts under ultradilute conditions to repress the linear products.[66–69]

2.1.11 Ring-closing addition

This efficient technique closes an iodo end group and styrenic end group of a linear polymer by a ring-closing addition to an end carbocation derived from a C=C bond in the presence of a tin complex.[70–73] Alternative closing methods such as UV-initiated C–C formation from an end C=C bond (CH_2=CH–polymer chain–CH=CH_2→[–CH_2–polymer chain–CH_2–]) have also been reported.[74]

2.1.12 Solid-phase synthesis and self-assembly

These methods are developed to efficiently synthesize cyclic DNAs. As shown in Figure 10,[75,76] in the solid-phase procedure, protected oligonucleotides are immobilized on a solid support; cyclization occurs spontaneously during deprotection of the oligonucleotide in good yield of up to 78 %.[75,76] Functionalized DNA oligomers have been reported to form ordered arrays via cyclic self-assembly with an average diameter of ~12.7 nm.[77] The cyclic array is more thermally stable than the linear array.[77]

2.2 Ring-expansion reactions

Ring-expansion polymerization methods continue to attract more interest due to their high potential in improving product purity and quantity. Theoretically, the method could produce highly pure cyclic polymers because it would not generate linear intermediates. However, the difficulty in controlling molecular weight has to be addressed. The commonly used ring-expansion methods are summarized in the following sections.

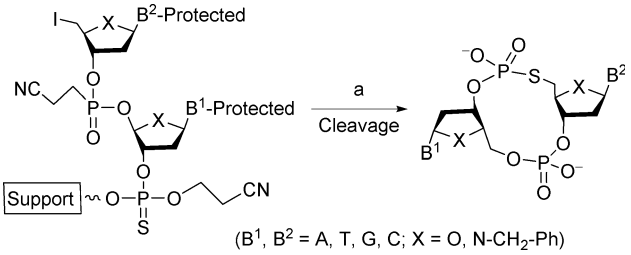

Figure 10. Synthesis of cyclic DNA by solid-phase reaction. *Reagents and conditions*: a) NH4OH (aq), rt, 24 h, 80 %. Reproduced with permission from Ref. [76]. Copyright 2007, American Chemical Society.

2.2.1 Ring-opening metathesis catalyzed by cyclic ruthenium complexes

The method was first reported by Grubbs et al., and demonstrated to be a powerful ring-expansion method (shown in

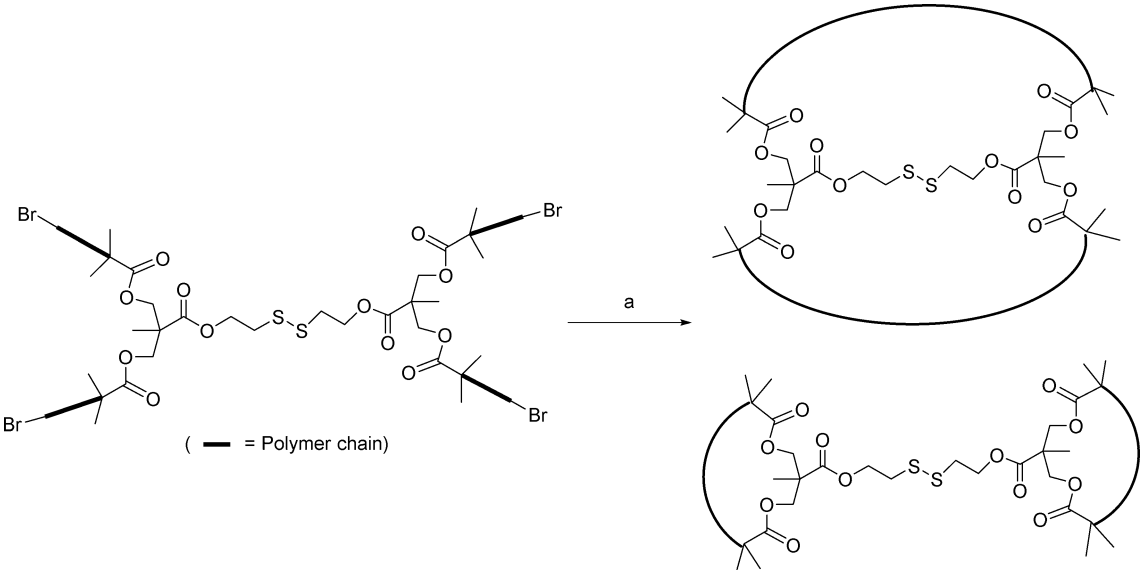

Figure 9. Formation of cyclic topology isomers via intramolecular ATRC. *Reagents and conditions*: CuBr/Cu/Me_6Tren, THF, rt, 28 h. Reproduced with permission from Ref. [65]. Copyright 2014, American Chemical Society.

Figure 11).[78] It made it practical to produce highly pure cyclic polyolefins in large scale from a relatively high monomer concentration.[78] The ruthenium-based catalysts are tunable to produce pure cyclic polyolefins.[79–82] The resulting cyclic polyolefins are liable to be functionalized to build polymer complexes, metallo-supramolecular cyclic polymers, and derived gels.[82–84] However, it is difficult to control the molecular weight with this method due to the absence of reliable chain ends, particularly for the much smaller cyclic polymers of less than ~85 kDa.[82–84] Nevertheless, the larger cyclic polymers can be controlled by optimizing reaction conditions. This issue is becoming more important and needs to be addressed successfully, because polymer samples with various sizes and narrow polydispersity index (PDI) need to be tested to investigate the real potential of the technique. In this regard, new olefin metathesis catalysts are expected to produce cyclic polymers with acceptable molecular weight control.

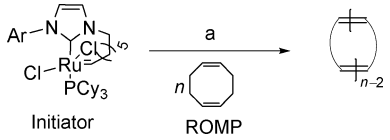

Figure 11. Synthesis of cyclic polymers by ring-opening metathesis reaction (ROMP). *Reagents and conditions*: a) 1,5-cyclooctadiene, CH_2Cl_2, 45 °C, 12 h, 83–95 %. Reproduced with permission from Ref. [79]. Copyright 2003, American Chemical Society.

2.2.2 Organotin-initiated ring expansion

In these reactions, organotins such as $R_2Sn(OR')_2$ initiate the polymerization by breaking a O–C bond in a cyclic ester to produce new expanded organotin complexes. The processes can be repeated and can form tin-containing cyclic polymers. Figure 12 shows an example for the ring-expansion reaction. Here, the molecular weights are difficult to control because they are not related to the monomer/initiator ratio.[74,85–91] Furthermore, the remaining tin species raise several issues regarding the polymer hydrolysis and toxicity, given their potential applications. Therefore, it is necessary to remove the retaining tin species while maintaining the cyclic structures. In this regard, a couple of methods have been developed, either to exchange the tin groups with other links[90] or further cross link the branch chains to form a new macrocycle.[74]

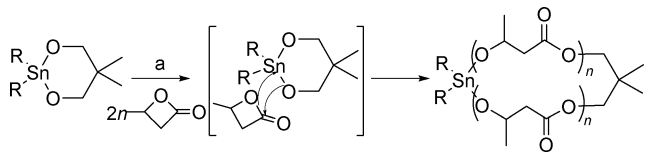

Figure 12. Synthesis of cyclic polymers by organotin initiator. *Reagents and conditions*: a) CH_2Cl_2, 75 °C, 6 d, 95 %. Reproduced with permission from Ref. [85]. Copyright 1995, American Chemical Society.

2.2.3 Reversible addition-fragmentation chain-transfer reaction

It has been reported that the molecular weights of the resulting cyclic polymers are related to reaction time. Therefore, the controlled-free-radical ring-expansion cyclic polymerization may produce polymers with well-controlled molecular weight and ring size. The interesting approach can extend to all the monomers that can conduct controlled radical polymerization to prepare functional cyclic polymers. Cobalt-60 γ-radiation and azobisisobutyronitrile (AIBN) have been used to initiate the chain transfer reactions, as shown in Figure 13.[92,93]

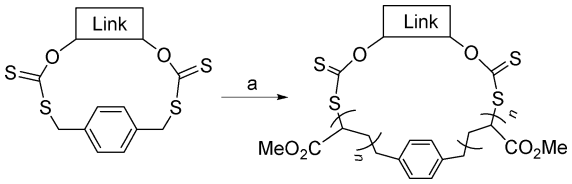

Figure 13. Reversible chain transfer reaction initiated by ^{60}Co-γ-irradiation. *Reagents and conditions*: a) methyl acrylate (MA), ^{60}Co γ-irradiation, THF, −30 °C, 4 h, 52 %. Reproduced with permission from Ref. [92]. Copyright 2003, American Chemical Society.

2.2.4 Zwitterionic ring-opening polymerization (ZROP)

Similar with other ring-opening polymerization (ROP) reactions, the driving force for zwitterionic ring opening is the ring strain and related steric considerations. The ZROP generally starts from an addition reaction of a neutral organic nucleophile with a strained monomer, followed by ring expansion to produce cyclic polymers, as described in Figure 14. Waymouth et al. summarized the recent progresses in *N*-heterocyclic-carbine-(NHC) and various amine-mediated ZROP, as well as the proposed mechanisms.[94] NHC-initiated reactions hold a high priority due to the variable NHC structure and highly efficient and fast reaction procedure, e.g. reactions take a few minutes under mild conditions (room temperature). Various cyclic polyesters have been prepared by the NHC-catalyzed ROP.[94]

Considering the depletion of fossil-based material resources and the ultimate fate of the large-scale commodity polymers, synthesis of cyclic polymers from renewable resources has become increasingly important. Therefore, within the reported cyclic polymers, cyclic polyesters from biodegradable monomers, such as lactide and ε-caprolactone, have attracted more interest within the community.[94–97] The use of metal-coordination initiators catalyzing ROP of cyclic ester monomers is widely recognized as an efficient process to produce linear polyesters with well-controlled molecular weights, compositions, and microstructures.[98,99] However, the residual metal impurities which are cytotoxic, may limit the wide applications of the derived polymers, particularly pharmaceutical and biomedical. Removal of the cytotoxic species from polymer products to meet the application requirements is compulsory, but the technology is difficult and costly.

On the other hand, various NHC-based organo-initiators have been developed for the ROP of cyclic ester monomers to

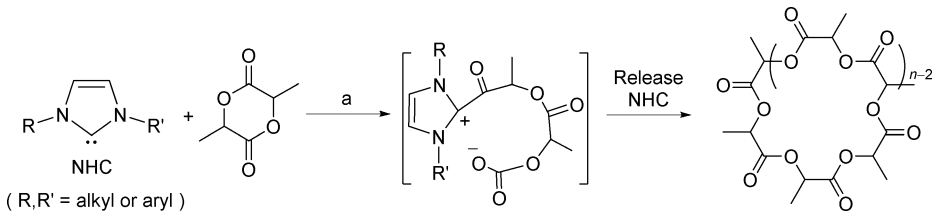

Figure 14. Synthesis of cyclic polymers by zwitterionic ring opening. *Reagents and conditions*:a) THF, 25 °C, 10 min, 81 ~ 97 %. Reproduced with permission from Ref. [95]. Copyright 2011, John Wiley and Sons.

produce corresponding cyclic polyesters.[94] NHC catalysts are generally air and moisture sensitive, and that makes it inconvenient to scale up the process. Zhu, et al have reported that an NHC catalyst produced in situ from 1-methyl-3-menthoxymethyl imidazolium chloride (Figure 15) is relatively robust and

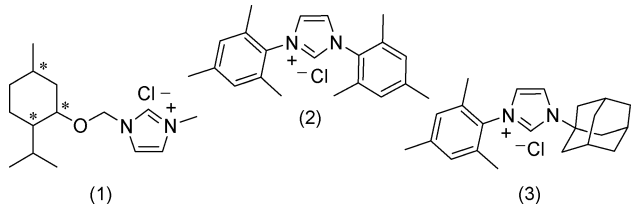

Figure 15. Structures of *N*-heterocyclic-carbine (NHC)-based catalyst precursors. Reproduced with permission from Ref. [96]. Copyright 2012, John Wiley and Sons.

highly active for the ROP to produce polylactones.[95–97] The NHC precursor is much cheaper and more active in comparison with the commonly used 1,3-bisarylimidazolium chloride (Figure 15. It was first reported that NHC carbene derived from enantiomeric forms of (+)-1-methyl-3-menthoxymethyl imidazolium chloride precursor displayed higher activity towards L-lactide (L-LA, with a product yield of 80 wt%, molecular weight (M_w) of 69404 and molecular weight density (MWD) of 1.89) than D-lactide (D-LA, with a product yield 40 wt%, M_w of 27224 and MWD of 1.64) with significantly high molecular weight.[95] The NHC catalyst also showed high activity for ε-caprolactone and δ-valearolactone zwitterionic ROP to form corresponding cyclic poly(ε-caprolactone), cyclic poly(δ-valearolactone), and cyclic poly(ε-caprolactone-co-δ-valearolactone) respectively.[82] The authors also found that the M_w of polycyclic lactide could be controlled either by changing ratios of [L-LA]/[catalyst] or performing the reaction at different temperatures. A higher mole ratio of [L-LA]/[catalyst] produced lower-M_w polymers. The results suggest that higher-M_w cyclic polymers are partially generated from an ROP of initially formed cyclic polymers with lower M_w, called macromonomers. A high mole ratio of [L-LA]/[catalyst] produces less amount of the macromonomer under the reported conditions and, thus, forms lower-M_w cyclic polymers. Under the same conditions, the polymerization conducted at room temperature produced higher-M_w polymers (M_w ~ 74000, MWD 2.02) than at 0 °C (M_w ~ 20700, MWD 1.46).[95]

3 Potential Applications of Cyclic Polymers

Compared with linear isomers, cyclic polymers always display different properties that could lead to unique applications. Unlike linear polymers which have been well explored and widely used in industry, cyclic polymers have many areas for improvement. These innovations include both synthetic methodologies and application investigations. To date, producing cyclic polymers in an industrial scale is impractical and, thus, the community should look for high-value-added products and find special applications where the normal linear polymers do not meet all the requirements. Some interesting properties and related potential applications are summarized below.

3.1 Macromolecular functional precursors

Well-designed cyclic polymers allow for further modifications to build up more complicated cyclic polymers. For example, various topologically different cyclic polymer composites have been prepared from the azide—alkyne-functionalized monocyclic polymer by click reactions.[1–12] The resulting multicyclopolymers have been able to form functional gels. As summarized in a recent review, these gels displayed good tensile strength and a large swelling capacity compared to the gels obtained from cross-linking linear polymers.[84] Unlike linear gels, which are well consistent with theoretical scaling predictions, the cyclic gels show a big deviation from the classic scaling models due to their inherent chemical structures.[84] It is highly expected that novel gel materials with advanced gel properties could be prepared by marrying the cyclic topology effects with the classical network concepts based on linear gels.

Potential differences in the biodistribution and pharmacokinetics of linear and cyclic polymers are also possible. An early work shows that water-soluble cyclic polyethylene-glycol-decorated (PEGylated) poly(acrylic acid) comb polymers had a significantly longer elimination time (up to 33% longer) and a great tumor accumulation in comparison with the linear counterparts in the same mass range. (Figure 16).[22] It is believed that the cyclic topology caused the increased blood circulation time and tumor uptake among polymers of similar molecular weights. After further development, optimized cyclic polymers could be identified to improve the targeted drug delivery system.

Janda et al. reported that a matrix composited by a cyclic peptide (11-mer) and poly(ethylene maleic anhydride) can specifically bind to a Botulinum neutrotoxin serotype A enzyme-linked immunosorbent assay (ELISA) without cross-interacting with other serotypes.[52] The selectivity has been demonstrated in the examined assay buffers, a variety of body fluids, and food stuffs with high sensitivity of 1 pg mL^{-1} in 3 h. The authors claimed that the cyclic-peptide-based capture system could be used for rapid, sensitive, and specific Botulinum neu-

trotoxin serotype A detection. Also, the methodology is robust, inexpensive, and simple.[52] Smaller constrained cyclic peptide oligomers have shown exciting potential in drug discovery applications such as for inflammation pain and cancer, and these have been highlighted in recent reports.[100–103]

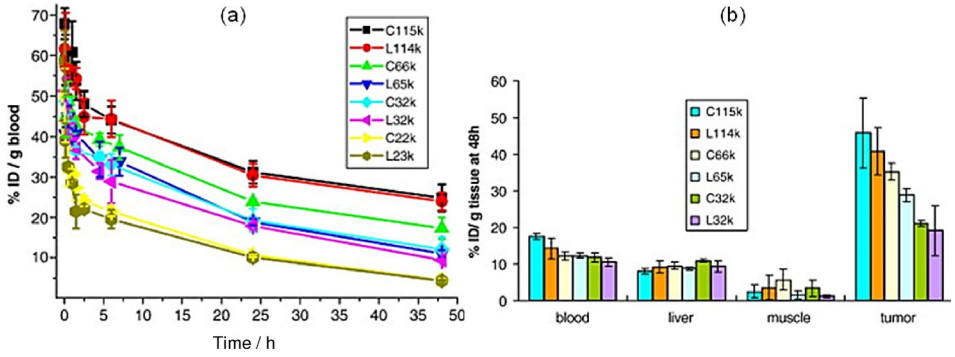

Figure 16. Blood circulation profiles (a, C = cyclic polymer; L = linear polymer; k = kDa) and tissue concentrations (b) of cyclic and linear polymers. Reproduced with permission from Ref. [22], "The influence of polymer topology on pharmacokinetics: differences between cyclic and linear PEGylated poly(acrylic acid) comb polymers". Copyright 2009, Elsevier.

3.2 Formation of thermally stable micelles

Yamamoto et al. reported that a self-assembled micelle from a cyclic polymer, cyclic poly(butyl acrylate)$_{2n}$-block-poly(ethylene oxide)$_m$, displayed significantly improved thermal stability compared with micelles formed from a linear polymer, poly(butyl acrylate)$_n$-block-poly(ethylene oxide)$_m$-block-poly(butyl acrylate)$_n$, due to a topology effect.[68] With similar compositions and structures of micelles, the micellar solution of linear polymers was not stable even at 25 °C, whereas the cyclic counterpart was stable until over 70 °C as shown in Figure 17.[68] Interestingly, the thermal stability of a micelle produced from linear and cyclic polymer mixtures is closely related to the mixing ratios of cyclic and linear polymers and, thus, could be tuned conveniently.[68] The topology structure of suppressed bridging effects by the cyclo-macromolecules is believed to cause the difference.[20–33] The remarkable difference could lead to important biological applications, such as drug delivery by designing heat-responsive molecular devices to enclathrate and release guest molecules.

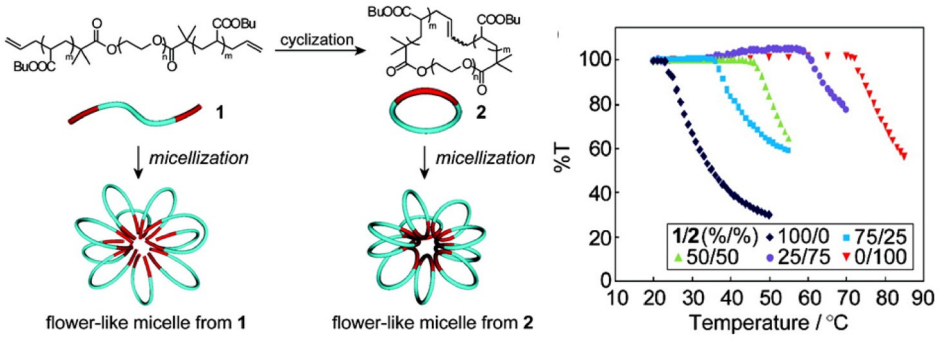

Figure 17. Thermal behavior of linear- and cyclic-polymer-derived micelles. Reproduced with permission from Ref. [68]. Copyright 2010, American Chemical Society.

Grayson et al. have reported the preparation of cyclic amphiphilic homopolymers by click cycloaddition.[18] The cyclic polymers dissolve in various polar solvents and are capable of forming micelles. The resulting micelles demonstrated the efficiency of encapsulate guests such as the water-soluble dye Rose Bengal, in nonpolar toluene solvent. The encapsulation capability was nearly identical to that of micelles produced from linear polymers.[18]

3.3 Enhancement of fluorescence

Recently, cyclic poly(4-vinylbenzyl)carbazole (PVBCZ) has been synthesized by successive combination of atom-transfer radical polymerization and an intramolecular end-to-end click reaction.[14] Cyclic PVBCZ displayed an enhanced fluorescence with a remarkably longer fluorescence life time in comparison with its linear counterpart. With the improved properties, a few potential applications have been perceived such as in organic optoelectronic devices and rapid identification of the cyclic structure.[14] Cyclic polymers containing azobenzene (–N=N–$C_6H_4^-$) species also exhibited increased fluorescence emission, as well as surface-relief-grafting formation when compared with their linear counterparts.[15,16] In addition, cyclic azobenzenes show faster *E*-to-*Z* and slower *Z*-to-*E* isomerization rate (referring to the N=N bond).[13,15,16,24]

3.4 Preparation of organic–inorganic hybrids

Recently, the NHC catalyst precursors have been successfully intercalated into clay (closite Na^+) by a cation-exchange reaction.[97] The intercalated precursor can be further deprotonated to form in-situ-generated NHC, which is active for ROP of lactides, to produce a cyclic polylactide-clay hybrid. According to X-ray diffraction (XRD) analysis, the cyclic poly(L-lactide)s are intercalated in the silicate galleries, as shown in Figure 18. However, it is difficult to determine the individual quality of intercalation and exfoliation.[97] Interestingly, palladium(0) nanoparticles have been supported on the organic–inorganic

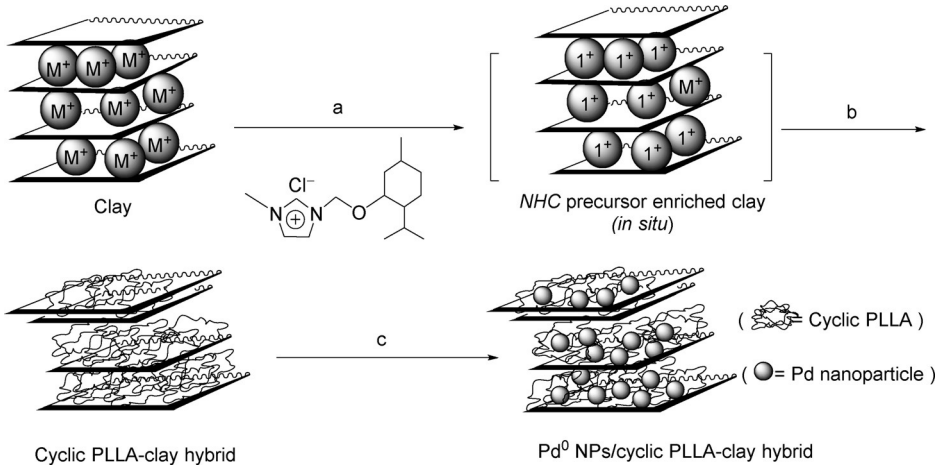

Figure 18. Synthesis of Pd NPs/cyclic PLLA/clay hybrids. *Reagents and conditions*: a) THF, 60 °C, 4 h; b) *n*-BuLi, L-LA, 0 °C–rt, 1 h, 80%; c) Na_2PdCl_4, H_2O, NaBH4, dimethylformamide, −10 °C, 2 h, 95–98%. Reproduced with permission from Ref. [97]. Copyright 2013, John Wiley and Sons.

hybrid, and the resulting catalyst composite showed a high efficiency and was a recyclable catalyst for the aminocarbonylation reaction of aryl halides with various amines.[97] The report showed a good application of cyclic polymers in catalysis due to their biodegradability and recyclability.

3.5 Novel substrates and inhibitors

Cyclic DNAs demonstrate significantly greater stability toward enzymatic degradation in biological media than that of their linear analogues and, therefore, they have high potential uses as decoys for transcription factors.[104] Small cyclic DNA GAGA-sequenced oligonucleotides have been used as minimal substrates and inhibitor scaffolds for ricin toxin A-chain catalysis with an activity 92-fold higher than that for the linear form.[76] The results demonstrate that cyclic DNAs are potentially promising substrates and inhibitors of ricin toxin A-chain.

4 Conclusion and Perspectives

Significant achievements have been made in the synthetic technology of cyclic polymers. Highly pure cyclic polymers could be produced from convenient ring-expansion polymerization reactions, such as metathesis, click chemistry, and zwitterionic ring-opening polymerization (ROP). Cyclic polymers with various topologies such as mono- and multicyclic polymers have been reported and well characterized with advanced analytical technology. Introducing click chemistry in DNA synthesis has made it more convenient in preparing various cyclic DNA and related structures. Due to the inherent cellular toxicity of Cu^I-based catalysts, in vivo applications of cyclic DNAs, produced from Cu-catalyzed click reactions, have not been fruitful. Therefore, removal of the Cu residue is highly desired.

On the other hand, the theoretical study of the methodologies described above is still very limited. Quantitative calculations will be important implementations and developments in Jacobson's and Stockmayer's theory, and this can be used to predict the equilibrium molecular size distributions of linear and cyclic molecules for polymer formation.[105] Jacobson and Stockmayer's quantitative theory of macrocyclization equilibrium is based on a major assumption of the Boltzmann factor for the distribution of end-to-end distances of a randomly coiled chain.[105] G. Ercolani and coworkers have implemented and reproposed the theory to make it more understandable to nonspecialists.[106]

Cyclic polymers always show unique properties in comparison with their linear counterparts due to well-known topology effects. More derived unique and useful properties are expected to be discovered in near future. In this regard, biomedical applications such as polymer–drug conjugates for drug delivery, applications in gel chemistry, and additives to tune linear polymer properties are likely to be discovered. In addition, cyclic polymers may also be used to prepare novel organic–inorganic hybrids, and the resulting materials could find further broad applications similar to linear polymer–inorganic hybrids, like catalyst supports.

High-value applications of cyclic polymers urgently need investigation to begin more interesting research. Therefore, great efforts have been made to prepare unique and useful cyclic materials to broaden their applications. However, functionalization of cyclic polymers remains a big challenge compared with linear polymers due to the compatibility issues of some functional groups with cyclization methodology. In addition, for metal-complex-catalyzed cyclic polymerization, the remaining toxic metal species have to be removed from product mixtures, similar to linear polymers. This issue is critical for cyclic polymer applications before scale-up. Finally, it is highly desirable to discover new applications for cyclic polymers, such as their use as additives for coating material and as macromonomers producing ultrahigh-molecular-weight linear polymers by ring-opening polymerization.

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