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Zwitterionic Ring-Opening Polymerization for the Synthesis of High Molecular Weight Cyclic Polymers

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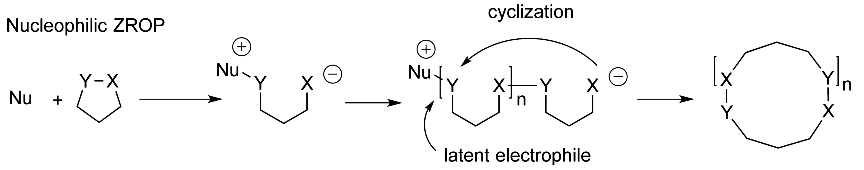

Cyclic polymers are an intriguing class of macromolecules. Because of the constraints of the cyclic topology and the absence of chain ends, the properties of these molecules differ from those of linear polymers in ways that remain poorly understood. Cyclic polymers present formidable synthetic challenges because the entropic penalty of coupling the chain ends grows exponentially with increasing molecular weight.

In this Account, we describe recent progress in the application of zwitterionic ring-opening polymerization (ZROP) as a strategy for the synthesis of high molecular weight, cyclic polymers. Zwitterionic ring-opening polymerization involves the addition of neutral organic nucleophiles to strained heterocyclic monomers; under appropriate conditions, cyclization of the resultant macrozwitterions generates cyclic macromolecules. We discuss the mechanistic and kinetic features of these zwitterionic ring-opening reactions and the conditions that influence the efficiency of the initiation, propagation, and cyclization to generate high molecular weight cyclic polymers.

N-Heterocyclic carbenes (NHC) are potent nucleophiles and relatively poor leaving groups, two features that are important for the generation of high molecular weight polymers. Investigations of the nature of the monomer and nucleophile have helped researchers understand the factors that govern the reactivity of these systems and their impact on the molecular weight and molecular weight distributions of the resulting cyclic polymers. We focus primarily on ZROP mediated by *N*-heterocyclic carbene nucleophiles but also discuss zwitterionic polymerizations with amidine, pyridine, and imidazole nucleophiles. The ZROP of N-carboxyanhydrides with N-hetereocyclic carbenes generates a family of functionalized cyclic polypeptoids. We can synthesize gradient lactone copolymers by exploiting differences in relative reactivity present in ZROP that differ from those of traditional metal-mediated polymerizations. These new synthetic methods have allowed us to investigate the influence of topology on the crystallization behavior, stereocomplexation, and solution properties of cyclic macromolecules.

I. Introduction

Despite more than 100 years of study of macromolecular structure and behavior, unresolved questions remain. Cyclic polymers differ from their linear topological congeners by only one bond, yet they exhibit properties that differ from linear chains in ways that are still not well understood. Experimental investigations of high molecular weight cyclic macromolecules are difficult because the synthetic challenges in generating cyclic macromolecules have limited access to appreciable quantities of pure materials.[1] The analytical challenges are formidable because there are a limited number of methods to characterize macromolecular topology. Traditional coupling routes to cyclic polymers by cyclization of linear precursor polymers under conditions of high dilution yield cyclic polymers.[1−4] The entropic penalties[5] associated with localizing two chain ends of a linear polymer into a region of space necessary for cyclization increases exponentially with molecular weight; this constitutes a severe challenge in generating high molecular weight cyclic polymers by coupling methods. Recent

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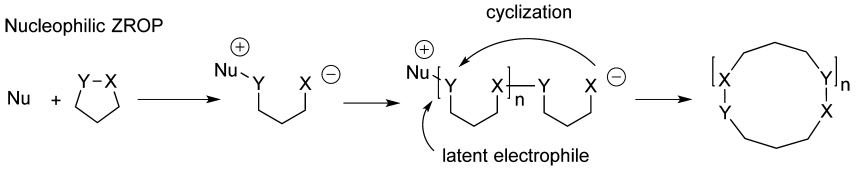
SCHEME 1. Nucleophilic Zwitterionic Ring-Opening Polymerization (NZROP) for the Synthesis of Cyclic Polymers



advances have provided cyclic polymers of intermediate molecular weight,[6,7] but for high molecular weight polymers the competitive generation of linear polymers due to coupling of chains is unavoidable.[8] Because trace linear contaminants have a significant impact on bulk physical properties of cyclic polymers,[9] herculean efforts are required to detect and remove linear contaminants.

To mitigate the entropic challenges in coupling the end groups of high molecular weight linear polymers, several innovative approaches have emerged. These approaches include cyclization of polymeric supports,[10] interfacial strategies,[11] ring-expansion approaches,[12,13] electrostatic assembly,[14] and zwitterionic ring-opening polymerization.[12,15,16]

Ring-expansion techniques from cyclic initiators[12,17,18] or catalysts[13] provide an attractive approach to cyclic macromolecules because monomer insertion into a reactive or weak bond expands the cycle and can, in principle,[19] avoid the formation of linear coproducts. The catalytic ring-expansion metathesis polymerization pioneered by Grubbs[13,20] generates high molecular weight polyolefins with molecular weights up to $M_n = 1200$ kDa. The ring-expansion ring-opening polymerization from cyclic tin initiators[12,17] generates cyclic polymers containing labile tin-alkoxides; subsequent chemistry can be carried out to generate cyclic polyesters and polycarbonates.[21,22]

This Account describes recent results from our group and others on the application of zwitterionic ring-opening polymerization (ZROP) as a strategy to generate high molecular weight cyclic polyesters. We focus on the kinetics and mechanisms of zwitterionic ring-opening polymerization and the limitations and opportunities that evolve from these mechanistic insights for the generation of well-defined cyclic macromolecules.

II. Zwitterionic Ring-Opening Polymerization

A. Historical Context. Zwitterionic polymerization is a process of enchainment where the ionic propagating end and its counterion are contained in the same polymer chain.[23] Excellent reviews by Johnston and Suzuki detail much of the early literature for the polymerization of vinyl monomers, carbonyl monomers, and strained ring monomers.[24,25] Szwarc had suggested as early as 1960 that charge cancellation of the zwitterionic chains might lead to cyclic structures.[26] Zwitterionic polymerization mediated by nucleophiles to generate anionic propagating species are most common,[25] but those mediated by neutral electrophiles are also known and were implicated as one of the mechanisms in the boron trifluoride initiated polymerization of 1,3,5-trioxane.[24,25]

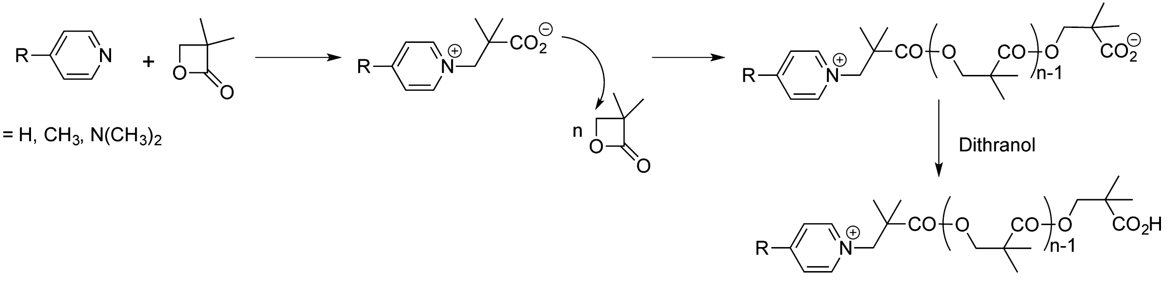
Zwitterionic polymerizations typically employ neutral nucleophilic initiators that react with monomer to generate a zwitterion (Scheme 1). Amines, pyridines, and phosphines can be used as initiators for the polymerization of reactive vinyl monomers and strained lactones.[12,23,24] Zwitterionic initiators have also been employed, as have zwitterionic monomers for step-growth polymerizations.[24]

To synthesize high molecular weight cyclic polymers by ZROP with nucleophilic initiators, propagation must be fast relative to cyclization; this is favored when the latent electrophile formed (Scheme 1) contains a relatively poor leaving group (low nucleofugality).[27] Under conditions where the zwitterionic intermediate is not capable of cyclization, other termination steps lead to linear polymers. Kricheldorf showed that for the zwitterionic polymerization of pivalactone initiated by pyridines and tertiary amines (Scheme 2),[28] cyclization was inefficient, and upon hydrolytic workup only protonated linear chains were observed. In other cases, the ring-opening polymerization of lactones generated cyclic structures.[12]

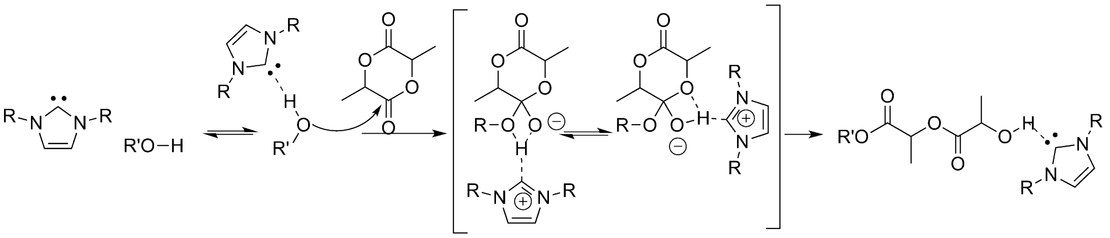
The ring-opening polymerization of ethylene oxide in DMSO mediated by *N*-heterocyclic carbenes (NHC) was proposed to proceed by a zwitterionic mechanism, but cyclized polymers were not observed.[29] Instead, addition of nucleophilic reagents to either quench or regulate the polymerization resulted in the incorporation of the nucleophilic reagent to each chain.[29]

B. *N*-Heterocyclic Carbene-Mediated Zwitterionic Ring-Opening Polymerization of Lactones. During the course of our investigations on the catalytic ring-opening polymerization of lactones mediated by NHCs in the presence of alcohol initiators,[15,30] we had proposed two possible mechanisms

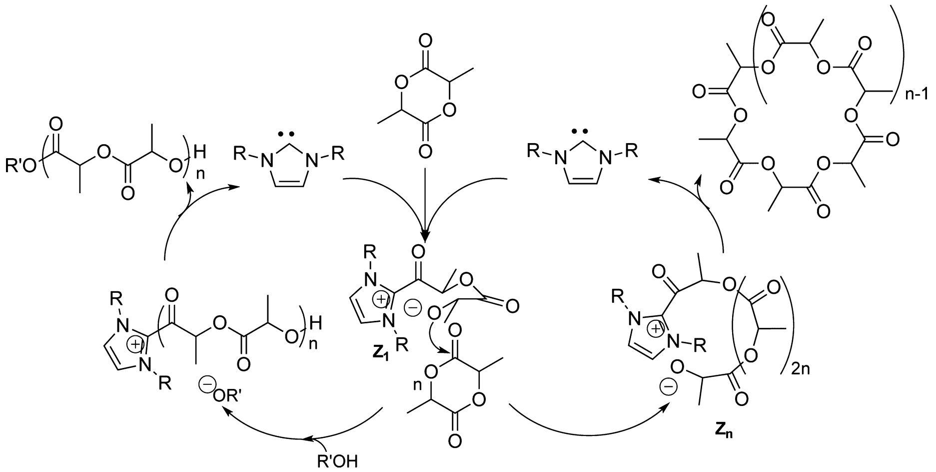
SCHEME 2. Zwitterionic Ring-Opening Polymerization of Pivalactone Initiated by Pyridine



SCHEME 3. Hydrogen Bonding Mechanism for the NHC-Mediated Synthesis of Linear Poly(lactide) in the Presence of an Alcohol Initiator



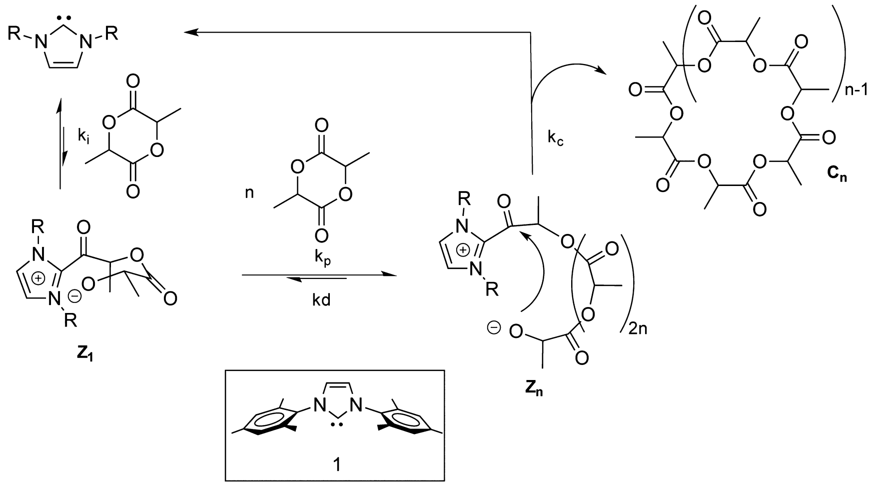
SCHEME 4. Tandem Zwitterionic Mechanism for the NHC-Mediated Synthesis of Linear Poly(lactide) in the Presence (left) and Absence (right) of an Alcohol Initiator



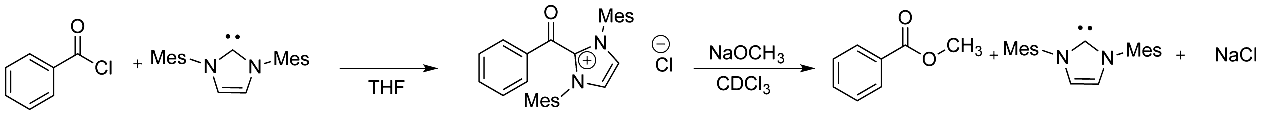
for enchainment:[15] a "chain-end" activating mechanism where the carbene activates the alcohol by H-bonding (Scheme 3), and a nucleophilic mechanism involving zwitterionic intermediates (Scheme 4). In the presence of alcohol initiators, the NHC-catalyzed polymerization of lactide is rapid (TOF $\approx$ 18 s^{-1}), yields narrow molecular weight polylactides ($M_w/M_n \leq 1.20$), and exhibits many of the features of a living polymerization.[15,30] DFT calculations[31] suggested that the zwitterionic intermediate (Scheme 4) was higher in energy than the H-bonded adduct (Scheme 3), implying that the H-bonding "chain-end activation" mechanism[15,32] (Scheme 3) is more likely when alcohols are used as initiators. However, at very low alcohol concentration and high ratios of monomer to alcohol ($[M]_0/[I]_0$) the molecular weights of the resultant polymers deviate from that predicted, implying that both mechanisms might compete.[15]

To test the competence of zwitterionic intermediates (Scheme 4), Szilard Csihony investigated the reactions of lactide with carbenes in the absence of alcohol initiators.[33,34] Investigations of a 1:1 mixture of lactide and IMes (1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene, NHC **1**) in d_8-THF did not yield detectable amounts of a zwitterionic intermediate; instead high molecular weight polylactide was generated. Subsequent investigations revealed that with

SCHEME 5. Proposed Mechanism for the Synthesis of High Molecular Weight Cyclic PLA with Carbene **1**



SCHEME 6. Formation and Reaction of Acyl-imidazolium **A** with Sodium Methoxide



A

excess lactide, the ring-opening polymerization in the absence of alcohol initiators generated high molecular weight cyclic poly(lactide) (PLA) ($M_n \leq 26\,000$ Da, $M_w/M_n \leq 1.35$).[16,34] Dilute solution viscosity studies, ^{1}H NMR, and MALDI-TOF MS indicated that the resulting PLA was cyclic.[34]

These results provide compelling, albeit indirect, evidence for the intermediacy of zwitterions and the viability of a nucleophilic mechanism for the ring-opening polymerization of lactide by nucleophilic carbenes. As suggested by Swarc[26] and Johnston,[24] we have proposed that the ionic attraction of the zwitterion compensates for the unfavorable entropy of cyclization,[5] enabling the generation of cyclic polymers even at relatively high (0.6−1.0 M) monomer concentrations.

Mechanistic investigations of the ZROP of lactide by IMes illustrated some unusual features; this system exhibits several characteristics of a kinetically controlled living polymerization but deviates from living behavior in several significant ways.[16,34] The polymerization is fast, reaching 90% conversion in less than 5 min at room temperature at an initial monomer concentration of 0.6 M ($[\mathbf{1}]_0 = 0.003$ M). The molecular weight of the PLAs increase linearly with increasing conversion, and the molecular weight distributions remain below $M_w/M_n = 1.3$ for monomer conversions below 70%. However, the experimental M_n exceeds that predicted from the initial ratio of monomer to carbene ($[M]_0/[I]_0$) and is relatively insensitive to changes in $[M]_0/[I]_0$. Molecular weights of cyclic PLA up to $M_n = 26\,000$ Da (DP = 180) could be readily prepared, but efforts to generate cyclic PLA with higher molecular weights were unsuccessful. Kinetic investigations suggested that this could be accounted for by the mechanism shown in Scheme 5.[16]

Kinetic studies revealed that initiation is second order in monomer, which can be rationalized by reversible formation of Z_1. Initiation is slower (k_i = 0.274 M^{-2} s^{-1}) than propagation ($k_p = 48.7$ M^{-1} s^{-1}), which is modeled as first order in monomer. At higher monomer conversions, the rate of depropagation ($k_d = 0.208$ s^{-1}) cannot be ignored due to the moderate equilibrium monomer concentration of lactide ($[M]_e$ = 0.014 M at 25 °C). Cyclization of the zwitterions is slower than propagation at modest monomer concentrations ($k_c = 0.0575$ s^{-1}), liberating the carbene and generating cyclic PLAs.

Independent evidence for the viability of the cyclization step was obtained by investigation of the reactivity of acyl imidazolium ions with alkoxides.[33] The acyl imidazolium **A** was generated from the reaction of **1** with benzoyl chloride (Scheme 6). Subsequent reaction of **A** with sodium methoxide rapidly yielded methyl benzoate and free carbene,

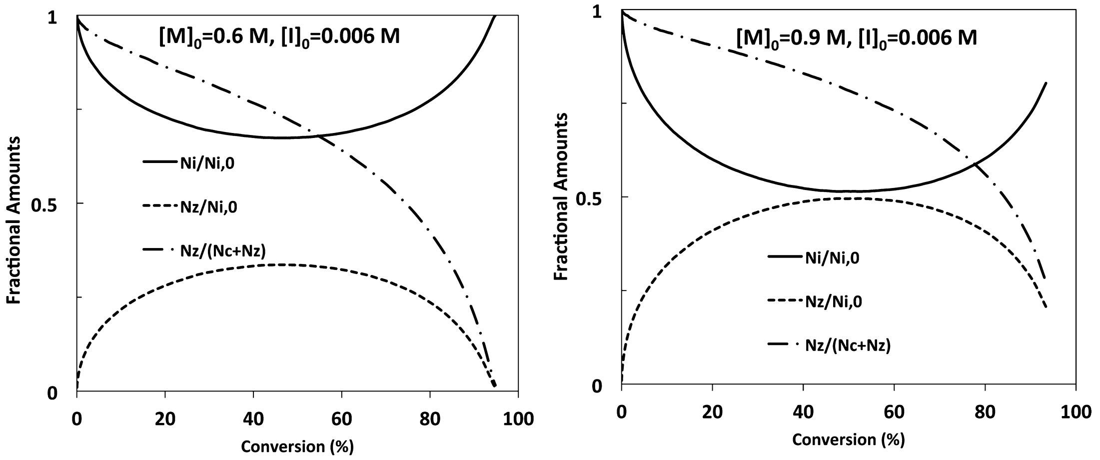


FIGURE 1. Representative simulations of intermediates at (a) $[M]_0 = 0.6$ M, $[I]_0 = 0.006$ M or (b) $[M]_0 = 0.9$ M, $[I]_0 = 0.006$ M and where N_i, N_z, and N_c are the number of initiators, zwitterions, and cyclized chains, respectively.

suggesting that these acyl imidazolium ions are readily attacked by alkoxides.

Stochastic kinetic simulations of the mechanism of Scheme 5 were used to predict the amounts of free carbene, active zwitterion, and cyclized chains throughout the polymerization (Figure 1).[16] These simulations imply that the initiator efficiency, defined as the fraction of carbenes that form active zwitterions, is less than 75% even at high monomer concentrations. The initiator efficiency decreases with decreasing monomer concentration, dropping to 25% at $[M]_0 = 0.6$ M.

These mechanistic and kinetic studies suggest that the ZROP of lactide is not a living polymerization but exhibits some of the characteristics of living behavior due to the slow rate of initiation, fast rate of propagation, and slow rate of cyclization. Because initiation is second order in monomer and slow, relatively few active zwitterions are generated in the initial stages of polymerization, but they rapidly consume monomer. Following a time-dependent initiation period, the concentration of active zwitterions remains relatively constant (Figure 1) as initiation becomes less probable. Carbenes that do not form active zwitterions initially and those liberated by cyclization do not initiate chains later in the polymerization due to the decreasing monomer concentration and the second-order monomer dependence of initiation. Because cyclization is slower than propagation, polydispersities remain narrow and the molecular weight increases with conversion, but the molecular weights are higher than that predicted from $[M]_0/[I]_0$, since not all of the initial carbenes generate active zwitterions. The molecular weights are not a simple function of $[M]_0/[I]_0$ because the number of active zwitterions is a complicated function of both $[M]_0$ and $[I]_0$. This model also explains why higher molecular weights are not readily obtained by changing $[M]_0/[I]_0$, since the molecular weights are limited by the relative rate of propagation versus cyclization.

Chain-growth experiments were carried out to test for the intermediacy of active zwitterions.[16] When a second charge of monomer is added at a point where the simulations suggested that few active zwitterions remained in solution (94% conversion, $N_z/N_{i,o} \leq 0.1$, Figure 1a), GPC analysis suggested that chain extension did not occur but that low molecular weight cycles were generated by re-initiation of carbenes and the added charge of monomer (Scheme 7a). In contrast, addition of a second charge of monomer at a point where a significant fraction of zwitterions were estimated to be present (59% conversion, $N_z/N_{i,o} \approx 0.5$, Figure 1b) resulted in both chain extension of the active zwitterions and re-initiation by the uninitiated carbenes (Scheme 7b). The low initiation efficiency and residual carbene concentration of this system precludes clean synthesis of block copolymers by sequential monomer addition.

The ZROP of lactide is stereospecific and generates crystalline, isotactic cyclic poly(lactide)s from either L-lactide or D-lactide.[35] The isotacticities of the resulting cyclic polymers ($f_{iii} = 0.81-0.90$, where f_{iii} = fraction of isotactic (iii) tetrads) are lower than that of isotactic linear PLLA and PDLA generated from other catalyst systems.[36] This is likely a consequence of competitive epimerization of either lactide monomer or polymer by the basic[37] NHC, as demonstrated in the stoichiometric ring-opening of lactide with CH_3OD with **1** in d_8-THF.[33]

Examination of the MALDI-TOF mass spectra of cyclic PLAs provides evidence for additional side reactions (Figure 2).[34] The cyclic PLA generated using carbene **1**

SCHEME 7. GPC Traces for Chain Extension by Sequential Addition of LA with Carbene **1**

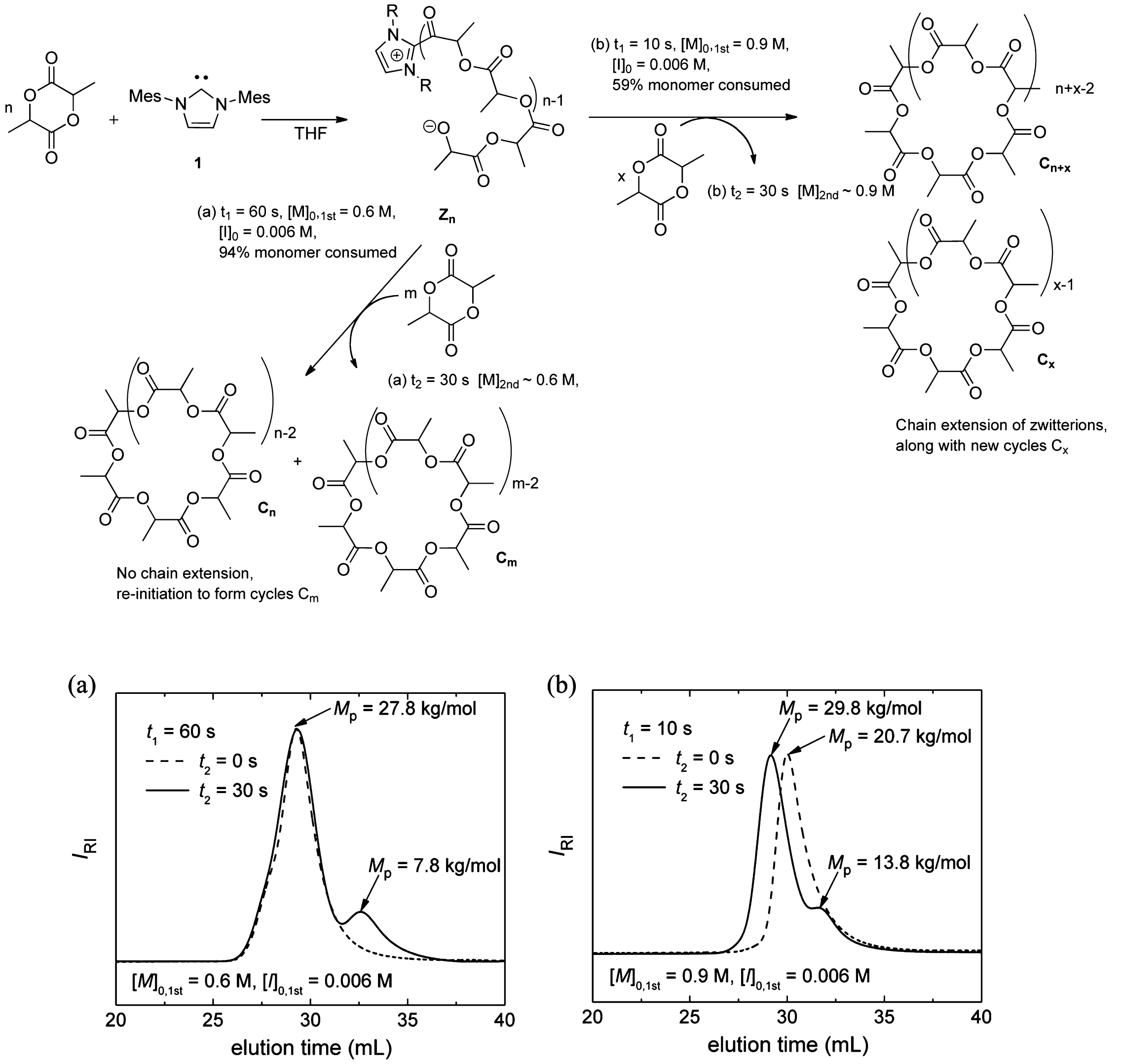


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exhibit ions with masses corresponding to singly charged sodium or potassium adducts of cyclic chains with peaks separated by 72 *m*/*z*, half that of the LA monomer (144 *m*/*z*).

The generation of odd-numbered PLAs can be accounted for by chain-scrambling processes (Scheme 8),[38] where the alkoxide of chain **A** attacks an internal ester of chain **B** to give two chains each with an overall odd number of lactate ester units. The presence of these odd-numbered chains strongly suggests that the propagating alkoxide is capable of attacking the ester groups of the open polymer chain. This attack could occur intermolecularly or intramolecularly, with competitive backbiting as an additional route to generating odd-numbered cycles.[38] Similar behavior was reported by Prasad.[39]

The ZROP of β-propiolactone (PL) or β-butyrolactone (BL) with the saturated carbene SIMes **2** at room temperature yields cyclic polymers.[40] In contrast to ZROP of lactide with the unsaturated carbene **1**, the polymerization of β-propiolactone (PL) with SIMes follows first-order kinetics with a linear increase in molecular weight with conversion that closely matches that predicted from $[M]_0/[I]_0$. Mechanistic studies revealed that the unsaturated carbene **3** reacts with β-butyrolactone (BL) to form a stable spirocycle that could be crystallographically characterized (Scheme 9). This spirocycle efficiently initiates the ZROP of the lactone by the reversible opening of the spirocycle to generate zwitterionic intermediates with an initiation efficiency close to 100%. The higher initiation efficiency for SIMes/BL relative to IMes/lactide is likely due to the slightly higher nucleophilicity

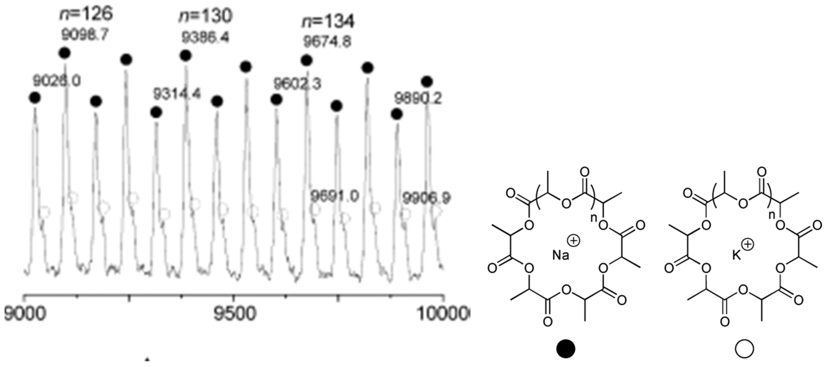
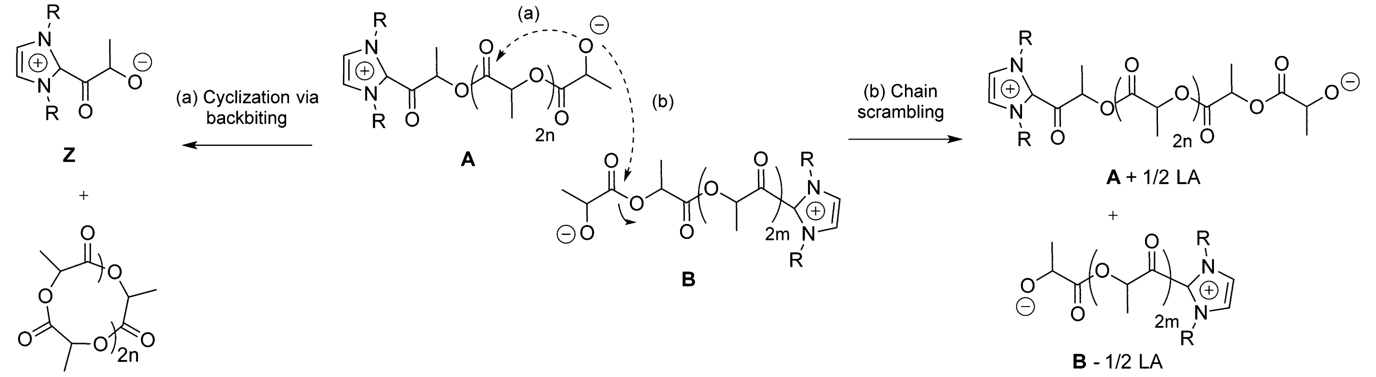
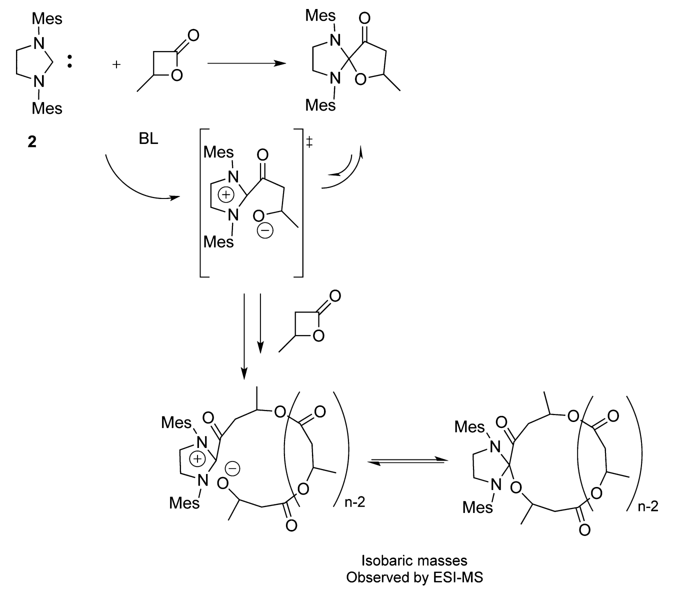


FIGURE 2. MALDI-TOF MS spectra of sodium and potassium adducts of PLA generated using carbene **1**. Reprinted with permission from ref 34. Copyright 2007 John Wiley and Sons.

SCHEME 8. Proposed Chain Scrambling of PLA during NHC-Mediated ZROP



SCHEME 9. Reaction of BL and Carbene **2**

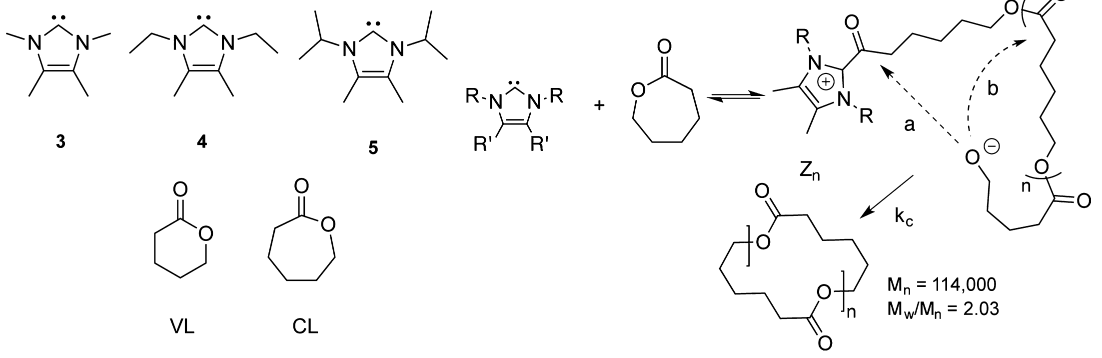


of SIMes **2** ($N = 23.35$) relative to IMes **1** ($N = 21.72$)[41] and the higher ring strain of the four-membered BL ring ($\Delta H_p = -82.3$ kJ/mol, $\Delta S_p = -74$ J/mol) relative to that of the six-membered lactide ring ($\Delta H_p = -22.9$ kJ/mol, $\Delta S_p = -41$ J/mol).[38]

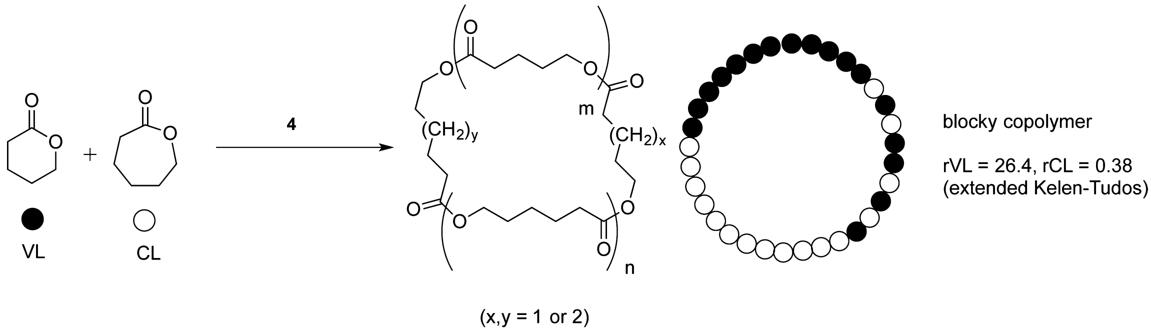
In situ monitoring of the polymerization by electrospray mass spectrometry (ESI-MS) yielded ions corresponding to macrocyclic spirocycles (or the isobaric zwitterions); subsequent treatment with CS_2 afforded the cyclic poly(lactones). The formation of NHC-spirocyclic intermediates has also been proposed by Zhang[42] in the polymerization of *N*-carboxyanhydride monomers. We have no evidence for neutral spirocycles when the unsaturated *N*-heterocyclic carbenes are used as initiators; typically the unsaturated imidazolium ions are not as readily attacked by alkoxides as the saturated imidazolinylidium ions.[43,44]

Attempts to generate cyclic poly(ε-caprolactone) (PCL) or poly(δ-valerolactone) (PVL) with carbene IMes **1** were unsuccessful.[45,46] However, the more nucleophilic[41] carbenes **3**–**5** are competent initiators for the zwitterionic ring-opening polymerization of ε-caprolactone or δ-valerolactone to generate cyclic PCL or PVL, respectively (Scheme 10).[47,48] In contrast to that observed in the ZROP of lactide with IMes **1**, the ZROP of ε-caprolactone with *N*-alkyl *N*-heterocyclic carbenes **3**–**5** generates much higher molecular weight cyclic PCLs, with molecular weights as high as $M_n = 114\,000$ Da (DP = 1000).[47] These molecular

SCHEME 10. Carbenes **3**–**5** Used in the Polymerization of δ-Valerolactone (VL) and ε-Caprolactone (CL)



SCHEME 11. Synthesis of Gradient Cyclic Poly(VL-*g*-CL)



weights are several multiples of the entanglement molecular weight of linear PCL (approximately 3000 Da), indicating that ZROP provides a synthetic strategy for generating highly entangled cyclic polymers.

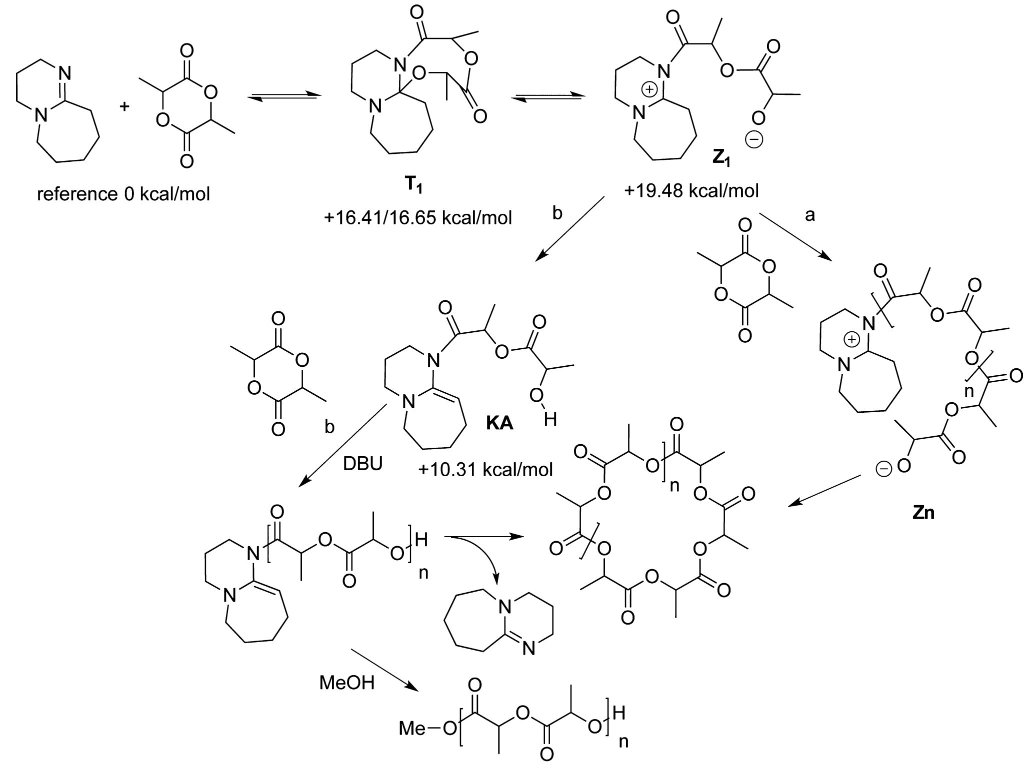
The ZROP of ε-caprolactone (CL)[47] and δ-valerolactone (VL)[48] with the more reactive carbenes **3**–**5** generates polylactones with higher molecular weights but broader molecular weight distributions ($M_n \leq 114\,000$, DP = 1000, $M_w/M_n = 1.3$–1.6) than the PLAs generated with NHC **1** ($M_n \leq 50\,000$, DP ≤ 350, $M_w/M_n = 1.03$–1.2). Kinetic investigations reveal that the polymerization of CL with carbene **3** exhibits first-order dependence in monomer and initiator, although with a noticeable induction period.

Initial kinetic modeling implies that the high molecular weights are partially a consequence of lower initiation efficiency for the formation of active zwitterions from the less reactive CL monomer. The broader polydispersities observed are likely a consequence of backbiting of the propagating alkoxide at internal esters of the macrozwitterions or nearby chains (path b, Scheme 10) in competition with cyclization at the acyl imidazolium terminus (path a, Scheme 10). These more basic NHCs (carbene pK_a in DMSO, **3** pK_a = 23.4 and **5** pK_a= 24.0)[49] polymerize lactide uncontrollably under similar conditions used for IMes **1**, suggesting that the nucleophilicity and basicity of the NHC nucleophile and the reactivity of the monomer are important parameters that influence the initiation efficiency and thus the rate of polymerization.

Attempts to generate cyclic polylactone block copolymers by sequential addition of monomer were frustrated by the low initiation efficiencies and the re-initiation of chains by uninitiated carbenes (Figure 1). However, we were able to devise a strategy for the generation of cyclic gradient polymers by exploiting the tendency of organic catalysts such as carbenes **3** and **4** to enchain δ-valerolactone more rapidly than ε-caprolactone (Scheme 11).[48]

To generate cyclic gradient copolymers by this strategy, the rate of propagation relative to cyclization needs to be high enough such that the kinetic lifetime of the zwitterion is sufficient to incorporate a significant fraction of both monomers. The faster rate of enchainment of VL relative to CL with NHC **4** leads to a cyclic gradient copolymer.[48] Analysis of the cyclic and linear gradient p(VL-*g*-CL) copolymers revealed that the structure and thermal properties were intermediate between those of the cyclic and linear PVL and PCL homopolymers, linear random p(VL-*r*-CL) copolymers, and diblock p(VL-*b*-CL) copolymers.[48,50]

SCHEME 12. Proposed Mechanism for the DBU-Mediated Polymerization of LA with DFT Computed Enthalpies



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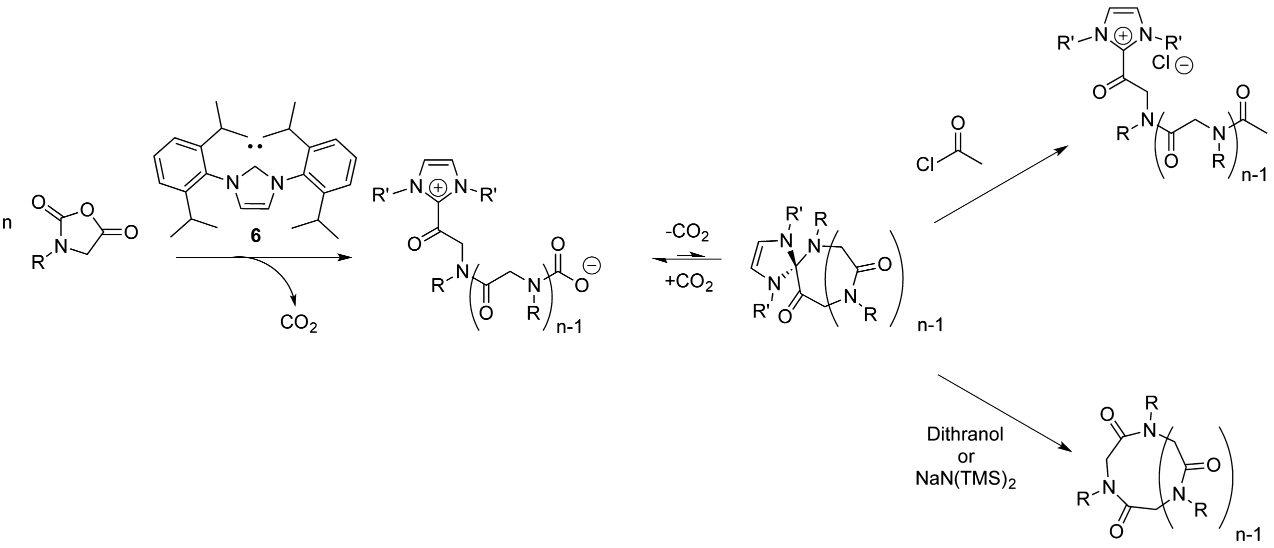
C. Amidine-Mediated Zwitterionic Ring-Opening Polymerization of Lactones. For efficient ZROP, initiation should be reasonably efficient and propagation should be fast relative to cyclization. This suggests that the initiating nucleophile should exhibit both high nucleophilicity and relatively poor leaving group ability. Mayr has quantified this behavior (nucleophilicity, Lewis basicity, and nucleofugality) for a variety of nucleophiles, including *N*-heterocyclic carbenes and amidines.[27,51]

We had previously shown that amidines, such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), were effective catalysts or cocatalysts for the ring-opening polymerization of lactones in the presence of alcohol initiators and had proposed that DBU acts as a general base to activate the alcohol chain end, similar to the "chain end" mechanism proposed for lactide (Scheme 3). However, amidines are also known to be potent nucleophiles.[52] To test whether amidines might also mediate the formation of cyclic polymers, we investigated the zwitterionic ring-opening of lactide with DBU and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) in the absence of alcohols.[53]

The zwitterionic ring-opening polymerization of lactide with DBU in CH_2Cl_2 occurs readily within 1 h (85% conversion) to afford PLAs with molecular weights of M_n = 56 000 Da; DBN is also effective, but slower. Analysis of the resulting polymers by dilute solution viscosity studies and MALDI-TOF MS revealed that the resulting polymers were predominantly cyclic but contained minor amounts (approximately <10%) of linear chains.[53] Theoretical studies suggested that the generation of linear chains is likely due to the deprotonation of the amidinium zwitterionic intermediate to generate neutral ketene-aminal, **KA**, which undergoes competitive enchainment with the amidinium zwitterion. Upon methanol workup, the **KA**-terminated polymers liberate DBU and linear PLA (Scheme 12). The generation of high molecular weight cyclic PLAs from DBU and DBN strongly implies that amidines are effective nucleophilic initiators for ZROP, but competitive reactions of the amidinium zwitterions leads to mixtures of cyclic and linear chains. That nucleophilic carbenes, amidines, and imidazoles[54] are effective suggests that any strong, neutral nucleophile could potentially generate cyclic polymers via a ZROP mechanism.

D. Zwitterionic Polymerization of Other Monomers. The ZROP of *N*-carboxyanhydrides (NCAs) thermally or with pyridine initiators generates low molecular weight cyclic polypeptides.[12,55] Zhang and co-workers demonstrated that

SCHEME 13. NHC-Mediated ZROP of NCA Monomers via Decarboxylation and Spirocycle Formation



the use of more potent nucleophiles such as *N*-heterocyclic carbene **6** provides a general strategy to a family of cyclic poly(peptoid)s of controlled molecular weight ($3000 \leq M_n \leq 30000$) and narrow molecular weight distributions ($M_w/M_n \leq 1.2$, Scheme 13).[42]

The carbene-initiated zwitterionic ring-opening polymerizations of NCAs exhibit living behavior as evidenced by the close agreement of the evolution of molecular weight with monomer conversion and the initial $[M]_0/[I]_0$[56] and the generation of cyclic block copolymers of Me-NCA and Bu-NCA by sequential monomer addition.[56] The high initiation efficiencies are likely a consequence of the favorable loss of CO_2 from the initially formed zwitterion. The nature of the solvent has a significant influence on the polymerization behavior. High molecular weight cyclic polymers were obtained in THF and toluene whereas polymerization in DMF or DMSO results in low molecular weight chains independent of the starting $[M]_0/[I]_0$.[42] More elaborate cyclic structures, such as amphiphilic block copolymers[57] and brush polymers and copolymers[58] were also reported.

Mechanistic and mass spectrometry investigations supported the formation of zwitterions or the isobaric spirocyclic[40] intermediates that retain the imidazolium end group. Cyclic polypeptoids were obtained by treatment of these intermediates with $NaN(TMS)_2$, under conditions of tandem MS[59] or MALDI-TOF ablation (Scheme 13).[42]

A zwitterionic mechanism was recently proposed by Chen for the polymerization of acrylic monomers with *N*-heterocyclic carbenes, where MALDI-TOF MS provided evidence for cyclic polymers from the NHC-mediated polymerization of γ-methyl-α-methylene-γ-butyrolactone.[60]

III. Properties of High Molecular Weight Cyclic Poly(lactone)s Generated via ZROP

While investigations of low molecular weight cyclic polymers have illuminated many differences between linear and cyclic chains,[1,14] the critical role of entanglement[9] is less well understood due to challenges in generating high molecular weight cyclic polymers. The ZROP of ε-caprolactone generates crystalline cyclic PCL with molecular weights ranging from $M_n = 41-114000$ Da. At these molecular weights, the cyclic PCL would be expected to be highly entangled ($[M]_e \approx 3000$ Da for linear PCL) providing an opportunity to investigate the influence of topology on the crystallization behavior of entangled cyclic polymers.[47] Investigations by wide-angle (WAXS) and small-angle (SAXS) X-ray scattering indicated that the crystal structure and lamellar thicknesses of linear and cyclic PCLs were similar; nevertheless, the cyclic PCL crystallized much faster than the linear PCL. Similar results were obtained by Schäler et al.[61] and Córdova et al.[62] for cyclic PCL obtained by alternative synthetic routes. The faster crystallization kinetics observed were attributed to the higher mobility of the cyclic chains in the melt.

The ZROP of L-lactide or D-lactide generates cyclic, isotactic PLLA or PDLA with molecular weights of $M_n = 26000-30000$ Da ($M_w/M_n \leq 1.4$).[35] These cyclic PLAs crystallize into lamellar crystals with a lamellar thickness and long-period spacing that is similar to the linear congeners and commensurate with the extended chain length of these cyclic PLAs. Despite the cyclic topology, blends of cyclic PDLA and PLLA were observed to form stable stereocomplexes[63] indicating that the endless cyclic topology does not inhibit stereocomplex formation.[35]

Cyclic poly(peptoid)s generated from the zwitterionic ring opening of NCAs exhibit a range of interesting behaviors. Cyclic poly(*N*-CHMePh-glycine) (M_n = 10 300 Da) exhibits more thermally stable helical conformations when constrained in a cyclic topology compared with the linear analogs.[64] Comparisons of thermoresponsive cyclic and linear random *N*-ethyl/*N*-butyl poly(peptoid)s indicted that the cyclic polymers have lower cloud point temperatures than their linear analogs.[64]

IV. Summary and Outlook

In this Account, we describe the current status of zwitterionic ring-opening polymerization as a strategy for the synthesis of high molecular weight cyclic polymers. Further advances are needed to generate high molecular weight cyclic polymers of a range of molecular weights so that unresolved questions of the influence of topology on melt configurations, the degree and nature of entanglements, the rheology and crystallization behavior can be resolved. That current theories cannot adequately explain or predict this behavior implies that we are far from a complete understanding of macromolecular behavior. Indications that even trace amounts of linear impurities influence the properties place severe demands on any synthetic technique to generate cyclic polymers of high topological purity. New analytical methods to detect and remove trace linear impurities in cycle polymer samples are direly needed.

Kinetic and mechanistic studies of ZROP have begun to illuminate the factors that influence the efficiency of initiation, the rate of propagation and cyclization, and the conditions under which high molecular weight cyclic polymers can be generated. Further advances will benefit from a better and more quantitative understanding of the relationship of the nucleophilicity, Lewis basicity, and nucleofugacity of the initiators to the kinetic reactivity of the electrophilic monomers, as well as the role of solvent on the efficiency of initiation, propagation, and cyclization. Little is known regarding the potential of zwitterionic strategies for generating knotted cyclic chains or catenanes, or even the influence of such topological isomerism[6] on the properties of the resulting materials and assemblies. As with many fields of polymer science, further advances will require new synthetic methods, new analytical techniques to assess topological connectivity and purity, and new theoretical approaches to unravel the influence of topology on macromolecular behavior.

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Robert M. Waymouth was born in 1960 in Warner Robins, GA. He received bachelor's degrees in mathematics and chemistry from Washington and Lee University and his Ph.D. from the California Institute of Technology in 1987 with Professor Robert H. Grubbs. Following a year of postdoctoral research with the late Professor Pino at the ETH in Zurich, he joined the faculty at Stanford University in 1988, where he is now the Robert Eckles Swain Professor of Chemistry. His research interests are in homogeneous catalysis and polymer chemistry.

FOOTNOTES

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The authors declare no competing financial interest.
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