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Recent Developments in Entropy-Driven Ring-Opening Metathesis Polymerization: Mechanistic Considerations, Unique Functionality, and Sequence Control

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ABSTRACT

Entropy-driven ring-opening metathesis polymerization (ED-ROMP) involves polymerization of olefin-containing macrocyclic monomers under entropically favorable conditions. Macrocycles can be prepared from a variety of interesting molecules which, when polymerized, impart unique functionality to the resulting polymer backbone such as degradable linkages, biological moieties, crystallizable groups, or supramolecular hosts. In addition, the sequence of atoms in the cyclic monomer is preserved within the polymer repeating units, allowing for facile preparation of sequence-defined polymers. In this review article, we consider how the mechanism of ROMP applies to ED-polymerizations, how olefinic macrocycles are synthesized, and how polymerization conditions can be tuned to maximize conversion. Recent works in the past 10 years are highlighted, with emphasis on methods which can be employed to achieve fast polymerization kinetics and/or selective head-to-tail regiochemistry, thus improving polymerization control. ED-ROMP, with its unique capability to produce polymers with well-defined polymer backbone microstructure, represents an essential complement to other, well-established, metathesis methodologies such as ROMP.

KEYWORDS: Degradable polymers, semi-crystalline polymers, host-guest chemistry, cyclic olefins, controlled polymerization

INTRODUCTION

The polymerization of cyclic monomers through ring-opening polymerization (ROP) has attracted significant research interest over the past decades due to the versatile structures and chemistries of the macromolecular products that can be reached.[1] To date, there is an extensive library of catalysts, monomers and polymerization mechanisms that can be employed, allowing for the production of a wide array of final polymers including polyethers, polyesters, polyamides and polycarbonates, with importance in applications ranging from degradable plastics, agriculture and through to pharmaceutical polymers.

In comparison to other widely used polymerization techniques, namely vinyl polymerizations, ROPs offer several advantages particularly within applications-based research. From the synthesis of polymers for drug delivery

and tissue engineering applications,[2–4] through to polymers for packaging and renewable plastics,[5,6] the ability to incorporate biocompatibility and biodegradability into the final materials is of importance for polymer performance, safety and recyclability.[7] As well, with ROP processes there is scope for achieving polymers with tunable crystallinities the incorporation of heteroatoms or functional moieties in the polymeric backbone.[8–10]

Entropy-driven ROP (ED-ROP) has also facilitated the synthesis of sequence-defined polymers. A repeating sequence of three or more units can be embedded into the structure of the macrocyclic monomer. Following polymerization, this sequence is preserved within the resulting polymer. In addition, careful tuning of reaction conditions can ensure that polymerization occurs in a head-to-tail fashion, thereby producing a polymer consisting of repeating segments of 3 or more units with regioregularity. Whilst the polymers themselves typically possess broad molecular weight distributions and thus are not "perfectly" defined, as we shall show, preliminary investigations have demonstrated that conserved sequences of repeating units can have a dramatic effect on the properties of the resulting material.

In this contribution, we consider the thermodynamic and kinetic parameters that influence monomer conversion, molecular weight, dispersity, and other factors during ED-ROP, with specific emphasis on how these apply to the mechanisms of metathesis chemistry. Methods of olefin-containing macrocycle synthesis are discussed, as the route of preparation determines the ultimate reactivity of the monomer during ED-ROMP. We build upon a 2009 review by Xue and Mayer[11] by highlighting recent reports on ED-ROMP to emphasize the usefulness of this technique for the preparation of polymers with unique backbone functionality, with pre-threaded supramolecular guest molecules, and with well-defined sequences, and other examples. Finally,

we suggest future challenges in this rapidly expanding and impactful field.

Thermodynamics of ring-opening polymerization

ROP is most typically utilized for small ring monomers, 3-8 atoms, and the ability of any given cyclic monomer to successfully polymerize has both thermodynamic and kinetic considerations.[12] In particular, macromolecular chain growth has an inherent reversibility of the propagation step ($k_p[\mathrm{M}] \approx k_d$; k_p and k_d are the rate constants of propagation and depropagation) and as a result, unreacted monomer can remain when the reaction comes to equilibrium.[12] This phenomenon can be described by the ratio of the enthalpy and entropy of polymerization, known as the ceiling temperature (T_c). The ability for a given monomer to readily undergo ring-opening polymerization is therefore dependent upon both thermodynamic parameters, related to the sign of the free enthalpy (ΔH_p) and entropy (ΔS_p), as well as the equilibrium monomer concentration ($[\mathrm{M}]_{eq}$). This can be expressed by Dainton and Ivin's equation:

$$\ln[\mathrm{M}]_{eq} = \Delta H_p/R\mathrm{T} - \Delta S_p^0/R \qquad \text{(Equation 1)}$$

In most conventional polymerizations of small three- to six-membered cyclic monomers, the driving force of the monomer-polymer conversion is alleviation of significant ring strain in the monomer species, and thus there is a decrease in enthalpy upon ring-opening ($\Delta H_p < 0$) and the monomers will easily polymerize (Figure 1).[12] In these cases, the overall free enthalpy of polymerization (ΔG_p) of the reaction is mostly dependent on ΔH_p, and the resulting monomer equilibrium concentration is low. It should be noted that there will also be an accompanying decrease in the entropy of the system ($\Delta S_p < 0$) due to a loss in translational degrees of freedom of the growing polymer chain, and thus the enthalpic contribution must prevail for polymerization to occur.

Ring strain is most significant for three- and four-membered rings, and as the ring size becomes larger, considering five- to eight-atom rings, alleviation of angular strain is the primary driving force. This is the case when sp^2 carbons are present such as in lactide, carbonates,[13] or trans-cyclooctene. An enthalpic contribution can also arise from transannular strain in substituted cyclooctenes,[14,15] among other examples. Therefore, a moderate enthalpic driving force remains and the monomers will readily polymerize; however, there can be nearly equal enthalpic and entropic contributions to the Gibbs free energy of polymerization, and the $[M]_{eq}$ becomes higher. In order to optimize for successful ROP, reaction conditions can be tuned to force the equilibrium of the reaction towards the macromolecule side of the equation. High monomer concentration and low reaction temperature can be employed to promote polymerization and counteract entropic factors. Recent reports on ROMP of cyclopentene exemplify the importance of reaction conditions for moderately-strained monomers.[16] The entropy of ROP can be further influenced by the elimination of a small molecule condensate, as is the case with *N*-carboxyanhydride polymerization.

Finally, as the ring size is increased even further, typically ≥ 14 atoms, there is minimal or negligible ring strain and atoms can adopt bonding configurations with near ideal bond angles and bond lengths.[17] Instead of relying on the enthalpic gain of alleviating ring strain, ED-ROMP is driven by two important forces: (1) a phenomenon known as the entropy of mixing;[11] and (2) an increase in conformational entropy as the macrocycle is opened to its linear form.[1,18] The first component describes the tendency of chemical reactions to progress towards mixtures of reactants and products in the absence of a significant enthalpic component. For ED-ROMP, this concept stipulates that, from an entropic perspective, the reaction prefers to settle amongst a most probable distribution of monomers, oligomers, and polymers. Absent ring-strain, there is little enthalpic difference between olefins in the monomeric and polymeric states. As such, the contribution of the entropy of mixing becomes significant, and the polymerization is driven towards an equilibrium of rings and chains. The entropy of mixing is complemented by a second entropic factor. As macrocycles are opened, the number of rotational and vibrational microstates of the repeating unit increases, resulting in an overall increase in the conformational entropy of the system. The contribution of these two entropic parameters explains why high monomer conversions during ED-ROMP can be readily achieved.

ROP

enthalpy (ring-strain)
$|\Delta H_p| > -T\Delta S_p$

3-8 atoms

low $[M]_{eq}$

ED-ROP

entropy
$|\Delta S_p| > \Delta H_p$

high concentration

high dilution

>8 atoms

high $[M]_{eq}$
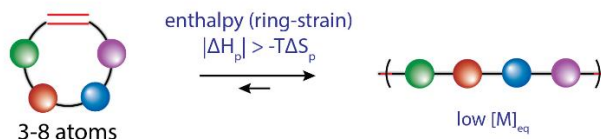
polymerization possible when $\Delta G_p < 0$
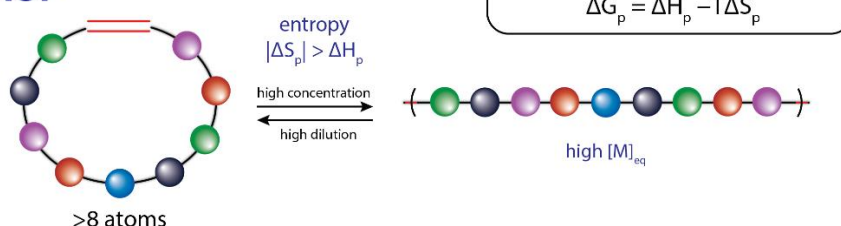$$\Delta G_p = \Delta H_p - T\Delta S_p$$

FIGURE 1. Small, highly-strained rings undergo ring-opening polymerization primarily due to the alleviation of ring strain. As the ring size increases, the polymerization is instead driven by an entropic gain originating from increased rotational and vibrational freedom in the polymeric state.

Entropy-driven ring-opening polymerization

In certain polymerizations, in addition to producing the desired linear macromolecular species, a variety of side reactions can also occur, such as chain transfer/segmentation and macrocyclization, and thus at the point of thermodynamic equilibrium, often the presence of macrocyclic side products can be detected.[19] Macrocyclization can arise by either end-to-end ring closure or back-biting reactions, and can be driven by the reaction conditions and the nature of initiator and catalyst. This process has historically been predicted according to the theory of Jakobson and Stockmeyer,[20] originally regarding intramolecular reactions in polycondensations:

$$[\text{M}(\gamma)]_{eq} \sim \gamma^{-5/2} \qquad \text{(Equation 2)}$$

This equation shows a critical monomer concentration $[\text{M}]_{eq}$ for a macrocycle $\text{M}(\gamma)$ of γ repeating units, and indicates that this equilibrium concentration will decrease as the ring size increases. Later, Kornfield *et al.*[18] further modelled this theoretically and computationally, additionally considering ring strain energy (thus enthalpy changes) as a contributor to the critical monomer concentration, $[\text{M}]_{eq,\infty}$. These combined theories describe the distribution of cyclic and linear polymers in solution at the polymerization equilibrium as a ring-chain equilibrium, which has significant dependence upon monomer concentration, and further the indication that in an equilibrated system, the majority of macrocycles will be strainless.

Entropy-driven ring-opening polymerization (ED-ROP) exploits this ring-chain equilibrium process for the reaction of strainless macrocycles to form linear polymers. Theory predicts that for a linear product to be achieved, the initial monomer concentration must exceed the critical concentration,[21,22] and importantly that due to the absence of any enthalpic driving force, there must be entropic favorability. In high dilution conditions, the equilibria will lie in favor of the cyclics, and the translational entropy, which is concentration dependent, will remain relatively high. However moving into high concentration or neat conditions, the equilibria will be in favor of the linear polymer. Moreover, increased temperature results in a lower Gibbs energy of polymerization via the $T\Delta S$ term, influencing the polymerization equilibrium in favor of the polymer.

Mechanisms of ED-ROP

Based on the nature of the monomer, initiator, and catalyst employed, there are several mechanisms by which ring-opening polymerizations can occur. ROPs always follow a chain-growth polymerization mechanism, although in some cases there are equilibrium rearrangements through the polymer backbone during polymerization driving the molecular weight distribution towards the most probable value ($M_w/M_n \approx 2.0$).[23] ROPs can largely be categorized as radical, anionic, cationic, coordination/insertion, enzymatic, or ring-opening metathesis, and these mechanisms can be universally applied to both ROP and ED-ROP. ED-ROP by methods other than ring-opening metathesis polymerization (ROMP) has been extensively reviewed elsewhere,[19,23,24] and will only be discussed briefly here.

Anionic ROP (AROP) is characterized by having a nucleophilic reagent as initiator of the polymerization, with chain growth usually occurring through continued nucleophilic attack of the chain end onto additional heterocyclic monomer.[25] The most typical example of AROP is the formation of polyesters through polymerization of 4-, 6- and 7-membered lactones; however, ED-ROP can also exploit the

anionic mechanism, such as the enzymatic synthesis of macrolides (>12 atom rings) by lipase,[26] or the use of metal methoxide catalysts to polymerize a variety of macrocycles.[27] Coordination-insertion or pseudoanionic ROP is another mechanism by which polyesters can be synthesized, typically catalyzed by metal-based catalysts such as stannous octoate ($Sn(Oct)_2$) or organocatalysts such as triazabicyclodecene (TBD).[28–30] In this polymerization mechanism, both the nucleophile and monomer are coordinated with the catalyst for a dual activation process. ED-ROP has been demonstrated through the coordination-insertion mechanism, for example the ring-opening of macrocyclic-oligoesters using di-*n*-butyltin oxide or zinc alkoxide as catalysts.[31,32] Alkene-substituted cyclic monomers can undergo radical ROP (rROP) in the absence of added catalyst by a thermal free radical process.[33] This reaction mechanism proceeds through homolytic dissociation across the double-bond to generate a carbon radical, followed by ring-opening to form the linear species. RROP can be utilized for the production of functionalized polyesters, to generate a main-chain olefin, or for the polymerization of heteroatom-containing rings, such as disulfides.[34] Most rROPs are enthalpically favorable due to the exchange of an alkene for a carbonyl. However, rROP can be entropy-driven in some cases.[35,36]

Ring-opening metathesis polymerization is an olefin metathesis chain-growth process, where cyclic olefins can be polymerized with the driving force of ring-strain relief, and is typically exemplified in the polymerization of highly strained norbornenes.[37] ROMP catalysts are transition metal complexes with carbon-metal double bonds (alkylines or benzylidenes), with the most well-known being the Grubbs series of ruthenium complexes,[15,38] and Schrock's Mo-based catalysts.[39,40] As shown in Figure 2, the mechanism of polymerization occurs through the formation of a metallocyclobutane intermediate, followed by a [2+2] cycloaddition, and finally a cycloreversion to generate the

linear species.[41] Interestingly, many ROMP reactions exist in an equilibrium between the forward polymerization and reversibility through backbiting reactions, ie. the ring-chain equilibrium.[37]
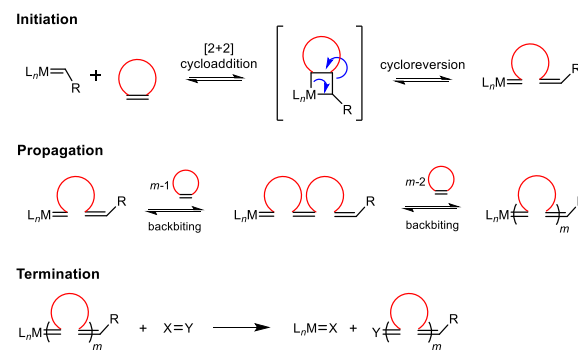
FIGURE 2. Mechanism of ROMP.

ROMP is an attractive polymerization tool due to its mild reaction conditions, typical narrow polydispersity values and efficient and clean polymer end-capping. Of particular importance is its fast reaction rate; for example, ROMP of exo-norbornene monomers can reach full conversion on the timescale of minutes. As well, Ru-based catalysts tend to be highly functional group tolerant, allowing for a wide range of monomer chemistries to be explored, and the resultant polymers can also be biodegradable as with other ROP processes, through the inclusion of cyclic ester or acetal comonomers.[42] Finally, ROMP has been demonstrated to be a valuable tool for entropy-driven polymerizations,[19,23] and will be the focus of the remainder of this review.

CONSIDERATIONS OF ED-ROMP

As outlined above, ED-ROMP involves the polymerization of olefinic macrocycles, in contrast to traditional ROMP where highly strained cyclic olefin monomers are used. It is somewhat counterintuitive that ROMP of macrocycles can give rise to high molecular weight polymers. Nonetheless, high conversions can be obtained during ED-ROMP, on timescales comparable to traditional ROMP, if proper reaction conditions and catalysts are employed.

ED-ROMP represents a competition of ring-opening (polymerization), ring-closing (cyclodepolymerization), and cross metathesis (chain transfer) reactions (Figure 3). A single Ru catalyst can perform all three of these transformations, and there is often little chemical selectivity of the catalyst towards olefins in the macrocyclic monomers, the polymer backbone, or on the polymer chain ends.[43] Clever methods have been devised to influence selectivity towards ring-opening which will be discussed in more detail below. In most cases, however, these reactions occur with equal probability, requiring careful tuning of reaction conditions to kinetically favor ring-opening over RCM or CM.

A: Possible metathesis reactions during ED-ROMP
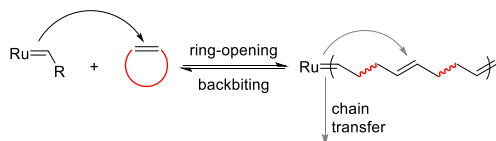
B: Propagation and side-reactions occur with equal probability
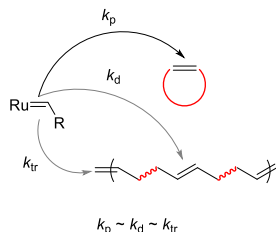

$$k_p \sim k_d \sim k_{tr}$$

FIGURE 3. Under equilibrium conditions, the metathesis catalyst does not distinguish between olefins in the monomer, the polymer backbone, or at the polymer chain ends. This leads to similar kinetics for propagation, depolymerization, and chain-transfer reactions.

As with other ED-ROP formulations, the most significant parameter that influences the ring-chain equilibrium is the initial concentration of cyclic monomer.[44,45] In general, high monomer concentration is required to achieve high DPs. This concept can be explained as follows: (1) ring-opening kinetics scale with olefin concentration; at high concentration of monomer and low polymerization conversion, the most abundant type of olefin is that of the monomer; (2) once ring-opening has occurred, the active catalyst must encounter another macrocyclic monomer for propagation to continue; thus, monomer olefin must be plentiful to prevent ring-closing; (3) as conversion increases, so does the concentration of backbone olefins; high monomer concentration in this case combats cyclo-reversion (depolymerisation) and chain transfer if the catalyst can locate additional monomer before it encounters a nearby polymeric olefin. Because monomer ring-opening grants a slight entropic gain to the system, this process occurs more rapidly than RCM (which has an entropic cost). As such, ED-ROMP kinetics are inherently biased towards polymerization at high monomer concentration and a maximum DP can be achieved if the polymerization is terminated prior to equilibration due to the differential kinetics of the various metathesis events.[46] Additionally, under concentrated monomer conditions, the translational entropy loss of ring-opening is limited due to the relatively slower diffusion of monomer. In contrast, low catalyst concentration is beneficial for ED-ROMP, as a low concentration of olefin end groups favors polymers and the number of these end groups is proportional to the catalyst loading.

A final consideration that is specific to ED-ROMP is olefin stereochemistry. The initial configuration of the monomeric olefin can contribute to its overall kinetic profile. It has been well established that certain alkene stereochemistry influences the rate of ring-opening, although this is largely attributed to a difference in ring strain between cycles containing either cis or trans isomers. This concept is exemplified by comparing the ring strain of cis- and trans-cycloctene, with the latter possessing a ring-strain 9.3 kcal/mol greater due to the "chair-like" conformation imposed on the ring by the geometry of the double bond.[14] For large, strainless macrocycles the influence of olefin stereochemistry does not originate from differential ring strain. Instead, a slight enthalpic benefit is associated with ring-opening of cis-olefinic macrocycles due to alleviation of steric repulsion between nearby bulky groups on the

same side of the double bond.[47,48] As the monomers are ring-opened and cyclo-reversion of the metallocyclobutane occurs, new olefins are produced in the polymer backbone with stereochemistry defined by the approach of the monomer relative to the catalyst-bound alkylidene. Under most reaction conditions using commercially available catalysts, mixtures of both cis and trans isomers are obtained. Certain catalysts have tendencies to produce different ratios of these isomers;[49–52] however, the overall composition of olefins trends towards the trans configuration over long reaction times, especially at high conversion where chain transfer (CM) reactions become more prevalent.[53] If a fully saturated backbone is desired, the polymer can be readily hydrogenated. The reader is directed to several excellent examples of olefin reduction following ROMP.[54–57]

ED-ROMP bears resemblance to acyclic diene metathesis (ADMET) in that the polymers obtained can share similar features with respect to the final polymer microstructure. In both cases, the structure of the repeating unit can be precisely programmed through the structure of the monomer. Indeed, the ADMET mechanism likely involves some degree of ring-closing of diene monomers to form macrocycles, which are polymerized via ED-ROMP during the metathesis reaction. Olefinic macrocycles are often prepared in this manner. However, polymerizations using ED-ROMP generally achieve higher conversions and produce polymers of marginally higher molecular weight and lower dispersity (Figure 4). Importantly, ED-ROMP also improves molecular weight control relative to ADMET, as the MW of the final polymer is proportional to the initial ratio of monomer to catalyst. Moreover, ADMET polymerization requires more metathesis events than ED-ROMP for polymers of similar MW, requiring more catalyst turnovers. Ru-methylidene (Ru=) species also arise during ADMET, which have been shown to decompose more rapidly than metal alkylidenes and benzylidenes.[58] As with ED-ROMP, the

equilibrium between monomer and polymer during ADMET is subject to the same driving forces, namely the initial concentrations of monomer and catalyst. For a comprehensive discussion on ADMET polymerization, the following reviews are recommended.[59–62]
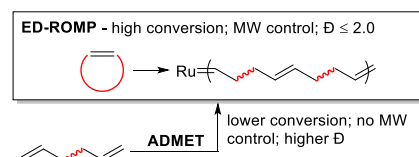
FIGURE 4. ED-ROMP and ADMET polymerization produce polymers with similar overall structures. However, ED-ROMP can be advantageous in that polymers with higher molecular weights and lower dispersities can be obtained.

MACROCYCLE SYNTHESIS

Macrocyclic compounds have great importance in many areas of chemistry research, for example in natural products synthesis, pharmaceutical chemistry, and in supramolecular self-assembly.[63–65] For this reason, over the past decades there has been a growing body of research focused on routes and reaction conditions for their synthesis. For ED polymerizations, the target macrocycles tend to be large-sized rings of greater than 14 atoms, which are kinetically unfavorable and strainless. As such, there is an entropic cost to their formation which is regained during polymerization. There is a range of chemistry that can be applied for the synthesis of macrocycles, and can be broadly assigned to two categories: the intramolecular cyclization of an oligomeric species, or the depolymerizing of longer polymer chains to yield the macrocycle; however, only the first strategy will be considered here. For intramolecular cyclization, the possible reactions follow the same overall requirements; namely the ring-closing of end-functional linear compounds at concentrations that favor cyclization over polymerization, in accordance with the ring-chain equilibrium discussed above.[66] To this end, reactions are

conducted under high dilution or pseudo-high dilution conditions, or in heterogenous systems utilizing solid supports to manipulate the reaction equilibrium.

Ring-closing metathesis (RCM)

Importantly, the family of olefin metathesis reactions also features one of utility for the synthesis of the macrocyclic compounds required for ED-ROMP. Ring-closing metathesis (RCM) describes the process of intramolecular metathesis of two terminal alkenes to yield an unsaturated ring, giving the cycloalkene as the E- or Z- isomer.[66,67] RCM has been used for the synthesis of ==cyclic and macrocyclic compounds== and is tolerant to a wide variety of functional groups, and is thus applicable for the synthesis of macrocycles featuring complex moieties to ultimately yield highly functionalized polymeric backbones.[68]

The mechanism of the ring-closing reaction is in accordance with the accepted mechanisms for olefin metathesis reactions (Figure 5).[67] Catalyzed by the same transition metal-based catalysts, initially there is the cycloaddition of one pendant alkene moiety with the catalyst to yield the metallacyclobutane intermediate, followed by the cycloreversion step to form the metal carbene intermediate. Through the second tethered alkene moiety, an intramolecular cyclization occurs to give the second conjoined metallacyclobutane and the final cycloreversion gives the cyclic alkene product.
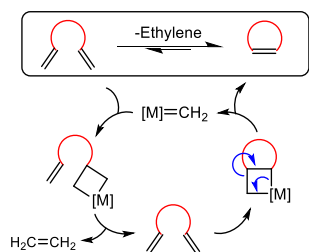

FIGURE 5. Mechanism of cyclic olefin synthesis by RCM.

This reaction is reversible in nature and is driven entropically by the evolution of ethylene gas, as well as dilute reaction conditions to promote the forward reaction. Stereoselectivity of the produced olefin occurs through either thermodynamic control or through use of a stereoselective catalyst. Small rings will favor the Z-isomer in order to minimize steric repulsion, whereas for macrocycles, the resultant ratio of E- and Z-olefins typically reflects the thermodynamic energy difference between the two isomers, which is approximately 9:1, E:Z, but can vary depending on the particular reaction.[69] It should be noted that while strategies have been elucidated to dictate the geometry of macrocycles synthesized through RCM,[70–72] during the polymerization step as the double bond reacts and undergoes the cycloreversion of the metallocyclobutane, the initial geometry is lost.[73] If it is of interest to dictate the stereochemistry at this stage, strategies can be employed such as prolonged reaction times to drive the thermodynamically favored *E*-isomer to high yields, or *Z*-isomers can be obtained through the use of catalysts which dictate the approach of the monomer to the catalyst-bound alkylidene.[74,75]

Macrocycles with pre-existing olefins

Macrolactonization reactions have historically been used to prepare a wide range of lactones and other cycloalkanes. These reactions are heavily used in the field of natural products synthesis, and for the synthesis of macrolactones for subsequent ring-opening polymerizations.[76,77] However, some researchers have also utilized the advantages of a macrolactonization approach for the synthesis of the macrocycles for ROMP, namely to exploit naturally occurring molecules featuring olefins as sustainable monomers, or for the cyclization of an olefin-containing molecule with a pre-determined stereochemistry. An example of the former was described by Domb et al.[78] who prepared an olefin-containing macrolactone from ricinoleic acid, a naturally obtained molecule from the castor oil plant, through

intramolecular coupling of the hydroxy- and carboxylic acid moieties. The use of this monomer in an ED-ROMP was subsequently described by Gautrot and coworkers,[79] who copolymerized it along with another naturally-derived macrocycle to generate renewably-sourced polymeric elastomers, which will be discussed in further detail below. Meyer et al.[80] sought to determine the impact of olefin stereochemistry on the mechanism and

"livingness" of ED-ROMP reactions. To facilitate a known geometry of the macrocyclic olefins, they prepared the monomers through macrolactonization of *trans*-alkene-containing oligomers of PLGA, and subsequently investigated the kinetics of reaction, as is discussed further below (Figure 6). These examples highlight the potential of this strategy for exploring green synthesis routes or enhanced control over monomer and polymer structure.
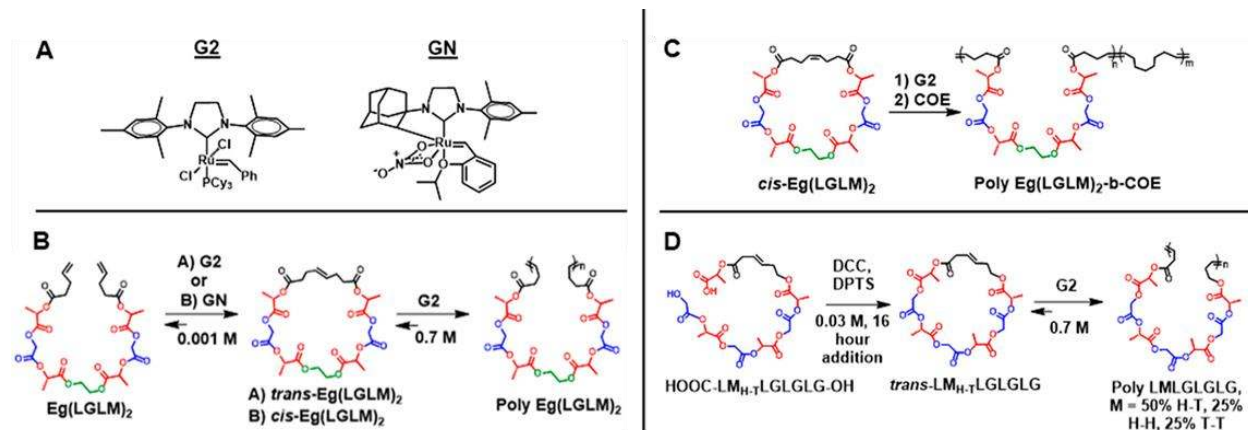
FIGURE 6. (A) Grubbs second generation (G2) and nitrato Grubbs (GN) catalyst structures. (B) Stereo-controlled ring-closing metathesis and ensuing polymerizations of Eg(LLCM)$_2$ macrocycle (C) Selectivity-enhanced entropy-driven ring-opening metathesis polymerization to prepare poly (EgLGLM)$_2$-b-COE. (D) Macrolactonization reactions of LMLGLGLG and SyLMLGLGL and subsequent polymerizations. (Reproduced from ref. 80. Copyright 2019 ACS Publications).

Macrocycles through cyclodepolymerization

Carothers, in the 1930s,[81] extensively studied the cyclodepolymerization (CDP) process in regards to condensation polymers, using thermal processes to recycle linear polymers into macrocyclic esters, and this has remained a valuable tool in polymer chemistry for a range of polycarbonates, polyurethanes, polyamides and more.[82,83] Interestingly, CDP can also be exploited as a tool for ED-ROMP through the preparation of macrocycles from alkene-containing linear polymers using high dilution conditions, by exploiting the same ring-chain equilibria as already discussed. Of importance, CDP can produce a cleaner reaction mixture than for RCM, as fewer end groups in solution result

in less linear side-products.[73] Grubbs et al.[84] demonstrated this process for the CDP of polyethers to yield unsaturated crown ethers. More recently, Hodge and coworkers have also exploited the CDP process to generate olefin-containing macrocycles from pre-formed polymers obtained commercially or through other polymerization routes.[85,86] While this field only contains a few reports concerning ROMP (the majority focus on the production of esters and carbonates), it represents a new potential area to be explored, particularly for polymer recycling processes.

Functional macrocycles by RCM

A prime advantage of ED-ROMP is the ability to include a wide variety of moieties along the polymer backbone through the polymerization of functionalized cyclic oligomers. To this end, there are two main considerations for the production of macrocycles: tolerance of the reaction conditions to a variety of functional groups and the functionalization of the chain ends to yield the diene species. Several catalysts have been reported to be tolerant to the presence of heteroatoms and complex or bulky functional groups, and as a result a range of examples of macrocyclic ED-ROMP precursors are emerging in the literature. Initially, RCM reactions were most commonly employed for the synthesis of complex five- to eight-membered lactams,[87,88] carbocyclic and heterocyclic vinyl chlorides,[89] alkenylboronates,[90] a variety of phosphorous,[91,92] sulfur[93–95] and fluorine[96,97] containing rings, cyclic di- and tri-nucleotides,[98,99] and more.[100] Following from these precedents, macrocycle synthesis evolved from simple unsaturated macrolactones and macrolactams,[68,101,102] to an even larger range of functional macrocycles such as fluorinated amino and azamacrolactones.[103] Even further, the wide availability of commercial alkene-terminal molecules has allowed for chain-end functionalization on virtually any small molecule. Gautrot et al.[104] prepared steroid-containing macrocycles by first reacting the base bile-acids with ω-undecylenyl alcohol or ω-undecenoyl chloride to generate the diene species, followed by the RCM reaction to yield the macrocycle. Ding et al.[105] synthesized a macrocyclic polyphosphoester through reaction of the diol with undecylenic acid to yield the α,ω-diolefin for subsequent RCM. In a different approach, macrocycles of poly(lactide) were synthesized by Sugai and coworkers,[106] who utilized an alkene-terminated ROP initiator to produce the linear oligomers, giving a one-step route to RCM precursors. In order to achieve a disulfide-bridged aliphatic polyester, Behrendt et al.[107] synthesized macrocycles based on L-cysteine which was end-functionalized with 11-bromoundec-1-ene, followed by the ring-closing

reaction in two steps. Finally, Meyer et al.[108] demonstrated the synthesis of sequence-encoded oligomers of lactic acid, glycolic acid and ε-caprolactone, which were functionalized with 4-pentenoic acid for preparation of the macrocycle by RCM.

It is also worth noting that in the field of natural products synthesis, ring-closing metathesis has been used to realize the synthesis of complex molecules such as the synthesis of the 15-membered heteroatom macrocyclic compound HCV Protease Inhibitor BILN 2061,[109] the formation of analogues of the peptide hormone Oxytocin,[110] macrolide analogues of the immunosuppressant Sanglifehrin,[111] the synthesis of the trisoxazole macrolactone of mycalolides A and B,[112] and more.[63] While these structures were not intended for further polymerization, these synthetic efforts highlight the full potential of RCM for a further broadening of functional macrocycles that can be envisioned in the future.

RECENT DEVELOPMENTS IN ENTROPY-DRIVEN RING-OPENING METATHESIS POLYMERIZATION

The continued evolution of new catalysts and wide variety of functionalized olefin-containing macrocycles has resulted in rapid growth of the field of ED-ROMP over the last decade for the synthesis of novel advanced polymeric materials.

Xie and coworkers[113] exploited ED-ROMP for the synthesis of degradable copolymers based on cyclooctene and a 27-atom azobenzene-containing macrocyclic olefin. The two monomers had different reactivities due to the strainless macrocycle and moderately strained cyclooctene, and thus the final composition could be tuned to feature linear blocks of poly(cyclooctene) bridged by the macrocycle. They showed that the polymers were hydrolytically degradable, with the macrocyclic spacer giving a degree of control over the degradation products, as confirmed by monomodal distributions of the lower molecular weight fragments by GPC. They reasoned that their method should facilitate the preparation of

multi-block copolymers by ED-ROMP in a one-pot procedure. Gautrot et al.[79] prepared shape memory polymers using ED-ROMP of macrocycles synthesized from naturally occurring bile acids (Figure 7). The use of an entropy-driven process was essential as only large, flexible and strainless macrocycles could incorporate the large steroidal moiety (or indeed other such bulky groups) into the polymeric

backbone. Using ED-ROMP, they copolymerized the macrocycles with a cyclic ricinoleic acid, investigating the physical effects of chemical modifications of the backbone. The resultant polymers were biodegradable, had high molecular weights (>200kDa), and tunable elasticity, T_g and shape recovery temperatures, with promising applications in biomedical devices.

FIGURE 7. Left, synthesis of macrocyclic bile acids and ED-ROMP copolymerization with ricinoleide. Right, shape memory phenomenon in bile acid-based polyesters with (a) warm drawing and (b) cold drawing experiments. (c) Shape memory effect in warm (red) and cold (blue) drawing mode. The cold drawing cycle is shorter, which simplifies its use and application in devices. (Reproduced from ref. 79. Copyright 2009 ACS Publications).

Shimizu and colleagues[114] synthesized a symmetrical 30-membered macrocycle featuring precisely alternating carbonate and stilbene groups to undergo subsequent ED-ROMP. When conducting the polymerization at concentrations over 1 M in monomer, they could reach moderate polymer molecular weights (45 kDa) and 60% yield of the linear species. They confirmed partial isomerization from the cis-configuration of the macrocycle into the more stable trans-configuration in the polymer (*trans:cis* 8:5), as is expected during ROMP due to secondary metathesis. In the macrocyclic form, the monomers were able to organize through hydrogen bonding and aryl stacking interactions to form columnar assemblies, thus providing materials capable of both

supramolecular self-assembly in the solid-state and linear polymerization in solution-state.

With the aim of demonstrating the utility of naturally derived macrocycles for generating unique macromolecules, Peng et al.[115] reported the ED-ROMP of lactonic sophorolipid, a macrocyclic glycolipid lactone obtained from yeast fermentation processes, which show bioactive properties. In this work, they aimed to fully investigate the kinetics of the polymerization reaction in order to perfectly tune the reaction for maximum polymer molecular weights and yields (in a typical scenario Mn > 100kDa, polymer yield 70%), by varying individual components such as solvent, catalyst loadings and monomer concentrations. Interestingly, when they used the second

generation Grubbs catalyst, despite slow initiation and secondary metathesis reactions, they observed characteristics of living polymerization, with the ratio of active propagating chains to total catalyst in polymerizations remaining constant resulting in plots of M_n vs monomer-to-initiator ratio that approximate linear behavior, thus providing a certain amount of control over the reaction and subsequent modifications and copolymerizations.

Mayer and coworkers[116] demonstrated the synthesis of metalated main-chain polypseudorotaxanes utilizing ED-ROMP (Figure 8). There is great interest in the formation of polymeric materials possessing dynamic crosslinks, such as linear chains encircled by slip-links (macrocycles), as they have novel and peculiar viscoelastic properties, however their research has been limited due to the complex
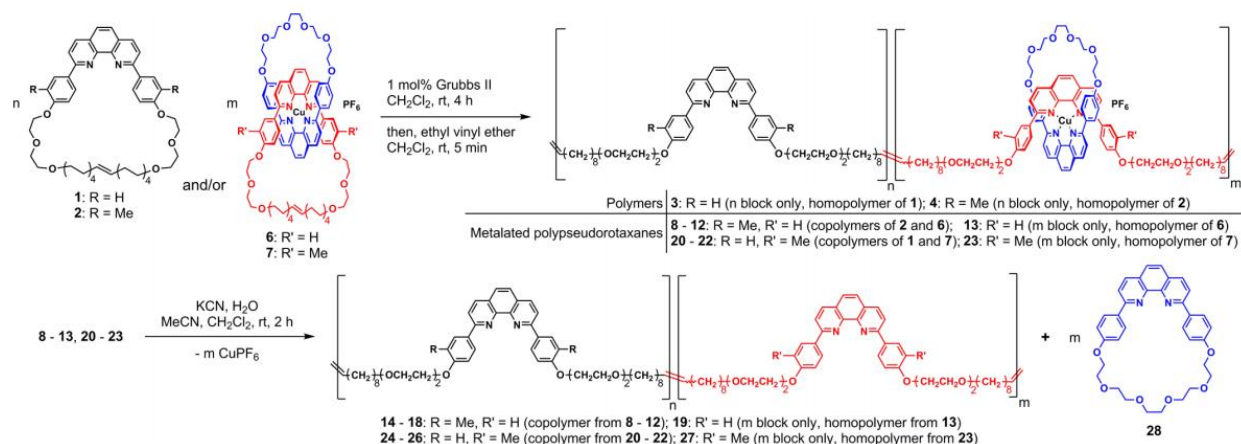

FIGURE 8. ED-ROMP homopolymerization and copolymerization of macrocycles and [2]Catenates. (Reproduced from ref. 116. Copyright 2014 ACS Publications).

synthetic methods required. Here, the authors demonstrated a simple route to the production of pseudorotaxane polymers, analogues of the desired materials, through copolymerization of prethreaded metalated monomers, [2]catenates, with noncatenated macrocycles to form linear polymers. They first prepared the interlocked rings using RCM of one diene with one non-reactive closed macrocycle to act as the slip-link, after which they copolymerized with varying ratios of the olefin-containing macrocycle, in order to tune the density of threaded macrocycles between zero and 100 (every backbone unit encircled). This work thereby provided an example of selective and precise control over threaded macrocycle density to generate pseudorotaxanes in a facile approach. In addition, this unique strategy offered higher threading densities than traditional complexation strategies where the

polymer is synthesized and subsequently mixed with metal salts and catenate, highlighting the usefulness of ROP as a strategy to prepare pseudorotaxane polymers.

In an interesting application of ED-ROMP as a polymerization tool, Grossweiler et al.[117] performed a fundamental study of force-rate characterization of spiropyran-based stress-responsive probes. The ring-opening reaction of spiropyran derivatives is mechanically accelerated, acting as colorimetric and fluorescent probes of molecular scale stress/strain mechanical events within a particular polymer. In order to quantify the forces involved in the activation of the probes by AFM, they copolymerized the target spiropyrans as macrocycles with an epoxy macrocycle as comonomer to facilitate adhesion of the material to the AFM probe. This work highlights

the versatility of the ED-ROMP reaction and applications that can be achieved through this polymerization technique.

With ED-ROMP, even large macrocyclic monomers can be readily polymerized. In a seminal example by Hodge et al., three families of macrocyclic olefins based on deoxycholic acid were polymerized, yielding polymers with various functionality including hydroxyl groups and methyl or t-butyl esters.[118] The macrocycles possessed novel structures wherein bile acid units were linked to a C20 fatty acid unit via the 3α- and 12α-positions, thus creating macrocycles with rings with a repeat unit of 29 ring atoms. Bile acid units were chosen to provide enhanced mechanical stiffness. The protected ester functionalities could be converted into carboxylic acids *via* treatment with trifluoroacetic acid. The resulting charged polymers were found to form transparent, hole-free films that could potentially be used for supporting cell growth. In a related example by the same group, bile-acid containing macrocyclic lactones were polymerized using ED-ROP *via* transesterifications (TEs) catalyzed by polymer-supported Candida antarctica lipase B (PS-CALB).[119] Polymerization occurred when the 3a- and 24-positions were linked by C14 or C20 chains or by a 23-atom chain, but not when the 3a- and 12a-positions were linked by a C20 chain. This suggested that the orientation of the bile acid derivative influenced the binding and thus transesterification efficiency of the enzyme. The polymers obtained differed in structure from those produced by ED-ROMP of the same macrocycles, highlighting the relatively higher selectivity of ED polymerization driven by olefin metathesis relative to TE.

As introduced above in section 4.2, Meyer and coworkers[108] developed a method for obtaining sequence-controlled polymers with customizable and controllable chain lengths through ED-ROMP. They prepared cyclic monomers containing ε-caprolactone, lactic, and glycolic acids (Figure 9), and the monomers were symmetrical with respect to the olefin

functionality. Polymerization by ED-ROMP yielded sequence-preserved copolymers with controllable molecular weights depending on the initial feed ratio of monomer and catalyst. NMR spectroscopic studies confirmed that the monomer sequences embedded in the macrocycles were retained during the polymerization process. This work therefore serves as a starting point for future investigations into other sequence controlled polymers derived from from backbone-functional monomers.
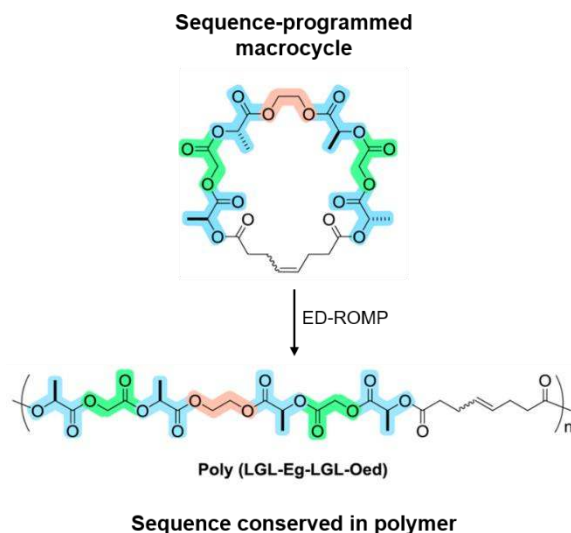

Figure 9. Synthesis of sequence-defined polymers via ED-ROMP using sequence-programmed macroycles. (Reproduced from ref. 108. Copyright 2015 ACS Publications).

Extending their work in the field of ED-ROMP, Craig and coworkers evaluated the mechanical strength and sonochemical properties of poly(catenane) copolymers.[120] Catenane-containing monomers or a topological control was copolymerized with (Z)-9,9-dichloro-bicyclo[6.1.0]non-4-ene (DCBCN) using ED-ROMP, yielding gem-dichlorocyclopropanated-polybutadiene (gDCC-PB) copolymers with 5 mol% of functional monomer. DCBCN was chosen as a co-monomer instead of cyclooctadiene to reduce backbiting reactions, and polymerizations were run for more than 3h to facilitate complete scrambling of the polymer

sequence by secondary metathesis. It should be noted that this type of polymer structure, with catenane moieties pre-formed prior to polymerization, could only be obtained using an ED-ROP methodology. Thus, the composition of the resulting polymer could be precisely controlled, as opposed to traditional supramolecular polymerization strategies. The relative strength of the catenane linkages relative to cyclic or linear controls was then assessed using sonochemical polymer mechanochemistry (sonication). It was found that the mechanical bonds of the catenanes were as strong or stronger than the covalent bonds along the polymer backbone.

Deng et al. leveraged ED-ROMP to synthesize main-chain liquid crystalline polymers.[121] Compared with a traditional ADMET polymerization (or similar step-growth protocols) of a mesogenic α,ω-diene, the ED-ROMP approach released no heat or volatiles during the reaction and was proven as a much more efficient tool to synthesize main-chain-functionalized polymers, in particular MCLCPs with much higher molecular weights over shorter reaction times. Moreover, in contrast to ADMET polymerization, the polymer molecular weight could be easily tuned by adjusting the ratio of Grubbs catalyst loading to the macrocyclic monomer.

In addition to mesogens, other interesting functionalities have been installed into the polymer backbone using ED-ROMP. Schlaad and coworkers prepared macrocycles based on L-cystine which were polymerized by ED-ROMP to produce polymers with redox-responsive disulfide backbone linkages.[107] The polymers could be degraded by hydrolysis of main chain esters or through reduction of the disulfide. In an exemplar study, complete depolymerization to the cyclic monomer was achieved in just 30 min by treating the polymer with an excess of dithioerythritol. In a subsequent study, ED-ROMP of an olefin/disulfide containing 16-atom macrocycle using the 3rd generation Grubbs catalyst was examined in greater detail (Figure

10).[122] Kinetic studies revealed that the catalyst deactivated during the polymerization, limiting the achievable (apparent) polymer molar mass. Higher molecular weights could be achieved via disulfide metathesis polymerization of the same macrocycle, yielding a polymer with an identical repeat unit structure but with thiol chain ends. In contrast, step-growth polymerizations by either ADMET or disulfide metathesis of acyclic diene and dithiol monomers were far less effective and yielded just low molar mass polymers or oligomers.
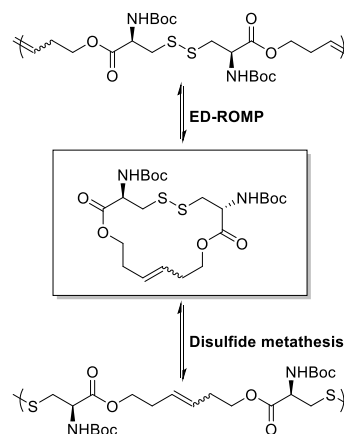

FIGURE 10. Synthesis of polymers with backbone disulfide functionality using either ED-ROMP or disulfide metathesis. (Adapted from ref. 122. Copyright 2019 Royal Society of Chemistry).

In a recent publication from Meyer and coworkers, ED-ROMP was exploited to prepare sequence-defined polymers to evaluate the influence of sequence, specifically the linker segment between the olefin and the repeating moiety, on the thermomechanical properties of the resulting polymers.[123] A library of sequence-controlled macrocycles was prepared, each of which contained a unique central moiety such as a five-carbon alkyl chain, diethylene glycol, a urea, a thioether, a triazole, a bioaromatic, and an extension of the ester sequence. The thermal and mechanical properties of these polymers depended on the ability of the linker to promote interchain interactions, as well as the weight fraction of the linker. For example, the incorporation of bio-aromatic linkages in the

polymer backbone resulted in increased Young's modulus and stiffness relative to linear alkyl analogues. In addition, polymer degradability was dominated by the relative hydrophobicity of the linker groups. Importantly, these differences in polymer properties arose from differences in linker chemistry only, as the macrocycle sequence was preserved following ED-ROMP.

SELECTIVE ED-ROMP

Early examples of ED-ROMP demonstrated that the structure of the resulting polymer could be precisely defined through macrocycle design. However, polymers prepared via ED-ROMP are generally contaminated by residual macrocyclic monomers (i.e., incomplete conversion), and their molecular weight distributions trend towards the most probable value of 2 due to secondary metathesis chemistry. Recent advances in macrocycle design have emerged to overcome these limitations by promoting monomer ring-opening over other metathesis reactions. This selectivity for ring-opening has been achieved through either kinetic control or by tuning olefin reactivity such that backbiting does not occur.

For example, the simple switch from a trans to a cis double bond in the macrocycle adds significant living character to what would otherwise be a solely entropy-driven equilibrium process. Meyer and coworkers demonstrated that lower dispersities, improved molecular weight control, and the ability to create block copolymers were possible for cis-olefin-containing monomers.[124] High monomer conversion (ca. 90%) was reached in only 10 min for the cis-monomer, while the trans- analogue required 2 h to reach the same conversion. The enhanced control afforded by ED-ROMP of cis-olefins appears to be a general phenomenon, as evidenced by improved polymerization control observed for a variety of macrocyclic monomers. Later termed selectivity-enhanced ED-ROMP (or SEED-ROMP), the differential reactivity between cis- and trans-macrocycles was further investigated by the Meyer group.[80] Computational analysis demonstrated that for

cis-olefin-containing monomers, the ratio of propagation rate to the rate of secondary metathesis is larger than for the corresponding trans-isomers (Figure 11). This preference arises from the fact that conformationally rigid cis-macromonomers present a higher population of reaction-favoring binding modes.
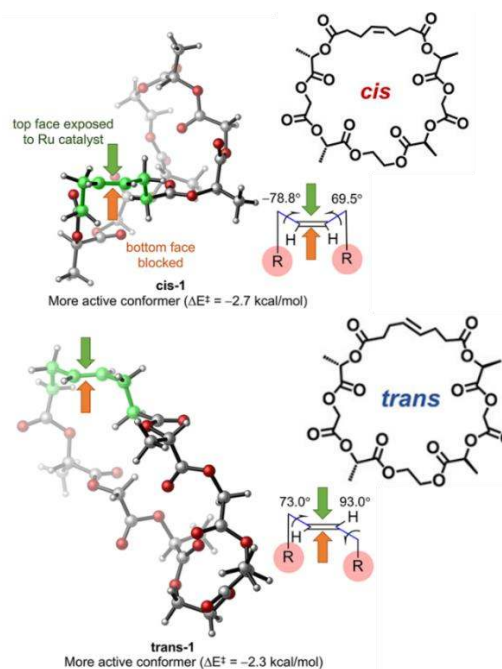

FIGURE 11. Origin of increased ring-opening kinetics of cis-olefinic macrocycles. (Reproduced from ref. 80. Copyright 2019 ACS Publications).

An alternative strategy to enhance the living character of ED-ROMP was recently developed by Gutekunst et al. which relies on chemical selectivity. This concept was inspired by work on relay RCM pioneered by Hoye and coworkers.[125] During relay RCM, a sequence of metathesis events is pre-determined by the arrangement of olefins or alkynes in the substrate. The movement of the metal catalyst is choreographed from one olefin to the next based on the reactivity of the various intermediates during the reaction cascade. In Hoye's seminal example, a relay substrate was developed which contained both internal alkenes and terminal alkenes. Metathesis on the geminally substituted terminal alkene was

favored over internal alkene metathesis due to the steric inaccessibility of the internal olefin.[126]

Furthering this strategy, Choi and coworkers reported tandem ring-opening/ring-closing metathesis polymerization of enyne monomers.[127] Employing the concept of relay metathesis, an internal alkene was placed 5 atoms away from an internal alkyne moiety, enabling intramolecular metathesis by providing a thermodynamic driving force, in this case, the generation of a conjugated diene and a cyclic moiety with low ring strain. Reaction of the catalyst with the alkyne generated a disubstituted alkylidene, which cannot undergo

further intermolecular metathesis but will rapidly react with nearby olefins on the substrate via intramolecular RCM. As a result, a substituted cyclopentene derivative is obtained, regenerating the reactive terminal alkylidene. This strategy succeeds as a consequence of the fast kinetics of 5- or 6-membered ring formation. The presence of additional enyne monomer allowed for propagation, resulting in the formation of a polymer with 5-membered cycles and diene moieties in the backbone. Due to the unique sequence of alkyne addition followed by RCM, the polymerization proceeded according to a chain-growth mechanism, facilitating molecular weight control.
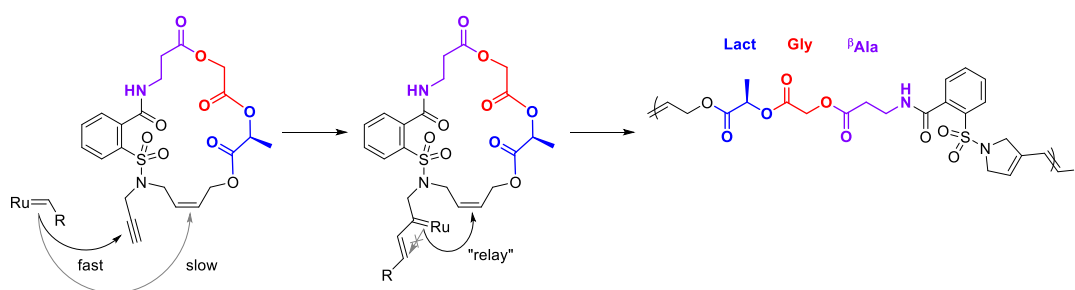

FIGURE 12. Relay metathesis applied to ED-ROMP to improve selectivity. (Reproduced from ref. 128. Copyright 2015 ACS Publications).

Translating Choi's strategy to ED-ROMP, Gutekunst et al. prepared peptide macrocycles with enyne active groups (Figure 12).[128] Exceptional molecular weight control was achieved for this system, and polymers with Đ < 1.4 were obtained at high conversions of cyclic monomer. Because controlled ED-ROMP is promoted by the unique chemistry of the relay metathesis "trigger", this method will likely be proven to be universal for a wide variety of macrocycles.

CONCLUSIONS AND FUTURE PERSPECTIVES

In summary, ED-ROMP has been well-established as an alternative technique to step-growth polymerization for the preparation of polymers with interesting backbone functionality, pre-threaded supramolecular guest molecules, well-defined sequences, or semi-crystalline segments. The availability of

modern Ru-based metathesis catalysts has facilitated a rapid expansion in this field in the past two decades, mediating the ring-opening of olefinic macrocyclic monomers of diverse chemistry. The rapid kinetics of metathesis reactions, especially those catalyzed by Grubbs' 3rd generation catalyst, and the selectivity of these reactions towards olefin substrates give ROMP an advantage over other ED-ROP strategies. This has allowed for the ring-chain equilibrium to be further biased towards the polymeric product. In addition, new strategies employing cis-olefin selectivity or relay-metathesis have further enhanced the efficiency of ED-ROMP.

Despite recent progress, most reports concerning ED-ROMP have been primarily proof-of-principle in nature. Whilst promising material properties have been realized via polymerization of olefinic macrocycles, many variations of ED-

ROMP have yet to be explored. The following points represent current and future challenges facing the field of ED-ROMP:

- Aqueous metathesis catalysts have become commercially available and several interesting reports have recently emerged demonstrating the feasibility of ROMP in aqueous milieu. To the best of our knowledge, no attempt has been made to carry out aqueous ED-ROMP, and polymerization of macrocyclic monomers in H_2O may enable the use of highly polar monomers or *in situ* phase separation.

- Only preliminary work has been reported on the synthesis of block copolymers by ED-ROMP *via* sequential polymerization. Undoubtedly, unique material or self-assembly properties could be achieved through the incorporation of polymer blocks derived from macrocyclic monomers.

- The current push for using renewable monomer feedstocks to reduce environmental burden provides the motivation to exploit naturally occurring unsaturated compounds or bulky natural products for synthesizing macrocyclic monomers and subsequent polymers with potentially interesting chemistries.

- Most studies on ED-ROMP (and ED-ROP in general) have been carried out with symmetrical macrocycles. A method to affect regiocontrol during polymerization would enable the use of asymmetric monomers.

The vast potential of ED-ROMP stems from the high degree of control it imparts over the chemical structure of the polymer backbone. As our understanding of how macrocycle structure and reaction conditions influence ED-ROMP, this degree of control of this powerful technique will continue to expand. The synthesis of polymers with low dispersities and controlled sequences has long been a fundamental aim in the field of polymer chemistry. Perhaps more than any other polymerization strategy, ED-ROMP has the capacity to realize this goal, and exciting next-generation materials will emerge to solve existing challenges of polymer science and beyond.

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GRAPHICAL ABSTRACT

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Recent Developments in Entropy-driven Ring-Opening Metathesis Polymerization: Mechanistic Considerations, Unique Functionality, and Sequence Control

ED-ROMP involves polymerization of olefin-containing macrocyclic monomers under entropically favorable conditions. In this review article, we consider how the mechanism of ROMP applies to ED-polymerizations, how olefinic macrocycles are synthesized, and how polymerization conditions can be tuned to maximize conversion. In addition, we highlight recent works, focusing on methods which can be employed to improve control during polymerization.