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Sequence-Controlled Copolymers Prepared via Entropy-Driven Ring-Opening Metathesis Polymerization

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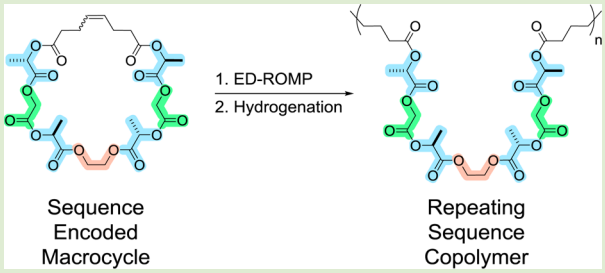
Supporting Information

ABSTRACT: A new general synthetic approach to sequenced macromolecules was developed and applied to the synthesis of polymers comprising lactic acid (**L**), glycolic acid (**G**), and ε-caprolactone (**C**)-derived monomer units. The new method employs entropy-driven ring-opening metathesis polymerization (ED-ROMP) to prepare copolymers with embedded sequences and controlled molecular weights. Cyclic macromonomer precursors were prepared by ring-closing metathesis of ethylene glycol (**Eg**)-linked sequenced oligomers bearing terminal olefins. ED-ROMP of the resulting macrocycles using Grubbs' second generation catalyst yielded **poly(CL-Eg-LC-Oed)**, **poly(CLL-Eg-LLC-Oed)**, **poly(LGL-Eg-LGL-Oed)**, and **poly(LGL-Eg-LGL-Hed)** (**Oed** = octenedioc acid; **Hed** = hexenedioc acid). Hydrogenation produced the saturated sequenced copolymers. Molecular weight was well-controlled and could be adjusted by varying the monomer-to-catalyst ratio. M_ns of 26−60 kDa were obtained (dispersities = 1.1−1.3). The methodology proved general for three different sequences and two olefinic metathesis groups.



The sophisticated interplay between structure and function has long been apparent in naturally occurring biological architectures. In these systems, a precisely sequenced framework prepared from a small pool of simple monomers imparts the properties responsible for the characteristic functions. The important relationship between sequence and properties would be expected to translate to synthetic polymers but has been less studied. Efforts in nonbiological polymers have historically focused on the more easily attainable and less sequence-controlled copolymer variants, that is, random, alternating, block, and gradient structures.[1−4] Recent advances have expanded the availability of more complex microstructures, and the concomitant studies of these new materials have established the potential for sequenced-based property control.[5−22]

We have long been interested in understanding the influence of sequence on polymer properties[23−32] and have focused significant attention on poly(lactic-*co*-glycolic acids) (PLGAs) and other α-hydroxy acid macromolecules due to their importance as nontoxic biodegradable bioengineering materials.[33−35] Our early efforts to prepare these materials relied on a segmer assembly polymerization (SAP) approach. Using this method, we prepared a library of sequenced copolymers and found that the rate of degradation and release of guest molecules is sequence-dependent.[30−32] Although these results were exciting and established the power of sequence in tuning properties, the full realization of the potential of these materials was limited by the lack of molecular weight control inherent in the step-growth SAP methodology. We, therefore, set out to develop a method to obtain sequence-controlled polymers with improved control of chain length without sacrificing the fundamental poly(alkylester) structure.

Herein, we report a strategy for making sequenced copolymers that utilizes entropy-driven ring-opening metathesis polymerization (ED-ROMP) and produces polymers with controlled molecular weights (Figure 1). ED-ROMP involves the ring-opening of a low-strain or unstrained cyclic olefin to produce an entropically favored polymer.[36−39]

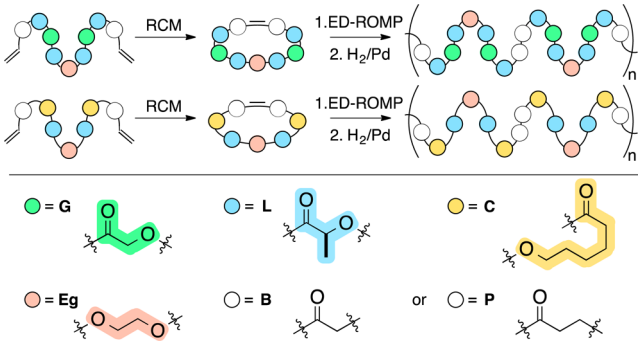


Figure 1. Preparation of sequenced copolymers by RCM and ED-ROMP. Monomer composition is highly customizable.

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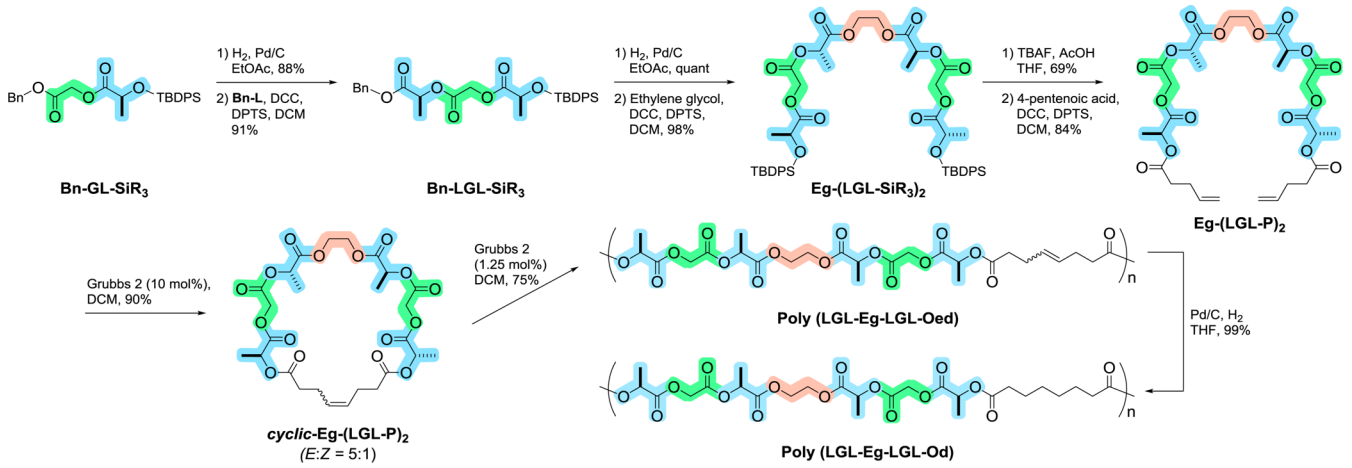
Scheme 1



There are several characteristics of ED-ROMP that make this an ideal approach to the problem of sequenced copolymers: sequence conservation, generality, and inherent molecular weight control. As with all ROMP reactions, the metathesis is highly selective and atom connectivity within the ring remains unchanged. Hillmyer and co-workers have cleverly exploited these characteristics to create sequenced copolymers from the ROMP of variously substituted cyclooctene rings.[7] Although this process resembles ED-ROMP in some aspects, the reaction is inherently limited to rings that exhibit ring strain.

Also related to the current work is the recent report by Hawker and co-workers in which a macrocyclic monomer with embedded sequence was polymerized using a novel relay ring-opening mechanism. In this system, which does not rely on ED-ROMP driving forces, a specialized trigger moiety was employed and is retained in the resulting polymer.[40]

Entropy is the primary driving force for the ED-ROMP reactions utilized in the current study. Concentration is used to favor chains over rings under conditions that allow for equilibration. Molecular weight control is possible because the number of chains is determined by the catalyst introduced. Final molecular weight is then a function of monomer-to-initiator ratio and the concentration, which determines the ring−chain equilibrium. The intrinsic molecular weight control differentiates ED-ROMP from the closely related, primarily step-growth acyclic diene metathesis polymerization (ADMET).[9,41,42]

ED-ROMP and the more general entropy driven ring-opening polymerization (ED-ROP) have been applied previously to a variety of macrocycles,[43−45] and the mechanism is well understood. To the best of our knowledge, this is the first example of ED-ROMP being explicitly used to produce polymers that display within them a series of sequenced monomers.

We began our investigation by first preparing cyclic precursors containing L-lactic acid (**L**), glycolic acid (**G**), and ε-caprolactone (**C**)-derived sequenced oligomers (segmers).[27,28,32] A typical synthesis begins with the doubly protected subunit **Bn-GL-SiR$_3$** (Scheme 1). Following hydrogenolysis to remove the benzyl group, carbodiimide-promoted coupling of **GL-SiR$_3$** with **Bn-L** produced the trimer **Bn-LGL-SiR$_3$**. Deprotection of the acid followed by coupling to ethylene glycol (**Eg**) yielded the palindromic segmer **Eg-(LGL-SiR$_3$)$_2$**. Removal of the silyl protecting group with TBAF/AcOH gave the fully deprotected diol **Eg-(LGL)$_2$**, which was coupled to either 4-pentenoic acid (**P**) or 3-butenoic acid (**B**, Scheme S1) to produce a diolefin-terminated segmer. This convergent synthetic approach allows for the facile assembly of segmers of any length and sequence from a common set of building blocks using standardized procedures. Optimized approaches could be easily substituted if a particular sequence was targeted for scale up.

Ring-closing metathesis (RCM)[46−48] with Grubbs' second generation catalyst (Grubbs 2) yielded the desired cyclic macromonomers. An analogous route was employed to prepare ***cyclic*-Eg-(LC-P)$_2$** and ***cyclic*-Eg-(LLC-P)$_2$** (Schemes S2 and S3, respectively). Although dilute conditions were used to inhibit oligomerization, the reaction was easily performed on a 2−3 g scale.

Once the requisite macrocycles had been constructed, ED-ROMP was carried out in the presence of Grubbs 2 (Scheme 1). To promote polymerization over nonproductive intramolecular ring formation, the reactions were conducted at high concentration (0.7 M). The polymerizations were quenched with ethyl vinyl ether to provide a series of polymers whose physical properties are shown in Table 1. The M_ns of the

Table 1. Polymer Molecular Weight and Thermal Data

Polymer	M/cat	T_g[a] (°C)	M_n (kDa)	M_w (kDa)	Đ
poly(CL-Eg-LC-Oed)-1	78	−27	26[b]	32[b]	1.3[b]
poly(CL-Eg-LC-Oed)-2	164	−27	39[b]	48[b]	1.3[b]
poly(CLL-Eg-LLC-Oed)-1	20		24[c]	32[c]	1.3[c]
poly(CLL-Eg-LLC-Oed)-2	19		29[c]	37[c]	1.3[c]
poly(CLL-Eg-LLC-Oed)-3	45		42[c]	53[c]	1.3[c]
poly(CLL-Eg-LLC-Oed)-4	45	−11	47[c]	60[c]	1.3[c]
poly(CLL-Eg-LLC-Oed)-5	75		48[c]	63[c]	1.3[c]
poly(CLL-Eg-LLC-Oed)-6	75		50[c]	65[c]	1.3[c]
poly(CLL-Eg-LLC-Oed)-7	125		60[c]	78[c]	1.3[c]
poly(CLL-Eg-LLC-Oed)-8	126		56[c]	71[c]	1.3[c]
poly(LGL-Eg-LGL-Oed)	78	18	33[b]	44[b]	1.3[b]
poly(LGL-Eg-LGL-Od)[d]	na	13	28[b]	41[b]	1.5[b]
poly(LGL-Eg-LGL-Hed)	80	32	33[b]	46[b]	1.4[b]
poly(LGL-Eg-LGL-Hd)[d]	na	23	27[b]	42[b]	1.5[b]

[a]First heating cycle at 10 °C/min. [b]SEC in THF, relative to PS standards. [c]SEC in THF, absolute molecular weight data. [d]Produced by hydrogenation of the corresponding **Oed** or **Hed** precursor.

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polymers ranged from 26 to 60 kDa. The T_gs of the polymers depended on both sequence and spacer composition, ranging from −11 °C for the **LLC** polymer to 32 °C for the **LGL** polymer with the **Hed** spacer (Figures S1 and S2). Interestingly, the T_gs of the two **poly(CL-Eg-LC-Oed)** samples were both −27 °C, despite a significant difference in molecular weight (Figure S2). Therefore, both polymers are in the regime where thermal properties are no longer affected by degree of polymerization. The SAP approach, which generally produced polymers of lower molecular weights, exhibited a range of T_gs for similar sequences.[27,28,32]

Based on our extensive experience characterizing SAP-produced α-hydroxy acid polymers with varying sequences[27,28,32] we can confirm conclusively that the sequences embedded in the macrocycles were retained during the polymerization process (Figures S3−S8). Using ^{1}H NMR spectroscopy, which we have previously shown is extremely sensitive to sequence in this class of polymers, we can rule out scrambling and epimerization.

To determine if these reactions conform to the expectations of an ED-ROMP process, kinetic studies of ***cyclic*-Eg-(LGL-P)$_2$** polymerizations were carried out by quenching aliquots at specific time intervals. SEC characterization of these aliquots confirmed that the M_n sharply increased at the onset of propagation and reached a maximum within 15 min (Figure 2a, Table S1). As expected during ED-ROMP, the M_n decreased and the dispersity ($Đ$) increased as secondary metathesis reactions became more prevalent. Secondary metathesis in this case means reaction of the catalytically active metal center with an internal double bond in the polymer chain. Secondary metathesis leads to ring−chain equilibration but does not scramble the embedded sequence.

Monomer conversion rose rapidly and then saturated at a level determined by ring−chain equilibrium, in this case 85.9% (Figure 2b). Conversion was monitored using ^{1}H NMR spectroscopy. The chemical shifts of the diastereotopic methylene protons of **G**, found at 4.9−4.55 ppm, were distinct for the ring-closed and ring-opened species (Figures 3 and S9). The effects of secondary metathesis are also well illustrated by the plot of molecular weight vs conversion (Figure 2c).

The initial linear phase was followed by a gradual drop in molecular weight at moderate conversions. Once the ring−chain equilibrium was reached the molecular weight continued to decrease due to secondary metathesis reactions. The dispersities gradually rose to 1.3. Importantly, we see evidence in these initial experiments for the desired molecular weight control. It is clear from the kinetic studies that the reaction is following the course expected for an ED-ROMP process. As such, molecular weight is governed by the monomer-to-catalyst ratio ([M]/[cat]) and the concentration of the reaction, which determine the proportion of monomers in chains with catalyst end groups.[37,49] Consistent with this expectation, we found that when the [M]/[cat] ratio was adjusted from 78:1 to 164:1 in the ED-ROMP of ***cyclic*-Eg-(LC-P)$_2$**, the M_n of the crude reaction mixture increased from 26 to 39 kDa (Table 1).

In a more detailed study of molecular weight control a series of polymerizations of ***cyclic*-Eg-(LLC-P)$_2$** were carried out (Table 1, Scheme S3, and Table S2). Four different [M]/[cat] ratios (20, 45, 75, and 125) were used in duplicate polymerizations and their absolute molecular weights were determined (Figure 4). Importantly, the M_ns increased consistently as a function of the [M]/[cat] ratio, although they did not track perfectly with those theoretically predicted.

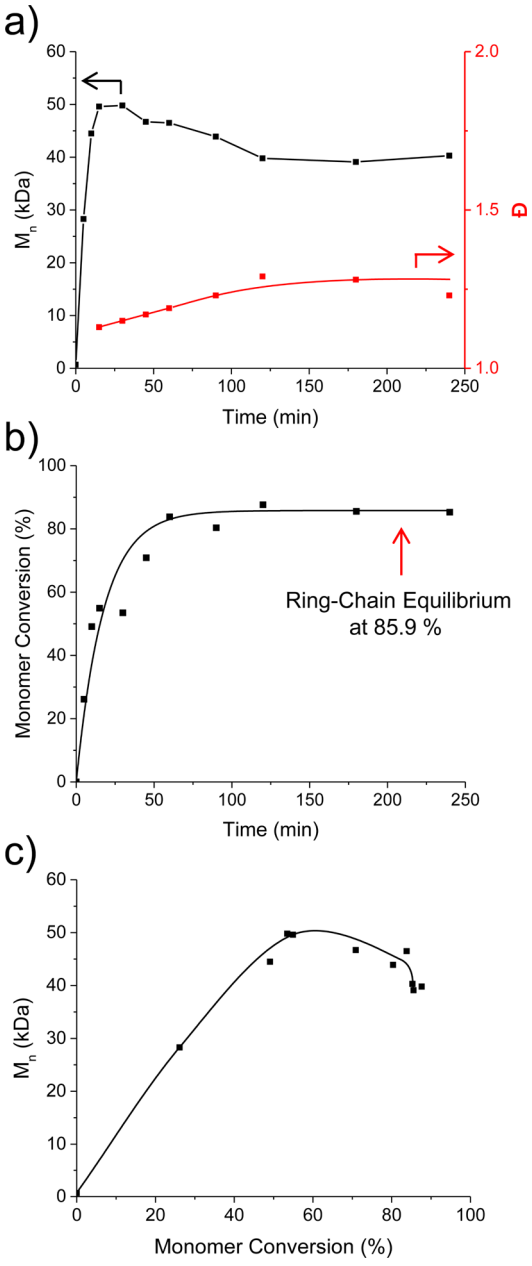

Figure 2. ED-ROMP of ***cyclic*-Eg-(LGL-P)$_2$**: (a) M_n vs time (black) and dispersity vs time (red); (b) monomer conversion (%) vs time; (c) M_n vs monomer conversion (%).

The pattern of the deviation, where molecular weights start higher than expected for low [M]/[cat] ratios and gradually decrease to lower than expected as the ratio of monomer to catalyst increases, has been observed previously for ED-ROMP polymerizations.[50] It is also important to note that the reactions were highly reproducible, duplicate conditions produced nearly identical molecular weights. Note: as the ring−chain equilibrium could not be calculated for this monomer because of an unfortunate overlap of NMR signals, the previously observed ratio of 85.9% was used to estimate the predicted values in Figure 4. Molecular weight predictions based on a reasonable range of ratios (80−90%) do not substantially change the analysis (Figure S10).

The olefinic group in the metathesis "linker" could be removed by hydrogenation. The saturated polymers containing

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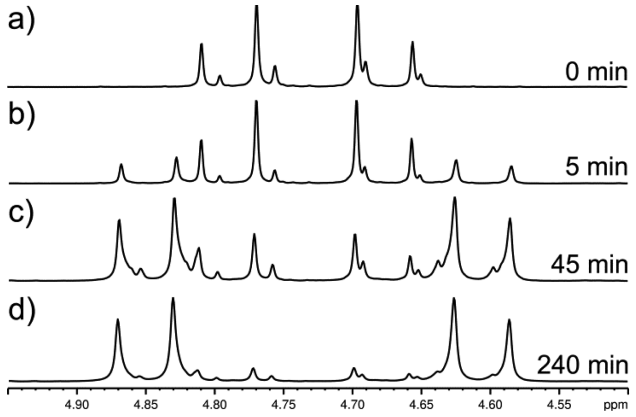

Figure 3. ^{1}H NMR (400 MHz) spectra of ED-ROMP of ***cyclic*-Eg-(LGL-P)$_2$** to **poly(LGL-Eg-LGL-Oed)**. Major resonances from *trans* isomers and minor resonances from *cis* isomers.

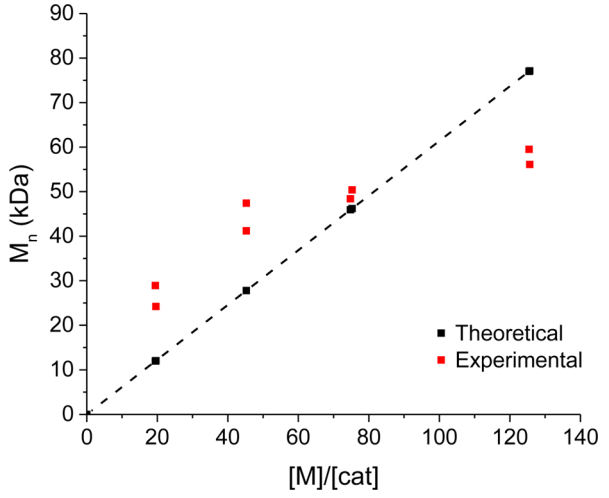

Figure 4. Molecular weight control study of the polymerization of ***cyclic*-Eg-(LLC-P)$_2$** to form **poly(CLL-Eg-LLC-Oed)** using varying [M]/[cat] ratios. The molecular weights determined are in red, while the dotted black line represents a theoretical living polymerization taking ring−chain equilibrium into account.

the LGL sequence were isolated as colorless solids with no visual evidence of catalyst contamination and conversions >97% (Schemes 1 and S1). Hydrogenation decreased the T_g of these polymers by 4−10 °C.

In summary, cyclic macromonomers containing ring-opened ε-caprolactone, lactic and glycolic acids were prepared by RCM and subsequently polymerized by ED-ROMP to yield sequence-preserved copolymers with molecular weight control. Kinetic studies confirmed the adherence of the reaction to the expected ED-ROMP pathway and the extension of the procedure to multiple sequences established that the polymerization conditions are sequence-independent.

The ED-ROMP approach to sequenced copolymers, which offers unique advantages over step-growth methods, should prove applicable to other sequences of α-hydroxy acids and to monomers beyond those described in this paper. It should be possible to execute ED-ROMP on any sequence that can be incorporated into an olefin-bearing macrocycle, a process greatly facilitated by the known propensity of RCM to generate large rings.[46] Although monomer production is somewhat limited by the need for high dilution, the production of gram-scale quantities sufficient for laboratory studies is not challenging. The tolerance of RCM for functional groups and the generality of the reaction should also make it possible to design the olefin-containing linker unit of the resulting copolymers to be compatible with the targeted properties and applications. Future studies will explore further the generality of this approach.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.5b00528.

Experimental section detailing polymer preparation, characterization, and reaction studies; ^{1}H NMR spectra of polymers; DSC data; and tables of conditions for ED-ROMP kinetics and molecular weight control experiments. (PDF)

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Notes

The authors declare no competing financial interest.

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