Functionalizable Stereocontrolled Cyclopolyethers by Ring-Closing Metathesis as Natural Polymer Mimics

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Abstract: Whereas complex stereoregular cyclic architectures are commonplace in biomacromolecules, they remain rare in synthetic polymer chemistry, thus limiting the potential to develop synthetic mimics or advanced materials for biomedical applications. Herein we disclose the formation of a stereocontrolled 1,4-linked six-membered cyclopolyether prepared by ring-closing metathesis (RCM). Ru-mediated RCM, with careful control of the catalyst, concentration, and temperature, selectively affords the six-membered-ring cyclopolymer. Under optimized reaction conditions, no metathetical degradation, macrocycle formation, or cross-linking was observed. Post-polymerization modification by dihydroxylation afforded a novel polymer family encompassing a poly(ethylene glycol) backbone and sugar-like functionalities (“PEGose”). This strategy also paves the way for using RCM as an efficient method to synthesize other stereocontrolled cyclopolyethers.

Control over the absolute configuration of a synthetic polymer main chain remains a significant challenge,[1,2] especially in light of the importance of this regularity in natural polymers.[3] This stereoregularity of the main chain plays a significant role in shaping the three-dimensional structure, and in-turn influencing the biological function of the natural macromolecules. In addition, rings are embedded in the backbones of many natural polymers, which restricts the bond rotation around the stereogenic centers.[4] These local conformational restrictions result in a specific compact structure along the polymer backbone: that is, the six-membered cyclic structures of cellulose and amylose backbones (Figure 1) form linear and helical structures, respectively. However, synthetic polymers that are made of similar 1,4-linked six-membered rings that would mimic these secondary structures present a unique challenge to synthetic chemists, especially if conventional polymerization techniques are employed.[5]

Ring-closing metathesis (RCM) has been predominantly used to prepare small cyclic molecules, including phosphineboranes, sulfides, amines, phenols, and oxazolines.[6] The use of RCM in polymer synthesis, however, remains rare,[7] with only a few examples of the preparation of polymeric nanoparticles,[8] cyclic polymers,[9] and cyclopolymers.[10] We hypothesized that this under-utilized post-polymerization technique could be employed for the synthesis of cyclopolyethers to mimic the topology of polysaccharides, where the configuration of all the stereogenic centers present in the polymers is controlled (Figure 1). While the broad functional group tolerance of metathesis catalysts suggests a broad reaction scope, poly(ethylene glycol) backbones are especially interesting given their role as gold standard stealth polymers in drug delivery.[11] We thus envisaged a sequence of ring-opening polymerization (ROP), ring-closing metathesis (RCM), and dihydroxylation (DH), as shown in Figure 1. An initial ROP of 3,4-epoxy-1-butene (EB) would afford polyepoxybutene (PEB), with the chirality of the parent epoxide leading to stereogenic control in the linear polymer. Ring-closing metathesis would then give a 1,4-linked functionalizable cyclopolyether (FCPE). Further functionalization, specifically diatereoselective dihydroxylation (DH), would produce a new stereocontrolled polymer that we have called “PEGose”, as it has the structural features of both sugars and
PEG, with the glycosidic bond of amylose replaced by a strong ether link.

For this structural control, it is imperative to start with enantiopure EB. Atactic PEB would lead to a non-stereoccontrolled cyclopolymer, where the 1,4-links would be indiscriminately cis (amylose-like) or trans (cellulose-like; Figure 2). Furthermore, the subsequent dihydroxylation reaction would not be diastereoselective on the trans 1,4-disubstituted six-membered rings. On the other hand, dihydroxylation of the cis-cyclopolymer will occur exclusively from the top face, which is not hindered by the two substituents.

The 13CNMR spectrum of the resultant PEB showed two signals for the stereogenic carbon atom, thus confirming the expected atacticity of the produced PEB (\(\alpha\)-PEB), as the catalyst is not stereoselective. Controlled low-molecular-weight polymers were produced, with \(M_{\text{GPC}}\) values of 2100 and 3200, respectively, and \(D < 1.2\). Although RCM on \(\alpha\)-PEB will not give a stereocontrolled cyclopolyether, it was used to establish the optimum RCM conditions. Although little difference in molecular weight was observed by gel-permeation chromatography (GPC) for the lowest molecular weight PEB samples, because of overlap with eluent peaks, the higher molecular weight samples (\(M_{\text{GPC}} 3200\)) showed a clear loss of molecular weight on ring closing, correlating well with the loss of a single ethylene molecule per repeat unit (Table 1). Optimal ring-closing conditions for PEB included the use of 5 mol % of the second-generation Hoveyda–Grubbs (HG2) catalyst at high concentrations of the polymer (\(\geq 0.2 \text{m}\) with respect to the monomer unit) in 1,2-dichloroethane (1,2-DCE; Table 1). Note that poor conversions were achieved with the first-generation Grubbs catalyst, likely because of the lower reactivity and thermal stability (see Table S2).\(^{[15]}\)

When concentrations were kept at 0.2 \(\text{m}\) (Table 1, entry 1), no cross-linking was observed, and the polymer dispersity and viscosity remained similar. However, at higher concentrations (0.4 \(\text{m}\)), competing ring-closing and polymer cross-linking occurs, as evidenced by the formation of a high-molecular-weight shoulder in the GPC traces (see Figure S1).\(^{[16]}\) This new polymer represents the first syntheticyclopolyether prepared, but its inherent atacticity prevents any overall topological control. Thus, isotactic-rich PEB (i-PEB) was synthesized by ROP of the \(R\) enantiomer of EB (95:5 e.r.), which was prepared from racemic EB by Jacobsen\(^{[17]}\)’s hydrolytic kinetic resolution (see page 3 in the Supporting Information).

The \(5^\text{th}\)CNMR spectrum of the resultant PEB showed two signals for the stereogenic carbon atom, thus confirming the expected atacticity of the produced PEB (\(\alpha\)-PEB), as the catalyst is not stereoselective. Controlled low-molecular-weight polymers were produced, with \(M_{\text{GPC}}\) values of 2100 and 3200, respectively, and \(D < 1.2\). Although RCM on \(\alpha\)-PEB

| Entry\(^{[a]}\) | [Olefin] | \(M_{\text{st}}\)^{[b]} | \(D_{\text{st}}\) \(^{[b]}\) | Conv. [%] \(^{[c]}\) | \(M_{\text{th}}\)^{[d]} | \(M_{\text{GPC}}\)^{[b]} | \(D\)^{[e]} |
|---|---|---|---|---|---|---|---|
| 1 | 0.2 | 3200 | 1.19 | 99 | 2540 | 2500 | 1.21 |
| 2 | 0.4 | 3200 | 1.19 | 99 | 2540 | 2900 | 1.3 |

\(^{[a]}\)Reactions performed in 1,2-DCE at reflux with 5 mol % of the HG2 catalyst for 72 h. \(^{[b]}\)\(M_s\) and \(D\) determined by GPC versus uncorrected PS standards. \(^{[c]}\)Determined by \(^1\)H NMR spectroscopy by integration of the olefin signals of the produced polymer. \(^{[d]}\)\(M_{\text{th}} = PE B\times 0.8\) because of the expected loss of one \(\text{C}_2\text{H}_4\) per monomer unit.

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tionally rigid isotactic derivative. This profile suggests a mechanism originally proposed by Coates and Grubbs: 1) a fast stage when the catalyst randomly closes adjacent olefins until only isolated olefins remain, and 2) a slow stage when the rings rearrange along the chain until all the olefins are cyclized. This requires that the cyclized olefins can undergo further metathetic reactions, thus enabling a reopening and exchange of the product rings. The two-stage reactivity is showcased through the RCM optimization, with the first stage completed in a similarly short time regardless of the solvent used (1,2-DCE, DCM, THF, CHCl₃) or catalyst loading (2–5%; see Tables S3–S6).

An illustration of this mechanism can be observed in the ¹³C NMR spectra of both the atactic and isotactic FCPE and PE (Figure 4), which demonstrate that greater than 99% of the olefins of PE are cyclized (Figure 4B,E). In the atactic FCPE (Figure 4B), the new olefin peaks appear as broad, overlapping resonances (δ = 125–132 ppm), which reflects the different ring configurations along the polymer backbone. On the other hand, i-FCPE showed only two sharp olefin resonances (Figure 4E), thereby confirming the stereocontrolled structure of the polymer (Figure 2, cis-cyclopolymer). However, the spectrum of i-FCPE after 94% conversion (Figure 4D), which was taken after 30 min, showed the 6% of uncyclized isolated olefin signals (δ = 118.3 and 135.6 ppm) and several cyclic olefin signals (δ = 125–132 ppm).

Most of these cyclic olefin peaks were not observed at the end of the reaction (after 7 days), which purports that in the initial metathesis stage when the catalyst randomly closes the olefins, different ring sizes were formed (Figure 5). In the subsequent slow stage, the rings rearrange along the chain until only the most thermodynamically stable six-membered rings are present.

Fixing the free rotation of the pendent olefins through RCM has an impact on the glass transition temperature (T_g) in both α- and i-PE. The organized structure of i-FCPE has a significantly higher T_g value than α-FCPE (−11°C from −26°C). This is consistent with the presence of cycles hindering segmental chain mobility in both structures.

To prepare the PEGose polymer, i-FCPE was dihydroxyalted under mild conditions using N-methylmorpholine N-oxide (NMO) and OsO₄ as a catalyst. This second post-polymerization functionalization was diastereoselective, as OsO₄ attacks on the less hindered side of the ring (Figure 2), as demonstrated by ¹³C NMR spectroscopy (Figure 6). The dihydroxylation produces a unique stereocontrolled polymer structure, with a hydrophilic surface (cis-diols) opposite the hydrophobic backbone. This distinctive structure could have potential applications in biomaterials, blood storage, or drug delivery.

Table 2: RCM of PEB with HG2 catalyst.

| Entry | PEB | Mn | θ | t (days) | FCPE | Mn | θ |
|-------|-----|----|---|---------|------|----|---|
|       | Mₐ |    |   |         | Mₐ |    |   |
| rac   | 4380 | 1.18 | −56 | 5 | 3500 | 2700 | 1.22 | −26 |
| R     | 3940 | 1.15 | −54 | 7 | 3150 | 2600 | 1.19 | −11 |

[a] [Olefin] = 0.2 M; the reaction conversion in 1,2-DCE at reflux with 5 mol% HG2 catalyst was monitored daily until > 99% by ¹H NMR spectroscopy. [b] Mₐ and D determined by GPC versus uncorrected PS standards. [c] Determined by differential scanning calorimetry. [d] Mₐ = PEB Mn × 0.8.

Figure 3. The RCM of i-PE, Mₐ = 3940 and D = 1.15, kinetic profile at 0.2 M using 5% HG2 catalyst in 1,2 DCE under reflux monitored by ¹H NMR spectroscopy.

Figure 4. ¹³C NMR spectra of the olefin region in CDCl₃ of: A) α-PEB, B) α-FCPE, C) i-PEB, D) metathesis product of i-PEB after 30 min (94% conversion), and E) metathesis product of i-PEB after 7 days (>99% conversion).

Figure 5. Proposed kinetic mechanism of the RCM of i-PEB.
Controlled dihydroxylation to form sugar-like structures with a poly-
delivery, with face polarity shaping the surface chemistry and self-assembly.\[18,20\] While amylose, \(\text{(C}_{6}\text{H}_{10}\text{O}_{5})_n\), and PEGose, \(\text{(C}_{6}\text{H}_{10}\text{O}_{4})_n\), have similar monomer units, PEGose is connected with an additional methylene bridge, which gives more flexibility to the polymer backbone. Circular dichroism (CD) was used to determine the influence of this CH\(_2\) unit on the secondary structure of the PEGose. Indeed, PEGose and amylose have the same prominent negative bands at \(\lambda = 182\) nm (Figure S25), which shows that this new PEGose has an extended pseudohelical structure similar to amylose.\[21\] Efforts to gain complementary X-ray characterization of this self-assembly are ongoing.

Although excess NMO affords complete dihydroxylation of the double bonds, the reaction also offers the ability to adjust the polymer polarity by limiting this co-oxidizing reagent. Reducing the NMO loading from 1.1 to 0.8 equivalents dramatically alters the polarity and solubility of the resultant polymer (Table 3), thereby offering a secondary (ethylene glycol) backbone that leads to a new PEGose architecture. The isotactic linear PEB leads, after RCM, to a cyclic polymer with well-defined cis substitution patterns. By taking advantage of the diastereoselectivity of the subsequent dihydroxylation reaction, we were able to create a cyclopolymer where the configuration of all the stereogenic centers is controlled, and which mimics the natural amylose. This new platform offers significant potential for future functionalization, drug conjugation, and biomedical mimicry, and is a significant focus of our future work, as is expanding this idea to other polymer backbones.

**Table 3: Controlled dihydroxylation to form cis-PEGose.**

| Entry | [Olefin]/[NMO] | Con. [%] | Soluble in | Insoluble in |
|-------|--------------|---------|------------|-------------|
| 1     | 1:1.1        | >99     | H\(_2\)O, DMSO | DMF         |
| 2     | 1:0.9        | 91      | DMF, MeOH  | acetone     |
| 3     | 1:0.8        | 80      | acetone    | EtOAc, CH\(_2\)Cl\(_2\) |

\[a\] Determined by \(^1\)H NMR spectroscopy through integration of the olefin signals relative to the polymer signals.

In conclusion, we have shown that RCM of linear, stereoregular polymers with pendant olefins can be used to prepare cycopolymers with excellent control over the ring size. Further functionalization of the latent olefin groups by dihydroxylation provides sugar-like structures with a poly-

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**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** cycopolymers · polyethylene glycol · post-polymerization modification · ring-closing metathesis · stereoregular synthesis

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Off the PEG: Ruthenium-catalyzed ring-closing metathesis (RCM) under careful control of the catalyst, concentration, and temperature allows the stereocontrolled synthesis of 1,4-linked six-membered cyclopolyethers. Post-polymerization modification by dihydroxylation (DH) affords polymers with a poly(ethylene glycol) backbone and sugar-like functionalities (“PEGose”).