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Partial Kinetic Resolution of Oxanorbornenes by Ring-Opening Metathesis Polymerization with a Chiral Ruthenium Initiator

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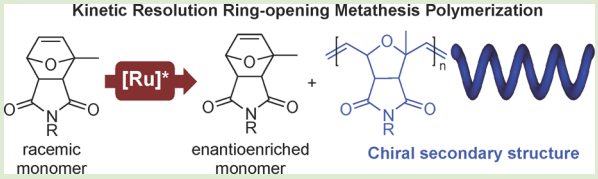
Supporting Information

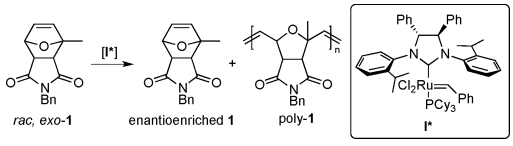
ABSTRACT: We report the first kinetic resolution by ring-opening metathesis polymerization (KR-ROMP). The polymerization profile showed a solvent-dependent variation of selectivity (S) over the course of the reaction. In tetrahydrofuran and dichloromethane, the resolution selectivity increased over the course of the reaction, while in toluene the selectivity was much higher in the beginning of the reaction and decreased throughout. Evidence suggests that the change in selectivity might be attributed to the chiral secondary structure of the growing polymer chain.



Of the many methods to synthesize enantiopure molecules, kinetic resolution (KR) polymerization is unique in that it simultaneously produces enantioenriched small molecule monomers and chiral polymers from a racemic monomer feed by preferentially polymerizing one enantiomer while leaving the unreacted monomer enantioenriched. KR polymerization is most commonly dictated by chiral metal catalysts and has been established for a variety of monomer classes, including epoxides,[1] lactide,[2] and α-olefins.[3] We have been interested in ruthenium-mediated ring-opening metathesis polymerization (ROMP) because its livingness and high functional group tolerance make it a powerful and versatile methodology to synthesize a wide array of well-defined polymeric materials.[4] Although there are examples of kinetic resolution of small molecules by ring-closing metathesis by our group[5] and others,[6,7] kinetic resolution using ROMP has not been demonstrated to the best of our knowledge. In this report, we disclose the first example of a partial kinetic resolution by ROMP (KR-ROMP) and propose an unusual ligand effect on the selectivity of the polymerization.

For this study, we focused on a system that is based on known initiator **I**, a member of a successful class of the ruthenium olefin metathesis catalysts that bear chiral monodentate N-heterocyclic carbenes (Scheme 1).[8] These catalysts are easily synthesized and have demonstrated selectivities up to 92% *ee* in asymmetric ring-closing metathesis (RCM) at low catalyst loading (<1 mol %). The enantioselectivity of the catalyst is derived from (4*R*,5*R*)-diphenyl NHC that imparts axial chirality to the N-aryl substituents and into the environment around the metal center. Monomer **1** is a 1-methyloxanorbornene derivative that contains structural homology to a number of pharmaceutically active compounds[9] and can also participate in alternating ring-opening metathesis copolymerization with *cis*-cyclooctene.[10] Furthermore, this monomer places the stereogenic carbon center directly adjacent to the olefin, which we hypothesized would make it susceptible to the KR-ROMP by **I**.

Scheme 1. Kinetic Resolution by Ring-Opening Metathesis Polymerization (KR-ROMP)



The KR-ROMP system was analyzed in a variety of solvents where the conversion, molecular weight and selectivity (S) were determined over the course of the reaction (Table 1, Supporting Information). The polymerization reaction profiles indicate that a chain-growth mechanism still prevails. The observed molecular weight is roughly 4-fold higher than the theoretical molecular weight by conversion, possibly caused by poor initiator efficiency. Further evidence for slow initiation comes from the higher polydispersity indices (PDI) of the isolated polymer (PDI_{THF} = 1.1−1.2; PDI_{DCM} = 1.2−1.3; PDI_{PhMe} = 1.3−1.4) compared to the polymers derived from unsubstituted norbornenes. The methylated 1-position on the monomer likely prevents easy ligation and reaction with the initiator.

The resolution selectivity ($S = k_{fast}/k_{slow}$) was examined next (Figure 1). In the cases where the reaction was performed in THF and DCM, the selectivity of the resolution doubled over the course of the reaction from S = 1.9 to S = 3.8 for THF and S = 1.9 to S = 3.0 for DCM (Table 1, experiments 1 and 2, Supporting Information). Conversely, the resolution in toluene

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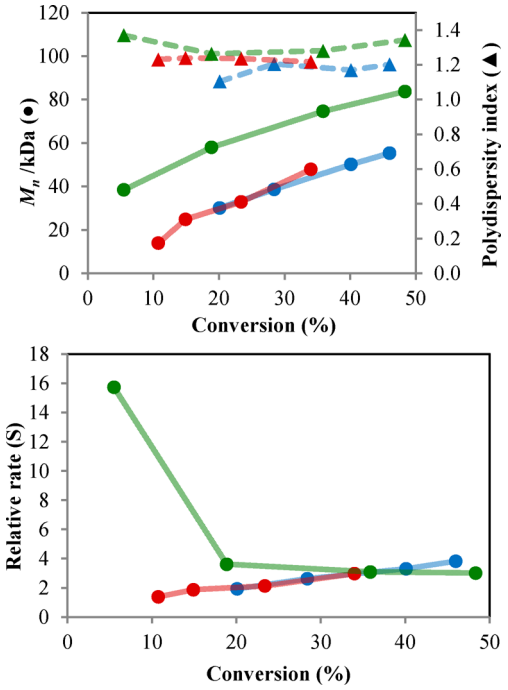

Figure 1. Solvent dependence on selectivity during the KR-ROMP of **1** by **I**. Conditions: solvent, 20 °C, $[\mathbf{1}]_0/[\mathbf{I}^*]_0 = 100$. Solvents: THF (blue), DCM (red), and toluene (green). *S* was calculated assuming first order kinetics of monomer consumption.

saw a *decrease* in the selectivity from $S = 16$ to $S = 3.0$ (Table 1, experiments 3 and 4, Supporting Information). It is common that solvent can greatly affect the enantioselectivity of a catalytic transformation, but in most cases of KR polymerizations, the *S* indicates relative rates of polymerization and is constant throughout the reaction.

Although a change in solvent can highly alter the enantioselectivity of metal catalyzed reactions, it has been shown in previous asymmetric ring-closing olefin metathesis reports that solvent does not significantly change the selectivity of the transformation.[8b] During the KR-ROMP the conformation of the growing polymer chain could further influence *S*. More so, an enantioenriched polymer could lead to higher ordered conformations. For example, in the solid state, polyoxanorbornenes with large tapered side groups have been shown to form a columnar helix mesophase.[11] Despite the fact that it has been shown that polyoxanorbornenes do not adopt helical conformations in solution, we hypothesized that moving steric bulk from the distal side groups to the main chain could induce chiral secondary structure in solution. To examine this possibility, we analyzed the chiroptical properties of the isolated polymers. Poly-**1** shows a negative Cotton effect that corresponds to the $\pi-\pi^*$ transition of the succinimide group. Because the polymer exhibits a Cotton effect while the enantioenriched monomer does not strongly suggests the polymer is adopting a higher ordered, chiral conformation, such as excess one-handed helicity (Figure 2). Additionally, the intensity of this Cotton effect is molecular weight dependent and increases with molecular weight. Optical activity of helical polymers increases with molecular weight as the helix becomes more well-developed.[12]

To investigate the solvent-induced change in *S*, we explored the possibility that the polymer conformation could also be altered in different solvents. Synthetic helical polymers can be

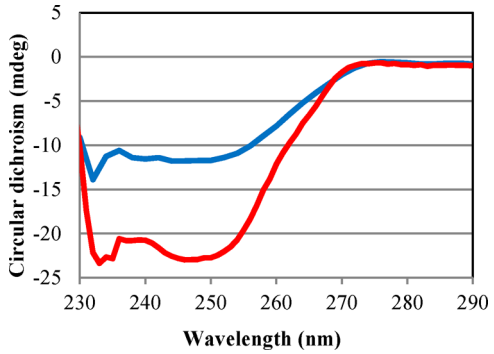

Figure 2. Circular dichroism spectra of poly-**1** in THF at 25 °C. The *ee* for both samples is 10%. The concentration of both samples is 1 mg/mL. M_w = 32.8 kDa (blue) and 43.6 kDa (red).

broadly classified as either static or dynamic helical polymers, depending on the inversion barrier of the helical conformation.[13] Static helical polymers have a relatively high energy barrier for helix inversion and are stable in solution, while dynamic helical polymers have a relatively low energy barrier for helix inversion and exist as a mixture of right- and left-handed helical domains that are separated by rarely occurring helix reversals. Even a slight incorporation of optically active repeat units can shift the equilibrium to excess one-handed helicity.

We synthesized monomer **2**, bearing an azobenzene moiety, to probe the effects of solvent on polymer secondary structure in toluene. Monomer **2** was polymerized by **I*** to poly-**2**, where the unreacted monomer possessed 17% *ee*.

The isolated polymer was analyzed by circular dichroism and demonstrated a solvent-dependent response where samples in THF and DCM had positive Cotton effect, while in toluene had negative Cotton effect (Figure 3). These data strongly

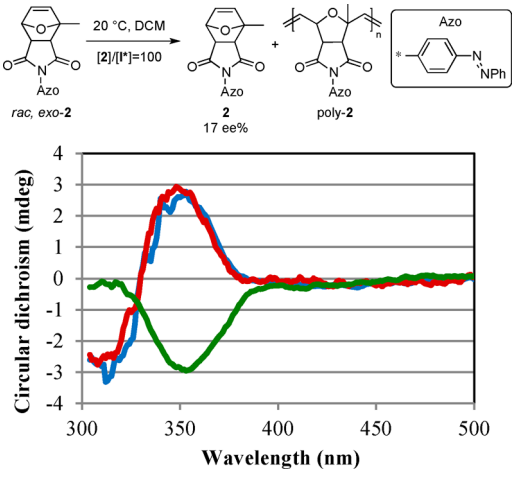

Figure 3. Solvent-dependent circular dichroism of poly-**2** at 25 °C. The polymer concentration for all samples is 1 mg/mL. Solvents: THF (blue), DCM (red), and toluene (green).

suggest that the helix-sense can be inverted through solvent interactions and the differences in helix-sense could correspond with change in *S* for each reaction solvent. We believe that the stereochemical model that best explains this phenomenon is one where the active chain end adopts different diastereomeric conformations in THF and DCM or toluene. This provides three chiral control elements around the ruthenium center: the

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NHC ligand, the last incorporated monomer and the helicity of the polymer chain (Figure 4). The NHC ligand is enantiopure,

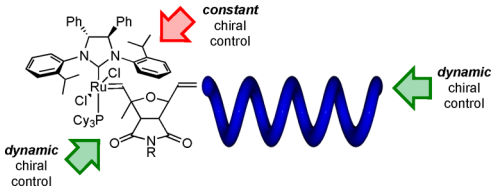

Figure 4. Chiral control elements for KR-ROMP.

and previous studies have demonstrated that solvent choice does not alter the enantioselectivity of asymmetric ring-closing metathesis performed with this family of ruthenium complexes.[7] The same monomer is always enriched in the polymer, but the proportion of the "fast" monomer increases, giving one possible dynamic control element. The polymer is constantly changing, also, as it grows and forms a chiral secondary structure which can influence the interaction of the ultimate monomer with the incoming monomer. Given the solvent-dependent nature of the helix-sense, this is reflected in the mercurial selectivity of the resolution. The selectivity increases in THF and DCM as the polymer chain grows, which contrasts to the degradation of selectivity as the polymer chain grows in toluene. In sum, this highlights that the *S* is most strongly dictated through chiral catalyst site control, but is to some degree also influenced by the conformation of the growing polymer chain's conformation in different solvents.

We have described the first partial kinetic resolution employing ring-opening metathesis polymerization. Using 1-methyloxanorbornene monomers, we have concluded that growing polymer chain probably adopts a higher-ordered conformation with excess one-handed helicity. The polymer helix has a marked effect on the selectivity of the polymerization: doubling the selectivity if the polymerization is conducted in DCM or THF, while drastically reducing selectivity to a fifth of its original value in toluene. While the selectivity of the resolutions still aspires toward synthetic utility, these results provide a promising guide for our future research. We believe that, through ligand design and careful solvent selection, we can harness both the high initial selectivity seen in resolutions conducted in toluene and the enhancement provided by the helical polymer. Additionally, helical polyoxanorbornenes provide a new polymer platform for novel chiroptical materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic methods, proton and ^{13}C NMR spectra, and UV−vis spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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