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Cyclic Alternating Ring-Opening Metathesis Polymerization (CAROMP). Rapid Access to Functionalized Cyclic Polymers

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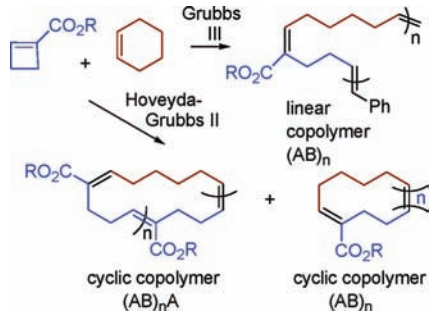
ABSTRACT



Catalysis of alternating ROMP with $(H_2IMes)Cl_2Ru{=}CHPh(OiPr)$, the second generation Hoveyda−Grubbs catalyst, provided an entirely cyclic alternating polymer. Conditions for the cyclic AROMP were used to prepare a polymer in which one of the repeat units bore a primary alkyl chloride that was used for further elaboration.

Cyclic polymers[1] exhibit thermodynamic,[1b] optical,[2] and biophysical[3] properties different from those of their linear counterparts. However, the potential applications of cyclic polymers that result from these altered properties have yet to be developed. Particularly intriguing are applications in drug delivery.[4]

The pharmacokinetics of cyclic polymers favor their use as vehicles for carrying drugs to solid tumors. Presumably because the minimum cross section of a cyclic polymer is larger than that of the corresponding linear polymer, cyclic polymers are filtered more slowly through the pores of the kidney. Relative to similar linear polymers of comparable molecular weights, they have reduced rates of clearance and extended plasma circulation times.[5] In addition, and again as a consequence of topology, cyclic polymers exhibit greater tumor accumulations than the related linear polymers; this difference has been attributed to the enhanced permeation and retention (EPR) effect.[6]

Cyclic polymers are formed as byproducts during the preparation of high molecular weight polymers by intramolecular reactions termed backbiting. In principle, the formation of cyclic polymers can be maximized by long reaction times; however, practical considerations may preclude this as a general strategy.

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It is likely that there is much to be learned about the synthesis of cyclic polymers.[7,1b] Notable recent contributions include strategies based on ring expansions and on "click chemistry.[8] The production of cyclic polymers in ROMP experiments has been optimized by the use of custom-synthesized catalysts.[9]

In 2009, we reported the preparation of copolymers of cyclobutene-1-carboxylic acid esters (**1**, monomer A) and cyclohexenes (**2**, Z = H or D, monomer B) by alternating ring-opening metathesis polymerization (AROMP)[10] with the third generation Grubbs catalyst (**3**) (Figure 1 and Scheme 1).[11]

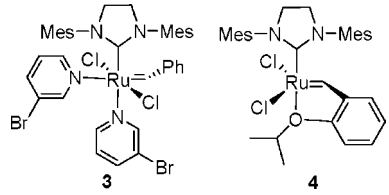
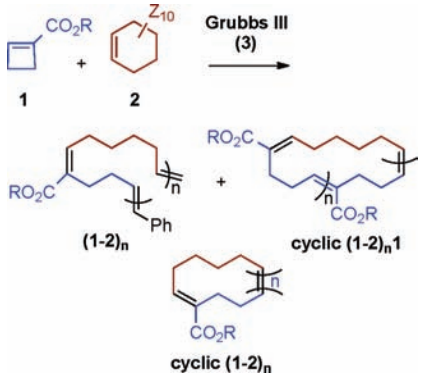


Figure 1. Catalysts used for AROMP and CAROMP.

Scheme 1



Analysis of the ^{1}H NMR spectrum of the product mixture derived from cyclobutenecarboxylic acid methyl ester (monomer **1a**) and cyclohexene D_{10} (**2-D$_{10}$**) led us to conclude that the anticipated alternating linear polymer PhCH═(AB)$_n$═CH$_2$, (**1a-2-D$_{10}$)$_n$** was formed, but that it was contaminated with cyclic polymer **cyclic(1a-2-D$_{10}$)$_n$1a** in which there was a single AA repeat and **cyclic(1a-2-D$_{10}$)$_n$**.

Although we were able to isolate the cyclic AROMP polymers from their linear coproducts, this method of preparation was clearly not ideal. Because we recognized the advantages of cyclic polymers for certain applications, we considered modifying the conditions of the AROMP reaction to maximize the backbiting reaction.

Noting the chelated structure of the readily available Hoveyda−Grubbs II catalyst,[12,13] we imagined that the transition state for backbiting at the styrene terminus might be stabilized by the ether oxygen−ruthenium interaction (Figure 2). We have therefore tested catalyst **4** for the production of increased amounts of cyclic polymer in the AROMP reaction.

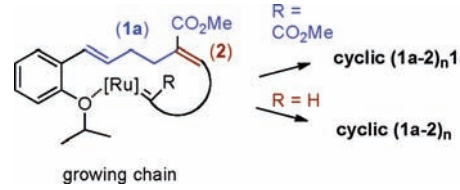


Figure 2. Proposed stabilization of a conformation disposed to backbiting in Hoveyda−Grubbs II AROMP.

For direct comparison of a Hoveyda−Grubbs II product with the largely linear and easily analyzed Grubbs III AROMP polymer **(1a-2-D$_{10}$)$_n$** isolated earlier, we treated a mixture of cyclobutene **1a** and cyclohexene D_{10} (**2-D$_{10}$**) with catalyst **4**. This reaction provided entirely cyclic copolymer **cyclic(1a-2-D$_{10}$)$_n$1a**+**cyclic(1a-2-D$_{10}$)$_n$**. (Table S1, Figures S1 and S2 in Supporting Information). The NMR spectrum showed no styrenyl protons. Furthermore, relative to the three proton methyl ester signal, the signal for the protons on the disubstituted olefin (5.4 ppm) integrated to one and that for the trisubstituted olefinic proton (6.8 ppm) was very small (approximately 0.07 H). These results supported the cyclic alternating polymer hypothesis; the alkene triplet at 6.8 ppm results from formation of an AA repeat, just as in the case of the catalyst **3** polymerization.[10] Electrospray mass spectrometry of the **cyclic(1a-2-D$_{10}$)$_n$1a**+**cyclic(1a-2-D$_{10}$)$_n$** prepared with Hoveyda−Grubbs II catalyst (**4**), (Figure 3), showed major peaks for both (AB)$_n$- and (AB)$_n$A-type cyclic structures. From the mass spectrum, the number average and weight average molecular weights are 639.54 and 686.09, respectively. The corresponding polydispersity index is 1.07.

Development of cyclic AROMP polymers for diverse applications is likely to build on experimentation with molecules that bear a variety of functional groups. A library of functionalized cyclic AROMP products could be accessible by ROMPing two libraries of monomers with the Hoveyda−Grubbs II catalyst. Alternatively, a CAROMP library could be obtained by elaboration of polymers derived from a single library of monomers and a single monomer bearing a functional group that can be modified in many ways.

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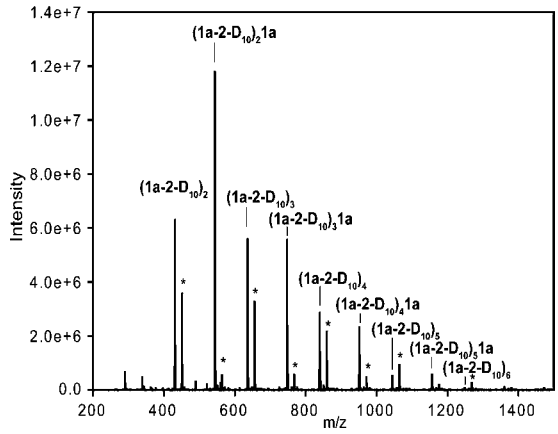
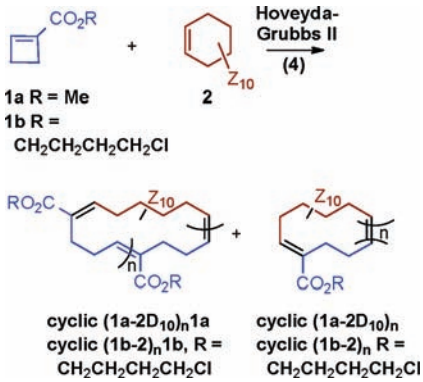


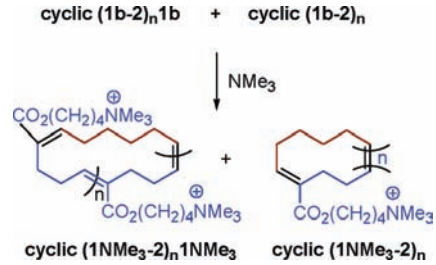
Figure 3. High-resolution LTQ-Orbitrap ESI mass spectroscopic analysis of **cyclic(1a-2-D_{10})1a**+**cyclic(1a-2-D_{10})$_n$** polymer. MNa^+. **cyclic(1a-2-D_{10})$_2$**: calcd 431.3767, found 431.3778. **cyclic(1a-2-D_{10})$_2$1a**: calcd 543.4291, found 543.4291. **cyclic(1a-2-D_{10})$_3$**: calcd 635.5701, found 635.5692. **cyclic(1a-2-D_{10})$_3$1a**: calcd 747.6226, found 747.6231. **cyclic(1a-2-D_{10})$_4$**: calcd 839.7636, found 839.7634. **cyclic(1a-2-D_{10})$_4$1a**: calcd 951.8160, found 951.8163. **cyclic(1a-2-D_{10})$_5$**: calcd 1043.9570, found 1043.9560. **cyclic(1a-2-D_{10})$_5$1a**: calcd 1156.0094, found 1156.0094. **cyclic(1a-2-D_{10})$_6$**: calcd 1248.1504, found 1248.1469. Asterisk (*) designates secondary cross-metathesis products derived from cyclic polymer.

As proof of principle of this latter approach, we have examined the CAROMP of monomer **1b** with cyclohexene (**2**) and demonstrated the efficient alkylation of an amine nucleophile with the resulting chloro-substituted polymer. The Hoveyda−Grubbs II procedure, applied to a solution of these monomers provided a mixture of **cyclic(1b-2)$_n$** and **cyclic(1b-2)$_n$1b** that contained no end groups as indicated by NMR (Table S1 and Figure S3 in Supporting Information). Its alternating structure, which includes an AA repeat, was confirmed by the integration of the peaks at 6.8 ppm (trisubstituted olefin protons) and at 5.4 ppm (disubstituted olefin protons) in the ^{1}H NMR spectrum (Figure S3 in Supporting Information). We estimate that the cyclic polymer (some, but not necessarily all, of which contains an AA repeat) is composed of 3−5 AB repeats. This value for n is in good agreement with the number average molecular weight of **cyclic(1b-2)$_n$1b**+**cyclic(1b-2)$_n$** determined by gel permeation

Scheme 2



Scheme 3



chromatography with polystyrene as a standard (see Supporting Information).

Because we were interested in comparing the physical and biological properties of clean cyclic polymer bearing trimethylammonium substituents with the corresponding polymer derived from the Grubbs III catalyst (mixture of linear and cyclic polymer), we derivatized **cyclic(1b-2)$_n$**+**cyclic(1b-2)$_n$1b** by treatment with trimethylamine. This reaction provided the water-soluble polymer **cyclic(1NMe$_3$-2)$_n$1NMe$_3$**+**cyclic(1NMe$_3$-2)$_n$** as indicated by NMR (Figure S4 in Supporting Information). Thus the CAROMP product from monomer **1b** and **2** could be used for the preparation of modified polymers.

In AROMP reactions, the commercially available Hoveyda−Grubbs II catalyst offers easy entry to cyclic polymers uncontaminated by their linear analogues. The use of a monomer that bears a primary alkyl chloride gives polymer that is easily and efficiently modified by nucleophilic substitution.

Expansion of this chemistry should allow cyclic polymers with alternating functionality to be used as templates for the construction of complex macromolecular structures with dense cores. For example, extension of side chain functional groups with further polymerization chemistry or by attachment of preformed polymers would provide alternating STAR polymers. These novel alternating STAR polymers could be used in a variety of applications that include drug delivery,[14] the formation of hydrogels and cell adhesion procedures,[15] and electronics.[16]

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Supporting Information Available: Detailed descriptions of the experimental procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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