Quantitative, Regiospecific, and Stereoselective Radical Ring-Opening Polymerization of Monosaccharide Cyclic Ketene Acetals

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ABSTRACT: Cyclic ketene acetals (CKAs) are among the most well-studied monomers for radical ring-opening polymerization (rROP). However, ring-retaining side reactions and low reactivities in homopolymerization and copolymerization remain significant challenges for existing CKAs. Here, we report that a class of monosaccharide CKAs can be facilely prepared from a short and scalable synthetic route and can undergo quantitative, regiospecific, and stereoselective rROP. NMR analyses and degradation experiments revealed a reaction mechanism involving a propagating radical at the C2 position of pyranose, with different monosaccharides exhibiting distinct stereoselectivity in the radical addition of the monomer. Furthermore, adding maleimide was found to improve the incorporation efficiency of the monosaccharide CKA in the copolymerization with vinyl monomers, producing unique degradable terpolymers with carbohydrate motifs in the polymer backbone.

Degradable polymers have shown great promise in biomedical applications[1, 2] and offer a potential solution to address the accumulation of persistent plastics in the environment.[3-6] During the past decade, significant efforts have been devoted to the development of degradable polymers.[7-24] Parallel to synthetic polymers, biopolymers in nature, *e.g.*, nucleic acids, proteins, and polysaccharides, are intrinsically biodegradable. Inspired by the structures and properties of biopolymers, chemists have sought to construct degradable polymers using biologically derived building blocks. In particular, carbohydrates have been considered a promising feedstock for polymer synthesis due to their natural abundance and unique material properties.[25-27] For example, carbohydrate polymers and native polysaccharides have been generated via anionic and cationic polymerizations.[28-38] Despite progress in the ionic polymerization of carbohydrate-derived monomers, radical polymerization, which is widely used to synthesize vinyl polymers and has demonstrated good functional group tolerance,[39] remains underutilized for producing carbohydrate-based degradable polymers.

Cyclic ketene acetals (CKAs) are one of the most extensively studied monomer classes for the synthesis of degradable polymers, thanks to their ability to introduce degradable ester groups into the polymer backbone via radical ring-opening polymerization (rROP).[7-9, 24] Despite the pioneering works by Bailey,[40] Dove,[41-45] Nicolas,[46-51] Sumerlin,[52, 53] and others,[7-9, 54] existing CKAs still suffer from two major limitations: (1) the ring-retaining side reaction that leaves non-degradable motifs in the polymer backbone and (2) low reactivity in the copolymerization with vinyl monomers, leading to uneven incorporation and necessitating a high feeding ratio of CKA (Figure 1A). For example, in a recent example reported by Buchard *et al.*,[55] 50% CKA in the feed was needed to achieve 11.9% incorporation of the ester group, with 21.1% non-degradable motifs derived from ring-retaining side reactions of the CKA also incorporated in the resulting polymer.

To address these challenges, we envisioned that fusing a five-membered CKA with a monosaccharide pyranose structure at C1−C2 could result in activated CKA monomers due to the anomeric effect and the additional twist of the ring structure caused by the 1,2-*cis* substitution, leading to higher reactivity in homopolymerization and copolymerization (Figure 1B). Furthermore, inspired by the high reactivity of the maleimide radical to CKAs,[52-54] we reasoned that maleimides could be added in the copolymerization of vinyl monomers and CKA to improve the incorporation of CKA (Figure 1B).

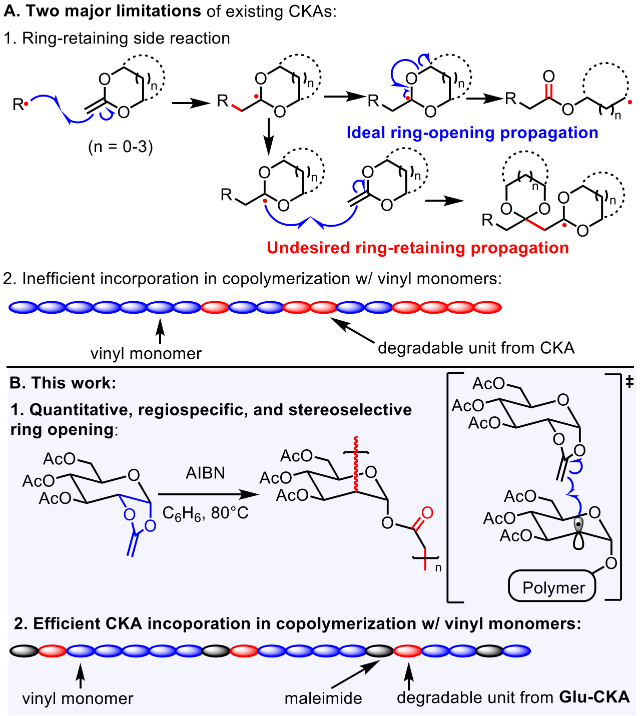


Figure 1. Overview of this work. (A) Limitations of existing CKAs. (B) Innovations of this work: 1) quantitative, regiospecific, and stereoselective ring-opening polymerization of monosaccharide CKAs; 2) efficient incorporation of monosaccharide CKAs in the copolymerization with vinyl monomers and maleimide.

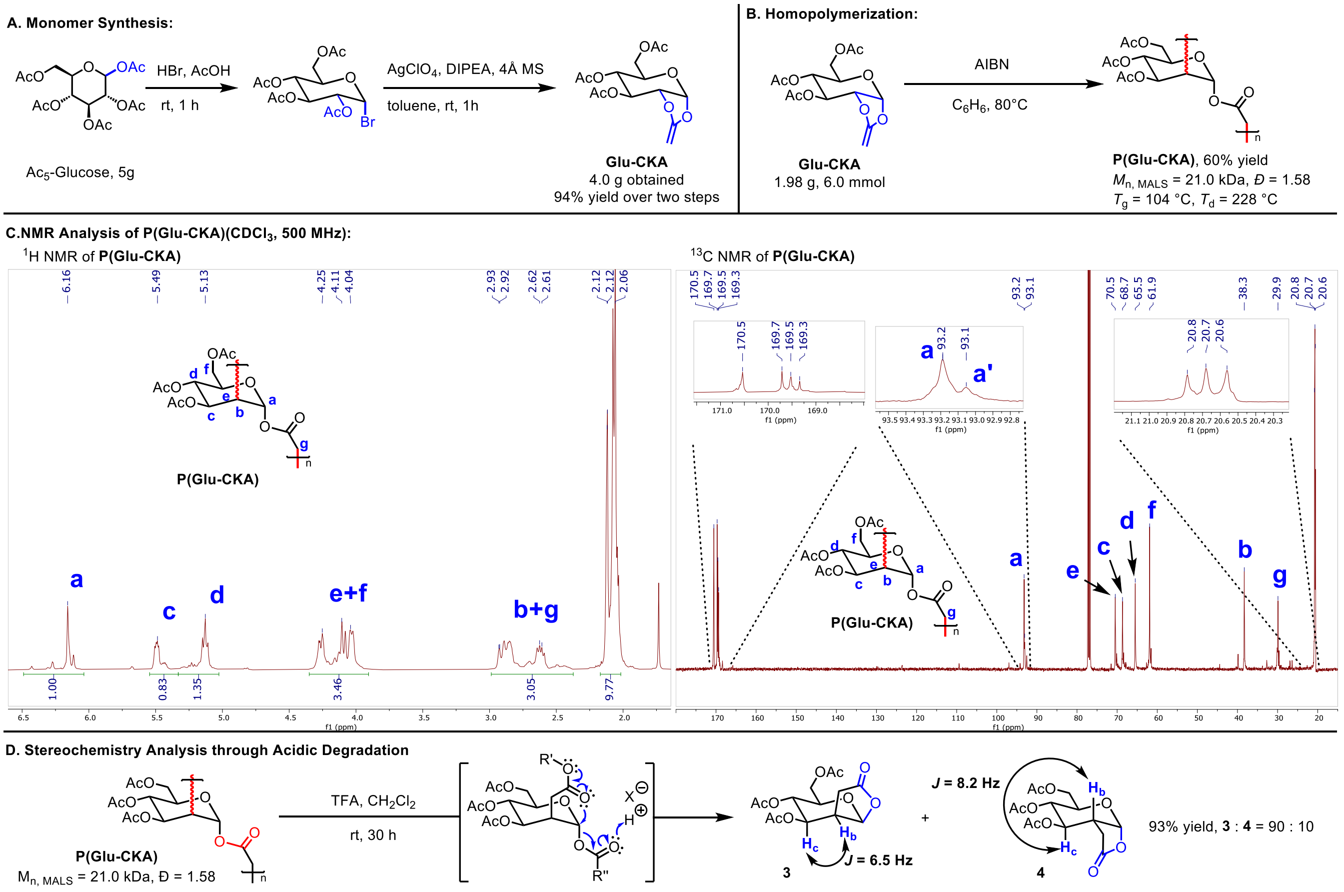


Figure 2. Synthesis and homopolymerization of Glu-CKA. (A) Synthetic route. (B) Homopolymerization of Glu-CKA. Reaction conditions: **Glu-CKA** (6.0 mmol), azobisisobutyronitrile (**AIBN**, 2.0 mol%, 0.12 mmol), C_6H_6 (30 mL, 0.2 M), 80 °C, under N_2 atmosphere, 24 h. Isolated yield is shown. (C) ^{1}H and ^{13}C NMR spectra of **P(Glu-CKA)**. Symbol **a'** indicates the anomeric carbon in minor diastereomeric repeating unit. (D) Acidic degradation of **P(Glu-CKA)**. Stereochemistry of **P(Glu-CKA)** was assigned by NOE and coupling constants analysis for **3** and **4**.

CKAs are typically synthesized through inefficient acid-catalyzed transacetalization-elimination process that often requires harsh reaction conditions and results in low yields.[7-9] Following the report by Hecht and Ko,[56, 57] we adopted a concise route to generate the desired **Glu-CKA** in multigram quantities in 94% yield over two steps. Starting from the readily available and inexpensive D-glucose pentaacetate, this route forms the CKA moiety via anomeric bromination followed by nucleophilic attack by the neighboring 2-*O*-acetate group and subsequent deprotonation. It requires no column chromatography, is readily scalable, and can be finished in three hours.

Free radical polymerization of **Glu-CKA** (0.20 M in benzene) initiated by 2.0 mol% azobisisobutyronitrile (AIBN) initiator gave a polymer **P(Glu-CKA)** ($M_{n,\,MALS} = 21.0$ kDa, $Đ = 1.58$, $T_g = 104$ ºC, $T_d = 228$ ºC) as a white solid in 60% yield. Both ^{1}H and ^{13}C NMR spectra of **P(Glu-CKA)** are surprisingly uncomplicated (Figure 2C). They suggested that the C2–O bond of **Glu-CKA** was quantitatively cleaved and a new C–C bond was formed at C2 (labeled as **b** in Figure 2C). No signals associated with the ring-retaining byproducts were detected. To assign the stereochemistry of this new stereogenic center, selective cleavage of the anomeric ester in **P(Glu-CKA)** was performed using trifluoroacetic acid (TFA), producing lactones **3** and **4** in a 90:10 ratio (Figure 2D). Both the coupling constant analysis of the ^{1}H NMR ($J_{\mathbf{bc}} = 6.5$ Hz) and the Nuclear Overhauser Effect spectroscopy (NOESY) (Figure S16) suggested that proton **b** in **3** is equatorial, whereas proton **b** in **4** is axial. Such assignments are also consistent with the spectra of **4** in the literature.[58] Similarly, basic degradation of **P(Glu-CKA)** using sodium methoxide also suggest that proton **b** is predominantly equatorial in **P(Glu-CKA)** (Figure S18). Hence, these analyses allowed us to assign the newly formed C–C bond at C2 to be predominantly axial and in the *S* configuration. Similar stereochemistry preference has been observed by Ngai and coworkers in the radical addition involving the C2 radical of glucose.[59-62]

To determine how the monosaccharide structure influences stereoselectivity, we next prepared **Man-CKA** and **Gal-CKA** using the similar method from D-mannose pentaacetate (81% yield) and D-galactose pentaacetate (90% yield), respectively (Figure S1). Free radical polymerization of these monomers generated **P(Man-CKA)** ($M_{n,\,MALS} = 16.7$ kDa, $Đ = 1.63$, $T_g =$ 102 ºC, $T_d = 225$ ºC) and **P(Gal-CKA)** ($M_{n,\,MALS} = 11.8$ kDa, $Đ$ = 1.38, T_g = 72 ºC, T_d = 220 ºC) in 58% and 40% yield, respectively (Figure 3A, Figure S6–11). The acidic degradation of **P(Man-CKA)** gave the same lactones **3** and **4** as the degradation products of **P(Glu-CKA)** in a 21:79 ratio. The acidic degradation of **P(Gal-CKA)** gave two new lactones **5** and **6** in an 80:20 ratio. ^{1}H NMR of **5** revealed a $J_{\mathbf{bc}} = 6.5$ Hz between protons **b** and **c**, in agreement with a vicinal axial-equatorial coupling. ^{1}H NMR of **6** revealed a $J_{\mathbf{bc}} = 10.6$ Hz between protons **b** and **c**, in agreement with a vicinal axial- axial interaction, which is consistent with the spectrum of the same compound in the literature.[58]

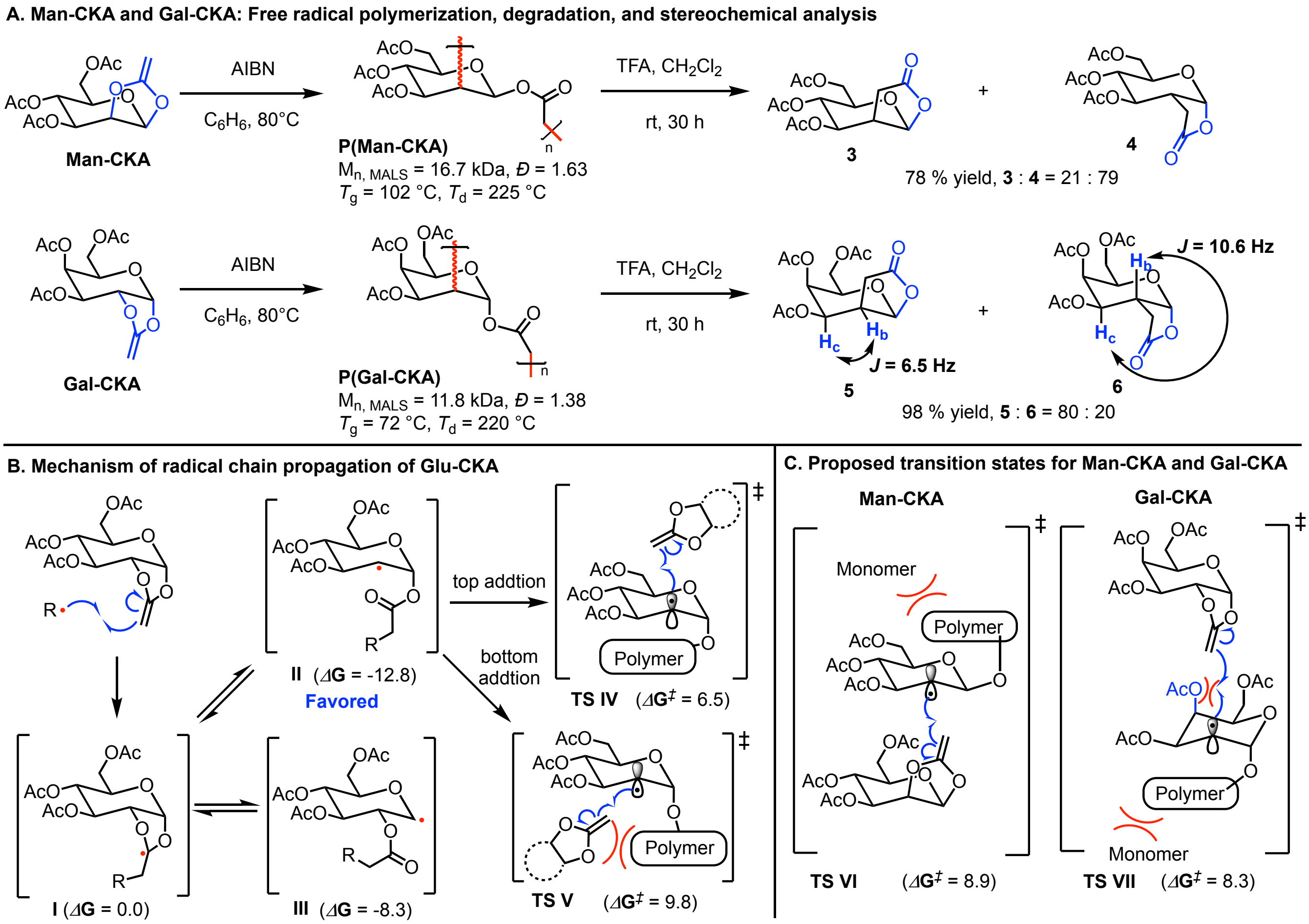


Figure 3. Stereochemical analysis of monosaccharide CKA polymerization. (A) Free radical polymerization, degradation, and stereochemical analysis for **Man-CKA** and **Gal-CKA**. (B) Mechanism of radical chain propagation pathway for **Glu-CKA**. ***ΔG***, ***ΔG***‡ indicate the Gibbs free energy and the activation energy, respectively (unit: kcal/mol). (C) Proposed transition states for **Man-CKA** and **Gal-CKA**.

DFT calculations provided further insights into the stereoselectivity of the polymerization of the monosaccharide CKAs. As shown in Figure 3B, intermediate **I** was generated from the radical addition of monomer **Glu-CKA**. Subsequent homocleavage of the C2–O bond and C1–O bond in **I** gave **II** and **III**, respectively. **II** is energetically favored over **III** by 4.5 kcal/mol (-12.8 kcal/mol *vs.* -8.3 kcal/mol), and **III** could also undergo 2,1-radical rearrangement to generate **II**.[63-67] The lower energy of **II** and the interconversion between **II** and **III** made **II** the predominant propagating species. The radical addition of **II** by the monomer could generate two potential diastereomers. Our calculations also suggested that the transition state for **Glu-CKA** to approach **II** from the top face of the pyranose (Figure 3B, **TS IV**) was 3.3 kcal/mol lower than that of a bottom face attack (Figure 3B, **TS V**), which could be attributed to the α-glycosidic bond in **II** that put the bulky polymer chain in the bottom face of the propagating radical. As a result, the bottom face attack of the monomer was blocked. Likewise, the radical addition of the chain propagating species by **Gal-CKA** also preferred the bottom face, but the steric hindrance by the axial acetate group at C4 slightly reduced the stereoselectivity of the polymerization compared to **Glu-CKA** (Figure 3C, **TS VII**). As to **Man-CKA**, the β-glycosidic linkage in the **TS VI** placed the polymer chain on top of the pyranose, making the monomer to prefer the radical addition from the bottom face. With these additional insights into the stereoselectivity, we chose to focus on **Glu-CKA**, which showed the highest stereoselectivity among the monomers examined, in the subsequent copolymerization studies.

Previous reports on the copolymerization of CKAs with activated vinyl monomers indicate that a high feeding ratio of the CKA is generally required.[7-9] We wonder if the enhanced reactivity observed in the homopolymerization of **Glu-CKA** could extend to copolymerization. In the copolymerization at the 1 : 1 feed ratio of **Glu-CKA** and methyl methacrylate (MMA), the rate of conversion of **Glu-CKA** was significantly lower than MMA (Figure 4B). To address this challenge, we wondered if adding a third maleimide monomer could improve the incorporation of **Glu-CKA**, as maleimide was found to possess a high reactivity toward CKAs related to the electron donor-acceptor complex formation.[52-54] Indeed, we found that the copolymerization of **Glu-CKA** and *N*-phenyl maleimide (MI) at 1:1 feeding ratio exhibited similar rates of conversion for both monomers throughout the reaction (Figure 4C). Furthermore, copolymerization at a feed ratio of **Glu-CKA** : MI : MMA = 1 : 1 : 1 showed similar rates of conversion for all three monomers throughout the reaction (Figure 4D). These results suggested that the addition of MI improved the incorporation of **Glu-CKA** in the copolymerization with MMA.

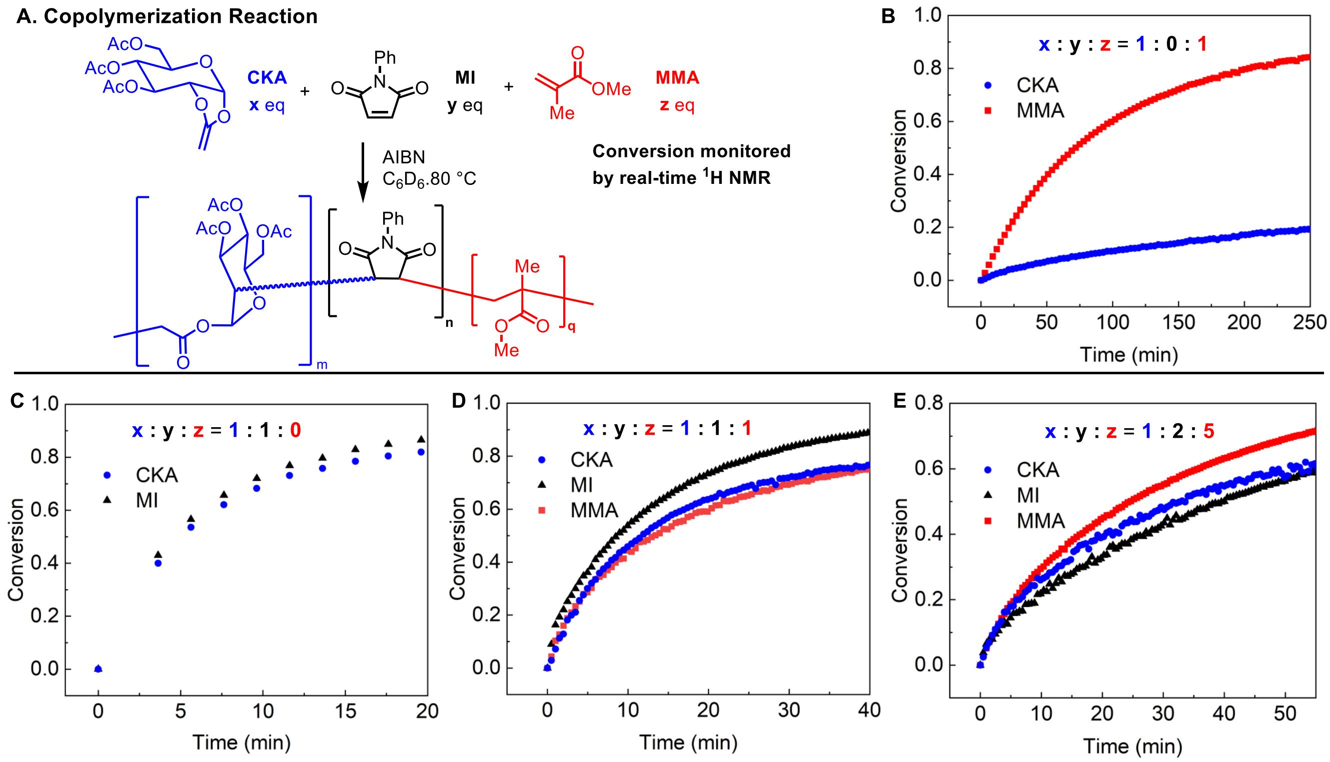
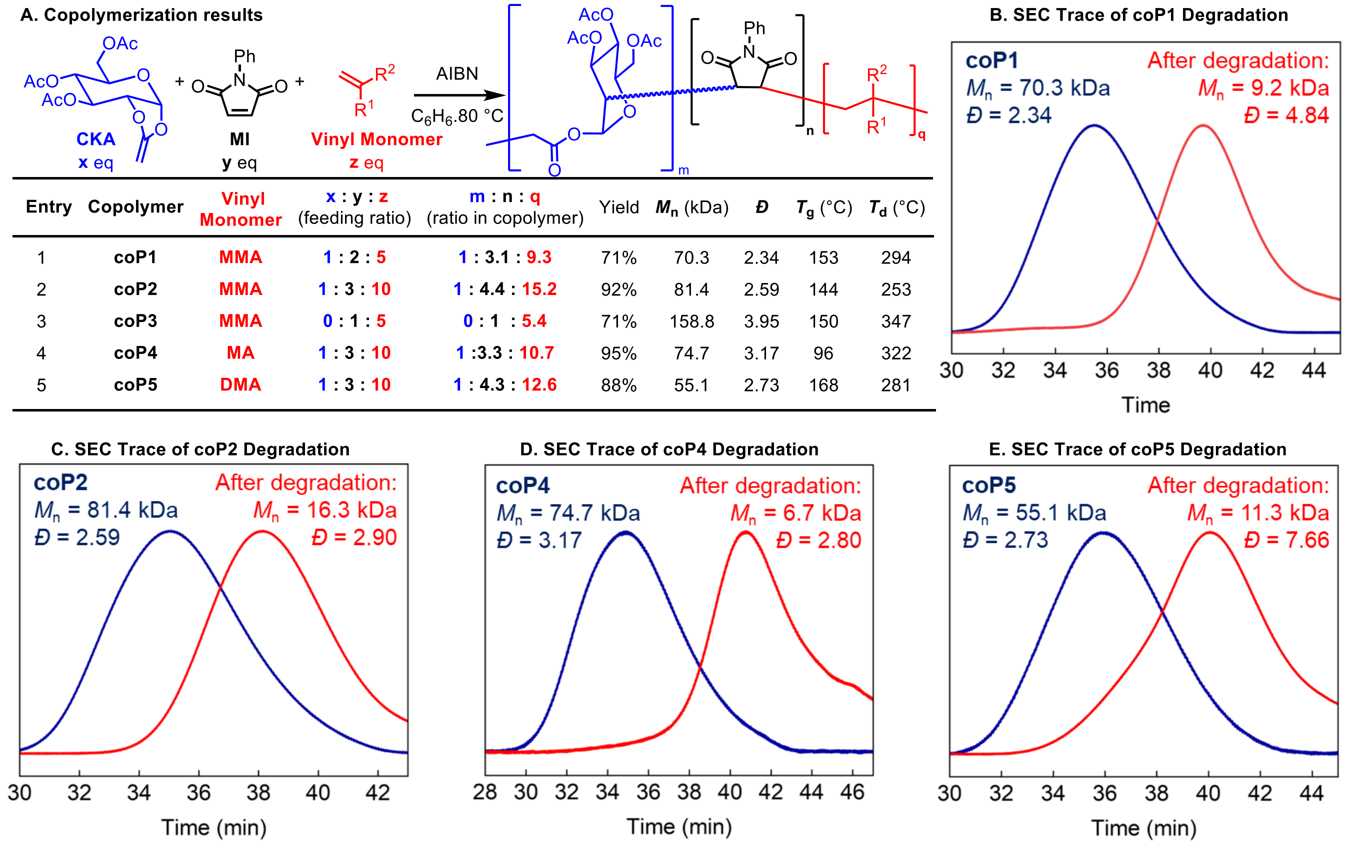


Figure 4. Real-time ^{1}H NMR monitoring of copolymerization. (A) Reaction scheme; (B)–(E) Real-time ^{1}H NMR monitoring of conversion as a function of reaction time: (B) **Glu-CKA** : MMA = 1 : 1; (C) **Glu-CKA** : MI = 1 : 1; (D) **Glu-CKA** : MI : MMA = 1 : 1 : 1 (E) **Glu-CKA** : MI : MMA = 1 : 2 : 5.

We then attempted copolymerization with a higher amount of MMA relative to **Glu-CKA** and MI. While the reaction at the feeding ratio of **Glu-CKA** : MI : MMA = 1 : 1 : 5 showed lower rate of conversion for **Glu-CKA** (Figure S19), copolymerization at the feeding ratio of **Glu-CKA** : MI : MMA = 1 : 2 : 5 (Figure 4E) demonstrated similar rates of conversion for all three monomers throughout the entire reaction, producing a terpolymer **coP1** in 71% yield (Figure 5A, entry 1). ^{1}H NMR analysis suggested the incorporated ratio of **Glu-CKA** : MI : MMA in **coP1** was 1 : 3.1 : 9.3. Diffusion Ordered Spectroscopy NMR (DOSY NMR) analysis confirmed that all three components are incorporated in the same copolymer (Figure S21). Basic degradation of **coP1** by sodium methoxide resulted in significant reduction of molecular weight (Figure 5B), indicating that ester groups were efficiently incorporated into the polymer backbone. Further lowering **Glu-CKA** ratio in the feed to **Glu-CKA** : MI : MMA = 1 : 3 : 10 did not affect the reactivity, producing terpolymer **coP2** with good degradability in 92% yield (Figure 5A, entry 2, and Figure 5C). In contrast to **coP1** and **coP2**, a control copolymer of MI and MMA only, **coP3**, was poorly degradable. The slight reduction of molecular weight of **coP3** under basic condition might be related to a small amount of retro-Michael reaction of the maleimide moieties[68] (Figure 5A, entry 3, and Figure S27). Next, we extend the monomers to methyl acrylate (MA) and *N*,*N*-dimethylacrylamide (DMA). Both the resultant terpolymers **coP4** (Figure 5A, entry 4) and **coP5** (Figure 5A, entry 5) showed incorporation ratios of **Glu-CKA** comparable to the feed ratio, as well as degradability under basic conditions (Figure 5D and 5E), suggesting that **Glu-CKA** possesses good reactivity in the copolymerization with acrylates and acrylamides when MI is added as the third monomer.

In conclusion, we demonstrated that monosaccharide cyclic ketene acetals enabled quantitative, regiospecific, and stereoselective rROP. The structure of the homopolymers were confirmed by NMR analyses and degradation experiments, with the radical species at C2 acting as the propagating species during the polymerization. Structure-activity studies revealed that the monosaccharide structure profoundly influences the stereochemical outcome of the reaction, with **Glu-CKA** identified as an optimal monomer for stereoselective polymerization. In the copolymerization with vinyl monomers, we demonstrated that adding maleimide could increase the incorporation of **Glu-CKA**, thereby improving the degradability of the resultant copolymers. Overall, this work provided a promising platform for generating degradable polymers and copolymers with main-chain carbohydrate motifs for a wide range of potential applications from biomaterials to sustainable plastics.



Entry	Copolymer	Vinyl Monomer	x : y : z (feeding ratio)	m : n : q (ratio in copolymer)	Yield	M_n (kDa)	Đ	T_g (°C)	T_d (°C)
1	coP1	MMA	1 : 2 : 5	1 : 3.1 : 9.3	71%	70.3	2.34	153	294
2	coP2	MMA	1 : 3 : 10	1 : 4.4 : 15.2	92%	81.4	2.59	144	253
3	coP3	MMA	0 : 1 : 5	0 : 1 : 5.4	71%	158.8	3.95	150	347
4	coP4	MA	1 : 3 : 10	1 :3.3 : 10.7	95%	74.7	3.17	96	322
5	coP5	DMA	1 : 3 : 10	1 : 4.3 : 12.6	88%	55.1	2.73	168	281

Figure 5. Synthesis and degradation of terpolymers of Glu-CKA, maleimide, and vinyl monomers. (A) Copolymerization results. (B)–(E) SEC traces of the terpolymer and their degradation products: (B) **coP1**, (C) **coP2**, (D) **coP3**, and (E) **coP4.** M_n and Đ were determined by the SEC analysis with DMF eluent, calibrated to polystyrene standards.[69]

ASSOCIATED CONTENT

Supporting information includes the supplementary figures, DFT calculations, characterization data, $^1H/^{13}C$/2D NMR spectra, DSC/TGA curves, and detailed experimental protocols (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): a provisional patent application based on this work has been filed by Boston College (63/624,378).

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69. Because the dn/dc values of the copolymers change over different copolymer compositions, MALS detector could not be used to accurately measure the M_n and $Đ$ of the statistical copolymers.

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