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Chemically Recyclable Pseudo-Polysaccharides from Living Ring-Opening Polymerization of Glucurono-1,6-lactones

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Cite This: J. Am. Chem. Soc. 2024, 146, 21868−21876
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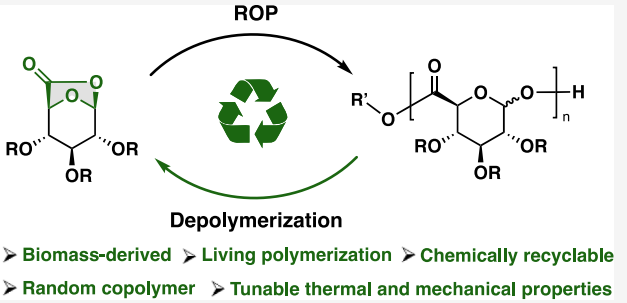
ABSTRACT: Recent advances in synthetic methods and monomer design have given access to precision carbohydrate polymers that extend beyond native polysaccharides. In this article, we present the synthesis of a class of chemically recyclable ester-linked pseudo-polysaccharides via the living anionic ring-opening polymerization of glucurono-1,6-lactones. Notably, the pseudo-polysaccharides exhibited defined chain-end groups, well-controlled molecular weights, and narrow molecular weight distributions, all hallmarks of living polymerization. Furthermore, we demonstrate that our approach is modular, as evidenced by tunable glass transition temperatures (T_g) and the ability to produce both amorphous and semicrystalline polymers by adjusting the monomer side chain structure. Lastly, we showcased the complete catalytic chemical recycling of these pseudo-polysaccharides back to the monomers. The flexibility of the polymerization and the recyclability of these pseudo-polysaccharides promote a sustainable circular economy while offering the potential to access polysaccharide-like materials with tunable thermal and mechanical properties.



INTRODUCTION

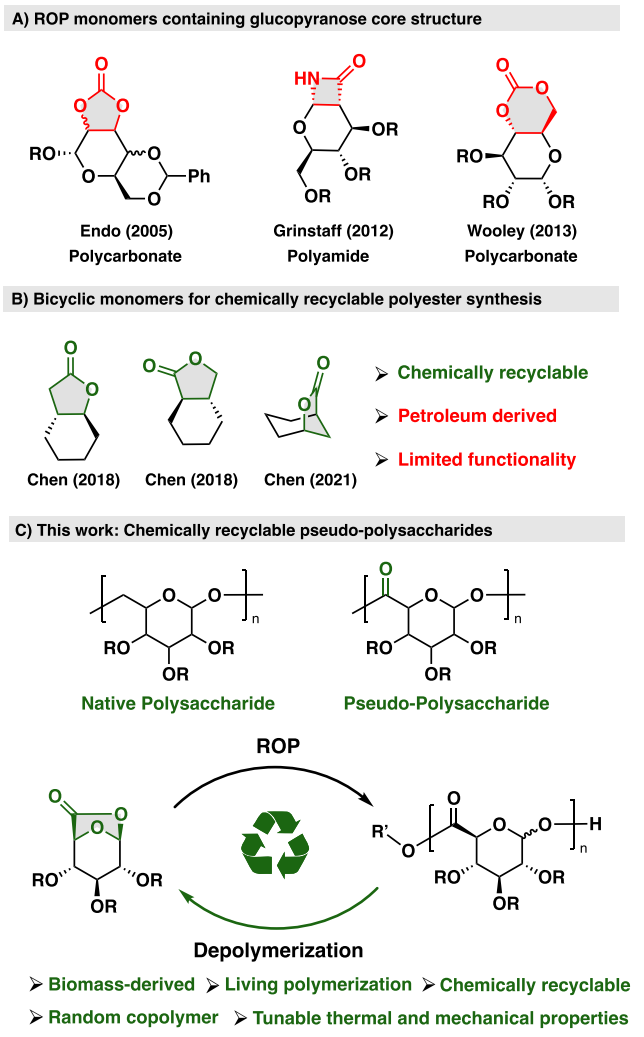
Polysaccharides rank among the most abundant biopolymers and play critical roles in nature, ranging from structural support to energy storage to facilitating cell signaling.[1] Their multifaceted functions have rendered them increasingly relevant in material science,[2−4] biomedicine,[5,6] food,[7] and energy.[8−10] While the traditional approach of isolating polysaccharides directly from natural sources has been widely adopted for a variety of applications, it often requires extensive purification and affords complex mixtures with significant batch-to-batch variations.[11] Consequently, this approach is unable to provide well-defined polysaccharides with controlled molecular weight and dispersity.[12] Chemists have resorted to chemical synthesis to overcome these limitations and meet the demand for structurally homogeneous polysaccharides that can be tailored for advanced applications, such as glycobiology and drug delivery. Various synthetic approaches, including enzymatic synthesis,[13,14] polycondensation,[15−18] iterative assembly,[19−25] and ring-opening polymerization (ROP),[26,27] have been employed. Nevertheless, the high complexity and structural diversity of polysaccharides, in terms of functional groups and stereochemistry, must be carefully considered.[28,29] This often hampers the aforementioned techniques, making the development of new synthetic methods for precision polysaccharides a significant challenge.

Recently, there has been a growing interest in polysaccharide-mimetics, often referred to as "pseudo-polysaccharides", which feature monosaccharide repeating units and non-native linkages (e.g., amide, carbonate, etc.).[30−37] These alternatives are gaining popularity over native polysaccharides because of their facile and controlled synthesis and their ability to approach and even surpass the functions of native polysaccharides in material and biomedical applications.[38,39] In their seminal work, Endo et al. reported the anionic ROP of five-membered glucopyranose carbonates, affording glucose-derived polycarbonates with moderate control.[40] Further advancing the polymerization of glucopyranose carbonates, Wooley et al. reported the organocatalytic living anionic ROP of six-membered bicyclic glucopyranose carbonates.[41] These glucose-derived polycarbonates exhibit tunable glass transition temperatures (T_g = 38 to 125 °C)[38] and have demonstrated strong potential in a variety of applications, including drug delivery, antimicrobial nanoparticles,[42−44] and hydrogels.[45] Further, Dane and Grinstaff reported the anionic ROP of bicyclic β-lactams derived from glucal.[46] This polymerization yielded enantiopure helical poly-amido-saccharides that have been leveraged for nanoparticle synthesis,[47] heparin mimetics,[48] protein stabilization,[49] and activation of immune response in mammalian cells[39] (Scheme 1A).

Received: May 11, 2024
Revised: July 2, 2024
Accepted: July 9, 2024
Published: July 25, 2024

https://doi.org/10.1021/jacs.4c06431
J. Am. Chem. Soc. 2024, 146, 21868−21876

Scheme 1. Development of Anionic ROP of Glucurono-1,6-lactones



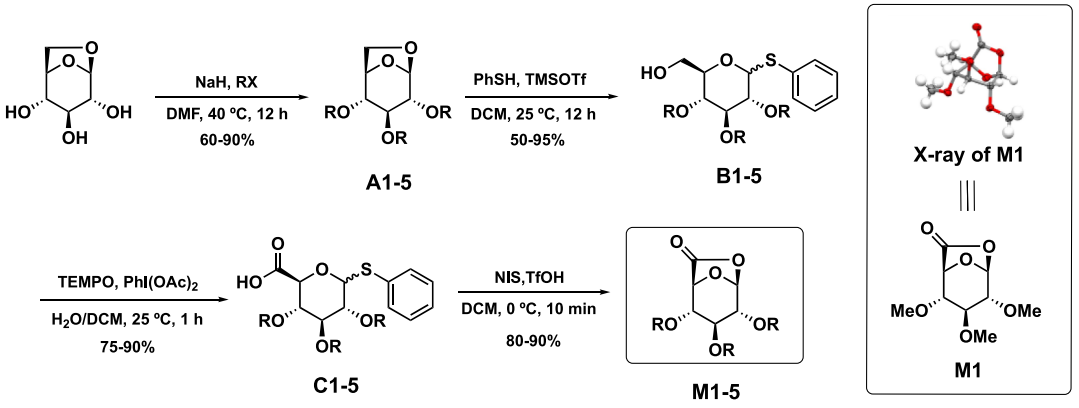
Recently, methodologies of utilizing bicyclic monomers have emerged, offering the advantages of promoting ring strain and increasing the magnitude of the enthalpic driving force.[50−61] For example, the Chen group has exploited ring fusion and hybridization techniques to enhance the polymerization of otherwise "nonstrained" γ-butyrolactones while also maintaining chemical recyclability of the resulting polymers (Scheme 1B).[62−65] Importantly, chemical recycling of polymers allowed access to virgin material without loss of properties—a long-standing challenge in plastic recycling. Nevertheless, the bicyclic monomers in Chen's reports were synthesized from petroleum-derived building blocks and also lacked functional side chains to modulate the thermal and mechanical properties of the resulting polymer. Herein, we explore the synthesis, polymerization, and chemical recycling of glucurono-1,6-lactones, a novel class of monosaccharide-derived bicyclic lactones, and their potential to create robust chemically recyclable pseudo-polysaccharides with tunable material properties. Prepared from renewable and inexpensive levoglucosan, this monomer could be accessed through a concise and scalable synthesis and features a pyranose core structure, allowing us to exploit the stereochemical complexity associated with polysaccharides. The living polymerization of this monomer enabled access to the unexplored polysaccharide-like materials, offering a tunable macromolecular platform with properties matching or exceeding those of native polysaccharides (Scheme 1C). Furthermore, achieving a circular life cycle from renewable and biomass-derived sources reduces waste and environmental pollution and facilitates the transition away from fossil-based feedstocks.

RESULTS AND DISCUSSION

Monomer Design and Synthesis. Our investigation began with the synthesis of glucurono-1,6-lactone (Scheme 2). Functionalization of the O2, O3, and O4 of commercially available levoglucosan (1,6-anhydro-β-D-glucopyranose) with various alkyl substitutions including methyl, ethyl, *n*-propyl, *n*-pentyl, and cyclopropylmethyl groups produced anhydrosugars **A1−5**. Subsequent nucleophilic ring-opening of **A1−5** following Kuzuhara's method[66,67] afforded thioglycosides **B1−5**. The C6 position of **B1−B5** was then oxidized into a carboxylic acid, followed by the final recyclization[68] to furnish the desired glucurono-1,6-lactones (**M1−M5**). This synthetic route is scalable to multigram scales with overall yields ranging from 24 to 57%. Further, the absolute structure of **M1** was confirmed by X-ray crystallography (Scheme 2, CCDC: 2354616).

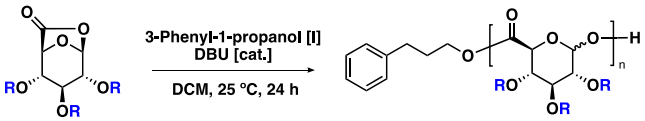
Polymerization Studies. Next, we attempted the polymerization of **M1** using 3-phenyl-1-propanol as an initiator and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the catalyst. Nevertheless, such conditions did not result in polymerization (Table 1, entry 1), which we attributed to the limited solubility of **M1**. We subsequently attempted the polymerization of **M2**,

Scheme 2. Synthesis of Glucurono-1,6-lactones



https://doi.org/10.1021/jacs.4c06431
J. Am. Chem. Soc. 2024, 146, 21868−21876

Table 1. Anionic ROP of Glucurono-1,6-lactones[a]



R: Me (M1), Et (M2), *n*-Pr (M3), *n*-Pen (M4), (M5), CL

entry	monomers	conc. (M)	$[M]_0$:$[I]_0$:[cat.]$_0$	conv. (%)[b]	M_n,Theo (kDa)[c]	M_n,NMR (kDa)[d]	M_n,SEC (kDa)[e]	α/β[f]	$Đ$[e]
1	M1	1.50	37.5:1:1						
2	M2	2.50	37.5:1:1	64	6.3	6.6	6.2	75/25	1.21
3	M3	2.72	37.5:1:1	84	9.6	9.2	11.2	87/13	1.12
4	M4	2.07	37.5:1:1	84	12.3	12.5	12.3	90/10	1.23
5	M5	2.83	37.5:1:1	72	9.2	8.7	9.8	83/17	1.17
6	M3	2.85	75:1:2	73	16.6	15.9	19.3	87/13	1.10
7	M4	2.35	75:1:2	89	26.3	24.9	21.6	90/10	1.14
8[g]	M4	2.38	150:1:2	88	51.1		37.7	90/10	1.10
9	M5	2.97	75:1:2	75	19.1	18.5	21.4	83/17	1.15
10	M5	3.00	150:1:2	69	35.1		34.1	83/17	1.14
11[g]	M5	3.04	300:1:2	78	79.2		29.7	83/17	1.14

[a]All polymerizations were conducted in dichloromethane with 3-phenyl-1-propanol and DBU in a glovebox at 25 °C. [b]Monomer conversion was estimated by ^{1}H NMR. [c]Theoretical molecular weight (M_n,Theo) was calculated based on the $[M]_0/[I]_0$ ratio and conversion. [d]M_n,NMR was estimated by ^{1}H NMR for polymers with sufficiently high signal-to-noise ratios. M_n of high molecular weight polymers cannot be determined using this method because of the low signal of the chain end group. [e]M_n, SEC, and $Đ$ were determined by SEC equipped with a multiangle laser light scattering detector. [f]α/β-anomeric ratios were estimated by ^{1}H NMR. [g]Polymerization was conducted for 48 h.

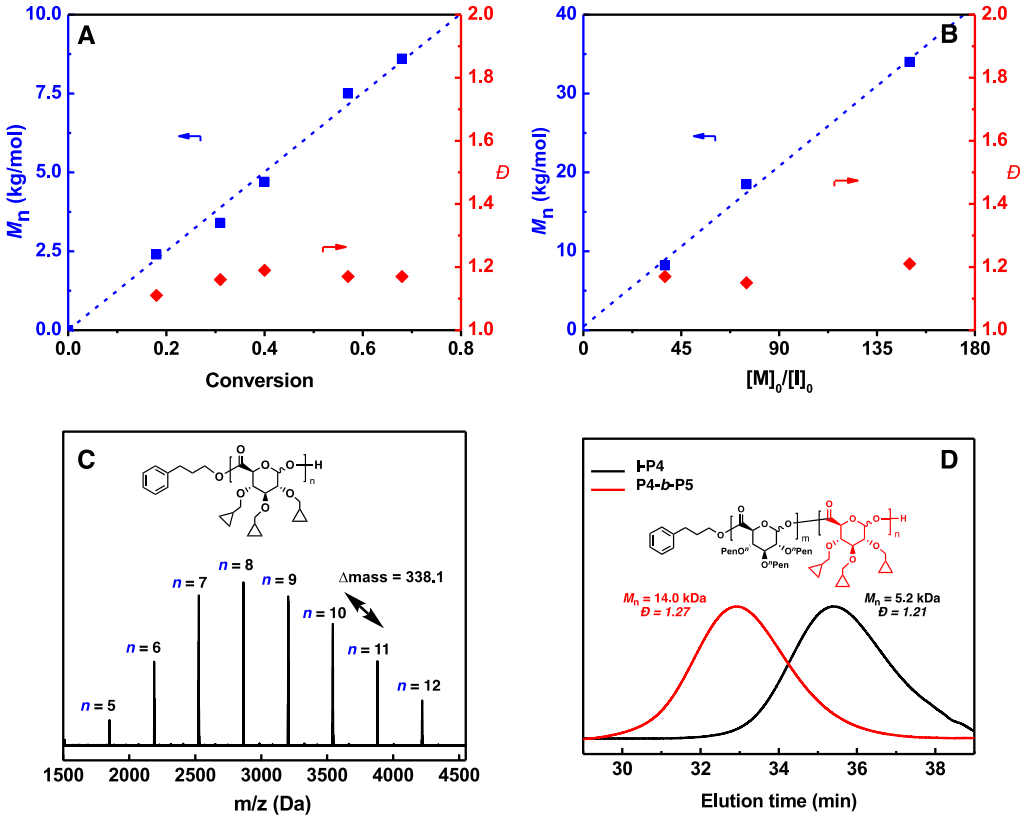


Figure 1. Characterization of the polymerization of glucurono-1,6-lactone monomers. (A) Relationship between M_n and conversion for the polymerization of **M5**. (B) Relationship between M_n and $[M]_0/[I]_0$ for the polymerization of **M5**. (C) MALDI-TOF mass spectrum of **P5**. (D) Chain extension of macroinitiator **I**−**P4** by **M5**.

which could attain a higher concentration of 2.5 M in dichloromethane due to its longer alkyl substitution. The polymerization of **M2** successfully produced a polymer, with the number-average molecular weight (M_n) obtained by size exclusion chromatography (SEC) corresponding well with the theoretical values (Table 1, entry 2). Inspired by these results,

https://doi.org/10.1021/jacs.4c06431
J. Am. Chem. Soc. 2024, 146, 21868−21876

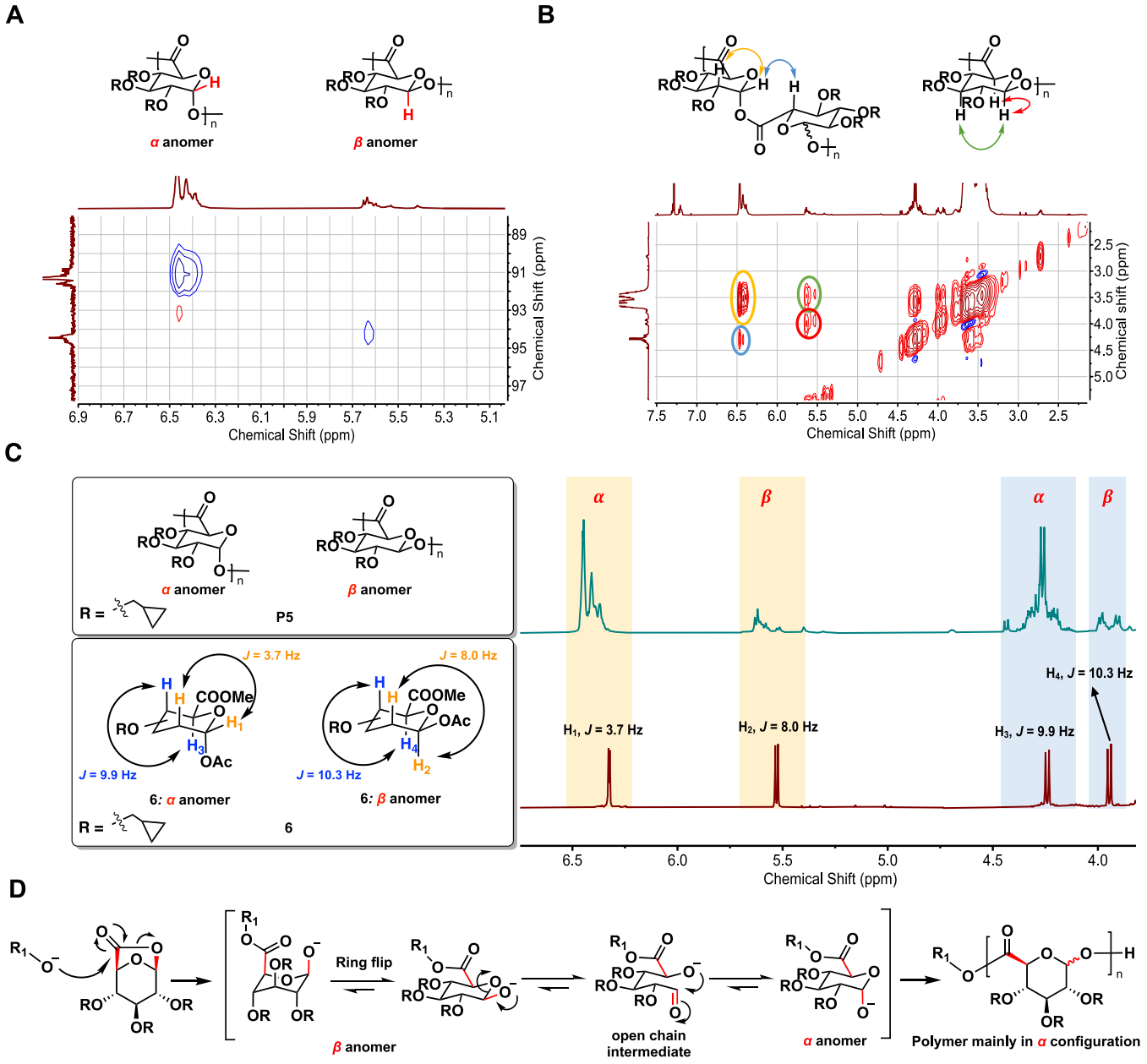


Figure 2. Stereochemical characterization of the pseudo-polysaccharides. (A) HSQC spectra of **P5** elucidates proton−carbon connectivity of α/β-anomers. (B) NOESY spectra of **P5** elucidates spatial correlations associated with α/β-anomers. (C) ^{1}H NMR spectra of **P5** and small molecule analogue **6** resembling the structure of the repeating unit. (D) Proposed mechanism of epimerization during propagation.

polymerizations of **M3**, **M4**, and **M5** were conducted under neat conditions as these monomers were liquids at room temperature. Increasing the initial monomer-to-initiator ($[M]_0/[I]_0$) ratio in these reactions resulted in polymers with higher M_n, while maintaining low dispersity (Table 1, entries 6−11). Notably, polymers with a degree of polymerization of over 100 were achieved (Table 1, entries 8 and 10). Further increasing the $[M]_0/[I]_0$ ratio to 300 did not lead to a higher M_n of the resulting polymer (Table 1, entry 11), suggesting insufficient polymerization control at this $[M]_0/[I]_0$ ratio, likely caused by chain transfer events.

We assessed the living characteristics of the polymerization using **M5** as the representative monomer. First, linear relationships between M_n and conversion and M_n and the $[M]_0/[I]_0$ ratio were observed, while low dispersities were maintained throughout the polymerization ($Đ$ < 1.2) (Figure 1A,B). In-depth analysis by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) of **P5**, a homopolymer of **M5**, showed a discrete set of peaks spaced by 338.1 Da, which corresponds to the molecular weight of the repeating unit. Furthermore, the chain-end groups of **P5** were identified as 3-phenyl-1-propanoxyl and hydrogen atom, respectively, indicative of high chain-end fidelity (Figure 1C). **P2**−**P4** showed consistent results (Figures S10−S12). Lastly, chain extension of a macroinitiator **I**−**P4** (M_n = 5.2 kDa, $Đ$ = 1.21), a homopolymer of **M4**, with **M5** showed a clear shift to a higher molecular weight region on the SEC chromatogram, affording a block copolymer **P4**-*b*-**P5** (M_n = 14.0 kDa, $Đ$ = 1.27) (Figure 1D). The formation of the block copolymer was further confirmed by diffusion ordered NMR spectroscopy (DOSY), which revealed a single diffusion peak (Figure S14). Taken together, these experiments indicate

https://doi.org/10.1021/jacs.4c06431
J. Am. Chem. Soc. 2024, 146, 21868−21876

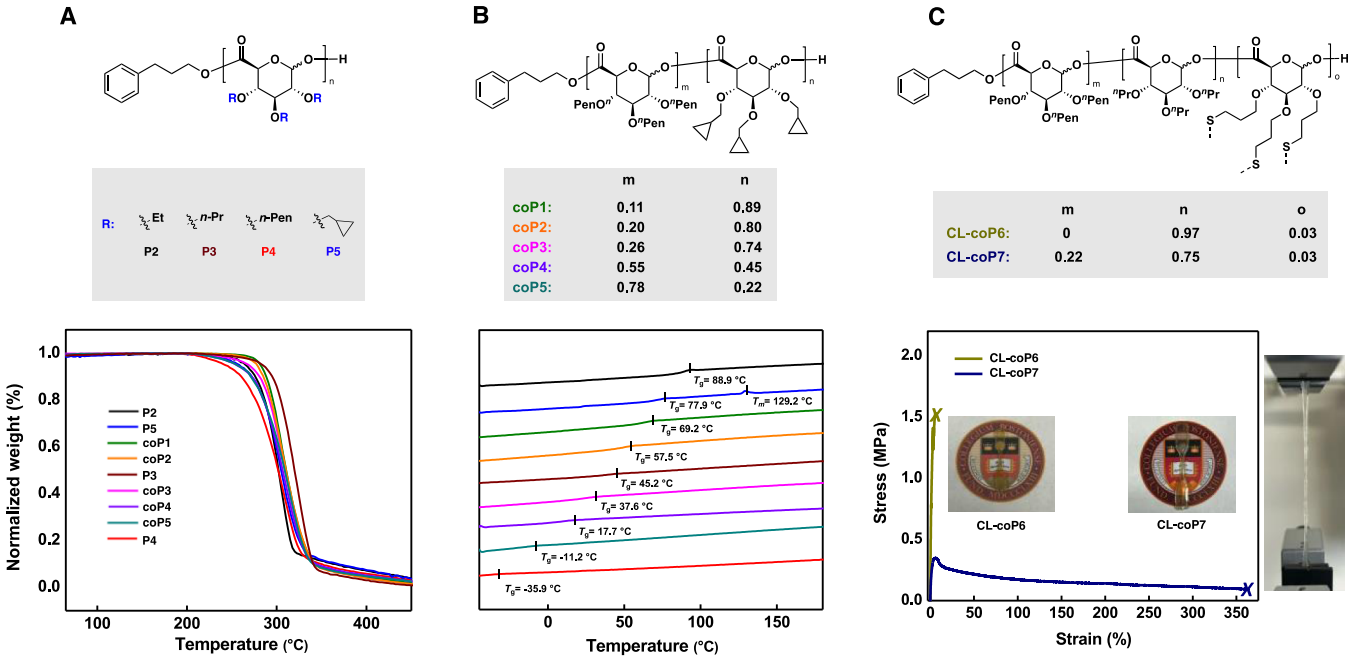


Figure 3. Thermal and mechanical properties of the pseudo-polysaccharides. (A) Normalized weight percent versus temperature obtained from TGA. (B) Glass transition temperatures of different copolymers with variable feed ratios obtained from DSC. (C) Tensile stress−strain curve of **CL-coP6** and **CL-coP7**.

that the anionic ROP of glucurono-1-6-lactones is a living polymerization.

Stereochemical Analysis of the Polymers. The glucurono-1,6-lactone monomers, locked in the β-anomeric configuration, were initially expected to form pseudo-polysaccharides predominantly with β-linkages. However, ^{1}H NMR analysis of **P5** revealed unexpected epimerization at the anomeric/C1 position, indicated by two anomeric signals at 5.5 and 6.4 ppm (Figures 2A,B and S7). To determine the stereochemistry of **P5**, we utilized two-dimensional NMR techniques, including heteronuclear single-quantum coherence (HSQC) and nuclear Overhauser effect spectroscopy (NOESY) experiments. HSQC provided insights into proton−carbon connectivity, showing correlations for the signals at 6.4 ppm in ^{1}H NMR and at 91 ppm in ^{13}C NMR and the signals at 5.6 ppm in ^{1}H NMR and at 94 ppm in ^{13}C NMR, putting the former in agreement with the chemical shifts of the α-anomer and the latter consistent with the β-anomer of glucosides (Figures 2A and S15).[69−71] Furthermore, NOESY experiments revealed key spatial relationships in the repeating unit of the polymer. Notably, the correlations of the proton signal at 6.4 ppm with the protons at C2 and C5 are consistent with the assignment of the α-anomer; the correlations of the proton signal at 5.6 ppm with the protons at C3 and C5 are consistent with the assignment of the β-anomer (Figures 2B and S16). To further elucidate the stereochemistry of the polymer, we synthesized the small molecule analogue **6**, which resembles the structure of the repeating unit of **P5**. The chemical shifts observed in the ^{1}H NMR spectrum of compound **6** aligned well with those of polymer **P5**. The coupling constants at C1 (α-anomer: J = 3.7 Hz, β-anomer: J = 8.0 Hz) and C5 (α-anomer: J = 9.9 Hz, β-anomer: J = 10.3 Hz) of **6** support our assignments. Further analyses of **6** using HSQC, correlation spectroscopy, and NOESY also corroborate these findings (Figures 2C and S17−S20). Additionally, epimerization at the C5 position did not occur based on the aligned peaks between **P5** and **6** at 4.24 and 3.94 ppm. Taken together, these results indicated a predominance of α-linkages in **P5** (83 mol %). We attributed the anomeric epimerization to the interconversion between the α-anomer and the β-anomer of the propagating anomeric alkoxide via an open-chain intermediate (Figure 2D). It is noteworthy that our observed rapid epimerization of the highly reactive nucleophilic anomeric alkoxide is consistent with past reports.[72−75] Interestingly, the α-linkage was predominant in all pseudo-polysaccharides generated from the polymerization of glucurono-1,6-lactones, and varying α/β ratios were observed as the protecting groups of O2, O3, and O4 varied (Table 1). More sterically hindered monomers, such as **M4**, were found to result in a high α/β ratio of 90:10 in the polymer (Table 1, entries 4, 7, and 8), compared to the lower α/β ratio (75:25) of the polymer generated from the less sterically hindered monomer **M2** (Table 1, entry 2). These results suggest that the propagation of the alkoxide anion is slower than its epimerization, allowing for the epimerization to proceed toward the thermodynamically more favored α-anomer.[74]

Material Properties of the Polymers. The thermal properties of the pseudo-polysaccharides generated from various monomers were measured using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). Both homopolymers (**P2**−**P5**) and statistical copolymers containing varying compositions of **M4** and **M5** (**coP1**−**coP5**) all showed 10% weight loss decomposition temperatures (T_d) ranging from 270 to 287 °C, similar to commercial polyesters (Figure 3A).[76,77] However, the glass transition temperatures (T_g) of the homopolymers varied greatly, with **P2**, **P3**, **P4**, and **P5** showing T_g values of 89, 45, −36, and 77 °C, respectively (Figure 3B). The lower T_g observed in **P4** was attributed to the highly flexible pentyl side chains, which disrupted the chain packing. Conversely, the more rigid cyclopropylmethyl group in **M5** facilitated chain packing and the formation of the crystalline domain, leading to a

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J. Am. Chem. Soc. 2024, 146, 21868−21876

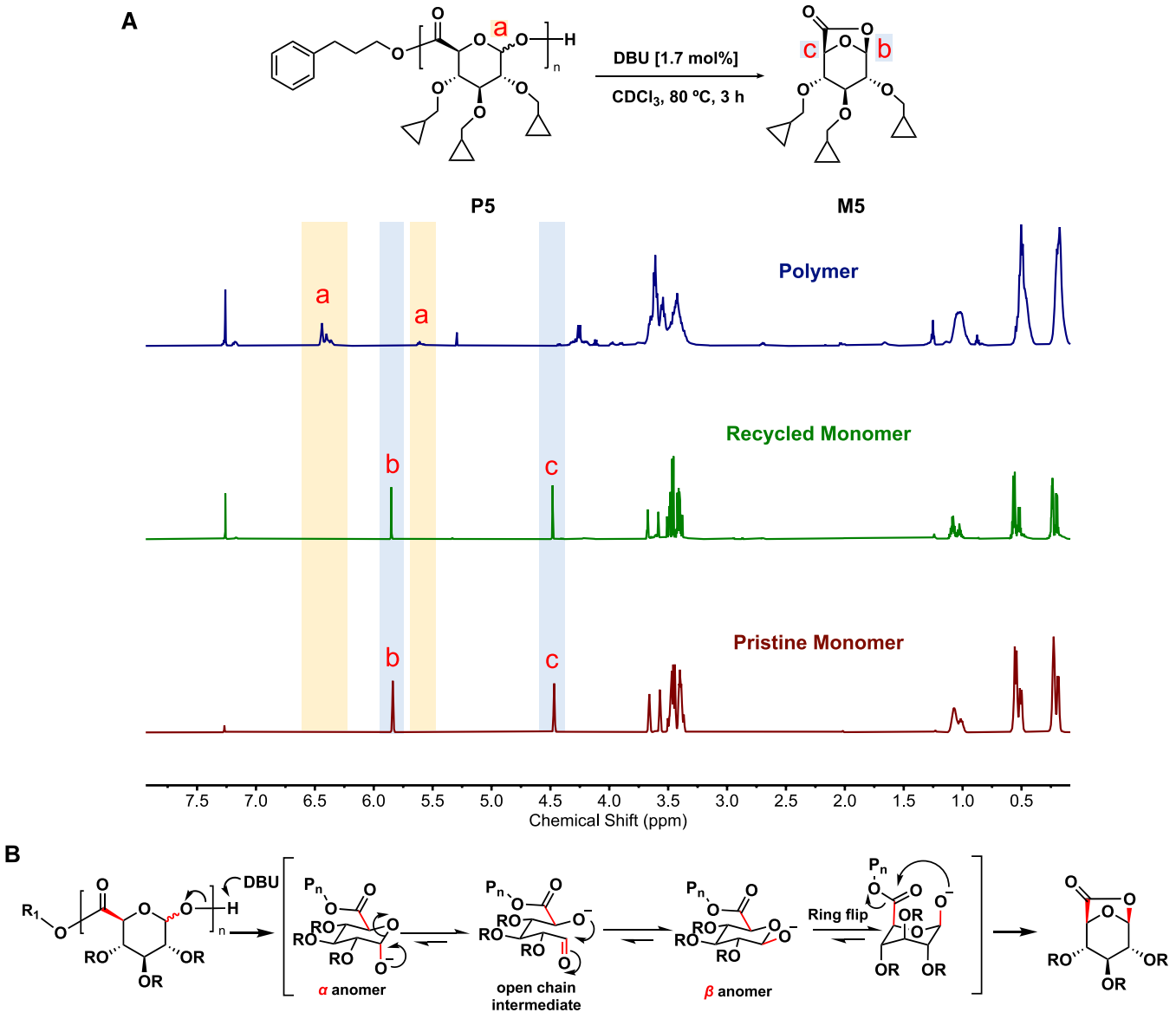

Figure 4. Depolymerization studies of the pseudo-polysaccharides. (A) ^{1}H NMR spectra of **P5**, the chemically recycled monomer, and pristine monomer **M5**. (B) Proposed depolymerization mechanism; β-anomer cyclization leads to productive monomer regeneration.

semicrystalline thermal behavior of **P5** with a melting temperature (T_m) of 129 °C. Importantly, the T_g of copolymers was found to be readily tunable in a broad temperature range from −36 to 89 °C in the statistical copolymers, which can be conveniently produced by varying the feed composition of two different monomers in the copolymerization. Notably, the compositions of the resulting copolymers (F_M^{end}) were consistent with the initial monomer feed ratios (f_M^0), suggesting that despite bearing different side chains, these monomers possessed similar reactivities in the copolymerization (Figure 3B, Table S4).

Capitalizing on the tunable thermal properties of the copolymers, we further investigated their mechanical properties. Given that **P3** and **P5** were hard but brittle and **P4** was a viscous oil, we hypothesized that a copolymer of two monomers would yield a material with desirable mechanical properties. To increase polymer entanglement and thereby enhance the mechanical strength, we used a cross-linker, **CL**, bearing allylic pendant groups, which could readily generate cross-linking within the material via UV-mediated thiol−ene click chemistry.[78] By examining various copolymer compositions, we found that a hard but brittle copolymer **coP6** could be generated using monomers **M3** and **CL** (F_{M3}^{end} = 0.97, F_{CL}^{end} = 0.03, F^{end} is defined as the final composition of the copolymer), with a Young's modulus of 199.06 ± 49.90 MPa, an ultimate tensile strength of 1.47 ± 0.05 MPa, and an elongation at break of 17.47 ± 3.80%. In stark contrast, an elastic copolymer **coP7** could be generated from the copolymerization of **M3**, **M4**, and **CL** (F_{M3}^{end} = 0.75, F_{M4}^{end} = 0.22, and F_{CL}^{end} = 0.03), with a Young's modulus of 21.57 ± 14.20 MPa, an ultimate tensile strength of 0.20 ± 0.06 MPa, and an elongation at break of 326.67 ± 33.23%. The drastic difference in mechanical properties between the two copolymers highlighted the tunability of the material properties of the pseudo-polysaccharides through the side chain modifications (Figure 3C).

Chemical Recycling. Chemically recyclable polymers hold significant potential as sustainable and environmentally friendly materials. We sought to explore whether the glucurono-1,6-lactone monomer could strike a balance between polymer-

https://doi.org/10.1021/jacs.4c06431
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ization and depolymerization thermodynamics and enable a circular monomer−polymer−monomer life cycle owing to its bicyclic nature. To test this hypothesis, depolymerization of **P5** (M_n = 8.0 kDa, $Đ$ = 1.17) was conducted under the presence of 1.7 mol % of DBU relative to the polymer repeating units in $CDCl_3$ and monitored by real-time ^1H NMR at 80 °C. Under this condition, quantitative depolymerization back to monomer **M5** was observed over 3 h (Figure 4A). Interestingly, SEC analysis of aliquoted samples during the depolymerization of **P5** showed no formation of oligomers, corroborating a head-to-tail depolymerization mechanism. The modest decrease in M_n as the conversion increased was attributed to midchain cleavage events arising from infrequent intermolecular transesterification (Figure S47). Subsequently, the depolymerization of **P5** was carried out on a gram scale with excellent yield (91%). Depolymerization of cross-linked copolymers **CL-coP6** and **CL-coP7** was also successful, resulting in 78% and 85% recovery yields of their respective monomers (for details, see depolymerization studies in the Supporting Information). It is noteworthy that following the depolymerization of **CL-coP7** and repolymerization, the mechanical properties of the repolymerized material were comparable to those of the pristine polymer (Figure S44).

While the pseudo-polysaccharides consist predominantly of α-linkages, the intramolecular ester linkage within the monomer requires a β-anomeric configuration. Therefore, monomer regeneration likely involves stereoinversion at the anomeric position when the chain-end hydroxyl group is deprotonated, followed by transesterification−cyclization of the β-anomeric alkoxide (Figure 4B). Although the α-anomeric alkoxide is thermodynamically favored, it is unable to undergo cyclization because it is located at a face of the ring different from that of the C6 carbonyl.

CONCLUSIONS

In conclusion, we have developed a versatile approach to chemically recyclable ester-linked pseudo-polysaccharides through anionic ROP of glucurono-1,6-lactones. Central to this method is the bicyclic glucurono-1,6-lactone monomer, which could incorporate a glucopyranose repeating unit into the main chain of the resulting pseudo-polysaccharides. This polymerization, carried out with an alcohol initiator and DBU as an organocatalyst, resulted in stereoselective polymerization to yield predominantly α-linkages, which was attributed to epimerization of the propagating glucosyl alkoxide anion. The polymerization maintained excellent livingness, enabling the synthesis of well-defined homopolymers, block copolymers, and statistical copolymers. We demonstrated that complete chemical recycling of these pseudo-polysaccharides back to their monomers could be readily achieved, suggesting a potential polymer circular economy. The versatility of this method is also highlighted by the tunable thermal and mechanical properties of these pseudo-polysaccharides, which offer the potential for creating novel polymeric materials surpassing native polysaccharides.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c06431.

Figures and tables, characterization data and $^1H/^{13}C$ NMR spectra, and detailed experimental protocols (PDF)

Accession Codes

CCDC 2354616 contains the Supporting Information crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Funding

This work was supported by an NSF CAREER award (CHE-1944512) to J.N. Financial assistance was also provided by a Beckman Young Investigator Award to J.N. from the Arnold and Mabel Beckman Foundation and a Camille Dreyfus Teacher-Scholar Award to J.N. from the Dreyfus Foundation. X-ray characterization was supported by an NIH Award (S10OD030360). NMR characterizations were supported by an NSF MRI award (CHE-2117246) and an NIH HEI-S10 award (1S10OD026910−01A1).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Dr. Bo Li, Prof. Ali Salifu, Dr. Thusitha Jayasundera, Marek Domin, Dr. Jing Jin, Dr. Xiaonan Li, Dr. Wenqi Wang, Na-Chuan Jiang, Gavin Giardino, and Matthew Chapman for characterization assistance and insightful discussions.

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https://doi.org/10.1021/jacs.4c06431
J. Am. Chem. Soc. 2024, 146, 21868−21876