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Synthesis and Polymerization of Bicyclic Ketals: A Practical Route to High-Molecular Weight Polyketals

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Supporting Information

ABSTRACT: Polyketals are an important class of materials for drug delivery to sensitive tissues as they degrade in vivo to nonacidic species. We report the synthesis of high-molecular weight cyclic polyketals by the cationic ring-opening polymerization of bicyclic ketal monomers, which were prepared by the metal-catalyzed rearrangement of epoxy ketones. Three different cyclic polyketals with high molecular weights were synthesized using this protocol.

Polyesters such as poly(lactic acid), poly(glycolic acid), and poly(ε-caprolactone) have great potential as drug-delivery vehicles because they are biocompatible and degrade to resorbable or excretable small molecules, which are subsequently metabolized or removed by the body.[1] However, polyesters degrade by hydrolysis of the ester linkages, thus forming significant quantities of hydroxy acids. These acidic species lower local pH in and around the degrading polyester,[2] which can aggravate inflammation in the recipient tissue.[3] Additionally, the acidic degradation products may damage or destroy the drug that is being delivered.[4] Due to these limitations, there has been recent interest in the synthesis of alternative biodegradable polymers that yield neutral products upon degradation.

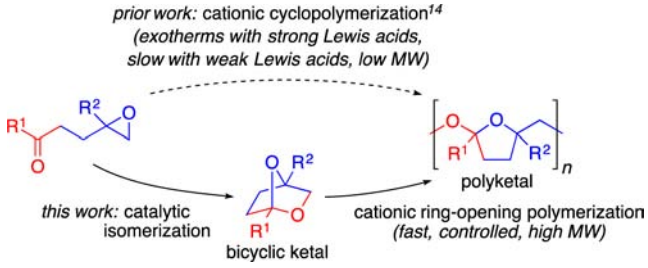
Polyketals are promising vehicles for drug delivery to pH-sensitive targets because they biodegrade into neutral ketone and alcohol species upon hydrolysis. Examples such as poly(1,4-phenylene acetone dimethylene ketal) (PPADK)[5] and poly(cyclohexane-1,4-diyl acetone dimethylene ketal) (PCADK)[6] have recently emerged as new materials for delicate applications, including delivery to inflammation-sensitive targets such as heart and lung tissue.[7] Both of these polyketals are synthesized by using the requisite diol and 2,2-dimethoxypropane via step-growth condensation polymerization, the challenging nature of which results in modest molecular weights (<5 kDa). Polymer molecular weight can play an important role in degradation and drug-release profiles;[8] therefore, the ability to synthesize high-molecular weight polymer is desirable. Additionally, macromolecule biodistribution properties such as blood circulation time and tumor accumulation have shown a dependence on molecular weight as well as polymer architecture and surface chemistry.[9]

A recent review of biodegradable polymers for drug delivery cited low molecular weights as one of the primary disadvantages of polyketals and polyacetals.[10] Polymerization techniques that form bonds other than the ketal linkage have been able to generate higher molecular weights than the aforementioned ketal polycondensations. Murthy has synthesized polyketals by acyclic diene metathesis with M_n up to 13 kDa,[11] and Frechét has reported the use of diamine-functionalized ketals for the synthesis of degradable, nontoxic polyketal-urethanes and polyketal-ureas with M_n as high as 42 kDa.[12] Miller recently reported the synthesis of high-molecular weight polyacetals (up to 40 kDa) using acid-catalyzed acetal metathesis,[13a] while Grubbs has reported a ring-opening metathesis route to polyacetals with M_n as high as 17 kDa.[13b]

An interesting new class of biodegradable cyclic polyketals synthesized via Lewis acid-catalyzed polymerization of epoxy ketones has recently been reported (Scheme 1).[14] In addition to the keto-diol degradation products being nonacidic, they show promise as cellular antiproliferative agents.[15] Unlike the previously mentioned polyketals and polyacetals, these cyclopolymers are formed by a chain-growth polymerization mechanism. The proposed enchainment process involves cationic activation of the epoxy portion of the monomer, followed by intramolecular cyclization of the ketone. Sequential monomer addition to the growing polymer and the lack of small-molecule byproducts eliminate the limitations of step-growth polymerizations. Although the reported molecular weights (up to 13 kDa) exceeded those of some of the existing polyketals, they are well below the desired molecular weight (~30−50 kDa).[9] In addition, reaction times were exceedingly long (48−72 h).

Due to these synthetic limitations, we decided to investigate a potentially more efficient synthetic method to yield higher-molecular weight material. An alternative pathway to the same cyclic polyketals is through the ring-opening polymerization of

Scheme 1. Methods for the Synthesis of Ketal Cyclopolymers from Epoxy Ketones



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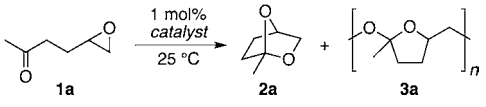
the corresponding bicyclic ketal (Scheme 1). The cationic polymerizations of analogous bicyclic acetals[16] and orthoesters[17] are established and are capable of producing polymers with very high molecular weights (up to 500 kDa).[18] We hypothesized that synthesis and subsequent ring-opening of bicyclic ketals could produce polyketals with significantly greater molecular weights than have been previously reported.

In addition to having polymerization ability, bicyclic acetals and ketals are key structures in certain natural product frameworks[19] and have also been used as intermediates for controlled synthesis of substituted furans.[20] Bicyclic acetals and ketals have been synthesized previously via intramolecular condensation of diols and carbonyl species.[21] Of particular interest to us were numerous studies reporting the isomerization of epoxy ketones or epoxy aldehydes of the correct chain length catalyzed by protic acids[22] or metal-based catalysts.[23] However, these isomerizations were performed with substrates bearing substituents that provided some amount of Thorpe-Ingold assistance for the cyclization. There are very few reports of bicyclic ketals with unsubstituted backbones,[24] likely owing to their proclivity for polymerization. We investigated the isomerization of the epoxy ketone 5,6-epoxyhexan-2-one (**1a**) to 1-methyl-2,7-dioxabicyclo[2.2.1]-heptane (**2a**) to identify a catalyst mild enough for the transformation (Table 1). Brønsted acids such as 2,4,6-collidine·HCl (entry 1) did not show any reactivity with the epoxide. The simple Lewis acid aluminum trichloride (entry 2) generated some of the desired bicyclic ketal, but the reaction was not selective and significant amounts of low molecular weight polymer were observed. Titanium tetrachloride [$TiCl_4(THF)_2$] completely transformed the epoxide, but only a small amount of **2a** was observed and significant quantities of unidentified species were produced (entry 3).

Table 1. Catalyst Screening for Epoxy Ketone Cyclization[a]

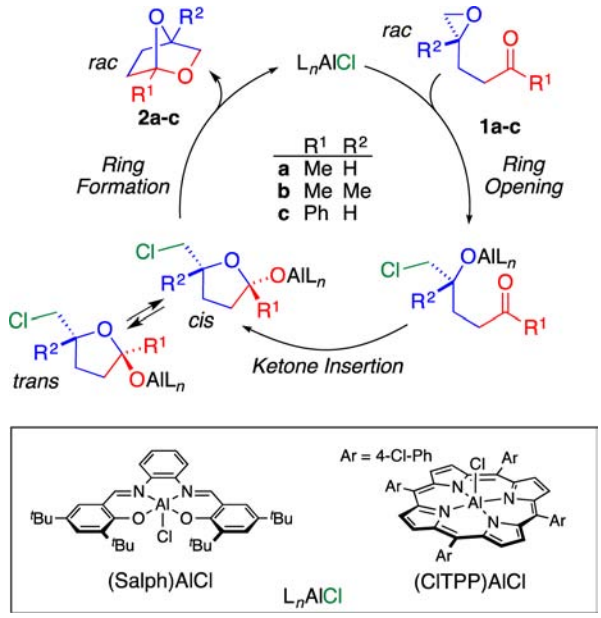


entry	catalyst	time (h)	**1a** (%)[b]	**2a** (%)[b]	**3a** (%)[b]
1	collidine·HCl	20	>99	<1	<1
2	$AlCl_3$	20	5	21	74
3[c]	$TiCl_4(THF)_2$	20	<1	<5	<1
4	(Salph)AlCl	20	55	29	16
5	(ClTPP)AlCl	20	73	27	<1
6[d]	(ClTPP)AlCl	144	<1	>99	<1

[a]Isomerization conditions: 1.0 mmol **1a**, 10 μmol catalyst ([**1a**]/[catalyst] = 100), 0.5 mL CH_2Cl_2, 25 °C. [b]Determined by ^{1}H NMR spectroscopy. [c]A variety of unidentified species were produced under these conditions. [d]Optimized conditions: 14 mmol **1a**, 70 μmol (ClTPP)AlCl ([**1a**]/[(ClTPP)AlCl] = 200), 7 mL 1,2,4-trichlorobenzene, 25 °C.

We felt that a homogeneous metal catalyst might selectively isomerize the epoxy ketone to the desired bicyclic ketal. Inoue demonstrated that porphyrin aluminum chloride species ring-open epoxides by coordination and subsequent nucleophilic attack by chloride or other nucleophiles.[25] Because the epoxide polymerizations using this complex are inherently slow, we proposed that intramolecular insertion of the ketone moiety into the metal alkoxide bond might occur more readily than epoxide enchainment. The resulting hemiacetal species could then ring-close with chloride elimination to form the bicyclic ketal and regenerate the catalyst (Scheme 2). Previously, our group has activated epoxides for ring-expansive carbonylation

Scheme 2. Proposed Mechanism: Catalytic Isomerization of Epoxy Ketones



with aluminum-based Lewis acids in salen and porphyrin frameworks.[26] Using the aluminum chloride form of these catalysts (Scheme 2), *N,N′*-phenylenebis(3,5-di-*tert*-butylsalicylidene-amino) aluminum chloride [(Salph)AlCl] and *meso*-tetra(4-chlorophenyl)porphyrinato aluminum chloride [(ClTPP)AlCl] were tested for the isomerization (Table 1, entries 4−5). The salen complex (Salph)AlCl was more selective than $AlCl_3$, but it generated polymer as well as leaving unreacted **1a** (entry 4). The porphyrin catalyst (ClTPP)AlCl (entry 5) proved to be the only selective catalyst for the isomerization, generating virtually no polymer by-products. Under optimized conditions (ClTPP)AlCl is able to fully and selectively convert epoxy ketone **1a** to cyclic ketal **2a** (entry 6).

The reaction proceeded well in chlorinated solvents, and 1,2,4-trichlorobenzene (bp = 214 °C) was chosen as a solvent because it allowed for the facile removal of product **2a** from the reaction mixture by vacuum transfer. The same catalyst and conditions facilitated the rearrangement of 5,6-epoxy-5-methyl-hexan-2-one (**1b**) to 1,4-dimethyl-2,7-dioxabicyclo[2.2.1]-heptane (**2b**). (ClTPP)AlCl also rearranged 4,5-epoxy-1-phenyl-pentan-1-one (**1c**) quantitatively to 1-phenyl-2,7-dioxabicyclo[2.2.1]heptane (**2c**); however, this bicyclic ketal was found to be unstable at 22 °C. For this reason, **2c** was purified by crystallization at −37 °C and used directly for polymerization.

With a series of bicyclic ketals now on hand, the polymerization behavior was investigated. Using bicyclic ketal **2a** as the model substrate, several Lewis acids were screened as catalysts for the polymerization (Table 2). Although $Zn(OTf)_2$ had previously been shown to produce the highest-molecular weight polymer in the direct polymerization of **1a**,[14] it did not produce any polymer from bicyclic monomer **2a** under the conditions tested (entry 1). $TiCl_4(THF)_2$ showed some activity but generated only oligomeric species (entry 2). Strong Lewis

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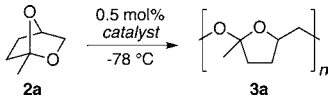
Table 2. Cationic Ring-Opening Polymerization of 2a[a]



entry	catalyst	yield (%)	M_n (kDa)[b]	M_w (kDa)[b]	M_w/M_n
1	$Zn(OTf)_2$	<1	–	–	–
2	$TiCl_4(THF)_2$	17	<1	<1	–
3	$BF_3{\cdot}OEt_2$	79	27	36	1.3

[a]Polymerization conditions: 2.0 mmol monomer, 10 μmol catalyst ([**2a**]/[catalyst] = 200), 0.4 mL CH_2Cl_2, −78 °C, 5 min. [b]Determined by GPC, in THF, vs polystyrene standards.

acids, such as $BF_3{\cdot}OEt_2$, were very active for the polymerization, achieving high yield and the highest molecular weight thus far observed in 5 min at −78 °C (entry 3).

Using $BF_3{\cdot}OEt_2$ as the catalyst, the bicyclic ketals were polymerized under a variety of conditions (Table 3). As a control, epoxy ketone **1a** was subjected to the polymerization conditions (entry 1), but no polymer was isolated. Using **2a** (entries 2−6), polymers with a range of molecular weights were synthesized. High monomer to catalyst loadings produced high molecular weight polymer, and a maximum M_n of 190 kDa was achieved (entry 6). This represents a significant increase over the highest previously reported molecular weight for this polyketal.[14] As seen in entries 5 and 6, this methodology is scalable, capable of producing multigram (>5 g) batches of polymer. An additional benefit is the rapid rate of the polymerization, reaching high conversions at low temperatures in minutes. The same conditions were successful for the polymerization of the other monomers as well. As seen in entries 7 and 8, the dimethyl derivative **2b** was polymerized with $BF_3{\cdot}OEt_2$ to good molecular weights (up to M_n = 58 kDa), although lower yields were isolated compared to those of monomer **2a**. Finally, despite the inability to isolate the phenyl ketal **2c** in pure form, it was possible to polymerize it to **3c** with moderate molecular weight (M_n = 15 kDa, entry 9). In comparison, the highest previously reported M_n for **3c** was 1.1 kDa.[14]

We have investigated the structure of the polymer formed by the cationic polymerization of **2a**. Depending on which ketal C−O bond of the monomer is cleaved, the resulting polymers may contain 5-membered furanose or 6-membered pyranose rings, or a combination of both (Figure 1). A study of the Lewis-acid catalyzed addition of nucleophiles to 2,7-dioxabicyclo[2.2.1]heptane (**2a** without the methyl substituent) revealed high selectivity for 5-membered furan rings,[27] as did the cationic polymerization of the same monomer.[28] Applying

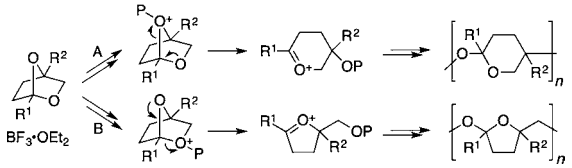


Figure 1. Proposed routes leading to pyranose (path A) or furanose (path B) ring structures (P = polymer chain).

the same Lewis-acid catalyzed reaction conditions to **2a** resulted in the formation of a *cis*/*trans* mixture of 5-membered furan rings.[29] We therefore propose that the polyketals synthesized by the cationic bicyclic ketal polymerization are a random *cis*/*trans* mixture of furanose rings. This result is consistent with other previous studies that report acid-catalyzed ring-opening of bicyclic acetals and ketals typically form 5-membered ring species.[30]

In conclusion, we demonstrate an efficient synthesis of cyclic ketal polymers with unprecedented control of molecular weights (including M_n up to 190 kDa) through a two-step process. First, we report a highly selective, catalytic rearrangement of epoxy ketones to bicyclic ketals (**2a−c**); and second, we demonstrate that $BF_3{\cdot}Et_2O$ initiates the rapid polymerization of the bicyclic ketals to high-molecular weight polymers. We believe the ability to synthesize polyketals with a broad range of molecular weights will lead to greater control over properties such as degradation, release profile, and biodistribution. Further studies will investigate mechanical properties and degradation and explore copolymer synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, NMR spectra of monomers and polymers. 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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Table 3. Polymerization Using $BF_3{\cdot}OEt_2$ as Catalyst[a]

entry	monomer	monomer (mmol)	[monomer]/ [$BF_3{\cdot}OEt_2$]	CH_2Cl_2 (mL)	time (min)	yield (%)	M_n (kDa)[b]	M_w (kDa)[b]	M_w/M_n
1	**1a**	2.0	200	0.40	5	<1	–	–	–
2	**2a**	2.0	15	0.40	5	70	8	11	1.4
3	**2a**	2.0	40	0.40	5	60	12	19	1.6
4	**2a**	3.8	1500	0.76	10	63	67	108	1.6
5	**2a**	66	2500	13.2	15	71	110	190	1.7
6	**2a**	66	4000	13.2	10	70[c]	190	380	2.0
7	**2b**	1.5	1000	0.30	20	31	38	50	1.3
8	**2b**	2.0	2000	0.40	5	24	58	85	1.5
9	**2c**	1.1	500	0.28	30	40	15	30	2.0

[a]All polymerizations performed at −78 °C. [b]Determined by GPC, in THF, vs polystyrene standards. [c]Yield approximate, due to trace solvent.

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assistance with NMR experiments to elucidate polymer structure.

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