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Divergent Mechanistic Avenues to an Aliphatic Polyesteracetal or Polyester from a Single Cyclic Esteracetal

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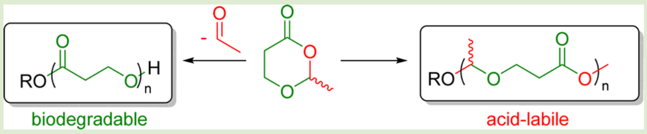
Supporting Information



ABSTRACT: The cyclic esteracetal 2-methyl-1,3-dioxane-4-one (MDO) was polymerized in bulk using diethyl zinc as the catalyst and benzyl alcohol as the initiator to yield either the corresponding polyesteracetal (PMDO) or the aliphatic polyester poly(3-hydroxypropionic acid) (PHPA) at low and high catalyst concentrations, respectively. Spectral analysis gave evidence for distinct propagating species in the two catalyst concentration regimes. At low zinc concentrations ring opening by attack of the initiating species at the acetal functionality, yielding a zinc carboxylate, followed by propagation to yield pure PMDO was implicated. At high zinc concentrations we propose that ring opening via attack at the ester functionality produced a labile zinc hemiacetal, which rapidly and irreversibly expelled acetaldehyde to form a propagating zinc alkoxide and ultimately pure PHPA. Initial rate studies indicated that the rate of PHPA formation had a second-order dependence on zinc concentration; in contrast, the rate of PMDO formation was first order in zinc concentration. High molar mass PMDO exhibited only a glass transition temperature (T_g) ≈ −30 °C, whereas high molar mass PHPA had a T_g ≈ −30 °C and a melting temperature (T_m) ≈ 77 °C. When PHPA and PMDO were subjected to neutral or slightly acidic environments, PMDO exhibited expedited degradation as compared with PHPA.

The development of polymers with pH responsiveness is important for needs in biomedicine, sensing, electronic materials, textile, and filtration applications.[1−8] Macromolecules can be strategically designed to respond to changes in pH through conformational changes triggered by reversible protonation or by irreversible chain degradation.[9] Simple polyesters are a well-understood example of the latter class but hydrolyze rather slowly at physiologically relevant pH ranges (4.5−7.4).[10,11] Polymers that degrade rapidly present tremendous opportunities for drug delivery[12−17] as well as for the development of new materials that break down in natural environments.[18,19]

Acetal or ketal functional groups are excellent candidates for facilitating degradation due to their acid-sensitive nature, and their incorporation in the main chain or as pendant groups of a nondegradable backbone has been reported.[20−23] Routes to polymers containing this functionality in their backbone include cationic,[24,25] step growth,[26−32] or metathesis[33,34] polymerizations. According to a 2010 patent disclosure, an alternating ester/acetal copolymer, poly(1,3-dioxolan-4-one), was accessed from the ring-opening polymerization (ROP) of a five-membered ring precursor. Furthermore, a statistical copolymer of 1,3-dioxolan-4-one (DOX) and lactide was reported. While the patent provided little in the way of characterization data for poly(1,3-dioxolan-4-one),[35] a more recent publication details the synthesis of a variety of copolymers of DOX and lactide and reports up to 36% DOX incorporation. A computational study of the ring strain in DOX suggests that DOX is slightly less strained than γ-butyrolactone, and the authors' reason that the unfavorable thermodynamics of polymerization can be offset by copolymerization with lactide. Finally, the degradation studies in distilled and oceanic water of a copolymer containing 4% DOX and 96% lactide displayed a 2% reduction in mass over the course of 40−50 days.[36]

Enticed by the marriage of the ester and acetal functionalities in a degradable polymer backbone, we set out to synthesize and study the ring-opening polymerization (ROP) of 2-methyl-1,3-dioxane-4-one (MDO). This six-membered monomer can be prepared by a simple Baeyer−Villiger oxidation of the commercial precursor 2-methyltetrahydrofuran-3-one (see Supporting Information (SI)). Alternatively MDO can be accessed from condensation of 3-hydroxypropionic acid with acetaldehyde,[37,38] both of which can be derived from biomass.[39]

We found that diethylzinc ($\mathrm{ZnEt_2}$), a catalyst commonly used in the ROP of lactones,[40−42] readily polymerizes neat MDO (~10 M) in the presence of benzyl alcohol as the initiator. At high loadings of catalyst ($[\mathrm{ZnEt_2}]_0$ = 30−100 mM) the reaction proceeds to essentially complete conversion within several hours. We discovered that catalyst concentration played an important role in the outcome of the polymerization. In fact, two repeating unit structures could be obtained from this one monomer solely by varying the catalyst concentration (Scheme 1).

At high loadings of $[\mathrm{ZnEt_2}]_0$ over a range of $[\mathrm{MDO}]_0/[\mathrm{BnOH}]_0$ ratios we generated polymers with molar masses from 7.9 to 43 kg mol^{-1} (representative polymerization: $[\mathrm{ZnEt_2}]_0$ = 100 mM, $[\mathrm{MDO}]_0$ = 10.1 M (neat), $[\mathrm{BnOH}]_0$ =

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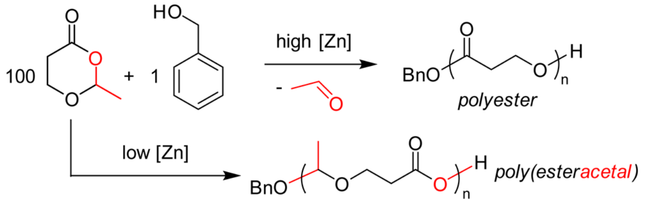
Scheme 1. Tunable ROP of MDO to Two Distinct Structures



100 mM, t_{polym} = 8 h, 23 °C). The polymer products were isolated as white solids by precipitation and exhibited narrow molar mass distributions ($Đ \leq 1.23$) as determined by size exclusion chromatography (SEC). However, the ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra of these polymers at full conversion showed almost no (<1%) incorporation of the acetal methyl and methine moieties present in MDO. Instead, the major resonances were in excellent agreement with poly(3-hydroxypropionic acid) (PHPA),[43] consistent with loss of acetaldehyde (as confirmed by ^{1}H NMR spectroscopy using diluted MDO, Figure S13, SI) under these conditions (Figure 1A and Scheme 1). This was further supported by melting transition temperatures (T_m) for the PHPA samples ranging from 59 to 77 °C and glass transition temperatures (T_g) ranging from −34 to −28 °C (Figure S6, SI), as well as a clear repeat unit of m/z = 72.02 by mass spectrometry (Figure S5, SI) consistent with the expected value.[41]

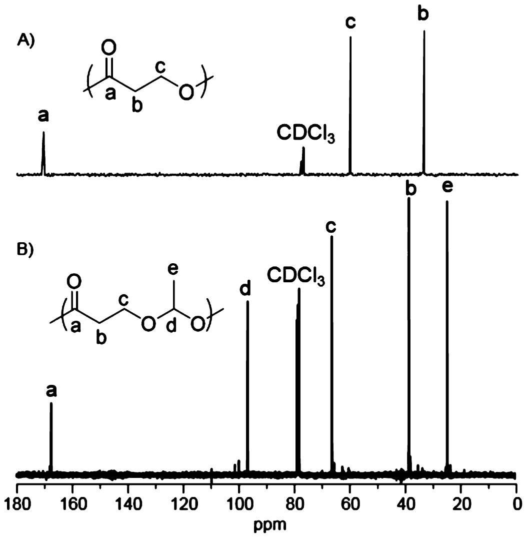


Figure 1. Representative ^{13}C NMR spectra and structural assignments of two distinct polymers synthesized by diethylzinc-catalyzed bulk polymerization of MDO. At higher catalyst concentrations (A, 30−100 mM) PHPA was formed, while at lower catalyst concentrations (B, 0.4−14 mM) PMDO was formed. Spectra are of samples HPA594 ($[ZnEt_2]_0$ = 31 mM, $[MDO]_0$ = 9.9 M, $[BnOH]_0$ = 15 mM, t_{polym} = 8 h, 23 °C, M_n = 43 kg/mol) and MDO66 ($[ZnEt_2]_0$ = 2 mM, $[MDO]_0$ = 10.1 M, $[BnOH]_0$ = 84 mM, t_{polym} = 72 h, M_n = 8 kg/mol).

Interestingly, at low $[ZnEt_2]_0$ loadings, the polymerization of MDO led to a retention of acetal structural units in the polymer backbone as expected in the ROP of cyclic esters. At $[ZnEt_2]_0$ = 0.4−14 mM a clear viscous material was isolated from the polymerization of MDO. At these low catalyst loadings, the MDO polymerization was slower and reached a limiting conversion of approximately 60% (see below). The splitting pattern of the diastereotopic methylene protons (ddd at δ = 3.85 ppm in $CDCl_3$, see Figure S7, SI) and the distinctive resonances in the ^{13}C NMR spectra when compared with PHPA (Figure 1B) were consistent with complete retention of the acetal functional group in the polyesteracetal PMDO (Scheme 1). Furthermore, the clearly defined ^{13}C resonances and the absence of resonances for polyacetaldehyde[44] suggest perfectly alternating ester and acetal units. The absence of a singlet at 5.1 ppm in the PMDO ^{1}H NMR spectrum, which is expected for methylene protons of a benzoyl ester end group, indicated an initiation process that did not proceed via attack of the initiator at the ester functionality. Instead, two doublets and a quartet were observed between 4.5 and 5 ppm, which is in good agreement with a benzyl acetal end group. From this we suggest that at low zinc concentrations benzyl alcohol initiates polymerization via attack at the acetal functionality, generating a propagating zinc carboxylate.

Using low concentrations of zinc, PMDO samples with molar masses ranging from 7.6 to 30 kg mol^{-1} were synthesized by varying $[MDO]_0/[BnOH]_0$ as described above for PHPA (representative polymerization: $[ZnEt_2]_0$ = 2 mM, $[MDO]_0$ = 10.1 M, $[BnOH]_0$ = 84 mM, t_{polym} = 72 h, 23 °C). SEC data for PMDO indicated that molar mass distributions ($Đ \approx 1.6$, see below) were broader than those observed for PHPA prepared from MDO at high zinc concentration. The PMDO samples exhibited low T_g values (−32 to −25 °C) but no melting transitions (Figure S10, SI). ESI-MS showed a clear MDO repeat unit at m/z = 116.05 (Figure S9, SI).

Bulk polymerization of MDO at high catalyst loadings was tracked by ^{1}H NMR analysis of aliquots from the reaction (see Figure S11, SI). The linear relationship between the natural logarithm of the monomer concentration versus time over the course of two half-lives suggests a reaction rate that is first-order in monomer (Figure S12, SI). At these diethyl zinc loadings, the polymerization of MDO to PHPA proceeds to >99% conversion with the concurrent elimination of acetaldehyde. This thermodynamic driving force is analogous to CO_2 expulsion observed during polymerization of *N*-carboxyanhydrides and cyclic carbonates.[45−47] Similarly, the expulsion of acetone has been observed during the 4-dimethylaminopyridine-catalyzed copolymerization of an epoxide with Meldrum's acid.[48]

Apparent molar masses and dispersities as a function of monomer conversion were tracked for both polymerizations by SEC. The linear correlation shown in Figure 2 is consistent with a controlled chain-growth mechanism for both PMDO and PHPA. The larger dispersity values in the case of PMDO are likely due to the relatively unfavorable polymerization thermodynamics; significant depolymerization even at low monomer conversion can lead to broader molar mass distributions.[49−53]

When monitoring MDO bulk polymerization at low catalyst loadings we determined that this reaction proceeds over several days and achieves ∼60% limiting conversion to PMDO at room temperature (Figure S11, SI), and the rate of conversion to PMDO also appears to be first order in monomer (Figure S12, SI). Using experimentally established densities the equilibrium monomer concentration for MDO under low catalyst concentration conditions was determined to be $[M]_{eq}$ = 4.53 M (23 °C). Values for $[M]_{eq}$ were then determined from 23 to 60 °C and used to compute the thermodynamic parameters for the ROP of MDO to PMDO. The ceiling temperature for the neat monomer was calculated to be 81 °C (ΔH_p^0 = −11.6 kJ/

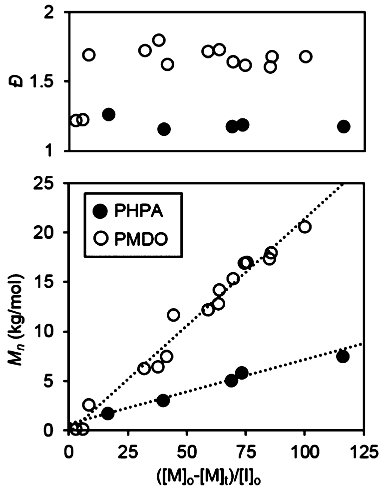


Figure 2. Number-average molar mass M_n and dispersity $Đ$ as determined by SEC calibrated with polystyrene standards. At high catalyst concentrations (●, $[ZnEt_2]_0$ = 87 mM) PHPA was formed. At low catalyst concentrations (○, $[ZnEt_2]_0$ = 1.0 mM), PMDO was formed, but the monomer was not completely consumed. For PHPA, $[MDO]_0$ = 9.3 M and $[BnOH]_0$ = 46 mM. For PMDO, $[MDO]_0$ = 10.1 M and $[BnOH]_0$ = 49 mM.

mol and $\Delta S_p^0 = -52$ J/(mol K), see Figure S14, SI), consistent with related six-membered lactones.[54,55]

To determine the order of both polymerizations in [Zn] we measured the initial polymerization rates over several high- and low-catalyst concentration ranges and created double logarithmic plots of k_{app} versus $[ZnEt_2]_0$ (Figure 3, also see Figures S15−S17, SI). These were broadly consistent with a first-order rate dependence on catalyst concentration under conditions where the acetal functionality is retained ($-d[MDO]/dt \propto [ZnEt_2]^{0.9\pm0.1}$) and a second-order rate dependence at loadings where acetaldehyde is eliminated ($-d[MDO]/dt \propto [ZnEt_2]^{1.9\pm0.2}$). Deviation from integer orders of reaction may be due to impurities or more complex aggregation phenomena, but this was not further investigated.[56−58]

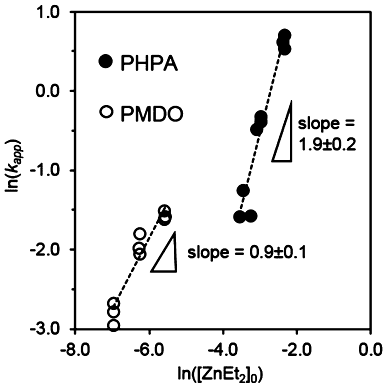
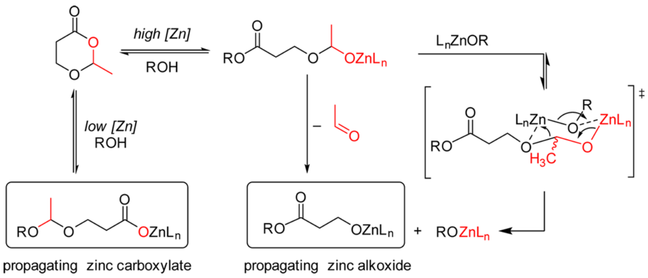


Figure 3. Kinetic plots used to determine the order of polymerization in $[ZnEt_2]_0$. Rate constants (k_{app}) were determined at various concentrations of $[ZnEt_2]_0$. The slope of ln(k_{app}) versus ln($[ZnEt_2]_0$) was used to establish the order of the reaction in $[ZnEt_2]_0$. At low catalyst loadings (○, $[ZnEt_2]_0$ = 0.93−3.7 mM, R^2 = 0.92) the acetal group was maintained, and the slope of the plot indicated that $-d[MDO]/dt \propto [ZnEt_2]^{0.9\pm0.1}$. At higher catalyst loadings (●, $[ZnEt_2]_0$ = 28−96 mM, R^2 = 0.93), the acetal group was eliminated, and the plot slope indicated that $-d[MDO]/dt \propto [ZnEt_2]^{1.9\pm0.2}$. In all cases polymerizations were conducted using $[MDO]_0$ = 10.1 M and $[BnOH]_0$ = 99 ± 7 mM at 23 °C.

We speculate that aggregation of zinc propagating centers coordinated through alkoxide oxygens[59] facilitates acetal elimination at higher relative catalyst concentrations, leading to PHPA. We envisioned that this proceeds through a six-membered transition state formed after coordination and ring opening of MDO, which then collapses to yield a 3-HPA repeat unit with concomitant release of acetaldehyde (Scheme 2).

Scheme 2. Proposed Mechanisms for the Polymerization of MDO



To assess if incorporation of the acetal moiety enhanced polymer susceptibility to degradation under acidic conditions, samples of PHPA and PMDO were subjected to degradation at pH 7.4, 6.4, 5.4, and 4.4 (Figure 4). PHPA did not degrade appreciably at any pH, consistent with other aliphatic polyesters over this short time scale.[8,60−62] In contrast, PMDO exhibited

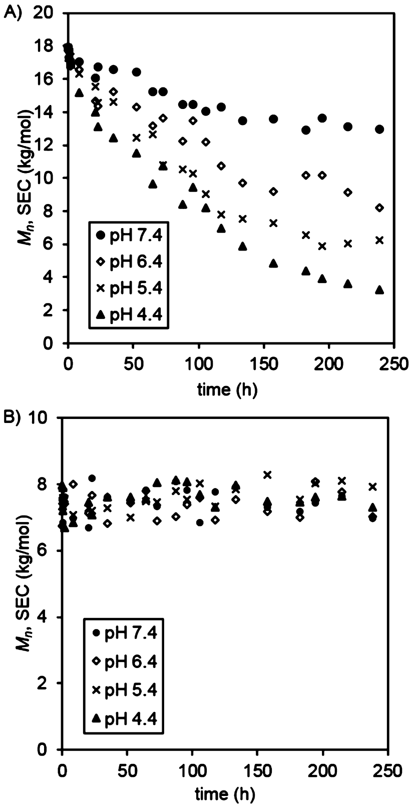


Figure 4. Degradation of (A) PMDO and (B) PHPA as a function of pH. Samples were subjected to degradation at room temperature in a 100 mM phosphate-citrate buffer, periodically lyophilized, and analyzed by SEC to determine changes in molar mass.

significant degradation at all pH levels, especially at low pH (4.4), where apparent molar mass decreased 6-fold over 240 h. This degradation rate is consistent with other systems incorporating acetal linkages as pendent groups[27] and parallels the enhanced degradation observed for lactide-1,3-dioxolane-4-one copolymers.[36] The rate of degradation we observed was, as expected, slower than for polymers incorporating more hydrolytically sensitive ketals.[29,30]

In summary, we have demonstrated the synthesis and characterization of the acid-labile polyesteracetal PMDO and the biodegradable polyester PHPA from a single monomer, MDO. Using diethylzinc as the catalyst, controlled polymerizations were achieved at both high and low catalyst concentrations. At high catalyst concentrations, the polymerization was driven toward the formation of PHPA due to the expulsion of acetaldehyde. This is notable as it achieves high conversions to PHPA with narrow molar mass distributions over practical time periods. Comparable molar mass distributions have only been achieved by the lanthanide-catalyzed solution polymerizations of β-propiolactone.[63] Macrocyclic,[43] condensation,[64] microbial,[65,66] and other ring-opening[67,68] syntheses generally give broader distributions than we observe in the case of MDO to PHPA. At low catalyst concentrations, acetal elimination could be entirely suppressed to deliver the acid-labile polymer PMDO. The formation of distinct products was rationalized by the first-order versus second-order dependency of the rate laws on initial diethylzinc concentration for PMDO and PHPA, respectively. A mechanistic hypothesis in good agreement with both the kinetics and ^{1}H NMR data was put forth for both PMDO and PHPA formation. Further investigation into the mechanism of ROP of cyclic esteracetals is currently underway in our laboratories. Findings described herein not only are intriguing in the context of homopolymer synthesis but also open up attractive avenues toward block- and random copolymer synthesis from a single monomer.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and all characterization data. 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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