Amine-catalyzed chain polymerization of ethyl glyoxylate from alcohol and thiol initiators

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ABSTRACT: Polyacetals have significant potential as degradable polymers, but aldehyde polymerizations are generally difficult to control. Here we show that polymerization of ethyl glyoxylate can be initiated from alcohols or thiols by activation with triethylamine to afford poly(ethyl glyoxylate) with controllable molecular weights and relatively low dispersities ($Đ$ = 1.3-1.4), as evidenced by MALDI-TOF mass spectrometry. Stabilization against depolymerization by chain-capping with benzyl chloroformate was found to proceed without side reactions observed from chain-capping with tolyl isocyanate. The use of the stronger base DBU leads to competing side reactions that limit polymer molecular weight.

Polymers that can be easily depolymerized or otherwise broken down or upcycled into useful molecules have potential applications in the formation of porous or patterned materials,[1-4] drug delivery agents,[1, 5-8] biodegradable plastics,[9-10] and stimuli responsive materials.[11-12] While a number of different polyesters and less-easily-degradable polyamides have been widely commercialized, a number of polymers with more labile backbone linkages, including acetals,[8, 11, 13-23] orthoesters,[24] pyrophosphates,[25] and *N*,*O*-acetals,[26] have been reported.

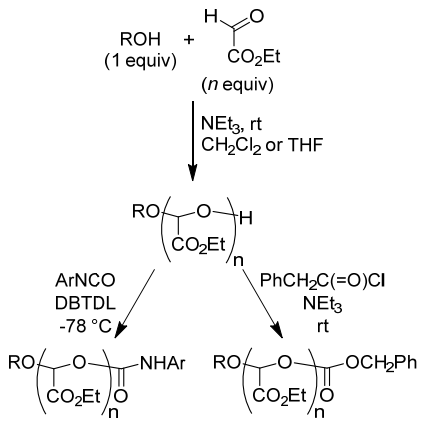
Polyacetals have been studied since the earliest days of polymer science,[27-28] and are particularly attractive for consideration as components of well-defined degradable polymer architectures because they can be prepared by addition polymerization of aldehydes and their C-O backbones are homologous to polyolefins and vinyl polymers but with a direct route for degradation through acetal hydrolysis or depolymerization due to hemiacetal instability. As demonstrated by Gillies,[15-16, 18-20, 29-32] Burel,[13-14, 33-34] Moore,[35-37] McNeil,[38] Kohl,[39-41] Boydston,[12, 42] Klumperman,[22] and others,[17, 43] polyacetals with low ceiling temperatures, particularly those prepared by polymerization of glyoxylate esters or *o*-phthalaldehyde, can depolymerize upon exposure to acid or removal of stabilizing end groups.

While poly(glyoxylate)s and related polyacetals have a great deal of potential in new degradable polymer materials, the polymerization of glyoxylate esters is not well understood. The most common method for polymerization of glyoxylates simply involves the addition of triethylamine to a solution of the monomer in dichloromethane with the subsequent addition of a reagent to cap the terminal hemiacetal unit, typically an isocyanate or a chloroformate, after a suitable period of time.[11, 13-20] Because of the high reactivity of EtG and its susceptibility to side reactions, reproducibly controlling these polymerizations has been difficult. However, Gillies and co-workers have recently demonstrated controlled polymerization of EtG using alkyllithiums and alkoxides as anionic initiators.[20]

While the amine-catalyzed polymerization of EtG has been described as an anionic polymerization, a more likely hypothesis is that initiation occurs by the activation of trace hydroxy-functional initiating species—water or glyoxylate hydrate (ethyl 2,2-dihydroxyacetate)—by hydrogen bonding with triethylamine, followed by addition of the activated oxygen to the monomer carbonyl group. Activation of alcohols for addition to carbonyl double bonds by hydrogen bonding with amines—without formation of free alkoxide—has previously been used in a range of organocatalyzed ring-opening polymerizations.[44-45] Propagation would then occur by the same mechanism through activation of the hemiacetal hydroxy end-group of the polymer chain.

To test this hypothesis, we have undertaken a study of the amine-catalyzed polymerization of ethyl glyoxylate from alcohol initiators (Scheme 1). If alcohols and other protic nucleophiles can be used as initiators for the polymerization of glyoxylates and other aldehydes, then the preparation of more complex polymer architectures that incorporate these monomers should be possible. For a hydroxy group activated by an amine, the nucleophilicity of the hydroxy group should increase as its acidity increases. Because the pK_a values of typical alkanols are

Scheme 1. Alcohol-initiated polymerization of ethyl glyoxylate.



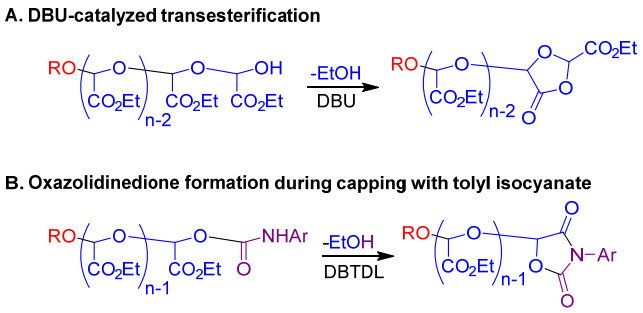
higher than those of hemiacetal and hydrate hydroxy groups, their use as initiators for aldehyde polymerization is non-ideal in that it creates the likelihood that propagation will be faster than initiation. However, using stable alkanol initiators rather than more reactive hemiacetals is much more convenient. Here we demonstrate that using NEt_3 with alkanol initiators, as well as one example of a thiol initiator, can allow control over poly(ethyl glyoxylate) molecular weight and end groups.

EtG was carefully purified by the process described by Gillies and co-workers to remove water, convert hydrate to glyoxylate, and crack glyoxylate oligomers.[15, 46] Polymerization studies carried out prior to the adoption of these procedures invariably resulted in low molecular weight products (number-average molecular weight, M_n < 2 kg/mol), most likely due to the presence of excess glyoxylate hydrate and/or water, which can also serve as initiators. 3-Methoxybenzyl alcohol (MBA) was initially chosen as an initiator to enable estimation of polymer molecular weight by ^{1}H NMR by integration of the methoxy proton peak. Both triethylamine and the stronger base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were investigated as catalysts.

Triethylamine-catalyzed EtG polymerization studies were carried out with [EtG]/[MBA] ratios from 25:1 to 150:1 ([NEt_3]/[MBA] = 1; CH_2Cl_2, rt, 30 min), with excess 4-tolyl isocyanate added to cap the chains at -78 °C. Size exclusion chromatography (SEC) analysis shows that apparent M_n increases from 1.4 to 7.0 kg/mol (vs PS standards) as the [EtG]/[MBA] ratio is increased from 25 to 150 and $Đ$ ranges from 1.5-1.9 (Table S1, Figure S1). For all polymerizations, ^{1}H NMR analysis showed conversions greater than 90%, suggesting that EtG polymerization occurs rapidly and that monomer/polymer equilibrium has been reached well before the end of the polymerization time. M_n values calculated from ^{1}H NMR spectra by comparison of the integrated area under the EtG repeating unit methylene peak (4.0 – 4.3 ppm) to the area under the MBA methylene peak (4.6 – 4.8 ppm) were very close to the theoretical values (Table S1, Figure S2). Polymerizations conducted under these conditions in either CH_2Cl_2 or THF ([EtG]/[MBA] = 50) showed comparable results (Table S1: MBA/TI-50, MBA/TI-50-THF). In attempting to follow the evolution of EtG conversion over time, it was found that conversions above 90% were observed after only 30 s at rt (Table S2). Dispersity increased ($Đ$ from 1.3 at 30 s to 1.6 at 60 min) at longer polymerization times, consistent with a reversible chain polymerization that undergoes a broadening of molecular weight distribution once a high conversion regime is reached.[47] The rapidity of polymerization also raises the likelihood that polymerization and depolymerization rates are much greater than chain-capping rates.

DBU-catalyzed polymerizations ([DBU]/[MBA] = 1) were found to result in polymers with low molecular weights (M_n < 1 kg/mol). MALDI-TOF MS analysis of the products shows the presence of many distinguishable series of peaks at m/z values expected for chain-end cyclization through transesterification of the terminal hemiacetal hydroxy group with a pendent EtG ester group (Scheme 2A; Figure S6). The MALDI-TOF MS for a polymerization run with DBU as the catalyst and no added initiator showed multiple series, all of which have m/z values that match species initiated from EtG hydrate or water (Figure S7). Gillies and co-workers have recently reported that DBU catalysis is effective for transesterification of PEtG side-chains with other alcohols.[48] These results suggest that using an amine such as NEt_3 that is basic enough to cause polymerization but not an effective transesterification catalyst under polymerization conditions is critical to controlling the polymerization process.

Scheme 2. Proposed chain end cyclization reactions during EtG polymerization.



MALDI-TOF MS analysis of polymers prepared with NEt_3 in CH_2Cl_2 and capped with tolyl isocyanate (Table S1: MBA/TI series) showed a single series of peaks with a spacing matching that of EtG (102 u), but the peak m/z values were 45 u less than those expected for PEtG chains with one MBA initiating group and one terminal tolyl carbamate end group, consistent with loss of EtOH (Figure S5A). Given the unimodal molecular weight distribution, we speculate that end-capping of PEtG with isocyanates in CH_2Cl_2 results in intramolecular cyclization of the carbamate nitrogen with a pendent PEtG ester group to an oxazolidinedione (Scheme 2B), as has been observed in reactions of ethyl glycolate with isocyanates,[49-52] though the formation of larger cyclic *N*-acyl carbamates cannot be ruled out. MALDI-TOF MS of the polymerization conducted under identical conditions in THF (MBA/TI-50-THF) showed two PEtG series: a higher intensity series consistent with formation of the putative oxazolidinedione end group, and a lower intensity series with m/z values matching those expected for MBA initiation and 4-tolyl isocyanate termination (Figure S5B). The lack of a clear identifiable ^{1}H NMR peak for the carbamate terminus of the polymer (Figure S4) necessitated using only the 3-methoxybenzyl end group peak to estimate M_n values, which were observed to increase as the [EtG]/[MBA] ratio increases and showed good correlation between $M_{n\ theor}$ and $M_{n\ NMR}$ at lower molecular weights (Table S2).

Using benzyl chloroformate as an end-capping agent with triethylamine as the catalyst resulted in a single series of peaks in the MALDI-TOF MS at m/z values expected for the sodium ion adducts of chains initiated by MBA and terminated with a benzyl carbonate group

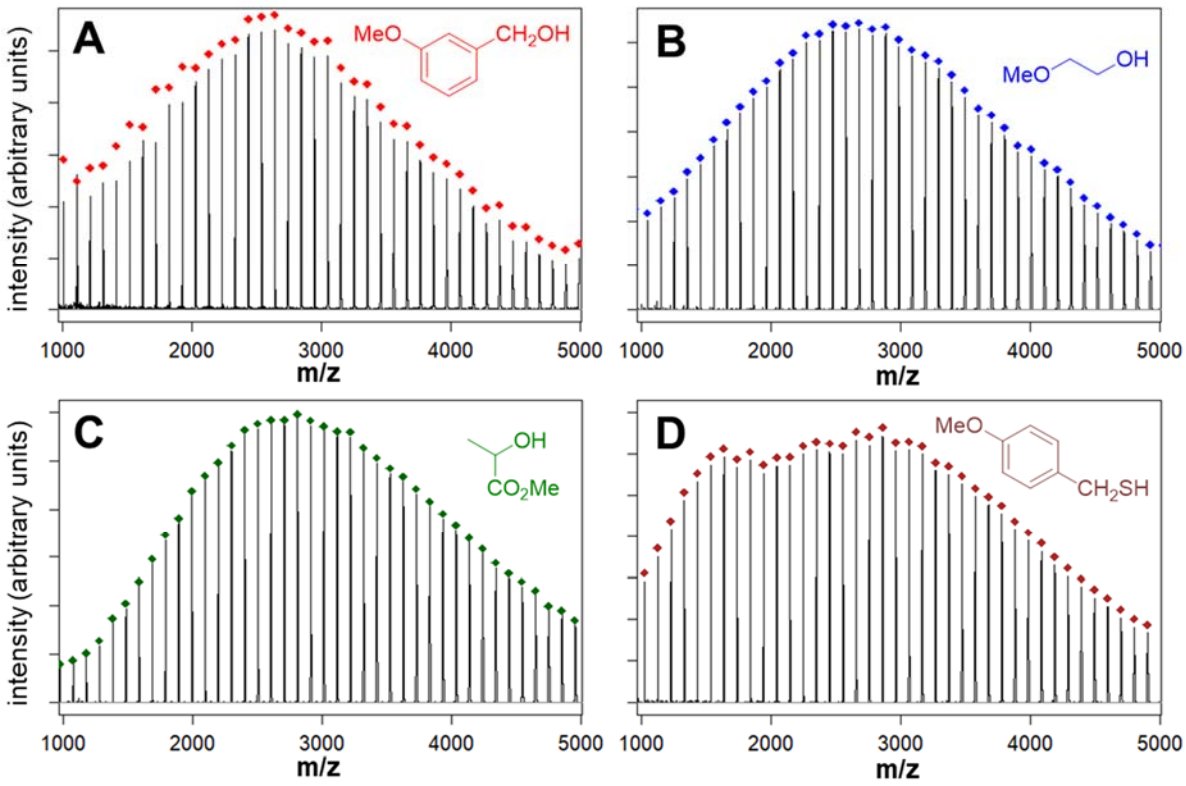


Figure 1. MALDI-TOF MS of PEtG prepared from different initiators and capped with benzyl chloroformate ([EtG]/[I] = 50, [NEt_3]/[I] = 1, CH_2Cl_2, 60 min, rt). Predicted m/z positions for sodium adducts of polymers with one head group derived from the intiator and capped with a benzyl carbonate are marked with diamonds. (A) 3-Methoxybenzyl alcohol (Conversion (NMR) = 93%; M_n (NMR) = 4.3 kg/mol; $Đ$ (SEC) = 1.3), (B) 2-methoxyethanol (Conversion (NMR) = 91%; M_n (NMR) = 4.1 kg/mol; $Đ$ (SEC) = 1.3), (C) methyl lactate (Conversion (NMR) = 90%; M_n (NMR) = 3.8 kg/mol; $Đ$ (SEC) = 1.3), (D) 4-methoxybenzyl thiol (Conversion (NMR) = 92%; M_n (NMR) = 4.1 kg/mol; $Đ$ (SEC) = 1.3). For detailed peak lists, see Tables S5-S8; for SEC data, see Figure S8.

(MBA/BC-50; Figure 1A, Table S4). A screen of other alcohol initiators—2-methoxyethanol (ME/BC-50; Figure 1B), and methyl lactate (ML/BC-50; Figure 1C)—shows effective initiation and chain capping without apparent side reactions is possible from a range of alcohols (Table S4). Peaks for macromolecules resulting from initiation by hydrate or water are not apparent (M+14 for MBA/BC; M+77 for ME/BC; M+49 for ML/BC; Tables S5-S7). A thiol initiator, 4-methoxybenzyl thiol, was also found to produce a single series of macromolecules (MBT/BC-50; Figure 1D). Because thiols are typically better nucleophiles and much more acidic than alcohols, they have the potential to be more effective initiators for aldehydes than alcohols. The MALDI-TOF MS data cannot rule out initiation by water/hydrate because peaks for these polymers would be predicted to appear at M-2 (Table S8), however the ^{1}H NMR spectra for MBT/BC-50 shows clearly visible peaks for the aromatic protons of the methyoxybenzyl initiating group (Figure S10). ^{1}H NMR spectra of each of these polymers show peaks corresponding to protons arising from the benzyl carbonate endgroup (benzylic CH_2, δ 5.2 ppm; ArH, δ 7.3-7.5 ppm) (Figures S9-S12). M_n values for all of these polymers were estimated to be approximately 4.0 kg/mol (by ^{1}H NMR end-group analysis), with $Đ$ (SEC vs PS standards) values ranging from 1.3-1.4 (Figure S8).

In summary, triethylamine-catalyzed polymerization of ethyl glyoxylate can effectively occur from hydroxy- and thiol-functionalized initiators. MALDI-TOF MS analysis of these polymerizations shows that chain-capping with benzyl chloroformate results in a single series of polymer chains with m/z values consistent with a controlled polymerization. However, the rapidity of the polymerization process in combination with the relatively slow chain-capping process has made it difficult to effectively measure polymerization kinetics and assess the "living ness" of these polymerizations. In the future, application of high-speed/high-throughput methods for kinetic analysis of these polymerizations, such as those demonstrated by Hedrick and Waymouth could be useful tools in better understanding these polymerizations.[53] These results suggest that hydroxy- and thiol-functionalized macroinitiators could also be used to prepare block copolymers of EtG, especially in consideration of the wide variety of thiol-terminated polymers that can be prepared through RAFT polymerization.[54]

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, ^{1}H NMR spectra, and MALDI-TOF MS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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